信州大学審査学位論文

ドナー・アクセプター型シクロプロパンを用いる高立体選択的反応の開発と生理活性リグナンの不斉全合成への応用

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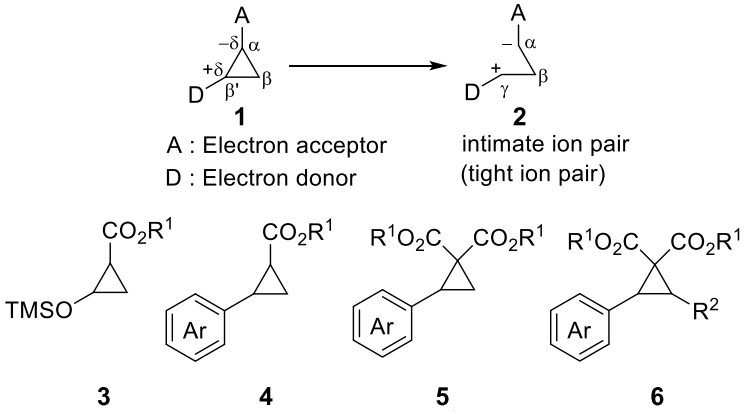
Contents

1. 序論

1.1. D-A シクロプロパン

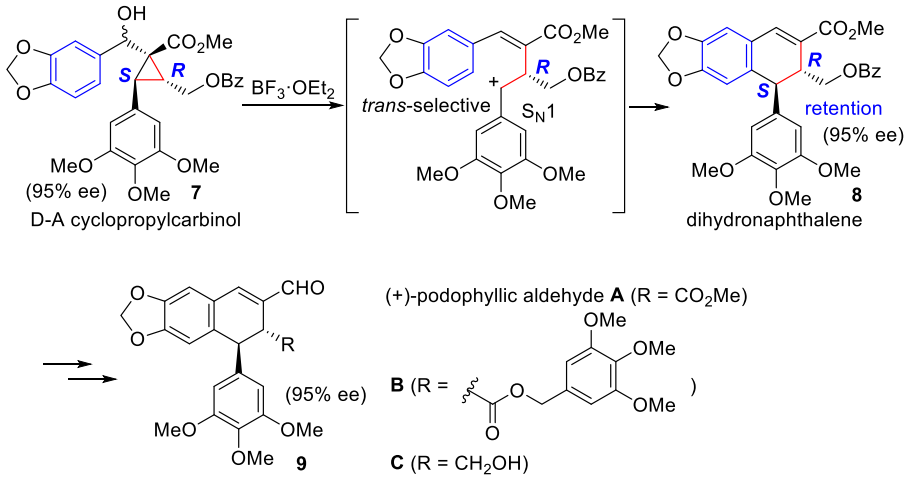
シクロプロパンは炭素小員環であり、堅固なエクリプス配座を有するため、立体配置をコントロールする足場として活用することができる。このシクロプロパンの C-C 結合は、電子供与性基（Donor）と電子求引性基（Acceptor）が 3 員環上に置換されている場合、容易に切断することができる。これをドナーアクセプター（D-A）シクロプロパン[1]と呼び、通常、**1** の構造を指す（Scheme 1.1）。電子供与性基が置換された炭素原子と電子求引性基が置換された炭素原子の間の結合は比較的弱く、負電荷は電子求引性基によって、正電荷は電子供与性基によって安定化される緊密イオン対を形成する概念が報告されている[2]。2 種の置換基が引き起こす push-pull 効果により、C-C 結合の分極が大きくなるため、開環反応を起こしやすく、高立体選択的合成への応用が可能な点で有機合成化学的に有用性が高い[1-3]。一般的には電子求引性基としてカルボニル基、電子供与性基としてシロキシ基やアリール基を有する D-A シクロプロパンが古くから研究されている。特にカルボニル基が同一炭素上に 2 つ置換されることでより活性の高いシクロプロパン **5** は有機合成化学への活用例が多く報告されている[1-3]。当研究室では **6** のような四置換シクロプロパンを不斉合成し、立体制御された分子間、または分子内反応の研究を行ってきた[4-6]。



Scheme 1.1. Examples of D-A cyclopropanes.

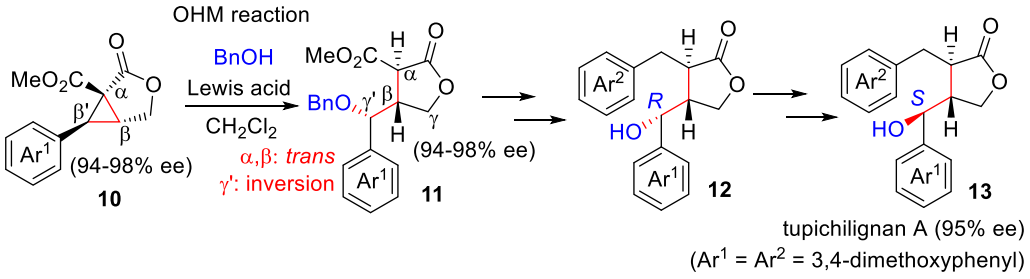
1.2. これまでの D-A シクロプロパンの研究

本論を述べるにあたって、当研究室で開発した重要な反応 2 種について説明する。まず、D-A シクロプロピルカルビノールの不斉転写分子内開環-環化反応がある。1-アリール-1,2-ジヒドロナフタレン骨格を有する天然物や生物活性化合物は多く知られており[7,8]、この開環-環化はこれらの全合成を前提に開発された反応である。この標的化合物として、細胞毒性およびアポトーシス誘導など有力な生物活性を有するポドフィリックアルデヒドを選択した[8d,e]。ポドフィリックアルデヒド類（**9A~C**）の不斉全合成は、光学活性なシクロプロピルカルビノール **7** からルイス酸として $BF_3{\cdot}OEt_2$ を用いた分子内開環-環化により、光学活性なジヒドロナフタレン **8** を得た後、数段階の置換基変換を経て達成した（Scheme 1.2）[6a]。この分子内開環-環化は、エナンチオ、ジアステレオ選択的に進行し、特にペンダントアリール基と隣接する置換基との立体配置はトランス体となる点が重要である。このトランス選択的な開環-環化の機構的研究についても報告している[6b]。

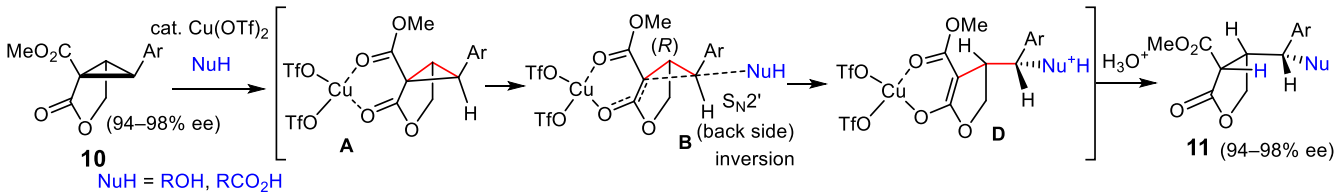


Scheme 1.2. Total synthesis of (+) podophyllic aldehydes using chiral transfer ring-opening cyclization.

もう 1 つはシクロプロパン開裂を伴う高立体選択的分子間付加反応である。これまで当研究室ではオキシホモマイケル（OHM）反応[5a]と Grignard 試薬を用いた 1,5-付加反応[5b]について報告したが、本論では前者の OHM 反応について述べる。OHM 反応は、D-A シクロプロパンに対しルイス酸存在下、アルコールを作用させると、シクロプロパン開裂を伴ったアルコールの付加が進行する。D-A シクロプロパンとして、光学活性なビシクロラクトン **10** を用いると、三連続不斉中心を有する光学活性トランス-α,β-二置換ラクトン **11** を与える（Scheme 1.3）。この反応は、まず、ルイス酸がカルボニルに配位し、次に S_N2 機構により背面からアルコールが攻撃することで、立体特異的にラクトン **11** を与える（Scheme 1.4）[5a]。アルコールとして BnOH を用いると、多様な生物活性を有する 7-ヒドロキシジベンジルリグナンラクトン[9]の不斉全合成に応用できる。その中で、リウマチや蛇に噛まれた傷に民間療法的に用いられてきた植物（*Tupista chinesis*）から 2006 年に単離されたツピキリグナン A (**13**)[10]の不斉全合成を達成した（Scheme 1.3）[5d]。本論の 4 章では、OHM 反応の scope and limitation についてと、ツピキリグナン A の合成を含めた生物活性 7-ヒドロキシジベンジルリグナンラクトンの全合成について報告する。



Scheme 1.3. Asymmetric total synthesis of 7*S*-tupichilignan A using OHM reaction.



Scheme 1.4. Plausible mechanism for OHM reaction.

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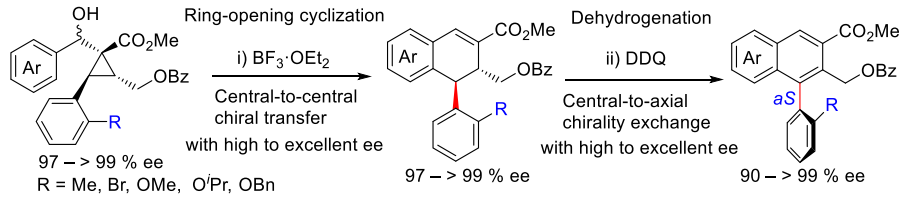
2. D-A シクロプロピルカルビノールを用いる中心から軸への不斉変換[1]

2.1. 概要

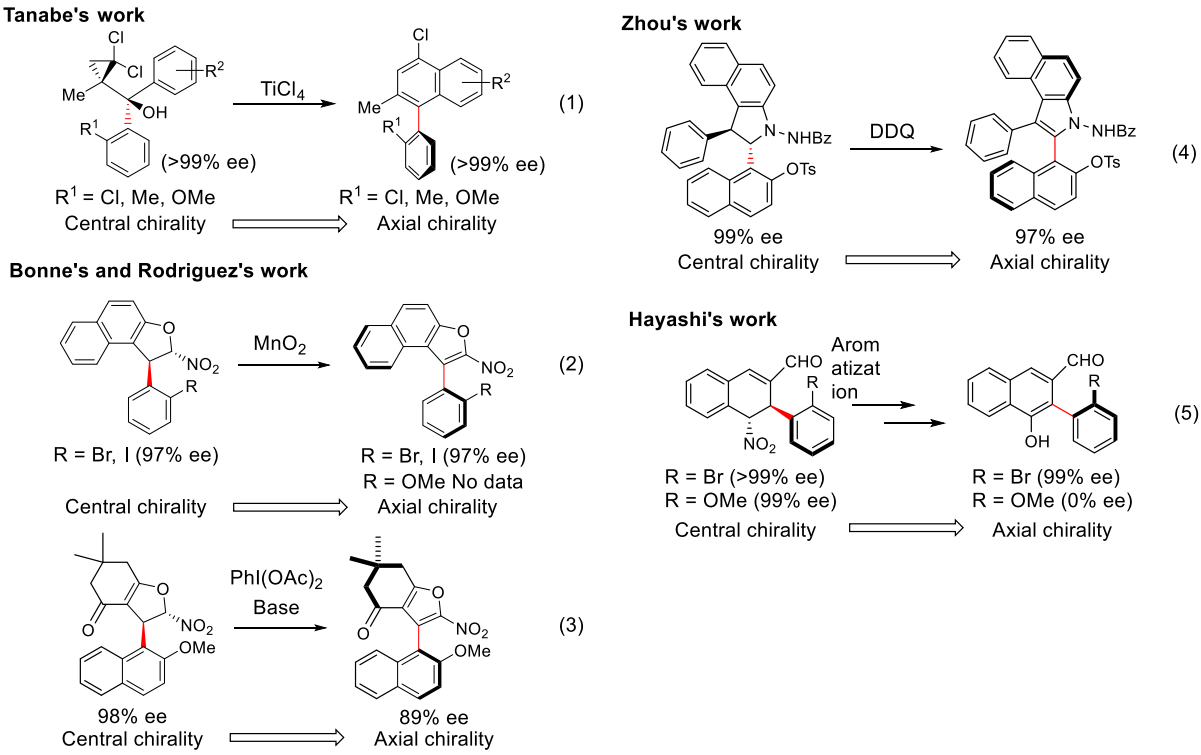


本研究では、ベンゼン環にオルト置換基を有する高光学活性 D-A シクロプロピルカルビノールから不斉転写型分子内開環-環化を経由する 1-アリールナフタレンへの変換により、高立体選択的な中心から軸への不斉変換を達成した。まず、分子内開環-環化により光学活性な D-A シクロプロピルカルビノール（97~>99% ee）からベンゼン環にオルト置換基（Me, Br, OMe, OBn, O^{i}Pr）を有する 1-アリール-1,2-ジヒドロナフタレンをエナンチオ、ジアステレオ選択的に得た（97~ >99 % ee）。続いて、不斉変換のステップとして、得られた光学活性 1-アリール-1,2-ジヒドロナフタレンの DDQ (2,3-dichloro-5,6-dicyano-*p*-benzoquinone) を用いた脱水素化により、軸不斉を有する 1-アリールナフタレンを高エナンチオ選択的に得ることができた（90~ >99 % ee）。特に重要な点は、ベンゼン環のオルト置換基にアルコキシ基を有する軸不斉 1-アリールナフタレンの高立体選択的な合成を達成したことである。さらに、不斉変換の方法を改善することで、高収率かつ高 ee でオルト位にアルコキシ基が置換されたナフタレンを得ることに成功した。

2.2. 序論

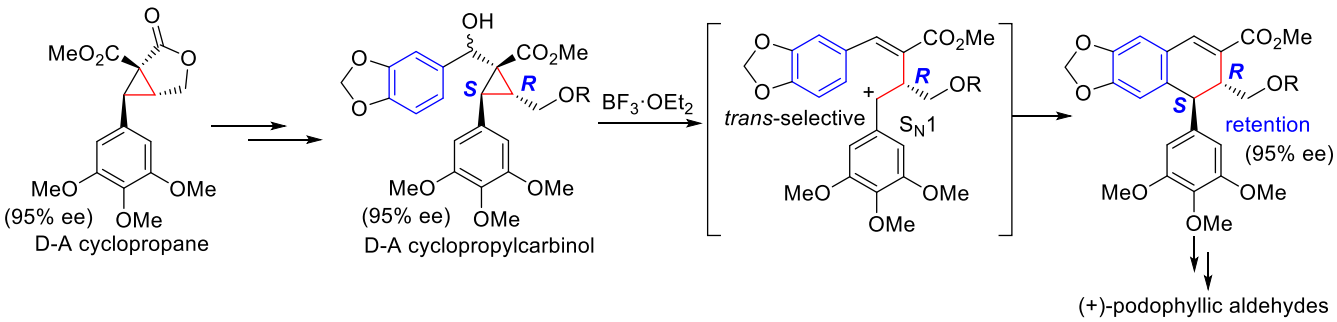
中心不斉から軸不斉への変換などキラリティーの種類を別の種類へと変換すること（以降、不斉変換と表記する）は現代の有機合成化学において長年注目されている分野である[2-8]。2004 年に、田辺らは光学活性ジクロロシクロプロピルカルビノールのベンズアヌレーションを用いた中心から軸への不斉変換を報告している [Scheme 2.1、reaction (1)][3m]。最近、Rodriguez らは酸化による中心から軸への不斉変換法を用いて、軸不斉を持つ光学活性なフランの合成を達成している [Scheme 2.1、reactions (2)、(3)[6b]][6]。Zhou らはオルト位のトシルオキシ基を用いた立体制御と DDQ 酸化により不斉変換を達成し、トシルオキシ基を変換することによる配位子への応用も報告している [Scheme 2.1、reaction (4)[7a]][7]。さらに、Zhou らはこの酸化による不斉変換のメカニズムを DFT 計算を用いて明らかにした。2020 年には、林らは 2-アリール-1,2-ジヒドロナフタレンから 2-アリールナフタレンへと段階的な芳香族化により、中心から軸への不斉変換法を報告した [Scheme 2.1、reaction (5)][8b]。Zhou ら、林らの報告では、これらの反転についてスペクトルデータや X 線結晶構造解析、計算化学により明確にした [Scheme 2.1、reactions (4)、(5)][7a,8b]。一方で、これらの研究では、不斉変換におけるエナンチオ選択性はオルト位にメトキシ基を有する基質の場合大きく減少し、他のオルトアルコキシ基を持つ置換基については報告されていない。ジヒドロベンゾフランからベンゾフランへの酸化における不斉変換についての Rodriguez らの報告には、オルトアルコキシ基置換のナフチル基の例はいくつか含まれているが、オルトアルコキシ基置換のフェニル基の例はない[6b]。林らの報告では、オルト位にメトキシ基が置換したフェニル基を持つ基質の場合、2-ア

リールジヒドロナフタレンのラセミ生成物が得られている[8b]。したがって、オルトアルコキシ置換フェニル基を有するビアリールの不斉交換の立体制御は、オルトアルコキシ置換ナフチル基を有するものよりも困難である。



Scheme 2.1. Central-to-axial chirality exchange in the synthesis of atropisomers.

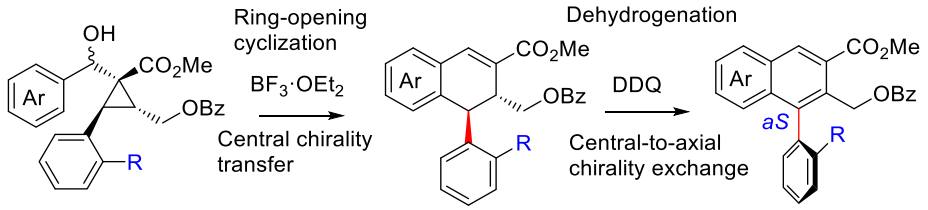
一方、ドナーアクセプター（D-A）シクロプロパンの環化反応は、炭素環および複素環の足場を合成するための方法として多く活用されている[9-11]。我々はシクロプロパンを用いた合成研究の一環として[12-14]、高光学活性 D-A シクロプロピルカルビノールの不斉転写分子内開環-環化[14]により、1-アリール-1,2-ジヒドロナフタレンを高エナンチオ、ジアステレオ選択的に得られたことを報告した。そして、この分子内開環-環化を鍵反応とし、ポドフィリックアルデヒドの不斉全合成を達成した（Scheme 2.2）[14a]。



Scheme 2.2. Our previously reported asymmetric total synthesis of (+)-podophyllic aldehydes.

このような背景から、我々は 1-アリール-1,2-ジヒドロナフタレンから 1-アリール-ナフタレンへの変換における中心から軸への不斉交換に注目した（Scheme 2.3）。本論では、高光学活性 D–A シクロプロピル

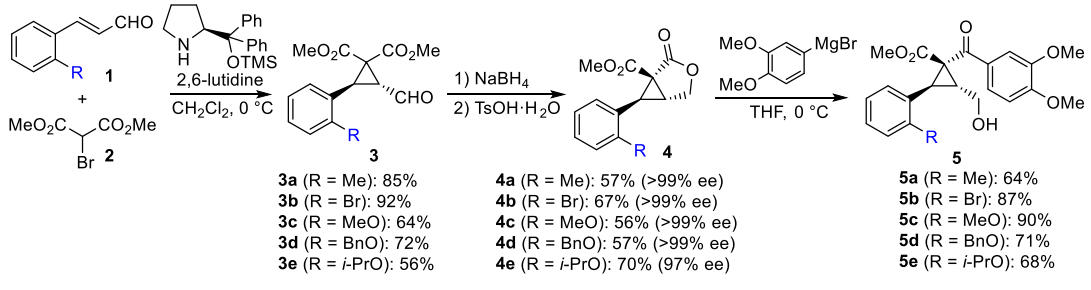
カルビノールの不斉転写分子内開環-環化とそれに続く DDQ による中心不斉を有するジヒドロナフタレンの脱水素化を用いた中心から軸への不斉交換により軸不斉アリールナフタレンの合成を達成した。特に、ペンダントアリール基にオルトアルコキシ置換基を有する基質を用いても、高いエナンチオ選択性で不斉変換に成功した。



Scheme 2.3. Synthesis of axially chiral aryl naphthalenes from centrally chiral aryl dihydronaphthalenes.

2.3. 結果・考察

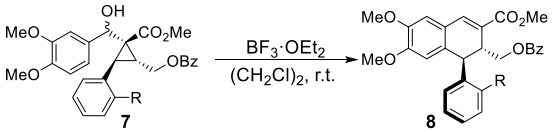
ポドフィリックアルデヒドの全合成についての我々の報告に従い、Scheme 2.4 の通りにペンダントアリール基にオルト置換基を有する光学活性 D-A シクロプロピルカルビノールの合成をした[14a]。まず、林-Jørgensen 触媒を用いた、オルト置換シンナムアルデヒド **1** とブロモマロン酸ジメチル (**2**) の不斉シクロプロパン化により、光学活性シクロプロピルアルデヒド **3** を高収率かつ高エナンチオ選択的に得た[13,15]。続いて、$NaBH_4$ を用いてアルデヒド **3** を還元した後、得られたアルコールを触媒量の *p*-トルエンスルホン酸（PTS）を用いてラクトン化し、ビシクロラクトン **4** を高収率かつ高 ee で得た[13]。ビシクロラクトン **4a-4d** の光学純度は、再結晶により >99% ee に上がった。一方で、ビシクロラクトン **4e** は再結晶が困難であったため、その光学純度は 97% ee のままとなった。これらのラクトン **4** の光学純度はキラル固定相を用いた HPLC 分析により決定した。ビシクロラクトン **4** に対し、THF 中で 3,4-ジメトキシフェニルマグネシウムブロミドを作用させることで、わずかに歪んだラクトン環において位置選択的なグリニャール反応が起こり、ケトン **5** を単一生成物として与えた。ケトン **5** の水酸基をベンゾイル基にて保護した後、得られたベンゾイルエステル **6** のカルボニル基を $NaBH_4$ で還元し、光学活性シクロプロピルカルビノール **7** を合成した。



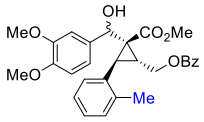
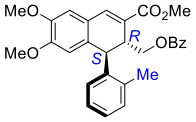
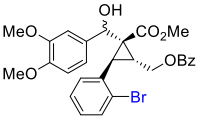
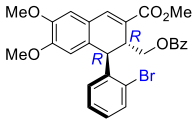
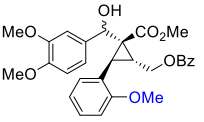
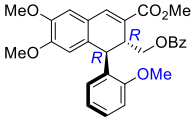
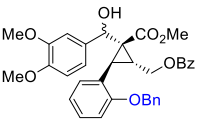
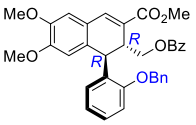
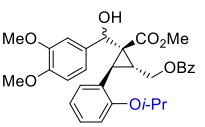
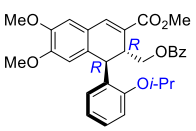
Scheme 2.4. Asymmetric synthesis of cyclopropylcarbinols.

続いて、これまでの我々の研究に従い[14]、1,2-ジクロロエタン中で光学活性シクロプロピルカルビノール **7** に対し $BF_3{\cdot}OEt_2$ を作用させると、不斉転写分子内開環-環化が起こり、1-アリール-1,2-ジヒドロナフタレン **8** を高ジアステレオ、エナンチオ選択的に得た（Table 2.1）。具体的には、ペンダントアリール基にオルト Me 置換基を有するシクロプロピルカルビノール **7a** の分子内開環-環化により、光学活性 1-アリール-1,2-ジヒドロナフタレン **8a** が単一生成物として 52%の収率、優れたトランスジアステレオ選択性と高い ee で得られた（Table 2.1、entry 1）。ジヒドロナフタレンの ee は、キラル固定相を用いた HPLC 分析によって決定し、シクロプロピルカルビノール（> 99% ee）からジヒドロナフタレン（> 99% ee）への完全な不斉転写が確認できた。Me の代わりにオルト Br 置換基を有する **7b** の開環-環化により、ジヒドロナフタレン **8b** が >99% ee で中程度の収率で得られた（entry 2）。より大きなオルト置換基は立体的に混雑するため、シクロプロパンの開環後にジヒドロナフタレンを与えるためのフリーデルクラフツアルキル化が進行しにくくなり、収率を低下させる可能性がある。オルト位にアルコキシ基を有する

Table 2.1. Synthesis of enantioenriched 1-aryl-1,2-dihydronaphthalenes **8** using a chirality-transferring ring-opening cyclization. [a]



7 **8**

Entry	Substrate **7**	Product **8**	Yield (%)[b]	ee of **8** [%][c]
1	 **7a**, >99% ee	 **8a**	52	>99
2[d]	 **7b**, >99% ee	 **8b**	45	>99
3[e]	 **7c**, >99% ee	 **8c**	79	>99
4	 **7d**, >99% ee	 **8d**	75	>99
5	 **7e**, 97% ee	 **8e**	91	97

[a] シクロプロピルカルビノール **7** （1.0 equiv.）の 1,2-ジクロロエタン溶液に、室温下 $BF_3{\cdot}OEt_2$（1.1 equiv.）加え、10 分間撹拌した。[b] 単離収率。[c] ee はキラル固定相を用いた HPLC 分析により決定した。[d] 83 ℃下で反応を行った。[e]

0 ℃下で反応を行った。

シクロプロピルカルビノール **7c–e** の場合、変換中に ee の損失なく、ジヒドロナフタレン **8c–e** がそれぞれ良好な収率で得られた（entry 3-5）。したがって、シクロプロピルカルビノール **7** の分子内開環-環化反応は、オルト置換基のサイズに関係なく、高いエナンチオ、ジアステレオ選択性で進行した。

ジヒドロナフタレン **8** は、中心不斉に加えて、回転異性体により軸不斉を示すと推測した。立体配置を解明するために、NMR を用いた実験をオルト Me 置換ジヒドロナフタレン **8a** で行った。**8a** の測定では、H(4)と H(Me)の間に NOE 相関が観察されたが、H(4)と H(6')の間に NOE 相関は確認されなかった（Figure 2.1）[16]。これらの結果から，ジヒドロナフタレン **8a** は，C(1′)と C(4)の間の結合軸において，ペンダントアリール基のオルト位の Me 置換基がジヒドロナフタレン環の外側に位置する軸配座（Me-outside）が最も安定であることが示唆された。このことは林らの報告と一致している[8,17]。ジヒドロナフタレン **8a** とジヒドロナフタレン **8b–8e** の類似性を考えると、他の基質においても R-outside が安定であると推測した。

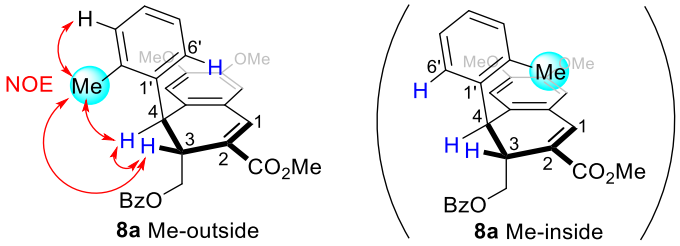
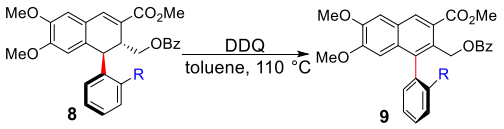


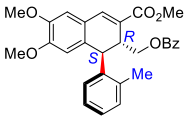
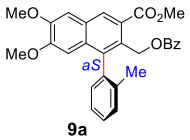
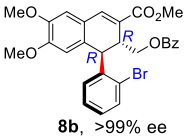
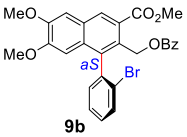
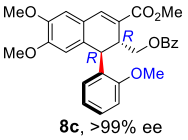
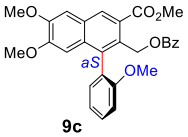
Figure 2.1. Conformational analysis of dihydronaphthalene **8a** by NOE experiment.

次に、ジヒドロナフタレン **8** の酸化的脱水素化を用いた不斉変換により、軸不斉を有する光学活性 1-アリールナフタレン **9** の構築を試みた[5,7]。ジヒドロナフタレン **8a** をトルエン（110 ℃）中、DDQ で処理すると、1-アリール-ナフタレン **9a** が収率 96%、95% ee で得られた（Table 2.2、entry 1）。光学純度は、中心から軸への不斉変換中に、>99% ee（中心不斉）から 95% ee（軸不斉）へとわずかに低下した。ee はキラル固定相を用いた HPLC 分析により決定した。酸化剤として DDQ の代わりに MnO_2 を使用した場合は、ジヒドロナフタレン **8a** の脱水素化は進行しなかった[6,8a]。よりかさ高い置換基として Br をペンダントアリール基のオルト置換基として導入した場合[6,8]、酸化的脱水素化は良好に進行し、目的の 1-アリールナフタレン **9b** が、ee の損失なく高収率で得られた（Table 2.2、entry 2）。したがって、オルト Br 置換基を有する基質において、完全な不斉変換が達成され、この結果は、他の報告と一致した[6-8]。アリール基にオルト OMe 置換基を有するジヒドロナフタレン **8c** の同様の変換（反応時間：3 時間）では、ナフタレン **9c** の ee は 74% ee に減少した（Table 2.2、 entry 3）。ただし、オルト OMe 置換基を持つナフタレン **9c** は、この方法により収率 93%、74% ee で得られたのに対し、林らの方法では、オルト OMe 置換基を有する基質の場合にラセミ生成物が得られている[8b]。1-アリールナフタレン **9c** の鏡像異性化障壁 (enantiomerization barrier) は、ナフタレンとアリール基の構造の違いのため、林らの不斉変換における 2-アリールナフタレンの異性化障壁よりもはるかに高いと予想される。したがって、オルト OMe 置換アリールナフタレン **9c** は、林らの研究によるラセミ体のオルト OMe 置換生成物と比較してある程度の ee を

示した。また、**8c** から **9c** への反応を完了させるためには 3 時間の反応が必要であった。しかし、1 時間で反応を停止させた場合、転化率は 79% だったが、得られたナフタレンは 79% ee であった。すなわち、反応時間を 1 時間から 3 時間に増やすと、DDQ を用いた脱水素化中にナフタレン **9c** の ee が 79% ee から 74% ee に減少することがわかった（Table 2.2, entries 3 and 4）。

Table 2. Dehydrogenation of dihydronaphthalenes **8** using DDQ at 110 °C. [a]



Entry	Substrate **8**	Product **9**	Time (h)	Yield[b] (%)	ee of **9** [%][c]
1	 **8a**, >99% ee	 **9a**	5	96	95
2	 **8b**, >99% ee	 **9b**	14	93	>99
3	 **8c**, >99% ee	 **9c**	3	93	74
4			1	58[d]	79

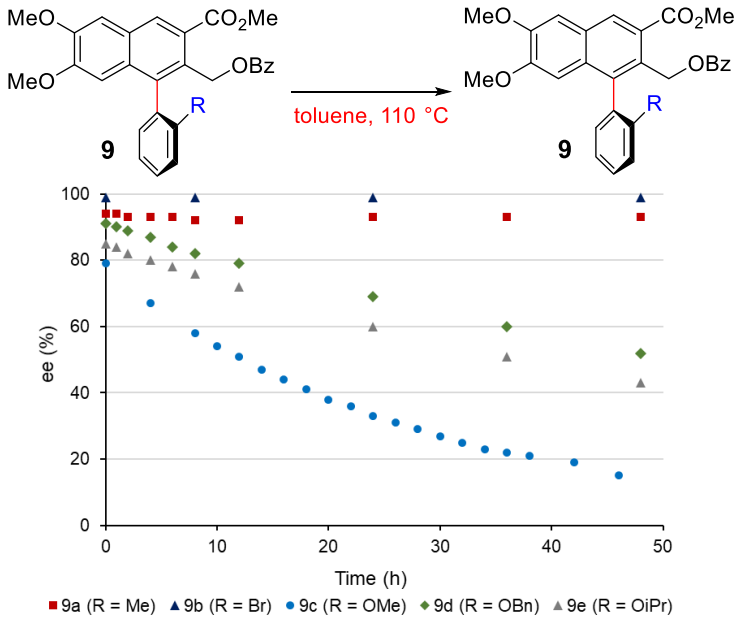
[a] ジヒドロナフタレン **8**（1.0 equiv.）のトルエン溶液に、室温下 DDQ（2.5 equiv.） を加え、110 ℃下で撹拌した。[b] 単離収率。[c] ee はキラル固定相を用いた HPLC 分析により決定した。[d] 反応転化率 79%。

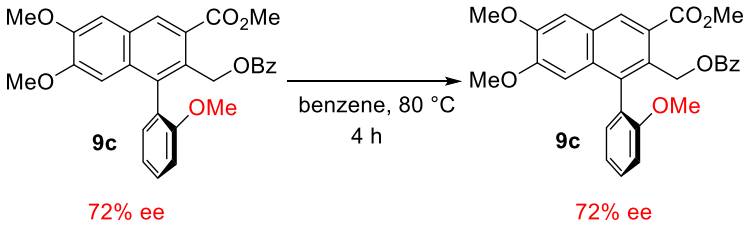
不斉交換の最適化をする前に、110 ℃と 95 ℃で軸不斉アリールナフタレン **9c** の ee を経時的に観察し、生成物の鏡像異性化障壁を調べた（SI、 S44 ページ参照）。ee の経時変化を観察したところ、光学活性なアリールナフタレン **9c**（79% ee）は 110 ℃でラセミ化が進行し、120 時間後にはほぼラセミ体（1% ee）になった。110 ℃および 95 ℃でのラセミ化実験データから Eyring 式を用いて **9c** の鏡像異性化のための Gibbs 自由エネルギー障壁 $\Delta G^{\ddagger}$を評価したところ、110 ℃のデータから 131kJ mol^{-1}、95 ℃のデータから 126kJ mol^{-1} となった。 また，110 ℃と 95 ℃の実験から，鏡像異性化の活性化エンタルピー$\Delta H^{\ddagger}$と活性化エントロピー$\Delta S^{\ddagger}$は，それぞれ 69.9 kJ mol^{-1} と -160 J mol^{-1} K^{-1} と評価された。このように鏡像異性化の障壁が比較的低いことから、110℃で部分的なラセミ化が起こったものと判断した。半減期は、110℃では 19.3 時間、95℃では 50 時間と推定された（SI、S44~S48 ページ参照）。

また、同様の ee の経時変化観察を、軸不斉ナフタレン **9b–e** においても行った。オルトアルコキシ基 OMe、O^{i}Pr、OBn をそれぞれ有する基質は、110 ℃ で 48 時間後に ee の減少を示した（Figure 2.2）。オルト Me 置換基を有するナフタレン **9a** の ee はわずかに減少したが、オルト Br 基を持つ基質は 110 ℃ でも光学純度を維持した。次に、ee 値の低下を防ぐために 110℃ 未満の温度でオルト OMe 基を有するナフタレン **9c** の ee を観察した。その結果、ベンゼン中 80 ℃にて 4 時間の撹拌ではオルト OMe を持つナフ

タレン **9c** の ee は保持された（Scheme 2.5）。この結果を踏まえ、ベンゼンまたは 1,2-ジクロロエタンの沸点（それぞれ 80°C または 83°C）で不斉変換を伴う脱水素化を行った。

Figure 2.2. Racemization of arylnaphthalenes **9** at 110 °C as a function of time.



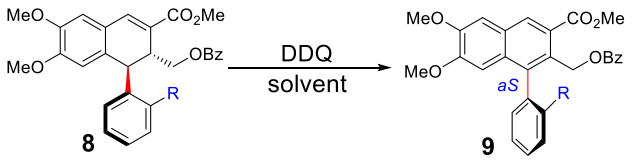


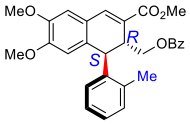
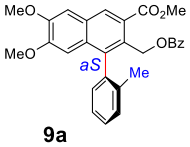
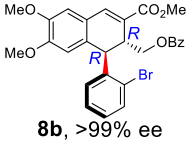
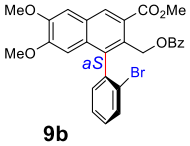
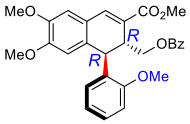
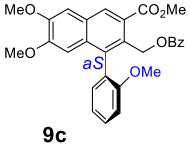
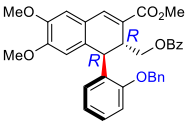
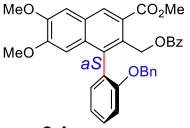
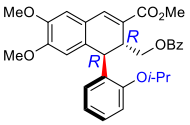
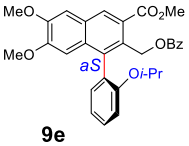
Scheme 2.5. Retention of the ee of *ortho*-OMe-substituted naphthalene **9c** in benzene at 80 °C.

Table 2.3 に示すように、すべての基質において ee が改善された。 ee はベンゼン、1,2-ジクロロエタン両方の溶媒でほぼ同じだったが、反応が完了するために必要な時間は、ベンゼンよりも 1,2-ジクロロエタンの方が短かった。これらの ee を Table 2.2 の値と比較すると、オルト Me 基を持つジヒドロナフタレン **8a** から軸不斉ナフタレン **9a** への不斉変換は、96% ee または 97% ee とわずかに改善された（Table 2.2, entries 1 and 2, Table 2.3, entries 1 and 2）。オルト Br 置換の基質 **8b** の場合、脱水素化は 80 °C または 83 °C で優れた ee（> 99%ee）かつ高収率で進行した（entries 3 and 4）。オルト OMe 置換のジヒドロナフタレン **8c** からナフタレン **9c** への不斉変換は、80 °C または 83 °C で良好に進行し、87% ee で **9c** を高収率で与えた（entries 5 and 6）。また、この反応は室温下でも進行し、反応時間は増大したが、ee は少し上昇した（entry 7）。0 °C では転化率が低下し、結果として **9c** が 66% の収率で得られ、ee は 92%とわずかに改善された（entry 8）。さらに温度を下げ、-45 °Cでの脱水素化も行ったが、反応は進行しなかった（entry 9）。生成物の収率と ee に基づくと、オルト OMe 置換基質 **8c** の DDQ を用いた脱水素化は、1,2-ジクロロエタン中、室温下で行う方法が最適であった（entry 7）。さまざまな温度、溶媒で基質 **8c** を用いた脱水

素化の最適化に関する詳細は、SI に記載した（SI、S5 ページの Table S1 を参照）。特に、調査したアルコキシ基の中で容易に脱保護され、直線的に立体が大きいオルト OBn 置換基をペンダントアリール基に導入した場合、ee はオルト OMe を有する基質と比較して高い値を示した（entries 10–13）。

Table 2.3. Central-to-axial chirality-exchange dehydrogenation of dihydronaphthalenes **8** in 1,2-dichloroethane or benzene. [a]



Entry	Substrate **8**	Product **9**	Solvent	Temp. (°C)	Time (h)	Yield[b] (%)	ee of **9** [%][c]
1			$(CH_2Cl)_2$	83	2	90	97
2	**8a**, >99% ee	**9a**	benzene	80	4	85	96
3			$(CH_2Cl)_2$	83	3	92	>99
4	**8b**, >99% ee	**9b**	benzene	80	4	92	>99
5			$(CH_2Cl)_2$	83	2.5	88	87
6			benzene	80	6	88	87
7	**8c**, >99% ee	**9c**	$(CH_2Cl)_2$	r.t.	48	90	91
8				0	144	66[d]	92
9				–45	24	0[e]	—
10			$(CH_2Cl)_2$	83	2.5	74	93
11			benzene	80	6	86	93
12	**8d**, >99% ee	**9d**	$(CH_2Cl)_2$	r.t.	48	84	98
13				0	144	69[f]	98
14			$(CH_2Cl)_2$	83	2	93	90
15	**8e**, 97% ee	**9e**	benzene	80	4	80	89

[a] ジヒドロナフタレンの 1,2-ジクロロエタンまたはベンゼン溶液に、室温下で DDQ を加え、指定の温度条件下で撹拌した。[b] 単離収率。[c] ee はキラル固定相を用いた HPLC 分析により決定した。[d] 反応転化率 84%。[e] 反応は進行せず、転化率 0%。[f] 反応転化率 89%。

1,2-ジクロロエタン中 83 °C でジヒドロナフタレン **8d** を脱水素化すると、ナフタレン **9d** が収率 74%、93% ee で得られた（entry 10）。ベンゼン中 80 °C では、同様の ee でナフタレン **9d** が収率 86%で得られ

た（entry 11）。反応を室温で行った場合、ナフタレン **9d** が収率 84%、98% ee で得られ、オルト OMe 置換のときと同様に ee が改善された（entry 12）。0 °C では、反応は完了せず（転化率 89%）、98% ee で **9d**（収率 69%）が得られた（entry 13）。よりかさ高いアルコキシ基オルト O^{i}Pr を有する基質 **8e**（97% ee）を用いた場合、83 °C または 80 °C での不斉変換により、それぞれ 90% ee および 89% ee のナフタレン **9e** が得られたが、**9d** のほどの ee は確認できなかった（entries 14 and 15）。したがって、オルト Me、オルト Br、およびオルト OBn 置換基質について、アリールジヒドロナフタレン（中心不斉）からアリールナフタレン（軸不斉）への有用性の高い（97〜> 99%ee）の不斉変換を達成した。

アリールナフタレン **9b** の絶対配置は、X 線結晶構造解析（Figure 2.3）により *aS*（アトロプ異性体の *S* 配置）として決定した[18]。反応の類似性に基づき、アリールナフタレン **9a** および **9c–e** も *aS* として決定した。この結果は、ジヒドロナフタレン **8** の最も安定した立体配座が「R-outside」であるため、DDQ を用いた脱水素化中に C(1')-C(4) 結合が回転（反転）することを示している。このことは、計算化学によって裏付けられた（SI、S72~S81 ページを参照）[19,20]。すなわち、この不斉変換では、ジヒドロナフタレン **8** の C(1')-C(4)結合軸の反転を伴い、この結果は林らの報告と一致した[7b]。

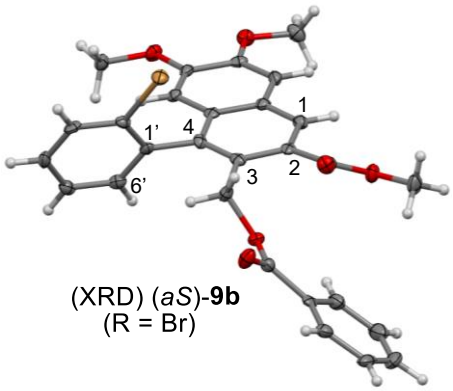
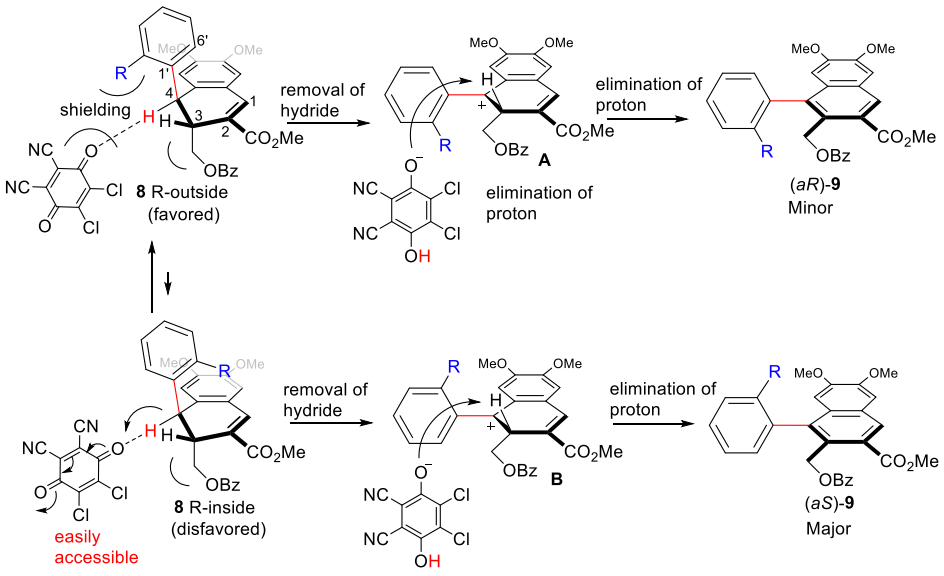


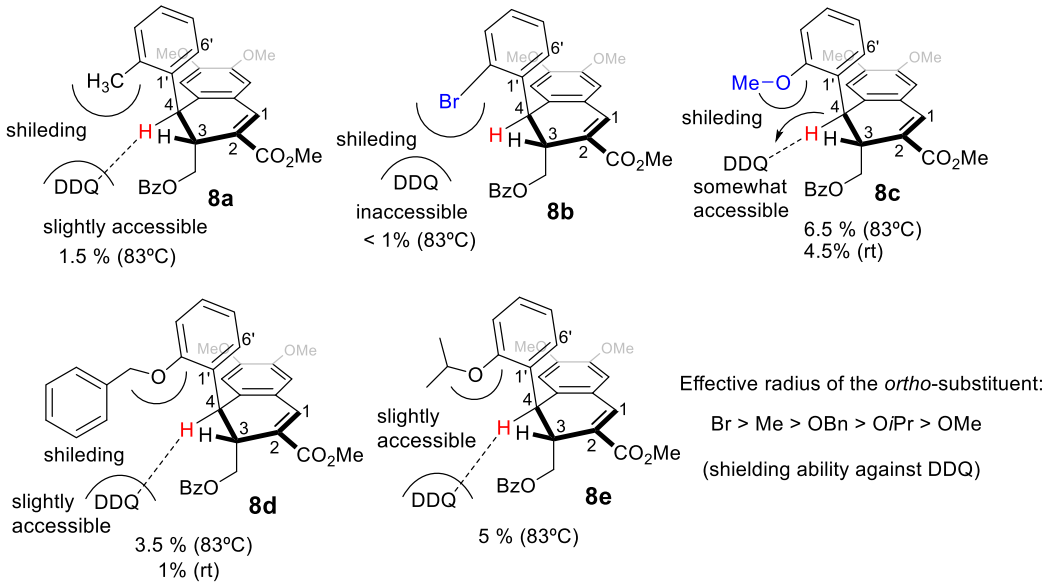
Figure. 2.3. Molecular structure of **9b** with thermal ellipsoids at 50% probability.



Scheme 2.6. Proposed mechanism for the central-to-axial chirality exchange.

次に、反応メカニズムと、高い立体選択性を誇る不斉変換の起源について考察した（Scheme 2.6）[6,7,21]。ジヒドロナフタレンの C(1′)-C(4) 結合の回転は、DDQ を用いたジヒドロナフタレン **8** の脱水素化中に起こった。R-outside では、DDQ がベンゼン環のオルト R 置換基による立体障害により C(4)の水素へ接近しにくくなるため、脱水素化の進行は妨げられる。一方、R-inside は R-outside よりも不利な立体配置であるが、R-inside の C(4)の水素は DDQ によって容易に除去される。したがって、ナフタレン(*aS*)-**9** は、C(1′)-C(4) 結合軸の反転を伴って、単一の軸不斉化合物として得られた。この結果は、Rodriguez らと Zhou らの両報告と一致した[6,7]。オルト置換基が、 R-outside における立体障害による C(4)での脱水素化を防ぐことに十分な大きさである場合、不斉変換は R-inside でのみ起こり、結果として優れた ee の軸不斉ナフタレンが得られる。

不斉変換において ee が下がる原因は 2 つ考えられる。1 つは (*aS*)-ナフタレン（Major）から (*aR*)-ナフタレン（Minor）への鏡像異性化障壁を超えることによるキラル軸の回転であり、もう 1 つは R-outside 配座において DDQ による脱水素化が進行し(*aR*)-ナフタレンを与えることである。どちらの原因もオルト置換基の有効半径に依存する。Sternhell の半径[22]（有効半径）による立体障害は、Br (1.86 ± 0.04 Å) と Me (1.80 ± 0.03 Å) が OMe (1.52 ± 0.03 Å) よりも大きく、Br (1.86 ± 0.04 Å) は Me (1.80 ± 0.03Å) よりわずかに大きいことを示している。鏡像異性化障壁は、有効半径の大きさに依存すると考えられる。つまり、*o*-Br> *o*-Me >> *o*-OMe となる。言い換えれば、鏡像異性化障壁は、オルト置換基の立体反発による有効半径の増加とともに増加する。オルト Br は、Me、OMe と比べ、大きな有効半径を持つため、110 °C 下でも ee を失うことなく、そして R-outside での脱水素化が進行することなく、完全な不斉変換を実現できた。対照的に、OMe の有効半径は Br および Me の有効半径よりもかなり小さいため、C(1′)-C(4) 軸回転による鏡像異性化障壁は 110 ℃で破られ、(*aS*)-**9** の ee が減少した。ただし、この問題は、83 ℃未満で反応を行うことで解決できる。後者の R-outside 配座 での脱水素化進行について考えると、R-outside 配座での C(4) 水素への DDQ の接近しやすさは、DDQ をシールドするオルト置換基の立体障害（有効半径）と相関する。上記のように、Br は ee を失うことなく、完全な不斉変換を実現するのに十分な大きさのオルト置換基である（Scheme 2.7、**8b**）。オルト Me も有効であるが、Br に比べて Me の有効半径がわずかに小さいため、R-outside 配座において 83 ℃で部分的に脱水素化される（1.5%）（Scheme 2.7、**8a**）。OMe の有効半径は Br、Me と比べかなり小さいため、83 ℃下で R-outside 配座に対し、さらに多くの脱水素化が起こり、目的の立体ではない(*aR*)-**9** (6.5%) が生成し、(*aS*)-**9** の ee は減少した（Scheme 2.7、**8c**）。オルトアルコキシ基を有する基質 **8c–d** の場合、脱水素化の温度を室温または 0 ℃ に下げると、R-outside 配座での脱水素化が減少し ee が向上した。さらに、オルト OBn の鎖状に広がった立体は、R-outside 配座における C(4) の水素へ接近する DDQ をよりシールドすることができるため、生成物の ee（93〜98% ee）を増加させる（Scheme 2.7、**8d**）。したがって、不斉変換における ee の損失（o-Br> o-Me >> o-OMe）は、Sternhell による有効半径に依存している。一方で O*i*Pr と OBn はまだ文献に報告されていない。ただし、本研究の 83 ℃での **9a-e** の ee の比較に基づき、これらのオルト置換基の有効半径は、Br> Me> OBn> O*i*Pr> OMe の傾向に従うと予想できる。



Scheme 2.7. Accessibility of DDQ to the hydrogen atom on C4 in the R-outside conformation of dihydronaphthalenes **8a**–**e**.

2.4. 結論

ベンゼン環にオルト置換基を持つ高光学活性 D–A シクロプロピルカルビノールから軸不斉を有する 1-アリールナフタレンに変換することにより、中心から軸へ優れた選択性で不斉交換する方法を確立した。この方法には、林–Jørgensen 触媒を用いた高エナンチオ選択的なシクロプロパン化、光学活性 D–A シクロプロピルカルビノールの不斉転写分子内開環-環化による高 ee の 1-アリール-1,2-ジヒドロナフタレンの合成も含む。得られた光学活性 1-アリール-1,2-ジヒドロナフタレンの脱水素化により、不斉変換を伴いベンゼン環上にオルト置換基を有する軸不斉 1-アリールナフタレンが高い ee で合成できた。したがって、この方法は、i）エナンチオ選択的シクロプロパン化を使用した中心不斉の構築、ii）開環-環化をによる中心不斉転写、iii）DDQ を用いた脱水素化による中心から軸への不斉変換、これら(i)~(iii) の中心から軸へのキラルリレーとみなすことができる。さらに、この不斉変換を改善して、ベンゼン環にオルト OBn 置換基を有する 1-アリールナフタレンを高 ee で得ることに成功した。

2.5. Supplementary data

実験方法、計算結果やその他補足事項は、別冊の Supporting information (SI) の S1~S81 ページを参照のこと。

2.6. 引用文献

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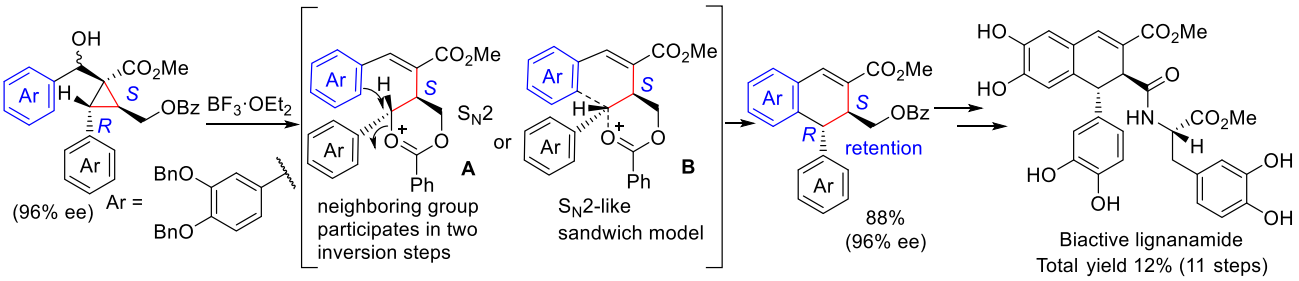
3. D-A シクロプロピルカルビノールの分子内開環-環化を用いる生理活性リグナンアミドの不斉全合成と機構解明

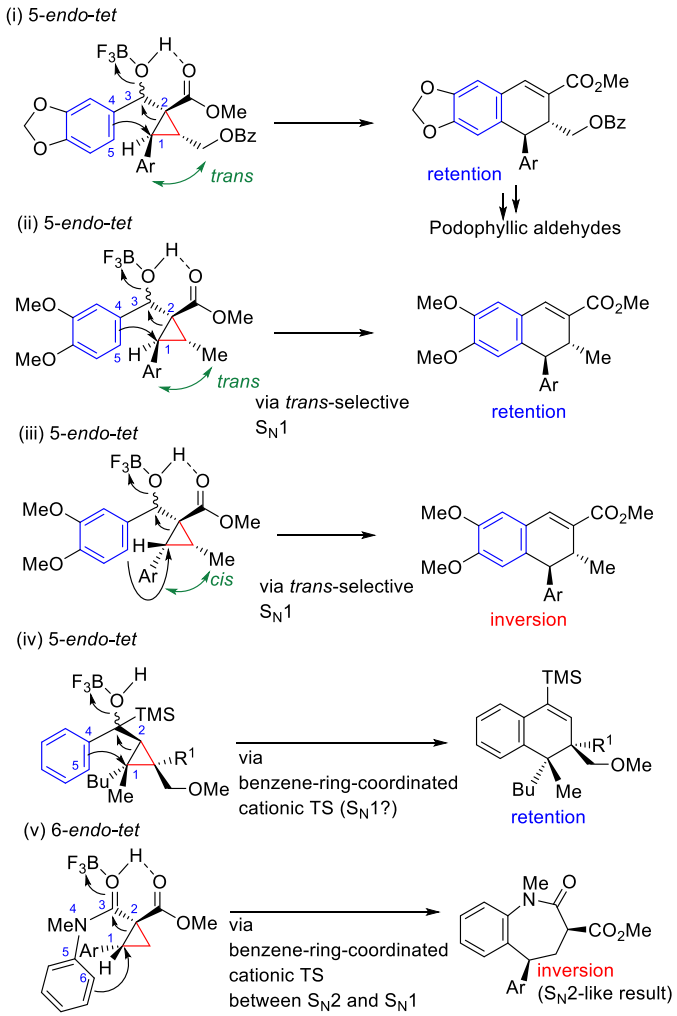
3.1. 概要



本研究では、乳がん細胞に対してより強い増殖抑制効果を示すリグナンアミド **1** のエナンチオ選択的全合成を達成した。重要な合成経路は、有機触媒によるエナンチオ選択的なシクロプロパン化と、ルイス酸を用いた 5-endo-tet 型環化反応である。特に分子内開環-環化は光学活性なシクロプロピルカルビノール（96% ee）に対してルイス酸として $BF_3{\cdot}OEt_2$ を作用させることで容易に、高収率かつ高トランス選択的にジヒドロナフタレン（96% ee）を与えた。 さらに、この重要な反応の機構を合成的に支持する結果を得た。合成結果によると、シクロプロピルカルビノールの 5-endo-tet 型環化反応は主に S_N1 機構で進行し、隣接する置換基の立体障害から高いトランス選択性が得られる。また、わずかであるが、(i)ベンゾイル基の酸素が S_N2 機構として、(ii)ベンゼン配位遷移状態が S_N1 的機構としてそれぞれ隣接基関与することがわかった。

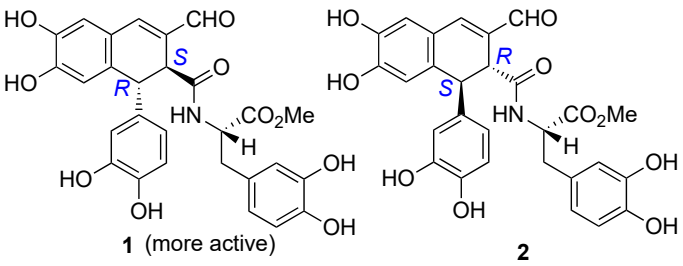
3.2. 序論

1-アリール-1,2-ジヒドロナフタレンは、自然界での有用性[1]と、それらの誘導体（ポドフィリックアルデヒドなど）は重要な生物活性を有するため[2]注目される化合物である。 たとえば、抗腫瘍性細胞毒性やアポトーシス誘導などの生物活性[2d]、トポイソメラーゼ阻害活性[2a]、および乳がん細胞に対する有効な抗増殖活性[2f,g]を示す化合物が報告されている。当研究室ではシクロプロパン骨格を用いる合成研究のとして[3-5]、ルイス酸を用いたドナーアクセプター（D-A）シクロプロピルカルビノールの高立体選択的な 5-endo-tet 型環化反応（開環-環化反応[5,6,7]）を鍵反応として、1-アリール-1,2-ジヒドロナフタレンを立体保持、高い ee で合成することに成功した [Scheme 3.1, (i)] [4d]。さらに、以前この反応について、トランス選択的な S_N1 機構を経由することを報告した [Scheme 3.1, (ii) and (iii)] [4e] D-A シクロプロパンの開環反応は、炭素環および複素環の足場合成のための汎用的な方法とされている[7] 。最近、D-A シクロプロパンの環拡大の機構研究が注目を浴びている[8,9]。Marek らは、ベンゼン環が配位したカチオン性遷移状態による多置換シクロプロピルカルビノールの開環環化により、ジヒドロナフタレン類縁体を高立体選択的に得たことを報告している [Scheme 3.1, (iv)][8]。Marek の機構は、このカチオン遷移状態を介した S_N1 的機構による立体保持を伴う 5-endo-tet 型環化反応に分類される。また、Ivanova, Trushcov, Alabugin らは、1 炭素伸長した 6-endo-tet 型環化反応による S_N2 的な反転を伴う 7 員環形成機構を報告し、その機構を計算化学で支持した[9]。6-endo-tet 型環化は立体特異的に進行し、ベンゼン環が配位したカチオン性遷移状態 (TS) を経て、反転を伴う 7 員環を形成した (S_N2 的結果) [Scheme 3.1, (v)]。



Scheme 3.1. Stereochemical pathways for some ring-opening cyclizations of cyclopropane derivatives.

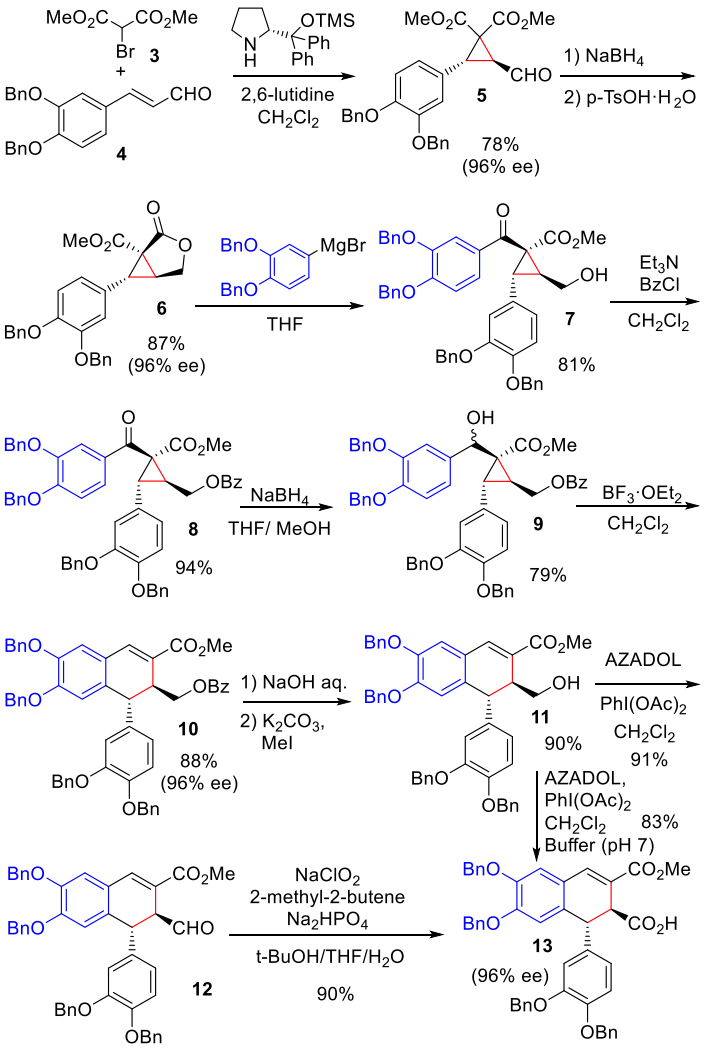
一方、L-DOPA とコーヒー酸の二量体とのハイブリッド化合物[2g,10]である生物活性リグナンアミドが合成され、乳がん細胞に対して顕著な抗増殖活性を示すことが報告されている。Magoulas らは、ラセミ体のジヒドロナフタレンセグメントと光学活性な L-DOPA セグメントとのカップリングを介して、リグナンアミド **1** および **2** を合成している（Scheme 3.2）[2g]。したがって、**1** および **2** の合成をそれぞれ達成するためには、ヘキサベンジル保護リグナンアミドのジアステレオマー混合物を分離する必要があった。これら 2 つのジアステレオマーの生物活性評価によると、リグナンアミド **1** は **2** よりも活性が高いと報告されている。しかし、リグナンアミド **1**、**2** のエナンチオ選択的な全合成はまだ報告されていない。 本研究では、D-A シクロプロピルカルビノールの開環環化反応を用いて、立体保持のまま、高 ee でリグナンアミド **1** の全合成に初めて成功したことを報告する。また、*trans*-および *cis*-異性体 **19a**, **19b** を用いた合成実験により、その鍵反応の機構を明らかにした。



Scheme 3.2. Lignanamides **1** and **2,** which exhibit antiproliferative activity.

3.3. 結果・考察

Scheme 3.3 に、ジヒドロナフタレンセグメント **13** の不斉合成について示した。ポドフィリックアルデヒドの全合成に関する以前の報告[4d]に従い、光学活性なジヒドロナフタレン **10** の合成を行った。最初に、Wang らにより報告されている、林- Jørgensen 触媒を用いた不斉シクロプロパン化により、3,4-ジベンジルオキシシンナムアルデヒド(**4**)とブロモマロン酸ジメチル(**3**)から光学活性シクロプロピルアルデヒド **5** を収率 78%、96% ee で得た[11]。THF /メタノール（1/1、v / v）中[12]、$NaBH_4$ を用いてシクロプロピルアルデヒド **5** を還元した後、得られたアルコールを触媒量の *p*-トルエンスルホン酸（*p*-TsOH·H_2O）でラクトン化すると、ビシクロラクトン **6** が収率 87%（96% ee）で得られた。ラクトン **6** の光学純度は、キラル固定相を用いた HPLC 分析により決定し、シクロプロパン化により得られたアルデヒド **5** の ee は、この HPLC 分析に基づいて決定した。ビシクロラクトン **6** に対し THF 中、3,4-ジベンジルオキシフェニルマグネシウムブロミドを作用させると、わずかに歪んだラクトン環に対し、位置選択的なグリニャール反応が起こり、ケトン **7** が高収率（81%）で得られた。ケトン **7** の水酸基をベンゾイル保護し、得られたベンゾイルエステル **8** のカルボニル基を THF /メタノール（1/1、v / v）[12] 中、$NaBH_4$ で還元すると、高光学活性シクロプロピルカルビノール **9** が収率 79%で得られた（dr = 10 / 1、96% ee)。シクロプロピルカルビノール **9** は 10：1 のジアステレオマー比で得られたが、両ジアステレオマーは続く分子内開環-環化により同様な立体のジヒドロナフタレン **10** を与える[13]。高光学活性シクロプロピルカルビノール **9** をジクロロメタン中、BF_3·OEt_2 を作用させると、分子内開環-環化がエナンチオ、ジアステレオ選択的に進行し、ジヒドロナフタレン **10** が収率 90%で 96% ee で得られた。ジヒドロナフタレン **10** の ee はキラル固定相を用いた HPLC 分析により決定した。

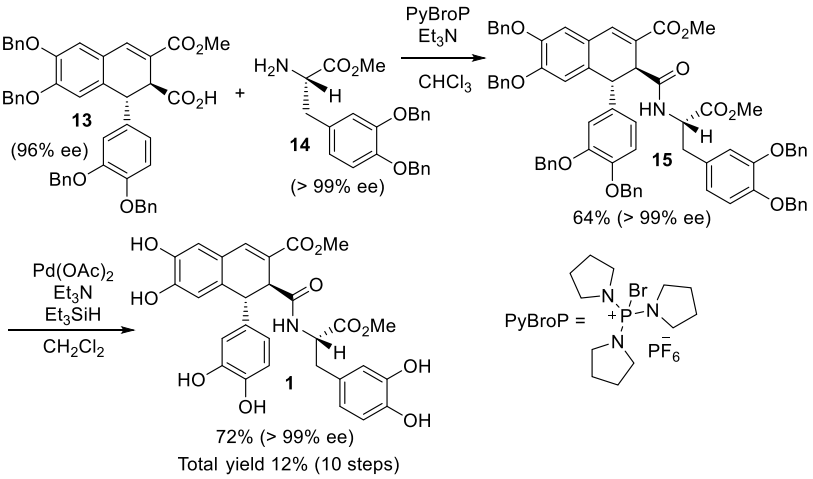


Scheme 3.3 Asymmetric total synthesis of dihydronaphthalene **13**.

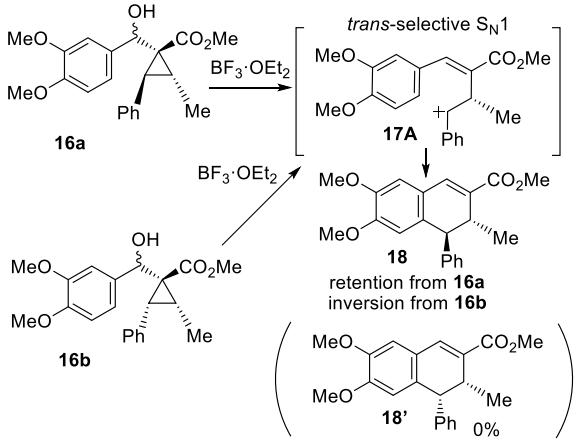
次に、ジヒドロナフタレン **10** をさらに変換し、ジヒドロナフタレン **13** へと導いた。THF/メタノール[12]中、NaOH 水溶液を用いて、ジヒドロナフタレン **10** のエステル部位を加水分解しカルボン酸を得た。得られたカルボン酸を DMF 中、K_2CO_3 存在下、MeI によりメチル化すると、アルコール **11** が 2 段階収率 90%で得られた。ジクロロメタン中、AZADOL[14]を用いたアルコール **11** の酸化により、アルデヒド **12** が収率 91%で得られた。 続いてアルデヒド **12** を Pinnick（Kraus）酸化に付すと[15]、カルボン酸であるジヒドロナフタレンセグメント **13** が収率 90%（96%ee）で得られた。一方、緩衝液（pH 7）を加え、ジクロロメタン中で AZADOL を用いてアルコール **11** を酸化すると、カルボン酸 **13** が収率 83%で直接得られた[16]。ジヒドロナフタレン **13** の光学純度は、前述のジヒドロナフタレン **10** の HPLC 分析に基づいて推定した。このように、温和な条件下で段階的または直接酸化することにより、アルコールからカルボン酸へと誘導できた。この直接酸化は、最も顕著な改善点である[4d]。他のアルコール **11** をより厳しい条件下で直接酸化する方法（例えば、Jones 酸化）は、ジヒドロナフタレンの脱水素化をもたらし、芳香族化を起こしてナフタレンを得る結果となった。

次に、Magoulas の方法に従い（Scheme 3.4）[2g]、PyBrOP と Et_3N の存在下でジヒドロナフタレン **13** とベンジル保護された DOPA セグメント **14** を縮合させると、目的のアミド **15** が 64%の収率（> 99%ee）

で得られた。シリカゲルを用いたカラムクロマトグラフィーにより、微量に含まれる別のジアステレオマーをアミド **15** から分離した。最後に、触媒量の $Pd(OAc)_2$ の存在下、アミド **15** を Et_3SiH および Et_3N を用いた脱ベンジル化[17]により、目的のリグナンアミド **1** が収率 72%で得られた（総収率：10 ステップで 12%）。



Scheme 3.4. Amide condensation of dihydronaphthalene segment **13** with protected L-DOPA segment **14**.

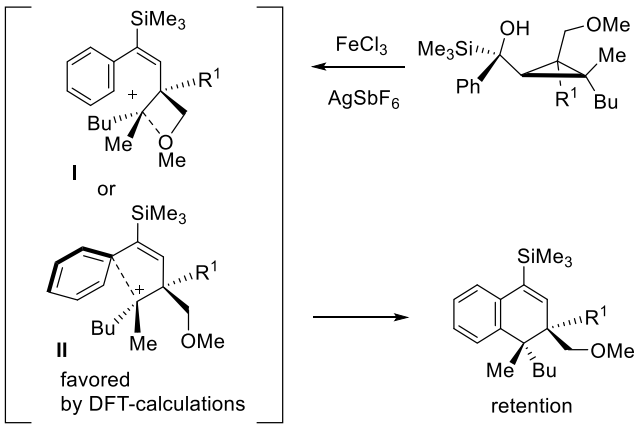


Scheme 3.5. Proposed mechanism for the ring-opening cyclization of *trans*- and *cis*-2-methyl-3-phenylcyclopropylcarbinols **16a** and **16b**.

全合成を達成するための鍵となる環化反応の機構については、シクロプロピルカルビノール **16a**、**16b** の開環環化によりトランス-ジヒドロナフタレン **18** が単一異性体として得られること（Scheme 3.5）を以前に報告した[4e]。この報告に基づき、我々は、全合成の鍵反応としてベンゼン環配位機構よりもトランス選択的 S_N1 機構を提案する。

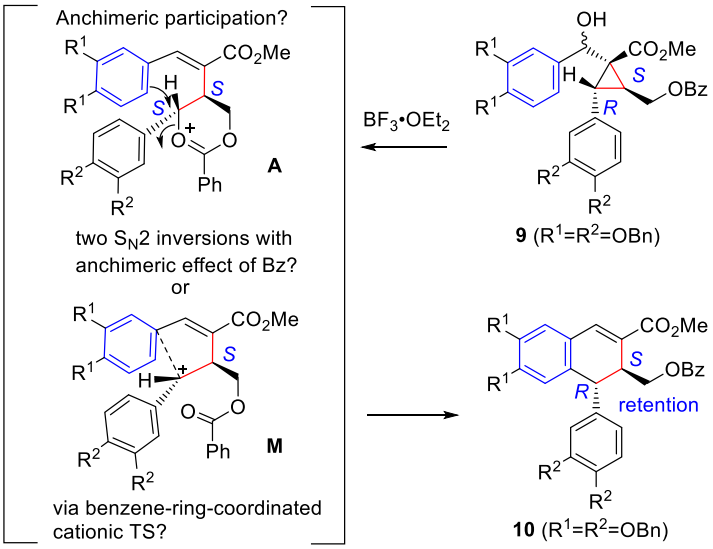
最近、Marek らはトリメチルシリル基を有するシクロプロピルカルビノールの同様の分子内開環-環化を報告している。この反応は立体保持で進行し、高い ee でジヒドロナフタレンを与える。Scheme 3.6 に示すように、Marek らは立体保持の生成物を与えるメカニズムとして、4 員環を形成することによってカ

チオン性炭素中心に配位する OMe 基の隣接基効果（Cation I）、あるいはベンゼン環の π 電子による別の隣接基効果（Cation II）を報告した[8]。彼らは DFT 計算により後者のメカニズムで進行することを裏付けた。このメカニズムは、以前の報告[4e]で述べたペリ環状反応のようなメカニズムに類似しており、シクロプロピルカルビノール **16b** からジヒドロナフタレン **18** へのトランス選択的なメカニズム（Scheme 3.5）においては説明できない。

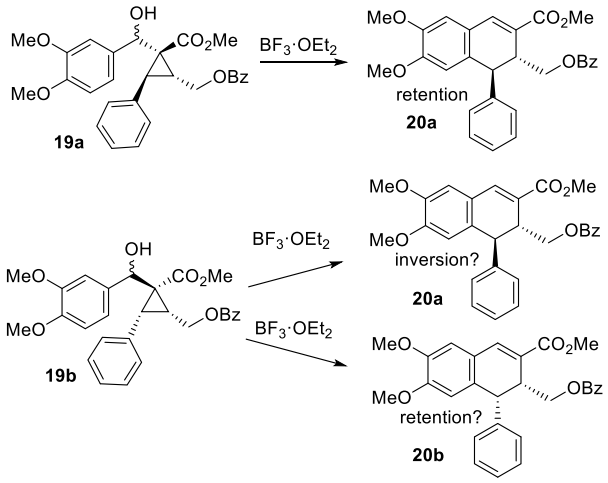


Scheme 3.6. Ring-opening cyclization mechanism reported by Marek.

Marek らの文献[8]に基づくと、今回報告した反応は、シクロプロピルカルビノール **9** のベンゾイル基を用いた 6 員環オキソニウムカチオンの形成に適していると思われる。シクロプロピルカルビノール **9** のベンゾイル基の隣接基効果により、2 回の S_N2 反転を経て反応が進行し、生成物 **10** が立体保持で得られると考えられる（Scheme 3.7）。最初の反転は 6 員環オキソニウムカチオン **A** を生成する際に起こり、2 回目の反転は S_N2 的な Friedel-Crafts アルキル化によってジヒドロナフタレン **10** を得るために起こると考えられる。一方、Marek の報告にあるベンゼン環配位カチオン遷移状態 **M** でも、立体制御が可能であると考えられる。

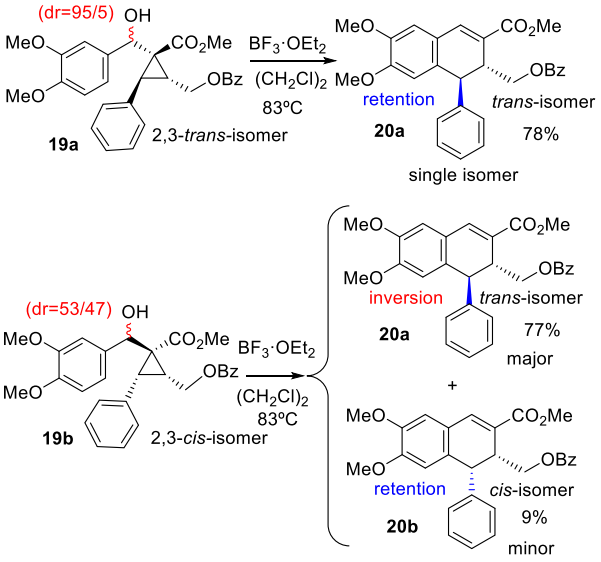


Scheme 3.7. Ring-opening cyclizations mechanism of cyclopropylcarbinol **9** involving anchimeric participation.



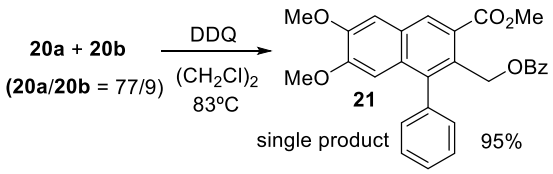
Scheme 3.8. Predictions of the stereochemical pathways in the ring-opening cyclization of *trans*- and *cis*-2-benzyloxy-3-phenylcyclopropylcarbinols **19a** and **19b**.

この鍵反応の機構を解明するために、CH_2OBz 基を有する *trans*-および *cis*-シクロプロピルカルビノール **19a, 19b** の開環-環化反応を行った。*trans*-シクロプロピルカルビノール **19a** は、前述のリグナンアミドの全合成（SI、S101-106 ページ参照）と同様の方法を用いて調製した。*cis*-異性体 **19b** は、(*Z*)-桂皮酸エチルから合成した（SI、S106-113 ページを参照）。*trans*-異性体 **19a** を BF_3・OEt_2 で 83 ℃で処理すると、*trans*-ジヒドロナフタレン **20a** が単一生成物として 78%の収率で得られた (Scheme 3.9)。同様に *cis*-異性体 **19b** を用いた場合では、*trans*-ジヒドロナフタレン **20a** と *cis*-ジヒドロナフタレン **20b** がそれぞれ 77% と 9%の収率で得られた (Scheme 3.9)。 *cis*-ジヒドロナフタレン **20b** は、主生成物 **20a** と分離不可能な副生成物 **20b** の混合物として得られ、それぞれの割合は ^{1}H-NMR スペクトルで決定した。分離できない異性体 **20a** および **20b** の混合物を DDQ[18] を用いて脱水素化すると、ナフタレン **21** が



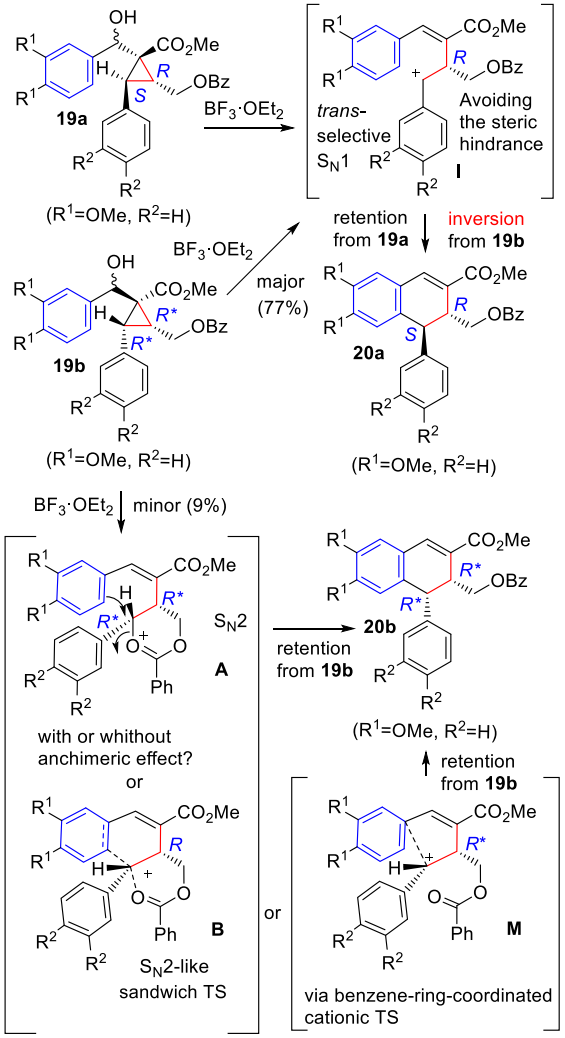
Scheme 3.9. Stereochemical pathways for the ring-opening cyclization of *trans*- and *cis*-2-benzoyloxy-3-phenylcyclopropylcarbinols **19a** and **19b**.

収率 95% で単一生成物として得られた (Scheme 3.10)。**20a** と **20b** の混合物がナフタレン **21** に変換されることから、副生成物は *cis*-ジヒドロナフタレン **20b** と推定された。このように，5-endo-tet 型環化反応において，わずかな立体保持は見られるものの、*cis* 配置 **19b** の大部分は立体反転を伴い *trans* 配置 **20a** に変換された。すなわち、*trans*-シクロプロピルカルビノール **19a** と *cis*-シクロプロピルカルビノール **19b** の開環環化反応は、主生成物として *trans*-ジヒドロナフタレン **20a** を与えた。



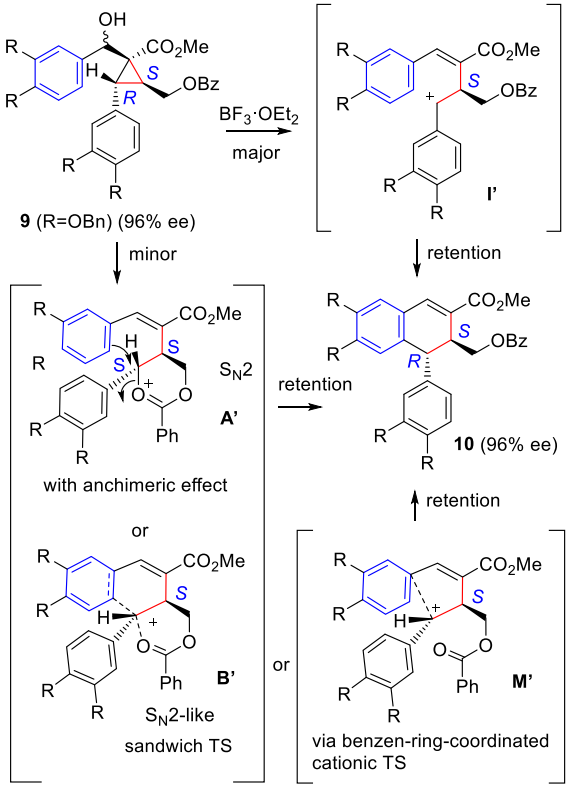
Scheme 3.10. Aromatization of a mixture of *trans*- and *cis*-dihydronaphthalene **20a** and **20b** using DDQ to afford naphthalene **21**.

これらの結果から、5-endo-tet 型の開環-環化反応について、反応機構を考察した（Scheme 3.11）。シクロプロピルカルビノール **19a**, **19b** の水酸基が脱離した後、シクロプロパンを開環すると、カチオン中間体 **I** が得られる。次に、カチオン **I** に対する Friedel-Crafts 型攻撃が起こり、CH_2OBz 基の立体障害を避けることで、*trans*-ジヒドロナフタレン **20a** を高い *trans* 選択性で得ることができる。このように、*cis* 異性体 **19b** の反応では、不斉中心の反転が確認された。しかし、*cis* 異性体 **19b** のごく一部は立体保持で進行し、*cis*-ジヒドロナフタレン **20b** を生成した。このマイナー経路には、隣接基関与による S_N2 機構の中間体 **A** または **B**、あるいは Marek による報告の機構と類似した遷移状態 **M** が関与すると考えられる[8]。すなわち、ベンゾイル基を有するシクロプロピルカルビノール **19a** および **19b** の 5-endo-tet 型環化反応は、主に隣接する CH_2OBz 基[20]が関与しない高トランス選択的 S_N1 機構を経由し進行した(Scheme 3.11)。この結果は、CH_2OBz 基の代わりにメチル基を持つ基質 **16b** の結果と一致する[4e,19]。しかし、*cis*-シクロプロピルカルビノール **16b** の開環-環化では *trans*-ジヒドロナフタレン **18** のみが得られたが、CH_2OBz 基を有するシクロプロピルカルビノール **19b** の反応では、少量の *cis*-ジヒドロナフタレン **20b** を得た。Marek の報告[8] では、シクロプロパンの開環により生成する 3 級カルボカチオンの存在が Friedel-Crafts アルキル化の際に立体を保持するために必要であるとされている（Scheme 3.6）。今回報告した 2 級カルボカチオンを経由する反応では、**19b** の反応により *trans*-異性体 **20a** が反転した主生成物となった。



Scheme 3.11. Explanation for the ring-opening cyclization mechanism of *trans*- and *cis*-2-benzoyloxy-3-phenylcyclopropylcarbinols **19a** and **19b**.

また、前述のリグナンアミド **1** の全合成において、*trans*-シクロプロピルカルビノール **9** を用いて 5-endo-tet 型環化反応を行い、*trans*-ジヒドロナフタレン **10** を得る場合にもこの機構が適用できる（Scheme 3.12）。*trans*-1,2-ジヒドロナフタレン **10** は, (i) 主経路では二級カチオン **I′**を経由するトランス選択的 S_N1 機構, (ii) 副経路では中間体 **A′**または隣接基関与する遷移状態 **B′**または **M′**を経由する機構により立体を保持して得られた(**A′**から **B′**や **M′**を経て **10** に至る過程は S_N2 機構の遷移状態と見なすことができる)。



Scheme 3.12. Explanation for the chirality-transferring 5-*endo*-*tet*-type ring-opening cyclization mechanism of *trans*-2-benzoyloxy-3-phenylcyclopropylcarbinol **9**.

3.4. 結論

以上のように、著者は有機触媒を用いた不斉シクロプロパン化を経由し、生理活性を有するリグナンアミド **1** を高い ee で不斉全合成することに成功した。高光学活性シクロプロピルカルビノールのルイス酸を用いた不斉転写開環-環化反応により、光学活性なジヒドロナフタレンを高エナンチオ、ジアステレオ選択的に得た。生物活性のあるリグナンアミド **1** は、10 段階を経て総収率 12%で得られた。不斉転写開環-環化反応の結果に基づき反応機構を考察したところ、重要なステップである 5-endo-tet 型環化反応は *trans* 選択的 S_N1 機構が主経路として進行し、隣接基が関与する機構は副経路であることが判明した。

3.5. Supplementary data

実験方法やその他補足事項は、別冊の Supporting information (SI) の S82~S116 ページを参照のこと。

3.6. 引用文献

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[13] Interestingly, instead of the Friedel–Crafts-type attack of the benzene ring, the nucleophilic attack of the OH group on the cationic benzyl position occurred to cyclize a furofuran ring in the efficient total synthesis of (+)-sesamin and (+)-sesamol: R. Ishikawa, N. Yoshida, Y. Akao, Y. Kawabe, M. Inai, T. Asakawa, Y. Hamashima, T. Kan, *Chem. Lett*. **2014**, *43*, 1572. The corresponding author of the report, T. Kan, is one of the persons to whom this report is dedicated.

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[20] At the 59th Symposium on the Chemistry of Natural Products held in Sapporo in 2017, Prof. Hidetoshi Yamada (one of persons to whom this report is dedicated) kindly suggested the anchimeric participation of a benzoylmethyl group in the ring-opening cyclization to us. This article can be considered an answer to his suggestion.

4. D-A シクロプロパンの高立体選択的 OHM 反応とツピキリグナン A の全合成

4.1. 概要

ドナー・アクセプター（D-A）シクロプロパンを用いて、ツピキリグナンの不斉全合成を達成した。林-Jørgensen 触媒を用いた不斉シクロプロパン化反応、ラクトンを有する D-A シクロプロパンのオキシホモマイケル（OHM）反応、γ-ラクトンの α-ベンジル化、*trans*-α,β-ジベンジル-γ-ラクトンの脱炭酸、酸化と立体選択的還元による 7 位の水酸基不斉中心の立体反転、これらは高い立体選択性を持って進行した。これまでツピキリグナンとして同定されていたジアステレオマーのスペクトルデータは、天然物の報告データと矛盾することが判明した。合成した両ジアステレオマーのスペクトルデータに基づき、ツピキリグナンの構造を修正し、ツピキリグナンの 7 位の絶対配置を *R* から *S* に変更した。

1.2. 序論

リグナンは、植物に広く存在し、その多様な生理活性から注目されている[1-3]。例えば、7*S*-ヒドロキシマタイレシノールなどの 7-ヒドロキシジベンジルリグナンラクトンは、統計的に有用な腫瘍増殖抑制効果を示すことから、抗がん剤の有力候補である（Figure 4.1）[2a-c]。 2006 年に、中国の民間療法でリウマチ疾患や蛇刺の治療に伝統的に使用されている *Tupistra chinensis* Baker から 7*R*-ヒドロキシマタイレシノールと同様の絶対配置を示すツピキリグナン A が単離されている[3]。しかし、ツピキリグナン A の全合成はまだ報告されておらず、7 位の水酸基を持つ炭素原子の絶対配置は構造活性相関（SAR）研究において興味深い分野となっている[2]。

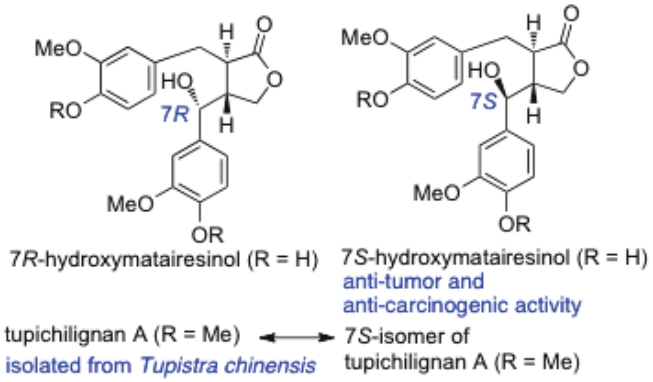
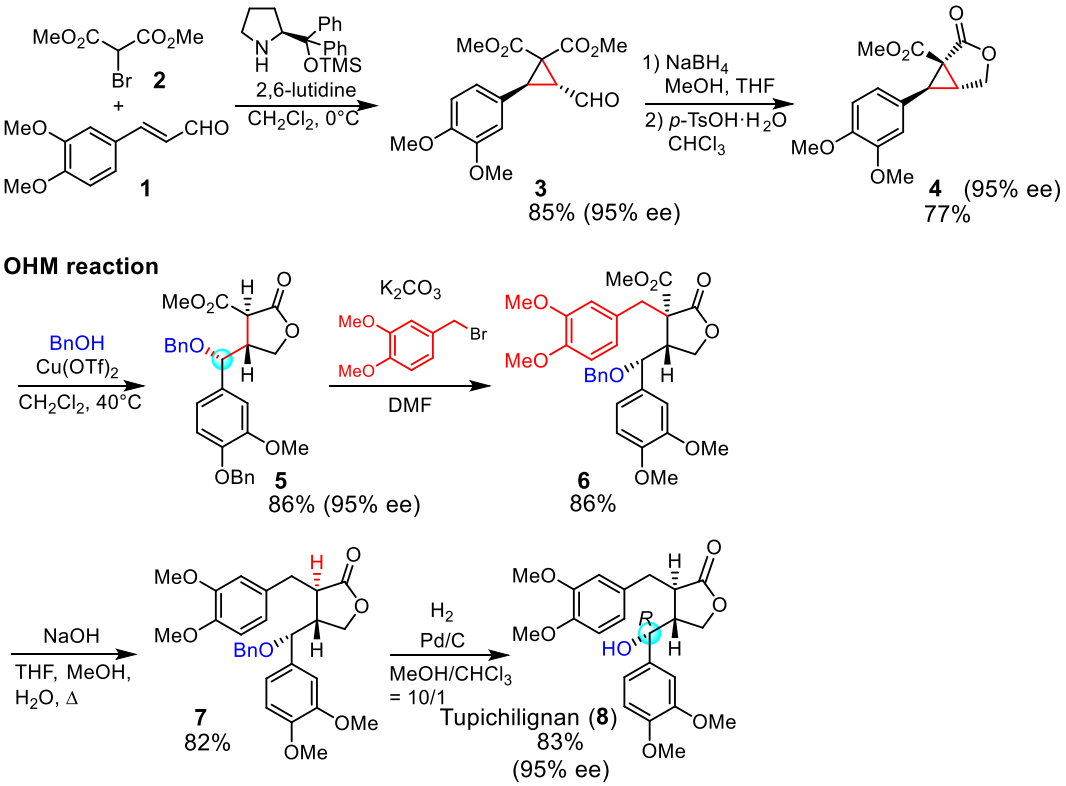


Figure 4.1. Structures of the isomers of hydroxymatairesinol and tupichilignan A.

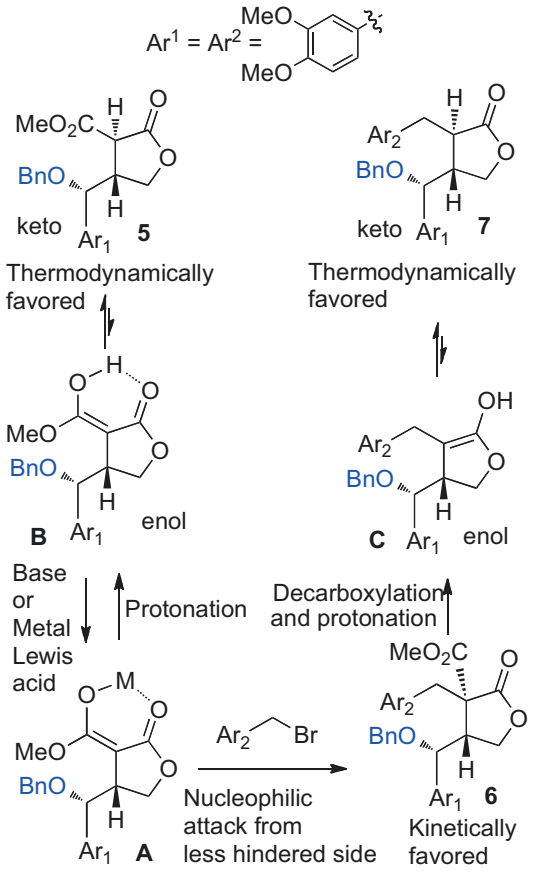
一方、最近の合成研究から、有機合成化学におけるドナー・アクセプター（D-A）シクロプロパンは注目された化合物である[4]。シクロプロパンを用いた合成研究の過程で、当研究室では既に、ラクトン環を有する D-A シクロプロパンへのオキシホモマイケル（OHM）付加反応を報告している[5,6]。 本論では、高光学活性ビシクロラクトンの OHM 反応を鍵反応として、ツピキリグナン A とその 7*S*-異性体の不斉全合成に初めて成功したことを報告する。

4.3. 結果・考察

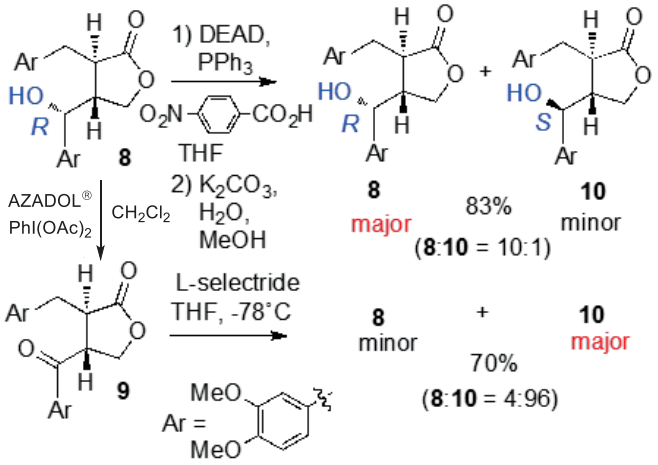


Scheme 4.1. Asymmetric total synthesis of tupichilignan A.

まず、林-Jørgensen 触媒を用いたジメトキシシンナムアルデヒド(**1**)とブロモマロン酸ジメチル (**2**) の不斉シクロプロパン化により、高光学活性シクロプロピルアルデヒド **3** が高い収率かつ高 ee で得られた (Scheme 4.1)[6f,h]。 アルデヒド **3** の $NaBH_4$ による還元とその後のラクトン化によりビシクロラクトン **4** が得られた。ビシクロラクトン **4** へのベンジルアルコールの高立体選択的 OHM 付加[6h] により、シクロプロパン開裂を伴い、立体反転で進行し、目的のラクトン **5** が高収率かつジアステレオ選択的に得られた。その後、ベンジルオキシラクトン **5** から生成したエノラートが、より立体障害の小さい面から 3,4-ジメトキシベンジルブロミドを攻撃して、目的物 **6** を単一異性体として得ることに成功した。得られたエステル **6** を脱炭酸し、プロトン化することにより *trans*-α,β-二置換ラクトン **7** を得た。ケト-エノール互変異性化により、熱力学的に有利なトランス配置の生成物 **7** が優れた dr で得られた(Scheme 4.2)。最後に、水素雰囲気下、触媒量の Pd-C を用いて **7** を脱ベンジル化すると、高収率でツピキリグナン A（**8**）が得られた。しかし、今回合成した 7*R*-異性体 **8** のスペクトルデータは、これまでツピキリグナン A として報告されていた天然物の報告データと矛盾していた（Table 4.1）[3]。^{1}H NMR スペクトルの H-7, H-8, H-9, H-7', H-8' の化学シフトは文献から得られたデータと大きく異なっていた。7*S*-および 7*R*-ヒドロキシマタイレシノールのスペクトルデータに基づいて[7]、我々は天然ツピキリグナン A の構造は 7*S*-異性体（**10**；Scheme 4.3）、すなわち **8** のエピマーであることを推測した。



Scheme 4.2. Explanation for stereoselective alkylation of **5**.

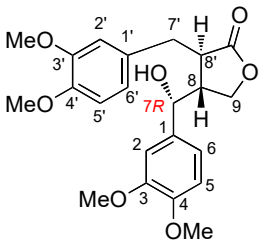


Scheme 4.3. Inversion of the configuration at the 7-position from the 7*R*-isomer **8** to the 7*S*-isomer **10** via ketone **9**.

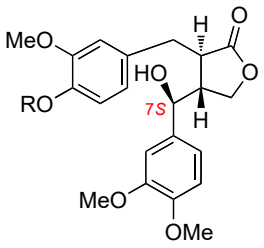
そこで、この仮説を検証するために、対応する 7*S*-異性体 **10** の合成を行った。まず、光延反応によって 7*R*-異性体 **8** の 7 位の立体を反転させようとしたが、原料 **8** と目的物 **10** の 10:1 混合物が生成した(Scheme 4.3)[8,9]。一方、アルコール **8** を酸化して得られたケトン **9** を L-selectride で還元すると、高い立体選択性 (dr＝96:4) とともに 7*S*-異性体 **10** が良好な収率で得られることがわかった。このようにして得られた 7*S*-異性体の ^{1}H NMR スペクトルデータは、天然のツピキリグナン A のものと一致した（Table 4.1)。また、7*S*-異性体の ^{13}C NMR スペクトルもツピキリグナン A のものと完全に一致した(Table 4.2)。

その結果、天然のツピキリグナン A の構造は、7*S*-異性体 **10** であることが確認された（Scheme 4.4）。

Table 4.1. Comparison of the ^{1}H NMR (400 MHz, $CDCl_3$) spectral data of reported tupichilignan A with those of the synthesized 7*R*- and 7*S*-isomers.



7*R*-isomer **8**

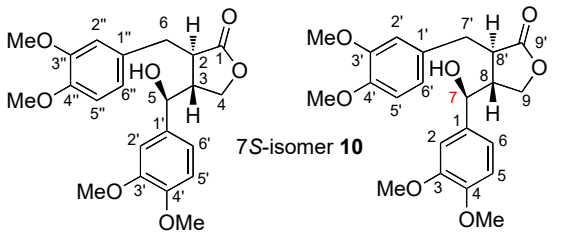


7*S*-isomer **10**

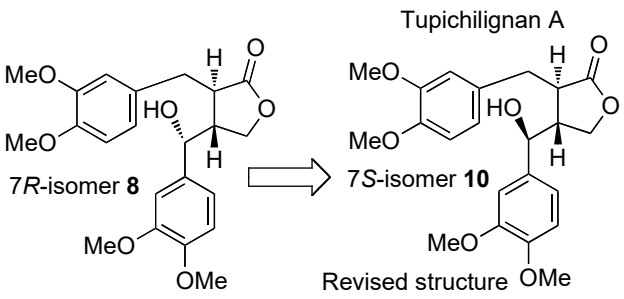
	7*R*-isomer **8** (synthesized)	Tupichilignan A (reported)	7*S*-isomer **10** (synthesized)
H-7	4.43 (1H, d)	4.64 (1H, d)	4.64 (1H, d)
H-8	2.55 (1H, quint)	2.62 (1H, quint)	2.62 (1H, quint)
H-9	4.38 (1H, dd) 4.10 (1H, dd)	3.92 (1H, m) 3.83 (1H, m)	3.97–3.90 (2H, m)
H-7'	2.84–2.68 (3H, m)	3.07 (1H, dd) 2.92 (1H, dd)	3.08 (1H, m) 2.93 (1H, dd)
H-8'		2.97 (1H, m)	2.97 (1H, m)
-OMe	3.88 (3H, s) 3.86 (3H, s) 3.82 (3H, s) 3.80 (3H, s)	3.88 (3H, s) 3.87 (3H, s) 3.85 (3H, s) 3.82 (3H, s)	3.88 (3H, s) 3.85 (3H, s)[a] 3.85 (3H, s)[a] 3.83 (3H, s)
Aromatic protons	6.87 (1H,d) 6.73 (1H, d) 6.70–6.67 (2H, m) 6.57 (1H, d) 6.53 (1H, dd)	6.81–6.63 (6H, m)	6.82–6.70 (4H, m) 6.71 (1H, d) 6.65 (1H, dd)

[a] For an easier comparison between observed and previously reported spectral data, the signal at 3.85 ppm (6H, s) is described here as two signals at 3.85 ppm (3H, s).

Table 4.2. Comparison of the ^{13}C NMR spectral data of tupichilignan A with those of the synthesized 7*S*-isomer **10.**

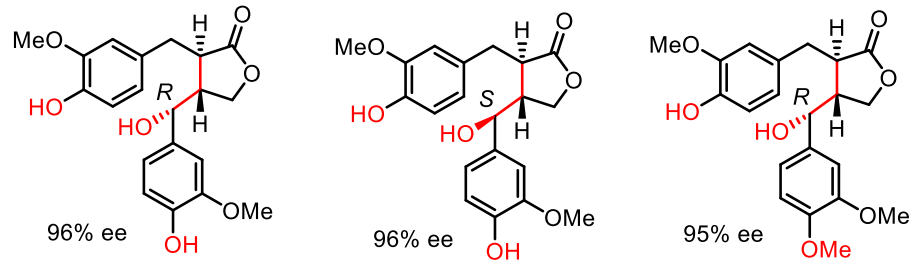


IUPAC numbering	Tupichilignan A (reported)[3]	7*S*-isomer **10** (synthesized)	Common numbering for lignans
C-1	179.1	179.1	C-9'
C-2	43.8	43.8	C-8'
C-3	45.1	45.1	C-8
C-4	68.3	68.3	C-9
C-5	75.3	75.4	C-7
C-6	34.9	34.9	C-7'
C–OMe	55.9 55.9 55.9 55.8	55.9(3) 55.8(9) 55.8 55.8	C–OMe
C-aromatic: C-1'~6' and C-1''~6''	149.3 149.1 148.9 147.8 134.0 130.1 121.7 118.2 112.8 111.1 111.0 109.0	149.3 149.1 148.9 147.8 134.0 130.1 121.8 118.2 112.8 111.1 111.0 109.0	C-aromatic: C-1~6 and C-1'~6'



Scheme 4.4. Revised structure of tupichilignan A.

ツピキリグナン A の合成経路を基に、さらに 3 種の生物活性を有するジベンジルリグナンラクトンの全合成も達成した（Scheme 4.5）。3,4-ジベンジルオキシシンナムアルデヒドから、7*R*-ヒドロキシマタイレシノール（96% ee）を 6 ステップ総収率 18%、この化合物の 7 位の水酸基の立体を反転させることで 7*S*-ヒドロキシマタイレシノール（96% ee）を 10 ステップ総収率 10%でそれぞれ合成に成功した。そして、7*R*-ヒドロキシアルクチゲニン（95% ee）も 6 ステップ総収率 41%で合成を達成した。（詳しい合成経路と各反応の収率は SI 121~134 ページを参照。）



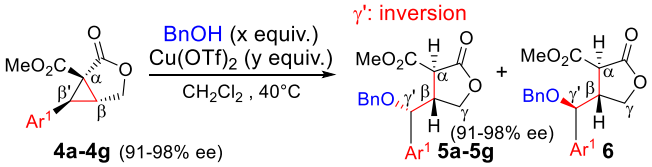
Scheme 4.5. Synthesized of three kinds of dibenzyl lignan lactones: 7*R*-hydroxymatairesinol, 7*S*-hydroxymatairesinol and 7*R*-hydroxyarctigenin.

本全合成の鍵反応である OHM 反応のようなシクロプロパンの開環を伴う D-A シクロプロパンへの求核剤の付加は他にもいくつか報告されている[10,11]。求核剤として、チオールやアミンを用いる報告例もあるが[10a,b]、2 つの不斉中心を持つビシクロシクロプロパンにチオールやアミンをホモマイケル付加した例は報告されていない。一方でシクロプロパン環上のアリール基の電子密度とホモマイケル付加における反応性との相関についての報告は少ない。そこで、OHM 反応の展開として、ラクトンを有する D-A シクロプロパンのホモマイケル反応について、その適用範囲、限界、（scope and limitation）および 3 種類の 7-ヒドロキシベンジルリグナンラクトンの包括的な全合成への応用を含め報告する。また、OHM 反応の scope and limitation については、i) 反応性とシクロプロパン環上のアリール基との相関、ii) チオールとアミンを用いたホモマイケル付加について検討した。

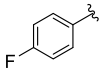
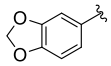
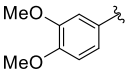
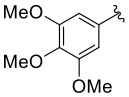
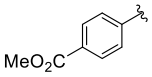
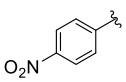
まず、ジベンジルリグナンラクトンの全合成と同様の合成法で、Ar^1 の置換様式がそれぞれ異なる光学活性ビシクロラクトン **4a-g** を合成し、OHM 反応におけるシクロプロパン環上のアリール基（Ar^1）の適用範囲を調べた（Table 4.3）。ジクロロメタン中、ルイス酸である $Cu(OTf)_2$ 存在下、ビシクロラクトン **4a**（Ar^1=Ph）とベンジルアルコールを 40 ℃にて反応させると、目的のラクトン **5a** が高ジアステレオ、エナンチオ選択的かつ高収率で得られた（Table 4.3、entry 1）。**4a** の反応と同様に、*p*-フルオロフェニル基を持つビシクロラクトン **4b** も優れた収率と高い立体選択性を示した（entry 3）。天然物の構造として多く見られる電子供与性アリール基を有するビシクロラクトン **4c**、**4d** および **4e** の OHM 反応は、2.0

equiv.の BnOH と 10 mol% の $Cu(OTf)_2$ を用い、短時間で反応を終了させることで高立体選択的に進行し、それぞれラクトン **5c**、**5d**、**5e** が高収率で得られた（entries 4-6）。この反応条件は、電子供与性アリール基を有する基質を用いた場合に見られる副反応、すなわち反応系内で付加した OBn の脱離とその後の S_N1 置換により起こるエピメリ化を抑制するためである[5a]。4-メトキシカルボニルフェニル基や 4-ニトロフェニル基などの電子吸引性アリール基を有するビシクロラクトンを用いても検討を行った。**4f**（Ar^1 = 4-メトキシカルボニルフェニル）の反応も同様に進行し、高い立体選択性でラクトン **5f** が得られたが、**4a-4e** を用いた場合と比較すると、より長い反応時間を必要とした（24 h）（entry 7）。さらに、**4g**（Ar^1 = 4-ニトロフェニル）の反応は、24 時間撹拌しても完了せず（転化率 46%）、収率が低くなった（entry 9）。ただし、この反応は溶媒をジクロロメタンから 1,2-ジクロロエタンに変え、反応温度を 70℃に上げると収率が向上した（74%）（entry 10）。一方、以前の我々の報告では、立体選択的な分子内開環-環化[3d]においてルイス酸として $Sc(OTf)_3$ を使用した。そこで、$Cu(OTf)_2$ の代わりに $Sc(OTf)_3$ を用いて、同条件の OHM 反応を **4a** に対し

Table 4.3. Scopes of aryl group on the cyclopropane ring for the OHM reaction of bicyclolactone **4**.[a]



4a-4g (91-98% ee) **5a-5g** **6**

Entry	Substrate **4** [ee of **4** (%)]	Ar^1	x	y	Time (h)	Product	Yield (%)[b]	dr(**5**/**6**)[c]	ee of **5** (%)[d]
1	**4a** (97)	Ph	1.0	0.1	4	**5a**	90	>99/1	97
2[e]	**4a** (97)		1.0	0.1	1/2	**5a**	91	>99/1	97
3	**4b** (91)		1.0	0.5	5	**5b**	88	>99/1	91
4	**4c** (94)		2.0	0.1	1/2	**5c**	81	>99/1	94
5	**4d** (95)		2.0	0.1	1/2	**5d**	90	>99/1	95
6	**4e** (95)		2.0	0.1	1/6	**5e**	95	>99/1	95
7	**4f** (98)		1.0	0.5	24	**5f**	81	>99/1	98
8[e]			1.0	0.1	5	**5f**	91	>99/1	98
9	**4g** (94)		1.0	0.5	24	**5g**	41[f]	>99/1	94
10[g]			1.0	0.5	24	**5g**	74	>99/1	94
11[e]			1.0	0.1	24	**5g**	58	>99/1	94
12[e,g]			1.0	0.1	3	**5g**	72	>99/1	94

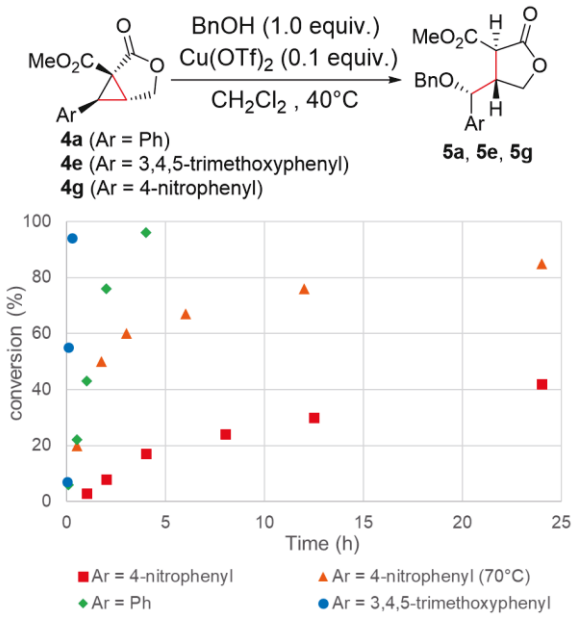
[a] ビシクロラクトン **4** (1.0 equiv.) と $Cu(OTf)_2$ (y equiv.) のジクロロメタン混合物に対し、ベンジルアルコール (x equiv.) を 0 ℃、アルゴン雰囲気下で加え、**4** が完全に消費されるまで 40 ℃にて撹拌した。[b] 単離収率。 [c] ^{1}H NMR スペクト

ルから決定した。[d] ラクトン **4** の β 位の絶対配置は固定されていることから、生成物 **5** の ee はラクトン **4** から推定した。[e] $Cu(OTf)_2$ の代わりに $Sc(OTf)_3$ を用いた。[f] 反応転化率 46%。 [g] ジクロロメタンの代わりに 1,2-ジクロロエタンを用い、70 ℃にて反応を行った。

行うと、30 分で反応が完了し、同様なラクトン **5a** を得られた（entry 2）。この結果から $Cu(OTf)_2$ の代わりに $Sc(OTf)_3$ を用いれば、電子求引性アリール基を有する基質の反応時間は短縮されると予想した。**4f** (Ar^1 = 4-メトキシカルボニルフェニル) の反応は 5 時間で終了し、収率も向上し（91%）、大きく改善された（entry 8）。**4g** の反応は、40 ℃下では、$Cu(OTf)_2$ と比較しわずかに改善したが、70 ℃下では 3 時間で **5g** が収率 72%で得られた（entries 11 and 12）。したがって、$Sc(OTf)_3$ を用いることで、反応が進行しにくい基質であっても、短時間で目的物を高収率で得ることができた。

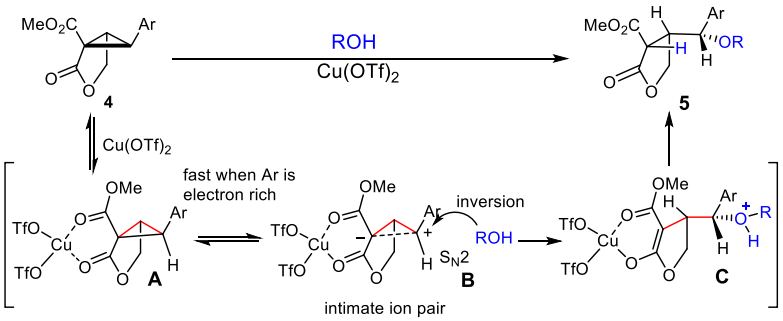
Table 4.3 の通り、シクロプロパン環上のアリール基の種類によって、OHM 反応の反応時間が大きく変化することがわかった。続いて、それぞれ異なるアリール基を持つビシクロラクトン **4a** (Ar^1 = Ph)、**4e** (Ar^1 = 3,4,5-トリメトキシフェニル)、**4g** (Ar^1 = 4-ニトロフェニル) を用いて、OHM 反応の経時変化を観察した。比較のため、試薬条件はすべて、$Cu(OTf)_2$ (0.1equiv) 、BnOH (1.0 equiv.) に統一した。これらの OHM 反応の転化率（%）を、各時間の ^{1}H NMR スペクトルから決定し、反応時間（h）に対してプロットした（Figure 4.2）。ビシクロラクトン **4a**（Ar^1 = Ph）の OHM 反応は 4 時間で完了した。Ar^1 = 3,4,5-トリメトキシフェニル基を持つビシクロラクトン **4d** は 10 分で反応が完了した。一方、 Ar^1 = 4-ニトロフェニル基を有する **4g** の反応は非常に遅く、40 ℃下では 24 時間で転化率は 42%にとどまった。温度を上げ、70 ℃にすると 24 時間後の転化率が 81%に向上した。

Figure 4.2. Conversion yields of the OHM reactions using **4a**, **4e** and **4g** as a function of time.



この反応時間の違いは、D-A シクロプロパンとルイス酸によって形成される緊密イオン対 (intimate ion pair) [11,12]の安定性が、アリール基の電子密度に深く関わるためであると考えられる（Scheme 4.6）。このことは Johnson らも報告しており、三置換の D-A シクロプロパンとアルデヒドの [3+2] 付加環化にお

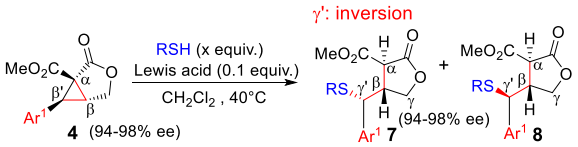
いて類似した結果を得ている[11]。ドナー側に 3,4,5-トリメトキシフェニル基のような電子豊富なアリール基を有する場合、緊密イオン対のカチオン性を安定化させるため、緊密イオン対の生成速度が速くなると考えられる。

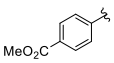


Scheme 4.6. Plausible mechanism for OHM reaction.

次にアルコールの代わりにチオールを用いてホモマイケル反応を試みた（Table 4.4）。同様の操作で $Cu(OTf)_2$ 存在下、ベンジルメルカプタンをシクロプロパン **4a** に作用させると、ベンジルアルコールと同様にして、チオールのホモマイケル反応が進行し、生成物 **7aa** を高立体選択的に与えた（Table 4.4, entry 1）。また、ベンゼンチオールを用いても、良好に反応が進行し、目的のラクトン **7ab** を与えた（entry 2）。電子供与性アリール基を有するシクロプロパン **4c-e** の場合もアルコールと同様にして 30 分で反応が完了し、それぞれ **6ca**、**6da**、**6ea** を高収率かつ立体選択的に得た（entries 3-5）。電子求引性アリール基を有するシクロプロパン **4f**、**4g** の場合は、前述の結果（Table 4.1, entries 7 and 11）からルイス酸として $Sc(OTf)_3$ を用い、さらに **4f** は溶媒を EDC、 温度 70 ℃にて行った。どちらの反応も 2 時間で完了し、高収率かつ立体選択的に **6fa**、**6ga** をそれぞれ与えた（entries 6 and 7）。

Table 4.4. The OHM reaction using thiols instead of the alcohol.[a]

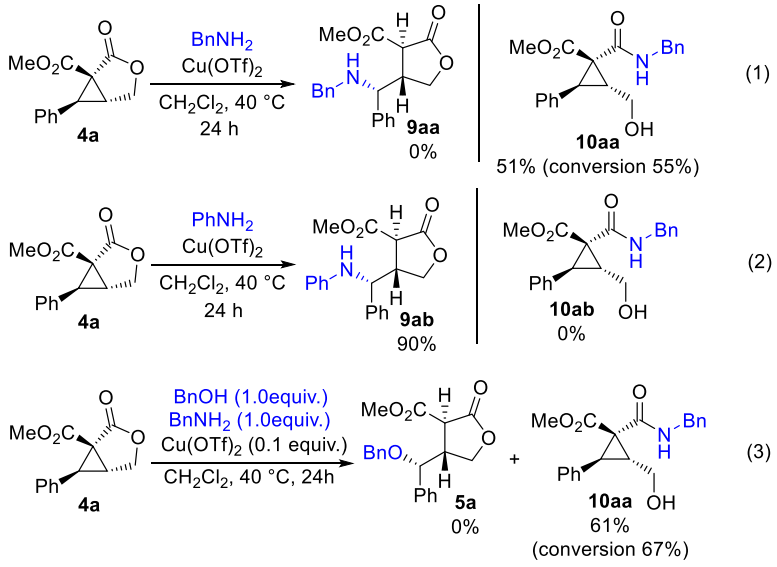


Entry	Substrate **4** [ee of **4** (%)]	Ar^1	Lewis acid	RSH	x	Time (h)	Product	Yield (%)[b]	dr(**7**/**8**)[c]	ee of **7** (%)[d]
1	**4a** (97)	Ph	$Cu(OTf)_2$	BnSH	1.0	5	**7aa**	74	>99/1	97
2				PhSH	1.0	2	**7ab**	70	>99/1	97
3	**4c** (94)		$Cu(OTf)_2$	BnSH	2.0	1/2	**7ca**	83	>99/1	94
4	**4d** (95)		$Cu(OTf)_2$	BnSH	2.0	1/2	**7da**	83	>99/1	95
5	**4e** (95)		$Cu(OTf)_2$	BnSH	2.0	1/2	**7ea**	81	>99/1	95
6	**4f** (98)		$Sc(OTf)_3$	BnSH	1.0	2	**7fa**	86	>99/1	98
7[e]	**4g** (94)		$Sc(OTf)_3$	BnSH	1.0	2	**7ga**	88	>99/1	94

[a] ビシクロラクトン **4** (1.0 equiv.) と $Cu(OTf)_2$ または $Sc(OTf)_3$ (0.1 equiv.) のジクロロメタン混合物に対し、チオール (x

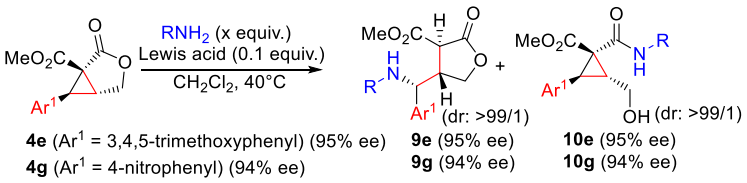
equiv.) を 0 ℃、アルゴン雰囲気下で加え、**4** が完全に消費されるまで 40 ℃にて撹拌した。[b] 単離収率。 [c] ^{1}H NMR スペクトルから決定した。[d] ラクトン **4** の β 位の絶対配置は固定されていることから、生成物 **5** の ee はラクトン **4** から推定した。 [e] ジクロロメタンの代わりに 1,2-ジクロロエタンを用い、70 ℃にて反応を行った。

次にビシクロラクトン **4a** に対し、$Cu(OTf)_2$ 存在下、ベンジルアミンまたはアニリンを作用させた。その結果、アニリンを用いた場合は同様なホモマイケル反応が進行し、目的のラクトン **9ab** を高収率かつ高立体選択的に与えた[Scheme 4.7, reaction (1)]。一方で、ベンジルアミンはシクロプロパン環に対するホモマイケル付加はまったく進行せず、ラクトンに対する 1,2-付加のみが進行し、シクロプロピルアミド **10aa** が得られた[Scheme 4.7, reaction (2)]。脂肪族アミンであるベンジルアミンが持つ塩基性がルイス酸を十分に不活性化させたため、ホモマイケル付加が進行しなくなったと考えられる。一方で芳香族アミンであるアニリンは、ルイス酸を十分に不活性化させるほどの塩基性を持たないため、ホモマイケル付加が進行したと考えられる。この仮説を裏付けるために、ベンジルアルコールとベンジルアミンを混合し、OHM 反応を行うと、ベンジルアルコールのホモマイケル付加はまったく進行しなかった[Scheme 4.7, reaction (3)]。3,4,5-トリメトキシフェニルを有する基質 **4e** と 4-ニトロフェニルを有する基質 **4g** の、ベンジルアミンまたはアニリンを用いたホモマイケル反応も行った（Table 4.5）。ベンジルアミンを用いた場合は、開環しやすい電子豊富なアリール基を有する基質であっても、Ar[1] の種類によらず、**4a** の反応と同様にシクロプロピルアミド **10ea**、**10ga** を 24 時間でそれぞれ中程度の収率で与えた（Table 4.5, entries 1 and 3）。一方、アニリンを用いた場合は、**4e** の反応ではアルコールとチオールを用いた場合と同様に、短時間でホモマイケル反応が完了し、高収率かつ高立体選択的にラクトン **9eb** を与えた（entry 2）。**4g** の反応は、$Cu(OTf)_2$ を用い、ジクロロメタン中 40 ℃にて反応を行ってもほとんど進行しなかったが、$Sc(OTf)_3$ を用いて、ジクロロエタン中 70 ℃にて行うと、これまでと同様にホモマイケル反応が進行し、ラクトン **9gb** を与えた（entries 4 and 5）。

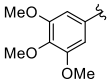
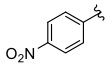


Scheme 4.7 The OHM reaction using amines instead of the alcohol.

Table 4.5. The OHM reaction of **4e** or **4g** using amines instead of the alcohol. [a]



4e (Ar^1 = 3,4,5-trimethoxyphenyl) (95% ee) **9e** (95% ee) **10e** (95% ee)
4g (Ar^1 = 4-nitrophenyl) (94% ee) **9g** (94% ee) **10g** (94% ee)

Entry	Substrate	Ar^1	Lewis acid	RNH_2	x	Time (h)	Yield of **9** (%)[b]	Yield of **10** (%)[b]
1	**4e**		$Cu(OTf)_2$	$BnNH_2$	2.0	24	0	75
2				$PhNH_2$	2.0	1/2	87	0
3	**4g**			$BnNH_2$	1.0	24	0	65
4				$PhNH_2$	1.0	24	10	0
5[c]			$Sc(OTf)_3$		1.0	8	70	0

[a] ビシクロラクトン **4** (1.0 equiv.) と $Cu(OTf)_2$ または $Sc(OTf)_3$ (0.1 equiv.) のジクロロメタン混合物に対し、アミン (x equiv.) を 0 ℃、アルゴン雰囲気下で加え、40 ℃にて撹拌した。[b] 単離収率。[c] ジクロロメタンの代わりに 1,2-ジクロロエタンを用い、70 ℃にて反応を行った。

4.4. 結論

結論として、ドナー・アクセプター型シクロプロパンを用いて、ツピキリグナン A として報告されている化合物 **8** およびその 7*S*-異性体 **10** の不斉全合成を達成した。有機触媒を用いたエナンチオ選択的シクロプロパン化、高立体選択的オキシホモマイケル付加、高立体選択的脱炭酸、7 位の水酸基の立体配置の反転が主要な反応である。合成した 7*R*- (**8**) および 7*S*-異性体 (**10**) のスペクトルデータを天然から単離されたツピキリグナン A のスペクトルと比較した結果、ツピキリグナン A の構造は 7S-異性体 **10** の構造に修正した。またこの合成法により 7*R*-ヒドロキシマタイレシノール、7*S*-ヒドロキシマタイレシノール、7*R*-ヒドロキシアルクチゲニンの合成も達成した。また、鍵反応である OHM 反応の scope and limitation として、i)シクロプロパン上のアリール基と反応性の相関、ii) チオールとアミンを用いたホモマイケル付加について検討した。アリール上の置換基の種類と反応性の相関については、ベンゼン環上の置換様式の違いで反応時間に大きな差が生じることがわかった。この結果は転化率の経時変化を観察することによっても明らかにした。一方、チオールとアミンのホモマイケル付加について、チオールとアニリンはアルコールと同様に進行した。しかし、比較的強い塩基性を持つ脂肪族アミン（ベンジルアミン）を用いた反応は、系内のルイス酸を不活性化させるため、シクロプロパン開裂を伴うホモマイケル付加が進行せず、ラクトンとの反応によりシクロプロピルアミドを与えた。

4.5. Supplementary data

実験方法、計算結果やその他補足事項は、別冊の Supporting information (SI) の S117~S154 ページを参照のこと。

4.6. 引用文献

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ありがとうございました。

2022 年 9 月

信州大学審査学位論文

Supporting Information

ドナー・アクセプター型シクロプロパンを用いる高立体選択的反応の開発と生理活性リグナンの不斉全合成への応用

総合医理工学研究科　総合理工学専攻

ファイバー工学分野　スマート材料工学ユニット

西井研究室　齊藤　泰千

2022 年 9 月

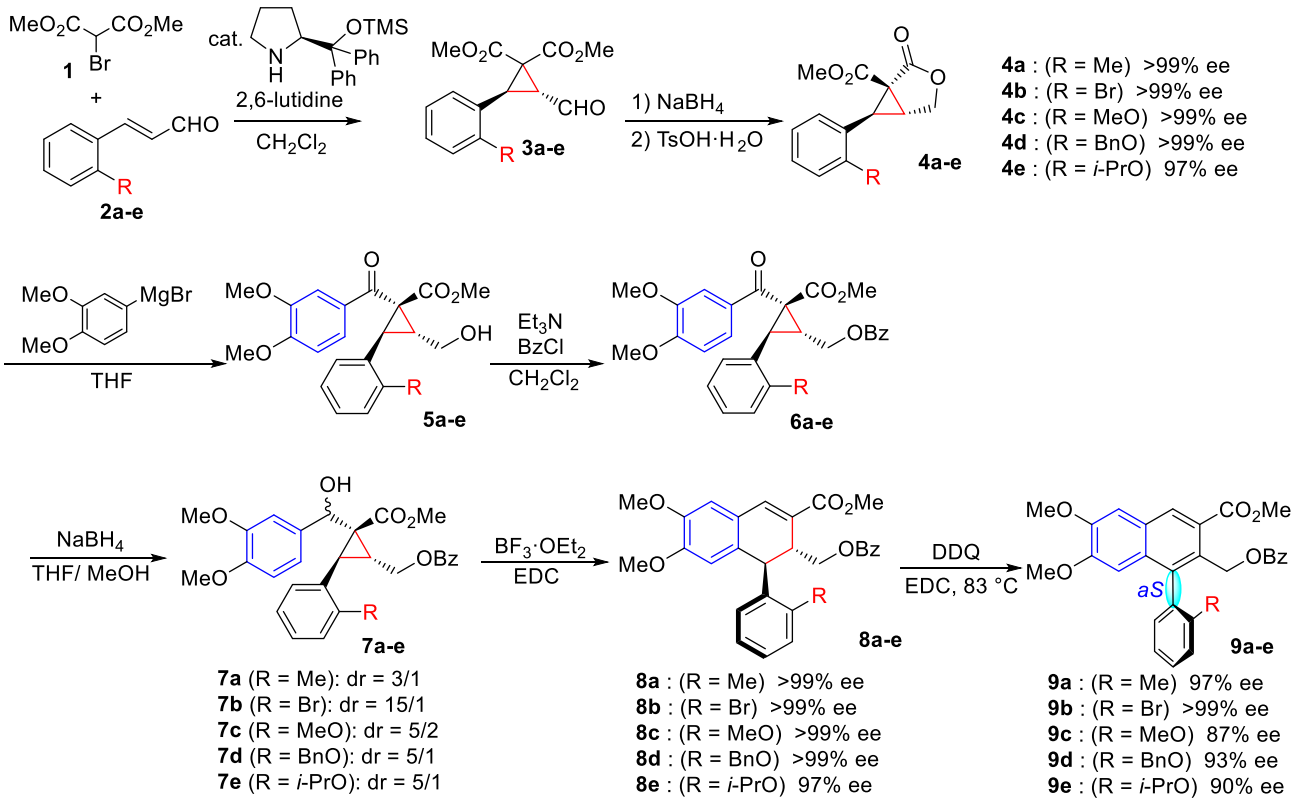
Contents:

1. D-A シクロプロピルカルビノールを用いる中心から軸への不斉変換

1.1. General methods and materials.

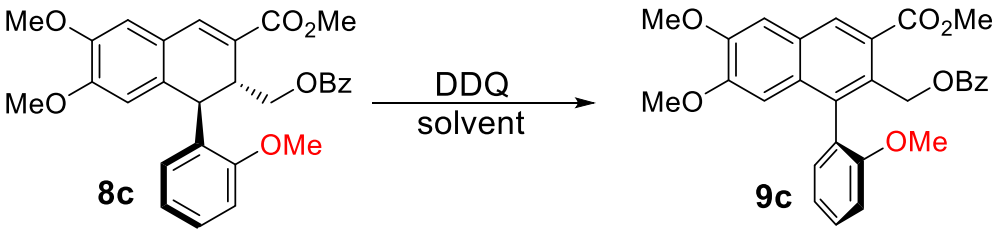
All reactions were carried out in oven-dried glassware under an argon atmosphere. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl. Column chromatography was performed with Kanto chemical CO., INC., silica gel 60 N (spherical, neutral, 40-50 μm). TLC analysis was performed on 0.25 mm Silica gel Merck 60 F_{254} plates. FT-IR spectra were recorded on a SHIMADZU IRTracer-100 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a BRUKER AVANCE NEO NanoBay (400 MHz for ^{1}H NMR, 101 M Hz for ^{13}C NMR) instrument. Chemical shifts (δ ppm) in $CDCl_3$ were reported downfield from TMS (= 0) for ^{1}H NMR. For ^{13}C NMR, chemical shifts were reported in the scale relative to $CDCl_3$ (77.16 ppm) as an internal reference. Mass spectra were obtained by electrospray ionization (ESI). HPLC analysis was performed on a JASCO GULLIVER SERIES.

1.2. Overview for the synthesis of axially chiral arylnaphthalenes.



1.3. Central-to-axial chirality exchange optimization.

Table S1. Optimization for dehydrogenation at various temperature. [a]



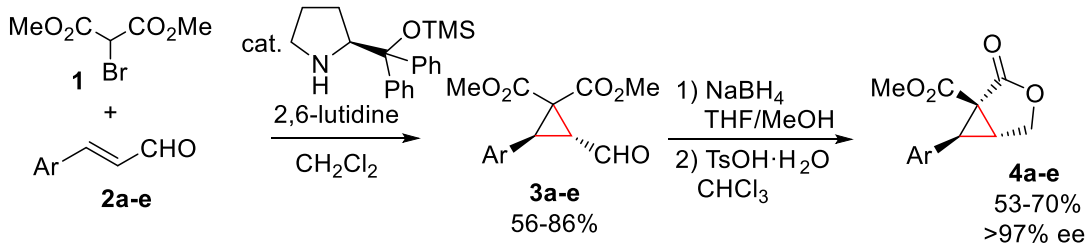
Entry	Solvent	Temp. (°C)	Time (h)	Conversion[b] (%)	Yield (%)[c]	ee (%)[d]
1	toluene	110	1	75	58	79
2		110	3	100	93	74
3	$(CH_2Cl)_2$	83	2.5	100	87	87
4	benzene	80	6	98	88	87
5	$CHCl_3$	61	3	100	90	89
6	CH_2Cl_2	40	24	100	76	90
7	$(CH_2Cl)_2$	r.t.	24	79	62	91
8		r.t.	48	100	90	91
9	benzene	r.t.	24	37	16	91
10	$(CH_2Cl)_2$	0	24	44	24	92
11		0	144	84	66	92
12	CH_2Cl_2	–45	24	0	0	—
13		–78	24	0	0	—

[a] Reactions were carried out with dihydronaphthalene **8c** (1.0 equiv.) in solvent, DDQ (2.5 equiv.) was added at room temperature, followed by being stirred at each temperature. [b] Determined by ^{1}H NMR spectral data. [c] Isolated yields. [d] The ee values of the compounds were determined by HPLC analysis on a chiral column.

Optimization for the chirality exchange of *o*-OMe substituted substrate **8c** at various temperature listed in Table S1. Although lower temperature (above 0 °C) enhanced the ee values, the reaction needed longer time to full conversion of starting material **8c** at lower temperature (entries 1–11). The desired product **9c** was obtained in 90% yield with 91% ee at r.t. in EDC (entry 8). Moreover, the same reaction at 0°C slightly enhanced the ee value of **9c** to 92% ee but decreased the yield to 66% yield (entry 11). The dehydrogenation did not occur at the temperature below 0 °C such as -45 or -78 °C.

1.4. Experimental procedures and characterization data for compounds.

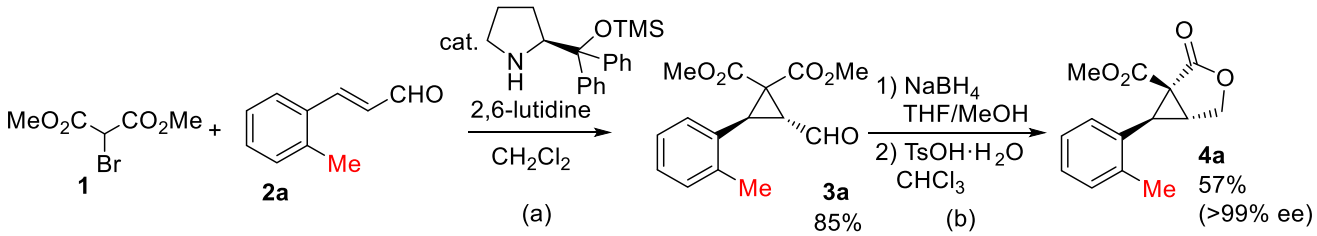
1.4.1. Asymmetric cyclopropanation using Hayashi-Jørgensen catalyst to afford enantioenriched cyclopropane 4.



Following our previous report,[a] bicyclolactone **4a**-**4e** were prepared from dimethyl bromomalonate **1** and cinnamaldehyde derivatives **2a**-**2e** in three steps: (i) Wang's asymmetric cyclopropanation,[b] (ii) chemoselective reduction of aldehyde, and (iii) lactonization.

Procedure and characterization were described in detail in supporting information of the previous literature: [a] Ito, J.; Sakuma, D.; Nishii, Y. *Chem. Lett*., **2015**, *44*, 297 (open access). [b] Xie, H.; Zu, L.; Li, H.; Wang, J.; Wang, W. *J. Am. Chem. Soc.* **2007**, *129*, 10886.

(1*S*,5*R*,6*S*)-1-methoxycarbonyl-6-(*o*-tolyl)-3-oxabicyclo[3.1.0]hexan-2-one (4a)



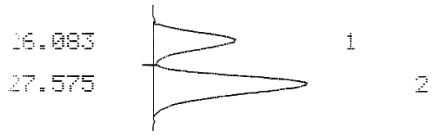
(a) A solution of Hayashi-Jørgensen catalyst (690 mg, 2.12 mmol, 20 mol%) in CH_2Cl_2 (2 mL) was added to a solution of aldehyde **2a** (1.54 g, 10.6 mmol) in CH_2Cl_2 (38 mL) at 0 ˚C under Ar atmosphere. Additionally, a solution of dimethyl bromomalonate **1** (2.35 g, 11.1 mmol) in CH_2Cl_2 (2 mL) and 2,6-lutidine (1.36 mL, 11.7 mmol) was added to the reaction mixture at the same temperature, followed by being stirred at 0 ˚C for 5 days. Then, the reaction was quenched with 1M-HCl aqueous solution (10 mL). Water (20 mL) was added to the mixture, which was extracted with $CHCl_3$ (ca. 20 mL x 3). The organic layers were washed with brine, dried over Na_2SO_4, and concentrated. The obtained crude oil was purified by column chromatography (SiO_2, hexane/AcOEt = 4/1) to give the product **3a** (2.49 g, 85%).

Aldehyde **3a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.52 (d, *J* = 4.4 Hz, 1H), 7.23 – 7.02 (m, 5H), 3.85 (s,

4H), 3.75 (d, J = 7.5 Hz, 1H), 3.49 (dd, J = 7.6, 4.4 Hz, 1H), 3.43 (s, 3H), 2.41 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 196.2, 166.6, 165.3, 138.6, 130.4, 130.2, 128.3, 127.8, 125.8, 53.4, 52.9, 44.1, 38.0, 35.1, 19.4.

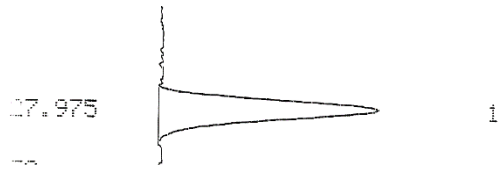
(b) The obtained aldehyde **3a** (2.49 g, 9.01 mmol) was dissolved with THF/MeOH (18 mL/2.7 mL). $NaBH_4$ (119 mg, 3.15 mmol) was added to the solution at 0 ˚C under an Ar atmosphere, followed by being stirred at same temperature for 15 minutes. Then, the reaction was quenched with sat. NH_4Cl aqueous solution (15 mL). Water (10 mL) was added to the mixture, which was extracted with AcOEt (ca. 5 mL x 5). The organic layers were washed with brine, dried over Na_2SO_4, and concentrated. The obtained crude oil was dissolved in $CHCl_3$ (90 mL), then p-TsOH·H_2O (171 mg, 0.901 mmol, 10 mol%) was added to the solution, followed by being stirred at 45 ˚C for 1 h. Then, the reaction was quenched with sat. $NaHCO_3$ (20 mL) aqueous solution. Water was added to the mixture, which was extracted with $CHCl_3$ (ca. 20 mL x 3). The organic layers were washed with brine, dried over Na_2SO_4, and concentrated. The obtained crude solid was purified by recrystallization (AcOEt/n-Hexane) to give product **4a** (1.26 g, 57%).

Product **4a**: colorless solid; mp = 127-130 ˚C; $[\alpha]_D^{22}$ = 2.06 (c = 1.00, chloroform, λ = 589 nm); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.31 – 7.06 (m, 4H), 4.52 (dd, J = 9.4, 4.9 Hz, 1H), 4.37 (d, J = 9.4 Hz, 1H), 3.47 (s, 3H), 3.38 (t, J = 5.3 Hz, 1H), 2.85 (d, J = 5.8 Hz, 1H), 2.37 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 170.3, 164.3, 138.5, 130.3, 130.2, 128.5, 128.0, 125.8, 67.4, 52.6, 37.2, 36.9, 28.0, 19.5; IR (KBr, neat): 3547, 3431, 3026, 2951, 1778, 1724, 1495, 1433, 1379, 1292, 1238, 1198, 1117, 1065, 1034, 970 cm^{-1}; HRMS (ESI) calcd for $C_{14}H_{14}O_4$ $(M+H)^+$ 247.0970, found 247.0965; HPLC analysis: >99% ee [Daicel CHIRALPAK IC (25 cm) at 25 °C, flow rate 0.85 mL/min; solvent: hexane/2-propanol, 10/1 (v/v); t_R(mixture of **4a** and optical isomer **4a′**) = 18.0 min and 19.2 min, t_R(**4a**) = 17.9 min.].



A 67.8/32.2 mixture of **4a** (1*S*,5*R*,6*S*) and **4a′** (1*R*,5*S*,6*R*): HPLC analysis using chiral column.

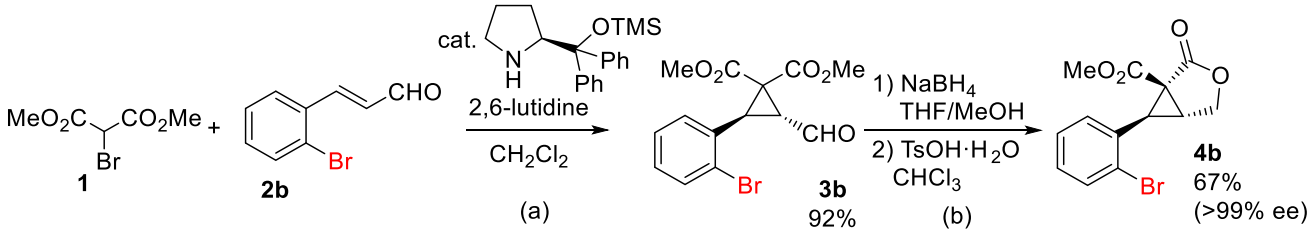
1	26.083	50717	1278	V	32.2286
2	27.575	106651	2374	V	67.7714



Enantioenriched **4a** (>99% ee): HPLC analysis using chiral column.

1	27.975	36493	842	100.0000

(1*S*,5*R*,6*S*)-1-methoxycarbonyl-6-(2-bromophenyl)-3-oxabicyclo[3.1.0]hexan-2-one (4b)

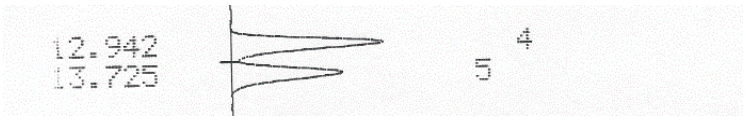


Following the procedure for the preparation of **4a**, (a) the cyclopropanation using cinnamaldehyde **2b** (3.99 g, 18.9 mmol), Hayashi-Jørgensen catalyst (923 mg, 2.83 mmol, 15 mol%), dimethyl bromomalonate **1** (4.19 g, 19.8 mmol) and 2,6-lutidine (1.36 mL, 11.7 mmol) gave crude oil (Reaction time for cyclopropanation: 3 days). The obtained crude oil was purified by column chromatography (SiO_2, hexane/AcOEt = 2/1) to give the cyclopropane **3b** (5.93 g, 92%). Then, (b) the reduction and the lactonization using **3b** gave crude solid. The obtained crude solid was purified by recrystallization (AcOEt/*n*-Hexane) to give product **4b** (3.62 g, 67%).

Aldehyde **3b**: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.53 (d, *J* = 4.4 Hz, 1H), 7.58 (dd, *J* = 7.9, 1.2 Hz, 1H), 7.30-7.23 (m, 1H), 7.19-7.12 (m, 2H), 3.89 – 3.82 (m, 1H), 3.85 (s, 3H), 3.52 (s, 3H), 3.39 (dd, *J* = 7.7, 4.4 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.8, 166.2, 165.3, 133.0, 132.3, 129.8, 129.7, 127.3, 125.9, 53.4, 53.1, 44.0, 39.0, 36.8.

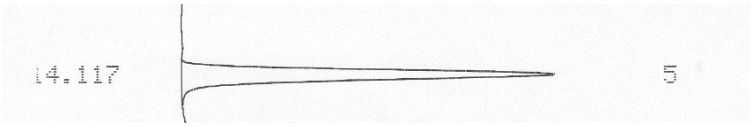
Product **4b**: colorless solid; mp = 134-136 ˚C; $[\alpha]_D^{22}$ = 5.02 (*c* = 1.00, chloroform, λ = 589 nm); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.59 (dd, *J* = 7.9, 1.1 Hz, 1H), 7.36-7.27 (m, 1H), 7.26-7.14 (m, 2H), 4.52 (dd, *J* = 9.4, 4.8 Hz, 1H), 4.40 (d, *J* = 9.2 Hz, 1H), 3.60 (s, 3H), 3.30 (t, *J* = 5.2 Hz, 1H), 2.96 (d, *J* = 5.9 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 169.7, 164.7, 132.9, 132.2, 130.2, 129.9, 127.3, 126.4, 67.0, 52.9, 39.1, 36.7, 29.7; IR (KBr, neat): 3532, 3424, 3076, 2951, 1786, 1721, 1476, 1441, 1373, 1356, 1283, 1261, 1196, 1171, 1123, 1096, 1069, 1036, 1005, 964, 773 cm^{-1}; HRMS (ESI) calcd for $C_{13}H_{11}BrO_4$ $(M+H)^+$ 310.9919, found 310.9913 ; HPLC analysis: >99% ee [Daicel CHIRALPAK IC (25 cm) at 25 °C, flow rate 0.40 mL/min; solvent: hexane/ethanol, 3/2 (v/v); t_R(mixture of **4b** and

optical isomer **4b′**) = 12.9 min and 13.7 min, t_R(**4b**) = 11.1 min.].



A 43.4/56.6 mixture of **4b** (1*S*,5*R*,6*S*) and **4b′** (1*R*,5*S*,6*R*): HPLC analysis using chiral column.

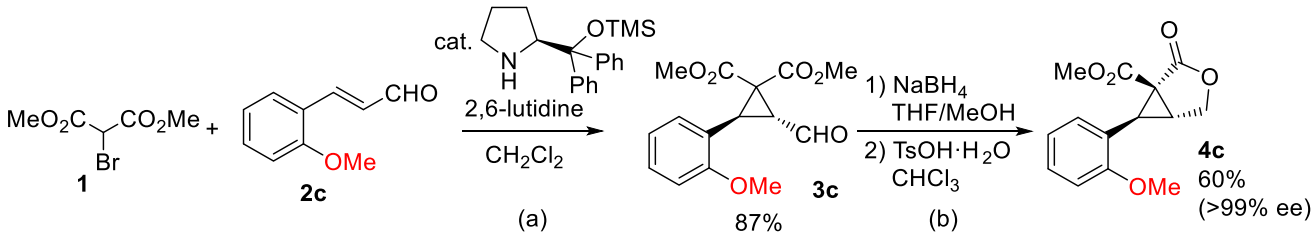
4	12.942	78303	3816	V	51.2880
5	13.725	60197	2781	V	39.4286



Enantioenriched **4b** (>99% ee): HPLC analysis using chiral column.

5	14.117	255586	11352	92.2895

(1*S*,5*R*,6*S*)-1-methoxycarbonyl-6-(2-methoxyphenyl)-3-oxabicyclo[3.1.0]hexan-2-one (4c)



Following the procedure for the preparation of **4a**, (a) the cyclopropanation using cinnamaldehyde **2c** (5.51 g, 34.0 mmol), Hayashi-Jørgensen catalyst (2.21 g, 6.80 mmol, 20 mol%), dimethyl bromomalonate **1** (7.53 g, 35.7 mmol) and 2,6-lutidine (4.75 mL, 40.8 mmol) gave crude oil (Reaction time for cyclopropanation: 5 days). The obtained crude oil was purified by column chromatography (SiO_2, hexane/AcOEt = 3/1) to give the cyclopropane **3c** (8.65 g, 87%). Then, (b) the reduction and the lactonization using **3c** gave crude solid. The obtained crude solid was purified by recrystallization (AcOEt/*n*-Hexane) to give product **4c** (4.66 g, 60%).

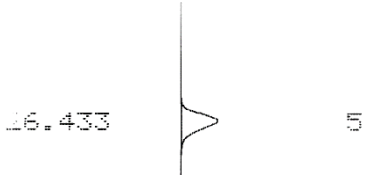
Aldehyde **3c**: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.46 (s, 1H), 7.28-7.24 (m, 2H), 7.03 (d, *J* = 7.2 Hz, 1H), 6.90-6.84 (m, 2H), 3.85-3.83 (m, 2H), 3.84 (s, 3H), 3.84 (s, 3H), 3.48 (s, 3H), 3.30 (d, *J* = 12.5 Hz, 1H). Aldehyde **3c** was reported by wang and co-workers, so see their report for other characterizations.[a] ([a] H. Xie, L. Zu, H. Li, J. Wang, W. Wang, *J. Am. Chem. Soc*. **2007**, *129*,10886–10894.)

Product **4c**: colorless solid; mp = 136-138 ˚C; $[\alpha]_D^{27}$ = 58.4 (*c* = 1.00, chloroform, λ = 589 nm); ^{1}H

NMR (400 MHz, $CDCl_3$) δ = 7.28 (t, *J* = 7.8 Hz, 1H), 7.13 (d, *J* = 7.5 Hz, 1H), 6.91 (t, *J* = 7.5 Hz, 1H), 6.86 (d, *J* = 8.2 Hz, 1H), 4.47 (dd, *J* = 9.3, 4.8 Hz, 1H), 4.34 (d, *J* = 9.3 Hz, 1H), 3.82 (s, 3H), 3.51 (s, 3H), 3.26 (t, *J* = 5.3 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 170.4, 164.7, 158.5, 129.56, 129.0, 120.6, 120.1, 110.3, 67.2, 55.6, 52.4, 36.5, 34.1, 28.5; IR (KBr, neat) 1776, 1729, 1600, 1470, 1435, 1377, 1361, 1308, 1290, 1254, 1200, 1090, 1063, 1007, 756, cm^{-1}; HRMS (ESI) calcd for $C_{14}H_{15}O_5$ $(M+H)^+$ 263.0919, found 263.0915. HPLC analysis: >99% ee [Daicel CHIRALPAK IC (25 cm) at 25 °C, flow rate 0.35 mL/min; solvent: hexane/ethanol, 1/1 (v/v); t_R(mixture of **4c** and optical isomer **4c′**) = 25.3 min and 26.5 min, t_R(**4c**) = 26.4 min.].

A 50.6/49.4 mixture of **4a** (1*S*, 5*R*, 6*S*) and **4a′** (1*R*, 5*S*, 6*R*): HPLC analysis using chiral column.

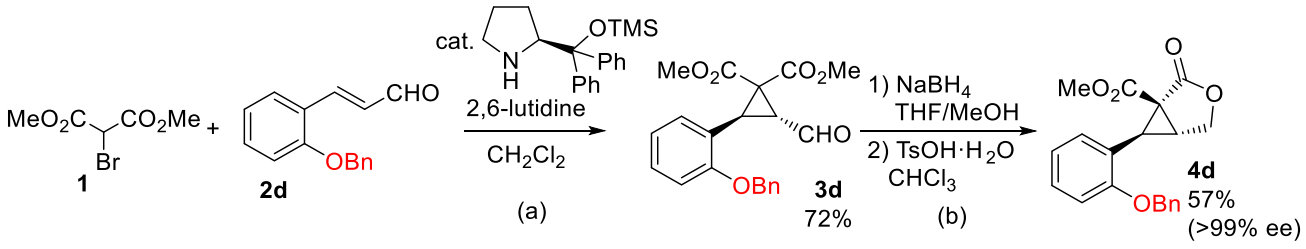
12	25.300	2744105	79562	V	47.7579
13	26.450	2816977	75411	V	49.0261



Enantioenriched **4a** (>99% ee): HPLC analysis using chiral column.

5	26.433	267303	7680	75.8883

(1*S*,5*R*,6*S*)-1-methoxycarbonyl-6-(2-(benzyloxy)phenyl)-3-oxabicyclo[3.1.0]hexan-2-one (4d)

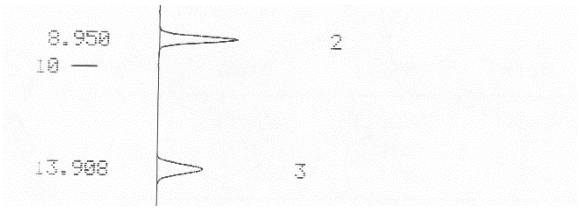


Following the procedure for the preparation of **4a**, (a) the cyclopropanation using cinnamaldehyde **2d** (3.00 g, 12.6 mmol), Hayashi-Jørgensen catalyst (820 mg, 2.52 mmol, 20 mol%), dimethyl bromomalonate **1** (2.79 g, 13.2 mmol) and 2,6-lutidine (1.61 mL, 13.9 mmol) gave crude oil (Reaction time for cyclopropanation: 5 days). The obtained crude oil was purified by column chromatography

(SiO_2, hexane/AcOEt = 4/1) to give the cyclopropane **3d** (3.34 g, 72%). Then, (b) the reduction and the lactonization using **3d** gave crude solid. The obtained crude solid was purified by recrystallization (AcOEt/*n*-Hexane) to give product **4d** (1.75 g, 57%).

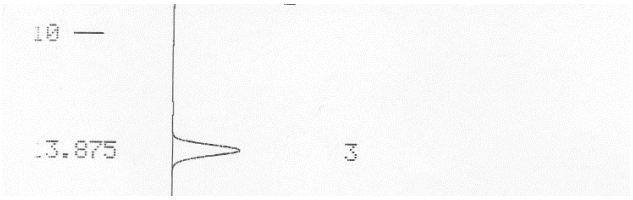
Aldehyde **3c**: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.44 (d, *J* = 4.6 Hz, 1H), 7.47 (d, *J* = 7.3 Hz, 2H), 7.39 (t, *J* = 7.3 Hz, 2H), 7.33-7.31 (m, 1H), 7.27-7.23 (m, 1H), 7.06 (d, *J* = 7.2 Hz, 1H), 6.96-6.86 (m, 2H), 5.12 (d, *J* = 11.7 Hz, 1H), 5.06 (d, *J* = 11.7 Hz, 1H), 3.90 (d, *J* = 7.8 Hz, 1H), 3.75 (s, 3H), 3.44 (s, 3H), 3.34 (dd, *J* = 7.9, 4.5 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 196.3, 166.6, 165.3, 157.6, 136.6, 129.2, 128.6, 128.3, 127.7, 127.1, 120.9, 120.3, 111.4, 77.2, 70.0, 52.9, 52.6, 43.6, 38.3, 32.1.

Product **4d**: colorless solid; mp = 165-168 ˚C; $[\alpha]_D^{23}$ = 1.30 (*c* = 1.00, chloroform, λ = 589 nm); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.49 (d, *J* = 7.4 Hz, 2H), 7.41 (t, *J* = 7.6 Hz, 2H), 7.35-7.23 (m, 2H), 7.15 (d, *J* = 7.2 Hz, 1H), 6.93 (t, *J* = 7.9 Hz, 2H), 5.11 (d, *J* = 4.3 Hz, 2H), 4.47 (dd, *J* = 9.3, 4.8 Hz, 1H), 4.33 (d, *J* = 9.3 Hz, 1H), 3.51 (s, 3H), 3.29 (t, *J* = 5.4 Hz, 1H), 3.04 (d, *J* = 6.0 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 170.1, 164.7, 157.6, 136.7, 129.6, 129.1, 128.7, 128.0, 127.1, 120.9, 120.4, 111.8, 70.2, 67.1, 52.4, 36.6, 34.1, 28.3; IR (KBr, neat) : 3036, 3007, 2965, 2905, 2862, 1775, 1715, 1603, 1587, 1501, 1450, 1373, 1292, 1209, 1116, 1096, 1008, 758 cm^{-1}; HRMS (ESI) calcd for $C_{20}H_{18}O_5$ $(M+Na)^+$ 361.1052, found 361.1046; HPLC analysis: >99% ee [Daicel CHIRALPAK IG (15 cm) at 25 °C, flow rate 0.80 mL/min; solvent: hexane/ethanol, 2/1 (v/v); t_R(mixture of **4d** and optical isomer **4d′**) = 9.0 min and 13.9 min, t_R(**4d**) = 13.9 min.].



A 46.2/53.8 mixture of **4d** (1*S*,5*R*,6*S*) and **4d′** (1*R*,5*S*,6*R*): HPLC analysis using chiral column.

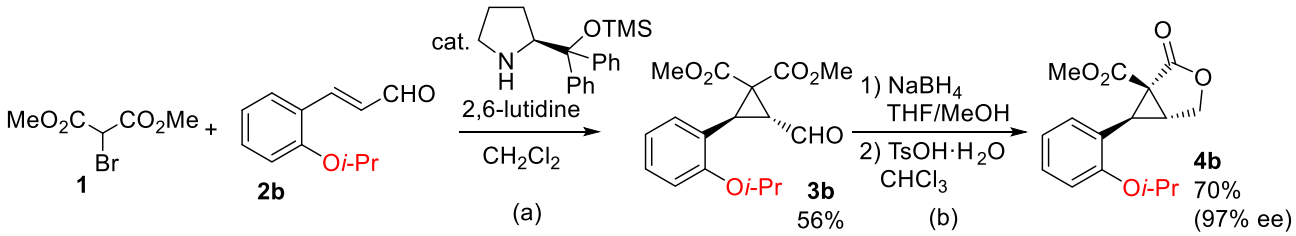
2	8.950	101391	5744	53.4708
3	13.908	87134	3333	45.9520



Enantioenriched **4d** (>99% ee): HPLC analysis using chiral column.

3	13.875	110598	4243	95.3922

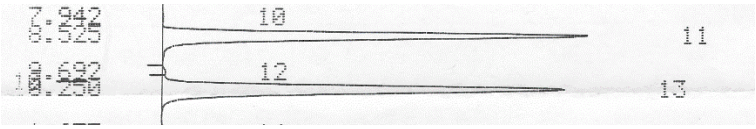
(1*S*,5*R*,6*S*)-1-methoxycarbonyl-6-(2-isopropoxyphenyl)-3-oxabicyclo[3.1.0]hexan-2-one (4e)



Following the procedure for the preparation of **4a**, (a) the cyclopropanation using cinnamaldehyde **2e** (2.20 g, 11.6 mmol), Hayashi-Jørgensen catalyst (755 mg, 2.32 mmol, 20 mol%), dimethyl bromomalonate **1** (2.57 g, 12.2 mmol) and 2,6-lutidine (1.49 mL, 12.8 mmol) gave crude oil (Reaction time for cyclopropanation: 5 days). The obtained crude oil was purified by column chromatography (SiO_2, hexane/AcOEt = 4/1) to give the cyclopropane **3e** (2.09 g, 56%). Then, (b) the reduction and the lactonization using **3e** gave crude solid. The obtained crude solid was purified by column chromatography (SiO_2, hexane/AcOEt = 2/1) to give the product **4e** (1.33 g, 70%).

Aldehyde **3e**: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.47 (d, *J* = 4.7 Hz, 1H), 7.24-7.20 (m, 1H), 7.03 (d, *J* = 7.1 Hz, 1H), 6.86-6.82 (m, 2H), 4.59-4.53 (m, 1H), 3.83 (s, 3H), 3.79 (d, *J* = 7.8 Hz, 1H), 3.48 (s, 3H), 3.29 (dd, *J* = 7.8, 4.8 Hz, 1H), 1.38 (d, *J* = 6.0 Hz, 3H), 1.31 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 196.4, 166.7, 165.5, 156.8, 129.0, 128.7, 121.5, 119.6, 112.3, 69.9, 52.9, 52.6, 43.6, 38.7, 32.4, 22.1, 21.6.

product **4e**: colorless amorphous solid; mp = 81-84 ˚C; $[\alpha]_D^{23}$ = 4.00 (*c* = 1.00, chloroform, λ = 589 nm); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.25 (t, *J* = 8.6 Hz, 1H), 7.12 (d, *J* = 7.6 Hz, 1H), 6.88 (t, *J* = 7.5 Hz, 1H), 6.84 (d, *J* = 8.2 Hz, 1H), 4.60-4.51 (m, 1H), 4.47 (dd, *J* = 9.2, 4.8 Hz, 1H), 4.35 (d, *J* = 9.2 Hz, 1H), 3.52 (s, 3H), 3.24 (dd, *J* = 5.4, 5.4 Hz, 1H), 2.95 (d, *J* = 6.1 Hz, 1H), 1.36 (d, *J* = 6.0 Hz, 3H), 1.33 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 170.3, 164.9, 156.8, 129.4, 129.2, 121.6, 119.7, 112.3, 70.2, 67.1, 52.3, 36.3, 34.8, 28.6, 22.3, 21.7; IR (KBr, neat); 2962, 1784, 1725, 1601, 1585, 1493, 1454, 1387, 1356, 1300, 1285, 1258, 1200, 1169, 1121, 1096, 1055, 1007, 959, 760 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{18}O_5$ $(M+K)^+$ 329.0791, found 329.0786; HPLC analysis: 97% ee [Daicel CHIRALPAK IG (15 cm) at 25 °C, flow rate 0.50 mL/min; solvent: hexane/ethanol, 2/1 (v/v); t_R(mixture of **4e** and optical isomer **4e′**) = 8.5 min and 10.3 min, t_R(**4e**) = 10.3 min for major and 8.6 min for minor.].



A 30.0/70.0 mixture of **4e** (1*S*,5*R*,6*S*) and **4e′** (1*R*,5*S*,6*R*): HPLC analysis using chiral column.

11	8.525	811893	52309	V	45.1620
12	9.692	6522	425	V	0.3628
13	10.250	896862	49591	V	49.8884

Enantioenriched **4e** (97% ee): HPLC analysis using chiral column.

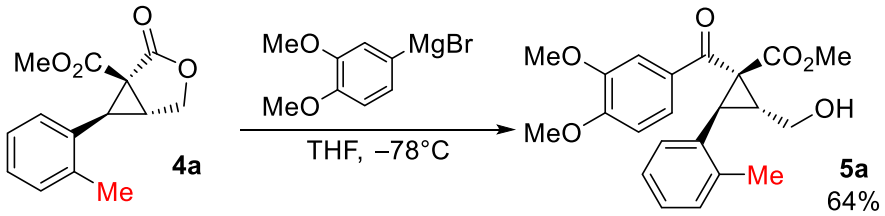
3	8.558	4800	332	V	1.3115
4	10.300	330633	18789		90.3324

Based on this enantiomeric ratio (90.33/1.31), 97% ee was estimated.

1.4.2. Synthesis of compounds 5 using Grignard reagents.

Methyl (1*R*,2*R*,3*S*)-1-(3,4-dimethoxybenzoyl)-2-(hydroxymethyl)

-3-(*o*-tolyl)cyclopropane-1-carboxylate (5a)

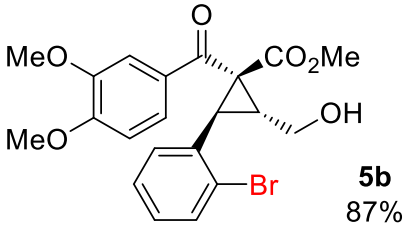


An oven-dried two-neckedround-bottomed flask was charged with Mg turnings (326 mg, 13.4 mmol), under Ar atmosphere. 4-bromo-1,2-dimethoxybenzene (582 mg, 2.68 mmol) THF solution (1.5 M) was added into the activated magnesium at room temperature. To this mixture, 1,2-dibromoethane (1 drops) was added at same temperature. After the reaction was initiated, 4-bromo-1,2-dimethoxybenzene (2.33 g, 10.7 mmol) THF solution (0.8 M) was added into the activated magnesium, stirring was continued until the complete consumption of Mg at same temperature. Mg was dissolved, then, THF was added to dilute the Grignard reagent to 0.5 M. This Grignard reagent THF solution (26.8 mL, 13.4 mmol) was added slowly to a solution of lactone **4a** (1.66 g, 6.72 mmol) in THF (47 mL) at -78 °C, followed by being stirred at same temperature for 10 min. After the reaction was completed, quenched with sat. NH_4Cl aqueous solution (20 mL). Water (30 mL) was added to the mixture, which was extracted with AcOEt (10 mL x 5). The organic layer was washed with brine, dried

(Na_2SO_4) and concentrated. The obtained crude oil was purified by column chromatography (SiO_2, hexane/AcOEt = 4/1) to give the product **5a** (1.66 g, 64%).

5a: colorless amorphous solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.62 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.58 (d, *J* = 2.0 Hz, 1H), 7.22 – 7.12 (m, 4H), 6.88 (d, *J* = 8.4 Hz, 1H), 3.94 (s, 6H), 3.84 (dd, *J* = 11.9, 5.7 Hz, 1H), 3.51 (dd, *J* = 11.9, 8.3 Hz, 1H), 3.39 (d, *J* = 8.0 Hz, 1H), 3.28 – 3.21 (m, 1H), 3.23 (s, 3H), 2.40 (s, 3H), 1.72 (br, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 191.7, 168.9, 153.6, 149.2, 138.8, 132.7, 130.5, 129.9, 128.4, 127.6, 125.6, 123.3, 110.8, 110.3, 60.9, 56.2, 56.1, 52.4, 46.1, 33.4, 32.2, 19.5; IR (KBr, neat) 3503, 3005, 2951, 2841, 1734, 1668, 1595, 1514, 1464, 1420, 1273, 1132, 1020, 748 cm^{-1}; HRMS (ESI) calcd for $C_{22}H_{24}O_6$ $(M+H)^+$ 385.1651, found 385.1646.

Methyl (1*R*,2*R*,3*S*)-1-(3,4-dimethoxybenzoyl)-2-(hydroxymethyl)-3-(2-bromophenyl)cyclopropane-1-carboxylate (5b)



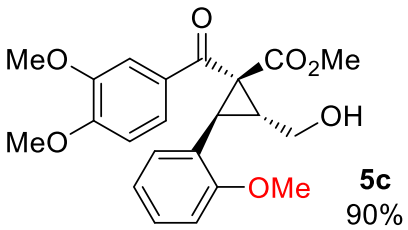
5b
87%

Following the procedure for the preparation of **5a**, the reaction of lactone **4d** (2.77 g, 8.89 mmol) with 3,4-dimethoxyphenylmagnesiumbromide THF solution (0.5 M) (35.6 mL, 17.8 mmol) gave the crude oil. The obtained crude oil was purified by column chromatography (SiO_2, hexane/AcOEt = 2/1) to give the product **5b** (3.49 g, 87%).

5b: colorless amorphous solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.62 – 7.57 (m, 2H), 7.55 (d, *J* = 7.8 Hz, 1H), 7.30 – 7.24 (m, 2H), 7.15-7.10 (m, 1H), 6.88 (d, *J* = 8.2 Hz, 1H), 3.94 (s, 3H), 3.94 (s, 3H), 3.56 – 3.48 (m, 2H), 3.32 (s, 3H), 3.14 (td, *J* = 8.2, 5.6 Hz, 1H), 1.67 (br, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 191.1, 169.0, 153.4, 149.1, 134.6, 132.8, 130.5, 129.0, 127.1, 126.0, 123.2, 110.8, 110.2, 77.4, 60.6, 56.2, 56.0, 52.5, 46.0, 34.4, 34.3; IR (KBr, neat) 3516, 2940, 2841, 1730, 1670, 1595, 1514, 1418, 1300, 1275, 1136, 1020, 758 cm^{-1}; HRMS (ESI) calcd for $C_{21}H_{21}BrO_6$ $(M+Na)^+$ 471.0419, found 471.0414.

Methyl (1*R*,2*R*,3*S*)-1-(3,4-dimethoxybenzoyl)-2-(hydroxymethyl)

-3-(2-methoxyphenyl)cyclopropane-1-carboxylate (5c)



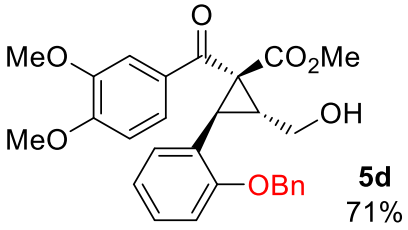
5c
90%

Following the procedure for the preparation of **5a**, the reaction of lactone **4c** (3.83 g, 14.6 mmol) with 3,4-dimethoxyphenylmagnesiumbromide THF solution (0.5 M) (58.4 mL, 29.2 mmol) gave the crude oil. The obtained crude oil was purified by column chromatography (SiO_2, hexane/AcOEt = 1/1) to give the product **5c** (5.26 g, 90%).

5c: colorless amorphous solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.68 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.59 (d, *J* = 2.0 Hz, 1H), 7.26 – 7.21 (m, 1H), 7.17 (d, *J* = 7.5 Hz, 1H), 6.97 – 6.80 (m, 3H), 3.95 (s, 3H), 3.94 (s, 3H), 3.84 (s, 3H), 3.82 – 3.70 (m, 1H), 3.56-3.50 (m, 1H), 3.37 (s, 3H), 3.33 (d, *J* = 8.0 Hz, 1H), 3.01-2.95 (m,1H), 2.06 (br, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 192.2, 169.3, 158.8, 153.6, 149.2, 130.4, 129.6, 128.8, 123.8, 123.2, 120.3, 111.0, 110.5, 110.2, 61.8, 56.2, 56.1, 55.6, 52.5, 45.4, 34.3, 29.8; IR (KBr, neat) 3480, 3011, 2945, 2837, 1728, 1667, 1597, 1514, 1464, 1418, 1300, 1273, 1209, 1132, 1022, 756 cm^{-1}; HRMS (ESI) calcd for $C_{22}H_{24}O_7$ $(M+H)^+$ 401.1600, found 401.1595.

Methyl (1*R*,2*R*,3*S*)-1-(3,4-dimethoxybenzoyl)-2-(hydroxymethyl)

-3-(2-(benzyloxy)phenyl)cyclopropane-1-carboxylate (5d)



5d
71%

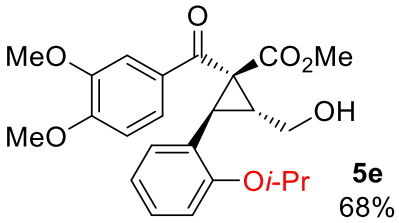
Following the procedure for the preparation of **5a**, the reaction of lactone **4d** (1.86 g, 5.50 mmol) with 3,4-dimethoxyphenyl magnesium bromide THF solution (0.5 M) (22.0 mL, 11.0 mmol) gave the crude oil. The obtained crude oil was purified by column chromatography (SiO_2, hexane/AcOEt = 2/1) to give the product **5d** (1.85 g, 71%).

5d: colorless amorphous solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.62 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.53 (d, *J* = 2.0 Hz, 1H), 7.45 (d, *J* = 7.2 Hz, 2H), 7.40 – 7.34 (m, 2H), 7.33 – 7.28 (m, 1H), 7.24 – 7.16 (m,

2H), 6.91 (t, J = 7.5 Hz, 2H), 6.81 (d, J = 8.4 Hz, 1H), 5.11 (d, J = 11.9 Hz, 1H), 5.06 (d, J = 11.9 Hz, 1H), 3.93 (s, 3H), 3.90 (s, 3H), 3.73 (dt, J = 12.6, 4.9 Hz, 1H), 3.51 – 3.41 (m, 2H), 3.31 (s, 3H), 3.03 (td, J = 8.1, 6.2 Hz, 1H), 1.86 (t, J = 5.5 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 192.1, 169.4, 158.0, 153.4, 149.1, 137.0, 130.7, 129.7, 128.7, 128.6, 127.9, 127.4, 123.5, 123.4, 120.5, 111.8, 110.8, 110.2, 70.3, 61.4, 56.13, 56.1, 52.4, 45.6, 34.4, 30.0; IR (KBr, neat) 3503, 3005, 2949, 2839, 1730, 1668, 1585, 1514, 1418, 1340, 1298, 1273, 1207, 1132, 1022, 756 cm^{-1}; HRMS (ESI) calcd for $C_{28}H_{28}O_7$ $(M+K)^+$ 451.1472, found 515.1467.

Methyl (1*R*,2*R*,3*S*)-1-(3,4-dimethoxybenzoyl)-2-(hydroxymethyl)

-3-(2-isopropoxyphenyl)cyclopropane-1-carboxylate (5e)



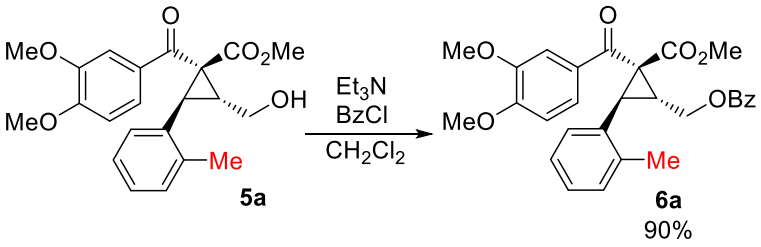
5e
68%

Following the procedure for the preparation of **5a**, the reaction of lactone **4e** (861 mg, 2.96 mmol) with 3,4-dimethoxyphenyl magnesium bromide THF solution (0.5 M) (11.8 mL, 5.92 mmol) gave the crude oil. The obtained crude oil was purified by column chromatography (SiO_2, hexane/AcOEt = 2/1) to give the product **5e** (861 mg, 68%).

5e: colorless amorphous solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.63 (dd, J = 8.4, 2.0 Hz, 1H), 7.57 (d, J = 2.0 Hz, 1H), 7.24 – 7.16 (m, 1H), 7.15 (d, J = 6.9 Hz, 1H), 6.92 – 6.79 (m, 3H), 4.61-4.54 (m, 1H), 3.94 (s, 6H), 3.78-3.73 (m 1H), 3.55-3.49 (m, 1H), 3.35 (s, 3H), 3.35 (d, J = 7.9 Hz, 1H), 1.96 (br, 1H), 1.38 (d, J = 6.1 Hz, 3H), 1.31 (J = 6.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 191.8, 169.4, 157.2, 153.4, 149.1, 130.6, 129.7, 128.5, 124.1, 123.4, 119.9, 112.7, 110.8, 110.2, 70.2, 61.6, 56.2, 56.1, 52.3, 45.4, 34.5, 30.1, 22.3, 22.0; IR (KBr, neat) 3524, 2976, 2938, 2841, 1732, 1670, 1597, 1514, 1454, 1418, 1340, 1298, 1273, 1207, 1128, 1022, 957, 756 cm^{-1}; HRMS (ESI) calcd for $C_{24}H_{28}O_7$ $(M+Na)^+$ 451.1733, found 451.1727.

1.4.3. Benzoyl protection.

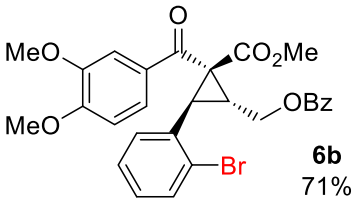
[(1*R*,2*R*,3*S*)-2-(3,4-dimethoxybenzoyl)-2-(methoxycarbonyl)-3-(*o*-tolyl)cyclopropyl]methyl benzoate (6a)



A CH_2Cl_2 solution of the alcohol **5a** (1.62 g, 4.22 mmol) was added triethylamine (0.76 mL, 5.49 mmol) at 0 °C, then dropped benzoyl chloride (0.64 mL, 5.49 mmol), followed by being stirred for 1h at same temperature. The reaction mixture was quenched with water, which was extracted with $CHCl_3$. The organic layer was washed with brine, dried (Na_2SO_4) and concentrated. The obtained crude was purified by column chromatography (SiO_2, Hexane/AcOEt = 4/1) to give the product **6a** (1.85 g, 90%).

6a: yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.81-7.79 (m, 2H), 7.61 – 7.47 (m, 3H), 7.34 (t, *J* = 7.8 Hz, 2H), 7.25 – 7.11 (m, 4H), 6.70 (d, *J* = 8.4 Hz, 1H), 4.73 (dd, *J* = 12.1, 5.6 Hz, 1H), 4.04 (dd, *J* = 12.1, 9.1 Hz, 1H), 3.85 (s, 6H), 3.55 (d, *J* = 7.8 Hz, 1H), 3.50 – 3.40 (m, 1H), 3.23 (s, 3H), 2.42 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 190.9, 168.7, 166.0, 153.4, 149.0, 138.8, 133.1, 132.3, 130.2, 129.9, 129.8, 129.7, 128.4, 128.3, 127.7, 125.6, 123.5, 110.7, 110.1, 77.4, 62.5, 56.1, 55.9, 52.4, 45.9, 32.5, 29.9, 19.4; IR (KBr, neat) 3020, 2953, 2841, 1721, 1668, 1595, 1516, 1456, 1420, 1300, 1275, 1173, 1024, 758, 714 cm^{-1}; HRMS (ESI) calcd for $C_{29}H_{28}O_7$ $(M+Na)^+$ 511.1733, found 511.1727.

[(1*R*,2*R*,3*S*)-3-(2-bromophenyl)-2-(3,4-dimethoxybenzoyl)-2-(methoxycarbonyl)cyclopropyl]methyl benzoate (6b)



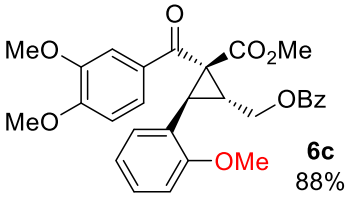
Following the procedure for the preparation of **6a**, the reaction of alcohol **5b** (3.49 g, 7.78 mmol) with benzoyl chloride (1.41 mL, 10.1 mmol) gave the crude oil. The obtained crude oil was purified by column chromatography (SiO_2, hexane/AcOEt = 2/1) to give the product **6b** (3.06 g, 71%).

6b: colorless amorphous solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.82 – 7.74 (m, 2H), 7.60 – 7.47 (m,

4H), 7.34 (t, J = 7.8 Hz, 2H), 7.30 – 7.24 (m, 2H), 7.16-7.12 (m, 1H), 6.69 (d, J = 8.9 Hz, 1H), 4.81 (dd, J = 12.2, 5.4 Hz, 1H), 4.03 (dd, J = 12.2, 9.3 Hz, 1H), 3.85 (s, 3H), 3.85 (s, 3H), 3.68 (d, J = 7.8 Hz, 1H), 3.41-3.35 (m,, 1H), 3.32 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 190.1, 168.8, 166.0, 153.3, 149.0, 134.2, 133.2, 132.9, 130.5, 130.3, 129.8, 129.7, 129.2, 128.3, 127.2, 126.0, 123.4, 110.7, 110.0, 77.5, 77.2, 76.8, 62.2, 56.1, 55.9, 52.6, 46.0, 34.4, 30.9; IR (KBr, neat) 2953, 2839, 1726, 1715, 1665, 1591, 1520, 1464, 1271, 1128, 1113, 1024, 714 cm^{-1}; HRMS (ESI) calcd for $C_{28}H_{25}BrO_7$ $(M+H)^+$ 553.0862, found 553.0856.

[(1*R*,2*R*,3*S*)-2-(3,4-dimethoxybenzoyl)-2-(methoxycarbonyl)

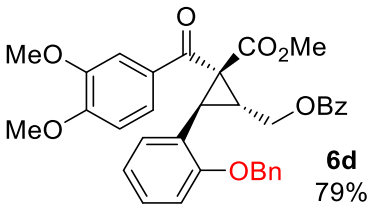
-3-(2-methoxyphenyl)cyclopropyl]methyl benzoate (6c)



Following the procedure for the preparation of **6a**, the reaction of alcohol **5c** (5.19 g, 13.0 mmol) with benzoyl chloride (2.34 mL, 16.9 mmol) gave the crude oil. The obtained crude oil was purified by column chromatography (SiO_2, hexane/AcOEt = 2/1) to give the product **6c** (5.78 g, 88%).

6c: colorless amorphous solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.82 – 7.76 (m, 2H), 7.58 (dd, J = 8.4, 2.0 Hz, 1H), 7.55 – 7.47 (m, 2H), 7.34 (dd, J = 10.8, 4.8 Hz, 2H), 7.26 – 7.16 (m, 2H), 6.94 – 6.88 (m, 1H), 6.84 (d, J = 8.2 Hz, 1H), 6.70 (d, J = 8.4 Hz, 1H), 4.74 (dd, J = 12.1, 5.5 Hz, 1H), 4.03 (dd, J = 12.1, 9.2 Hz, 1H), 3.85 (s, 3H), 3.85 (s, 3H), 3.83 (s, 3H), 3.29 (s, 3H), 3.32 – 3.23 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 191.0, 169.2, 166.1, 159.0, 153.2, 149.0, 133.1, 130.6, 129.9, 129.8, 129.6, 128.9, 128.3, 123.5, 122.9, 120.2, 110.8, 110.4, 110.0, 62.7, 56.1, 56.0, 55.8, 52.4, 45.7, 30.7, 29.5; IR (KBr, neat) 2999, 2955, 2839, 1721, 1668, 1585, 1514, 1464, 1418, 1275, 1024, 756, 714 cm^{-1}; HRMS (ESI) calcd for $C_{29}H_{28}O_8$ $(M+H)^+$ 505.1862, found 505.1857.

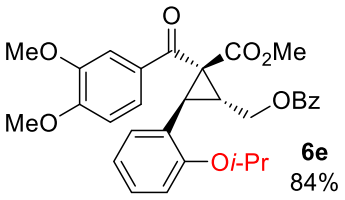
[(1*R*,2*R*,3*S*)-3-(2-(benzyloxy)phenyl)-2-(3,4-dimethoxybenzoyl)-2-(methoxycarbonyl)cyclopropyl]methyl benzoate (6d)



Following the procedure for the preparation of **6a**, the reaction of alcohol **5d** (1.80 g, 3.78 mmol) with benzoyl chloride (0.68 mL, 4.91 mmol) gave the crude oil. The obtained crude oil was purified by column chromatography (SiO_2, hexane/AcOEt = 2/1) to give the product **6d** (1.725 g, 79%).

6d: colorless amorphous solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.81 – 7.74 (m, 2H), 7.59 – 7.46 (m, 5H), 7.40 – 7.28 (m, 5H), 7.21 (dd, *J* = 11.7, 4.4 Hz, 2H), 6.91 (dd, *J* = 16.3, 8.1 Hz, 2H), 6.68 (d, *J* = 8.4 Hz, 1H), 5.14 (d, *J* = 12.2 Hz, 1H), 5.06 (d, *J* = 12.2 Hz, 1H), 4.75 (dd, *J* = 12.1, 5.3 Hz, 1H), 3.99 (dd, *J* = 12.2, 9.5 Hz, 1H), 3.84 (d, *J* = 1.0 Hz, 6H), 3.74 (d, *J* = 8.0 Hz, 1H), 3.37-3.31 (m, 1H), 3.24 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 190.9, 169.2, 166.0, 158.0, 153.1, 148.9, 137.2, 133.03, 130.8, 129.8, 129.8, 129.6, 128.8, 128.5, 128.2, 127.7, 127.2, 123.2, 123.1, 120.5, 111.8, 110.7, 110.0, 70.1, 62.5, 56.0, 55.9, 52.3, 45.9, 30.8, 29.8; IR (KBr, neat) 3065, 3005, 2951, 2839, 1722, 1670, 1597, 1514, 1450, 1418, 1298, 1275, 1111, 1024, 754, 714 cm^{-1}; HRMS (ESI) calcd for $C_{35}H_{32}O_8$ $(M+K)^+$ 619.1734, found 619.1729.

[(1*R*,2*R*,3*S*)-2-(3,4-dimethoxybenzoyl)-2-(methoxycarbonyl)-3-(2-isopropoxyphenyl)cyclopropyl]methyl benzoate (6e)



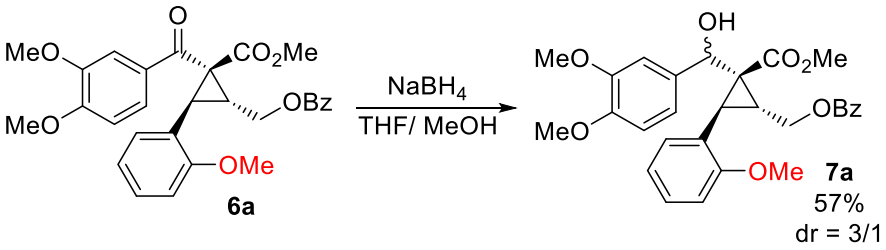
Following the procedure for the preparation of **6a**, the reaction of alcohol **5e** (861 mg, 2.01 mmol) with benzoyl chloride (0.36 mL, 2.61 mmol) gave the crude oil. The obtained crude oil was purified by column chromatography (SiO_2, hexane/AcOEt = 2/1) to give the product **6e** (867 mg, 84%).

6e: colorless liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.79-7.77 (m, 2H), 7.56 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.54 – 7.47 (m, 2H), 7.37 – 7.30 (m, 2H), 7.23 – 7.14 (m, 2H), 6.90 – 6.79 (m, 2H), 6.69 (d, *J* = 8.4

Hz, 1H), 4.80 (dd, *J* = 12.1, 5.3 Hz, 1H), 4.55 (dt, *J* = 12.1, 6.0 Hz, 1H), 3.98 (dd, *J* = 12.1, 9.5 Hz, 1H), 3.85 (s, 6H), 3.60 (d, *J* = 8.0 Hz, 1H), 3.29 (s, 3H), 3.31 – 3.24 (m, 1H), 1.42 (d, *J* = 6.0 Hz, 3H), 1.31 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 190.8, 169.3, 166.0, 157.2, 153.1, 149.0, 133.1, 130.7, 129.8, 129.8, 129.7, 128.6, 128.2, 123.8, 123.4, 119.8, 112.6, 110.7, 110.0, 70.1, 62.7, 56.1, 56.0, 52.3, 45.7, 30.9, 29.9, 22.4, 21.9; IR (KBr, neat) 3065, 2976, 2841, 1724, 1670, 1597, 1514, 1452, 1298, 1275, 1111, 1024, 959, 756, 714 cm^{-1}; HRMS (ESI) calcd for $C_{31}H_{32}O_8$ $(M+Na)^+$ 555.1995, found 555.1989.

1.4.4. Synthesis of cyclopropylcarbinol 7.

[(1*R*,2*R*,3*S*)-2-((3,4-dimethoxyphenyl)(hydroxy)methyl)-2-(methoxycarbonyl) -3-(*o*-tolyl)cyclopropyl]methyl benzoate (7a)



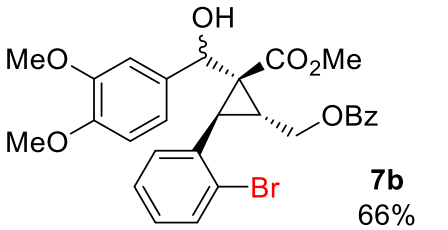
$NaBH_4$ (806 mg, 21.3 mmol) was added to a solution of cyclopropane **6a** (1.05 g, 2.13 mmol) in THF/MeOH (THF = 4.3 mL, MeOH = 4.3 mL) at 0 °C under an Ar atmosphere, followed by being stirred at same temperature. After the reaction was completed, quenched with sat. NH_4Cl aqueous solution (30 mL). Water (30 mL) was added to the mixture, which was extracted with $CHCl_3$ (ca. 20 mL x 5). The organic layers were washed with brine, dried (Na_2SO_4), and concentrated. The obtained crude oil was purified by column chromatography (SiO_2, hexane/AcOEt = 4/1) to give the product **7a** (596 mg, 57%, dr = 3/1).

7a: (3/1 mixture of diastereoisomers) yellow liquid; (Selected data for major of **7a**.) ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.01-7.98 (m, 2H), 7.58 – 7.52 (m, 1H), 7.45-7.41 (m, 2H), 7.15-7.08 (m, 5H), 7.02 (dd, J = 8.3, 1.8 Hz 1H), 6.69 (d, *J* = 8.4 Hz, 1H), 5.66 (d, *J* = 6.0 Hz, 1H), 4.85 – 4.74 (m, 2H), 3.86 (s, 3H), 3.78 (s, 3H), 3.20 (s, 3H), 3.08 – 2.99 (m, 2H), 2.82 (d, *J* = 6.0 Hz, 1H), 2.33 (s, 3H); ^{13}C NMR (101MHz, $CDCl_3$) δ = 19.7, 26.9, 31.8, 41.6, 51.6, 55.8, 55.8, 63.5, 71.6, 110.3, 110.8, 118.6, 125.5, 127.0, 127.4, 128.4, 129.7, 130.1, 133.0, 133.2, 134.5, 135.1, 138.0, 148.5, 148.8, 166.7, 170.8. (Selected data for minor of **7a**.) ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.95-7.92 (m, 2H), 7.58 – 7.52 (m, 1H), 7.45-7.40 (m, 2H), 7.16-7.08 (m, 5H), 6.97 (dd, *J* = 8.5, 2.3 Hz, 1H), 6.67 (d, *J* = 9.3 Hz, 1H),

5.66 (d, J = 6.0 Hz, 1H), 4.68 – 4.59 (m, 2H), 4.52 (dd, J = 12.1, 7.8 Hz, 1H), 4.35 (d, J = 11.6 Hz, 1H), 3.85 (s, 3H), 3.78 (s, 3H), 3.20 (s, 3H), 2.88 (d, J = 7.5 Hz, 1H), 2.55 (s, 3H).

IR (KBr, neat) 3545, 3003, 2953, 2837, 1721, 1668, 1595, 1514, 1464, 1420, 1275, 1024, 714 cm^{-1}; HRMS (ESI) calcd for $C_{29}H_{30}O_7$ $(M+Na)^+$ 513.1889, found 513.1884. Diastereomeric ratio (dr) was estimated by the measurement of ^1H NMR spectral data.

[(1*R*,2*R*,3*R*)-3-(2-bromophenyl)-2-((3,4-dimethoxyphenyl)(hydroxy)methyl)-2-(methoxycarbonyl)cyclopropyl]methyl benzoate (7b)

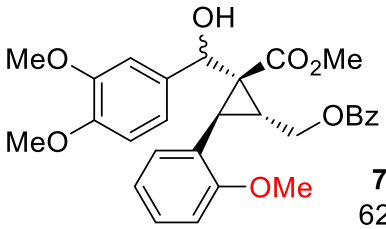


7b
66%
dr = 15/1

Following the procedure for the preparation of **7a**, the reaction of cyclopropane **6b** (2.79 g, 5.04 mmol) with $NaBH_4$ (1.91 g, 50.4 mmol) gave the crude oil. The obtained crude oil was purified by column chromatography (SiO_2, hexane/AcOEt = 5/2) to give the product **7b** (1.859 g, 66%, dr = 15/1).

7b: (15/1 mixture of diastereoisomers) colorless amorphous; (Selected data for major of **7b**.) ^1H NMR (400 MHz, $CDCl_3$) δ = 8.00 – 7.95 (m, 2H), 7.58 – 7.49 (m, 2H), 7.42 (t, J = 7.7 Hz, 2H), 7.24 – 7.20 (m, 2H), 7.10-7.07 (m, 2H), 7.01 (dd, J = 8.3, 1.9 Hz, 1H), 6.70 (d, J = 8.3 Hz, 1H), 5.88 (d, J = 5.6 Hz, 1H), 4.82 (dd, J = 11.7, 7.6 Hz, 1H), 4.73 (dd, J = 11.7, 7.1 Hz, 1H), 3.85 (s, 3H), 3.77 (s, 3H), 3.27 (s, 3H), 3.21 (d, J = 7.7 Hz, 1H), 3.05-2.93 (m, 2H), 1.71 (br, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 170.4, 166.7, 148.9, 148.4, 136.1, 134.9, 133.1, 132.4, 130.3, 130.1, 129.7, 128.7, 128.4, 127.1, 126.0, 118.6, 110.9, 110.4, 70.8, 63.2, 55.9, 55.8, 51.9, 42.0, 34.2, 27.5; IR (KBr, neat) 3487, 3001, 2949, 2835, 1717, 1518, 1464, 1271, 1140, 1026, 712 cm^{-1}; HRMS (ESI) calcd for $C_{28}H_{27}BrO_7$ $(M+Na)^+$ 577.0838, found 577.0832. Diastereomeric ratio (dr) was estimated by the measurement of ^1H NMR spectral data.

[(1*R*,2*R*,3*S*)-2-((3,4-dimethoxyphenyl)(hydroxy)methyl)-2-(methoxycarbonyl)-3-(2-methoxyphenyl)cyclopropyl]methyl benzoate (7c)



7c
62%
dr = 5/2

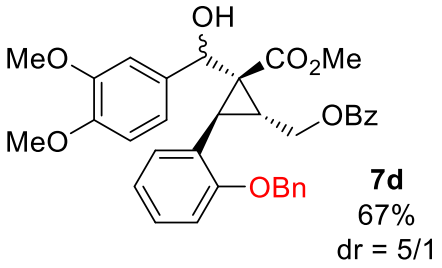
Following the procedure for the preparation of **7a**, the reaction of cyclopropane **6c** (5.78 g, 11.5 mmol) with $NaBH_4$ (4.33 g, 115 mmol) gave the crude oil. The obtained crude oil was purified by column chromatography (SiO_2, hexane/AcOEt = 2/1) to give the product **7c** (3.61 g, 62%, dr = 5/2).

7c: (5/2 mixture of diastereoisomers) colorless amorphous; (Selected data for major of **7c**.) ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.04-8.02 (m, 2H), 7.45-7.42 (m, 2H), 7.25 – 7.11 (m, 3H), 7.08 (dd, *J* = 8.3, 1.9 Hz, 1H), 6.93 – 6.83 (m, 2H), 6.77 (dd, *J* = 16.8, 8.3 Hz, 2H), 5.38 (d, *J* = 6.5 Hz, 1H), 4.72 (d, *J* = 7.4 Hz, 1H), 4.66 (dd, *J* = 11.9, 7.5 Hz, 1H), 3.86 (s, 3H), 3.82 (s, 3H), 3.70 (s, 3H), 3.26 (s, 3H), 2.97 (d, *J* = 7.8 Hz, 1H), 2.86-2.81 (m, 1H), 1.67 (br, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 171.2, 166.6, 158.5, 148.6, 148.2, 134.9, 133.0, 130.1, 129.7, 129.4, 128.4, 124.4, 120.1, 118.8, 110.6, 110.4, 109.9, 72.3, 63.6, 55.9, 55.8, 55.3, 51.5, 41.3, 29.8, 28.3.

(Selected data for minor of **7c**.) ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.00-7.98 (m, 2H), 7.58-7.42 (m, 5H), 7.25 – 7.11 (m, 3H), 6.98 (dd, *J* = 8.3, 1.3 Hz, 1H), 6.68 (d, *J* = 8.3 Hz, 1H), 4.78 – 4.73 (m, 1H), 4.54 (dd, *J* = 12.0, 8.1 Hz, 1H), 4.21 (d, *J* = 7.7 Hz, 1H), 3.88 (s, 3H), 3.84 (s, 3H), 3.79 (s, 3H), 3.18 (s, 3H), 3.09 (dd, *J* = 14.7, 7.7 Hz, 1H), 2.86-2.81 (m, 1H), 1.67 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 171.0, 166.4, 158.6, 148.8, 148.1, 135.1, 133.2, 129.8, 129.7, 129.3, 128.7, 128.2, 123.6, 120.4, 117.8, 110.7, 110.1, 109.8, 73.5, 63.4, 55.8, 55.8, 55.5, 51.6, 41.9, 31.1, 27.5.

IR (KBr, neat) 3482, 3001, 2951, 2835, 1717, 1603, 1518, 1464, 1273, 1142, 1026, 756, 714 cm^{-1}; HRMS (ESI) calcd for $C_{29}H_{30}O_8$ $(M+Na)^+$ 529.1838, found 529.1833.Diastereomeric ratio (dr) was estimated by the measurement of ^{1}H NMR spectral data.

[(1*R*,2*R*,3*S*)-3-(2-(benzyloxy)phenyl)-2-((3,4-dimethoxyphenyl)(hydroxy)methyl)-2-(methoxycarbonyl)cyclopropyl]methyl benzoate (7d)



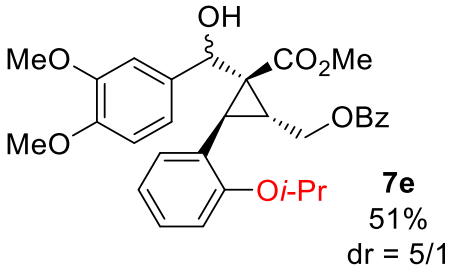
7d
67%
dr = 5/1

Following the procedure for the preparation of **7a**, the reaction of cyclopropane **6d** (0.50 g, 0.86 mmol) with $NaBH_4$ (305 mg, 8.06 mmol) gave the crude oil. The obtained crude oil was purified by column chromatography (SiO_2, hexane/AcOEt = 5/2) to give the product **7d** (337 mg, 67%, dr = 5/1).

7d: (5/1 mixture of diastereoisomers) colorless amorphous; (Selected data for major of **7d**.) ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.98 – 7.96 (m, 2H), 7.56-7.32 (m, 8H), 7.21-7.14 (m, 2H), 7.01 (d, *J* = 1.9 Hz, 1H), 6.96 (dd, *J* = 8.4, 1.8 Hz, 1H), 6.93-6.85 (m, 2H), 6.64 (d, *J* = 8.3 Hz, 1H), 5.47 (d, *J* = 5.9 Hz, 1H), 5.05 (d, *J* = 11.5 Hz, 1H), 4.99 (d, *J* = 11.5 Hz, 1H), 4.62 (dd, *J* = 11.8, 7.3 Hz, 1H), 4.54 (dd, *J* = 11.8, 7.4 Hz, 1H), 3.82 (s, 3H), 3.72 (s, 3H), 3.25 (s, 3H), 3.07 (d, *J* = 7.9 Hz, 1H), 2.95-2.86 (m, 1H), 2.69 (d, *J* = 5.9 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 171.2, 166.6, 157.9, 148.7, 148.2, 137.3, 135.1, 133.0, 130.2, 129.7, 129.3, 128.7, 128.4, 128.2, 128.2, 127.7, 124.9, 120.4, 118.5, 111.2, 110.8, 110.1, 71.3, 70.3, 63.5, 55.9, 55.8, 51.7, 41.9, 29.6, 27.3.

(Selected data for minor of **7d**.) ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.98 – 7.96 (m, 2H), 7.56-7.32 (m, 8H), 7.21-7.14 (m, 2H), 7.07 (d, *J* = 1.9 Hz, 1H), 6.93-6.85 (m, 3H), 6.62 (d, *J* = 8.1 Hz, 1H), 5.47 (d, *J* = 5.9 Hz, 1H), 5.16 (d, *J* = 11.9 Hz, 1H), 5.11 (d, *J* = 11.9 Hz, 1H), 4.72-4.67 (m, 2H), 4.45 (dd, *J* = 12.0, 8.3 Hz, 1H), 3.79 (s, 3H), 3.77 (s, 3H), 3.20 (s, 3H), 3.07 (d, *J* = 7.9 Hz, 1H), 2.95-2.86 (m, 1H). IR (KBr neat) 3497, 2951, 2837, 1721, 1603, 1516, 1450, 1273, 1140, 1026, 712 cm^{-1}; HRMS (ESI) calcd for $C_{35}H_{34}O_8$ $(M+Na)^+$ 605.2151, found 605.2146. Diastereomeric ratio (dr) was estimated by the measurement of ^{1}H NMR spectral data.

[(1*R*,2*R*,3*S*)-2-((3,4-dimethoxyphenyl)(hydroxy)methyl)-3-(2-isopropoxyphenyl)-2-(methoxycarbonyl)cyclopropyl]methyl benzoate (7e)



7e
51%
dr = 5/1

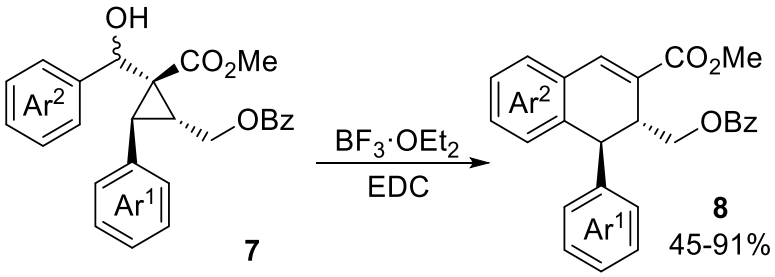
Following the procedure for the preparation of **7a**, the reaction of cyclopropane **6e** (1.13 g, 1.68 mmol) with $NaBH_4$ (636 mg, 16.8 mmol) gave the crude oil. The obtained crude oil was purified by column chromatography (SiO_2, hexane/AcOEt = 5/2) to give the product **7e** (463 mg, 51%, dr = 5/1).

7e: (5/1 mixture of diastereoisomers) colorless amorphous; (Selected data for major of **7e**.) ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.99-7.97 (m, 2H), 7.57 – 7.50 (m, 1H), 7.43-7.40 (m, 2H), 7.20 – 7.07 (m, 3H), 7.03 (dd, *J* = 8.3, 1.6 Hz, 1H), 6.89 – 6.78 (m, 2H), 6.71 (d, *J* = 8.3 Hz, 1H), 5.67 (d, *J* = 5.4 Hz, 1H), 4.67-4.57 (m, 2H), 4.52 (dd, *J* = 11.8, 7.7 Hz, 1H), 3.86 (s, 3H), 3.77 (s, 3H), 3.27 (s, 3H), 3.03 (d, *J* = 7.9 Hz, 1H), 3.00 (d, *J* = 5.5 Hz, 1H), 2.90 (q, *J* = 7.6 Hz, 1H), 1.68 (br, 1H), 1.39 (d, *J* = 6.0 Hz, 3H), 1.36 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 171.2, 166.7, 156.7, 148.8, 148.3, 135.0, 133.0, 130.2, 129.8, 129.5, 128.4, 128.1, 125.1, 119.7, 118.5, 111.8, 110.8, 110.1, 71.4, 69.7, 63.6, 55.9, 55.8, 51.7, 41.8, 29.6, 27.9, 22.4, 22.0.

(Selected data for minor of **7e**.) ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.02 – 7.93 (m, 2H), 7.57-7.50 (m, 1H), 7.43-7.40 (m, 2H), 7.20 – 7.07 (m, 3H), 6.98 (dd, *J* = 8.3, 1.3 Hz, 1H), 6.89 – 6.78 (m, 2H), 6.67 (d, *J* = 8.3 Hz, 1H), 4.79 (dd, *J* = 12.0, 6.6 Hz, 1H), 4.73 (d, *J* = 7.3 Hz, 1H), 4.70 – 4.56 (m, 2H), 4.52 (dd, *J* = 11.8, 7.7 Hz, 1H), 4.13 (d, *J* = 7.3 Hz, 1H), 3.83 (s, 3H), 3.79 (s, 3H), 3.18 (s, 3H), 2.84 (d, *J* = 7.6 Hz, 1H), 1.68 (br, 1H), 1.44 (d, *J* = 6.2 Hz, 3H), 1.42 (d, *J* = 6.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.0, 166.4, 156.8, 148.9, 148.1, 135.2, 133.2, 129.9, 129.8, 128.6, 128.4, 124.1, 119.9, 118.0, 110.7, 109.9, 73.5, 69.8, 55.9, 51.6, 42.2, 31.4, 27.6, 22.2, 21.9.

IR (KBr, neat) 3503, 2976, 2359, 1717, 1601, 1518, 1456, 1273, 1140, 1026, 957, 752, 714 cm^{-1}; HRMS (ESI) calcd for $C_{31}H_{34}O_8$ $(M+Na)^+$ 557.2151, found 557.2146. Diastereomeric ratio (dr) was estimated by the measurement of ^{1}H NMR spectral data.

1.4.5. Experimental procedure for ring-opening cyclization of 7 to afford *trans*-dihydronaphthalenes 8.

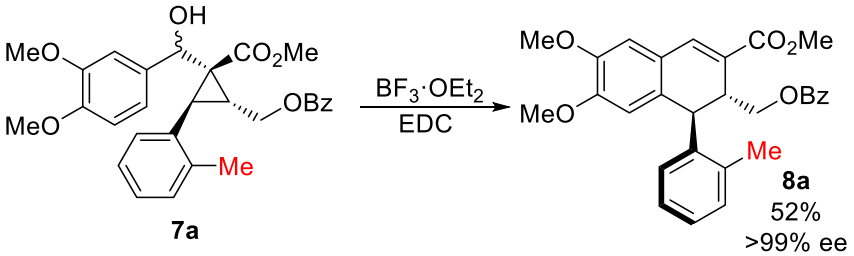


$BF_3{\cdot}OEt_2$ (1.1 equiv.) was added to a solution of cyclopropylcarbinol **7** (1.0 equiv.) in 1,2-dichloroethane (EDC) at room temperature or reflux temperature, followed by being stirred at same temperature for 5-10 min. The reaction was quenched with water at 0 °C. The organic layer was washed with water and extracted with $CHCl_3$. The organic layer was washed with brine, dried (Na_2SO_4) and concentrated. The obtained crude oil was purified by column chromatography to give the dihydronaphthalenes **8** (45-91%). The relative structure of **8** was determined by analogy with the NMR spectral data of a *trans*-dihydronaphthalene synthetic intermediate (**11a** in the literature: *Chem. Lett*. **2014**, *39*, 194.) in the total synthesis of (±) cyclogalgravin[a] and NOESY observations. The NOESY chart was attached in S15.

[a] Sakuma, D.; Ito, J.; Sakai, R.; Taguchi, R.; Nishii, Y. *Chem. Lett*. **2014**, *39*, 194 (open access).

Methyl (3*R*,4*S*)-3-((benzoyloxy)methyl)-6,7-dimethoxy-4-(*o*-tolyl)

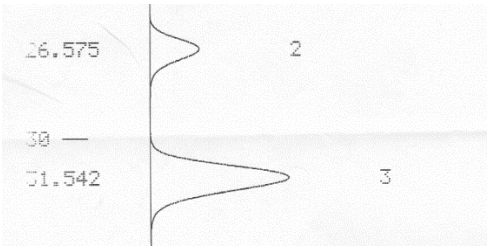
-3,4-dihydronaphthalene-2-carboxylate (8a)



$BF_3{\cdot}OEt_2$ (0.14 mL, 1.13 mmol) was added to a solution of cyclopropylcarbinol **7a** (473 mg, 0.964 mmol) in 1,2-dichloroethane (EDC) (10 mL) at room temperature, followed by being stirred at same temperature for 10 min. The reaction was quenched with H_2O (20 ml) at 0 °C, and the mixture was extracted with $CHCl_3$ (10 ml x 3). The combined organic layer was washed with brine (20 ml), dried over Na_2SO_4, and evaporated. The obtained crude oil was purified by column chromatography (SiO_2, hexane/AcOEt/ = 4/1) to give the dihydronaphthalene **8a** (237 mg, 52% yield).

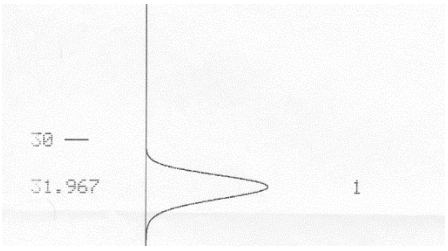
8a: colorless amorphous solid; $[\alpha]_D^{23}$ = 14.8 (*c* = 1.00, chloroform, λ = 589 nm); ^{1}H NMR (400 MHz,

$CDCl_3$) δ = 7.89-7.86 (m, 2H), 7.73 (s, 1H), 7.58 – 7.51 (m, 1H), 7.42-7.38 (m, 2H), 7.19 (d, *J* = 7.4 Hz, 1H), 7.07 (td, *J* = 7.4, 1.2 Hz, 1H), 6.94 (t, *J* = 7.1 Hz, 1H), 6.88 (s, 1H), 6.57 (s, 1H), 6.44 (d, *J* = 6.9 Hz, 1H), 4.55 (s, 1H), 4.41 (dd, *J* = 10.9, 4.8 Hz, 1H), 4.33 (dd, *J* = 10.9, 7.8 Hz, 1H), 3.92 (s, 3H), 3.79 (s, 3H), 3.68 (s, 3H), 3.38 (dd, *J* = 7.7, 4.8 Hz, 1H), 2.61 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 167.2, 166.7, 151.3, 148.3, 140.8, 138.8, 134.9, 133.1, 130.9, 130.6, 130.2, 129.7, 128.4, 128.3, 126.5, 126.1, 125.2, 123.7, 112.9, 111.7, 66.4, 56.2, 56.11, 51.9, 41.9, 39.5, 19.9; IR (KBr, neat) 3447, 2949, 1717, 1653, 1635, 1603, 1570, 1558, 1541, 1516, 1489, 1437, 1350, 1273, 1244, 1213, 1140, 1113, 758, 714 cm^{-1}; HRMS (ESI) calcd for $C_{29}H_{28}O_6$ $(M+Na)^+$ 495.1784, found 495.1778; HPLC analysis: >99% ee [Daicel CHIRALPAK IG (15 cm) at 25 °C; flow rate = 0.85 mL/min; solvent: hexane/2-propanol = 10/1 (v/v); t_R(mixture of **8a** and optical isomer **8a′**) = 26.6 min and 31.5 min, t_R(**8a**) = 32.0].



A 77.0/23.0 mixture of **8a**(3*R*,4*S*) and optical isomer **8a′** (3*S*,4*R*): HPLC analysis using chiral column.

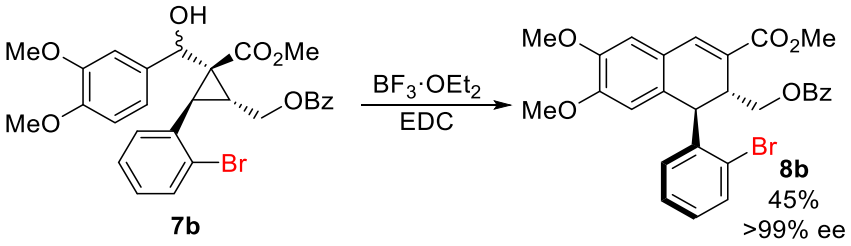
2	26.575	868449	14252	22.9992
3	31.542	2906366	40382	76.9697



Enantioenriched **8a** (>99% ee): HPLC analysis using chiral column.

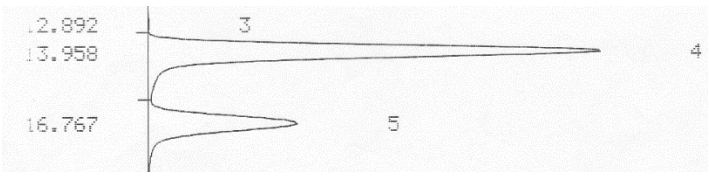
1	31.967	2843007	38446	100.0000

Methyl (3*R*,4*R*)-3-((benzoyloxy)methyl)-4-(2-bromophenyl)-6,7-dimethoxy -3,4-dihydronaphthalene-2-carboxylate (8b)



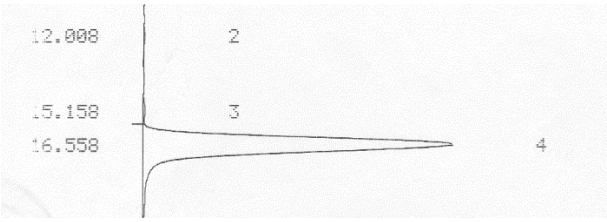
$BF_3{\cdot}OEt_2$ (0.16 mL, 1.23 mmol) was added to a solution of cyclopropylcarbinol **7b** (600 mg, 1.12 mmol) in 1,2-dichloroethane (EDC) (11 mL) at 83 °C, followed by being stirred at same temperature for 10 min. The reaction was quenched with H_2O (20 ml) at 0 °C, and the mixture was extracted with $CHCl_3$ (10 ml x 3). The combined organic layer was washed with brine (20 ml), dried over Na_2SO_4, and evaporated. The obtained crude oil was purified by column chromatography (SiO_2, hexane/AcOEt = 3/1) to give the dihydronaphthalene **8b** (277 mg, 45% yield).

8b: colorless amorphous solid; $[\alpha]_D^{24}$ = 11.0 (*c* = 1.00, chloroform, λ = 589 nm); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.81 – 7.75 (m, 2H), 7.72 (s, 1H), 7.61 – 7.56 (m, 1H), 7.50 (dd, *J* = 10.5, 4.3 Hz, 1H), 7.35 (t, *J* = 7.8 Hz, 2H), 7.08 – 6.98 (m, 2H), 6.87 (s, 1H), 6.63 (s, 1H), 6.55 – 6.50 (m, 1H), 4.78 (s, 1H), 4.51 (dd, *J* = 10.9, 4.8 Hz, 1H), 4.41 (dd, *J* = 10.9, 6.6 Hz, 1H), 3.91 (s, 3H), 3.81 (s, 3H), 3.71 (s, 3H), 3.50 (t, *J* = 5.5 Hz, 1H); ^{13}C NMR (101MHz, $CDCl_3$) δ = 167.1, 166.6, 151.3, 148.4, 141.5, 138.5, 132.2, 130.0, 129.9, 129.8, 129.7, 128.2, 128.1, 127.5, 125.1, 123.8, 123.7, 112.6, 111.6, 66.6, 56.1, 51.9, 44.8, 39.1, 31.6, 22.7, 14.1; IR (KBr, neat) 3020, 2953, 2841, 1722, 1670, 1597, 1514, 1464, 1450, 1437, 1420, 1272, 1215, 1173, 1144, 1111, 1070, 1026, 752, 711 cm^{-1}; HRMS (ESI) calcd for $C_{28}H_{25}BrO_6$ $(M+Na)^+$ 559.0732, found 559.0727; HPLC analysis: >99% ee [Daicel CHIRALPAK IC (25 cm) at 25 °C; flow rate = 0.40 mL/min; solvent: hexane/ethanol = 10/1 (v/v); t_R(mixture of **8b** and optical isomer **8b′**) = 14.0 min and 16.8 min, t_R(**8b**) = 16.6].



A 29.4/70.6 mixture of **8b**(3*R*,4*R*) and optical isomer **8b'** (3*S*,4*S*): HPLC analysis using chiral column.

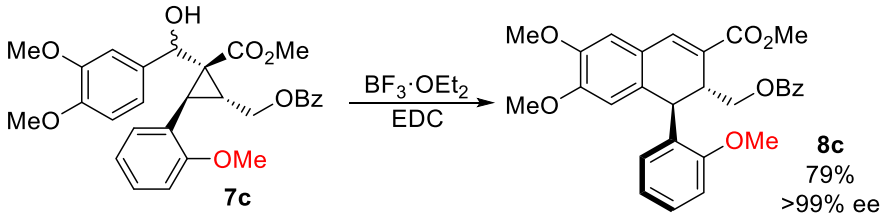
4	13.958	9441715	266545	LLL	70.4907
5	16.767	3933224	88078	V	29.3650



Enantioenriched **8b** (>99% ee): HPLC analysis using chiral column.

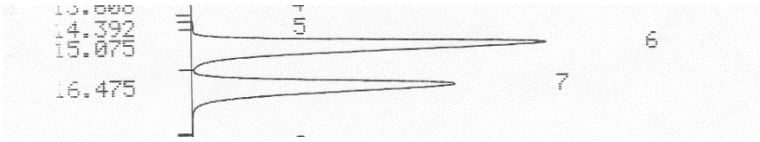
4	16.558	4294055	98048	LLL	99.3835

Methyl (3*R*,4*R*)-3-((benzoyloxy)methyl)-6,7-dimethoxy-4-(2-methoxyphenyl) -3,4-dihydronaphthalene-2-carboxylate (8c)



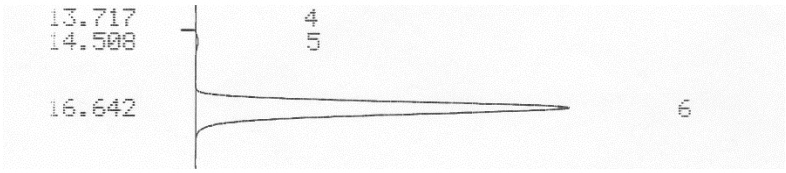
$BF_3{\cdot}OEt_2$ (0.79 mL, 6.30 mmol) was added to a solution of cyclopropylcarbinol **7a** (2.90 g, 5.72 mmol) in 1,2-dichloroethane (EDC) (57 mL) at room temperature, followed by being stirred at same temperature for 10 min. The reaction was quenched with H_2O (10 ml) at 0 ℃, and the mixture was extracted with $CHCl_3$ (15 ml x 3). The combined organic layer was washed with brine (50 ml), dried over Na_2SO_4, and evaporated. The obtained crude oil was purified by column chromatography (SiO_2, hexane/AcOEt = 3/1) to give the dihydronaphthalene **8c** (2.20 g, 79% yield).

8c: colorless solid; mp = 146-150 ˚C; $[\alpha]_D^{27}$ = 126.0 (*c* = 1.00, chloroform, λ = 589 nm); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.91 – 7.83 (m, 2H), 7.69 (s, 1H), 7.56 – 7.49 (m, 1H), 7.42 – 7.34 (m, 2H), 7.14 (td, *J* = 8.1, 1.7 Hz, 1H), 6.87 (d, *J* = 8.9 Hz, 1H), 6.86 (s, 1H), 6.69 (td, *J* = 7.5, 1.0 Hz, 1H), 6.64 (s, 1H), 6.40 (dd, *J* = 7.6, 1.6 Hz, 1H), 4.82 (s, 1H), 4.49 (dd, *J* = 10.8, 4.7 Hz, 1H), 4.28 (dd, *J* = 10.8, 7.4 Hz, 1H), 3.91 (s, 3H), 3.86 (s, 3H), 3.79 (s, 3H), 3.70 (s, 3H), 3.49 – 3.43 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 167.3, 166.5, 156.2, 151.1, 148.1, 138.34, 132.8, 131.2, 130.5, 130.4, 129.6, 128.8, 128.2, 127.5, 125.3, 124.3, 120.6, 112.8, 111.5, 110.17, 77.4, 77.1, 76.8, 66.4, 56.1, 56.0, 55.3, 51.8, 39.0, 38.6; IR (KBr, neat); 3017, 2951, 2835, 1717, 1632, 1603, 1570, 1514, 1489, 1437, 1408, 1368, 1348, 1273, 1240, 1211, 1138, 1084, 1053, 1026, 1003, 756, 712 cm^{-1}; HRMS (ESI) calcd for $C_{29}H_{28}O_7$ $(M+Na)^+$ 511.1733, found 511.1727; HPLC analysis: >99% ee [Daicel CHIRALPAK IG (15 cm) at 25 °C; flow rate = 0.35 mL/min; solvent: hexane/ethanol = 2/1 (v/v); t_R(mixture of **8c** and optical isomer **8c′**) = 15.1 min and 16.5 min, t_R(**8c**) = 16.6].



A 44.9/55.1 mixture of **8c**(3*R*,4*R*) and optical isomer **8c′** (3*S*,4*S*): HPLC analysis using chiral column.

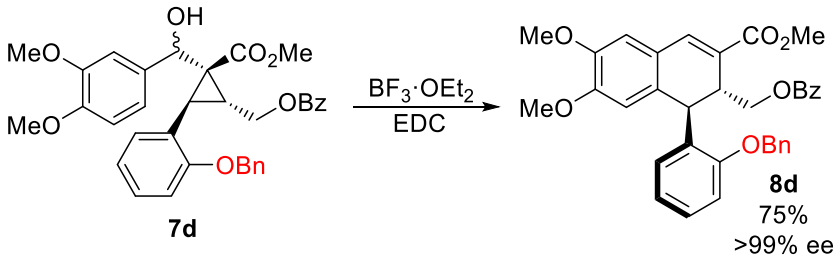
6	15.075	4984975	186813	LLL	54.7205
7	16.475	4050485	139070	V	44.4626



Enantioenriched **8c** (>99% ee): HPLC analysis using chiral column.

6	16.642	5370271	183399	98.2444

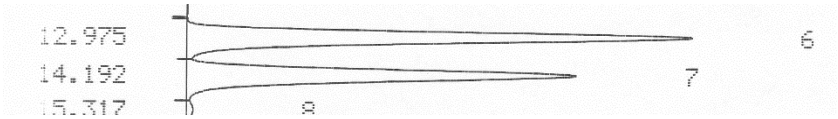
Methyl (3*R*,4*R*)-3-((benzoyloxy)methyl)-4-[2-(benzyloxy)phenyl]-6,7-dimethoxy -3,4-dihydronaphthalene-2-carboxylate (8d)



$BF_3{\cdot}OEt_2$ (70 μL, 0.556 mmol) was added to a solution of cyclopropylcarbinol **7d** (294 mg, 0.505 mmol) in 1,2-dichloroethane (EDC) (5.0 mL) at room temperature, followed by being stirred at same temperature for 10 min. The reaction was quenched with H_2O (10 ml) at 0°C, and the mixture was extracted with $CHCl_3$ (8 ml x 3). The combined organic layer was washed with brine (10 ml), dried over Na_2SO_4, and evaporated. The obtained crude oil was purified by column chromatography (SiO_2, hexane/AcOEt = 3/1) to give the dihydronaphthalene **8d** (214 mg, 75% yield).

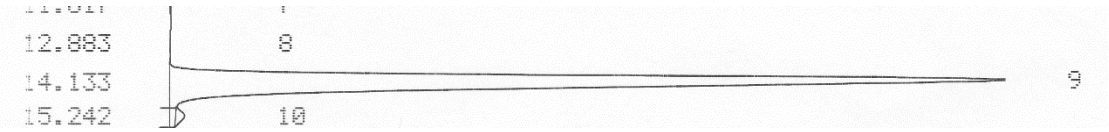
8d: colorless solid; mp = 112-118 ˚C; $[\alpha]_D^{23} = 0.85$ (*c* = 1.00, chloroform, λ = 589 nm); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.67 (s, 1H), 7.65 (dd, *J* = 8.3, 1.2 Hz, 2H), 7.51 (d, *J* = 7.3 Hz, 2H), 7.47 – 7.41 (m, 1H), 7.38 (dd, *J* = 10.2, 4.7 Hz, 2H), 7.33 – 7.21 (m, 3H), 7.12 (td, *J* = 8.1, 1.7 Hz, 1H), 6.94 (d, *J* = 7.6 Hz, 1H), 6.83 (s, 1H), 6.71 (td, *J* = 7.5, 0.8 Hz, 1H), 6.63 (s, 1H), 6.45 (dd, *J* = 7.6, 1.5 Hz, 1H), 5.22 (d, *J* = 12.0 Hz, 1H), 5.16 (d, *J* = 12.0 Hz, 1H), 4.82 (s, 1H), 4.38 (d, *J* = 5.6 Hz, 2H), 3.89 (s, 3H), 3.75 (s, 3H), 3.71 (s, 3H), 3.59 (t, *J* = 5.3 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 167.4,

166.6, 155.4, 151.1, 148.1, 138.4, 137.2, 132.8, 131.9, 130.8, 130.2, 129.6, 128.9, 128.8, 128.2, 127.7, 127.5, 125.4, 124.7, 120.8, 112.8, 111.8, 111.6, 70.4, 67.2, 56.2, 56.1, 51.9, 39.3, 39.0; IR (KBr, neat) 3065, 3032, 3003, 2949, 2833, 2364, 2322, 1717, 1636, 1603, 1570, 1514, 1487, 1450, 1348, 1271, 1234, 1138, 1113, 1026, 754, 712, 755, 712 cm^{-1}; HRMS (ESI) calcd for $C_{35}H_{32}O_7$ $(M+H)^+$ 565.2226, found 565.2221; HPLC analysis: >99% ee [Daicel CHIRALPAK IG (15 cm) at 25 °C; flow rate = 0.35 mL/min; solvent: hexane/ethanol = 2/1 (v/v); t_R(mixture of **8d** and optical isomer **8d′**) = 13.0 min and 14.2 min, t_R(**8d**) = 14.1].



A 45.2/54.8 mixture of **8d**(3*R*,4*R*) and optical isomer **8d′** (3*S*,4*S*): HPLC analysis using chiral column.

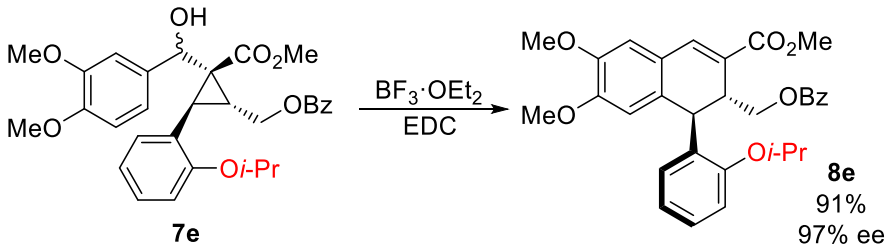
6	12.975	6079716	247543	V	53.0049
7	14.192	5014067	190776	V	43.7142



Enantioenriched **8d** (>99% ee): HPLC analysis using chiral column.

8	12.883	2201	125		1.9570E-02
9	14.133	10831751	408581	TTT	96.3305

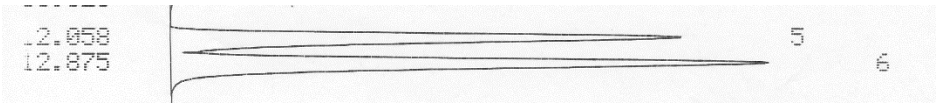
Methyl (3*R*,4*R*)-3-((benzoyloxy)methyl)-4-(2-isopropoxyphenyl)-6,7-dimethoxy -3,4-dihydronaphthalene-2-carboxylate (8e)



$BF_3{\cdot}OEt_2$ (36 μL, 0.289 mmol) was added to a solution of cyclopropylcarbinol **7e** (141 mg, 0.263 mmol) in 1,2-dichloroethane (2.6 mL) at room temperature, followed by being stirred at same temperature for 10 min. The reaction was quenched with H_2O (5 ml) at 0 °C, and the mixture was extracted with $CHCl_3$ (5 ml x 3). The combined organic layer was washed with brine (5 ml), dried

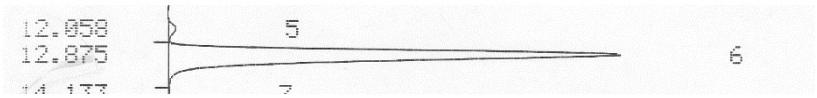
over Na_2SO_4, and evaporated. The obtained crude oil was purified by column chromatography (SiO_2, hexane/AcOEt = 5/2) to give the dihydronaphthalene **8e** (124 mg, 91%, 97% ee).

8e: colorless amorphous solid; $[\alpha]_D^{23}$ = 6.99 (*c* = 1.00, chloroform, λ = 589 nm); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.68-7.66 (m, 3H), 7.48 (t, *J* = 7.4 Hz, 1H), 7.31 (t, *J* = 7.8 Hz, 2H), 7.15 – 7.07 (m, 1H), 6.88 (d, *J* = 8.2 Hz, 1H), 6.85 (s, 1H), 6.69 – 6.61 (m, 2H), 6.41 (dd, *J* = 7.6, 1.4 Hz, 1H), 4.77 – 4.65 (m, 2H), 4.51 – 4.40 (m, 2H), 3.91 (s, 3H), 3.80 (s, 3H), 3.68 (s, 3H), 3.52 (t, *J* = 5.3 Hz, 1H), 1.44 (d, *J* = 4.2 Hz, 3H), 1.43 (d, *J* = 4.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 167.5, 166.7, 154.6, 151.1, 148.1, 138.4, 132.9, 132.2, 131.1, 130.3, 129.7, 129.0, 128.2, 127.5, 125.5, 124.9, 119.9, 112.7, 112.2, 111.62, 69.8, 67.6, 56.2, 56.1, 51.8, 39.5, 38.8, 22.5, 22.2; IR (KBr, neat) 2976, 1717, 1603, 1570, 1485, 1456, 1273, 1234, 1115, 752, 711 cm^{-1}; HRMS (ESI) calcd for $C_{31}H_{32}O_7$ $(M+Na)^+$ 539.2046, found 539.2040; HPLC analysis: 97% ee [Daicel CHIRALPAK IC (25 cm) at 25 °C; flow rate = 0.40 mL/min; solvent: hexane/ethanol = 1/1 (v/v); t_R(mixture of **8e** and optical isomer **8e′**) = 12.1 min and 12.9 min, t_R(**8e**) = 12.9].



A 55.5/44.5 mixture of **8e**(3*R*,4*R*) and optical isomer **8e′** (3*S*,4*S*): HPLC analysis using chiral column.

5	12.058	2679111	124861	V	44.0714
6	12.875	3343563	145936	V	55.0017

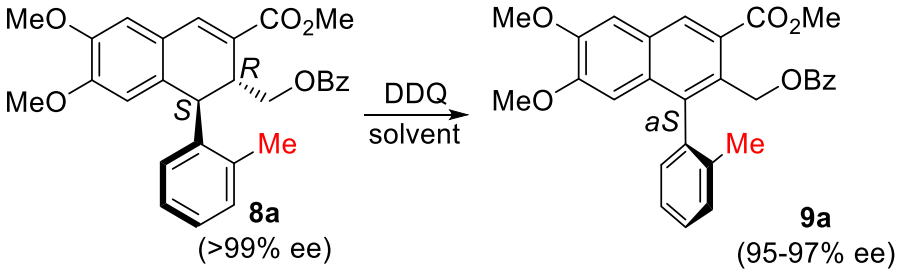


Enantioenriched **8e** (97% ee): HPLC analysis using chiral column.

5	12.058	156921	7467	V	1.4951
6	12.875	10209377	442502	TTT	97.2702

1.4.6. Central-to-axial chirality exchange by dehydrogenation using DDQ.

Methyl (*S*)-3-((benzoyloxy)methyl)-6,7-dimethoxy-4-(*o*-tolyl)-2-naphthoate (9a)



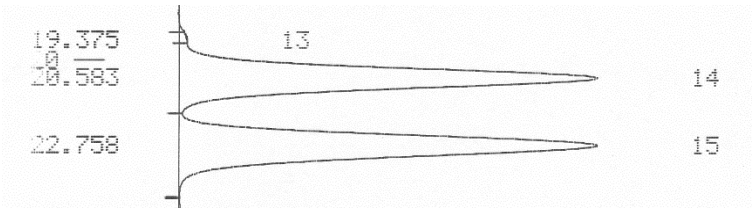
i) (Table 2, Entry 1): A solution of dihydronaphthalene **8a** (47 mg, 0.100 mmol) in Toluene (6.8 mL) and DDQ (57 mg, 0.250 mmol, 2.5 equiv.) was stirred at 110 ˚C under an argon atmosphere for 5 h. After cooled to room temperature, sat. $NaHCO_3$ aqueous solution (10 mL) was added to the reaction mixture, which was extracted with AcOEt (ca. 10 mL × 4). Its organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel eluting with *n*-Hexane-AcOEt (4/1) to afford **9a** (45 mg, 96% yield) as a light-yellow solid.

ii) (Table 3, Entry 1): A solution of dihydronaphthalene **8a** (47 mg, 0.100 mmol) in 1,2-dichloroethane (6.8 mL) and DDQ (57 mg, 0.250 mmol, 2.5 equiv.) was stirred at 83 ˚C under an argon atmosphere for 2 h. After cooled to room temperature, sat. $NaHCO_3$ aqueous solution (10 mL) was added to the reaction mixture, which was extracted with AcOEt (ca. 10 mL × 4). Its organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel eluting with *n*-Hexane-AcOEt (4/1) to afford **9a** (42 mg, 90% yield) as a light-yellow solid.

iii) (Table 3, Entry 2): A solution of dihydronaphthalene **8a** (47 mg, 0.100 mmol) in benzene (6.8 mL) and DDQ (57 mg, 0.250 mmol, 2.5 equiv.) was stirred at 80 ˚C under an argon atmosphere for 2 h. After cooled to room temperature, sat. $NaHCO_3$ aqueous solution (10 mL) was added to the reaction mixture, which was extracted with AcOEt (ca. 10 mL × 4). Its organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel eluting with *n*-Hexane-AcOEt (4/1) to afford **9a** (40 mg, 85% yield) as a light-yellow solid.

9a: light-yellow solid; mp = 130-133 ˚C; $[\alpha]_D^{23}$ = 1.05 (*c* = 1.00, chloroform, λ = 589 nm); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.37 (s, 1H), 7.96 – 7.89 (m, 2H), 7.54 – 7.48 (m, 1H), 7.42 – 7.27 (m, 5H), 7.24 (s, 1H), 7.17 (d, *J* = 7.2 Hz, 1H), 6.51 (s, 1H), 5.46 (d, *J* = 11.7 Hz, 1H), 5.39 (d, *J* = 11.7 Hz,

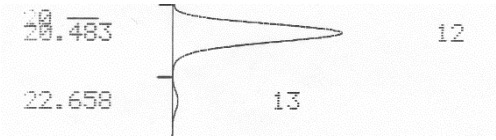
1H), 4.03 (s, 3H), 3.81 (s, 3H), 3.68 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 168.9, 166.3, 151.5, 150.5, 140.2, 137.5, 136.9, 132.9, 130.4, 130.3, 130.1, 123.0, 129.7, 128.4, 128.34, 127.9, 127.4, 126.2, 107.3, 105.4, 63.3, 56.2, 55.8, 52.4, 19.9; IR (KBr, neat) 3447, 2947, 1719, 1506, 1472, 1435, 1364, 1315, 1204, 1152, 1113, 1072, 1020, 851, 764 cm^{-1}; HRMS (ESI) calcd for $C_{29}H_{26}O_6$ $(M+K)^+$ 509.1366, found 509.1361; HPLC analysis [Daicel CHIRALPAK IG (15cm) at 25°C, hexane/2-propanol = 10/1 (v/v), flow rate 0.85 mL/min]: t_R[mixture of (*aS*)-**9a** and (*aR*)-**9a**] = 20.6 min and 22.8 min, i) (Table 2, Entry 1) t_R[(*aS*)-**9a**] = 20.5 min for major and 22.7 min for minor, ee = 95%, ii) (Table 3, Entry 1) t_R[(*aS*)-**9a**] = 21.2 min for major and 23.8 min for minor, ee = 97%, iii) (Table 3, Entry 2) t_R[(*aS*)-**9a**] = 20.9 min for major and 23.3 min for minor, ee = 96%.



A 57.2/42.8 mixture of (*aS*)-**9a** and (*aR*)-**9a**: HPLC analysis using chiral column.

14	20.583	9574521	205433	LLL	47.8020
15	22.758	9991837	205346	V	49.8855

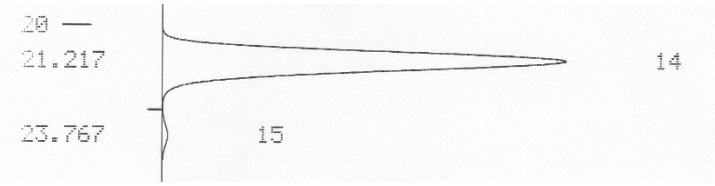
i) Table 2, Entry 1 (Solvent = toluene, Reaction temperature = 110 °C)



(*aS*)-**9a** (95% ee): HPLC analysis using chiral column.

12	20.483	1835541	41534	LLL	87.7450
13	22.658	60835	1350	V	2.9081

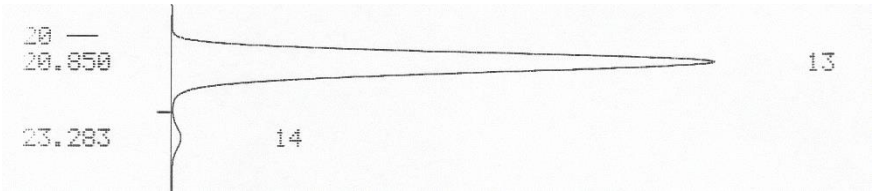
ii) Table 3, Entry 1 (Solvent = 1,2-dichloroethane, Reaction temperature = 83 °C)



(*aS*)-**9a** (97% ee): HPLC analysis using chiral column.

14	21.217	9768530	208740	V	92.1103
15	23.767	157547	2880	V	1.4856

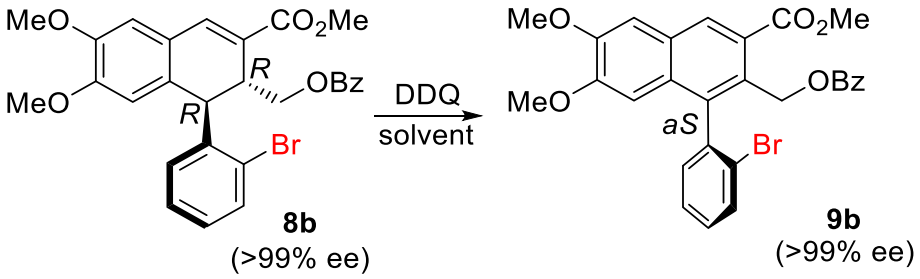
iii) Table 3, Entry 2 (Solvent = benzene, Reaction temperature = 80 °C)



(*aS*)-**9a** (96% ee): HPLC analysis using chiral column.

13	20.850	12128935	265935	V	92.9227
14	23.283	236344	4464	V	1.8107

Methyl (*S*)-3-((benzoyloxy)methyl)-4-(2-bromophenyl)-6,7-dimethoxy-2-naphthoate (9b)



8b (>99% ee)

9b (>99% ee)

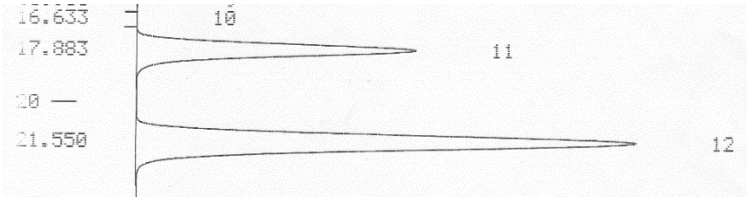
i) (Table 2, Entry 2): Following the procedure for the preparation of **9a**, the dehydrogenation of dihydronaphthalene **8b** (54 mg, 0.100 mmol) using DDQ (57 mg, 0.250 mmol) in toluene (6.8 mL) at 110 °C gave the crude oil. The obtained crude oil was purified by column chromatography (SiO_2, hexane/AcOEt = 4/1) to give the product **9b** (48 mg, 93% yield). (Reaction temperature = 110 °C, Reaction time = 14 h).

ii) (Table 3, Entry 3): Following the procedure for the preparation of **9a**, the dehydrogenation of dihydronaphthalene **8b** (54 mg, 0.100 mmol) using DDQ (57 mg, 0.250 mmol) in 1,2-dichloroethane (6.8 mL) at 83 °C gave the crude oil. The obtained crude oil was purified by column chromatography (SiO_2, hexane/AcOEt = 4/1) to give the product **9b** (48 mg, 92% yield). (Reaction temperature = 83 °C, Reaction time = 3 h).

iii) (Table 3, Entry 4): Following the procedure for the preparation of **9a**, the dehydrogenation of dihydronaphthalene **8b** (54 mg, 0.100 mmol) using DDQ (57 mg, 0.250 mmol) in benzene (6.8 mL) at 80 °Cgave the crude oil. The obtained crude oil was purified by column chromatography (SiO_2, hexane/AcOEt = 4/1) to give the product **9b** (48 mg, 92% yield). (Reaction temperature = 80 °C, Reaction time = 4 h).

9b: yellow solid; mp = 136-138 ˚C; $[\alpha]_D^{23}$ = 0.385 (*c* = 1.00, chloroform, λ = 589 nm); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.42 (s, 1H), 7.98 – 7.91 (m, 2H), 7.76-7.75 (m, 1H), 7.56 – 7.46 (m, 1H), 7.45 –

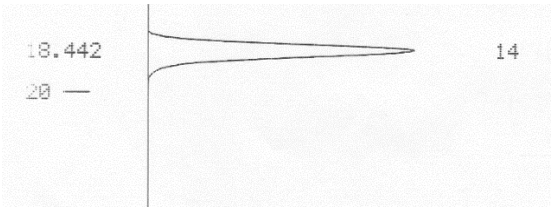
7.30 (m, 5H), 7.27-7.25 (m, 1H), 6.48 (s, 1H), 5.60 (d, J = 11.8 Hz, 1H), 5.29 (d, J = 11.8 Hz, 1H), 4.03 (s, 3H), 3.83 (s, 3H), 3.71 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 168.6, 166.2, 151.6, 150.5, 139.5, 138.9, 133.1, 132.9, 132.1, 130.6, 130.3, 130.0, 129.8, 128.4, 128.2, 127.7, 127.2, 124.8, 107.3, 105.1, 77.5, 77.2, 76.84, 63.1, 56.1, 55.8, 52.4; IR (KBr, neat) 2951, 2830, 2361, 2322, 1717, 1622, 1506, 1433, 1369, 1315, 1265, 1246, 1200, 1178, 1152, 1111, 1072, 1024, 950, 849, 787 cm^{-1}; HRMS (ESI) calcd for $C_{28}H_{23}BrO_6$ $(M+Na)^+$ 557.0576, found 557.0570; HPLC analysis [Daicel CHIRALPAK IG (15cm) at 25°C, hexane/ethanol = 10/1 (v/v), flow rate 0.87 mL/min]: t_R(mixture of (*aS*)-**9b** and (*aR*)-**9b**) = 17.9 min and 21.6 min, i) (Table 2, Entry 2) t_R[(*aS*)-**9b**] = 18.4 min, ee = >99%, ii) (Table 3, Entry 3) t_R[(*aS*)-**9b**] = 16.6 min for major and 19.9 min for minor, ee = 99%, iii) (Table 3, Entry 4) t_R[(*aS*)-**9b**] = 16.7 min for major and 20.1 min for minor, ee = 99%.



A 31.9/67.5 mixture of (*aS*)-**9b** and (*aR*)-**9b**: HPLC analysis using chiral column.

11	17.883	5929048	169869	LLL	31.8563
12	21.550	12566651	303899		67.5196

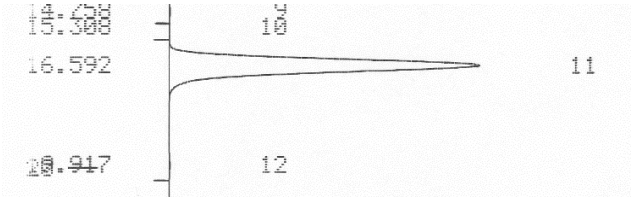
i) Table 2, Entry 2 (Solvent = toluene, Reaction temperature = 110 °C)



(*aS*)-**9b** (>99% ee): HPLC analysis using chiral column.

14	18.442	10842924	304396	EEE	98.5339

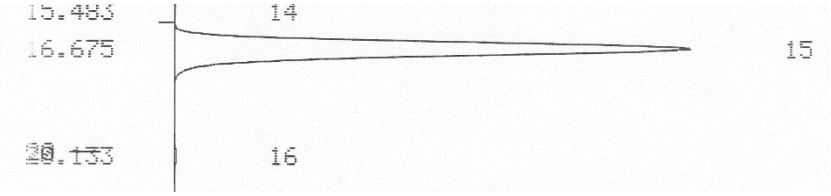
ii) Table 3, Entry 3 (Solvent = 1,2-dichloroethane, Reaction temperature = 83 °C)



(*aS*)-**9b** (>99% ee): HPLC analysis using chiral column.

11	16.592	4946604	158436	TTT	97.7077
12	19.917	14270	424	V	0.2819

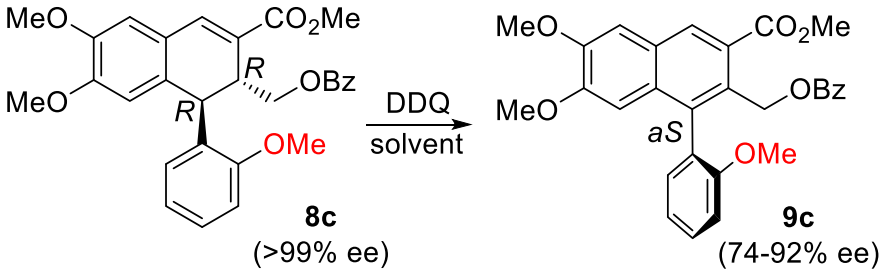
iii) Table 3, Entry 4 (Solvent = benzene, Reaction temperature = 80 °C)



(*aS*)-**9b** (>99% ee): HPLC analysis using chiral column.

15	16.675	15911312	505731	TTT	98.2915
16	20.133	56479	1557		0.3489

Methyl (*S*)-3-((benzoyloxy)methyl)-6,7-dimethoxy-4-(2-methoxyphenyl)-2-naphthoate (9c)



8c (>99% ee) **9c** (74-92% ee)

Following the procedure for the preparation of **9a**, the dehydrogenation of dihydronaphthalene **8c** (50 mg, 0.102 mmol) using DDQ (57 mg, 0.250 mmol) in solvent (6.8 mL) gave the crude oil. The obtained crude oil was purified by column chromatography (SiO_2, hexane/AcOEt = 4/1) to give the product **9c** (x mg, y% yield).

i) (Table 2, Entry 3): Solvent = toluene, Reaction temperature = 110 °C, Reaction time = 3 h, x = 47, y = 93.

ii) (Table 2, Entry 4): Solvent = toluene, Reaction temperature = 110 °C, Reaction time 1 h, x = 29, y = 58, Conversion = 75%.

iii) (Table 3, Entry 5): Solvent = 1,2-dichloroethane, Reaction temperature = 83 °C, Reaction time = 2.5 h, x = 44, y = 88.

iv) (Table 3, Entry 6): Solvent = benzene, Reaction temperature = 80 °C, Reaction time = 6 h, x = 44, y = 88.

v) (Table 3, Entry 7): Solvent = 1,2-dichloroethane, Reaction temperature = r.t., Reaction time = 48 h, x = 45, y = 90.

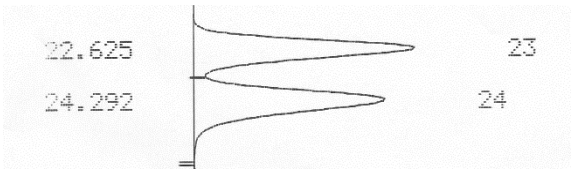
vi) (Table 3, Entry 8): Solvent = 1,2-dichloroethane, Reaction temperature = 0 °C, Reaction time = 144 h, x = 33, y = 66, Conversion = 84%.

vii) (Table S1, Entry 5): Solvent = chloroform, Reaction temperature = 61 °C, Reaction time = 3 h, x

= 45, y = 90.

viii) (Table S1, Entry 6): Solvent = dichloromethane, Reaction temperature = 40 °C, Reaction time = 24 h, x = 38, y = 76.

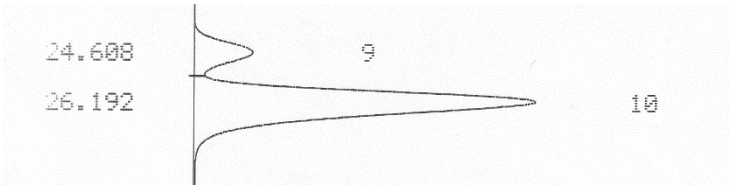
9c: lignt-yellow solid; mp = 152-156 ˚C; $[\alpha]_D^{27}$ = 21.3 (*c* = 1.00, chloroform, λ = 589 nm); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.35 (s, 1H), 7.97 – 7.90 (m, 2H), 7.50 (m, 1H), 7.44 (m, 1H), 7.37 (t, *J* = 7.7 Hz, 2H), 7.26 (s, 1H), 7.22 (s, 1H), 7.19 (dd, *J* = 7.4, 1.7 Hz, 1H), 7.08 – 6.99 (m, 2H), 6.64 (s, 1H), 5.65 (d, *J* = 11.8 Hz, 1H), 5.31 (d, *J* = 11.8 Hz, 1H), 4.02 (s, 3H), 3.82 (s, 3H), 3.70 (s, 3H), 3.63 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 169.0, 166.3, 157.3, 151.2, 150.3, 137.3, 132.8, 132.0, 130.5, 130.5, 130.0, 129.9, 129.7, 128.7, 128.4, 127.3, 126.5, 120.9, 111.2, 107.2, 105.7, 77.5, 77.2, 76.8, 63.6, 56.1, 55.8, 55.6, 52.4; IR (KBr, neat) 3404, 2951, 2839, 1713, 1620, 1599, 1580, 1508, 1495, 1472, 1450, 1435, 1402, 1366, 1314, 1263, 1177, 1113, 1020 cm^{-1}; HRMS (ESI) calcd for $C_{29}H_{26}O_7$ $(M+Na)^+$ 509.1576, found 509.1571; HPLC analysis [Daicel CHIRALPAK IG (15cm) at 25°C, hexane/ethanol = 10/1 (v/v), flow rate 0.87 mL/min]: t_R(racemic **9c**) = 22.6 min and 24.3 min, i) (Table 2, Entry 1) t_R[(*aS*)-**9c**] = 26.2 min for major and 24.6 min for minor, ee = 74%, ii) (Table 2, Entry 4) t_R[(*aS*)-**9c**] = 25.0 min for major and 23.3 min for minor, ee = 79%, iii) (Table 3, Entry 5) t_R[(*aS*)-**9c**] = 26.4 min for major and 24.7 min for minor, ee = 87%, iv) (Table 3, Entry 6) t_R[(*aS*)-**9c**] = 25.7 min for major and 24.4 min for minor, ee = 87%, v) (Table 3, Entry 7) t_R[(*aS*)-**9c**] = 26.0 min for major and 24.6 min for minor, ee = 91%, vi) (Table 3, Entry 8) t_R[(*aS*)-**9c**] = 23.4 min for major and 25.0 min for minor, ee = 92%, vii) (Table S1, Entry 5) t_R[(*aS*)-**9c**] = 25.8 min for major and 24.4 min for minor, ee = 89%, viii) (Table S1, Entry 6) t_R[(*aS*)-**9c**] = 25.7 min for major and 24.2 min for minor, ee = 90%.



A racemic **9c**: HPLC analysis using chiral column.

23	22.625	2294013	54160	V	42.9154
24	24.292	2357999	46931	V	44.1124

i) Table 2, Entry 3 (Solvent = toluene, Reaction temperature = 110 °C, Reaction time 3 h)

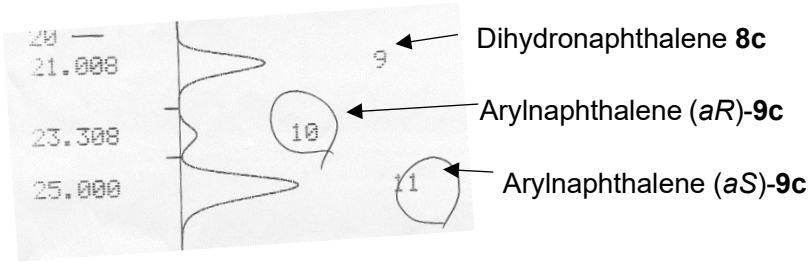


(*aS*)-**9c** (74% ee): HPLC analysis using chiral column.

9	24.608	2684031	57217	V	12.7831
10	26.192	18228216	334539	TTT	86.8145

ii) Table 2, Entry 4 (Solvent = toluene, Reaction temperature = 110 °C, Reaction time 1 h) [a]

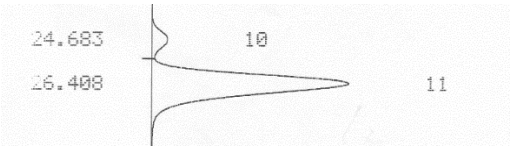
[a] Crude oil was analyzed.



(*aS*)-**9c** (79% ee): HPLC analysis using chiral column.

9	21.008	1870137	42838	V	35.0196
10	23.308	369088	8426	V	6.9114
11	25.000	3069988	57714	V	57.4877

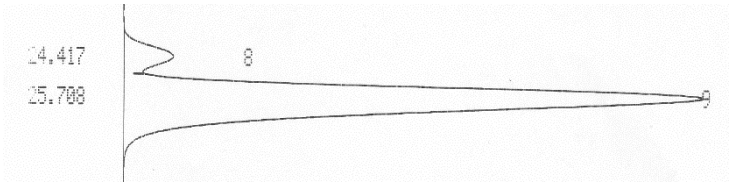
iii) Table 3, Entry 5 (Solvent = 1,2-dichloroethane, Reaction temperature = 83 °C)



(*aS*)-**9c** (87% ee): HPLC analysis using chiral column.

10	24.683	439328	9556	V	6.2500
11	26.408	6499803	118190	TTT	92.4682

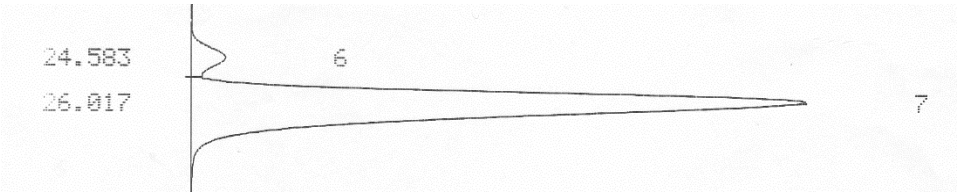
iv) Table 3, Entry 6 (Solvent = benzene, Reaction temperature = 80 °C)



(*aS*)-**9c** (87% ee): HPLC analysis using chiral column.

8	24.417	3349342	76216	V	6.5109
9	25.708	47868323	879863	V	93.0528

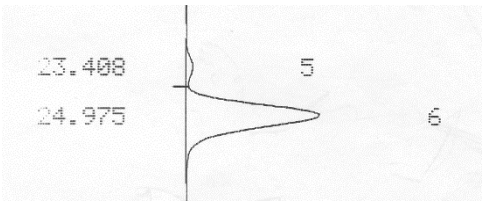
v) Table 3, Entry 7 (Solvent = 1,2-dichloroethane, Reaction temperature = r.t.)



(*aS*)-**9c** (91% ee): HPLC analysis using chiral column.

6	24.583	1489080	33632	V	4.3963
7	26.017	32116070	603706	V	94.8191

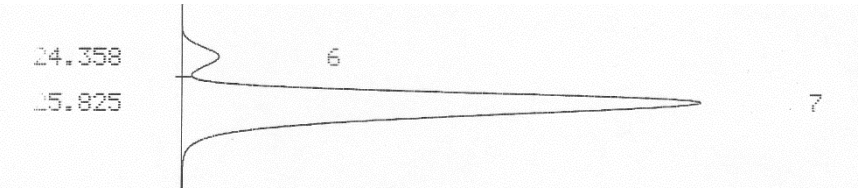
vi) Table 3, Entry 8 (Solvent = 1,2-dichloroethane, Reaction temperature = 0 °C)



(*aS*)-**9c** (92% ee): HPLC analysis using chiral column.

5	23.408	136661	3182	V	3.7442
6	24.975	3459675	65711	V	94.7876

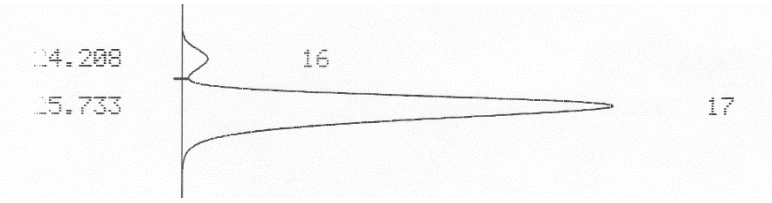
vii) Table S1, Entry 5 (Solvent = chloroform, Reaction temperature = 61 °C)



(*aS*)-**9c** (89% ee): HPLC analysis using chiral column.

6	24.358	1640141	36408	V	5.6609
7	25.825	27100925	508367	V	93.5384

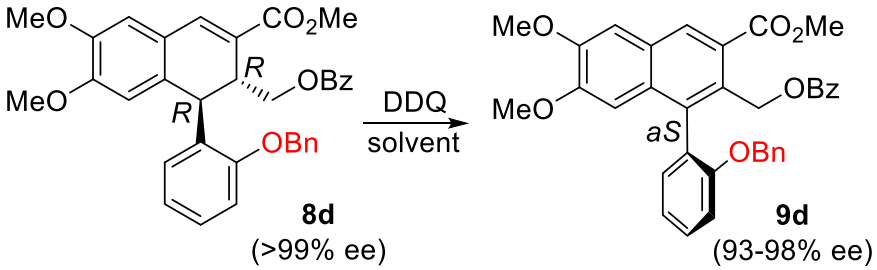
iii) Table S1, Entry 6 (Solvent = dichloromethane, Reaction temperature = 40 °C)



(*aS*)-**9c** (90% ee): HPLC analysis using chiral column.

16	24.208	1152416	25325	V	4.7930
17	25.733	22629861	422573	V	94.1203

Methyl (*S*)-3-((benzoyloxy)methyl)-4-(2-(benzyloxy)phenyl)-6,7-dimethoxy-2-naphthoate (9d)



8d (>99% ee) **9d** (93-98% ee)

Following the procedure for the preparation of **9a**, the dehydrogenation of dihydronaphthalene **8d** (57 mg, 0.101 mmol) using DDQ (57 mg, 0.250 mmol) in solvent (6.8 mL) gave the crude oil. The obtained crude oil was purified by column chromatography (SiO_2, hexane/AcOEt = 5/1) to give the product **9d** (x mg, y% yield).

i) (Table 3, Entry 10): Solvent = 1,2-dichloroethane, Reaction temperature = 83 °C, Reaction time = 2.5 h, x = 42, y = 74.

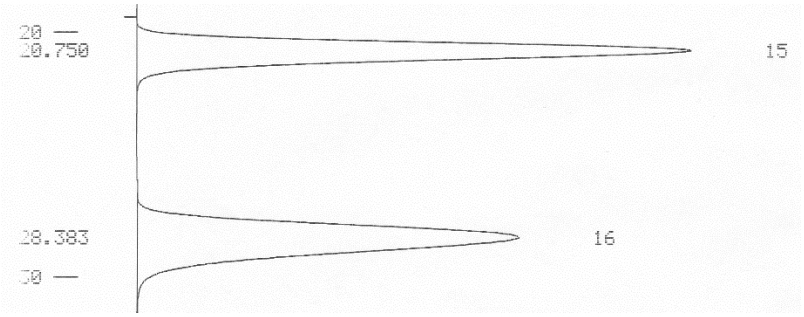
ii) (Table 3, Entry 11): Solvent = benzene, Reaction temperature = 80 °C, Reaction time = 6 h, x = 49, y = 86.

iii) (Table 3, Entry 12): Solvent = 1,2-dichloroethane, Reaction temperature = r.t., Reaction time = 48 h, x = 48, y = 84.

iv) (Table 3, Entry 13): Solvent = 1,2-dichloroethane, Reaction temperature = 0 °C, Reaction time = 144 h, x = 48, y = 84.

9d: light-yellow amorphous solid; $[\alpha]_D^{23}$ = 0.955 (*c* = 1.00, chloroform, λ = 589 nm); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.37 (s, 1H), 7.91 (d, *J* = 7.2 Hz, 2H), 7.49 (t, *J* = 7.4 Hz, 1H), 7.35 (dd, *J* = 14.3, 6.7 Hz, 3H), 7.25 – 7.20 (m, 2H), 7.16 – 7.10 (m, 3H), 7.05 (t, *J* = 8.0 Hz, 2H), 7.01 – 6.94 (m, 2H), 6.62 (s, 1H), 5.64 (d, *J* = 11.8 Hz, 1H), 5.38 (d, *J* = 11.8 Hz, 1H), 4.95 (s, 2H), 4.03 (s, 3H), 3.81 (s, 3H), 3.65 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 169.0, 166.3, 156.2, 151.2, 150.3, 137.3, 137.2, 132.8, 132.0, 130.6, 130.4, 123.0, 129.8, 129.7, 128.7, 128.4, 128.3, 127.6, 127.3, 127.2, 126.6, 121.2, 113.0, 107.2, 105.7, 103.8, 69.8, 63.7, 56.1, 55.7, 52.4; IR (KBr, neat) 3063, 3003, 2951, 2373, 2322, 1717, 1622, 1601, 1582, 1506, 1472, 1450, 1375, 1315, 1244, 1198, 1150, 1069, 1024, 756 cm^{-1}; HRMS (ESI) calcd for $C_{35}H_{30}O_7$ $(M+Na)^+$ 585.1889, found 585.1884; HPLC analysis [Daicel CHIRALPAK IG (15cm) at 25°C, hexane/2-propanol = 5/1 (v/v), flow rate 0.85 mL/min]: t_R[mixture of (*aS*)-**9d** and (*aR*)-**9d**] = 20.8 min and 28.4 min, i) (Table 3, Entry 10) t_R[(*aS*)-**9d**] = 30.0 min for major and 22.2 min for minor, ee = 93%, ii) (Table 3, Entry 11) t_R[(*aS*)-**9d**] = 30.9 min for major and

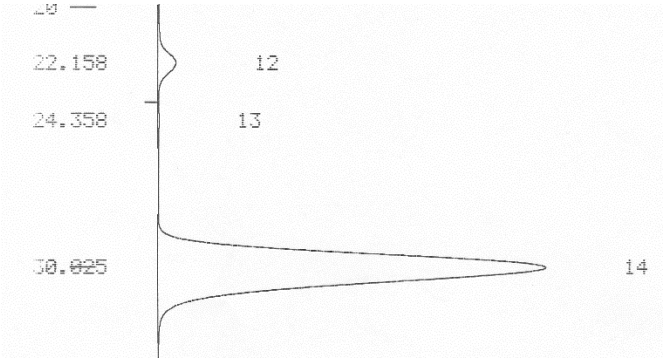
22.6 min for minor, ee = 98%, iii) (Table 3, Entry 12) t_R[(*aS*)-**9d**] = 30.9 min for major and 22.7 min for minor, ee = 98%, iv) (Table 3, Entry 13) t_R[(*aS*)-**9d**] = 32.7 min for major and 23.9 min for minor, ee = 98%.



A 49.5/45.5 mixture of [(*aS*)-**9d**] and [(*aR*)-**9d**]: HPLC analysis using chiral column.

15	20.750	34380538	687558	V	45.5078
16	28.383	37421133	473802		49.5325

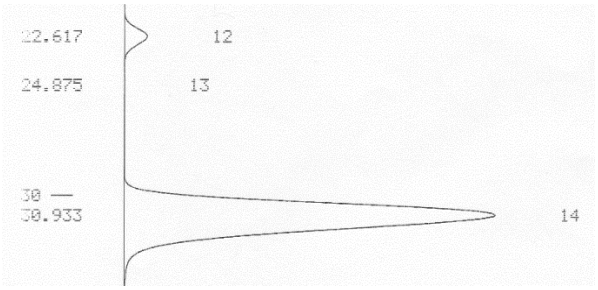
i) Table 3, Entry 10 (Solvent = 1,2-dichloroethane, Reaction temperature = 83 °C)



(*aS*)-**9d** (93% ee): HPLC analysis using chiral column.

12	22.158	601110	10417	V	3.2361
13	24.358	18385	334	V	9.8974E-02
14	30.025	17790127	225843		95.7727

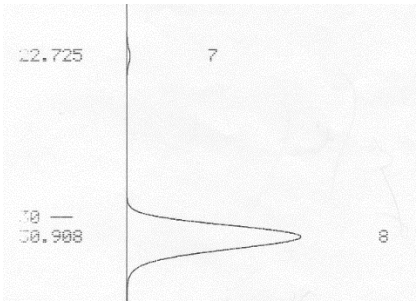
ii) Table 3, Entry 11 (Solvent =benzene, Reaction temperature = 80 °C)



(*aS*)-**9d** (93% ee): HPLC analysis using chiral column.

12	22.617	1766016	32529	3.6936
13	24.875	32282	615	6.7518E-02
14	30.933	45430986	524995	95.0181

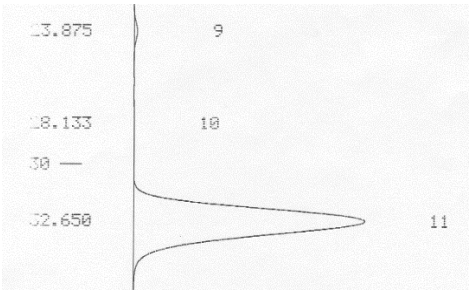
iii) Table 3, Entry 12 (Solvent = 1,2-dichloroethane, Reaction temperature = r.t.)



(*aS*)-**9d** (98% ee): HPLC analysis using chiral column.

7	22.725	114370	2119	1.1712
8	30.908	9551660	119060	97.8107

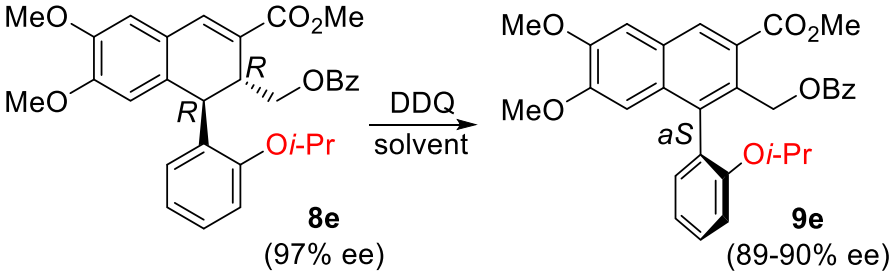
iv) Table 3, Entry 13 (Solvent = 1,2-dichloroethane, Reaction temperature = 0 °C)



(*aS*)-**9d** (98% ee): HPLC analysis using chiral column.

9	23.875	137254	2417	0.9418
10	28.133	8230	126	5.6467E-02
11	32.650	14236471	162435	97.6838

Methyl (*S*)-3-((benzoyloxy)methyl)-4-(2-isopropoxyphenyl)-6,7-dimethoxy-2-naphthoate (9e)



8e (97% ee) → **9e** (89-90% ee)

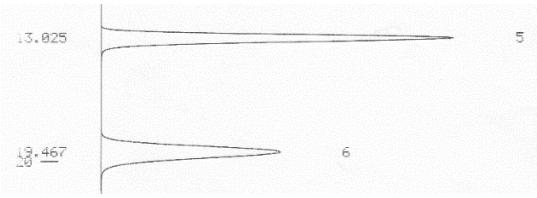
Following the procedure for the preparation of **9a**, the dehydrogenation of dihydronaphthalene **8e** (30 mg, 58.2 μmol) using DDQ (33 mg, 0.145 mmol) in solvent (4.0 mL) gave the crude oil. The obtained crude oil was purified by column chromatography (SiO_2, hexane/AcOEt = 4/1) to give the product **9e** (x mg, y% yield).

i) (Table 3, Entry 14): Solvent = 1,2-dichloroethane, Reaction temperature = 83 °C, Reaction time = 2

h, x = 28, y = 93.

ii) (Table 3, Entry 15): Solvent = benzene, Reaction temperature = 80 °C, Reaction time = 4 h, x = 24, y = 80.

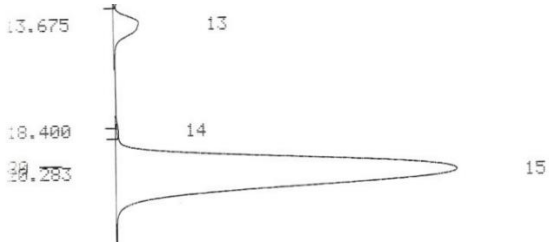
9e: light-yellow amorphous solid; $[\alpha]_D^{23}$ = 0.396 (*c* = 1.00, chloroform, λ = 589 nm); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.33 (s, 1H), 7.98 – 7.90 (m, 2H), 7.50 (t, *J* = 7.4 Hz, 1H), 7.43 – 7.33 (m, 3H), 7.22 (s, 1H), 7.18 (dd, *J* = 7.4, 1.7 Hz, 1H), 7.06 – 6.97 (m, 2H), 6.66 (s, 1H), 5.65 (d, *J* = 11.8 Hz, 1H), 5.31 (d, *J* = 11.8 Hz, 1H), 4.45 – 4.33 (m, 1H), 4.03 (s, 3H), 3.80 (s, 3H), 3.70 (s, 3H), 1.03 (d, *J* = 6.0 Hz, 3H), 0.99 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 169.0, 166.2, 155.6, 150.9, 150.1, 137.6, 132.7, 132.2, 130.4, 130.4, 129.6, 129.5, 128.4, 128.2, 128.1, 127.6, 127.2, 120.5, 113.9, 107.0, 105.8, 77.4, 77.3, 77.1, 76.8, 70.0, 63.7, 56.0, 55.6, 52.2, 22.0, 21.8; IR (KBr, neat) 3431, 2976, 2361, 1719, 1506, 1491, 1472, 1450, 1433, 1244, 1198, 1175, 1150, 1117, 1069, 1024, 953, 756 cm^{-1}; HRMS (ESI) calcd for $C_{31}H_{30}O_7$ $(M+Na)^+$ 537.1889, found 537.1884; HPLC analysis [Daicel CHIRALPAK IG (15cm) at 25 °C, hexane/2-propanol = 5/1 (v/v), flow rate 0.85 mL/min]: t_R[mixture of (*aS*)-**9e** and (*aR*)-**9e**] = 13.0 min and 19.5 min, i) (Table 3, Entry 14) t_R[(*aS*)-**9e**] = 20.3 min for major and 13.7 min for minor, ee = 90%, ii) (Table 3, Entry 15) t_R[(*aS*)-**9e**] = 30.9 min for major and 22.6 min for minor, ee = 89%.



A 45.3/54.3 mixture of (*aS*)-**9e** and (*aR*)-**9e**: HPLC analysis using chiral column.

5	13.025	8991274	301268		54.2934
6	19.467	7508532	152931		45.3400

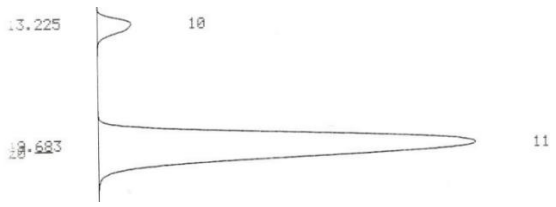
i) Table 3, Entry 14 (Solvent = 1,2-dichloroethane, Reaction temperature = 83 °C)



(*aS*)-**9e** (90% ee): HPLC analysis using chiral column.

13	13.675	1937742	32758	LLL	4.7182
14	18.400	10720	503	L S	2.6102E-02
15	20.283	38142230	457062	LLL	92.8731

ii) Table 3, Entry 15 (Solvent =benzene, Reaction temperature = 80 °C)



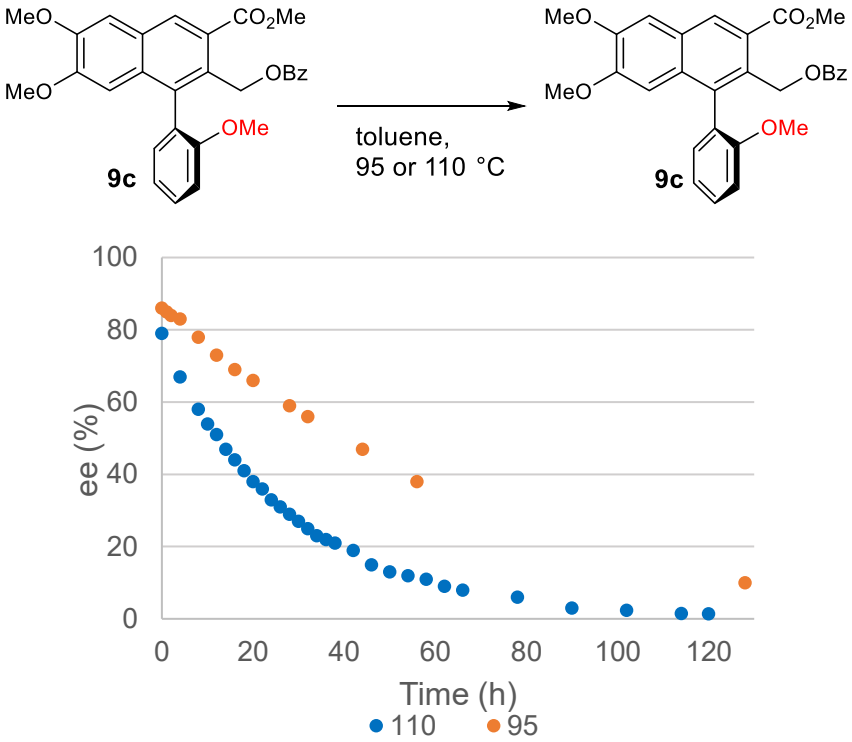
(*aS*)-**9e** (89% ee): HPLC analysis using chiral column.

10	13.225	2897191	54659	5.3644
11	19.683	51033824	609218	94.4939

1.5. Observation of arylnaphthalene 9c racemization as a function of time.

1.5.1. Charts.

Figure S1. Racemization of arylnaphthalene **9c** at 95 or 110 °C as a function of time.



1.5.2. Evaluation (estimation) of enantiomerization barrier and half life time.

Table S2. Racemization of arylnaphthalene **9c** at 110 °C in toluene as a function of time.

Time		ee data	exponential	residue
Time (h)	t(s)	ee (%)	eefit	residual^2
0	0	79	78.1	0.010253165
4	14400	67	67.79823932	0.009510239
8	28800	58	58.85532976	0.012613603

10	36000	54	54.83646976	0.012957068
12	43200	51	51.09203242	0.000166078
14	50400	47	47.60327913	0.007743526
16	57600	44	44.35275085	0.002828026
18	64800	41	41.32418068	0.002563247
20	72000	38	38.5024125	0.006642587
22	79200	36	35.87332511	0.000445737
24	86400	33	33.42376155	0.005441632
26	93600	31	31.14146326	0.000645544
28	100800	29	29.01500876	7.76769E-06
30	108000	27	27.03375645	4.22036E-05
32	115200	25	25.18779139	0.001410624
34	122400	23	23.46787567	0.009517723
36	129600	22	21.86540216	0.000823481
38	136800	21	20.37235148	0.018759175
42	151200	19	17.68514163	0.090992239
46	165600	15	15.35238751	0.008278464
50	180000	13	13.32733473	0.008242156
54	194400	12	11.56939602	0.015451649
58	208800	11	10.04333778	0.083200237
62	223200	9	8.718573854	0.008800075
66	237600	8	7.568552582	0.023268359
78	280800	6	4.951251394	0.183312273
90	324000	3	3.239046053	0.019047672
102	367200	2.4	2.11894297	0.032913773
114	410400	1.5	1.386185697	0.008635797
120	432000	1.4	1.121172627	0.055531932

relaxation time(τ/s)	reaction rate constant (k/s^{-1})	ln k
101800	9.82318E-06	-11.53076538

If reaction rate constant is reciprocal of relaxation time

Half life time T

ee=78.1exp(-t/101800)

Half of ee: ee=39.55, t is estimeted as T

or T＝ln2/k＝0.693/k

T(sec)＝69507.9

T(hour) = 19.5965

Figure S2.

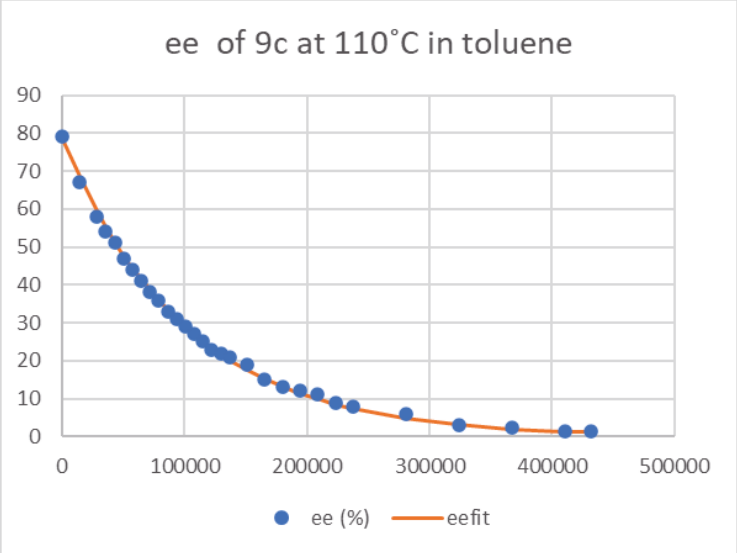


Table S3. Racemization of arylnaphthalene **9c** at 95 °C in toluene as a function of time.

Time		ee data	exponential	residue
Time (h)	t(s)	ee (%)	eefit	residual^2
0	0	86	86.1	0.01
1	3600	85	84.91152207	9.20982E-05
2	7200	84	83.73944925	0.000808175
4	14400	83	81.44361626	0.029184703
8	28800	78	77.03905494	0.011838659
12	43200	73	72.87269718	0.000222
16	57600	69	68.93166069	6.76849E-05
20	72000	66	65.20375983	0.009606036

28	100800	59	58.34188195	0.007341006
32	115200	56	55.1866881	0.011812076
44	158400	47	46.70851116	0.001807782
56	201600	38	39.53281289	0.061829351

relaxation time(τ/s)	reaction rate constant(k/s^{-1})	ln k
259000	3.861E-06	-12.46458334

If reaction rate constant is reciprocal of relaxation time

Half life time T

ee = 86.1exp(-t/259000)

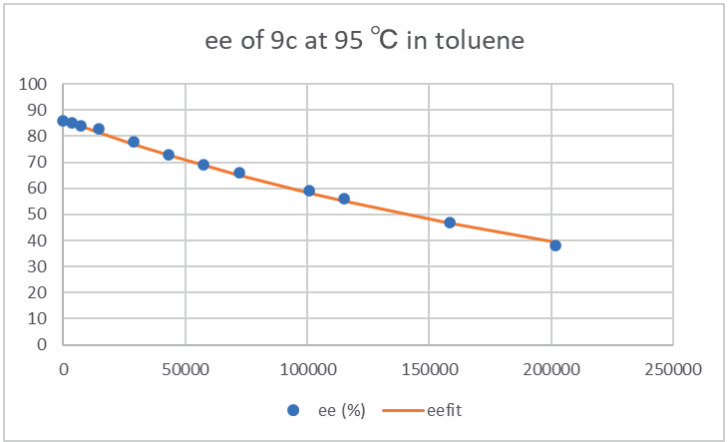
Half of ee: ee=43.05, t is estimeted as T

or T = ln2/k = 0.693/k

T(sec) = 180180

T(hour) = 49.8575

Figure S3.



Eyring equation: $k = (\kappa k_B T/h) \exp(-\Delta G^{\ddagger}/RT)$

$$\ln(k/T) = -(\Delta H^{\ddagger}/R)(1/T) + \ln(\kappa k_B/h) + (\Delta S^{\ddagger}/R)$$

[k: reaction rate constant, R: gas constant, k_B: Boltzmann constant, h: Planck's constant, κ: transmission coefficient (κ = 1)]

Table S4. Evaluation of $\Delta G^{\ddagger}$ for enantiomerization of **9c** using the Eyring equation.

	95 °C (T = 368.15 K)	110 °C (T = 383.15 K)
$1/T$	0.002716284	0.002609944
k: reaction rate constant	3.861E-06	9.82318E-06
ln k	-12.46458334	-11.53076538
$\kappa k_B T / h$	7.67303E+12	7.98566E+12
ln ($\kappa k_B T / h$)	29.66873306	29.70866915
$\Delta G^{\ddagger}/RT$	41.19949844	41.23943453
$\Delta G^{\ddagger}$ (kJ mol^{-1})	126.0427174	131.3053904

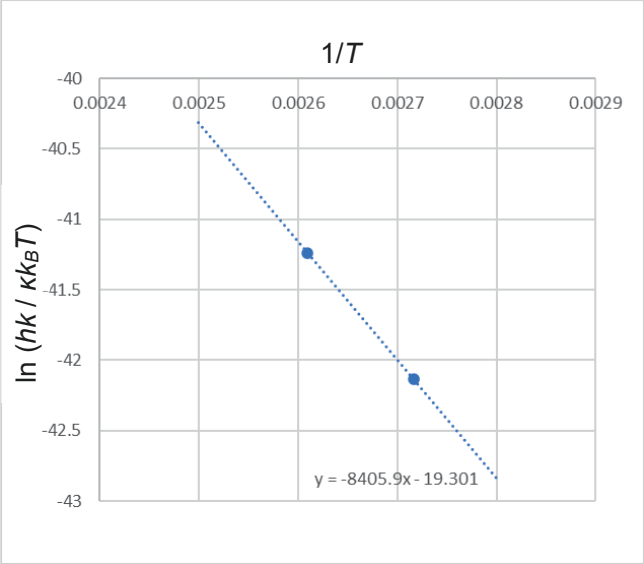
Evaluation of $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$.

$$\ln(k/T) = -(\Delta H^{\ddagger}/R)\,(1/T) + \ln(\kappa k_B/h) + (\Delta S^{\ddagger}/R)$$

$$\ln(hk/\kappa k_B T) = -(\Delta H^{\ddagger}/R)\,(1/T) + (\Delta S^{\ddagger}/R)$$

	95 °C (T = 368.15 K)	110 °C (T = 383.15 K)
$1/T$	0.002716	0.002609
ln (hk / $\kappa k_B T$)	-42.1333164	-41.23943453

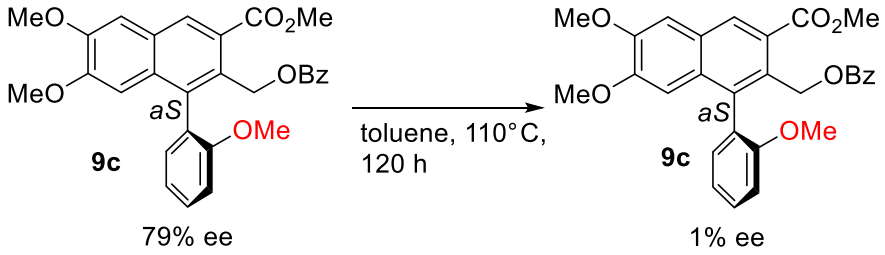
Figure S4. ln (hk / $\kappa k_B T$) versus $1/T$



$\Delta H^{\ddagger}$ /R	8406
$\Delta H^{\ddagger}$ (kJ mol^{-1})	69.85386
$\Delta S^{\ddagger}$ /R	-19.301
$\Delta S^{\ddagger}$ (J mol^{-1} K^{-1})	-160.39131

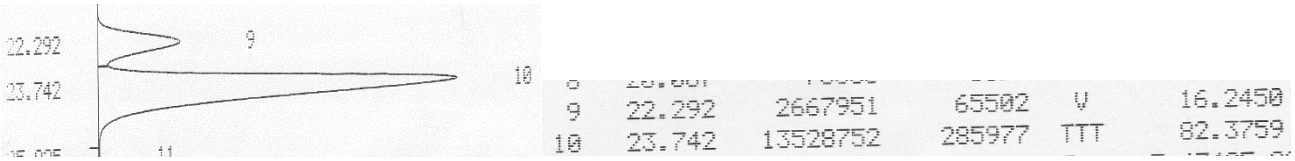
1.5.3. HPLC analysis.

Observation of 9c racemization in toluene at 110 °C.



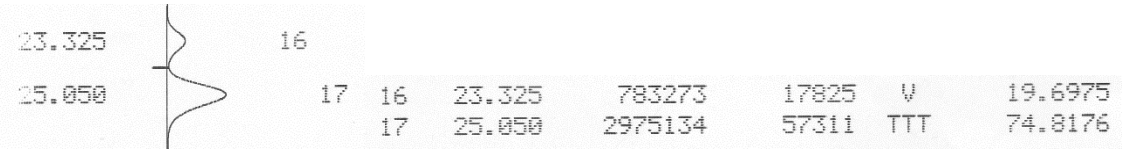
HPLC analysis [Daicel CHIRALPAK IG (15cm) at 25°C, hexane/ethanol = 10/1, flow rate 0.87 mL/min]

Stirred for 4 h.



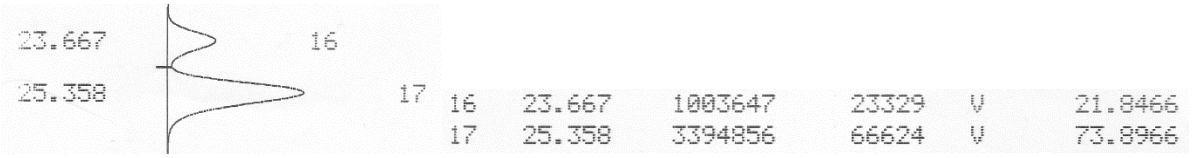
Based on this enantiomeric ratio (82.38/16.25), 67% ee was estimated.

Stirred for 8 h.



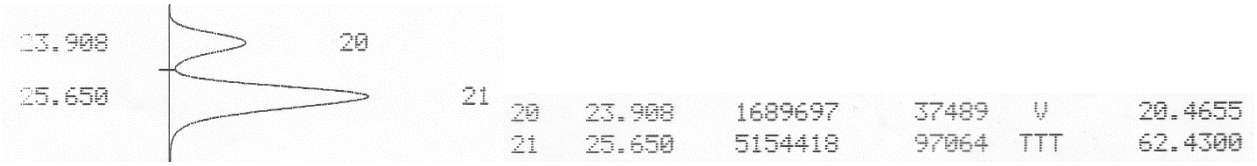
Based on this enantiomeric ratio (74.82/19.70), 58% ee was estimated.

Stirred for 10 h.



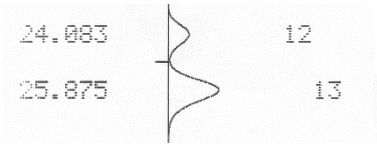
Based on this enantiomeric ratio (73.90/21.85), 54% ee was estimated.

Stirred for 12 h.



Based on this enantiomeric ratio (62.43/20.47), 51% ee was estimated.

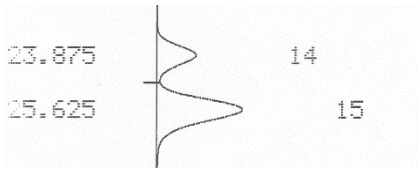
Stirred for 14 h.



12	24.083	471089	10537	V	21.3058
13	25.875	1317079	24800	V	59.5670

Based on this enantiomeric ratio (59.57/21.31), 47% ee was estimated.

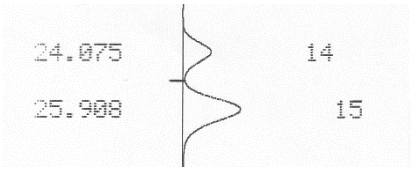
Stirred for 16 h.



14	23.875	840966	19141	V	26.2837
15	25.625	2179529	41908	V	68.1194

Based on this enantiomeric ratio (68.12/26.28), 44% ee was estimated.

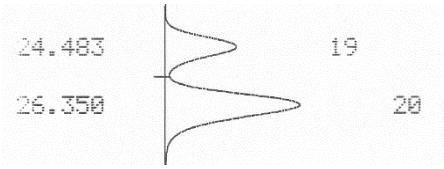
Stirred for 18 h.



14	24.075	638626	14078	V	27.8158
15	25.908	1530787	28215	V	66.6744

Based on this enantiomeric ratio (66.67/27.82), 41% ee was estimated.

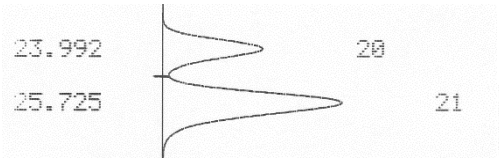
Stirred for 20 h.



19	24.483	1627026	34911	V	28.8091
20	26.350	3652820	66247	TTT	64.6792

Based on this enantiomeric ratio (64.68/28.81), 38% ee was estimated.

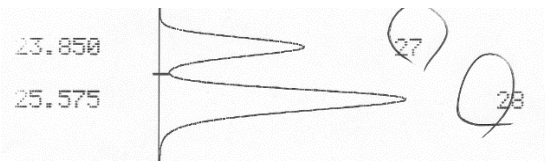
Stirred for 22 h.



20	23.992	2177102	49040	V	30.0879
21	25.725	4604896	87951	TTT	63.6404

Based on this enantiomeric ratio (63.64/30.09), 36% ee was estimated.

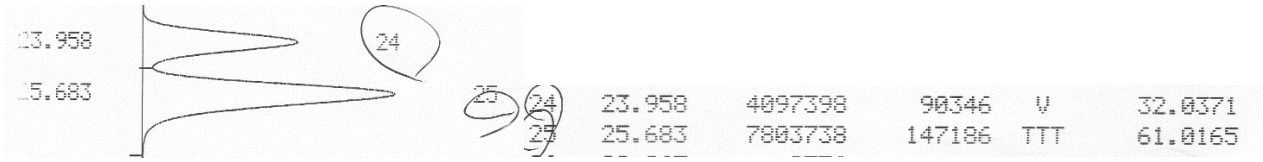
Stirred for 24 h



27	23.850	3283836	72960	V	31.1214
28	25.575	6559499	124294	TTT	62.1653

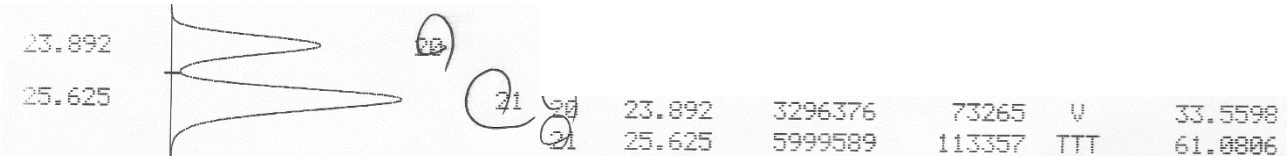
Based on this enantiomeric ratio (62.17/31.12), 33% ee was estimated.

Stirred for 26 h.



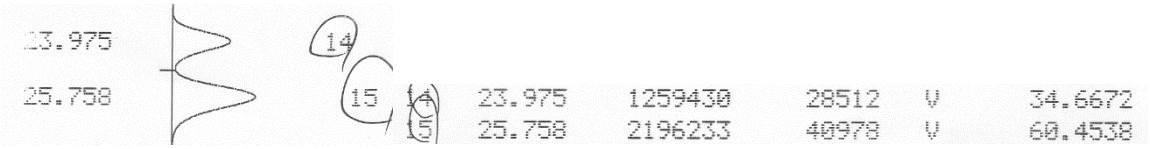
Based on this enantiomeric ratio (61.02/32.04), 31% ee was estimated.

Stirred for 28 h.



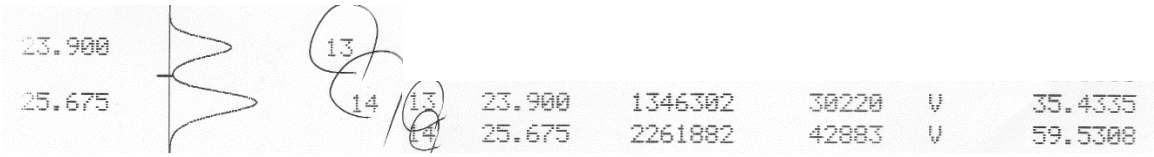
Based on this enantiomeric ratio (61.08/33.56), 29% ee was estimated.

Stirred for 30 h.



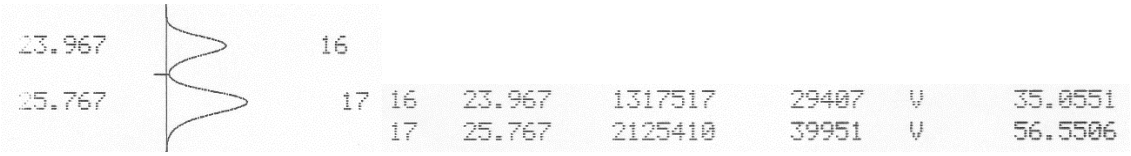
Based on this enantiomeric ratio (60.45/34.67), 27% ee was estimated.

Stirred for 32 h.



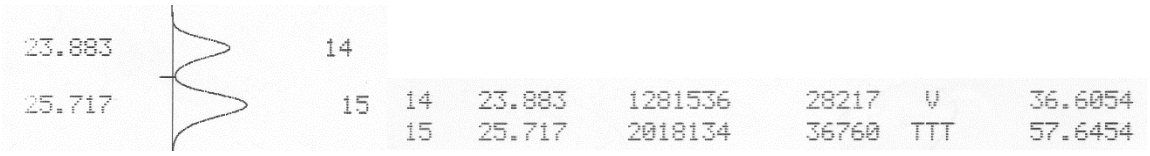
Based on this enantiomeric ratio (59.53/35.43), 25% ee was estimated.

Stirred for 34 h.



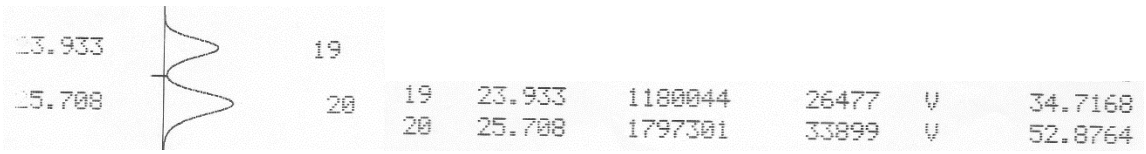
Based on this enantiomeric ratio (56.55/35.06), 23% ee was estimated.

Stirred for 36 h



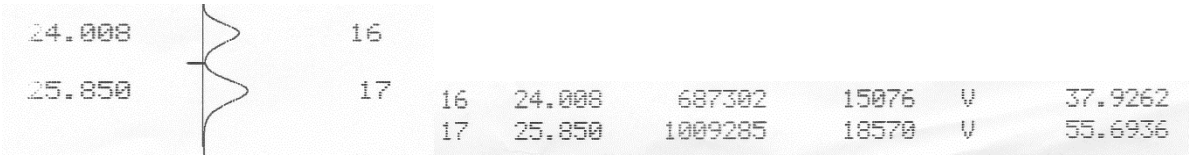
Based on this enantiomeric ratio (57.65/36.61), 22% ee was estimated.

Stirred for 38 h.



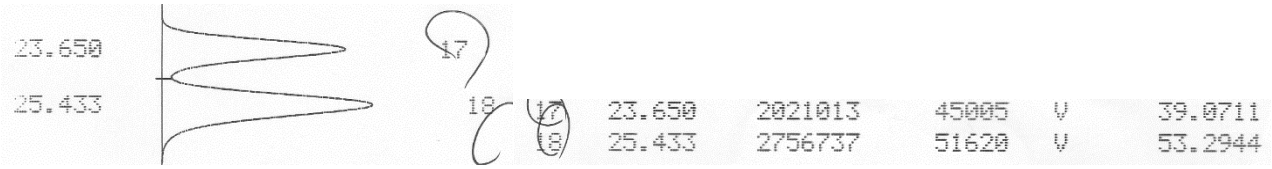
Based on this enantiomeric ratio (52.88/34.72), 21% ee was estimated.

Stirred for 42 h.



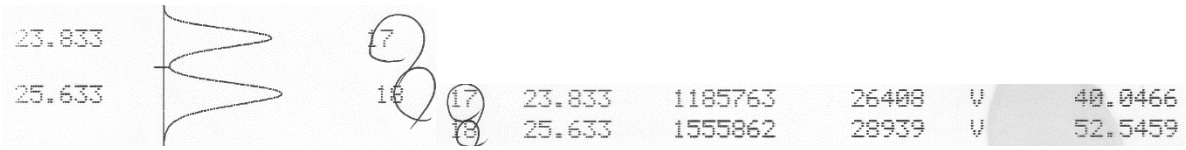
Based on this enantiomeric ratio (55.69/37.93), 19% ee was estimated.

Stirred for 46 h.



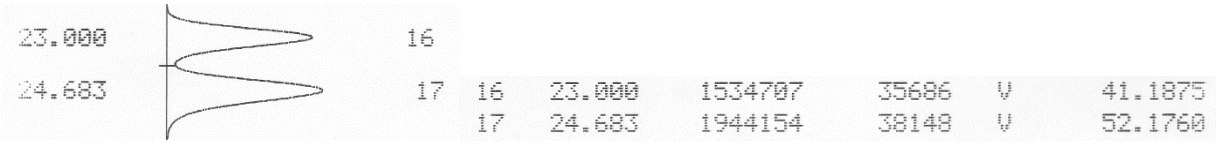
Based on this enantiomeric ratio (53.29/39.07), 15% ee was estimated.

Stirred for 50 h.



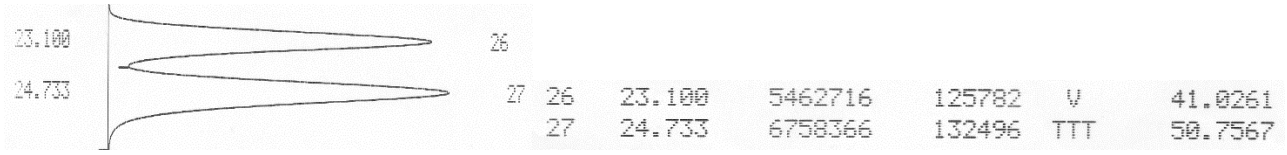
Based on this enantiomeric ratio (52.55/40.05), 13% ee was estimated.

Stirred for 54 h.



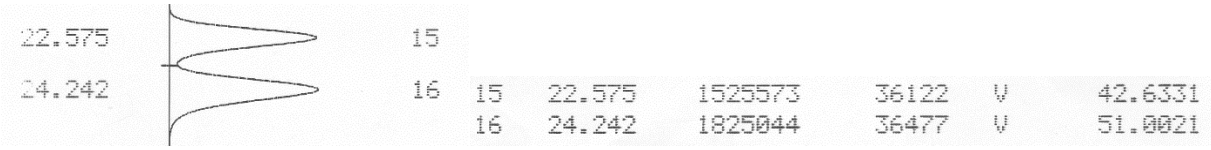
Based on this enantiomeric ratio (52.18/41.19), 12% ee was estimated.

Stirred for 58 h.



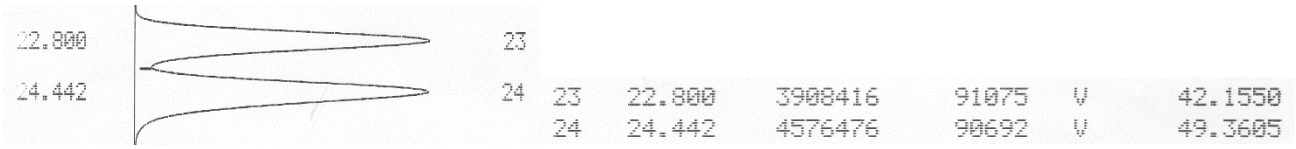
Based on this enantiomeric ratio (50.76/41.03), 11% ee was estimated.

Stirred for 62 h.



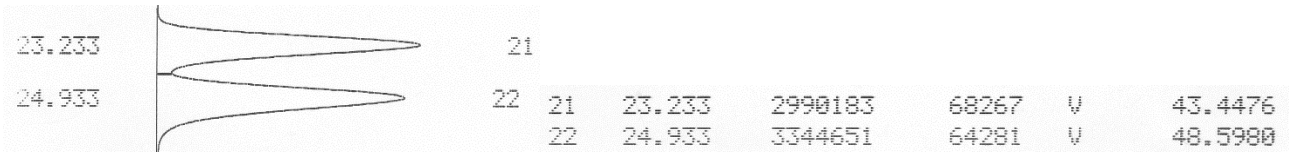
Based on this enantiomeric ratio (51.00/42.63), 9% ee was estimated.

Stirred for 66 h.



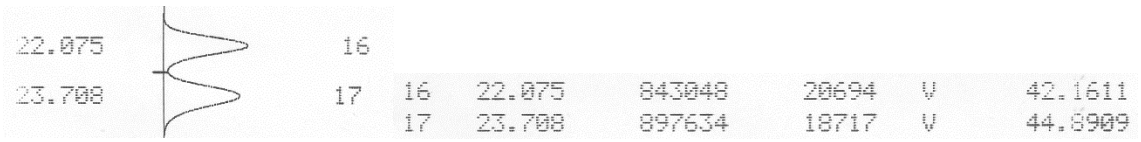
Based on this enantiomeric ratio (49.36/42.16), 8% ee was estimated.

Stirred for 78 h.



Based on this enantiomeric ratio (48.60/43.45), 6% ee was estimated.

Stirred for 90 h.

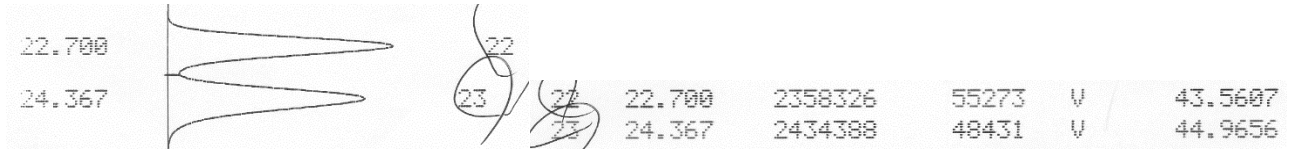


Based on this enantiomeric ratio (44.89/42.16), 3% ee was estimated.

Stirred for 102 h.

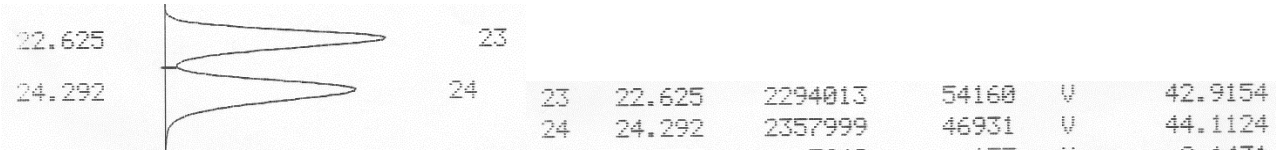
Based on this enantiomeric ratio (44.83/42.69), 2% ee was estimated.

Stirred for 114 h.



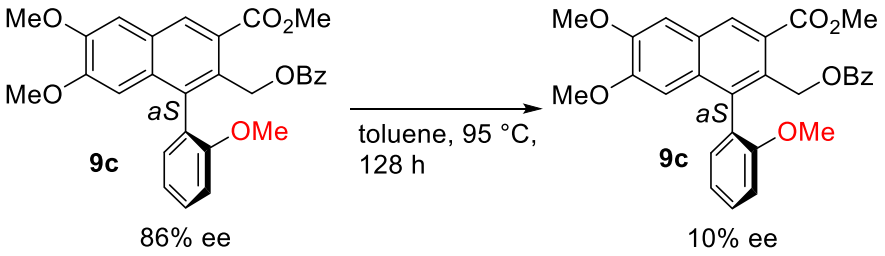
Based on this enantiomeric ratio (44.97/43.56), 2% ee was estimated.

Stirred for 120 h.



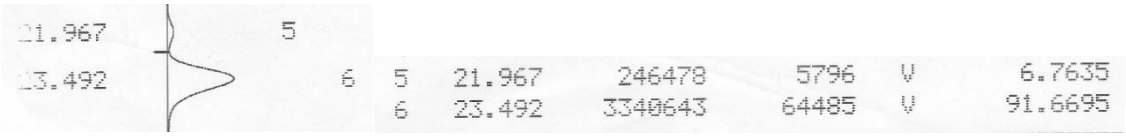
Based on this enantiomeric ratio (44.11/42.92), 1% ee was estimated.

Observation of 9c racemization in toluene at 95 °C.



HPLC analysis [Daicel CHIRALPAK IG (15cm) at 25°C, hexane/ethanol = 10/1, flow rate 0.87 mL/min]

0 h

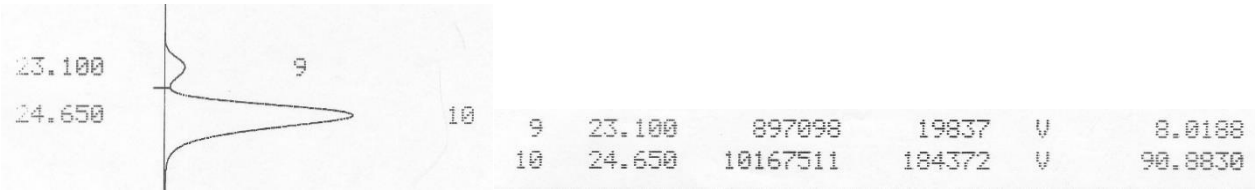


Based on this enantiomeric ratio (91.7/6.8), 86% ee was estimated.

Stirred for 1 h.

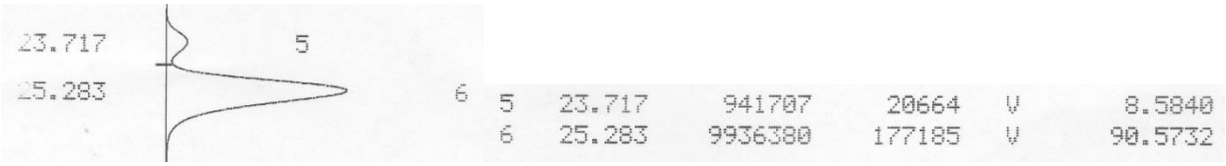
Based on this enantiomeric ratio (91.7/7.0), 85% ee was estimated.

Stirred for 2 h.



Based on this enantiomeric ratio (90.9/8.0), 84% ee was estimated.

Stirred for 4 h.

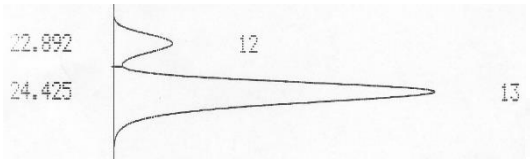


Based on this enantiomeric ratio (90.6/8.6), 83% ee was estimated.

Stirred for 8 h.

Based on this enantiomeric ratio (88.4/10.8), 78% ee was estimated.

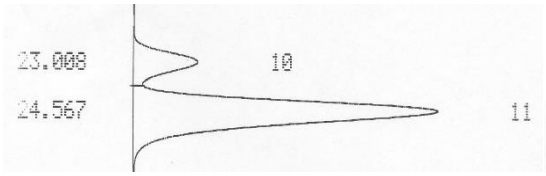
Stirred for 12 h.



12	22.892	1800773	41658	V	13.3702
13	24.425	11410669	226148	V	84.7209

Based on this enantiomeric ratio (84.7/13.3), 73% ee was estimated.

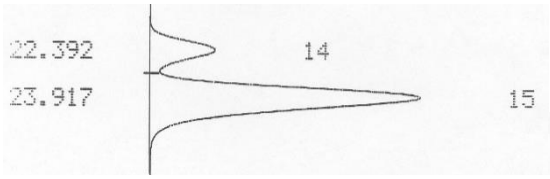
Stirred for 16 h.



10	23.008	1769464	40533	V	15.0915
11	24.567	9827939	191890	V	83.8208

Based on this enantiomeric ratio (83.8/15.1), 69% ee was estimated.

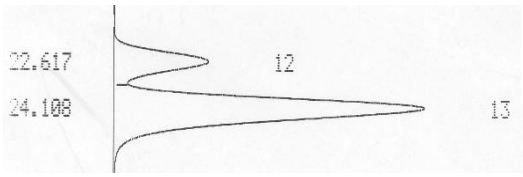
Stirred for 20 h.



14	22.392	1445857	33668	V	16.8129
15	23.917	7052651	140352	V	82.0105

Based on this enantiomeric ratio (82.0/16.8), 66% ee was estimated.

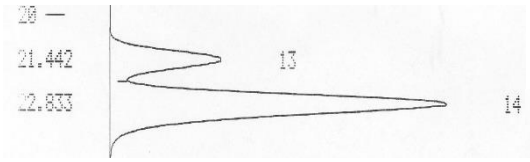
Stirred for 28 h.



12	22.617	2844447	65919	V	19.9337
13	24.108	10963313	216751	V	76.8303

Based on this enantiomeric ratio (76.8/19.9), 59% ee was estimated.

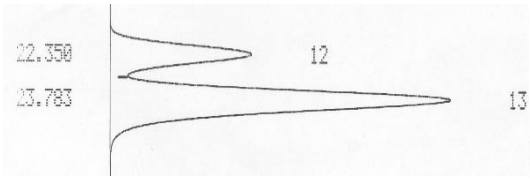
Stirred for 32 h.



13	21.442	3662533	88219	V	21.9857
14	22.833	12806213	266659	V	76.8742

Based on this enantiomeric ratio (76.9/22.0), 56% ee was estimated.

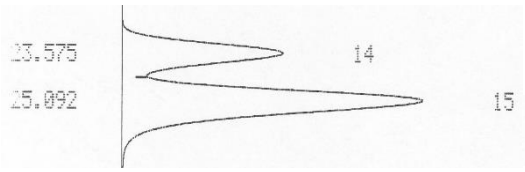
Stirred for 44 h.



12	22.350	4612678	109863	V	26.1168
13	23.783	12851583	264720	V	72.7651

Based on this enantiomeric ratio (72.8/26.1), 47% ee was estimated.

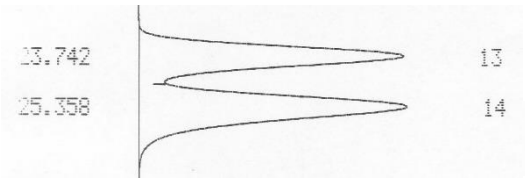
Stirred for 56 h.



14	23.575	4807951	104900	V	30.5262
15	25.092	10750302	196273	V	68.2547

Based on this enantiomeric ratio (68.3/30.5), 38% ee was estimated.

Stirred for 128 h.



13	23.742	7430912	160267	V	44.5679
14	25.358	9066649	162404	V	54.3785

Based on this enantiomeric ratio (54.4/44.6), 10% ee was estimated.

1.6. Observation of arylnaphthalenes 9a, 9b, 9d and 9e racemization in toluene 110 °C as a function of time.

1.6.1. Chart and Table.

Figure S5. Racemization of arylnaphthalenes **9** in toluene at 110 °C as a function of time.

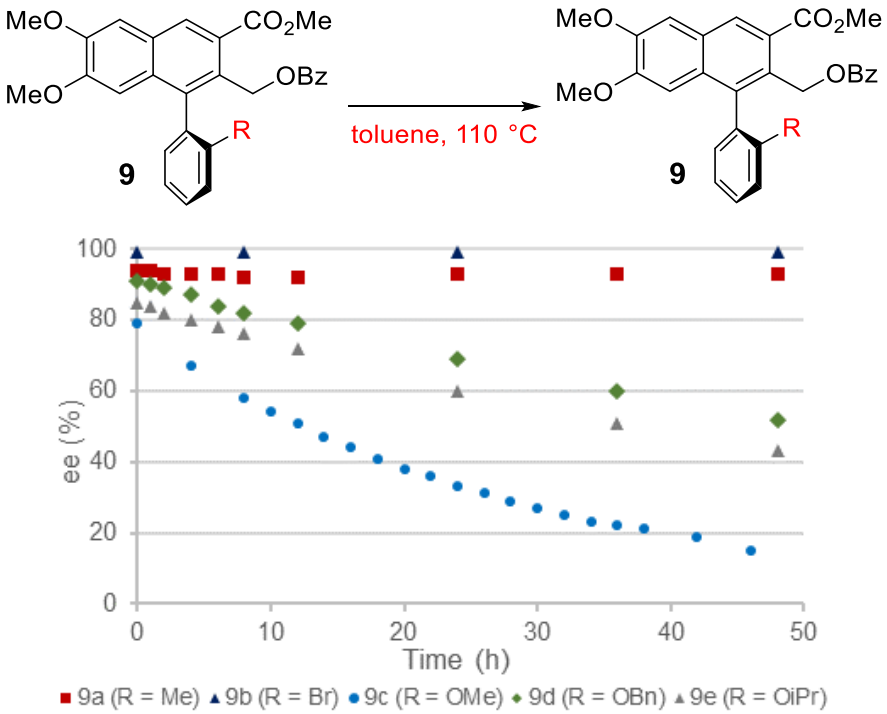
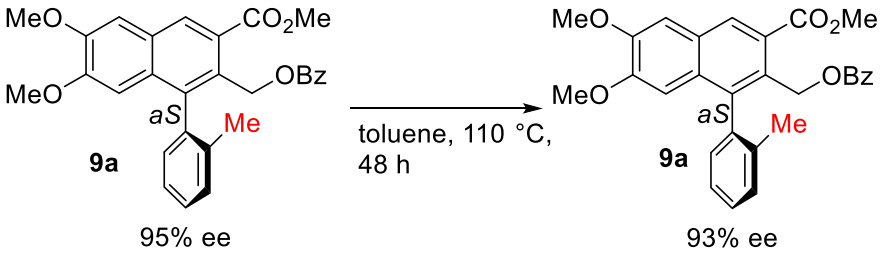


Table S5. Racemization of arylnaphthalenes **9a, 9b, 9d, 9e** in toluene at 110 °C as a function of time.

Time (h)	ee of **9a** (R = Me) (%)	ee of **9b** (R = Br) (%)	ee of **9d** (R = OBn) (%)	ee of **9e** (R = O*i*-Pr) (%)
0	94	>99	91	85
1	94		90	84

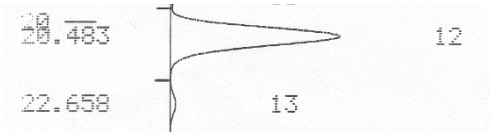
2	93		89	82
4	93		87	80
6	93		84	78
8	92	>99	82	76
12	92		79	72
24	93	>99	69	60
36	93		60	51
48	93	>99	52	43

1.6.2. HPLC analysis.



HPLC analysis [Daicel CHIRALPAK IG (15cm) at 25 °C, hexane/2-propanol = 10/1 (v/v), flow rate 0.85 mL/min]

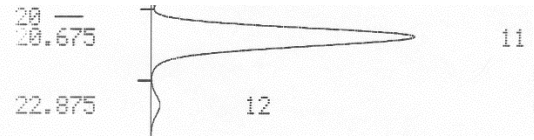
Stirred for 1 h.



12	20.483	1835541	41534	LLL	87.7450
13	22.658	60835	1350	V	2.9081

Based on this enantiomeric ratio (87.75/2.91), 94% ee was estimated.

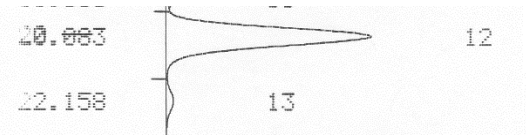
Stirred for 2 h.



11	20.675	3219650	71284	LLL	89.1363
12	22.875	125239	2452	V	3.4673

Based on this enantiomeric ratio (89.14/3.47), 93% ee was estimated.

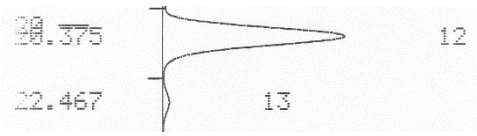
Stirred for 4 h.



12	20.083	2180073	50287	LLL	85.7740
13	22.158	77306	1689	V	3.0416

Based on this enantiomeric ratio (85.77/3.04), 93% ee was estimated.

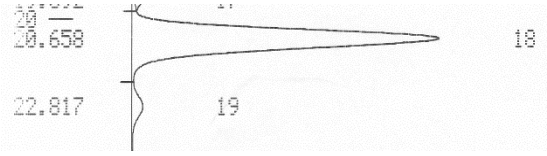
Stirred for 6 h.



12	20.375	1959605	44699	LLL	89.4544
13	22.467	67450	1477	V	3.0790

Based on this enantiomeric ratio (89.45/3.08), 93% ee was estimated.

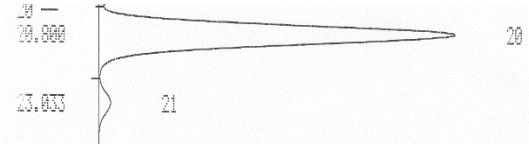
Stirred for 8 h.



18	20.658	4186893	94895	LLL	87.1486
19	22.817	164459	3230	V	3.4232

Based on this enantiomeric ratio (87.15/3.42), 92% ee was estimated.

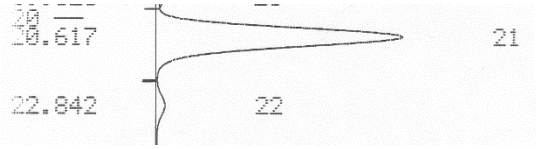
Stirred for 12 h.



20	20.800	7146723	159629	LLL	87.8528
21	23.033	280426	5484	V	3.4472

Based on this enantiomeric ratio (87.85/3.45), 92% ee was estimated.

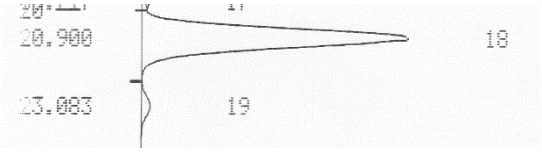
Stirred for 24 h.



21	20.617	2842419	62293	LLL	77.4218
22	22.842	110236	2152	V	3.0026

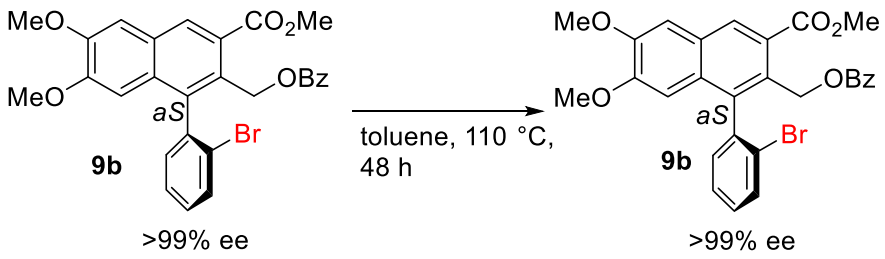
Based on this enantiomeric ratio (77.42/3.00), 93% ee was estimated.

Stirred for 48 h.



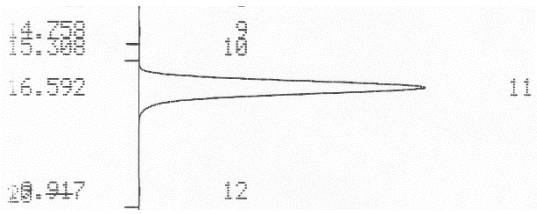
18	20.900	1793068	39958	LLL	79.3988
19	23.083	61655	1316	V	2.7301

Based on this enantiomeric ratio (79.40/2.73), 93% ee was estimated.



HPLC analysis [Daicel CHIRALPAK IG (15cm) at 25°C, hexane/ethanol = 10/1, flow rate 0.87 mL/min]

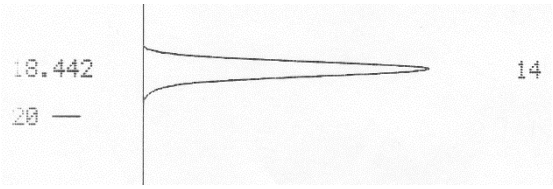
Stirred for 8 h.



9	14.758	14343	493	V	0.2833
10	15.308	5398	217	V	0.1066
11	16.592	4946604	158436	TTT	97.7077
12	19.917	14270	424	V	0.2819

Based on this enantiomeric ratio (97.71/0.28), >99% ee was estimated.

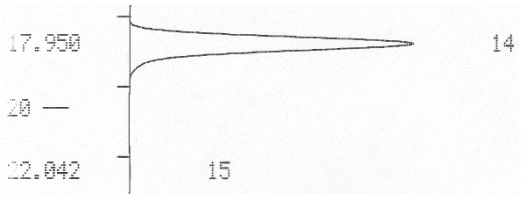
Stirred for 24 h.



14	18.442	10842924	304396	EEE	98.5339

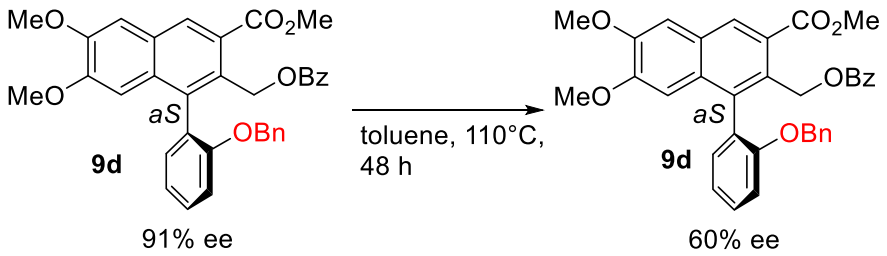
Based on this HPLC analysis, >99% ee was estimated.

Stirred for 48 h.



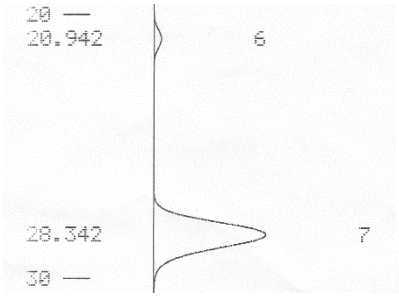
14	17.950	5702562	169771	V	97.9932
15	22.042	16322	453	V	0.2805

Based on this enantiomeric ratio (97.99/0.28), >99% ee was estimated.



HPLC analysis [Daicel CHIRALPAK IG (15cm) at 25°C, hexane/2-propanol = 5/1, flow rate 0.85 mL/min]

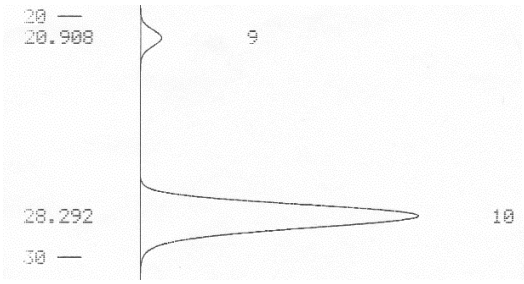
Before observation. (0 h)



6	20.942	109620	2161	4.3695
7	28.342	2300982	32287	91.7173

Based on this enantiomeric ratio (91.72/4.37), 91% ee was estimated.

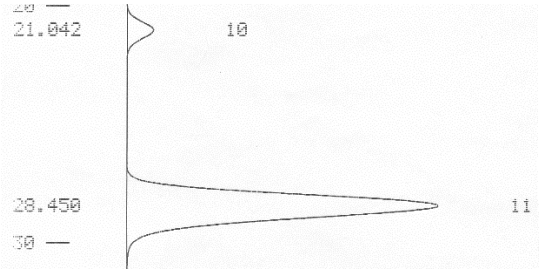
Stirred for 1 h.



9	20.908	339296	6717	5.0274
10	28.292	6270449	87051	92.9104

Based on this enantiomeric ratio (92.91/5.03), 90% ee was estimated.

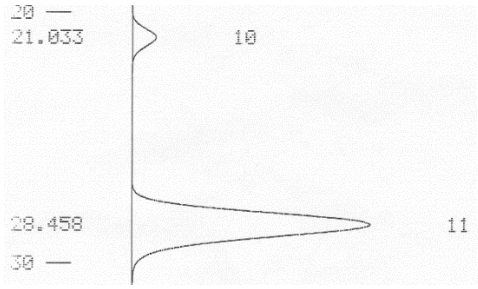
Stirred for 2 h.



10	21.042	436947	8564	5.6008
11	28.450	7165593	99622	91.8484

Based on this enantiomeric ratio (91.85/5.60), 89% ee was estimated.

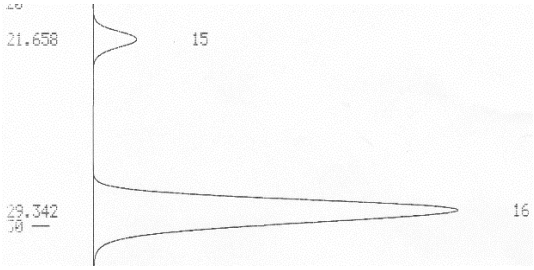
Stirred for 4 h.



10	21.033	371280	7308	6.5285
11	28.458	5151607	71773	90.5852

Based on this enantiomeric ratio (90.59/6.53), 87% ee was estimated.

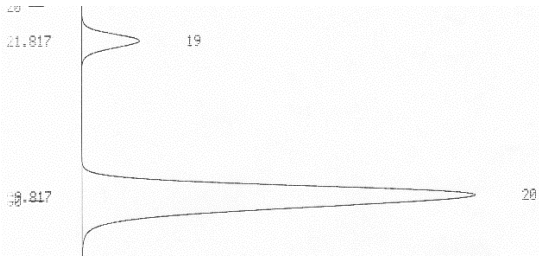
Stirred for 6 h.



15	21.658	972530	18467	7.5840
16	29.342	11536119	153459	89.9614

Based on this enantiomeric ratio (89.96/7.58), 84% ee was estimated.

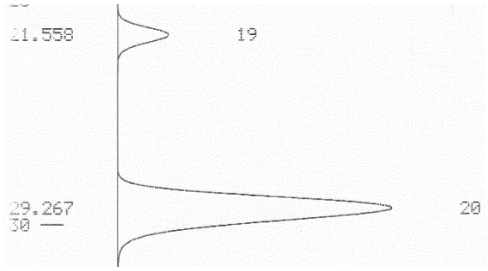
Stirred for 8 h.



19	21.817	1455165	27901	8.4759
20	29.817	15123183	190722	88.0881

Based on this enantiomeric ratio (88.09/8.48), 82% ee was estimated.

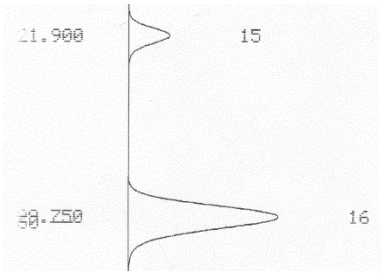
Stirred for 12 h.



19	21.558	1711352	34057		10.2287
20	29.267	14377597	184363		85.9341

Based on this enantiomeric ratio (85.93/10.23), 79% ee was estimated.

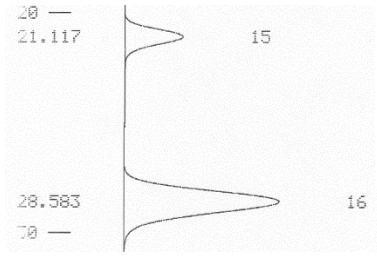
Stirred for 24 h.



15	21.900	682454	13393		14.8868
16	29.750	3718445	49269		81.1127

Based on this enantiomeric ratio (81.11/14.89), 69% ee was estimated.

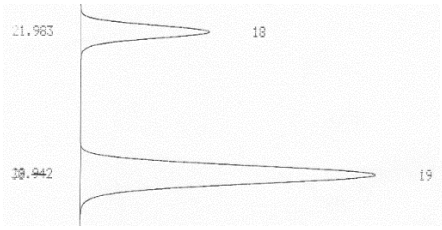
Stirred for 36 h.



15	21.117	989750	20085		19.0455
16	28.583	3946315	53213		75.9378

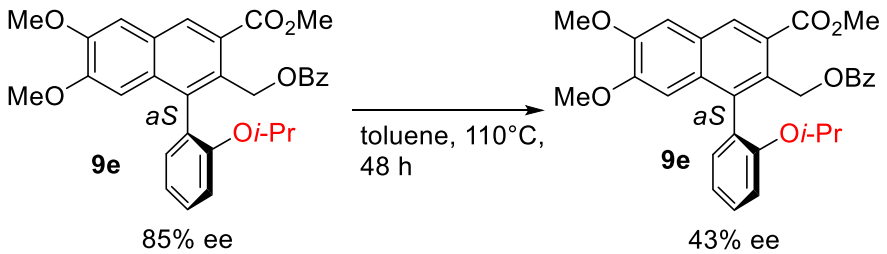
Based on this enantiomeric ratio (75.94/19.05), 60% ee was estimated.

Stirred for 48 h.



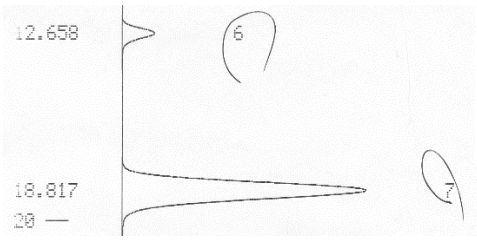
18	21.983	1793222	33862		22.0261
19	29.942	5748346	77914		70.6066

Based on this enantiomeric ratio (70.61/22.03), 60% ee was estimated.



HPLC analysis [Daicel CHIRALPAK IG (15cm) at 25°C, hexane/2-propanol = 5/1, flow rate 0.85 mL/min]

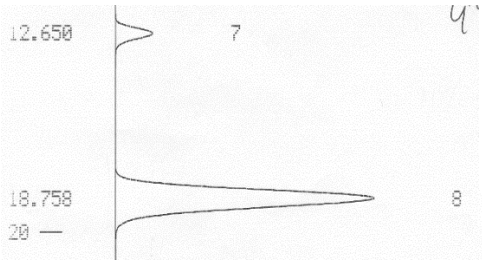
Before observation. (0 h)



6	12.658	317996	10888	7.3915
7	18.817	3924290	82212	91.2165

Based on this enantiomeric ratio (91.22/7.39), 85% ee was estimated.

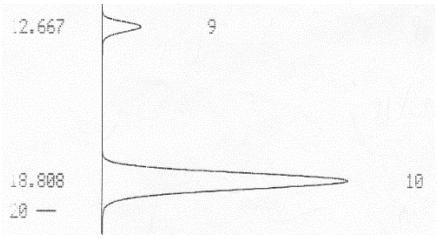
Stirred for 1 h.



7	12.650	370170	12732	8.1066
8	18.758	4166866	88248	91.2527

Based on this enantiomeric ratio (91.25/8.11), 84% ee was estimated.

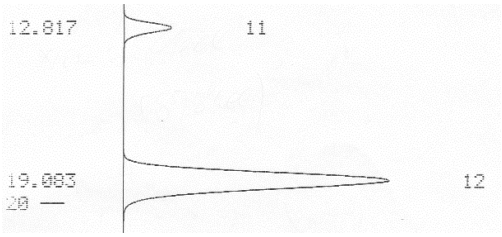
Stirred for 2 h.



9	12.667	446013	15294	8.6551
10	18.808	4644792	97276	90.1340

Based on this enantiomeric ratio (90.13/8.66), 82% ee was estimated.

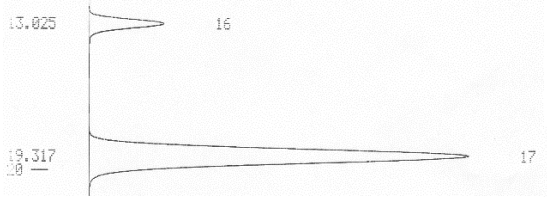
Stirred for 4 h.



11	12.817	439282	14780	9.6181
12	19.083	4029152	82964	88.2187

Based on this enantiomeric ratio (88.22/9.62), 80% ee was estimated.

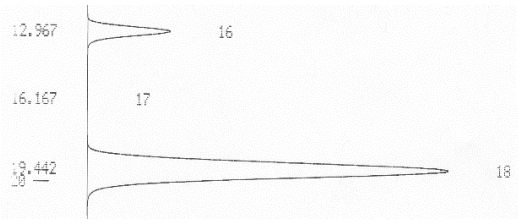
Stirred for 6 h.



16	13.025	1021813	33486	10.7490
17	19.317	8231860	169607	86.5956

Based on this enantiomeric ratio (86.60/10.75), 78% ee was estimated.

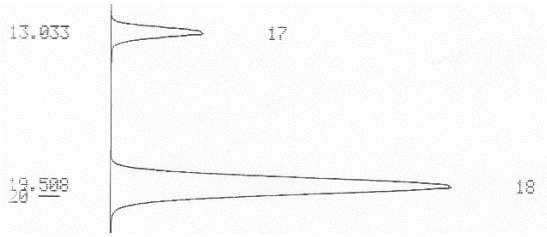
Stirred for 8 h.



16	12.967	1219653	39650	11.8424
17	16.167	4215	120	4.0926E-02
18	19.442	8771298	173287	85.1659

Based on this enantiomeric ratio (85.17/11.84), 76% ee was estimated.

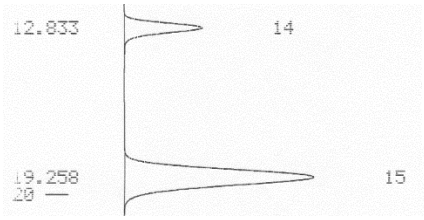
Stirred for 12 h.



17	13.033	2024017	65568	13.7401
18	19.508	12196341	242701	82.7950

Based on this enantiomeric ratio (82.80/13.74), 72% ee was estimated.

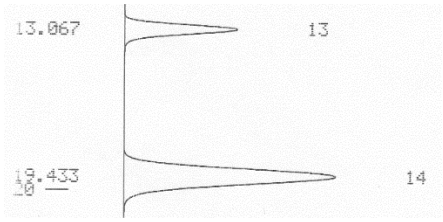
Stirred for 24 h.



14	12.833	778619	25502	19.3442
15	19.258	3081483	61776	76.5569

Based on this enantiomeric ratio (76.56/19.34), 60% ee was estimated.

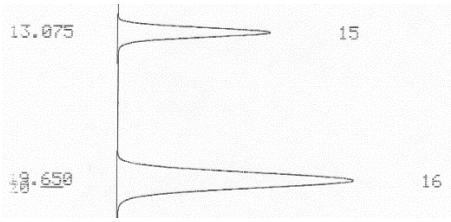
Stirred for 36 h.



13	13.067	1113233	37281	23.6012
14	19.433	3402503	69917	72.1351

Based on this enantiomeric ratio (72.14/23.60), 51% ee was estimated.

Stirred for 48 h.

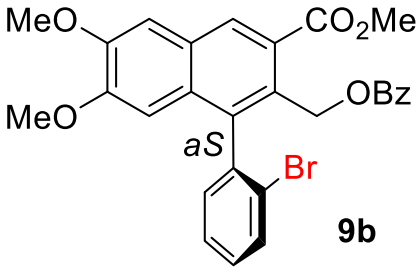


15	13.075	1576021	51266	26.3995
16	19.650	3962597	79374	66.3764

Based on this enantiomeric ratio (66.38/26.40), 43% ee was estimated.

1.7. Data of X-ray single crystal analysis.

X-ray Crystallography for **9b**.



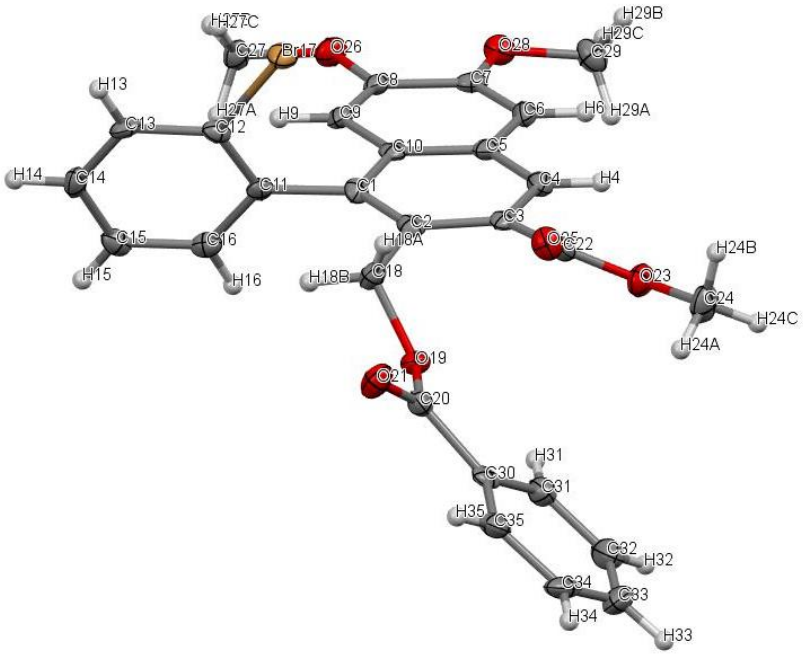


Figure S6. ORTEP for X-ray crystal structures of **9b**.
Thermal ellipsoids are set at 50% probability.

Table S6. Crystal data and structure refinement for **9b**.

Empirical Formula	$C_{28}H_{23}BrO_6$
Formula Weight	535.37
Crystal Color	clear light colourless
Crystal System	orthorhombic
Space Group	$P2_12_12_1$
Lattice Parameters	a = 7.6567(3) Å
	b = 13.7351(4) Å
	c = 22.7161(7) Å

	α = 90°
	β = 90°
	γ = 90°
	V = 2388.95(14) Å^3
Z value	4
Density(calc)	1.489 g/cm^3
Absorption coefficient	1.768 mm^{-1}
F_{000}	1092
Diffractometer	XtaLAB Mini II
Radiation type	Mo K¥α
Radiation wavelength	0.71073 Å
Temperature	93 K
Radiation monochromator	graphite
No. of Reflections Measured	Total: 141354
	Unique: 4245 (R_{int} = 0.0689)
	Parsons quotients (Flack x parameter): 1248
Theta range for data collection	1.793 to 25.439˚
Index ranges	-7<=h=<9
	-16<=k=<16
	-27<=i=<27
Completeness to theta = 25.30°	99.88%
Absorption correction type	gaussian
Max. and min. transmission	0.993 to 0.996
No. Observations	4245
No. Variables	320
Reflection/Parameter Ratio	21.53
Residuals: R_1 (I>2.00s(I))	0.1006
Residuals: R (All reflections)	0.0597
Residuals: wR_2 (All reflections)	0.1231
Goodness-of-fit on F^2	1.092

Flack parameter (Parsons' quotients = 1248)	-0.018(8)
Maximum peak in Final Diff. Map	0.921 $e\text{Å}^{-3}$
Minimum peak in Final Diff. Map	-0.527 $e\text{Å}^{-3}$

Table S7. Atomic coordinates for **9b**.

Atom	x	y	z
Br17	-0.00428(9)	0.64052(4)	0.52732(2)
O19	0.4378(6)	0.5815(3)	0.36449(17)
O23	0.2228(6)	0.3545(3)	0.31545(17)
O28	0.2991(6)	0.1298(3)	0.61179(18)
O21	0.3548(7)	0.7204(3)	0.31995(18)
O26	0.3731(6)	0.2804(3)	0.67437(17)
O25	0.1086(6)	0.5041(3)	0.32597(19)
C16	0.5232(10)	0.5975(4)	0.5629(3)
C14	0.4305(10)	0.7382(5)	0.6163(3)
C13	0.2642(9)	0.7277(4)	0.5944(3)
C20	0.4283(9)	0.6422(5)	0.3182(3)
C27	0.4223(9)	0.3621(4)	0.7105(2)
C29	0.2762(10)	0.0437(4)	0.5774(3)
C12	0.2291(8)	0.6499(5)	0.5575(3)
C15	0.5622(9)	0.6732(4)	0.6001(3)
C8	0.3362(8)	0.3011(5)	0.6166(3)
C7	0.2942(9)	0.2157(5)	0.5821(3)
C10	0.3034(8)	0.4048(4)	0.5311(3)
C22	0.1822(9)	0.4347(5)	0.3468(3)
C30	0.5181(10)	0.6009(4)	0.2650(2)
C2	0.2854(9)	0.5062(4)	0.4437(3)
C4	0.2265(9)	0.3333(4)	0.4364(3)
C5	0.2612(9)	0.3210(5)	0.4969(3)
C3	0.2353(8)	0.4243(5)	0.4101(3)

C9	0.3403(8)	0.3916(4)	0.5918(3)
C34	0.5826(10)	0.6180(6)	0.1622(3)
C24	0.1642(11)	0.3566(5)	0.2549(3)
C32	0.6392(10)	0.4693(5)	0.2105(3)
C33	0.6382(11)	0.5247(6)	0.1606(3)
C18	0.3164(9)	0.6017(4)	0.4132(3)
C6	0.2563(9)	0.2270(4)	0.5235(3)
C1	0.3155(9)	0.4976(4)	0.5032(3)
C35	0.5205(9)	0.6580(5)	0.2147(3)
C31	0.5784(10)	0.5059(5)	0.2633(3)

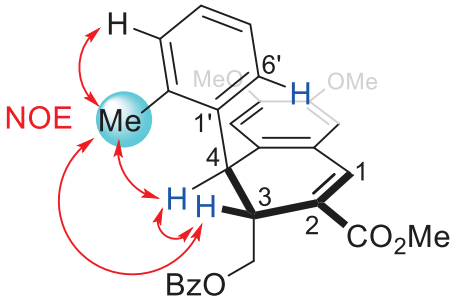
Table S8. Atomic coordinates involving hydrogen atoms for **9b**.

Atom	x	y	z
H16	0.611549	0.554609	0.552216
H14	0.455491	0.789028	0.641978
H13	0.177040	0.771972	0.604236
H27A	0.532436	0.387339	0.697215
H27B	0.432568	0.341412	0.750678
H27C	0.334834	0.411880	0.707528
H29A	0.357233	0.044052	0.545165
H29B	0.159049	0.041542	0.562428
H29C	0.297018	-0.012519	0.601562
H15	0.675138	0.681055	0.614377
H4	0.197209	0.279375	0.413710
H9	0.367735	0.445268	0.614907
H34	0.585612	0.655746	0.128175
H24A	0.219336	0.409649	0.234699
H24B	0.039744	0.365013	0.253932
H24C	0.194479	0.296378	0.236036
H32	0.681639	0.405923	0.208977

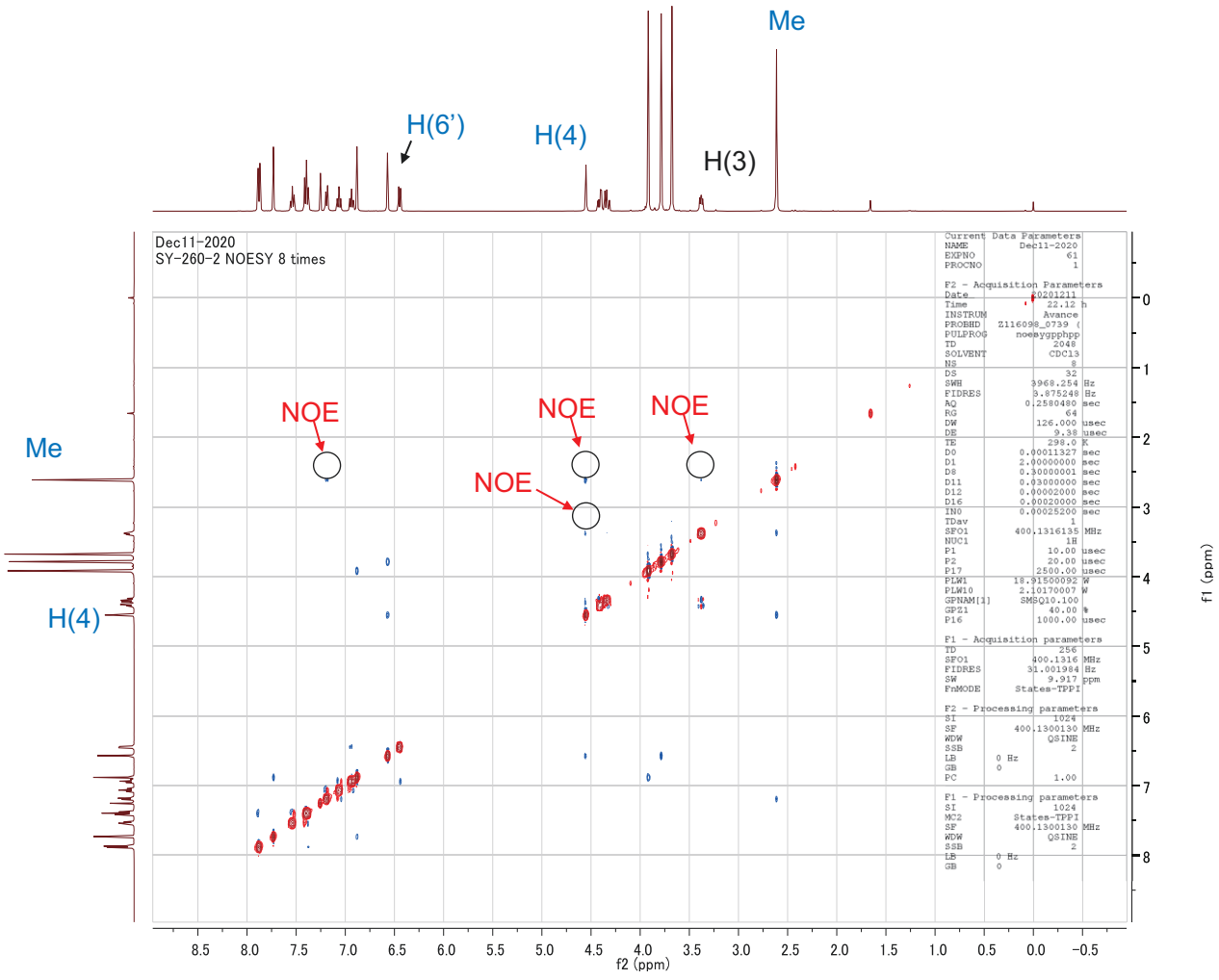
H33	0.676027	0.497922	0.125192
H18A	0.207458	0.627919	0.398289
H18B	0.367007	0.648446	0.440320
H6	0.227243	0.172861	0.500949
H35	0.481261	0.722052	0.215899
H31	0.577939	0.467568	0.297071

1.8. NOE analysis of dihydronaphthalene 8a.

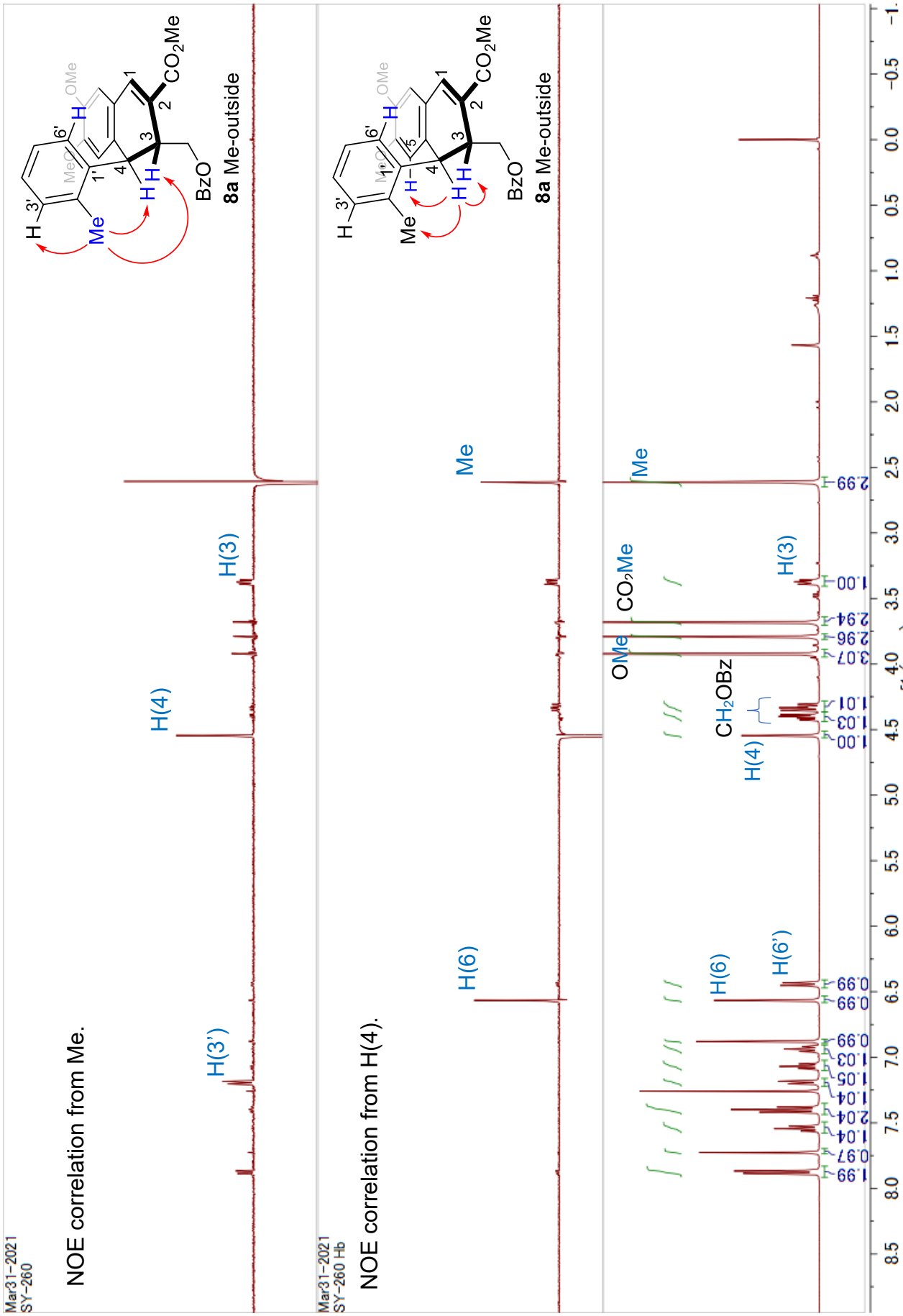
8.1. 2D-NOESY



8a Me-outside



8.2. 1D-NOE


NOE correlation from Me.
8a Me-outside
H(4)
H(3)
H(3')
NOE correlation from H(4).
8a Me-outside
Me
H(6)
OMe
CO2Me
CH2OBz
H(4)
H(3)
H(6)
H(6')
f1 (ppm)

1.9. Computational studies.

All calculations were carried with GRRM17[1-4] based on Gaussian16 program.[5] Structure optimizations were carried out at the M06-2X level in the gas phase using the 6-31+G(d,p) basis set.[6] The vibrational frequencies were computed at the same level to check whether each optimized structure is an energy minimum (no imaginary frequency) or a transition state (single imaginary frequency). The Gibbs free energy used for discussion in this study was calculated by adding the gas-phase Gibbs free energy correction.

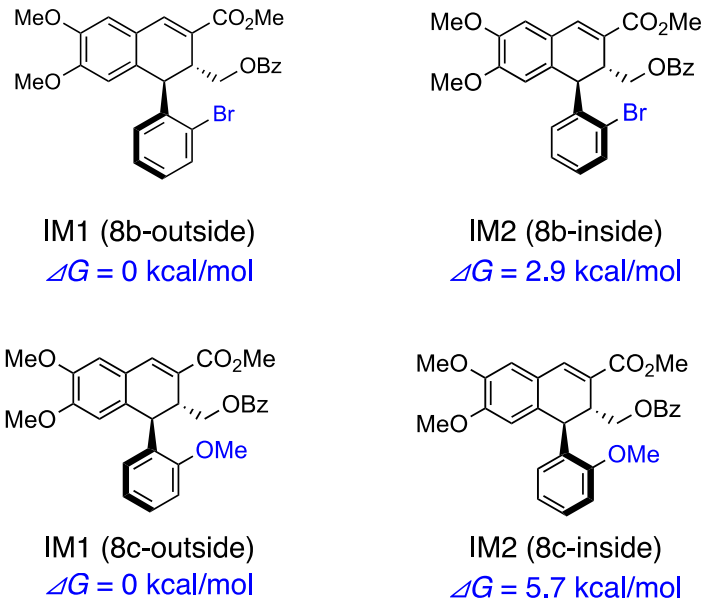


Figure S7. Energy profile for the conformation of dihydronaphthalenes **8b**, **8c** around the axis between the naphthalene and benzene moieties.

・IM1 (**8b**-outside)

Gibbs Free Energy: -1534.15117422628 A.U

C	-2.410718641482	0.020222372045	-2.233537046475
C	-1.417743940370	-0.549745583830	-1.438456919738
C	-0.836758407928	0.175993261714	-0.399599745905
C	-1.265933354339	1.478729185168	-0.127354838205
C	-2.277543314786	2.044452715694	-0.918478365677
C	-2.838334857347	1.338989004791	-1.967577189811
H	-1.063187300465	-1.556469518669	-1.634696441136
C	-0.640687781992	2.222158280389	0.959977440343
H	-2.632933374902	3.053883254954	-0.730110562430
C	0.499174702339	1.806423151322	1.538044094186
H	-1.102443494765	3.143875430937	1.307099813688
O	-3.836447358820	1.907576991931	-2.710877532815
O	-3.015977637959	-0.603005044242	-3.272345525692
C	-3.439884942144	2.273652986343	-4.027780642648
H	-3.113436283767	1.397161837172	-4.595921355616
H	-4.316672837493	2.715897843707	-4.501564324738
H	-2.631153227980	3.014476005280	-3.986709622767
C	-2.637984221361	-1.940465008508	-3.541958423306
H	-3.236813207927	-2.253308337423	-4.396428122208
H	-1.572427891089	-2.002430161621	-3.791490444831
H	-2.855812382005	-2.588008495576	-2.684887368896
C	2.364960861377	0.963933693970	0.079969853122
H	3.036907484682	1.664739518867	0.581135742760
H	2.941542890699	0.069720540104	-0.179930806164
C	1.070504943017	2.641562203821	2.623530160939
O	0.552977102235	3.627672391021	3.099686927414
O	2.269248390558	2.179451151690	3.037971004955

C	2.880753924577	2.933995650258	4.084948645025
H	2.238827518875	2.942497273579	4.968218792469
H	3.823742065705	2.433581929785	4.297844341907
H	3.051350817253	3.962466191412	3.760007878141
O	1.904520013169	1.647871198288	-1.076555982877
C	1.515767800946	0.967940888964	-2.192793753832
C	1.895722532649	-0.338512921792	-2.512206376809
C	0.689809945119	1.684571006299	-3.066275110959
C	1.425691083755	-0.920214010733	-3.691401666189
H	2.540253356036	-0.916650978264	-1.859941186213
C	0.233604668988	1.094429452084	-4.237037709622
H	0.403446812277	2.693689060680	-2.787057291389
C	0.593862058020	-0.216717045228	-4.557801800395
H	1.725018397106	-1.936927658833	-3.929592696989
H	-0.413678991249	1.658946737851	-4.901623038553
H	0.237088470855	-0.676627737476	-5.473837358195
C	1.232193841593	0.580825649052	1.044322757795
H	1.738150494343	0.112322669767	1.895487913479
C	0.246718329946	-0.458097783303	0.444831174008
H	0.819707376520	-1.119335115506	-0.211717093158
C	-0.310859063854	-1.327322792162	1.561835764325
C	-1.577984248054	-1.115889623044	2.112046600258
C	0.456725132325	-2.359907478294	2.111078585802
C	-2.047921762402	-1.883246028021	3.174613325732
H	-2.201459911592	-0.329710949161	1.696311166426
C	0.006808940115	-3.139844854549	3.170222773366
C	-1.255215121687	-2.896797533645	3.706125286656
H	-3.033769711167	-1.688357637020	3.583728655625
H	0.635601249592	-3.929880069686	3.565612529677
H	-1.612361127306	-3.501818699458	4.533020823924

Br	2.183278231901	-2.743035653334	1.402766909601

・IM2 (**8b**-inside)

Gibbs Free Energy: -1534.14653583899 A.U

C	-2.807057335248	0.449632974844	-1.911177261666
C	-1.784666519300	-0.338582371372	-1.389348659082
C	-0.832784526487	0.203841502051	-0.524132407132
C	-0.912798301156	1.550441723664	-0.155862878013
C	-1.959752044162	2.335851026686	-0.665153011938
C	-2.890389354839	1.808951677039	-1.539926070804
H	-1.696806787242	-1.382990276386	-1.671839766063
C	0.076064309002	2.122732064894	0.745741749497
H	-2.052027901908	3.381936682470	-0.385633528341
C	1.167627246616	1.444009486194	1.127438918708
H	-0.096071988008	3.115504328375	1.155415774789
O	-3.911469244073	2.592234737351	-2.005189954273
O	-3.751215467547	0.010553131225	-2.778818550571
C	-3.772792121888	2.969975801020	-3.369615545530
H	-3.737188225969	2.088795076113	-4.017989275317
H	-4.648358757523	3.571938145019	-3.614342938313
H	-2.864818025701	3.571485748577	-3.505044728696
C	-3.665571889182	-1.335088274303	-3.207562382448
H	-4.491096254406	-1.480693395202	-3.903167657550
H	-2.712413703240	-1.522420054847	-3.716725906251
H	-3.773397408828	-2.024871200361	-2.362726598465
C	2.638964028614	0.298405642784	-0.512452455254
H	3.513209823057	0.757031555438	-0.045961253007
H	2.936872775890	-0.675498572015	-0.919245247682
C	2.057373694191	2.077927224835	2.130068593352

O	1.876265643465	3.157395394686	2.649151278784
O	3.121705311675	1.301654693267	2.429945072257
C	4.001055150248	1.838104275223	3.418958872593
H	3.460617924971	2.004403711831	4.353028236233
H	4.784300174373	1.093942032095	3.553094597101
H	4.421010742421	2.786742559836	3.078007787796
O	2.249008083600	1.196667589438	-1.545170294736
C	1.538760922100	0.761572896824	-2.630572712096
C	1.752872395055	-0.466011520001	-3.262962823684
C	0.582304745327	1.646659655977	-3.134405018700
C	0.970322380339	-0.817604368656	-4.363709700404
H	2.520096745788	-1.146717118164	-2.908955316250
C	-0.182394704108	1.290342357664	-4.239360310924
H	0.439806343107	2.594172909670	-2.624970126623
C	-0.003257010137	0.050085845927	-4.854356204656
H	1.139175114780	-1.775034304789	-4.847824462435
H	-0.931741701169	1.981418365489	-4.613886040600
H	-0.604783780182	-0.229753220264	-5.713135487491
C	1.528125875253	0.101016922270	0.538853172756
H	1.967113049919	-0.522365397379	1.327076685251
C	0.335655811375	-0.673515659507	-0.099774389046
H	0.720768860725	-1.068198757781	-1.043569452242
C	-0.092127445552	-1.932689308327	0.643139072450
C	0.075886422389	-3.163204264883	-0.008413129535
C	-0.657312870231	-1.968992421554	1.920677454211
C	-0.298071621984	-4.370693487486	0.573306485742
H	0.514580893725	-3.162336781222	-1.003891577454
C	-1.038766981691	-3.167202266594	2.519629046139
C	-0.863033656659	-4.371114938405	1.845298552623
H	-0.150345799581	-5.301338205898	0.035310823407

H	-1.475118304442	-3.150800906878	3.512283572991
H	-1.163997016802	-5.300391451559	2.317806598872
Br	-0.928363890329	-0.382631524127	2.907070043256

・IM1 (**8c**-outside)

Gibbs Free Energy: -3990.9229413342 A.U

C	-2.977146565802	-0.264690426226	-1.594254617898
C	-2.038908188770	-1.058663895165	-0.931895277745
C	-0.999925911411	-0.476635127684	-0.206545217133
C	-0.899306245860	0.917047556921	-0.133744724486
C	-1.844636560447	1.713451942892	-0.796834707220
C	-2.870668904930	1.140718096589	-1.525603654119
H	-2.111080747821	-2.140786543523	-0.963998738161
C	0.219688852475	1.513135555429	0.583116005213
H	-1.777568950757	2.797467431413	-0.764978174213
C	1.283936271226	0.785674769002	0.963925290362
H	0.223732283782	2.586166562383	0.761232570887
O	-3.800344166714	1.936172320474	-2.138674601768
O	-4.019507119518	-0.745071316008	-2.316124407681
C	-3.672731039947	1.983709584359	-3.555313263617
H	-3.806119011464	0.990037281878	-3.993759544269
H	-4.456099219780	2.652066855242	-3.913810810719
H	-2.690590188365	2.385888391335	-3.832477280013
C	-4.192581310019	-2.148016094184	-2.368213752712
H	-5.084563838737	-2.316992090375	-2.970003818142
H	-3.332214895160	-2.635195111426	-2.841541080735
H	-4.343018354213	-2.562550415006	-1.365010746271
C	2.237442918038	-1.015812970892	-0.551342850300
H	3.236878203741	-0.582145752498	-0.457144272153

H	2.344900781592	-2.102562572334	-0.621271725701
C	2.419948301775	1.510221958782	1.582769310208
O	2.431278466836	2.681885209801	1.888920778955
O	3.496095988684	0.708781056708	1.756082077414
C	4.635833570186	1.345965503506	2.333518608437
H	4.388358413187	1.743144141866	3.320031893626
H	5.400305137424	0.574380182496	2.408650452476
H	4.974409546316	2.166753570414	1.697094988584
O	1.604981061151	-0.635061016495	-1.764147836932
C	1.702380688698	0.645619032508	-2.229048201618
C	2.721647852625	1.539786442310	-1.892995059899
C	0.701592308133	1.033259835528	-3.124982106429
C	2.723044234051	2.818059702021	-2.450584904210
H	3.500089165609	1.267065903553	-1.188999315185
C	0.721643919700	2.307282489827	-3.680082961875
H	-0.090175002021	0.323818766596	-3.349364707231
C	1.730619631956	3.211421953859	-3.344648692445
H	3.511060407868	3.511493698378	-2.173381172911
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H	1.740317900457	4.208623970521	-3.771438941454
C	1.381932701350	-0.697365930985	0.682407494356
H	1.898597489132	-1.177138680633	1.520376794599
C	-0.023383669179	-1.342982577319	0.560469820344
H	0.105435104427	-2.277917377228	0.002383035715
C	-0.552823691526	-1.719344423570	1.938157788696
C	-1.539628127476	-1.003293518035	2.607908647588
C	0.005903303949	-2.842907645635	2.580324386728
C	-1.970675021240	-1.375959357451	3.883947798730
H	-1.983806846124	-0.139559343069	2.121542997091
C	-0.420962820010	-3.229810342132	3.849403859758

C	-1.411242279822	-2.487719765191	4.497987856586
H	-2.739246606592	-0.798259902216	4.386119821971
H	0.004574830034	-4.096914001833	4.340020885466
H	-1.738467901114	-2.791456984907	5.487408265689
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H	2.282486712942	-5.019719799433	1.738780263503
H	2.064266950915	-4.397774099042	3.397509160490
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・IM2 (**8c**-inside)

Gibbs Free Energy: -3990.91386960163 A.U

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C	0.184732399351	-3.184207543535	-0.368859555574
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H	0.019959634083	-5.746860171564	1.847248239790
O	-0.895713681288	-1.324835345318	2.539277323025
C	-1.369012654773	-1.558162025671	3.850082311542
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H	-2.226617316422	-2.241500684138	3.841446663502
H	-0.580342408715	-1.968229810768	

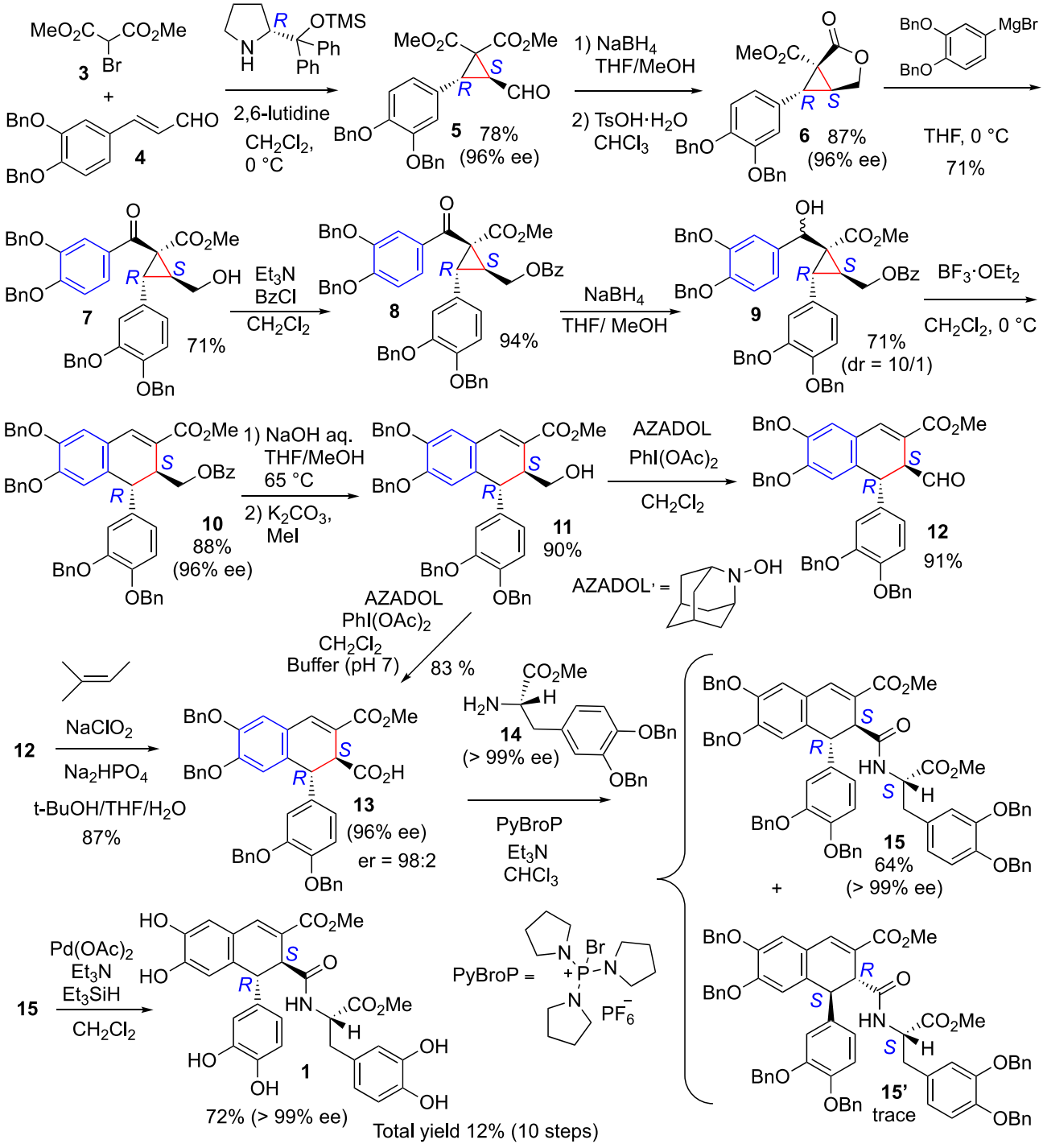
2. D-A シクロプロピルカルビノールの分子内開環-環化を用いる生理活性リグナンアミドの不斉全合成と機構解明

2.1. General method and materials.

All reactions were carried out in oven-dried glassware under an argon atmosphere and monitored by thin-layer chromatography using 0.25 mm Silica gel Merck 60 F_{254} plates. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl. Column chromatography was performed with Kanto chemical CO., INC., silica gel 60 N (spherical, neutral, 40-50 μm). TLC analysis was performed on 0.25 mm Silica gel Merck 60 F_{254} plates. FT-IR spectra were recorded on a SHIMADZU IR Tracer-100 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a BRUKER AVANCE NEO NanoBay (400 MHz for ^{1}H NMR, 101 M Hz for ^{13}C NMR) instrument. Chemical shifts (δ ppm) in $CDCl_3$ were reported downfield from TMS (= 0) for ^{1}H NMR. For ^{13}C NMR, chemical shifts were reported in the scale relative to $CDCl_3$ (77.16 ppm) as an internal reference. Mass spectra were obtained by atmospheric pressure chemical ionization (APCI). HPLC analysis was performed on a JASCO GULLIVER SERIES.

2.2 Overview.

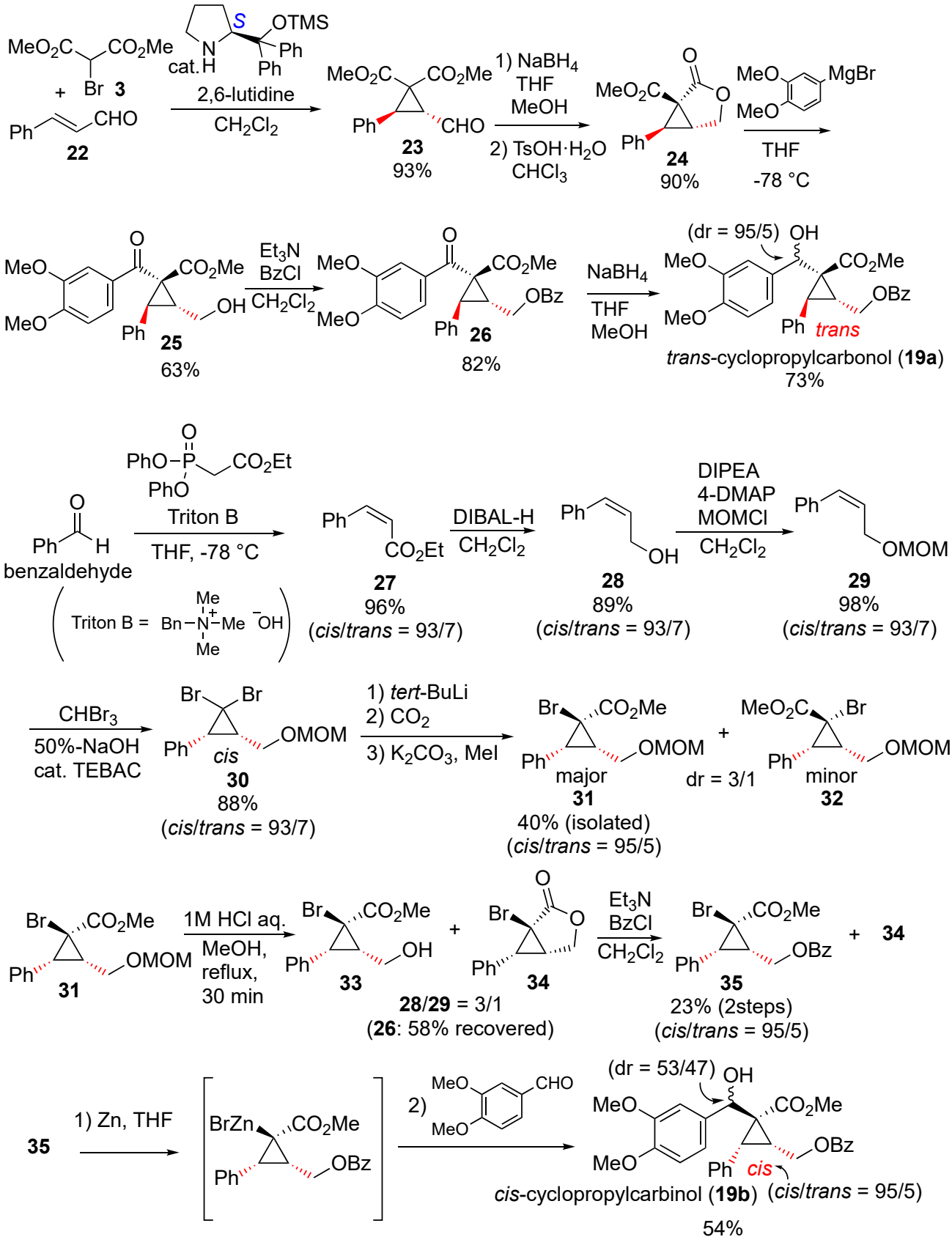
2.2.1. Asymmetric total synthesis of a bioactive lignanamide 1.



The first enantioselective total synthesis of a bioactive lignanamide **1** was achieved with high ee. Key synthetic steps include an organocatalytic enantioselective cyclopropanation and a Lewis-acid-mediated chirality-transferring 5-*endo*-*tet* type cyclization that proceeds with a very high degree of stereoinduction. Details of the preparative procedures for asymmetric total synthesis of a bioactive

lignanamide are described in page S85-S100.

2.2.2. Synthesis of *trans*- and *cis*-cyclopropylcarbinol 19a and 19b.



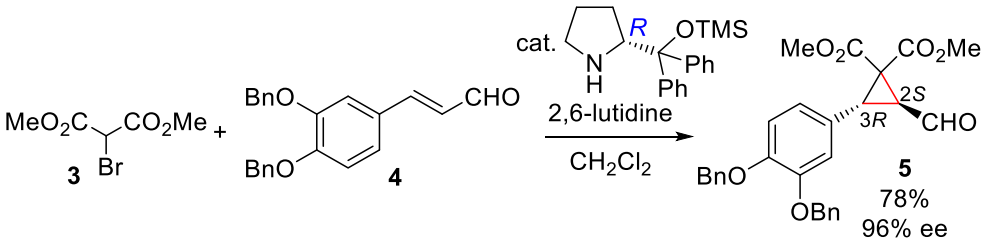
To elucidate the mechanism of the key reaction, *trans*-Cyclopropylcarbinol **19a** was prepared by the similar method described in the aforementioned total synthesis of the lignanamide (see SI, page S101-106). *cis*-Isomer **19b** was synthesized from ethyl *cis*-cynnamate analog (see SI, page S106-113).

2.3. Experimental procedures and characterization data for compounds.

2.3.1. Asymmetric total synthesis of a bioactive lignanamide 1.

Asymmetric cyclopropanation using Hayashi-Jørgensen catalyst to afford enantioenriched cyclopropane 5.

Dimethyl (2*S*,3*R*)-2-formyl-3-(3,4-dibenzyloxyphenyl)cyclopropane-1,1-dicarboxylate (5)



Following Wang's report,[a] we synthesized cyclopropane **5** using dibenzyloxycinnamaldehyde **4**, dimethyl bromomalonate **3** and (*R*)-Hayashi-Jørgensen catalyst.

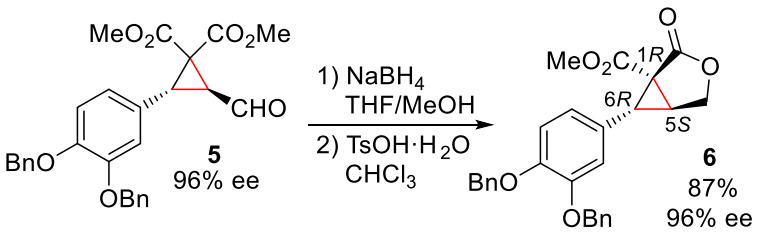
A solution of (*R*)-Hayashi-Jørgensen catalyst (456 mg, 1.41 mmol) in CH_2Cl_2 (7.5 ml) was added to a solution of aldehyde **4** (1.95 g, 5.62 mmol) in CH_2Cl_2 (33 ml) at 0 ˚C under Ar atmosphere, additionally, a solution of dimethyl bromomalonate **3** (1.38 g, 6.47 mmol) in CH_2Cl_2 (6 ml) and 2,6-lutidine (0.76 ml, 6.47 mmol) was added to the reaction mixture at the same temperature, followed by being stirred at 0˚C for 92 h. Then, the reaction was quenched with 1M-HCl aqueous solution (10 mL). Water (30 ml) was added to the mixture, which was extracted with $CHCl_3$ (20 mL x 3). The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The obtained crude oil was purified by column chromatography (SiO_2, hexane/AcOEt = 2/1) to give the product **5** (2.07 g, 78%, 96% ee). Based on the HPLC analysis of lactone **6** that was derived from **5**, ee of **5** was estimated as 96% ee.

Product 5: yellow oil; ^{1}H NMR (400MHz, $CDCl_3$) δ 3.29 (dd, J = 4.6, 7.5Hz, 1H), 3.42 (s, 3H), 3.74

(d, J = 7.5Hz, 1H), 3.82 (s, 3H), 5.12 (s, 2H), 5.12 (s, 2H), 6.72-6.75 (m, 1H), 6.84-6.86 (m, 2H), 7.28-7.49 (m, 10H), 9.45 (d, J = 4.6Hz, 1H); ^{13}C NMR (101MHz, $CDCl_3$) δ 196.5, 167.0, 165.5, 149.2, 149.2, 137.4, 128.9 (C2), 128.3 (C2), 127.8, 127.7, 125.6, 121.9, 115.7, 115.2, 71.8, 71.6, 53.7, 53.3, 45.0, 39.0, 35.8; IR (KBr, neat): 3030, 2957, 2866, 1734, 1709, 1587, 1522, 1433, 1389, 1302, 1234, 1207, 1167, 1138, 1024, 739, 696 cm^{-1}.

[a] H. Xie, L. Zu, H. Li, J. Wang, W. Wang, *J. Am. Chem. Soc.* **2007**, *129*, 10886.

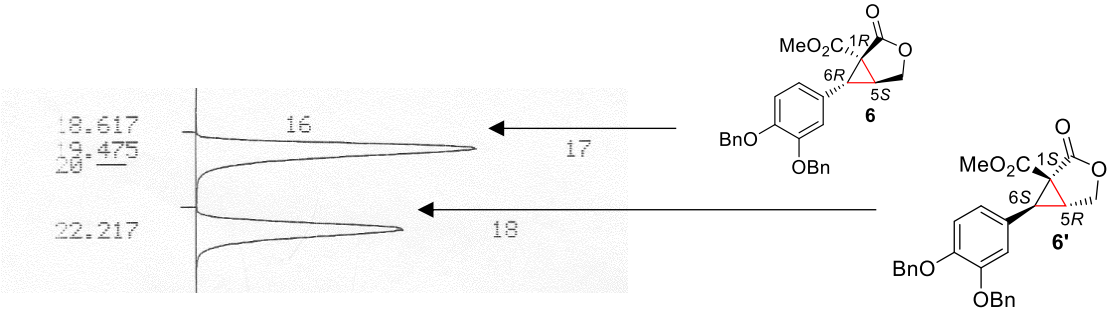
(1*R*,5*S*,6*R*)-1-Methoxycarbonyl-6-(3,4-dibenzyloxyphenyl)-3-oxabicyclo[3,1,0]-hexan-2-one (6)



$NaBH_4$ (21 mg, 0.555 mmol) was added to a solution of cyclopropane **5** (756 g, 1.59 mmol) in THF/MeOH (THF: 4.2 mL; MeOH: 3.2 mL) at 0°C under an Ar atmosphere followed by being stirred for 15 minutes. Then, the reaction was quenched with sat. NH_4Cl aqueous solution (10 mL). Water (10 mL) was added to the mixture, which was extracted with AcOEt (ca. 10 mL x 5). The organic layer was washed with brine, dried (Na_2SO_4), and concentrated. The obtained crude oil was resolved in $CHCl_3$ (17 mL), then *p*-TsOH·H_2O (16 mg, 82 μmol) was added to the solution, followed by being stirred at 45°C for 2 h. Then, the reaction was quenched with sat. $NaHCO_3$ aqueous solution (10 mL). Water (10 mL) was added to the mixture, which was extracted with $CHCl_3$ (ca. 10 mL x3). The organic layer was washed with brine, dried (Na_2SO_4), and concentrated. The obtained crude oil was purified by column chromatography (SiO_2, hexane/AcOEt = 1/1) to give the product **6** (616 mg, 87%, 96% ee). The ee was observed by HPLC analysis of **6** with chiral column (Daicel CHIRALPAK IC).

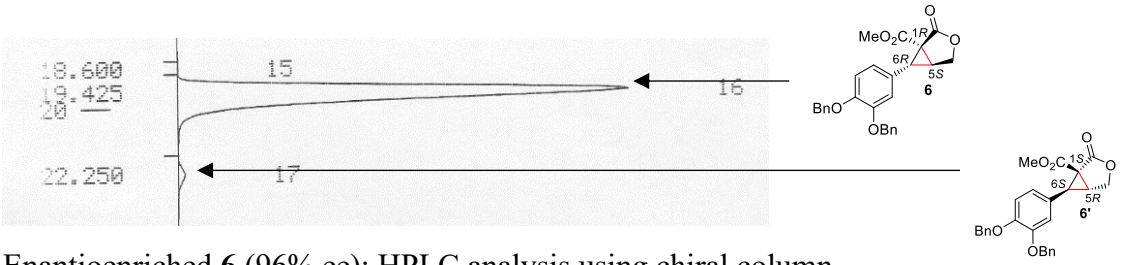
Product **6**: colorless solid; mp 107-111˚C; $[\alpha]_D^{23}$ = 27.4 (c = 1.00, chloroform, λ = 589 nm); ^{1}H NMR

(400 MHz, $CDCl_3$) δ 7.47-7.28 (m, 10H), 6.86 (d, J = 8.3 Hz, 2H), 6.75 (dd, J = 8.3, 2.0 Hz, 1H), 5.13 (s, 2H), 5.12 (s, 2H), 4.44 (dd, J = 9.3, 4.8 Hz, 1H), 4.30 (d, J = 9.4 Hz, 1H), 3.47 (s, 3H), 3.17 (t, J = 5.1 Hz, 1H), 2.81 (d, J = 5.6 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.1, 164.0, 148.9, 148.7, 137.0, 128.6, 128.5, 127.9, 127.9, 127.3, 127.3, 124.8, 121.8, 115.5, 114.5, 77.4, 77.1, 76.8, 71.3, 71.1, 67.3, 52.7, 37.9, 37.56, 27.8; HRMS (APCI) calcd for $C_{27}H_{24}O_6$ $(M+H)^+$ 445.1821, found 445.1646. HPLC analysis: 96% ee [Daicel CHIRALPAK IC (25cm) at 25°C, flow rate 0.5 ml/min, solvent: hexane / ethanol = 1/1, t_R(mixture of **6** and optical isomer **6′**) = 19.48 min and 22.22 min, t_R(**6**) = 19.43 min for major and 22.25 min for minor].



Mixture of **6** and isomer **6′**: HPLC analysis using chiral column.

17	19.475	9660621	290434	LLL	55.0150
18	22.217	7447234	213617	V	42.4103



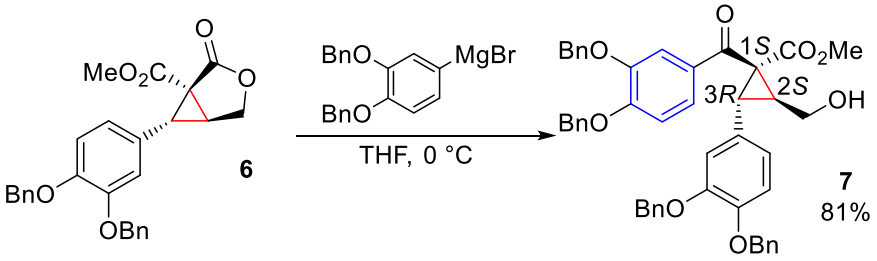
Enantioenriched **6** (96% ee): HPLC analysis using chiral column.

16	19.425	15871930	470760	LLL	95.9176
17	22.250	266497	7188	V	1.6105

Based on this enantiomeric ratio (95.92/1.61), the ee value was estimated as 96% ee.

Methyl (1*S*,2*S*,3*R*)-1-[(3,4-dibenzyloxyphenyl)carbonyl]

-3-(3,4-dibenzyloxyphenyl)-2-(hydroxymethyl)cyclopropanecarboxylate (7)

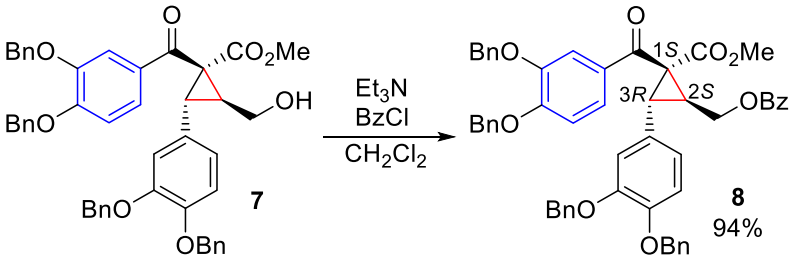


An oven-dried two-neckedround-bottomed flask was charged with Mg turnings (233 mg, 9.9 mmol), under Ar atmosphere. 4-bromo-1,2-dibenzyloxybenzene (553 mg, 1.50 mmol) THF solution (1.0 M) was added into the activated Mg at 66 °C. After the reaction was initiated, 4-bromo-1,2-dibenzyloxybenzene (2.77 g, 7.50 mmol) THF solution (1.0 M) was added at same temperature, followed by being stirred until the Mg was completely consumed at reflux temperature. Then, THF was added to dilute the Grignard reagent to 0.5 M. This Grignard reagent THF solution (18.0 mL, 9.00 mmol) was added slowly to a solution of lactone **6** (2.00 g, 4.50 mmol) in THF (15.8 mL) at -78 °C (ice-salt bath), followed by being stirred at same temperature for 15 min. After the reaction was completed, quenched with sat. NH_4Cl aqueous solution (15 mL). Water (20 mL) was added to the mixture, which was extracted with AcOEt (10 mL x 5). The organic layer was washed with brine, dried (Na_2SO_4) and concentrated. The obtained crude oil was purified by column chromatography (SiO_2, hexane/AcOEt = 3/2) to give the product **7** (2.69 g, 81%).

Product **7**: colorless amorphous solid; $[\alpha]_D^{24}$ = 82.7 (*c* = 1.00, chloroform, λ = 589 nm); ^{1}H NMR (400MHz, $CDCl_3$) δ 7.56-7.59 (m, 2H), 7.28-7.47 (m, 20H), 6.93-6.95 (m, 2H), 6.80-6.88 (m, 2H), 5.09-5.24 (m, 8H), 3.29-3.36 (m, 1H), 3.22 (m, 1H), 3.21 (s, 3H), 2.95 (m, 1H), 1.51 (brs, 1H); ^{13}C NMR (101MHz, $CDCl_3$) δ 192.2, 169.0, 153.8, 149.1, 149.0, 148.7, 137.7 (2C), 137.2, 136.8, 130.9, 129.1, 129.0, 128.9 (2C), 128.5, 128.4, 128.2, 128.1, 127.8, 127.7 (2C), 127.6, 124.0, 122.3, 116.3, 115.1, 114.6, 113.4, 71.7, 71.6, 71.4, 71.3, 61.4, 52.8, 46.9, 34.3, 33.8; IR (KBr, neat): 3455, 3065, 3034, 2947, 2864, 1952, 1871, 1811, 1730, 1668, 1593, 1516, 1454, 1429, 1385, 1277, 1136, 1024,

912, 854, 813, 733, 694 cm^{-1}.

Methyl (1*S*,2*S*,3*R*)-2-(benzoyloxymethyl)-3-(3,4-dibenzyloxyphenyl) -1-[(3,4-dibenzyloxyphenyl)carbonyl]cyclopropanecarboxylate (8)

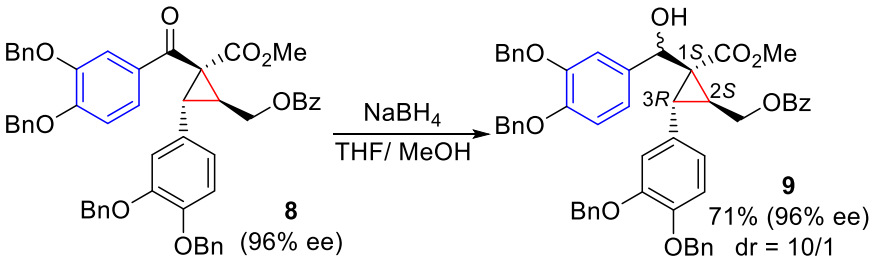


A CH_2Cl_2 (1.0 mL) solution of the alcohol **7** (361 mg, 0.502 mmol) was added triethylamine (0.11 mL, 0.79 mmol) at 0 °C, then dropped benzoyl chloride (87 μL, 0.75 mmol), followed by being stirred for 4 h at same temperature. The reaction mixture was quenched with water, which was extracted with $CHCl_3$. The organic layer was washed with brine, dried (Na_2SO_4) and concentrated. The obtain crude was purified by column chromatography (SiO_2, Hexane/AcOEt = 2/1) to give the product **8** (394 mg, 94%).

Product **8**: colorless amorphous solid; $[\alpha]_D^{25}$ = 57.6 (*c* = 1.00, chloroform, λ = 589 nm); ^{1}H NMR (400MHz, $CDCl_3$) δ 7.77-7.81 (m, 2H), 7.27-7.59 (m, 25H), 6.91-6.93 (m, 1H), 6.78-6.88 (m, 3H), 5.05-5.16 (m, 8H), 4.56 (dd, *J* = 5.9, 12.1 Hz, 1H), 3.94 (dd, *J* = 8.7, 12.1 Hz, 1H), 3.49 (d, *J* = 7.7 Hz, 1H), 3.16-3.24 (m, 1H), 3.17 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.7, 168.6, 166.0, 153.4, 148.8, 148.7, 148.5, 137.4 (2C), 137.3, 136.8, 136.5, 133.1, 130.6, 129.8, 128.8, 128.7, 128.6 (2C), 128.3, 128.2, 128.1, 127.9 (2C), 127.6, 127.5 (2C), 127.4, 127.2, 123.6, 121.9, 115.8, 114.9, 113.9, 112.9, 71.4, 71.3, 71.0, 70.9, 62.4, 52.6, 46.7, 33.1, 30.4; IR (KBr, neat): 3065, 3032, 2949, 2868, 1958, 1877, 1813, 1721, 1668, 1593, 1514, 1454, 1427, 1381, 1267, 1024, 910, 854, 812, 737, 696 cm^{-1}; HRMS (APCI) calcd for $C_{54}H_{46}O_9$ $(M+H)^+$ 839.3215, found 839.3464.

Methyl (1*S*,2*S*,*3SR*)-2-(benzoyloxymethyl)-3-(3,4-dibenzyloxyphenyl)

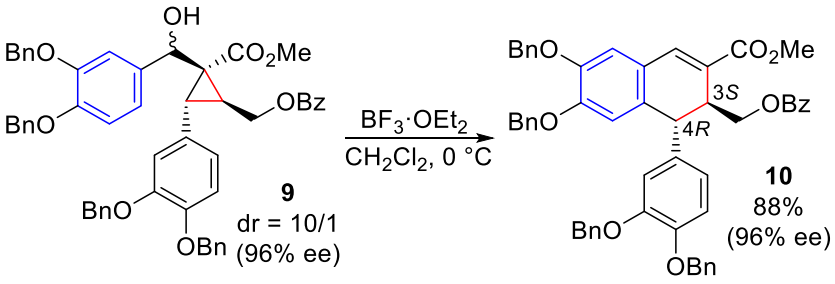
-1-[(*R*) and (*S*)-1-hydroxy-1-(3,4-dibenzyloxyphenyl)methyl]cyclopropanecarboxylate (9)



$NaBH_4$ (143 mg, 3.78 mmol) was added to a solution of cyclopropane **8** (394 mg, 0.470 mmol) in THF/MeOH (THF = 1.5 mL, MeOH = 1.5 mL) at 0 °C under an Ar atmosphere, followed by being stirred at same temperature for 30 min. Then, the reaction was quenched with sat. NH_4Cl aqueous solution (20 mL). Water (10 mL) was added to the mixture, which was extracted with AcOEt (ca. 10 mL x 5). The organic layer was washed with brine, dried (Na_2SO_4), and concentrated. The obtained crude oil was purified by column chromatography (SiO_2, hexane/AcOEt = 4/1) to give the product **9** (314 mg, 79%, 96% ee, dr = 10/1). Diastereomeric ratio (dr) was estimated by the measurement of ^1H NMR spectral data. The optical purity of cyclopropylcarbinol **9** was estimeted based on aforementioned HPLC analysis of lactone **6**.

Product **9**: (10/1 mixture of diastereomers) colorless amorphous solid; $[\alpha]_D^{26} = 6.42$ (Selected data for major of **9**.) ^1H NMR (400MHz, $CDCl_3$) (Selected data for Major of **7**) δ 8.07-8.03 (m, 2H), 7.57-7.53 (m, 1H), 7.20-7.45 (m, 22H), 7.16 (d, *J* = 1.9 Hz, 1H), 7.01 (dd, *J* = 1.9, 8.2 Hz, 1H), 6.86 (d, *J* = 8.4 Hz, 1H), 6.78 (d, *J* = 8.2 Hz, 1H), 6.74 (d, *J* = 1.7 Hz, 1H), 6.65 (dd, *J* = 1.7, 8.4 Hz, 1H), 4.95-5.16 (m, 9H), 4.65 (dd, *J* = 6.1, 6.8 Hz, 1H), 4.52 (dd, *J* = 6.1, 6.8 Hz, 1H), 3.29 (d, *J* = 7.2, 1H), 3.11 (s, 3H), 2.72-3.78 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.1, 166.7, 148.8, 148.6, 147.9, 137.4(2C), 137.3, 135.8, 133.3, 130.2, 129.8, 129.4, 128.5, 127.9 (2C), 127.5, 127.4 (3C), 121.7, 119.7, 115.7, 115.0, 114.7, 114.1, 72.6, 71.4, 71.4, 71.2, 63.4, 51.7, 41.8, 33.9, 28.8; IR (KBr, neat) 3489, 3063, 3032, 2947, 2868, 1956, 1877, 1811, 1717, 1603, 1585, 1514, 1452, 1381, 1271, 1134, 1069, 1024, 910, 854, 814, 735, 714, 696 cm^{-1}.

Methyl (3*S*,4*R*)-3-[(benzoyloxy)methyl]-6,7-dibenzyloxy-4-(3,4-dibenzyloxyphenyl) -3,4-dihydronaphthalene-2-carboxylate (10)

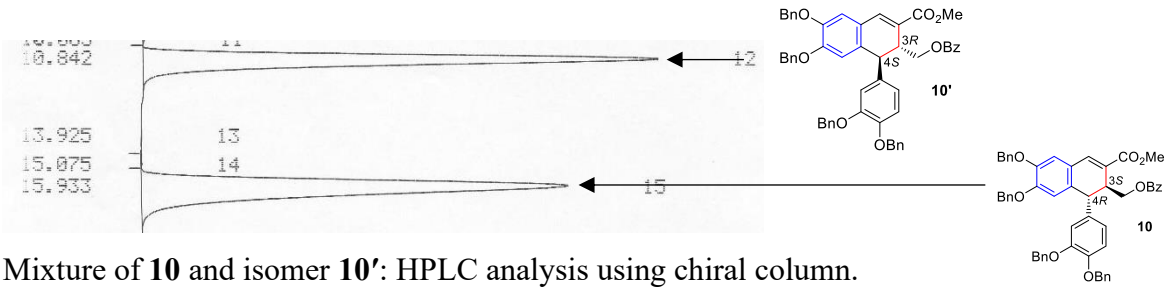


$BF_3{\cdot}OEt_2$ (45 μL, 0.394 mmol) was added to a solution of cyclopropylcarbinol **9** (300 mg, 0.357 mmol) in CH_2Cl_2 (3.6 mL) at 0 °C under an Ar atmosphere, followed by being stirred at same temperature for 30 min. The reaction was quenched with H_2O (5 ml) at 0 ℃, and the mixture was extracted with $CHCl_3$ (5 ml x 3). The combined organic layer was washed with brine (10 ml), dried over Na_2SO_4, and evaporated. The obtained crude oil was purified by column chromatography (SiO_2, hexane/AcOEt = 3/1) to give the dihydronaphthalene **10** (225 mg, 88%, 96% ee). The ee was observed by HPLC analysis of **10** with chiral column (Daicel CHIRALPAK IC). The relative structure of **10** was determined by analogy with the NMR spectral data of a *trans*-dihydronaphthalene synthetic intermediate (**11a** in the literature: *Chem. Lett*. **2014**, *39*, 194.) in the total synthesis of (±)-cyclogalgravin[a] and NOESY observations. The NOESY chart was attached in S15.

[a] Sakuma, D.; Ito, J.; Sakai, R.; Taguchi, R.; Nishii, Y. *Chem. Lett*. **2014**, *39*, 194 (open access).

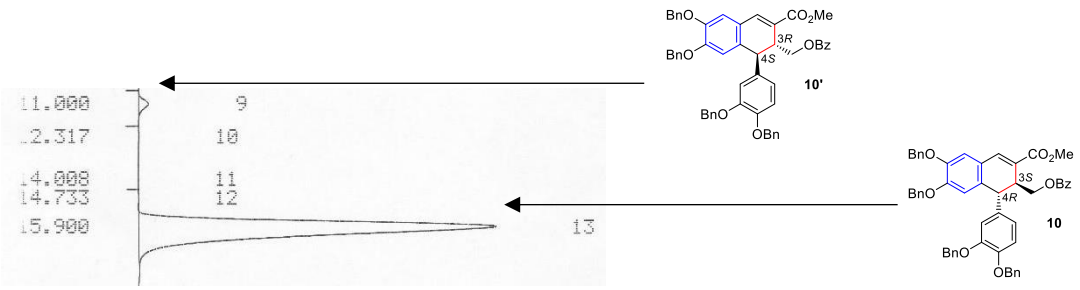
Dihydronaphthalene **10**: colorless amorphous solid; $[\alpha]_D^{27}$ = -66.4 (*c* = 1.00, chloroform, λ = 589 nm); ^{1}H NMR (400MHz, $CDCl_3$) δ 7.80-7.84 (m, 2H), 7.22-7.55 (m, 24H), 6.89 (s, 1H), 6.76 (d, *J* = 8.3 Hz, 1H), 6.67 (s, 1H), 6.48 (dd, *J* = 2.1, 8.4 Hz, 1H), 6.44 (d, *J* = 2.1 Hz, 1H), 5.16 (brs, 2H), 5.09 (brs, 2H), 5.02 (brs, 2H), 4.98 (brs,2H), 4.33 (dd, *J* = 4.9, 10.8 Hz, 1H), 4.23 (dd, *J* = 7.5, 10.8 Hz, 1H), 4.14 (brs,1H), 3.70 (s, 3H), 3.44 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.1, 166.5, 151.1, 148.5, 148.0, 147.7, 138.2, 137.5, 137.3, 137.2, 136.9, 136.7, 133.0, 131.1, 130.1, 129.6, 128.7, 128.6, 128.5(2C), 128.4, 128.0 (2C), 127.8, 127.7, 127.4, 127.3 (2C), 124.8, 124.1, 120.4, 115.9, 115.6, 114.9, 114.8, 71.7, 71.3, 71.2, 71.1, 66.2, 51.9, 45.1, 41.2; IR (KBr, neat): 3063, 3032, 2947, 2870, 1962,

1873, 1811, 1709, 1632, 1601, 1568, 1508, 1454, 1371, 1271, 1238, 1134, 1082, 1015, 920, 847, 808, 735, 696 cm^{-1}; HRMS (APCI) calcd for $C_{54}H_{46}O_8$ $(M+H)^+$ 822.3187, found 822.3448. HPLC analysis: 96% ee [Daicel CHIRALPAK IG (15cm) at 25°C, flow rate 0.5 ml/min, solvent: hexane / dichloromethane = 1/1, t_R(mixture of **10** and optical isomer **10′**) = 10.8 min and 15.9 min, t_R(**10**) = 15.9 min for major and 11.0 min for minor].



Mixture of **10** and isomer **10′**: HPLC analysis using chiral column.

12	10.842	18185755	627112	V	44.3406
13	13.925	15020	543		3.6622E-02
14	15.075	8168	337	L	1.9914E-02
15	15.933	21495000	518919	LLL	52.4093



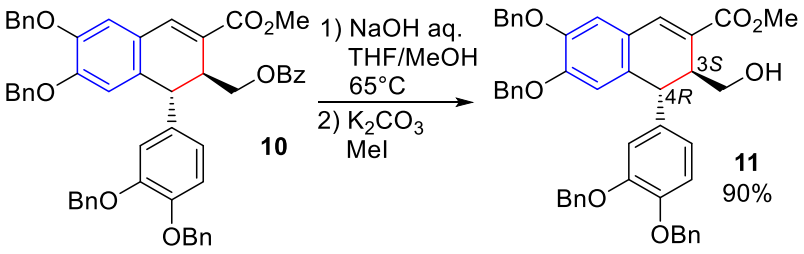
Enantioenriched **10** (96% ee): HPLC analysis using chiral column.

9	11.000	327804	12507	V	1.8518
10	12.317	25963	997	V	0.1467
11	14.008	10572	308	V	5.9723E-02
12	14.733	10056	343	V	5.6804E-02
13	15.900	16828403	433457		95.0642

Based on this enantiomeric ratio (95.06/1.85), the ee value was estimated as 96% ee.

Methyl (3*S*,4*R*)-6,7-dibenzyloxy-4-(3,4-dibenzyloxyphenyl)

-3-(hydroxymethyl)-3,4-dihydronaphthalene-2-carboxylate (11)

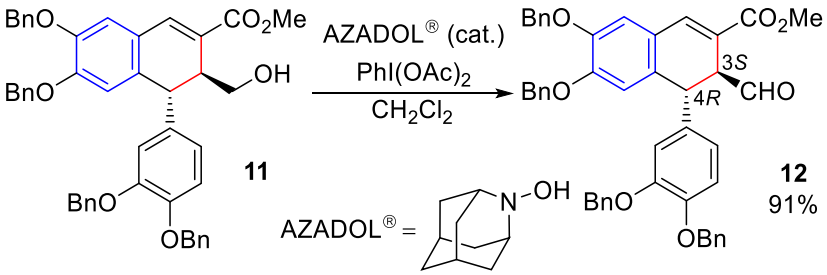


3.0 M NaOH aqueous solution (1.55 mL) was added to a solution of **10** (255 mg, 0.310 mmol) in THF/MeOH (THF = 0.78 mL, MeOH = 0.78 mL) at room temperature, followed by being stirred at 65 °C for 1 h. After the reaction was completed, 1 M HCl aq. was added. Then THF/MeOH was removed by rotary evaporation. Water (5 mL) was added to the mixture, which was extracted with $CHCl_3$ (ca. 5 mL x 3). The organic layer was washed with brine, dried (Na_2SO_4), and concentrated. The obtained crude oil was dissolved in DMF (1.8 mL), then K_2CO_3 (98 mg, 0.709 mmol) was added to the solution at 0 °C, followed by being stirred at same temperature for 30 min. Then MeI (60 μL, 0.709 mmol) was added and the solution was stirred at same temperature at 3 h. After the reaction was completed, the reaction was quenched with sat. NH_4Cl aqueous solution (5 mL). Water was added to the mixture, which was extracted with AcOEt (ca. 5 mL x 5). The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The obtained crude oil was purified by purified by column chromatography (SiO_2, hexane/AcOEt = 1/1) to give the product **11** (200 mg, 90%).

Product **11**: colorless amorphous solid; $[\alpha]_D^{26}$ = -38.1 (*c* = 0.50, chloroform, λ = 589 nm); ^{1}H NMR (400MHz, $CDCl_3$) δ 7.14-7.37 (m, 21H), 6.78 (s, 1H), 6.63-6.65 (m, 2H), 6.35-6.38 (m, 2H), 5.07 (s, 2H), 4.89-4.98 (m, 6H), 4.14 (s, 1H), 3.62 (s, 3H), 3.57 (dd, *J* = 5.5, 10.5 Hz, 1H), 3.27 (t, *J* = 9.5 Hz, 1H), 3.06 (dd, *J* = 5.5, 8.4 Hz, 1H), 1.97 (brs,1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.0, 151.1, 148.5, 147.85, 147.6, 137.6, 137.5, 137.4, 137.2, 136.7, 131.3, 128.6, 128.6, 128.6, 128.5, 128.0, 127.8, 127.7, 127.5, 127.4, 127.4, 127.3, 125.0, 124.8, 120.4, 115.9, 115.6, 114.9, 71.7, 71.4, 71.2, 71.0, 63.9, 51.9, 45.1, 43.9; IR (KBr, neat): 3416, 3063, 3030, 2945, 2870, 1954, 1869, 1811, 1701, 1627, 1600, 1566,

1608, 1454, 1435, 1414, 1379, 1240, 1132, 1080, 1016, 916, 850, 735, 696, 613 cm^{-1}; HRMS (APCI) calcd for $C_{54}H_{46}O_8$ $(M+H)^+$ 822.3187, found 822.3448.

Methyl (3*S*,4*R*)-6,7-dibenzyloxy-4-(3,4-dibenzyloxyphenyl) -3-formyl-3,4-dihydronaphthalene-2-carboxylate (12)

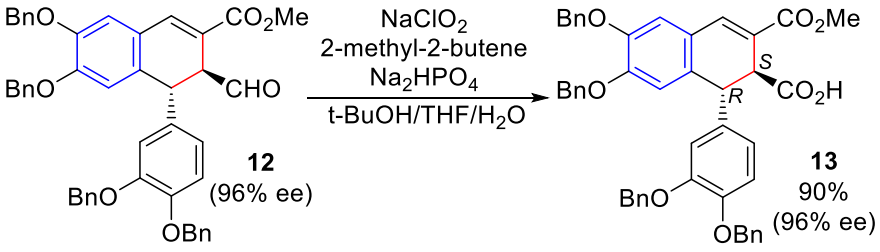


AZADOL® (0.9 mg, 6.0 μmol) and iodobenzene diacetate (50 mg, 0.156 mmmol) were added to a solution of **11** (86 mg, 0.120 mmmol) in CH_2Cl_2 (1.0 mL) at 0 °C under an Ar atmosphere, followed by being stirred at room temperature for 1.5 h. Then sat $NaHCO_3$ aqueous solution was added to the solution. Further, sat. $Na_2S_2O_3$ aqueous solution was added and the mixture was stirred for 15 min. The mixture was extracted with $CHCl_3$. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The obtained crude oil was purified by purified by column chromatography (SiO_2, hexane/AcOEt = 3/1) to give the product **12** (78 mg, 91%).

Product **10**: colorless amorphous solid; $[\alpha]_D^{22}$ = -100.1 (*c* = 0.50, chloroform, λ = 589 nm); ^{1}H NMR (400MHz, $CDCl_3$) δ 9.53 (s, 1H), 7.61 (s, 1H), 7.24-7.45 (m, 20H), 6.87 (s, 1H), 6.75 (d, *J* = 8.1 Hz, 1H), 6.70 (s, 1H), 6.43-6.47 (m, 2H), 5.15 (s, 2H), 5.09 (s.2H), 5.04 (s, 1H), 5.01 (s,1H), 4.98 (s, 2H), 4.56 (brs,1H), 3.79 (brs,1H), 3.76 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.8, 167.1, 151.5, 148.7, 148.1, 148.0, 139.4, 137.5, 137.2, 137.1, 136.6, 136.0, 131.3, 128.7, 128.6, 128.5, 128.1(2C), 127.9, 127.8, 127.5, 127.4, 127.3, 124.2, 120.4, 120.0, 115.9, 115.1, 115.0, 114.8, 71.6, 71.4, 71.2, 71.0, 54.6, 52.2, 42.0; IR (KBr, neat): 3063, 3030, 2947, 2868, 1956, 1877, 1811, 1719, 1701, 1630, 1601, 1566, 1508, 1454, 1437, 1416, 1369, 1238, 1134, 1078, 1014, 916, 854, 735, 696, 611 cm^{-1}; HRMS (APCI)

calcd for $C_{47}H_{40}O_7$ $(M+H)^+$ 716.2769, found 716.2990.

(1*R*,2*S*)-6,7-dibenzyloxy-1-(3,4-dibenzyloxyphenyl)-3-(methoxycarbonyl) -1,2-dihydronaphthalene-2-carboxylic acid (13)



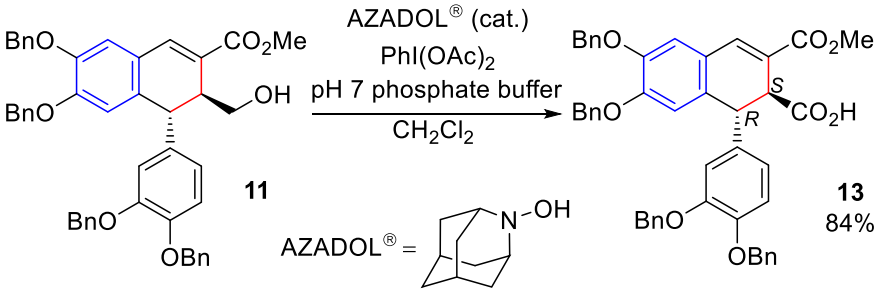
2-methyl-2-butene (0.28 mL, 2.65 mmol) was added to a solution of **12 (**190 mg, 0.265 mmol) in *t*-BuOH (2.7 mL), THF (2.7 mL) and 1.0 M Na_2HPO_4 aqueous solution (4.0 mL). Then $NaClO_2$ (36 mg, 0.398 mmmol) was added to the solution at 0 °C, followed by being stirring at room temperature for 2 h. After the reaction was completed, sat. $Na_2S_2O_3$ aqueous solution was added and the mixture was stirred for 10 min. Brine was added to the mixture, which was extracted with $CHCl_3$. The organic layers were dried over Na_2SO_4, and concentrated. The obtained crude oil was purified by column chromatography (SiO_2, $CHCl_3$/MeOH = 100/1) to give the product **13** (175 mg, 90%, 96% ee) The optical purity of dihydronaphthalene segment **13** was estimeted based on aforementioned HPLC analysis of dihydronaphthalene **10**.

Dihydronaphthalene segment **13**: colorless amorphous solid; $[\alpha]_D^{24}$ = -93.0 (*c* = 0.50, chloroform, λ = 589 nm); ^{1}H NMR (400MHz, $CDCl_3$) δ 3.71 (s, 3H), 3.88 (d, *J* = 1.8 Hz, 1H), 4.54 (brs, 1H), 4.94-5.04 (m, 4H), 5.07-5.14 (m,4H), 6.40-6.47 (m, 2H), 6.67 (s, 1H), 6.73 (d, *J* = 8.3 Hz, 1H), 6.87 (s, 1H), 7.22-7.44 (m, 20H), 7.49 (s, 1H); ^{13}C NMR (101MHz, $CDCl_3$) δ 45.3, 47.5, 52.5, 71.3, 71.5, 71.7, 72.0, 115.0, 115.2, 115.5, 116.1, 120.7, 121.8, 124.7, 127.65, 127.66, 127.7, 127.9, 128.1, 128.2, 128.4 (2C), 128.8, 128.9 (2C), 129.0, 131.2, 136.1, 136.9, 137.49, 137.55, 137.8, 138.5, 148.3, 148.5, 148.9, 151.6, 168.0, 177.5.

NMR-spectral data of synthesized **13** was consistent with reported data of synthesized racemic **13**[a].

[a] G. E. Magoulas, A. Rigopoulos, Z. Piperigkou, C. Gialeli, N. K. Karamanos, P. G. Takis, A. N. Troganis, A. Chrissanthopoulos, G. Maroulis, D. Papaioannou, *Bioorg. Chem*. **2016**, *66*, 132.

The direct oxidation of alcohol 11 to carboxylic acid 13.

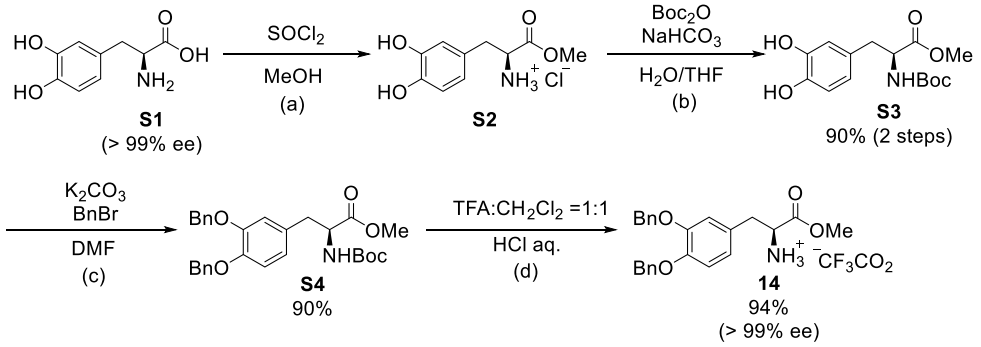


Following Arai's report,[a] we synthesized carboxylic acid **13** using alcohol **11**.

To a solution of alcohol **11** (440 mg, 0.61 mmol) in CH_2Cl_2/pH 7.0 phosphate buffer (1:1, v/v, 2.4 mL) at 0 °C were sequentially added AZADOL® (9.3 mg, 61 μmol) and $PhI(OAc)_2$ (471 mg, 1.46 mmol). The resultant solution was stirred at room temperature for 3 h. The reaction was quenched with saturated aqueous $Na_2S_2O_3$ solution at 0 °C. The mixture was extracted with AcOEt, and the aqueous layers were extracted with AcOEt. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The obtained crude oil was purified by column chromatography (SiO_2, $CHCl_3$/MeOH = 100/1) to give the product **13** (380 mg, 84%, 96% ee). The optical purity of dihydronaphthalene segment **13** was estimeted based on aforementioned HPLC analysis of dihydronaphthalene **10**.

[a] M.Sasaki, K. Iwasaki, K. Arai, *Org. Lett*. **2018**, *20*, 7163.

Preparation for DOPA segment 14.



Following Magoulas's report,[a] DOPA segment **14** was prepared. For these experimental procedures and characterizations, see this report.

[a] G. E. Magoulas, A. Rigopoulos, Z. Piperigkou, C. Gialeli, N. K. Karamanos, P. G. Takis, A. N. Troganis, A. Chrissanthopoulos, G. Maroulis, D. Papaioannou, *Bioorg. Chem*. **2016**, *66*, 132.

(a) To an ice-cold suspension of L-DOPA **S1** (500 mg, 2.54 mmol) in MeOH (6 mL), $SOCl_2$ (1 mL, 13.8 mmol) was added dropwise. The reaction mixture was stirred at room temperature for 16 h, evaporated to dryness and co-evaporated with toluene several times to remove excess $SOCl_2$.

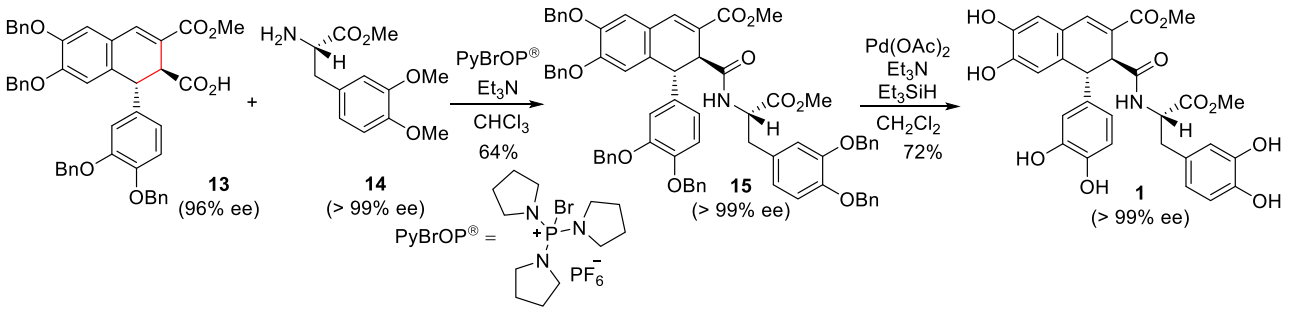
(b) The obtained compound **S2** was dissolved in THF (2.8 mL). A sat. $NaHCO_3$ aqueous solution (3.8 mL) and a solution of di-*tert*-butyl-dicarbonate (554 mg, 2.54 mmol) in THF (1.0 mL) were added to the mixture at 0 °C, followed by being stirring at room temperature for 1 h and then evaporated to remove organic solvent. Water was added to the mixture, which was extracted with AcOEt (ca. 10 mL x 5). The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. Compound **S3** was obtained as a colorless solid (709 mg, 90%).

(c) Compound **S3** was dissolved in DMF (2.2 mL), then K_2CO_3 (98 mg, 0.709 mmol) was added to the solution at 0 °C, followed by being stirred at same temperature for 30 min. Then MeI (60 μL, 0.709 mmol) was added and the solution was stirred at same temperature at 3 h. After the reaction was completed, the reaction was quenched with sat. NH_4Cl aqueous solution (5 mL). Water was added to the mixture, which was extracted with AcOEt (ca. 5 mL x 5). The organic layer was washed with

brine, dried over Na_2SO_4, and concentrated. The obtained crude oil was purified by purified by column chromatography (SiO_2, hexane/AcOEt = 1/1) to give the product **S4** (200 mg, 90%).

(d) To a solution of **S4** (102 mg, 0.203 mmol) in CH_2Cl_2 (1.0 mL), TFA (0.34 mL) was added and the mixture was stirred at ambient temperature for 1 h. Then, it was evaporated to dryness and triturated with Et_2O. The resulting precipitate was filtered under vacuo and dried to afford DOPA segment **14** (74 mg, 94%).

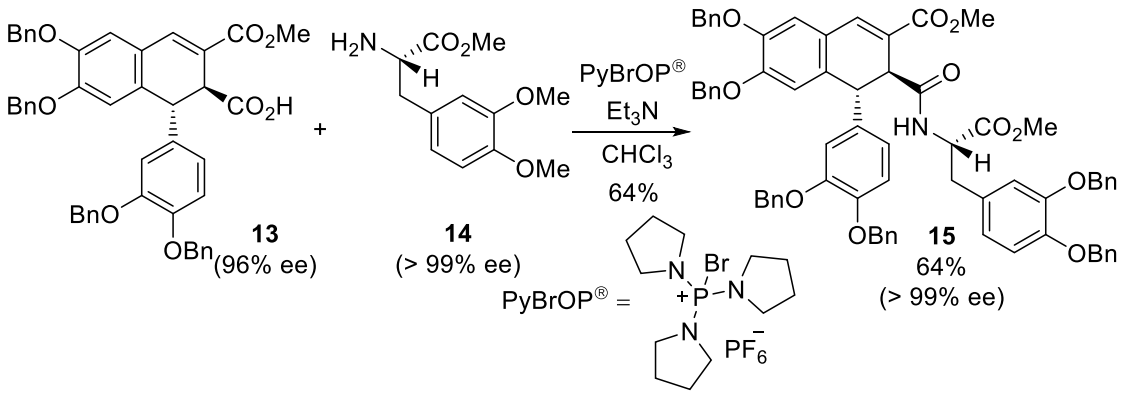
Enantioselective synthesis of lignan amide 1.



Following Magoulas's report[a], lignan amide **1** was prepared from enantioenriched dihydronaphthalene segment **13** and amine **14** in 2 steps.

[a] G. Magoulas, A. Rigopoulos, Z. Piperigkou, C. Gialeli, N. Karamanos, P. Takis, A. Troganis, A. Chrissanthopoulos, G. Maroulis, D. Papaioannou, *Bioorganic Chemistry*, **2016**, *66*, 132.

Methyl (1*R*,2*S*)-6,7-bis(benzyloxy)-1-(3,4-bis(benzyloxy)phenyl)-2-(((*S*)-3-(3,4-bis(benzyloxy)phenyl)-1-methoxy-1-oxopropan-2-yl)carbamoyl)-1,2-dihydronaphthalene-3-carboxylate (15)



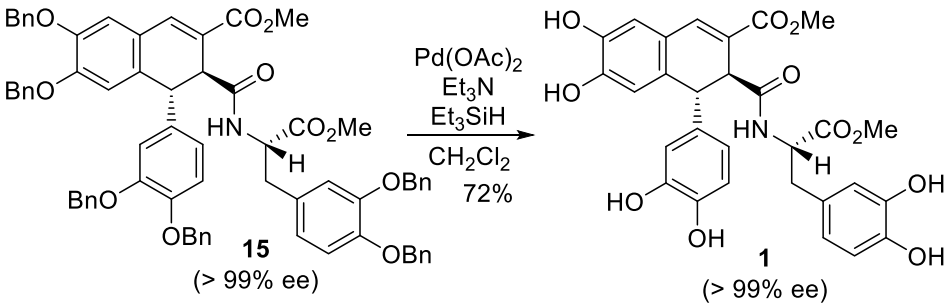
To an ice-cold solution of amine **14** (36 mg, 92 μmol), dihydronaphthalene **15** (52 mg, 71 μmol) and Et_3N (40 μL, 0.28 mmol) in $CHCl_3$ (0.5 mL), PyBrOP (53 mg, 0.11 mmol) was added. The mixture was stirred at 0°C for 10 min and then at ambient temperature for additional 30 min. Then, the reaction mixture was diluted with $CHCl_3$, washed twice with water, dried over Na_2SO_4 and evaporated. The obtained crude oil was purified by column chromatography (SiO_2, hexane/AcOEt = 3/1) to give the product **15** (50 mg, 64%).

Product **15**: colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (s, 1H), 7.50 – 7.24 (m, 30H), 6.89 (d, *J* = 8.2 Hz, 1H), 6.88(s, 1H), 6.77-6.73 (m, 3H), 6.68 (d, *J* = 7.9 Hz, 1H), 6.59 (dd, *J* = 8.2, 1.9 Hz, 1H), 6.51 (dd, *J* = 8.3, 2.0 Hz, 1H), 6.48 (d, *J* = 2.0 Hz, 1H), 5.19 – 4.96 (m, 12H), 4.72-4.67 (m, 1H), 4.56 (s, 1H), 3.75 (d, *J* = 1.5 Hz, 1H), 3.70 (s, 3H), 3.51 (s, 3H), 3.04 – 2.93 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.4, 170.9, 167.5, 151.4, 148.9, 148.3, 147.9, 147.6, 147.5, 138.7, 137.3, 137.2, 137.1, 137.0, 136.4, 136.2, 132.1, 129.2, 128.4, 128.3, 128.2, 127.8, 127.7, 127.7, 127.6, 127.5, 127.3, 127.2, 127.2, 127.1, 127.1, 123.5, 122.1, 121.4, 120.2, 115.9, 115.6, 115.0, 114.6, 114.50, 71.4, 71.2, 71.1, 71.1, 70.9, 70.6, 53.2, 52.0, 51.9, 48.2, 44.7, 37.2; IR (NaCl,neat): 3032, 2949, 1737, 1693, 1504, 1238, 1136, 1018, 734, 696 cm^{-1}; HRMS (APCI) calcd for $C_{71}H_{63}O_{11}N$ $(M+H)^+$ 1106.4474, found 1106.4897.

NMR-spectral data of synthesized **15** was consistent with reported data [a].

[a] G. Magoulas, A. Rigopoulos, Z. Piperigkou, C. Gialeli, N. Karamanos, P. Takis, A. Troganis, A. Chrissanthopoulos, G. Maroulis, D. Papaioannou, *Bioorganic Chemistry*, **2016**, *66*, 132.

Lignanamide 1.



To a solution of $Pd(OAc)_2$ (21 mg, 95 μmol) in CH_2Cl_2 (0.5 mL) Et_3N (13 μL, 95 μmol) was added and the mixture was stirred for 10 min. Then, a solution of **14** (44 mg, 40 μmol) in CH_2Cl_2 (0.9 mL) was added dropwise over 30 min. The resulting mixture was stirred for 10 min followed by the dropwise addition of Et_3SiH (0.15 mL, 0.95 mmol) over 1 h. Finally, the reaction was stirred at ambient temperature overnight. Addition of MeOH followed by filtration and evaporation of the filtrate gave an oily residue which was diluted AcOEt, washed twice with an aqueous solution 5% citric acid and once with water, dried over Na_2SO_4 and evaporated to dryness. The obtained crude oil was purified by column chromatography (SiO_2, $CHCl_3$/MeOH = 4/1) to give the lignan amide **1** (17 mg, 72%).

Lignan amide **1**: yellow solid; ^{1}H NMR (400 MHz, *d*$_4$-MeOH) δ 7.59 (s, 1H), 6.79 (s, 1H), 6.68 (d, *J* = 8.0 Hz, 1H), 6.61 (d, *J* = 8.0 Hz, 1H), 6.51 (d, *J* = 2.0 Hz, 1H), 6.44 (s, 1H), 6.40 – 6.32 (m, 3H), 4.48 (dd, *J* = 7.6, 5.7 Hz, 1H), 4.06 (d, *J* = 2.8 Hz, 1H), 3.69 (s, 3H), 3.68 (d, *J* = 3.0 Hz, 1H), 3.56 (s, 3H), 2.88 – 2.84 (m, 1H), 2.76 – 2.71 (m, 1H); ^{13}C NMR (101 MHz, MeOD) δ 173.0, 171.8, 167.6, 147.9, 145.0, 144.6, 144.1, 143.9, 143.6, 139.7, 135.2, 130.4, 127.6, 123.2, 121.0, 120.3, 118.6, 115.9, 115.9, 115.7, 115.0, 114.8, 114.4, 53.5, 51.2, 51.0, 49.3, 46.2, 36.3; IR (NaCl, neat): 3371, 2953, 1726,

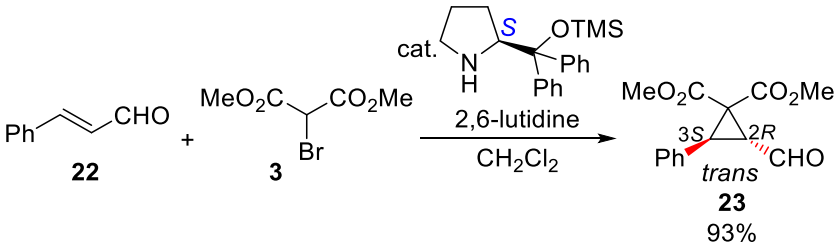
1681, 1651, 1610, 1585, 1517, 1438, 1367, 1261, 1197 cm^{-1}; HRMS (APCI) calcd for $C_{29}H_{26}O_{11}N$ $(M-H)^+$ 564.1500, found 564.1357.

NMR-spectral data of synthesized **1** was consistent with reported data of the lignan amide[a].

[a] G. Magoulas, A. Rigopoulos, Z. Piperigkou, C. Gialeli, N. Karamanos, P. Takis, A. Troganis, A. Chrissanthopoulos, G. Maroulis, D. Papaioannou, *Bioorganic Chemistry*, **2016**, *66*, 132.

2.3.2. Synthesis of *cis*- or *trans*-cyclopropylcarbinol and mechanistic support for the ring-opening cyclization.

Dimethyl (2*R*, 3*S*)-2-formyl-3-phenylcyclopropane-1,1-dicarboxylate (23)



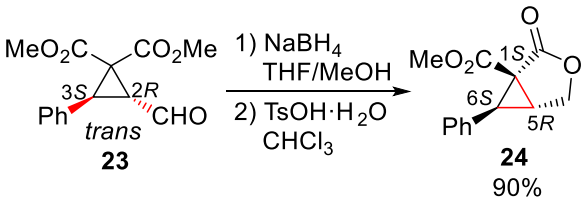
(Known compound) Following Wang's report,[a] we synthesized cyclopropane **23** using cinnamaldehyde **22**, dimethyl bromomalonate **3** and (*S*)-Hayashi-Jørgensen catalyst. Procedure and characterization were described in detail in Wang's report: [a] H. Xie, L. Zu, H. Li, J. Wang, W. Wang, *J. Am. Chem. Soc.* **2007**, *129*, 10886.

A solution of (*S*)-Hayashi-Jørgensen catalyst (1.71 g, 5.25 mmol, 0.15 equiv.) in CH_2Cl_2 (5 mL) was added to a solution of *trans*-cinnamaldehyde **22** (4.63 g, 35.0 mmol) in CH_2Cl_2 (130 ml) at 0 ˚C under Ar atmosphere, additionally, a solution of dimethyl bromomalonate **3** (7.39 g, 35.0 mmol) in CH_2Cl_2 (5 ml) and 2,6-lutidine (4.48 mL, 38.5 mmol, 1.1 equiv.) was added to the reaction mixture at the same temperature, followed by being stirred at 0˚C for 3 days. Then, the reaction was quenched with 1M-HCl aqueous solution (10 mL). Water (200 ml) was added to the mixture, which was extracted with

$CHCl_3$ (50 mL x 3). The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The obtained crude oil was purified by column chromatography (SiO_2, hexane/AcOEt = 4/1) to give the cyclopropane **23** (8.58 g, 93%).

Cyclopropane 23: yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.50 (d, *J* = 4.5 Hz, 1H), 7.34 – 7.26 (m, 3H), 7.24 – 7.22 (m, 2H), 3.83 (s, 3H), 3.83 (d, *J* = 7.5 Hz, 1H), 3.47 (s, 3H), 3.40 (dd, *J* = 7.5, 4.5 Hz, 1H).

(1*S*, 5*R*, 6*S*)-1-methoxycarbonyl-6-phenyl-3-oxabicyclo[3.1.0]hexan-2-one (24)



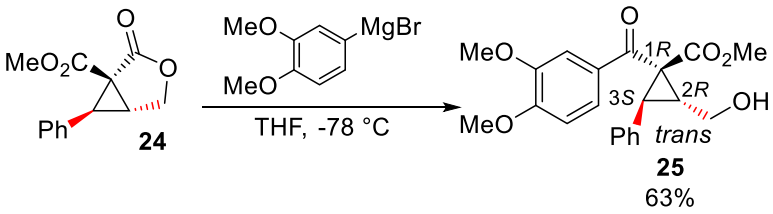
(Known compound) Procedure and characterization were described in detail in supporting information of the previous literature: [a] Ito, J.; Sakuma, D.; Nishii, Y. *Chem. Lett*., **2015**, *44*, 297 (open access). [b] S. Takada, K. Iwata, T. Yubune, Y. Nishii, *Tetrahedron Lett*. **2016**, *57*, 2422. [c] S. Takada, T. Saito, K. Iwata, Y. Nishii, *Asian J. Org. Chem*. 2016, 5, 1225.

$NaBH_4$ (85 mg, 2.25 mmol, 0.35 equiv.) was added to a solution of cyclopropane **23** (1.68 g, 6.42 mmol) in THF/MeOH (THF: 13 mL; MeOH: 2 mL) at 0 °C under an Ar atmosphere followed by being stirred for 15 min. Then, the reaction was quenched with sat. NH_4Cl aqueous solution (10 mL). Water (20 mL) was added to the mixture, which was extracted with AcOEt (ca. 10 mL x 5). The organic layer was washed with brine, dried (Na_2SO_4), and concentrated. The obtained crude oil was resolved in $CHCl_3$ (64 mL), then *p*-TsOH·H_2O (122 mg, 0.642 mmol, 0.1 equiv.) was added to the solution, followed by being stirred at 45°C for 60 min. Then, the reaction was quenched with sat. $NaHCO_3$ aqueous solution (10 mL). Water (30 mL) was added to the mixture, which was extracted with $CHCl_3$ (ca. 20 mL x3). The organic layer was washed with brine, dried (Na_2SO_4), and concentrated. The

obtained crude oil was purified by column chromatography (SiO_2, hexane/AcOEt = 2/1) to give the product **24** (1.34 g, 90%).

Product **24**: colorless solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.21 (m, 5H), 4.50 (dd, *J* = 9.4, 4.8 Hz, 1H), 4.37 (d, *J* = 9.4 Hz, 1H), 3.51 (s, 3H), 3.31 (t, *J* = 5.2 Hz, 1H), 2.92 (d, *J* = 5.6 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.1, 164.1, 131.9, 128.7, 128.6, 128.3, 67.4, 52.7, 37.9, 37.7, 27.8.

Methyl (1*R*, 2*R*, 3*S*)-1-(3,4-dimethoxybenzoyl)-2-(hydroxymethyl) -3-phenylcyclopropane-1-carboxylate (25)



Following our previous report,[a,b] compound **25** was prepared from bicyclolactone **24** using 1,2-dimethoxyphenylmagnesiumbromide.

[a] Ito, J.; Sakuma, D.; Nishii, Y. *Chem. Lett*., **2015**, *44*, 297 (open access). [b] T. Saito, Y. Shimizu, Y. Araki, Y. Ohgami, Y. Kitazawa, Y. Nishii, *Eur. J. Org. Chem.* **2022**, e202101213.

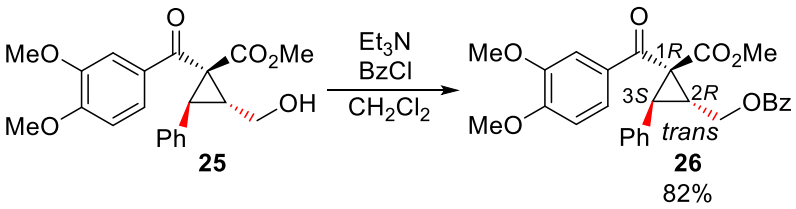
An oven-dried two-neckedround-bottomed flask was charged with Mg turnings (73 mg, 3.00 mmol), under Ar atmosphere. 4-bromo-1,2-dimethoxybenzene (163 mg, 0.750 mmol) THF solution (1.5 M) was added into the activated magnesium at room temperature. To this mixture, 1,2-dibromoethane (1 drops) was added at same temperature. After the reaction was initiated, 4-bromo-1,2-dimethoxybenzene (488 mg, 2.25 mmol) THF solution (0.8 M) was added into the activated magnesium, stirring was continued until the complete consumption of Mg at same temperature. Mg was dissolved, then, THF was added to dilute the Grignard reagent to 0.5 M. This Grignard reagent THF solution (3.75 mL, 3.00 mmol) was added slowly to a solution of lactone **24** (348 mg, 1.50 mmol)

in THF (5.3 mL) at -78 °C, followed by being stirred at same temperature for 10 min. After the reaction was completed, quenched with sat. NH_4Cl aqueous solution (10 mL). Water (10 mL) was added to the mixture, which was extracted with AcOEt (10 mL x 5). The organic layer was washed with brine, dried (Na_2SO_4) and concentrated. The obtained crude oil was purified by column chromatography (SiO_2, hexane/AcOEt = 2/1) to give the product **25** (350 mg, 63%).

Product **25**: light-brown amorphous solid; ^1H NMR (400 MHz, $CDCl_3$) δ 7.64 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.57 (d, *J* = 2.0 Hz, 1H), 7.36 – 7.19 (m, 5H), 6.89 (d, *J* = 8.4 Hz, 1H), 3.94 (s, 3H), 3.93 (s, 3H), 3.90 – 3.78 (m, 1H), 3.53 – 3.40 (m, 1H), 3.35 (d, *J* = 7.9 Hz, 1H), 3.29 (s, 3H), 3.11 (td, *J* = 8.2, 5.7 Hz, 1H), 1.99 (brs, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 191.9, 168.8, 153.7, 149.2, 134.5, 130.3, 129.0, 128.3, 127.4, 123.6, 110.9, 110.3, 61.2, 56.2, 56.1, 52.5, 46.7, 33.7, 33.6; IR (KBr, neat): 3513, 2953, 2841, 1732, 1668, 1595, 1514, 1273, 1022 cm^{-1}; HRMS (ESI) calcd for $C_{21}H_{22}O_6$ $(M+Na)^+$ 393.1309, found 393.1289.

Methyl (1*S*, 2*S*, 3*R*)-2-(benzoyloxymethyl)-3-phenyl

-1-[(3,4-dimethoxyphenyl)carbonyl]cyclopropanecarboxylate (26)



To a CH_2Cl_2 (2.0 mL) solution of the alcohol **25** (250 mg, 0.670 mmol) was added triethylamine (97 µL, 0.880 mmol, 1.3 equiv.) at 0 °C, then dropped benzoyl chloride (120 µL, 0.880 mmol, 1.3 equiv.), followed by being stirred for 4 h at same temperature. The reaction mixture was quenched with water, which was extracted with $CHCl_3$. The organic layer was washed with brine, dried (Na_2SO_4) and concentrated. The obtain crude was purified by column chromatography (SiO_2, Hexane/AcOEt = 4/1)

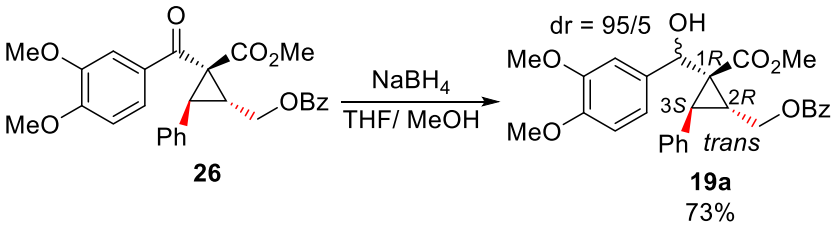
to give the product **26** (260 mg, 82%).

Product **26**: colorless amorphous solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (dd, *J* = 8.3, 1.3 Hz, 2H), 7.58 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.54 – 7.49 (m, 2H), 7.37 – 7.22 (m, 8H), 6.71 (d, *J* = 8.4 Hz, 1H), 4.71 (dd, *J* = 12.1, 5.7 Hz, 1H), 4.04 (dd, *J* = 12.1, 9.1 Hz, 1H), 3.86 (s, 3H), 3.85 (s, 3H), 3.62 (d, *J* = 7.7 Hz, 1H), 3.35 (ddd, *J* = 9.0, 7.7, 5.7 Hz, 1H), 3.27 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.7, 168.7, 166.0, 153.4, 149.1, 134.3, 133.1, 130.2, 129.8, 129.7, 129.0, 128.4, 128.3, 127.5, 123.5, 110.7, 110.1, 62.4, 56.1, 55.9, 52.6, 46.7, 33.3, 30.1; IR (KBr, neat): 3028, 2953, 2841, 1732, 1714, 1666, 1595, 1514, 1289, 1024 cm^{-1}; HRMS (ESI) calcd for $C_{28}H_{26}O_7$ $(M+Na)^+$ 497.1571, found 497.1537.

Methyl (1*R*, 2*R*, *3S*)-2-(benzoyloxymethyl)-3-phenyl

-1-[(*R*) and (*S*)-1-hydroxy-1-(3,4-dimethoxyphenyl)methyl]cyclopropanecarboxylate

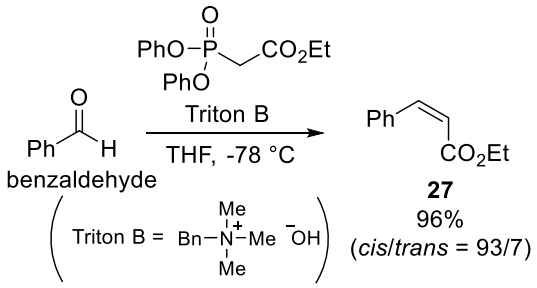
(*trans*-cyclopropylcarbinol) (19a)



$NaBH_4$ (87 mg, 2.30 mmol) was added to a solution of cyclopropane **26** (220 mg, 0.460 mmol) in THF/MeOH (THF = 2.0 mL, MeOH = 2.0 mL) at 0 °C under an Ar atmosphere, followed by being stirred at room temperature for 20 min. Then, the reaction was quenched with sat. NH_4Cl aqueous solution (10 mL). Water (5 mL) was added to the mixture, which was extracted with AcOEt (ca. 10 mL x 5). The organic layer was washed with brine, dried (Na_2SO_4), and concentrated. The obtained crude oil was purified by column chromatography (SiO_2, hexane/AcOEt = 4/1) to give the cyclopropylcarbinol **19a** (159 mg, 73%, dr = 95/5). Diastereomeric ratio (dr) was estimated by the measurement of ^{1}H NMR spectral data.

Cyclopropylcarbinol **19a**: (95/5 mixture of diastereomers) light-yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) (Selected data for Major of **7**) δ 8.04 (dd, *J* = 8.3, 1.2 Hz, 2H), 7.60 – 7.52 (m, 1H), 7.43 (t, *J* = 7.7 Hz, 2H), 7.30 – 7.17 (m, 6H), 7.12 (d, *J* = 1.9 Hz, 1H), 7.05 (dd, *J* = 8.3, 1.8 Hz, 1H), 6.78 (d, *J* = 8.3 Hz, 1H), 5.22 (d, *J* = 7.2 Hz, 1H), 4.79 (dd, *J* = 11.9, 7.1 Hz, 1H), 4.73 (dd, *J* = 11.9, 7.3 Hz, 1H), 3.86 (s, 3H), 3.83 (s, 3H), 3.42 (d, *J* = 7.2 Hz, 1H), 3.25 (s, 3H), 2.97 (d, *J* = 7.6 Hz, 1H), 2.90 (q, *J* = 7.3 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.0, 166.7, 148.8, 148.4, 135.9, 135.0, 133.2, 130.1, 129.8, 128.78, 128.5, 128.2, 127.0, 118.6, 110.8, 110.2, 72.6, 63.5, 55.9, 55.9, 51.7, 42.0, 34.1, 28.2; IR (NaCl, neat) 3498, 3024, 2951, 2835, 1714, 1697, 1602, 1514, 1269, 1026 cm^{-1}; HRMS (ESI) calcd for $C_{28}H_{28}O_7$ $(M+Na)^+$ 499.1727, found 499.1683.

Ethyl (*Z*)-cinnamate (27)



(Known compound) Following Ando's report,[a,b] we synthesized ethyl (*Z*)-cinnamate **27**.

A solution of ethyl diphenylphosphonoacetate (Horner-Emmons reagent) (10.9 g, 34.1 mmol) in THF (340 mL) was treated with Triton B (40% in methanol) (18.6 mL, 40.9 mmol, 1.2 equiv.) at -78 °C for 15 min. Benzaldehyde (3.44 mL, 34.1 mmol) was then added, and the resulting mixture was stirred at -78 °C. The reaction was quenched with sat. NH_4Cl, and the mixture was extracted with AcOEt (30 mL × 5). The combined extracts were washed with water (100 mL × 2) followed by brine, dried (Na_2SO_4), and concentrated. After determining the *cis*/*trans* ratio of the crude mixture by 400 MHz ^{1}H NMR, ethyl (*Z*)-cinnamate **27** was isolated by flash chromatography (SiO_2, hexane/AcOEt = 20/1) as a colorless oil (5.58 g, 93%, *cis*/*trans* = 93/7). The *cis*/*trans* ratio did not change by flash

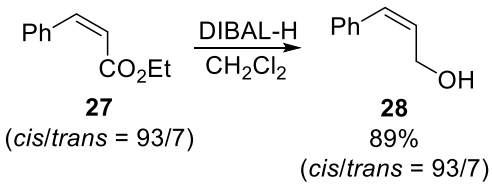
chromatography.

Ethyl (*Z*)-cinnamate **27**: (*cis*/*trans* = 93/7) colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) (Selected data for ethyl (*Z*)-cinnamate) δ 7.62 – 7.54 (m, 2H), 7.42 – 7.28 (m, 3H), 6.95 (d, *J* = 12.6 Hz, 1H), 5.95 (d, *J* = 12.6 Hz, 1H), 4.17 (q, *J* = 7.1 Hz, 2H), 1.24 (t, *J* = 7.1 Hz, 3H).

^{1}H NMR spectral data of **27** was consistent with reported data[a].

[a] K. Ando, *J. Org. Chem.* **1997,** *62,* 1934. [b] K. Ando, *J. Org. Chem.* **1998,** *63,* 8411.

(*Z*)-cinnamyl alcohol (28)



27 (*cis*/*trans* = 93/7)

28 89% (*cis*/*trans* = 93/7)

Following the reported preparation, we synthesized alcohol **28**[a].

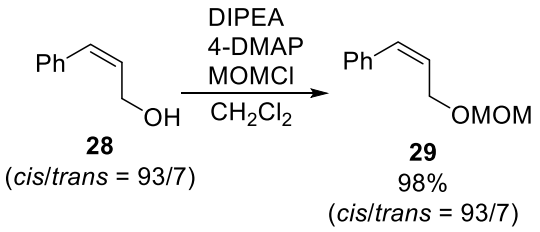
To a stirred solution of ethyl cinnamate **27** (5.76 g, 32.7 mmol) in anhydrous CH_2Cl_2 (68 mL) was added dropwise diisobutylaluminum hydride (1.0 M in hexane, 71.9 mL, 71.9 mmol, 2.2 equiv) under argon at −78 °C. The mixture was stirred at −78 °C for 15 min, and the reaction was quenched with 1M-HCl aqueous solution. The resulting mixture was allowed to warm to ambient temperature and stirred for additional 30 min. The aqueous layers were extracted with $CHCl_3$ (50 mL · 3), and the combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The obtained crude oil was purified by column chromatography (SiO_2, hexane/AcOEt = 4/1) to give the (*Z*)-cinnamyl alcohol **28** (3.90 g, 89%, *cis*/*trans* = 93/7). The *cis*/*trans* ratio did not change by column chromatography.

(*Z*)-cinnamyl alcohol **28**: (*cis*/*trans* = 93/7) colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) [Selected data for (*Z*)-cinnamyl alcohol] δ 7.41 – 7.16 (m, 5H), 6.58 (d, *J* = 11.7 Hz, 1H), 5.88 (dt, *J* = 11.8, 6.4 Hz, 1H), 4.44 (t, *J* = 4.9 Hz, 2H), 1.49 (t, *J* = 5.0 Hz, 1H).

^{1}H NMR spectral data of **28** was consistent with reported data[a].

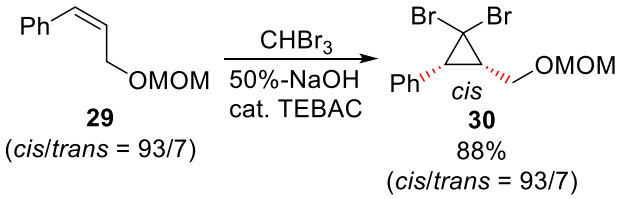
[a] D. J. Vyas, M. Oestreich, *Chem. Commun*., **2010**, *46*, 568.

cis-cinnamyl(methoxymethyl)ether (29)



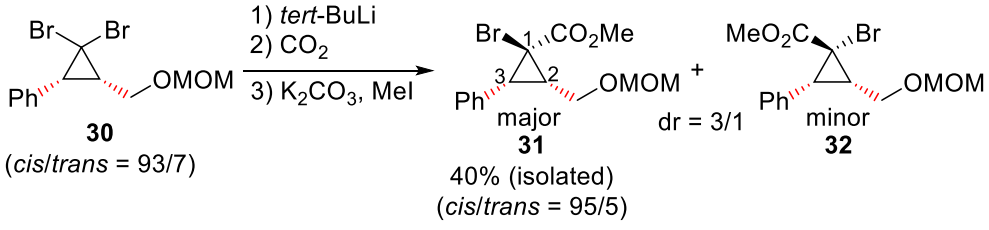
To a stirred solution of *cis*-cinnamyl alcohol **28** (3.83 g, 28.6 mmol), diisopropylethylamine (14.6 mL, 85.8 mmol, 3.0 equiv.), and 4-dimethylaminopyridine (349 mg, 2.86 mmol, 0.1 equiv.) in CH_2Cl_2 (57 mL) was added chloromethyl methyl ether (3.22 mL, 42.9 mmol, 1.5 equiv.) at 0 ºC. After the reaction mixture was stirred at room temperature for 15 h, water (100 mL) was added to the reaction mixture. The aqueous layer was extracted with Et_2O (30 mL × 5) and the combined organic layer was washed with brine. The extract was dried (Na_2SO_4), filtered, and concentrated under reduced pressure afforded. The residue was purified by column chromatography (hexane/AcOEt=20/1) to afford **29** (5.00 g, 98%, *cis*/*trans* = 93/7) as a colorless liquid. The *cis*/*trans* ratio did not change by column chromatography. Product **29**: (*cis*/*trans* = 93/7) colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) (Selected data for *cis*-isomer) δ 7.37 – 7.31 (m, 2H), 7.28 – 7.19 (m, 4H), 6.61 (d, *J* = 11.8 Hz, 1H), 5.90 – 5.82 (m, 1H), 4.67 (s, 2H), 4.35 (dd, *J* = 6.3, 1.8 Hz, 2H), 3.37 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 136.7, 131.7, 128.9, 128.7, 128.4, 127.3, 96.3, 64.6, 55.5; IR (NaCl, neat): 3024, 2932, 2884, 2822, 1601, 1576, 1495, 1447, 1400, 1211, 1150, 1105, 1065, 1038, 988, 957, 918, 773, 700 cm^{-1}; HRMS (ESI) calcd for $C_{54}H_{46}O_9$ $(M+NaKH)^+$ 241.0601, found 241.0580.

***cis*-1,1-dibromo-2-[(methoxymethoxy)methyl]-3-phenylcyclopropane (30)**



50%-NaOH aqueous solution (NaOH: 8.24 g, 206 mmol; water: 8.24 mL) was added dropwise to a solution of compound **29** (3.66 g, 20.6 mmol) and triethylbenzylammoniumchiloride (TEBAC) (468 mg, 2.06 mmol) in $CHBr_3$ (20 mL, 206 mmol) at 40 °C with vigorous stirring, and followed by being stirred at 60 °C for 24 h. The reaction mixture was diluted with water (100 ml), which was filtered through celite. The aqueous layer was extracted with Et_2O (30 mL × 5) and the combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (hexane/AcOEt=20/1) to afford dibromocyclopropane **30** (6.34 g, 88%, *cis*/*trans* = 93/7) as a light-yellow liquid. The *cis*/*trans* ratio did not change by column chromatography. Dibromocyclopropane **30**: (*cis*/*trans* = 93/7) light-yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$) (Selected data for *cis*-isomer **30**) δ 7.36 – 7.24 (m, 5H), 4.69 (d, *J* = 1.6 Hz, 2H), 3.67 (dd, *J* = 10.9, 6.7 Hz, 1H), 3.55 (dd, *J* = 10.9, 7.5 Hz, 1H), 3.42 (s, 3H), 3.08 (d, *J* = 11.1 Hz, 1H), 2.43 – 2.33 (m, 1H); IR (NaCl, neat): 2990, 2945, 2930, 2884, 1497, 1447, 1396, 1213, 1153, 1107, 1045, 918, 743, 698 cm^{-1}.

Methyl (1*R, 2*S**, 3*R**)-1-bromo-2-[(methoxymethoxy)methyl]-3-phenylcyclopropane -1-carboxylate (31)**

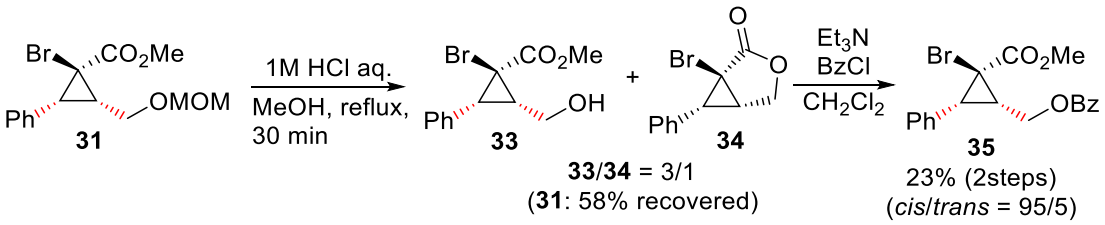


A pentane solution of *tert*-BuLi (1.6 M, 2.25 mL, 3.60 mmol, 1.2 equiv.) was added dropwise to a solution of dibromocyclopropane **30** (1.05 g, 3.00 mmol) in THF (15 ml) at -100 °C under an Ar atmosphere, followed by being stirred at the same temperature for 30 min. Then, CO_2 gas was added to the reaction mixture at -100 °C, followed by being stirred for 1 h. The reaction mixture was allowed to warm to rt, then water (20 ml) was added to the mixture, which was extracted with Et_2O (ca. 10 mL × 5). To the aqueous layer was added 1M-HCl aqueous solution at 0 °C until the carboxylic acid was sufficiently formed. The mixture was extracted with AcOEt (10 mL × 5) and the combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The obtained oil was dissolved in DMF. To a DMF- solution (7.5 mL) of the obtained carboxylic acid (800 mg, 2.54 mmol), K_2CO_3 (527 mg, 3.81 mmol) was added, and then, MeI (0.24 mL, 3.86 mmol) was added, followed by being stirred at room temperature for 2h. Water was added to the mixture, which was extracted with Et_2O. The organic layer was washed with brine, dried (Na_2SO_4) and concentrated. The obtained crude oil was purified by column chromatography (SiO_2, hexane/AcOEt = 6/1) to give the product **31** (398 mg, 40%, *cis*/*trans* = 95/5). Only the product **31** was isolated and the *cis*/*trans* ratio slightly changed to 95/5 by column chromatography.

Product **31**: (*cis*/*trans* = 95/5) light-yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) (Selected data for *cis*-isomer **31**) δ 7.33 – 7.17 (m, 5H), 4.65 (s, 2H), 3.95 (dd, *J* = 11.0, 6.8 Hz, 1H), 3.90 (dd, *J* = 11.0, 7.6 Hz, 1H) 3.62 (s, 3H), 3.38 (s, 3H), 3.29 (d, *J* = 10.6 Hz, 1H), 2.48 (dt, *J* = 10.7, 7.2 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.4, 132.8, 129.4, 128.5, 127.5, 96.9, 63.5, 55.5, 53.1, 40.1, 36.4, 32.1; IR (NaCl, neat): 2993, 2949, 2886, 1732, 1498, 1435, 1314, 1223, 1152, 1105, 1049, 920, 800, 731, 700 cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{17}BrO_4$ $(M+K)^+$ 426.9942, found 426.9910.

Minor product **32**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.16 (m, 5H), 4.50 (d, *J* = 6.6 Hz, 1H), 4.43 (d, *J* = 6.6 Hz, 1H), 3.73 (s, 3H), 3.41 – 3.33 (m, 1H), 3.24 (dd, *J* = 10.8, 6.6 Hz, 1H), 3.16 (s, 3H), 2.94 – 2.84 (m, 1H), 2.16 – 2.05 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.5, 135.5, 129.0, 128.4, 126.9, 96.3, 65.7, 55.1, 52.0, 30.6, 27.7, 23.7.

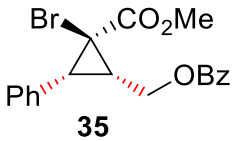
Synthesis of methyl (1*S, 2*R**, 3*R**)-1-bromo-2-benzolyoxymethyl-3-phenylcyclopropane carboxylate (35).**



To a solution of cyclopropane **31** (555 mg, 1.69 mmol) in MeOH (20 mL) was added 1.0 M HCl aqueous solution (2.3 mL) at 0 °C. followed by being stirred at reflux temperature for 30 min. Then the mixture was cooled to 0 °C and quenched with sat. $NaHCO_3$ aqueous solution (10 mL). Water was added to the mixture, which was extracted with Et_2O (5 mL × 5). The organic layer was washed with brine, dried (Na_2SO_4) and concentrated. Unreacted compound **31** was removed by column chromatography (SiO_2, hexane/AcOEt = 4/1) of obtained crude oil to give the mixture of alcohol **33** and lactone **34** (195 mg, **33**/**34** = 3/1). The compound **31** was recovered 58% (323 mg). The obtained mixture [195 mg, (alcohol **33**: 77 wt%, 0.526 mmol)] was resolved in CH_2Cl_2 (1.6 mL), then triethylamine (77 µL, 0.552 mmol, 1.05 equiv.) and benzoyl chloride (64 µL, 0.552 mmol, 1.05 equiv.) was added to the solution at 0 °C, followed by being stirred at same temperature for 2 h. Then, water (3 mL) was added to the reaction, which was extracted with $CHCl_3$ (ca. 5 mL x 3). The organic layer was washed with brine, dried (Na_2SO_4), and concentrated. The obtained crude oil was purified by column chromatography (SiO_2, hexane/AcOEt = 50/1) to give the product **35** (151 mg, 23%, *cis*/*trans* = 95/5). The *cis*/*trans* ratio did not change by column chromatography.

Mixture of alcohol **33** and lactone **34** (**33**/**34** = 3/1): ^{1}H NMR (400MHz, $CDCl_3$) (Selected data for alcohol **33**) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.18 (m, 5H), 4.01 (ddd, *J* = 12.2, 9.0, 6.6 Hz, 1H), 3.85 – 3.76 (m, 1H), 3.73 (s, 3H), 3.22 (d, *J* = 10.6 Hz, 1H), 2.42 (ddd, *J* = 10.6, 9.2, 6.7 Hz, 1H), 2.29 (dd, *J* = 9.1, 4.1 Hz, 1H); (Selected data for lactone **34**) δ 7.39 – 7.27 (m, 5H), 4.51 (dd, *J* = 10.1, 5.1 Hz, 1H), 4.06 (d, *J* = 10.1 Hz, 1H), 3.30 (d, *J* = 9.0 Hz, 1H), 2.86 (dd, *J* = 9.0, 4.8 Hz, 1H).

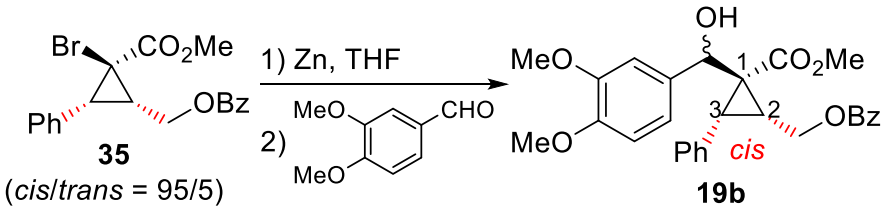
Methyl (1*R, 2*S**, 3*R**)-1-bromo-2-[(benzoyloxy)methyl]-3-phenylcyclopropane -1-carboxylate (35)**



35
(*cis*/*trans* = 95/5)

colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) (Selected data for *cis*-isomer) δ 8.11 – 8.04 (m, 2H), 7.62 – 7.54 (m, 1H), 7.47 (t, *J* = 7.7 Hz, 2H), 7.35 – 7.26 (m, 3H), 7.25 – 7.20 (m, 2H), 4.80 (dd, *J* = 12.0, 6.7 Hz, 1H), 4.65 (dd, *J* = 12.0, 8.0 Hz, 1H), 3.62 (s, 3H), 3.37 (d, *J* = 10.6 Hz, 1H), 2.63 (ddd, *J* = 10.5, 7.9, 6.8 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.3, 166.4, 133.3, 132.4, 130.1, 129.8, 129.3, 128.8, 128.6, 127.8, 60.8, 53.3, 40.1, 34.9, 32.1; IR (NaCl, neat): 3061, 3028, 2951, 1724, 1603, 1497, 1450, 1315, 1271, 1113, 1026, 962, 804, 712 cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{17}BrO_4$ $(M+K)^+$ 426.9942, found 426.9910.

Methyl (1*S, 2*R**, *3R**)-2-(benzoyloxymethyl)-3-phenyl -1-[*R** and *S**-1-hydroxy-1-(3,4-dimethoxyphenyl)methyl]cyclopropanecarboxylate (*cis*-cyclopropylcarbinol) (19b)**



35
(*cis*/*trans* = 95/5)

19b
54% (dr = 53/47)
(*cis*/*trans* = 95/5)

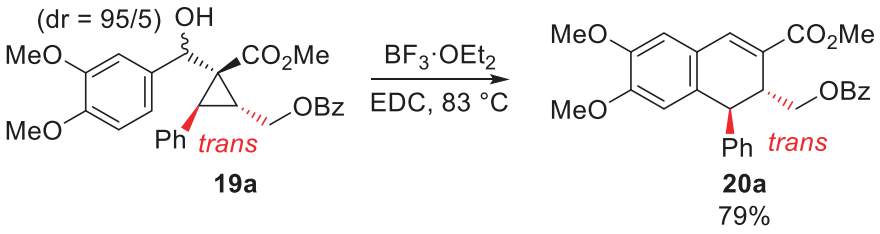
Following our previous report[a], we synthesized *cis*-cyclopropylcarbinol **19b**.

In order to activate the surface of Zn, a little amount of TMSCl (3 μL, 25 μmol, 6 mol%) was added to Zn (67 mg, 1.03 mmol, 2.5 equiv.) in THF (0.3 mL) at room temperature under Ar atmosphere, followed by being stirred at room temperature for 30 min. A solution of cyclopropane **35** (160 mg, 0.411 mmol, 1.3 equiv.) in THF (0.5 mL) was added to the mixture at room temperature, and being stirred at the same temperature for 30 min. A THF solution (0.5 ml) of 3,4-dimethoxybenzaldehyde (53 mg, 0.316 mmol, 1.0 equiv.) was added to the mixture at room temperature, followed by being stirred at reflux temperature for 2.5 h. The reaction mixture was quenched with 1M-HCl aqueous solution (3 mL). Water (10 mL) was added to the mixture, which was extracted with Et_2O (5 mL x 5). The organic layer was washed with brine, dried (Na2SO4), and concentrated. The obtained crude oil was purified by column chromatography (SiO_2, hexane/AcOEt = 4/1) to give cyclopropylcarbinol **19b** (80 mg, 53%, dr = 53/47). Diastereomeric ratio (dr) was estimated by the measurement of ^{1}H NMR spectral data.

Cyclopropylcarbinol **19b**: (53/47 mixture of diastereomers) colorless oil; ^{1}H NMR (400MHz, $CDCl_3$) (Selected data for major of **19b**) δ 8.04 – 7.99 (m, 2H), 7.58 (dd, *J* = 10.5, 4.4 Hz, 1H), 7.45 (t, *J* = 7.7 Hz, 2H), 7.32 – 7.27 (m, 2H), 7.24 (t, *J* = 5.9 Hz, 3H), 7.01 (dd, *J* = 5.7, 1.9 Hz, 2H), 6.81 (d, *J* = 8.8 Hz, 1H), 5.38 (s, 1H), 4.79 – 4.66 (m, 2H), 3.89 (s, 3H), 3.86 (s, 3H), 3.40 (s, 3H),3.04 (brs, 1H) , 3.03 (d, *J* = 9.7 Hz, 1H), 2.16 (dt, *J* = 9.6, 7.5 Hz, 1H); (Selected data for minor of **31**) δ 8.08 – 8.01 (m, 2H), 7.62 – 7.55 (m, 1H), 7.47 (t, *J* = 7.7 Hz, 2H), 7.36 – 7.23 (m, 7H), 7.14 (d, *J* = 1.9 Hz, 1H), 7.06 (dd, *J* = 8.3, 1.7 Hz, 1H), 6.72 (d, *J* = 8.3 Hz, 1H), 4.86 (dd, *J* = 11.8, 7.2 Hz, 1H), 4.77 (dd, *J* = 11.8, 7.7 Hz, 1H), 4.50 (d, *J* = 9.4 Hz, 1H), 4.04 (d, *J* = 9.6 Hz, 1H), 3.90 (s, 3H), 3.84 (s, 3H), 3.37 (s, 3H), 3.00 (d, *J* = 9.6 Hz, 1H), 2.21 (dt, *J* = 9.4, 7.5 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.3, 171.9, 166.6, 166.6, 149.0, 148.9, 148.8, 148.5, 134.6, 134.3, 134.0, 133.7, 133.2, 133.1, 130.3, 130.3, 129.7, 129.7, 129.6, 128.7, 128.5, 128.5, 127.3, 127.0, 119.3, 118.1, 110.9, 110.8, 110.3, 109.7, 78.5, 73.1, 61.9, 61.9, 56.0, 56.0, 55.9, 55.9, 51.7, 51.6, 38.7, 38.5, 33.7, 30.7, 28.2, 26.0; IR (NaCl, neat): 3501, 3022, 2951, 2835, 1715, 1602, 1516, 1450, 1271, 1236, 1142, 1026, 912, 808, 756, 714, 3065, 3032, 2949, 2868, 1958, 1877, 1813, 1721, 1668, 1593, 1514, 1454, 1427, 1381, 1267, 1024, 910, 854, 812, 737, 696 cm^{-1}; HRMS (ESI) calcd for $C_{28}H_{28}O_7$ $(M+Na)^+$ 499.1727, found 499.1682.

[a] D. Sakuma, K. Yamada, K. Sasazawa, Y. Nishii, *Chem. Lett*. **2015**, *44*, 818.

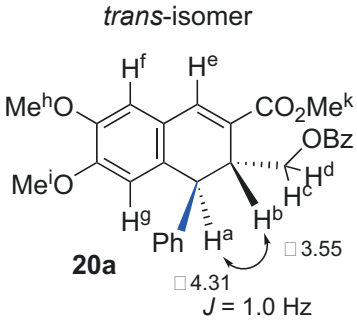
Ring-opening cyclization of *trans*-cyclopropylcarbinol 19a



Following our previous reports[a,b], we synthesized dihydronaphthalene **20a**.

$BF_3{\cdot}OEt_2$ (14 μL, 1.15 mmol, 1.1 equiv.) was added to a solution of *trans*-cyclopropylcarbinol **19a** (50 mg, 1.05 mmol) in 1,2-dichloroethane (EDC) (1.0 mL) at 83 °C, followed by being stirred at same temperature for 1 min. The reaction was quenched with H_2O (3 mL) at 0 °C, and the mixture was extracted with $CHCl_3$ (5 mL x 3). The combined organic layer was washed with brine (5 mL), dried over Na_2SO_4, and evaporated. The obtained crude oil was purified by column chromatography (SiO_2, hexane/AcOEt/ = 4/1) to give the dihydronaphthalene **20a** (38 mg, 79%).

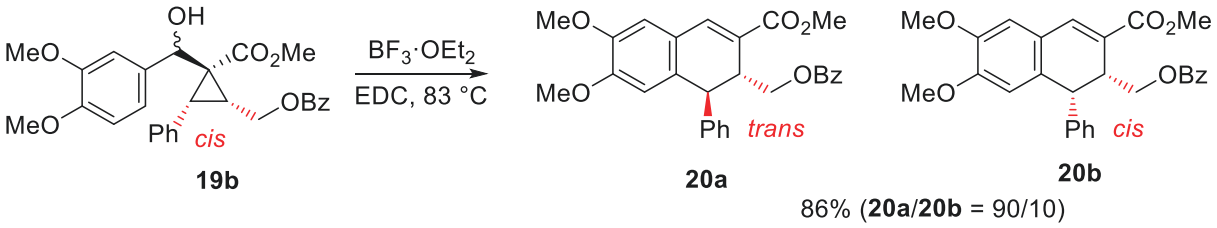
Product **20a**: colorless amorphous solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91-7.81 (m, 2H of Bz), 7.70 (s, 1H = H^e), 7.57-7.52 (m, 1H of Bz), 7.42-7.38 (m, 2H of Bz), 7.24-7.16 (m, 3H of Ph), 7.02-6.97 (m, 2H of Ph), 6.86 (s, 1H = H^f), 6.66 (s, 1H = H^g), 4.41 (dd, J = 10.8, 4.9 Hz, 1H = H^c), 4.33-4.29 (m, 1H = H^d), 4.31 (d, J = 1.0 Hz, 1H = H^a) 3.91 (s, 3H of OMe^h), 3.81 (s, 3H of OMe^i), 3.70 (s, 3H of OMe^k), 3.55 (ddd, J = 7.4, 4.9, 1.0 Hz, 1H = H^b); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.2, 166.6, 151.1, 148.3, 143.6, 138.6, 133.1, 130.2, 130.2, 129.7, 128.6, 128.4, 127.6, 126.7, 124.6, 123.8, 112.9, 111.9, 66.2, 56.2, 56.1, 51.9, 45.8, 41.3; IR (KBr, neat): 3003, 2949, 2835, 1716, 1602, 1516, 1273, 1240 cm^{-1}; HRMS (ESI) calcd for $C_{54}H_{46}O_9$ $(M+Na)^+$ 481.1622, found 481.1642.



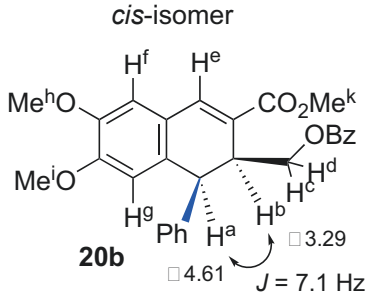
[a] J. Ito, D. Sakuma, Y. Nishii, *Chem. Lett*. **2015**, *44*, 297. [b] K. Sasazawa, S. Takada, T. Yubune,

N. Takaki, R. Ota, Y. Nishii, *Chem. Lett*. **2017**, *46*, 524.

Ring-opening cyclization of *cis*-cyclopropylcarbinol 19b

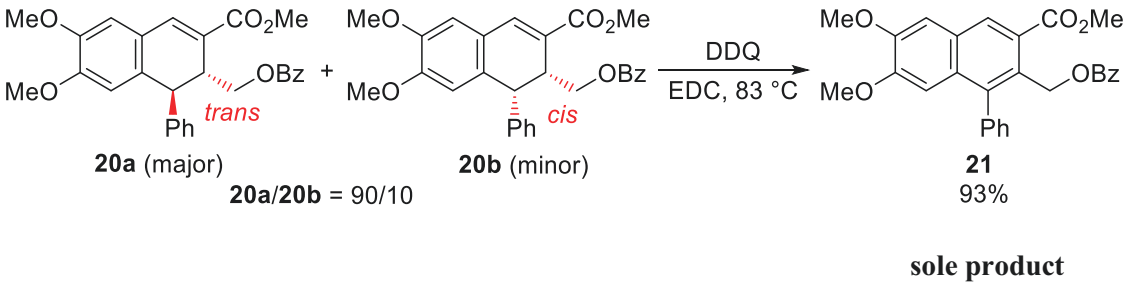


Following the procedure for the cyclization of **19a** to afford **20a**, the similar reaction using *cis*-isomer **19b** instead of **19a** furnished an inseparable mixture of *trans*-dihydronaphthalene **20a** and *cis*-dihydronaphthalene **20b** (**20a**/**20b** = 90/10) in 86 % yield. Selected data for **20b**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (s, 1H = H^e), 7.49-7.44 (m, 1H of Bz), 7.37-7.31 (m, 2H of Bz), 7.24-7.11 (m, 3H of Ph), (2H of Bz and 2H of Ph cannot be assigned due to the overlapping peaks of the other isomer.), 6.81 (s, 1H = H^f), 6.71 (s, 1H = H^g), 4.61 (d, *J* = 7.1 Hz, 1H = H^a), 4.47 (dd, *J* = 11.6, 3.1 Hz, 1H = H^c), 4.00, dd, *J* = 11.6, 4.5 Hz, 1H = H^d), 3.88 (s, 3H of OMe^h), 3.78 (s, 3H of OMe^i), 3.70 (s, 3H of OMe^k), 3.29 (ddd, *J* = 7.1, 4.5, 3.1 Hz, 1H = H^b).



Dehydrogenation of mixture of dihydronaphthalene 20a and 20b (20a/20b =90/10).

Methyl 3-[(benzoyloxy)methyl]-6,7-dimethoxy-4-phenyl-2-naphthoate (21)



Following our previous report,[a] we synthesized naphthalene **21**.

A solution of dihydronaphthalene **20a** and *cis*-isomer **20b** (**20a**/**20b** = 90/10) (30 mg, 65 μmol) in 1,2-dichloroethane (4.4 mL) and DDQ (37 mg, 0.164 mmol, 2.5 equiv.) was stirred at 83 ℃ under an argon atmosphere for 2.5 h. After cooled to room temperature, sat. $NaHCO_3$ aqueous solution (5 mL) was added to the reaction mixture, which was extracted with AcOEt (ca. 5 mL×5). The combined organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, hexane/AcOEt/ = 4/1) to afford naphthalene **21** (27 mg, 93%) as a single product.

Product **21**: colorless amorphous solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (s, 1H), 7.99 – 7.91 (m, 2H), 7.49 (dt, *J* = 22.0, 7.7 Hz, 4H), 7.39 (t, *J* = 7.7 Hz, 2H), 7.33 (dd, *J* = 7.7, 1.6 Hz, 2H), 7.24 (s, 1H), 6.68 (s, 1H), 5.47 (s, 2H), 4.03 (s, 3H), 3.82 (s, 3H), 3.70 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.9, 166.2, 151.2, 150.4, 140.9, 138.1, 132.9, 130.5, 130.4, 130.3, 129.9, 129.7, 128.7, 128.4, 128.3, 128.1, 128.0, 127.4, 107.1, 106.0, 63.4, 56.2, 55.8, 52.4; IR (KBr, neat): 3061, 3020, 2951, 2831, 1722, 1715, 1622, 1504, 1472, 1433, 1244, 1200, 1150, 1111, 1070, 1024, 758, 711 cm^{-1}; HRMS (ESI) calcd for $C_{28}H_{24}O_6$ $(M+K)^+$ 495.1204, found 495.1240.

[a] T. Saito, Y. Shimizu, Y. Araki, Y. Ohgami, Y. Kitazawa, Y. Nishii, *Eur. J. Org. Chem.* **2022**, e202101213.

Thus, dehydgenation of the mixture of these inseparable isomers **20a** and **20b** using DDQ furnished naphthalene **21** as sole product in 95% yield. Based on the transformation of the mixture of **20a** and **20b** to naphthalene **21**, the minor product was assigned to *cis*-dihydronaphthalene **20b.**

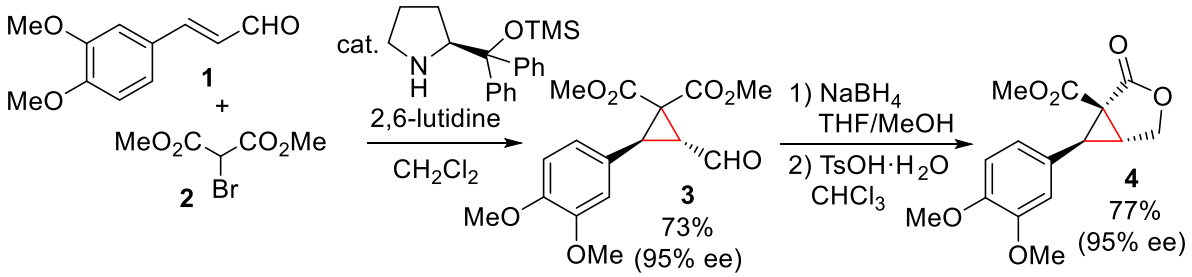
3. D-A シクロプロパンの高立体選択的 OHM 反応とツピキリグナン A の全合成

3.1. General methods and materials.

All reactions were carried out in oven-dried glassware under an argon atmosphere. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl. Column chromatography was performed with Kanto chemical CO., INC., silica gel 60 N (spherical, neutral, 40-50 μm). TLC analysis was performed on 0.25 mm Silica gel Merck 60 F_{254} plates. FT-IR spectra were recorded on a SHIMADZU IRTracer-100 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a BRUKER AVANCE NEO NanoBay (400 MHz for ^{1}H NMR, 101 M Hz for ^{13}C NMR) instrument. Chemical shifts (δ ppm) in $CDCl_3$ were reported downfield from TMS (= 0) for ^{1}H NMR. For ^{13}C NMR, chemical shifts were reported in the scale relative to $CDCl_3$ (77.16 ppm) as an internal reference. Mass spectra were obtained by electrospray ionization (ESI). HPLC analysis was performed on a JASCO GULLIVER SERIES.

3.2. Experimental procedures and characterization data for compounds.

3.2.1. Total synthesis of tupichilignan A.



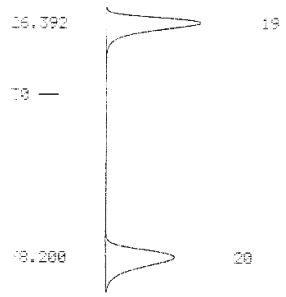
(a) A solution of (*S*)-Hayashi-Jørgensen catalyst (1.10 g, 3.30 mmol) in CH_2Cl_2 (3.3 ml) was added to a solution of aldehyde **1** (2.50 g, 13.0 mmol) in CH_2Cl_2 (6.5 ml) at 0 ˚C under Ar atmosphere, additionally, a solution of dimethyl bromomalonate **2** (4.00 g, 15.6 mmol) in CH_2Cl_2 (3.3 ml) and 2,6-lutidine (1.60 ml, 14.3 mmol) was added to the reaction mixture at the same temperature, followed by being stirred at 0 ˚C for 5 days. Then, the reaction was quenched with 1M-HCl aqueous solution (20 mL). Water (20 ml) was added to the mixture, which was extracted with $CHCl_3$ (20 mL x 3). The organic layers were washed with brine, dried over Na_2SO_4, and concentrated. The obtained crude oil was purified by column chromatography (SiO_2, hexane/AcOEt = 2/1) to give the product **3** (3.10 g, 73%, 95% ee). Based on the HPLC analysis of lactone **4** that was derived from **3**, the ee was estimated as 96% ee.

3: colorless liquid; $[\alpha]_D^{21}$ = -35.9 (*c* = 1.00, chloroform, λ = 589 nm); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.35 (dd, *J* = 4.6, 7.5 Hz, 1H), 3.51 (s, 3H), 3.79 (d, *J* = 7.5 Hz, 1H), 3.83 (s, 3H), 3.86 (s, 3H), 3.89 (s, 3H), 6.73-6.79 (m, 3H), 9.48 (d, *J* = 4.6 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 35.4, 38.6, 44.5, 52.9, 53.3, 55.8, 55.9, 110.9, 111.5, 120.6, 124.4, 148.8 (aromatic C x 2), 165.1, 166.6, 196.0; IR (KBr, neat) 3474, 2955, 1738, 1715, 1591, 1520, 1454, 1435, 1146, 1026, 816 cm^{-1}. On the basis of the HPLC analysis of lactone **4** derived from **3**, the ee was estimated as 95% ee.

(b) The obtained aldehyde **3** (3.10 g, 9.50 mmol) was dissolved with THF/MeOH (9.5 mL/9.5 mL). $NaBH_4$ (126 mg, 3.30 mmol) was added to the solution at 0 ˚C under an Ar atmosphere, followed by being stirred at same temperature for 15 minutes. Then, the reaction was quenched with sat. NH_4Cl aqueous solution (20 mL). Water (20 mL) was added to the mixture, which was extracted with AcOEt (ca. 15 mL x 5). The organic layer was washed with brine, dried (Na_2SO_4), and concentrated. The obtained crude oil was resolved in $CHCl_3$ (95 mL), then *p*-TsOH·H_2O (90 mg, 0.480 mmol) was added to the solution, followed by being stirred at 45°C for 2 h. Then, the reaction was quenched with sat. $NaHCO_3$ aqueous solution (10 mL). Water (20 mL) was added to the mixture, which was extracted with $CHCl_3$ (ca. 20 mL x 3). The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The obtained crude oil was purified by column chromatography (SiO_2, hexane/AcOEt = 3/2) to give product **4** (2.17 g, 77%, 95% ee).

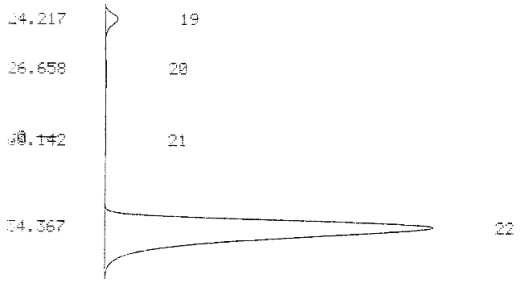
4: colorless solid; mp = 111-114°C; $[\alpha]_D^{24}$ = -30.5 (*c* = 1.00, chloroform, λ = 589 nm); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.90 (d, J = 5.6 Hz, 1H), 3.26 (m, 1H), 3.56 (s, 3H), 3.86 (s, 3H), 3.87 (s, 3H), 4.37 (d, *J* = 9.3 Hz, 1H), 4.50 (dd, *J* = 9.3, 4.9 Hz, 1H), 6.79-6.83 (m, 2H), 6.77 (s, 3H) ; ^{13}C NMR (101 MHz, CDCl3) δ 28.3, 38.2, 38.3, 53.1, 56.2, 56.4, 67.7, 111.2, 112.3, 121.3, 124.4, 149.2, 149.4, 164.51, 170.5; IR (KBr, neat) 2959, 1794, 1722, 1520, 1441, 1258, 1240, 1141, 1015 cm^{-1}; HRMS (APCI) calcd for $C_{15}H_{16}O_6$ $(M+H)^+$ 293.1020 , found 293.1008; HPLC analysis: 95% ee [Daicel CHIRALPAK IC (25 cm) at 25 °C; flow rate = 0.8 mL/min; solvent: hexane/ethanol = 2/1 (v/v); t_R(mixture of **4** and optical isomer **4′**) = 26.4 min and 38.2 min, t_R(**4**) = 34.4 min for major and 24.2 min for minor].

[a] Y. Kimura, Y. Sone, T. Saito, T. Mochizuki, Y. Nishii, *Asian J. Org. Chem*. **2017**, *6*, 977–980.



A 48.7/49.0 mixture of **4** (1*S*, 5*R*, 6*S*) and optical isomer **4′** (1*R*, 5*S*, 6*R*): HPLC analysis using chiral column.

19	26.392	3227639	72273	49.0101
20	38.200	3207033	52178	48.6972

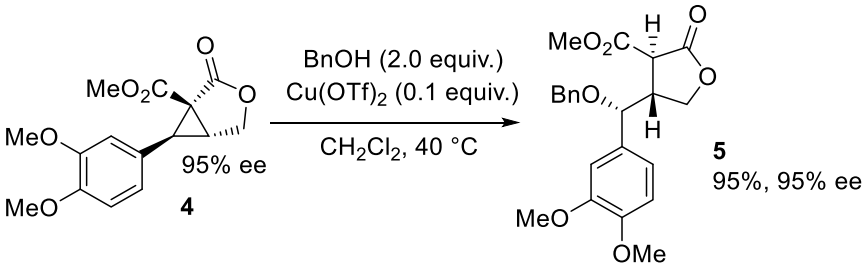


Enantioenriched **4** (95% ee): HPLC analysis using chiral column.

19	24.217	357368	9102	2.2406
20	26.658	20832	333	0.1306
21	30.142	11138	147	6.9831E-02
22	34.367	15137019	242478	94.9061

Based on this enantiomeric ratio (94.91/2.24), 95% ee was estimated.

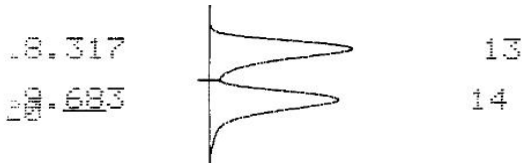
(α*S*, β*R*)-α-Methoxycarbonyl-β-(*R*)-(benzyloxy)(3,4-dimethoxyphenyl)methyl -γ-butyrolactone (5)



An experiment for total synthesis of 7-hydroxyarctigenin. Benzylalcohol (0.35 mL, 3.4 mL) was added to a solution of cyclopropane **4** (500mg, 1.7 mmol) in CH_2Cl_2 (3.4 mL) at 0°C under an Ar atmosphere. Additionally, $Cu(OTf)_2$ (62 mg, 0.17mmol) was added to the mixture at the same temperature, followed by being stirred at 40 °C for 7 h. The reaction mixture was cool down to 0 °C, water was added to the mixture, which was extracted with $CHCl_3$. The organic layers were washed with brine, dried (Na_2SO_4) and concentrated. The obtained crude was purified by column chromatography (SiO_2,

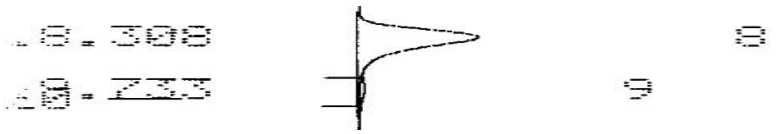
hexane/AcOEt = 2/1) to give the product **5** (628 mg, 92%).

5: colorless solid; mp = 92-94 °C; $[\alpha]_D^{24}$= 147.5 (*c* = 1.00, chloroform, λ = 589 nm); ^{1}H NMR (400MHz,$CDCl_3$) δ 3.31-3.42 (m, 2H), 3.56 (s, 3H), 3.89 (s, 3H), 3.90 (s, 3H), 4.23 (d, J = 11.8 Hz, 1H), 4.24-3.30 (m, 2H), 4.46 (dd, J = 7.4, 9.2 Hz, 1H), 4.53 (d, J = 11.8 Hz, 1H), 6.80-6.89 (m, 3H), 7.24-7.26 (m, 2H), 7.30-7.39 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 47.0, 49.6, 53.3, 56.3(7), 56.3(9), 69.8, 70.8, 80.6, 109.9, 111.5, 120.2, 128.4, 128.5,129.0, 130.6, 137.8, 149.8, 150.0, 167.9, 172.0; IR (KBr,neat) 3537, 3078, 2959, 1768, 1740, 1591, 1516, 1452, 1242, 1142, 1026, 745, 692 cm^{-1}; HRMS (APCI) calcd for $C_{22}H_{24}O_7$ $(M-H)^-$ 399.1438 , found 399.1432; HPLC analysis: 95% ee [Daicel CHIRALPAK IC (25cm) at 25˚C, flow rate 1.0 ml/min, solvent: hexane / ethanol = 2/1, t_R(racemic) = 18.3 min and 19.7 min, t_R(**5**) = 18.3 min for major and 19.7 min for minor].



A 48.2/47.9 mixture of **5** and optical isomer **5′** : HPLC analysis using chiral column.

13	18.317	898713	25248	V	48.2119
14	19.683	891995	22900	V	47.8515

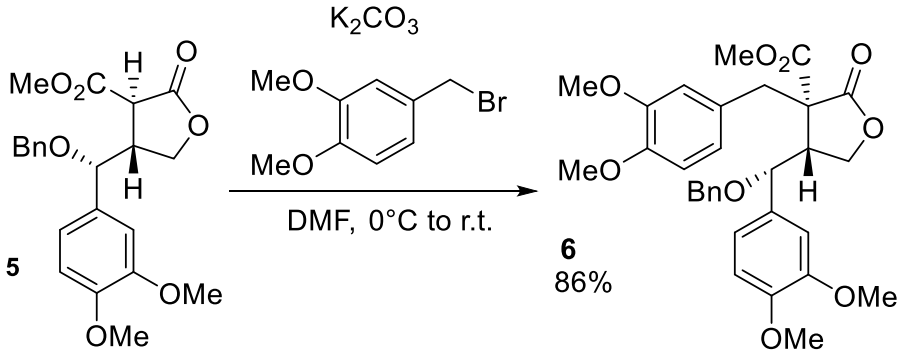


Enantioenriched **5** (95% ee): HPLC analysis using chiral column.

8	18.308	454629	12302	TTT	91.6157
9	19.733	8723	333	T	1.7578

Based on this enantiomeric ratio (91.6/1.8), 95% ee was estimated.

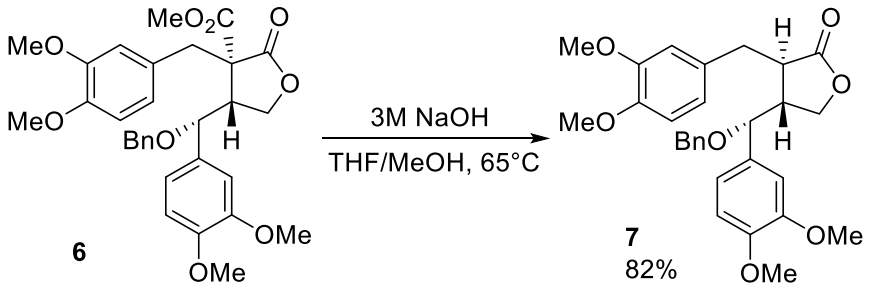
(α*R*, β*R*)-α-(3,4-dimethoxyphenyl)methoxycarbonyl-β-(*R*)-(benzyloxy)(3,4-dimethoxyphenyl)methyl-γ-butyrolactone (6)



A DMF (0.65 ml) solution of **5** (260 mg, 0.649 mmol) was added to a suspension of K_2CO_3 (269 mg, 1.95 mmol) in DMF (1.0 ml) at 0 ˚C. Then, the DMF solution of 3,4-dimethoxybenzyl bromide (225 mg, 0.97mmol) was added to the mixture at 0 ˚C, and followed by being stirred at room temperature for 3h. 1M-HCl aqueous solution (10 ml) was added to the reaction mixture, which was extracted with AcOEt (ca. 10 ml x 5). The organic phase was washed with brine, dried (Na_2SO_4), and concentrated. The obtained crude oil was purified by column chromatography (SiO_2, hexane/AcOEt = 2/1) to give the product **6** (307 mg, 86%).

6: colorless liquid; $[\alpha]^{24}_D = 40.1°$ (*c* 1.00, chloroform, λ = 589 nm); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.75-2.81 (m, 1H), 2.86 (d, J = 14.5 Hz, 1H), 3.36(d, J = 14.5 Hz, 1H), 3.80 (s, 3H), 3.83 (s, 3H), 3.87 (s, 3H), 3.91 (s, 3H), 4.15 (d, J = 11.3 Hz, 1H), 4.18 (t, J = 8.4 Hz, 1H), 4.37 (dd, J = 3.1, 9.1 Hz, 1H), 4.46 (dd, J = 8.7, 10.8 Hz, 1H), 6.42 (dd, J = 2.0, 8.1 Hz, 1H) , 6.58 (d, J = 1.9 Hz, 1H), 6.71 (d, J = 8.2 Hz, 1H), 6.80 (dd, J = 1.9, 8.1 Hz, 1H), 6.88 (d, J = 8.2 Hz, 1H), 7.24-7.26 (m, 2H), 7.29-7.36 (m, 3H) ; ^{13}C NMR (101 MHz, $CDCl_3$) δ 36.6, 48.1, 53.0, 56.2, 56.3(1), 56.3(3), 56.4, 57.8, 68.1, 70.9, 77.9, 109.9, 111.3, 111.5, 114.0, 123.5, 128.0, 128.3, 128.4 (aromatic C x 2), 128.8 (aromatic C x 2), 131.7, 137.9, 148.7, 149.4, 149.6, 149.8, 170.0, 176.0 ; IR (KBr, neat) 3549, 2936, 1776, 1740, 1591, 1518, 1464, 1238, 1142, 1028 cm^{-1}; HRMS (APCI) calcd for $C_{31}H_{34}O_9$ (M) 550.2197 , found 550.2187.

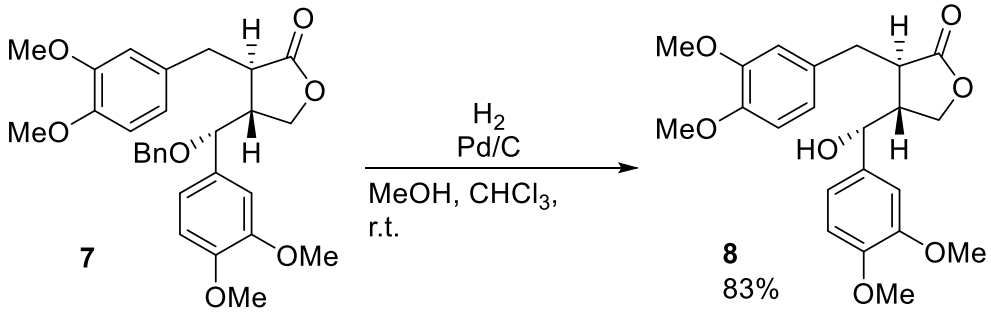
(α*R*, β*R*)-α-(3,4-dimethoxyphenyl)-β-(*R*)-(benzyloxy)(3,4-dimethoxyphenyl)methyl -γ-butyrolactone (7)



3M-NaOH aqueous solution (2.65 mL, 7.95 mmol) was dropwise added to a solution of **6** (875 mg, 1.59 mmol) in THF / Methanol (8/1, 28 mL) at 0 ˚C, and followed by being stirred at 65 ˚C for 3h. 1M-HCl aqueous solution (15 mL) was added to the reaction mixture, then additional water (40 mL) was added to the reaction mixture, which was extracted with AcOEt (ca. 20 ml x 5). The organic phase was washed with brine, dried (Na_2SO_4), and concentrated. The obtained crude oil was purified by column chromatography (SiO_2, hexane/AcOEt = 4/1) to give the product **7** (643 mg, 82%).

7: colorless solid; mp = 112-114 °C; $[\alpha]^{25}_D$ = -41.0° (*c* 1.00, chloroform, λ = 589 nm); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.53-2.62 (m, 2H), 2.65-2.69 (m, 1H), 2.75 (dd, J = 6.9, 13.1 Hz, 1H), 3.76 (s, 3H), 3.81 (s, 3H), 3.84 (s, 3H), 3.90 (s, 3H), 4.03 (d, J = 7.5 Hz, 1H), 4.09 (d, J = 11.6 Hz, 1H), 4.12 (dd, J = 7.9, 9.3 Hz, 1H), 4.32 (dd, J = 6.5, 9.3 Hz, 1H), 4.37 (d, J = 11.6 Hz, 1H), 6.44 (dd, J = 1.9, 8.1 Hz, 1H) , 6.50 (d, J = 1.9 Hz, 1H), 6.62 (d, J = 1.9 Hz, 1H), 6.67-6.68 (m, 1H), 6.69-6.70 (m, 1H), 6.81 (d, J = 8.1 Hz, 1H), 7.20-7.22 (m, 2H), 7.29-7.36 (m, 3H) ; ^{13}C NMR (101 MHz, $CDCl_3$) δ 35.1, 44.0, 46.2, 56.1(5), 56.2(3), 56.2(6), 56.3(2), 69.1, 70.9, 81.3, 109.7, 111.3(7), 111.4(2), 112.6, 119.9, 121.7, 128.4 (aromatic C x 3), 128.9 (aromatic C x 2), 130.3, 131.6, 138.0, 148.3, 149.4, 149.5, 149.8, 179.3 (C=O); IR (KBr, neat) 3003, 2936, 2835, 1769, 1593, 1516, 1464, 1263, 1155, 746 cm^{-1}; HRMS (APCI) calcd for $C_{29}H_{32}O_7$ (M) 492.2143 , found 492.2142.

(α*R*, β*R*)-α-(3,4-dimethoxyphenyl)-β-(*R*)-(3,4-dimethoxyphenyl)(hydroxy)methyl -γ-butyrolactone (8)

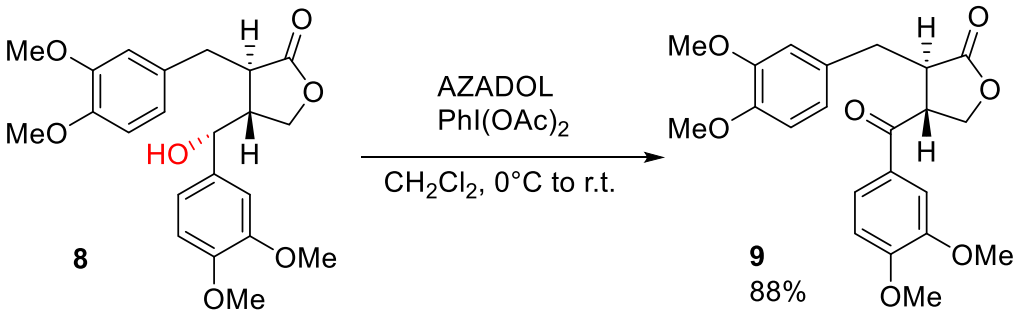


Pd/C (19 mg, 10 mol%) was added to a solution of compound **7** (90 mg, 0.18mmol) in MeOH/$CHCl_3$ [10 ml, 10/1 (v/v)] at room temperature, followed by being stirred at the same temperature for 9 h under hydrogen atmosphere (balloon). After a filtration, the filtrate solution was concentrated. The obtained crude oil was purified by column chromatography (SiO_2, hexane/AcOEt = 3/2) to give a product **8** (61 mg, 83%).

8: colorless solid; mp = 83-85 °C; $[\alpha]^{26}_D$ = 5.55° (*c* 1.00, chloroform, λ = 589 nm); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.88 (brd, J = 2.8 Hz, 1H, OH), 2.55 (quint, J = 7.2 Hz, 1H, H-8), 2.72, (m, 1H, H-8'), 2.75 (dd, J = 5.0, J_{gem}=13.3 Hz, 1H, H-7'), 2.80 (dd, J = 7.7, J_{gem}=13.3 Hz, 1H, H-7'), 3.80 (s, 3H, OMe), 3.83 (s, 3H, OMe), 3.86 (s, 3H, OMe), 3.88 (s, 3H, OMe), 4.11 (dd, J = 7.8, J_{gem}=9.4 Hz, 1H, H-9), 4.38 (dd, J = 6.4, J_{gem} = 9.4 Hz, 1H, H-9), 4.43 (dd, J = 2.8, 7.2 Hz, 1H, H-7), 6.53 (dd, J = 2.0, 8.1 Hz, 1H), 6.57 (d, J = 2.0 Hz, 1H), 6.65-6.67 (m, 2H), 6.73 (d, J = 8.1 Hz, 1H), 6.79 (d, J = 8.1 Hz, 1H) ; ^{13}C NMR (101 MHz, $CDCl_3$) δ 35.0, 43.9, 46.5, 56.2 (OMe x 2), 56.2, 56.3, 68.6, 74.3, 109.3, 111.3(7), 111.4(2), 112.7, 113.6, 121.7, 130.4, 134.7, 148.3, 149.2, 149.3, 149.4, 179.5 ; IR (NaCl, neat) 3505, 2936, 2837, 1767, 1593, 1518, 1466, 1420, 1263, 1140, 1026, 812, 764 cm^{-1}, HRMS (APCI) calcd for $C_{22}H_{26}O_7$ $(M-H)^-$ 401.1595 , found 401.1609; Because the absolute configuration of β-position of lactones would never change, we speculate the ee value of **8** as 95% ee on the basis of ee value of lactone **5.**) The spectral data of **8** were inconsistent with reported data for tupichilignan A[a].

[a] W Bin, L Mei, L Lan, Y Chang, *Chem. Pharm. Bull.* **2006**, *54*, 954.

(3*R*,4*R*)-4-(3,4-dimethoxybenzoyl)-3-(3,4-dimethoxybenzyl)dihydrofuran-2(3*H*)-one (9)

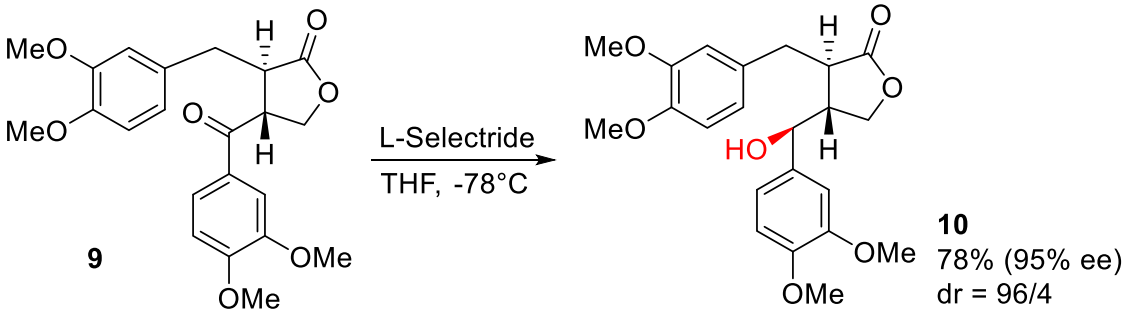


A CH_2Cl_2-solution (0.2 mL) of compound **8** (59 mg, 147 μmol) was added to a solution of 2-hydroxy-2-azaadamantane (AZADOL) (1.1 mg, 7.3 μmol) in CH_2Cl_2 (0.4 mL) at 0˚C under an Ar atmosphere, additionally, (Diacetoxyiodo)benzene (62 g, 191 μmol) was added to the reaction mixture at the same

temperature, followed by being stirred at room temperature for 1 h. The mixture was diluted with saturated aqueous $NaHCO_3$ (1.0 mL) and saturated aqueous $Na_2S_2O_3$ (1.0 mL), then additional water (30 mL) was added to the reaction mixture, which was extracted with AcOEt (ca. 10 ml x 5). The organic phase was washed with brine, dried (Na_2SO_4), and concentrated. The obtained crude oil was purified by column chromatography (SiO_2, hexane/AcOEt = 1/1) to give the product **9** (52 mg, 88%).

9: colorless solid; mp = 73-75 °C; $[\alpha]^{21}_D$ = 20.1° (*c* 1.00, chloroform, λ = 589 nm); ^{1}H NMR (400 MHz, CDCl3) δ 2.99-3.09 (m, 2H), 3.52-3.59 (m, 1H), 3.74 (s, 3H), 3.80 (s, 3H), 3.91 (s, 3H), 3.95 (s, 3H), 4.03-4.15 (m, 2H), 4.36-4.42 (m, 1H), 6.59-6.67 (m, 3H), 6.81 (d, J = 8.4 Hz, 1H), 7.23 (dd, J = 2.0, 8.4 Hz, 1H), 7.35 (d, J = 2.0 Hz, 1H) ; ^{13}C NMR (101 MHz, $CDCl_3$) δ 34.7, 45.1, 47.0, 56.1, 56.2, 56.4, 56.6, 68.7, 110.3, 110.7, 111.5, 112.7, 122.0, 123.3, 130.0, 130.3, 148.4, 149.8, 149.4, 154.6, 177.7, 195.4; IR (NaCl, neat) 3534, 2938, 1771, 1670, 1593, 1518, 1466, 1422, 1265, 1159, 1024, 762 cm^{-1}; HRMS (APCI) calcd for $C_{22}H_{24}O_7$ $(M+H)^+$ 401.1595 , found 401.1602.

(α*R*, β*R*)-α-(3,4-dimethoxyphenyl)-β-(*S*)-(3,4-dimethoxyphenyl)(hydroxy)methyl -γ-butyrolactone (10: tuphichilignan A)

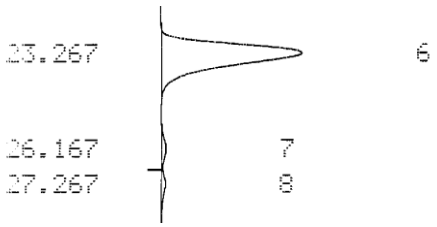


A 1.0 M-hexane-solution of L-selectride (221 μL, 221 μmol) was dropwise added to a solution of **9** (73 mg, 184 μmol) in THF (1.0 mL) at -78 ˚C under an Ar atmosphere, followed by being stirred at the same temperature for 5 minutes. 1M-HCl aqueous solution (5 ml) was added to the reaction mixture at 0˚C, which was extracted with AcOEt (ca. 10 ml x 3). The organic phase was washed with brine, dried (Na_2SO_4), and concentrated. The obtained crude oil was purified by column chromatography (SiO_2, hexane/AcOEt = 3/2) to give the product **10** (57 mg, 78%, dr = 96:4).

10: colorless solid; mp = 73-75 °C; $[\alpha]^{24}_D$ = -17.7° (*c* 1.00, chloroform, λ = 589 nm); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.51 (brs, 1H), 2.62(quint, J = 7.2 Hz, 1H), 2.91 (dd, J = 5.3, 13.3 Hz, 1H), 2.97 (m, 1H), 3.06 (dd, J = 5.3, 13.3 Hz, 1H), 3.83 (s, 3H), 3.85 (s, 6H), 3.88 (s, 3H), 3.90-3.99 (m, 2H), 4.64 (d, J = 6.3 Hz, 1H), 6.63 (dd, J = 2.0, 8.1 Hz, 1H), 6.69 (d, J = 1.9 Hz, 1H), 6.73-6.82 (m, 4H) ; ^{13}C

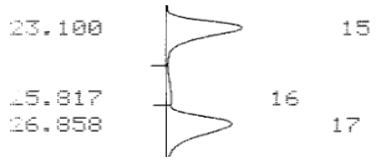
NMR (101 MHz, $CDCl_3$) δ 34.9, 43.8, 45.1, 55.8(1) (C x 2), 55.8(9), 55.9(3), 68.3, 75.4, 109.0, 111.0, 111.1, 112.8, 118.2, 121.8, 130.1, 134.0, 147.8, 148.9, 149.1, 149.3, 179.1 ;IR (NaCl, neat) 3505, 2938, 2837, 1759, 1592, 1518, 1466, 1420, 1263, 1236, 1188, 1140, 1026, 812, 764 cm^{-1}; HRMS (APCI) calcd for $C_{22}H_{26}O_7$ (M) 402.1673 , found 402.1675 ; 95% ee: HPLC analysis [Daicel CHIRALPAK IC (25cm) at 25˚C, flow rate 0.6 ml/min, solvent: hexane / ethanol = 2/1, t_R(a mixture of **10** and **10'**) = 23.10 min and 26.858 min, t_R(**10**) = 27.27 min for minor and 23.27 min for major, t_R(**10'**) = 23.56 min for minor and 27.03 min for major]. The spectral data of **10** were good accordance with reported data for tupichilignan A.[a]

[a] W Bin, L Mei, L Lan, Y Chang, *Chem. Pharm. Bull.* **2006**, *54*, 954.



6	23.267	1437046	33033		90.8036
7	26.167	45520	1039	V	2.8763
8	27.267	38728	869	V	2.4471

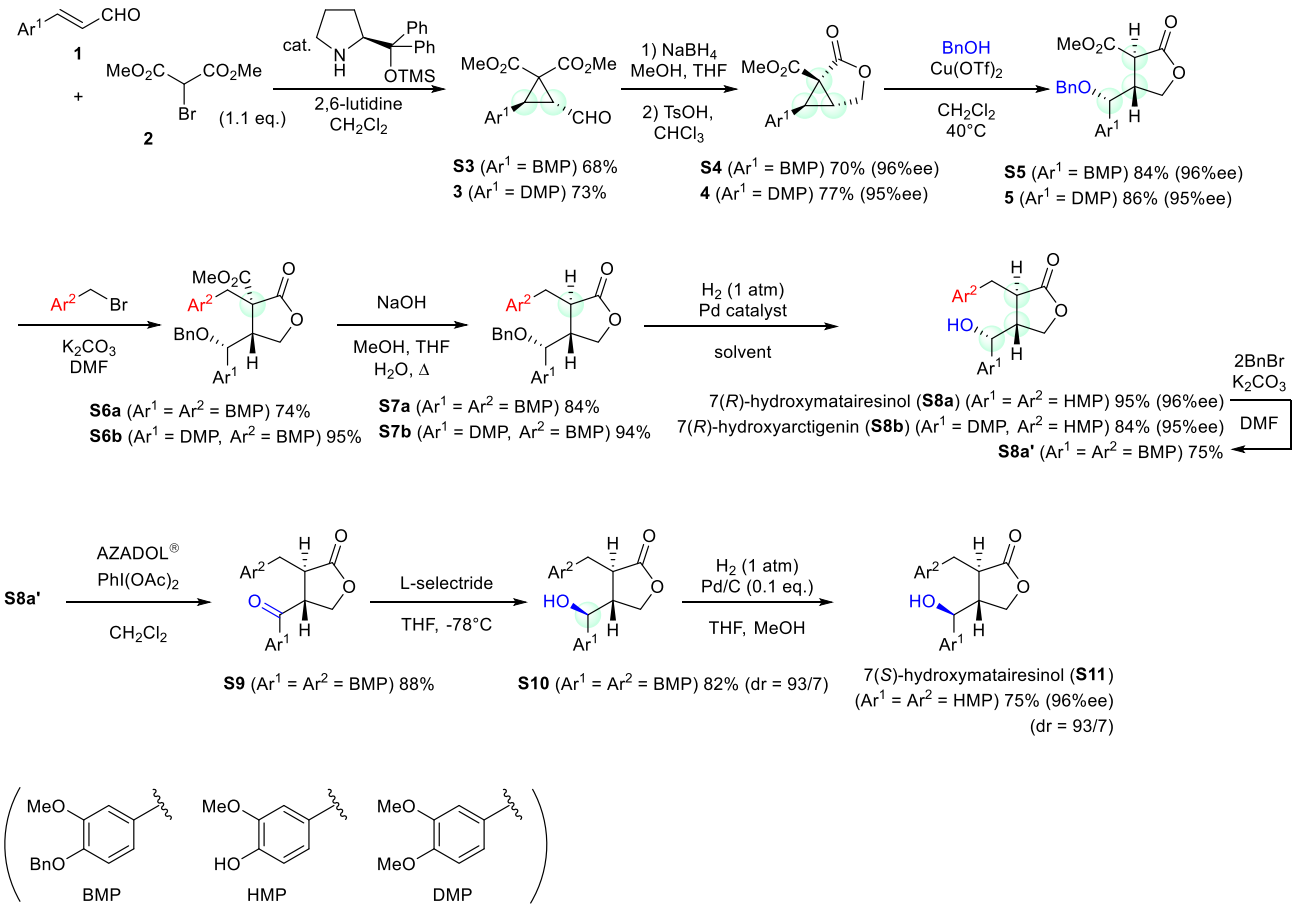
Based on this enantiomeric ratio (90.80/2.45), 95% ee was estimated.



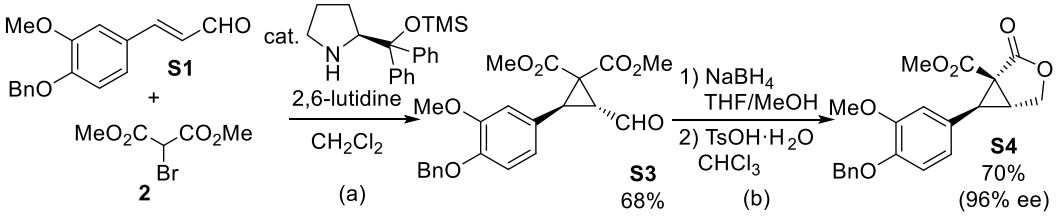
15	23.100	1525819	35113	V	45.6377
16	25.817	122178	2100	V	3.6544
17	26.858	1592935	30204	V	47.6452

10/optical isomer **10′** = 45.6377/47.6452 = 49/51

3.2.3. Total synthesis of hydroxymatairesinol and hydroxyarctigenin.



(1*S*,5*R*,6*S*)-1-methoxycarbonyl-6-(4-(benzyloxy)-3-methoxyphenyl)-3-oxabicyclo[3.1.0]hexan -2-one (S4)



(a) A solution of (*S*)-Hayashi-Jørgensen catalyst (349 mg, 1.07 mmol) in CH_2Cl_2 (3 mL) was added to a solution of aldehyde **S1** (1.15 g, 4.29 mmol) in CH_2Cl_2 (10 ml) at 0˚C under Ar atmosphere, additionally, a solution of dimethyl bromomalonate **2** (1.09 g, 5.15 mmol) in CH_2Cl_2 (3 mL) and 2,6-lutidine (0.70 mL, 4.72 mmol) was added to the reaction mixture at the same temperature, followed by being stirred at 0˚C for 5 days. Then, the reaction was quenched with 1M-HCl aqueous solution (6 mL). Water (10 ml) was added to the mixture, which was extracted with $CHCl_3$ (20 mL x 3). The

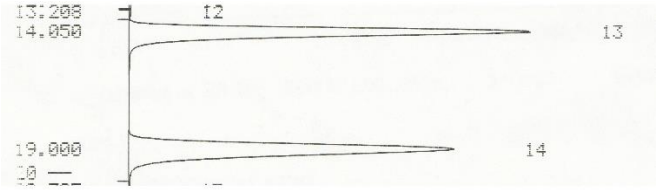
organic layers were washed with brine, dried over Na_2SO_4, and concentrated. The obtained crude oil was purified by column chromatography (SiO_2, hexane/AcOEt = 2/1) to give the product **S3** (1.16 g, 68%, 96% ee). Based on the HPLC analysis of lactone **S4** that was derived from **S3**, the ee was estimated as 96% ee.

Aldehyde **S3**: colorless solid; mp 84-88 ˚C, $[\alpha]^{28}_D = 22.2$ (*c* = 1.00, chloroform, λ = 589 nm); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.46 (d, *J* = 4.6 Hz, 1H), 7.29-7.42 (m, 5H), 6.80 (d, J = 8.3 Hz, 1H), 6.75 (d, *J* = 2.0 Hz, 1H), 6.69 (dd, *J* = 2.0, 8.3, 1H), 5.12 (s, 2H), 3.87 (s, 3H), 3.83 (s, 3H), 3.77 (d, *J* = 7.5 Hz, 1H), 3.48 (s, 3H), 3.33 (dd, *J* = 4.6, 7.5 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 196.0, 166.5, 165.0, 149.5, 147.9, 136.8, 128.5 (aromatic C x 2), 127.9, 127.3 (aromatic C x 2), 125.0, 120.5, 113.7, 112.0, 70.9, 56.0, 53.3, 52.9, 44.5, 38.5, 35.4; IR (KBr, neat) 2961, 2876, 1736, 1705, 1591, 1520, 1439, 1300, 1250, 1207, 1148, 1034, 739 cm^{-1}; HRMS (APCI) calcd for $C_{22}H_{22}O_7$ $(M-H)^-$ 397.1282, found 397.1292. On the basis of the HPLC analysis of lactone **S4** derived from **S3**, the ee was estimated as 96% ee.

(b) The obtained aldehyde **S3** (1.00 g, 2.50 mmol) was dissolved with THF/MeOH (5 mL/5 mL). $NaBH_4$ (33 mg, 0.880 mmol) was added to the solution at 0 ˚C under an Ar atmosphere, followed by being stirred at same temperature for 15 minutes. Then, the reaction was quenched with sat. NH_4Cl aqueous solution (5 mL). Water (10 mL) was added to the mixture, which was extracted with AcOEt (ca. 10 mL x 5). The organic layer was washed with brine, dried (Na_2SO_4), and concentrated. The obtained crude oil was resolved in $CHCl_3$ (25 mL), then *p*-TsOH·H_2O (124 mg, 0.250 mmol) was added to the solution, followed by being stirred at 45°C for 1 h. Then, the reaction was quenched with sat. $NaHCO_3$ aqueous solution (10 mL). Water (10 mL) was added to the mixture, which was extracted with AcOEt (ca. 5 mL x 5). The organic layers were washed with brine, dried over Na_2SO_4, and concentrated. The obtained crude oil was resolved in $CHCl_3$ (65 mL), then *p*-TsOH·H_2O (24 mg, 0.160 mmol) was added to the solution, followed by being stirred at 45˚C for 2 h. Then, the reaction was quenched with sat. $NaHCO_3$ aqueous solution (5 mL). Water (10 mL) was added to the mixture, which was extracted with $CHCl_3$ (ca. 10 mL x 3). The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The obtained crude oil was purified by column chromatography (SiO_2, hexane/AcOEt = 3/2) to give product **S4** (644 mg, 70%, 96% ee). The ee was observed by HPLC analysis of **S4** with chiral column (Daicel CHIRALPAK IC).

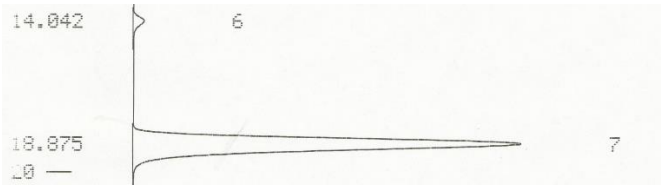
S4: colorless solid; mp 119-121 ˚C; $[\alpha]_D^{24} = 58.8$ (*c* = 1.00, chloroform, λ = 589 nm); ^{1}H NMR (400

MHz, $CDCl_3$) δ 2.87 (d, J = 5.6 Hz, 1H), 3.24 (t, J = 5.0 Hz, 1H), 3.10 (s, 3H), 3.87 (s, 3H), 4.35 (d, J = 9.1 Hz, 1H), 4.48 (dd, J = 4.8, 9.3 Hz, 1H), 5.13 (s, 2H), 6.71 (dd, J = 2.0, 8.3, 1H), 6.79 (d, J = 2.0, 1H), 6.82 (d, J = 8.1, 1H), 7.30-7.43 (m, 5H) ; ^{13}C NMR (101 MHz, $CDCl_3$) δ 28.2, 38.1, 38.3, 53.1, 56.5, 67.7, 71.3, 112.8, 114.0, 121.2, 125.1, 127.7 (aromatic C x 2) , 128.3, 129.0 (aromatic C x 2), 137.2, 148.5, 149.9, 164.5, 170.5 ; IR (KBr, neat) 2953, 1784, 1721, 1520, 1439, 1256, 1234, 1142, 1103, 1072, 1016 cm^{-1} ; HRMS (APCI) calcd for $C_{21}H_{20}O_6$ $(M+H)^+$ 369.1333 , found 369.1373, HPLC analysis: 96% ee [Daicel CHIRALPAK IC (25 cm) at 25 °C; flow rate = 0.6 mL/min; solvent: hexane/ethanol = 1/1 (v/v); t_R(mixture of **S4** and optical isomer **S4′**) = 14.1 min and 19.0 min, t_R(**S4**) = 18.9 min for major and 14.0 min for minor].



A 50.2.7/47.6 mixture of **S4** (1*S*,5*R*,6*S*) and optical isomer **S4′** (1*R*,5*S*,6*R*): HPLC analysis using chiral column.

13	14.050	3325581	128925	LLL	47.5546
14	19.000	3508624	104345	TTT	50.1720

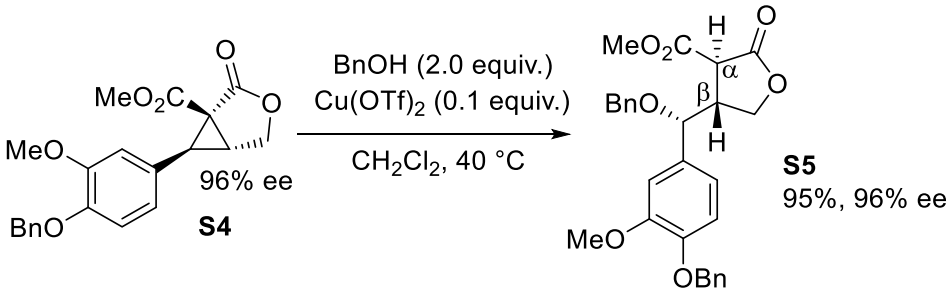


Enantioenriched **S4** (96% ee): HPLC analysis using chiral column.

6	14.042	81747	3195	2.0522
7	18.875	3861115	116299	96.9328

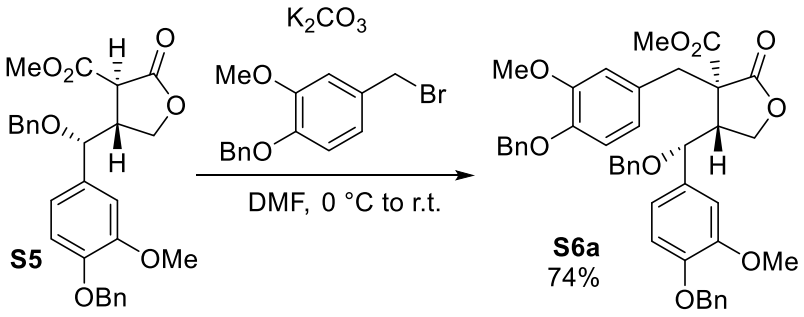
Based on this enantiomeric ratio (96.9/2.1), 96% ee was estimated.

(α*S*, β*R*)-α-Methoxycarbonyl-β-(*R*)-(benzyloxy)(4-benzyloxy-3-methoxyphenyl)methyl -γ-butyrolactone (S5)



Benzyl alcohol (225 μL, 2.17 mmol) was added to a solution of cyclopropane **S4** (400 mg, 1.09 mmol) in CH_2Cl_2 (5.0 mL) at 0°C under an Ar atmosphere. Additionally, $Cu(OTf)_2$ (39 mg, 0.109 mmol) was added to the mixture at the same temperature, followed by being stirred at 40 °C for 7 h. The reaction mixture was cool down to 0 °C, water was added to the mixture, which was extracted with $CHCl_3$. The organic phase was washed with brine, dried (Na_2SO_4) and concentrated. The obtained crude was purified by column chromatography (SiO_2, hexane/AcOEt = 2/1) to give the product **S5** (436 mg, 84%). **S5**: colorless solid; mp = 141-144 °C; $[\alpha]_D^{28}$= -45.1 (*c* 1.00, chloroform, λ = 589 nm); ^{1}H NMR (400MHz,$CDCl_3$) δ 3.31-3.39 (m, 2H), 3.50 (s, 3H), 3.89 (s, 3H), 4.21 (d, J = 11.8 Hz, 1H), 4.22-4.27 (m, 2H), 4.45 (dd, J = 7.5, 9.3 Hz, 1H), 4.51 (d, J = 11.8 Hz, 1H), 5.12 (s, 2H), 6.75 (dd, J = 2.0, 8.2, 1H), 6.83 (d, J = 2.0, 1H), 6.88 (d, J = 8.2, 1H), 7.23-7.25 (m, 2H), 7.31-7.46 (m, 8H) ; ^{13}C NMR (101 MHz, $CDCl_3$) δ 47.0, 49.6, 53.2, 56.5, 69.9, 70.8, 71.4, 80.6, 110.4, 114.2, 120.0, 127.7 (aromatic C x 2), 128.3(8), 128.4(2) (aromatic C x 2), 128.4(5), 128.9(7) (aromatic C x 2), 129.0(2) (aromatic C x 2), 131.2, 137.3, 137.8, 148.9, 150.6, 167.9, 172.0 ; IR (KBr,neat) 2886, 1767, 1740, 1593, 1510, 1271, 1163, 1142, 1024, 743, 696 cm^{-1} ; HRMS (APCI) calcd for $C_{28}H_{28}O_7$ $(M-H)^-$ 475.1751, found 475.1728. Based on the fixed absolute configuration at the β-position of lactone **S4** (94% ee), ee of **S5** was determined as 96% ee.

(α*R*, β*R*)-α-[4-(benzyloxy)-3-methoxyphenyl]methoxycarbonyl-β-(*R*)-(benzyloxy)(4-benzyloxy-3-methoxyphenyl)methyl-γ-butyrolactone (S6a)

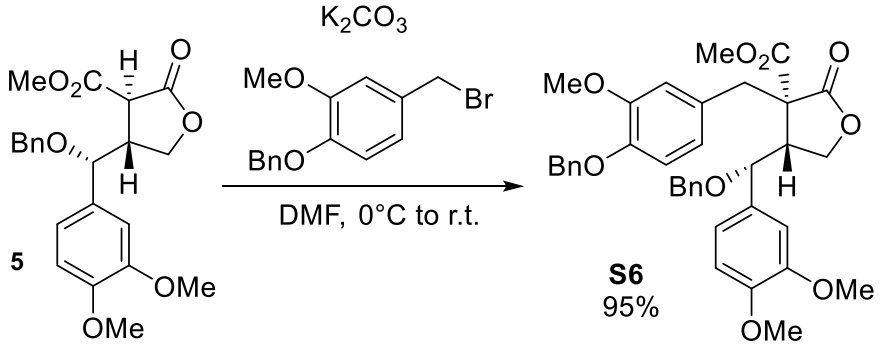


A DMF (0.65 ml) solution of **S5** (418 mg, 0.877 mmol) was added to a suspension of K_2CO_3 (364 mg, 2.63 mmol) in DMF (1.0 ml) at 0 ˚C. Then, the DMF solution of 3-benzyloxy-4-methoxybenzyl bromide (403 mg, 1.32 mmol) was added to the mixture at 0 ˚C, and followed by being stirred at room temperature for 3h. 1M-HCl aqueous solution (5 ml) was added to the reaction mixture, which was extracted with AcOEt (ca. 10 ml x 5). The organic phase was washed with brine, dried (Na_2SO_4),

and concentrated. The obtained crude oil was purified by column chromatography (SiO_2, hexane/AcOEt = 2/1) to give the product **S6a** (456 mg, 74%).

S6a: colorless liquid; $[\alpha]^{27}_D$ = 38.3 (*c* = 1.00, chloroform, λ = 589 nm); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.75 (ddd, J = 5.8, 8.2, 10.8 Hz, 1H), 2.82 (d, J = 14.5 Hz, 1H), 3.33 (d, J = 14.5 Hz, 1H), 3.48 (s, 3H), 3.78 (s, 3H), 3.82 (s, 3H), 4.13 (d, J = 11.2 Hz, 1H), 4.17 (t, J = 8.4 Hz, 1H), 4.34 (d, J = 5.7 Hz, 1H), 4.36 (d, J = 11.2 Hz, 1H), 4.44 (dd, J = 8.8, 10.8 Hz, 1H), 5.08 (s, 2H), 5.17 (d, J = 3.2 Hz, 2H), 6.31 (dd, J = 1.9, 8.1 Hz, 1H), 6.60 (d, J = 1.9 Hz, 1H), 6.67-6.72 (m, 3H), 6.87 (d, J = 8.0 Hz, 1H), 7.23-7.45 (m, 15H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 36.6, 48.1, 53.0, 56.4(0), 56.4(4), 57.8, 68.1, 70.9, 71.4(7), 71.5, 78.0, 110.5, 114.2, 114.3, 114.5, 119.5, 123.5, 127.7 (aromatic C x 4), 128.2(7), 128.2(9), 128.4 (aromatic C x 3), 128.6, 128.8 (aromatic C x 2), 129.0 (aromatic C x 2), 129.1 (aromatic C x 2), 132.2, 137.3, 137.5, 137.9, 147.9, 148.7, 150.1, 150.5, 170.0, 175.9; IR (NaCl neat) 2934, 1778, 1738, 1591, 1504, 1454, 1146, 1018, 737, 700 cm^{-1}; HRMS (APCI) calcd for $C_{43}H_{42}O_9$ (M) 702.2823 , found 702.2844.

(α*R*, β*R*)-α-[4-(benzyloxy)-3-methoxyphenyl]methoxycarbonyl-β-(*R*)-(benzyloxy)(3,4-dimethoxyphenyl)methyl-γ-butyrolactone (S6b)

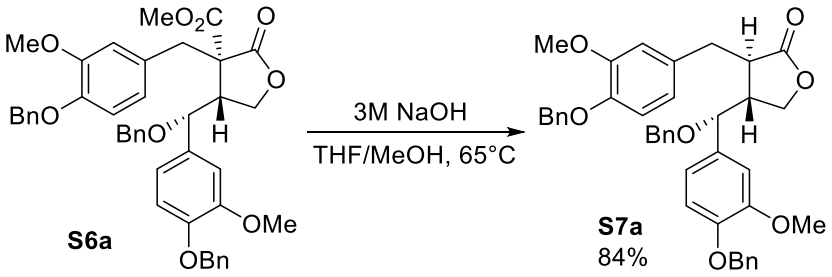


Following the procedure for the preparation of **11a**, the reaction of lactone **5d** (302 mg, 0.755 mmol) with 3-benzyloxy-4-methoxybenzyl bromide (157 mg, 1.13 mmol) gave the crude oil. The obtained crude oil was purified by column chromatography (SiO_2, hexane/AcOEt = 2/1) to give the product **11c** (450 mg, 95%).

11c: colorless solid; mp = 65-69 °C; $[\alpha]^{24}_D$ = 47.6° (*c* 1.00, chloroform, λ = 589 nm); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.74-2.80 (m, 1H), 2.83 (d, J = 14.5 Hz, 1H), 3.34 (d, J = 14.5 Hz, 1H), 3.50 (s, 3H), 3.81 (s, 6H), 3.90 (s, 3H), 4.12-4.20 (m, 2H), 4.35-4.38 (m, 2H), 4.45 (dd, J = 8.8, 10.9 Hz, 1H), 5.09 (d, J = 2.2 Hz, 2H), 6.35 (dd, J = 1.7, 8.2 Hz, 1H), 6.61 (d, J = 1.8 Hz, 1H), 6.70-6.72 (m, 2H), 6.77

(dd, J = 1.9, 8.2 Hz, 1H), 6.86 (d, J = 8.2 Hz, 1H), 7.23-7.41 (m, 10H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 36.6, 48.1, 53.0, 56.3, 56.4, 56.5, 57.7, 68.1, 70.9, 71.5, 78.0, 109.9, 111.5, 114.2, 114.5, 119.7, 123.5, 127.6 (aromatic C x 2), 128.2, 128.3, 128.4 (aromatic C x 2), 128.7, 128.8 (aromatic C x 2), 129.0 (aromatic C x 2), 131.6, 137.5, 137.9, 147.9, 149.6, 149.8, 150.1, 169.9, 175.9; IR (KBr, neat) 2931, 1776, 1739, 1514, 1265, 1143, 1028, 739, 698 cm^{-1}; HRMS (APCI) calcd for $C_{37}H_{38}O_9$ (M) 626.2510 , found 626.2545.

(α*R*, β*R*)-α-[4-(benzyloxy)-3-methoxyphenyl]-β-(*R*)-(benzyloxy)(4-benzyloxy-3-methoxyphenyl)methyl-γ-butyrolactone (S7a)

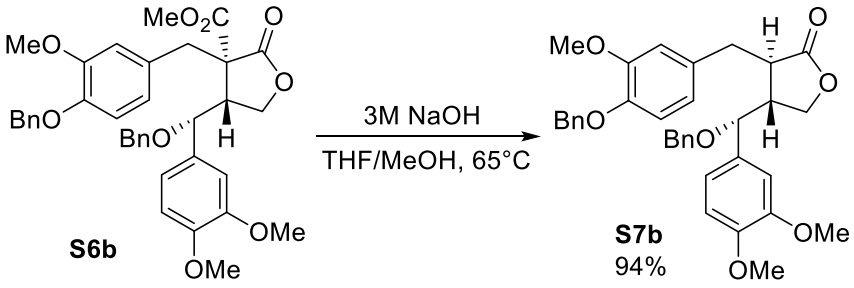


3M-NaOH aqueous solution (0.108 mL, 3.24 mmol) was dropwise added to a solution of **S6a** (456 mg, 649 mmol) in THF / Methanol (8/1, 12 mL) at 0 ˚C, and followed by being stirred at 65 ˚C for 3h. 1M-HCl aqueous solution (5 mL) was added to the reaction mixture, then additional water (20 mL) was added to the reaction mixture, which was extracted with AcOEt (ca. 10 ml x 5). The organic phase was washed with brine, dried (Na_2SO_4), and concentrated. The obtained crude oil was purified by column chromatography (SiO_2, hexane/AcOEt = 3/2) to give the product **S7a** (351 mg, 84%).

S7a: colorless solid; mp = 119-123 °C; $[\alpha]^{24}_D$ = 49.2° (*c* 1.00, chloroform, λ = 589 nm); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.52 (quint, J = 6.8, 7.2 Hz, 1H), 2.58 (dd, J = 4.0, 12.6 Hz, 1H), 2.64-2.74 (m, 2H), 3.76 (s, 3H), 3.80 (s, 3H), 3.97 (d, J = 7.2 Hz, 1H), 4.03 (d, J = 11.5 Hz, 1H), 4.10 (dd, J = 7.9, 9.3 Hz, 1H), 4.30 (dd, J = 6.8, 9.3 Hz, 1H), 4.36 (d, J = 11.5 Hz, 1H), 5.11 (s, 2H), 5.16 (s, 2H), 6.35 (dd, J = 2.0, 8.1 Hz, 1H), 6.54 (d, J = 2.0 Hz, 1H), 6.59 (dd, J = 1.9, 8.1 Hz, 1H), 6.63 (d, J = 1.9 Hz, 1H), 6.69 (d, J = 8.2 Hz, 1H), 6.82 (d, J = 8.2 Hz, 1H), 7.19-7.21 (m, 2H), 7.25-7.46 (m, 13H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 35.1, 43.9, 46.2, 56.3, 56.4, 69.0, 71.0, 71.5 (MeO-, C x 2), 81.2, 110.3, 113.2, 114.2, 114.4, 119.8, 121.7, 127.6(6) (aromatic C x 2), 127.7(4) (aromatic C x 2), 128.2, 128.4 (aromatic C x 4), 128.9 (aromatic C x 4), 129.0 (aromatic C x 2), 131.0, 132.2, 137.4, 137.6, 138.0, 147.4, 148.6, 150.1, 150.5, 179.3; IR (KBr, neat) 2916, 1763, 1589, 1514, 1454, 1422, 1261, 1234, 1165, 1136, 1026,

744, 696 cm^{-1}; HRMS (APCI) calcd for $C_{41}H_{40}O_7$ (M) 644.2769 , found 644.2766.

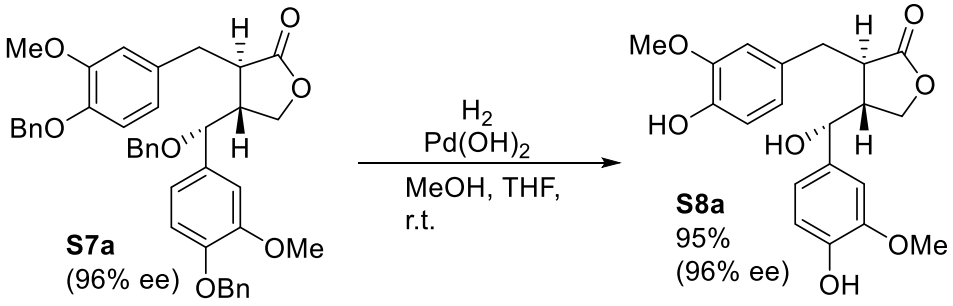
(α*R*, β*R*)-α-[4-(benzyloxy)-3-methoxyphenyl]-β-(*R*)-(benzyloxy)(3,4-dimethoxyphenyl)methyl -γ-butyrolactone (S7b)



Following the procedure for the preparation of **S7a**, the reaction of **S6b** (432 mg, 0.690 mmol) gave the crude oil. The obtained crude oil was purified by column chromatography (SiO_2, hexane/AcOEt = 4/1) to give the product **S7b** (369 mg, 94%).

S7b: colorless liquid; $[\alpha]^{28}_D$ = 57.5° (*c* 1.00, chloroform, λ = 589 nm); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.54 (quint, J = 7.1, 7.3 Hz, 1H), 2.58 (dd, J = 4.4, 12.1 Hz, 1H), 2.65-2.76 (m, 2H), 3.77 (s, 3H), 3.80 (s, 3H), 3.90 (s, 3H), 3.99 (d, J = 7.3 Hz, 1H), 4.06 (d, J = 11.5 Hz, 1H), 4.10 (dd, J = 7.9, 9.3 Hz, 1H), 4.31 (dd, J = 6.8, 9.3 Hz, 1H), 4.36 (d, J = 11.5 Hz, 1H), 5.12 (s, 2H), 6.38 (dd, J = 1.9, 8.1 Hz, 1H) , 6.54 (d, J = 1.9 Hz, 1H), 6.62 (d, J = 1.9 Hz, 1H), 6.66 (dd, J = 1.9, 8.1 Hz, 1H), 6.70 (d, J = 8.1 Hz, 1H), 6.80 (d, J = 8.1 Hz, 1H), 7.20-7.22 (m, 2H), 7.28-7.36 (m, 6H), 7.41-7.43 (m, 2H) ; ^{13}C NMR (101 MHz, $CDCl_3$) δ 35.1, 43.9, 46.2, 56.2(5), 56.2(8), 56.3, 69.0, 70.9, 71.5, 81.2, 109.8, 111.5, 113.1, 114.4, 119.8, 121.7, 127.6 (aromatic C x 2), 128.2, 128.4 (aromatic C x 3), 128.9 (aromatic C x 4), 131.0, 131.6, 137.6, 138.0, 147.4, 149.5, 149.8, 150.1, 179.3; IR (NaCl, neat) 3001, 2835, 1767, 1591, 1514, 1419, 1263, 1140, 1026, 810, 742, 698 cm^{-1}; HRMS (APCI) calcd for $C_{35}H_{36}O_7$ (M) 568.2456 , found 568.2463.

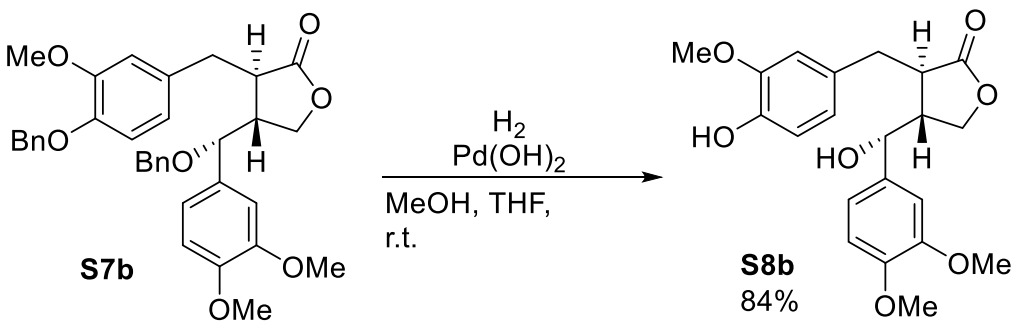
(α*R*, β*R*)-α-(4-hydroxy-3-methoxybenzyl)-β-(*R*)-hydroxy(4-hydroxy-3-methoxyphenyl)methyl-γ-butyrolactone (S8a: 7*R*-hydroxymatairesinol)



$Pd(OH)_2$ (16 mg, 22.9 μmol, 20 wt%) was added to a solution of compound **S7a** (148 mg, 0.229 mmol) in MeOH/THF [0.45 mL, 1/1 (v/v)] at room temperature, followed by being stirred at the same temperature for 9 h under hydrogen atmosphere (balloon). After a filtration, the filtrate solution was concentrated. The obtained crude oil was purified by column chromatography (SiO_2, hexane/AcOEt = 1/1) to give a product **S8a** (81 mg, 95%, 96% ee).

S8a: colorless solid; mp = 66-68 °C; $[\alpha]^{28}_D$ = -1.14° (*c* 1.00, chloroform, l = 589 nm); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.02 (brd, J = 2.7 Hz, 1H, OH), 2.51 (tdd, J = 6.0, 7.7, 13.6 Hz, 1H), 2.62 (td, J = 5.3, 7.9 Hz, 1H), 2.71 (dd, J = 8.0, 11.9 Hz, 1H), 2.78 (dd, J = 5.2, 12.8 Hz, 1H), 3.77 (s, 3H), 3.79 (s, 3H,), 4.18 (dd, J = 7.5, 9.4 Hz, 1H), 4.39 (dd, J = 2.8, 7.9 Hz, 1H), 4.42 (dd, J = 5.6, 9.5 Hz, 1H), 5.50 (s, 1H), 5.60 (s, 1H), 6.44 (d, J = 1.9 Hz, 1H), 6.49 (dd, J = 1.9, 8.0 Hz, 1H), 6.55 (d, J = 1.9 Hz, 1H), 6.63 (dd, J = 1.9, 8.0 Hz, 1H), 6.77 (d, J = 8.0 Hz, 1H), 6.83 (d, J = 8.0 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 35.3, 44.3, 46.5, 56.1 (MeO-, C x 2), 68.8, 74.7, 108.4, 111.5, 114.3, 114.5, 119.6, 122.4, 129.7, 133.9, 144.8, 146.0, 147.0, 147.3, 179.5; IR (KBr, neat) 3445, 2938, 1751, 1604, 1518, 1452, 1433, 1375, 1273, 1153, 1029, 733 cm^{-1}; HRMS (APCI) calcd for $C_{20}H_{22}O_7$ $(M-H)^-$ 373.1282 , found 373.1298. 96% ee: Because the absolute configuration of β-position of lactones would never change, we speculate the ee value of **S8a** as 96% ee on the basis of ee value of lactone **S4**.

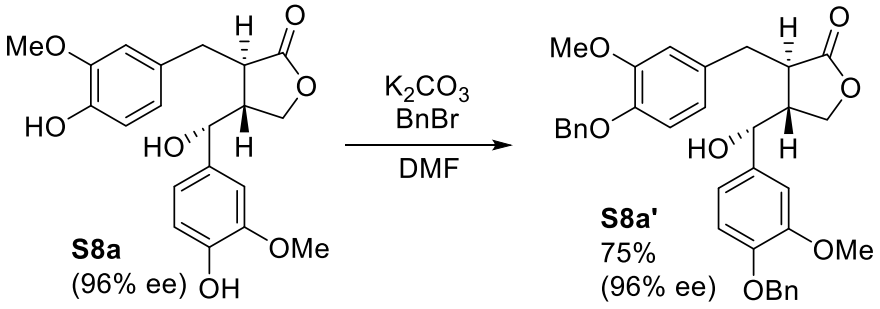
(α*R*, β*R*)-α-(4-hydroxy-3-methoxyphenyl)-β-(*R*)-(3,4-dimethoxyphenyl)(hydroxy)methyl -γ-butyrolactone (S8b: 7*R*-hydroxyarctigenin)



Following the procedure for the preparation of **S8a**, the reaction of **S7b** (355 mg, 0.625 mmol) gave the product **S8b** (204 mg, 84%).

S8b: colorless solid; mp = 75-78 °C; $[\alpha]^{27}_D$ = 11.0° (*c* 1.00, chloroform, λ = 589 nm); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.89 (brd, J = 2.7 Hz, 1H, OH), 2.54 (quint, J = 6.6, 7.3 Hz, 1H), 2.66 (td, J = 5.6, 7.3 Hz, 1H), 2.75 (s, 1H), 2.77 (d, J = 4.0 Hz, 1H), 3.77 (s, 3H), 3.81 (s, 3H,), 3.88 (s, 3H), 4.14 (dd, J = 7.7, 9.4 Hz, 1H), 4.40 (dd, J = 6.0, 11.7 Hz, 1H), 4.41 (d, J = 6.1 Hz, 1H), 5.51 (s, 1H), 6.49-6.51 (m, 2H), 6.62 (d, J = 1.9 Hz, 1H), 6.68 (dd, J = 1.9, 8.1 Hz, 1H), 6.77-6.80 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 35.2, 44.1, 46.4, 56.2 (MeO-,C x 2), 56.3, 68.7, 74.4, 109.2, 111.3, 111.7, 114.5, 118.7, 122.5, 129.7, 134.6, 144.9, 147.1, 149.3, 149.6, 179.6; IR (KBr, neat) 3437, 2935, 2360, 1762, 1605, 1518, 1267, 1155, 1024, 813, 746 cm^{-1}; HRMS (APCI) calcd for $C_{21}H_{24}O_7$ $(M-H)^-$ 387.1438, found 387.1425. Because the absolute configuration of β-position of lactones would never change, we speculate the ee value of **S8b** as 95% ee on the basis of ee value of lactone **4.**

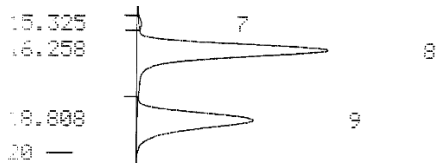
(α*R*, β*R*)-α-[4-(benzyloxy)-3-methoxyphenyl]-β-(*R*)-(4-benzyloxy-3-methoxyphenyl)(hydroxy)methyl-γ-butyrolactone (S8a′)



A DMF (0.6 ml) solution of **S8a** (100 mg, 0.267 mmol) was added to a suspension of K_2CO_3 (81 mg, 588 μmol) in DMF (0.2 ml) at 0 ˚C. Then, the DMF solution of benzyl bromide (70 μl, 588 μmol) was added to the mixture at 0 ˚C, and followed by being stirred at room temperature for 3h. 1M-HCl aqueous solution (10 ml) was added to the reaction mixture, which was extracted with AcOEt (ca. 10 ml x 5). The organic phase was washed with brine, dried (Na_2SO_4), and concentrated. The obtained crude oil was purified by column chromatography (SiO_2, hexane/AcOEt = 3/2) to give the product **S8a′** (111 mg, 75%).

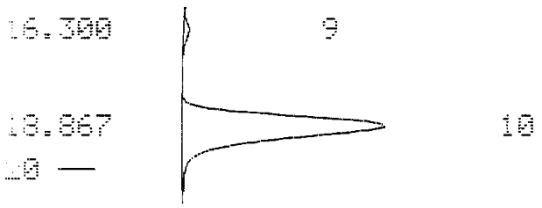
S8a′: colorless solid; mp = 53-55 °C; $[\alpha]^{24}_D$ = 20.5° (*c* 1.00, chloroform, λ = 589 nm); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.00 (brs, 1H), 2.51 (quint, J = 6.8, 14.4 Hz, 1H), 2.67-2.79 (m, 3H), 3.79 (s, 3H),

3.80 (s, 3H), 4.08 (dd, J = 7.9, 9.4 Hz, 1H), 4.33-4.37 (m, 2H), 5.11 (s, 2H), 5.14 (s, 2H), 6.43 (dd, J = 2.0, 8.1 Hz, 1H), 6.56-6.59 (m, 2H), 6.67 (d, J = 2.0 Hz, 1H), 6.72 (d, J = 8.1 Hz, 1H), 6.78 (d, J = 8.1 Hz, 1H), 7.27-7.37 (m, 6H), 7.41-7.43 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 35.1, 43.9, 46.5, 56.3 (MeO-, C x 2), 68.5, 71.4, 71.5, 74.4, 109.8, 113.2, 114.3, 114.4, 118.5, 121.7, 127.7 (aromatic C x 4), 128.3, 128.4, 128.9 (aromatic C x 2), 129.0 (aromatic C x 2), 131.1, 135.1, 137.3, 137.6, 147.4, 148.4, 150.1, 150.3, 179.4; IR (KBr, neat) 3418, 2926, 1742, 1591, 1516, 1259, 1230, 1138, 1032, 858, 810, 744, 696 cm^{-1}; HRMS (APCI) calcd for $C_{34}H_{34}O_7$ (M) 554.2299 , found 554.2340; HPLC analysis: 96% ee [Daicel CHIRALPAK IC (25cm) at 25˚C, flow rate 0.6 ml/min, solvent: hexane / ethanol = 1/2, t_R(racemic) = 16.26 min and 18.81 min, t_R(**S8a′**) = 19.83 min for major and 22.73 min for minor].



A 59.2/40.8 mixture of **S8a'** and optical isomer **S8a′′**: HPLC analysis using chiral column.

8	16.258	934775	26449	TLT	56.2950
9	18.808	643160	16057	T	38.7330

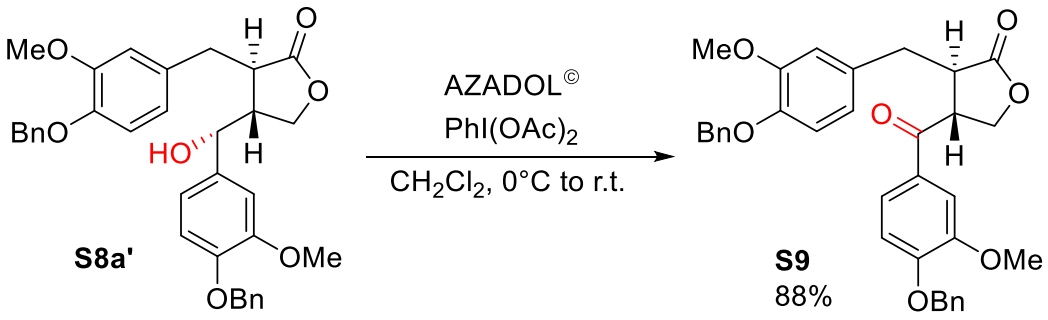


Enantioenriched **S8a′ (**96%ee) : HPLC analysis using chiral column.

9	16.300	7852	262	1.7130
10	18.867	411075	10131	89.6787

Based on this enantiomeric ratio (89.7/1.71), 96% ee was estimated.

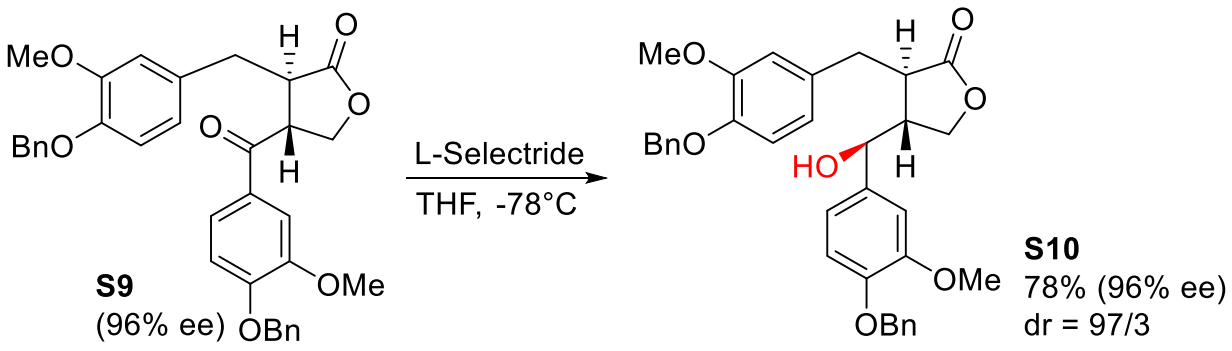
(3*R*,4*R*)-4-(4-(benzyloxy)-3-methoxybenzoyl)-3-(4-(benzyloxy)-3-methoxybenzyl) dihydrofuran-2(3*H*)-one (S9)



A CH_2Cl_2-solution (0.1 mL) of compound **S8a′** (50 mg, 92 μmol) was added to a solution of 2-hydroxy-2-azaadamantane (AZADOL©) (0.7 mg, 4.6 μmol) in CH_2Cl_2 (0.3 mL) at 0˚C under an Ar atmosphere, additionally, (Diacetoxyiodo)benzene (39 mg, 120 μmol) was added to the reaction mixture at the same temperature, followed by being stirred at room temperature for 1h. The mixture was diluted with saturated aqueous $NaHCO_3$ (1.0 mL) and saturated aqueous $Na_2S_2O_3$ (1.0 mL), then additional water (10 mL) was added to the reaction mixture, which was extracted with AcOEt (ca. 5 ml x 5). The organic phase was washed with brine, dried (Na_2SO_4), and concentrated. The obtained crude oil was purified by column chromatography (SiO_2, hexane/AcOEt = 2/1) to give the product **S9** (44 mg, 88%).

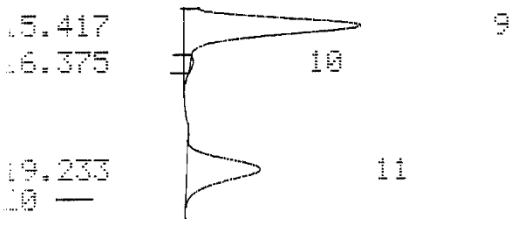
S9: colorless solid; mp = 109-112 °C; $[\alpha]^{24}_D$ = 7.33° (*c* 0.50, chloroform, λ = 589 nm); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.97 (dd, J = 6.7, 14.2 Hz, 1H), 3.02 (dd, J = 5.6, 14.2 Hz, 1H), 3.55 (ddd, J = 5.6, 6.7, 8.7 Hz, 1H), 3.70 (s, 3H), 3.90 (s, 3H), 4.03 (td, J = 8.2, 8.7 Hz, 1H), 4.08 (d, J = 8.2 Hz, 1H), 4.35 (t, J = 8.2 Hz, 1H), 5.03 (s, 2H), 5.22 (s, 2H), 6.53 (dd, J = 1.7, 8.0 Hz,1H), 6.62 (d, J = 1.7 Hz, 1H), 6.65 (d, J = 8.0 Hz, 1H), 6.81 (d, J = 8.4 Hz, 1H), 7.14 (dd, J = 1.8, 8.4 Hz, 1H), 7.26-7.42 (m, 11H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 34.7, 45.0, 46.9, 56.2, 56.5, 68.7, 71.3, 71.4, 111.1, 112.3, 113.2, 114.4, 122.0, 123.2, 127.6 (aromatic C x 2), 127.7 (aromatic C x 2), 128.3, 128.7, 128.9 (aromatic C x 2), 129.2 (aromatic C x 2), 129.4, 130.6, 136.3, 137.5, 147.5, 150.1, 150.3, 153.7, 177.7, 195.4; IR (KBr, neat) 3034, 2938, 2878, 1784, 1674, 1593, 1512, 1428, 1263, 1141, 1016, 810, 742 cm^{-1}; HRMS (APCI) calcd for $C_{34}H_{32}O_7$ $(M+H)^+$ 553.2221 , found 553.2260.

(α*R*, β*R*)-α-[4-(benzyloxy)-3-methoxyphenyl]-β-(*S*)-(4-benzyloxy-3-methoxyphenyl)(hydroxy)methyl-γ-butyrolactone (S10)



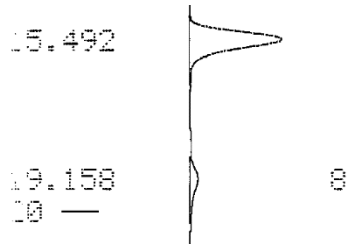
A 1.0 M-hexane-solution of L-selectride (152 μL, 152 μmol) was dropwise added to a solution of **S9** (70 mg, 127 μmol) in THF (0.25 mL) at -78 ˚C under an Ar atmosphere, followed by being stirred at the same temperature for 30 minutes. 1M-HCl aqueous solution (1 ml) was added to the reaction mixture at 0˚C, which was extracted with AcOEt (ca. 5 ml x 3). The organic phase was washed with brine, dried (Na_2SO_4), and concentrated. The obtained crude oil was purified by column chromatography (SiO_2, hexane/AcOEt = 4/3) to give the product **10a** (58 mg, 82% yield, dr = 93:7). **S10**: colorless solid; mp = 70-73 °C; $[\alpha]^{24}_D$ = 0.26° (*c* 0.50, chloroform, λ = 589 nm); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.95 (d, J = 2.7 Hz, 1H), 2.60 (td, J = 6.9, 14.1 Hz, 1H), 2.88 (dd, J = 5.3, 13.3 Hz, 1H), 2.94 (td, J = 5.3, 6.8 Hz, 1H), 3.05 (dd, J = 5.2, 13.3 Hz, 1H), 3.82 (s, 3H), 3.84 (s, 3H), 3.88 (d, J = 8.2 Hz, 1H), 3.92 (dd, J = 7.0, 9.3 Hz, 1H), 4.61 (dd, J = 2.6, 6.7 Hz, 1H), 5.11 (s, 2H), 5.14 (s, 2H), 6.55 (dd, J = 2.0, 8.2 Hz, 1H), 6.65 (dd, J = 2.0, 8.2 Hz, 1H), 6.71 (d, J = 2.0 Hz, 1H), 6.74 (d, J = 8.2 Hz, 1H), 6.75 (dd, J = 2.0 Hz, 1H), 6.81 (d, J = 8.2 Hz, 1H), 7.27-7.37 (m, 6H), 7.41-7.43 (m, 4H) ; ^{13}C NMR (101 MHz, $CDCl_3$) δ 34.9, 35.4, 44.0, 56.4, 56.5, 68.8, 71.4(7), 71.5(2), 75.6, 110.0, 113.8, 114.3, 114.4, 118.6, 122.2, 127.6(6), 127.6(9), 127.4, 128.2(4), 128.2(7), 128.4, 128.9(5), 128.9(8), 129.0, 131.2, 135.0, 137.3, 137.6, 137.7, 147.4, 148.6, 150.0, 150.4, 179.6; IR (KBr, neat) 3504, 3213, 2933, 1767, 1593, 1516, 1419, 1381, 1334, 1263, 1139, 1026, 810, 742, 696 cm^{-1}; HRMS (APCI) calcd for $C_{34}H_{34}O_7$ (M) 554.2299 , found 554.2322.

HPLC analysis: 96% ee [Daicel CHIRALPAK IC (25cm) at 25˚C, flow rate 0.6 ml/min, solvent: hexane / ethanol = 1/2, t_R(mixture of **S10** and optical isomer **S10′**) = 15.42 min and 19.23 min, t_R(**S10**) = 15.49 min for major and 19.12 min for minor].



A 66.6/33.4 mixture of **S10** and optical isomer **S10′**: HPLC analysis using chiral column.

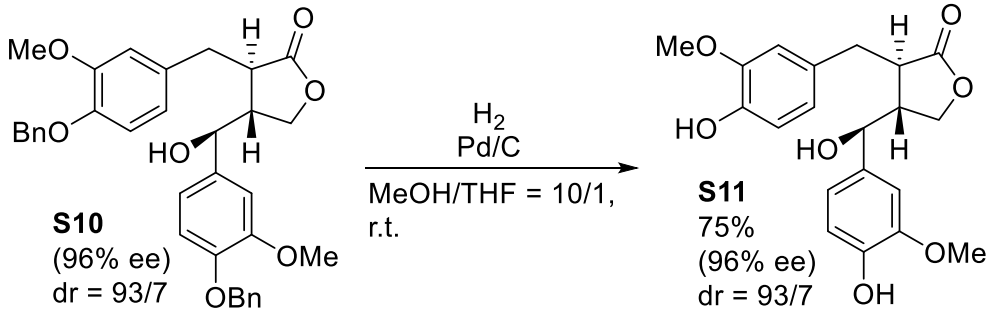
9	15.417	294718	8885	TTT	45.9648
10	16.375	2231	121	T	0.3480
11	19.233	147421	3691		22.9921



Enantioenriched **S10 (**96% ee) : HPLC analysis using chiral column.

7	15.492	286304	9225		80.7291
8	19.158	30317	700		8.5486

(α*R*, β*R*)-α-(4-hydroxy-3-methoxybenzyl)-β-(*S*)-hydroxy(4-hydroxy-3-methoxyphenyl)methyl-γ-butyrolactone (S11: 7*S*-hydroxymatairesinol)



Pd-C (10 mg, 10 mol%) was added to a solution of ester **S10** (50 mg, 90 μmol) in MeOH/THF (0.7 ml, 10/1) at room temperature, followed by being stirred at the same temperature for 9 h under hydrogen atmosphere (balloon). After a filtration, the filtrate solution was concentrated. The obtained crude oil was purified by column chromatography (SiO_2, hexane/AcOEt = 3/4) to give a product **S11** (25 mg, 75%, dr = 93/7).

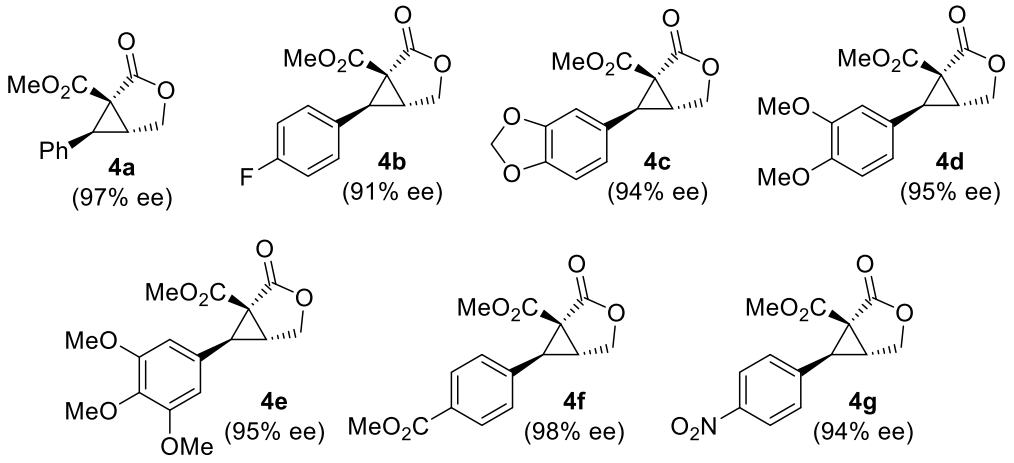
S11: colorless liquid; $[\alpha]^{24}_D$ = -30.6° (*c* 0.50, chloroform, λ = 589 nm); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.56-2.63 (m, 1H), 2.89-2.95 (m, 2H), 3.01 (dd, J = 8.1, 15.3 Hz, 1H), 3.81 (s, 3H), 3.84 (s, 3H), 3.93 (d, J = 8.1 Hz, 1H), 3.95 (d, J = 6.7 Hz, 1H), 4.63 (d, J = 6.5 Hz, 1H), 5.53 (s, 1H), 5.65 (s, 1H), 6.60

(dd, J = 1.9, 8.2 Hz, 1H), 6.61 (s, 1H), 6.67 (d, J = 1.8 Hz, 1H), 6.71 (dd, J = 1.9, 8.2 Hz, 1H), 6.78 (d, J = 7.8 Hz, 1H), 6.85 (d, J = 8.0 Hz, 1H) ; ^{13}C NMR (101 MHz, $CDCl_3$) δ 35.5, 44.1, 45.6, 56.2(5), 56.2(9), 69.0, 75.7, 108.7, 112.3, 114.4, 114.8, 119.2, 122.9, 129.9, 133.9, 144.8, 146.0, 147.0, 147.2, 179.8; IR (NaCl, neat) 3447, 2937, 2845, 2360, 1751, 1604, 1518, 1431, 1375, 1273, 1124, 1032, 821, 655 cm^{-1}; HRMS (APCI) calcd for $C_{20}H_{22}O_7$ $(M-H)^-$ 373.1282 , found 373.1314.

Because the absolute configuration would never change during the debenzylation, we speculate the ee value of **S11** as 96% ee on the basis of ee value of **S10.**

3.2.3. scope and limitation of OHM reaction.

Preparations of bicyclic D–A cyclopropanes 4a-g.



Following our previous reports,[a-d] bicyclolactones **4a-g** were prepared.

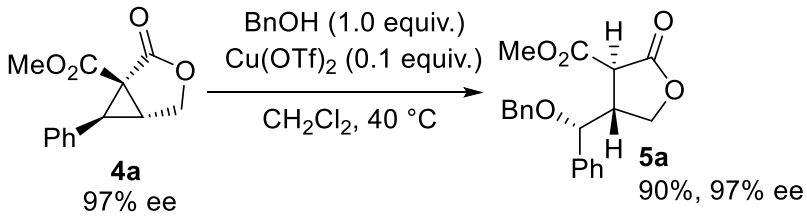
For procedures for the syntheses of **4a-g** and their characterizations, see supporting information of these literatures.

[a] J. Ito, D. Sakuma, Y. Nishii, *Chem. Lett*. **2015**, *44*, 297 (open access article). [b] S. Takada, K. Iwata, T. Yubune, Y. Nishii, *Tetrahedron Lett*. **2016**, *57*, 2422. [c] S. Takada, T. Saito, K. Iwata, Y. Nishii, *Asian J. Org. Chem*. **2016**, *5*, 1225. [d] Y. Sone, Y. Kimura, R. Ota, T. Mochizuki, J. Ito, Y. Nishii, *Eur. J. Org. Chem*. **2017**, 2842.

6	14.042	81747	3195	2.0522
7	18.875	3861115	116299	96.9328

Based on this enantiomeric ratio (96.9/2.1), 96% ee was estimated.

(α*S*, β*R*)-α-Methoxycarbonyl-β-(*R*)-(benzyloxy)phenylmethyl-γ-butyrolactone (5a)

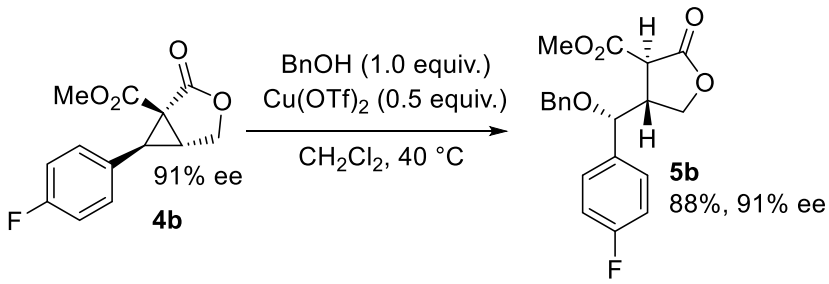


Benzyl alcohol (22 μL, 0.215 mmol) was added to a mixture of cyclopropane **4a** (50 mg, 0.215 mmol) and $Cu(OTf)_2$ (8 mg, 21.5 μmol) in CH_2Cl_2 (2.2 mL) at 0°C under an Ar atmosphere, followed by being stirred at 40°C for 4 h. After the reaction was completed, the mixture was cool down to 0°C. Water (3 mL) was added to the mixture, which was extracted with $CHCl_3$ (2 mL x 3). The organic layer was washed with brine, dried (Na_2SO_4) and concentrated. The obtained crude oil was purified by column chromatography (SiO_2, hexane/AcOEt = 4/1) to give the product **5a** (66 mg, 90 %, 97% ee).

5a: colorless solid; mp 80-82˚C; $[\alpha]_D^{24} = 96.5$ (*c* = 1.00, chloroform, λ = 589 nm); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.31-3.41 (m, 1H), 3.44 (d, *J* = 9.5 Hz, 1H) , 3.55 (s, 3H), 4.22 (d, *J* = 11.8 Hz, 1H), 4.28 (dd, *J* = 9.2, 8.3 Hz, 1H), 4.36 (d, *J* = 6.7 Hz, 1H), 4.41 (dd, *J* = 9.2, 8.0, 1H), 4.54 (d, *J* = 11.8, 1H), 7.23-7.25 (m, 1H), 7.29-7.43 (m, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 45.6, 48.0, 51.8, 68.1, 69.5, 79.0, 125.9, 126.9, 127.0, 127.6, 127.9, 136.4, 136.9, 147.9, 166.1, 170.5 ; IR (KBr, neat) 3350, 3063, 3030, 2872, 1780, 1741, 1496, 1454, 1207, 1022, 698 cm^{-1}; HRMS (APCI) calcd for $C_{20}H_{20}O_5$ $(M-H)^-$ 339.1227, found 339.1239. The ee of **5a** (97% ee) was determined by HPLC analysis in our previous report.[a] On the basis of spectral data, the absolute configuration of **5a** was determined by analogy with the similar compound **5e** (CCDC 1456448) that was assigned by X-ray crystallographic analysis in our previous report.[a]

[a] S. Takada, K. Iwata, T. Yubune, Y. Nishii, *Tetrahedron Lett*. **2016**, *57*, 2422.

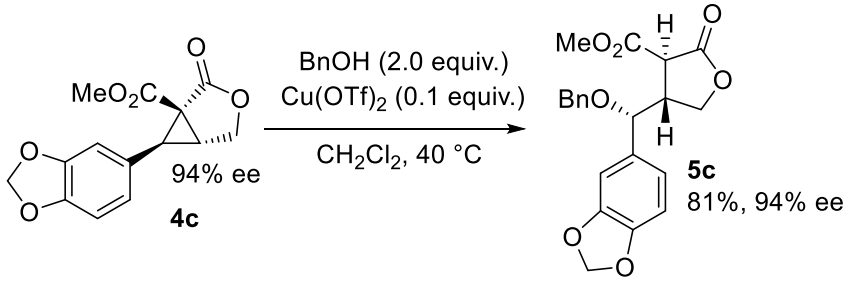
(α*S*, β*R*)-α-Methoxycarbonyl-β-(*R*)-(benzyloxy)(4-fluorophenyl)methyl-γ-butyrolactone (5b)



Following the procedure for the preparation of **5a**, the reaction of bicyclolactone **4b** (54 mg, 0.215 mmol) with benzyl alcohol (22 μL, 0.215 mmol) in the presence of $Cu(OTf)_2$ (39 mg, 0.108 mmol) gave the product **5b** (72 mg, 88%). (Reaction time = 5 h)

5b: colorless solid; mp 51-52˚C; $[\alpha]_D^{26}$ = 148.5 (*c* = 1.00, chloroform, λ = 589 nm); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.28-3.36 (m, 1H), 3.40 (d, *J* = 9.4 Hz, 1H), 3.57 (s, 3H), 4.14 (d, *J* = 11.8 Hz, 1H), 4.25 (dd, *J* = 9.0, 8.2 Hz, 1H), 4.33 (d, *J* = 6.8 Hz, 1H), 4.42 (dd, *J* = 9.2, 7.8, 1H), 4.52 (d, *J* = 11.8, 1H), 7.07-7.13 (m, 2H), 7.21-7.25 (m, 2H), 7.27-7.39 (m, 5H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 47.0, 49.3, 53.3, 69.5, 70.9, 79.9, 116.3, (d, $J_{C\text{-}F}$ = 21.6 Hz), 128.4, 128.5, 129.0, 129.1 (d, JC-F = 8.3 Hz), 134.2 (d, $J_{C\text{-}F}$ = 3.0 Hz), 137.5, 163.2 (d, $J_{C\text{-}F}$ = 247 Hz), 167.9, 171.8; IR (KBr, neat) 3537, 3064, 3030, 2953, 2916, 2868, 1782, 1741, 1604, 1508, 1454, 1222, 1170, 1020, 840, 740 cm^{-1}; HRMS (APCI) calcd for $C_{20}H_{19}FO_5$ $(M\text{-}H)^+$ 357.1133, found 357.1135. Based on the fixed absolute configuration at the β-position of lactone **4b** (91% ee), ee of **5b** was determined as 91% ee.

(α*S*, β*R*)-α-Methoxycarbonyl-β-(*R*)-(benzyloxy)(3,4-methylenedioxyphenyl)methyl -γ-butyrolactone (5c)

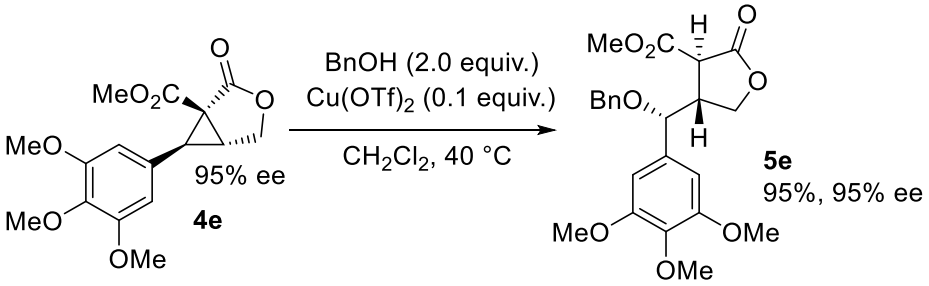


Following the procedure for the preparation of **5a**, the reaction of bicyclolactone **4c** (59 mg, 0.215 mmol) with benzyl alcohol (44 μL, 0.43 mmol) in the presence of $Cu(OTf)_2$ (8 mg, 22 μmol) gave the product **5c** (67 mg, 81%). (Reaction time = 0.5 h)

5c: colorless solid; mp 112-113˚C; $[\alpha]_D^{26}$ = 122.0 (*c* = 1.00, chloroform, λ = 589 nm); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.26-3.34 (m, 1H), 3.40 (d, *J* = 9.2 Hz, 1H), 3.61 (s, 3H), 4.20 (d, *J* = 11.8 Hz, 1H), 4.24-4.28 (m, 2H), 4.43 (dd, *J* = 9.2, 7.9 Hz, 1H), 4.53 (d, *J* = 11.8 Hz, 1H), 5.99 (s, 2H), 6.72-6.75

(dd, *J* = 1.5, 8.0 Hz, 1H), 6.80-6.83 (m, 2H), 7.22-7.25 (m, 2H), 7.29-7.38 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 47.0, 49.5, 53.2, 69.6, 70.8, 80.3, 101.7, 107.2, 108.8, 121.2, 128.4, 128.5, 129.0, 132.2, 137.7, 148.3, 148.9, 167.3, 171.9; IR (KBr, neat) 3533, 3446, 3084, 3014, 2954, 2887, 2864, 1772, 1743, 1489, 1436, 1247, 1134, 1016, 929, 810, 744, 690 cm^{-1}; HRMS (APCI) calcd for $C_{21}H_{20}O_7$ $(M-H)^-$ 383.1125, found 383.1120. Based on the fixed absolute configuration at the β-position of lactone **4c** (94% ee), ee of **5c** was determined as 94% ee.

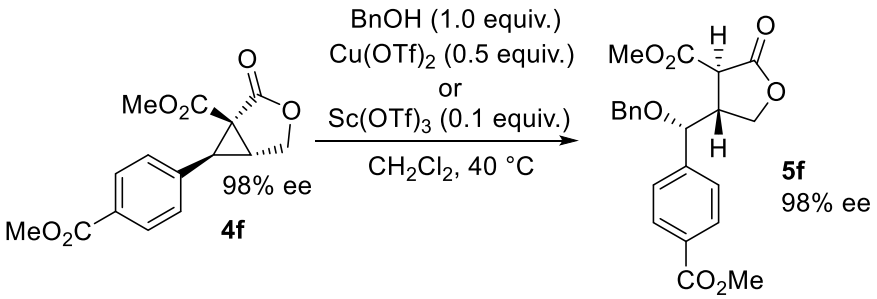
(α*S*, β*R*)-α-Methoxycarbonyl-β-(*R*)-(benzyloxy)(3,4,5-trimethoxyphenyl)methyl -γ-butyrolactone (5e)



Following the procedure for the preparation of **5a**, the reaction of bicyclolactone **4e** (69 mg, 0.215 mmol) with benzyl alcohol (44 μL, 0.43 mmol) in the presence of $Cu(OTf)_2$ (8 mg, 22 μmol) gave the product **5e** (88 mg, 95%). (Reaction time = 10 min)

5e: colorless solid; mp 143-145˚C; $[\alpha]_D^{26}$ = 100.1 (*c* = 1.00, chloroform, λ = 589 nm); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.30-3.38 (m, 1H), 3.44 (d, J = 9.6 Hz, 1H), 3.60 (s, 3H), 3.87 (s, 9H), 4.24-4.29 (m, 2H), 4.28 (d, J = 6.3 Hz, 1H), 4.44 (dd, J = 9.1, 8.0 Hz, 1H), 4.56 (d, J = 11.8 Hz, 1H), 6.50 (s, 2H), 7.24-7.28 (m, 2H), 7.33-7.39 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 46.9, 49.5, 53.3, 56.7, 61.2, 69.6, 71.0, 80.7, 104.1, 128.4, 128.5, 129.0, 133.9, 137.7, 138.5, 154.1, 167.9, 171.8; IR (KBr, neat) 3001, 2945, 2843, 1770, 1737, 1593, 1508, 1327, 1247, 1134, 1024, 754 cm^{-1}; HRMS (APCI) calcd for $C_{23}H_{26}O_8$ $(M-H)^-$ 429.1555, found 429.1559. Based on the fixed absolute configuration at the β-position of lactone **4e** (95% ee), ee of **5e** was determined as 95% ee.

(α*S*, β*R*)-α-Methoxycarbonyl-β-(*R*)-(benzyloxy)(4-methoxycarbonylphenyl)methyl -γ-butyrolactone (5f)



Benzyl alcohol (21 μL, 0.207 mmol) was added to a mixture of cyclopropane **4f** (60 mg, 0.207 mmol) and Lewis acid [$Cu(OTf)_2$ (37 mg, 0.103 mmol) or $Sc(OTf)_3$ (10 mg, 21 μmol)] in CH_2Cl_2 (2.1 mL) at 0 °C under an Ar atmosphere, followed by being stirred at 40 °C. Then, the mixture was cool down to 0°C. Water (3 mL) was added to the mixture, which was extracted with $CHCl_3$ (2 mL x 3). The organic layer was washed with brine, dried (Na_2SO_4) and concentrated. The obtained crude oil was purified by column chromatography (SiO_2, hexane/AcOEt = 6/1) to give the product **5f** (x mg, y %, 94% ee).

(a) Lewis acid: $Cu(OTf)_2$ (37 mg, 0.103 mmol)

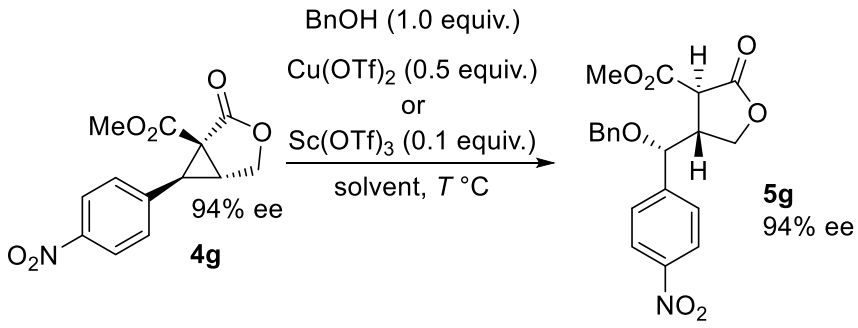
Reaction time = 24 h, x = 66, y = 81.

(b) Lewis acid: $Sc(OTf)_3$ (10 mg, 21 μmol)

Reaction time = 5 h, x = 75, y = 91.

5f: colorless solid; mp = 104-106°C; $[\alpha]_D^{25}$= 103.2 (*c* = 1.00, chloroform, λ = 589 nm); ^{1}H NMR (400MHz,$CDCl_3$) δ 3.26-3.36 (m, 1H), 3.47 (d, J = 9.4 Hz, 1H), 3.67 (s, 3H), 3.94 (s, 3H), 4.21 (d, J = 11.8 Hz, 1H), 4.27 (dd, J = 8.2, 8.8 Hz, 1H), 4.35 (dd, J = 8.2, 9.2 Hz, 1H), 4.44 (d, J = 6.3 Hz, 1H), 4.55 (d, J = 11.7 Hz, 1H), 7.22-7.26 (m, 2H), 7.31-7.38 (m, 3H), 7.40 (d, J = 8.2 Hz, 2H), 8.08 (d, J = 8.2 Hz, 2H) ; ^{13}C NMR (101 MHz, $CDCl_3$) δ 46.7, 49.2, 52.7, 53.4, 69.0, 71.3, 79.7, 127.2, 128.5, 128.7, 129.1, 130.7, 131.1, 137.3, 143.6, 166.9, 167.7, 171.6; IR (KBr,neat) 3001, 2953, 2873, 1775, 1742, 1717, 1610, 1501, 1433, 1287, 1175, 1111, 1020, 741 cm^{-1}; HRMS (ESI) calcd for $C_{22}H_{22}O_7$ $(M+Na)^+$ 421.1258, found 421.1263. Based on the fixed absolute configuration at the β-position of lactone **4f** (98% ee), ee of **5f** was determined as 98% ee.

(α*S*, β*R*)-α-Methoxycarbonyl-β-(*R*)-(benzyloxy)(4-nitrophenyl)methyl-γ-butyrolactone (5g)



Benzyl alcohol (19 μL, 0.180 mmol) was added to a mixture of cyclopropane **4g** (50 mg, 0.180 mmol) and Lewis acid [$Cu(OTf)_2$ (35 mg, 90 μmol) or $Sc(OTf)_3$ (9 mg, 18 μmol)] in solvent (CH_2Cl_2 or 1,2-dichloroethane) (1.8 mL) at 0 °C under an Ar atmosphere, followed by being stirred at *T* °C. Then, the mixture was cool down to 0°C. Water (3 mL) was added to the mixture, which was extracted with $CHCl_3$ (2 mL x 3). The organic layer was washed with brine, dried (Na_2SO_4) and concentrated. The obtained crude oil was purified by column chromatography (SiO_2, hexane/AcOEt = 6/1) to give the product **5g** (x mg, y %, 94% ee).

(a) Lewis acid: $Cu(OTf)_2$ (35 mg, 90 μmol), solvent: CH_2Cl_2, *T* = 40.

Reaction time = 24 h, x = 28, y = 41.

(b) Lewis acid: $Cu(OTf)_2$ (35 mg, 90 μmol), solvent: 1,2-dichloroethane, *T* = 70.

Reaction time = 24 h, x = 51, y = 74.

(c) Lewis acid: $Sc(OTf)_3$ (9 mg, 18 μmol), solvent: CH_2Cl_2, *T* = 40.

Reaction time = 24 h., x = 40, y = 58.

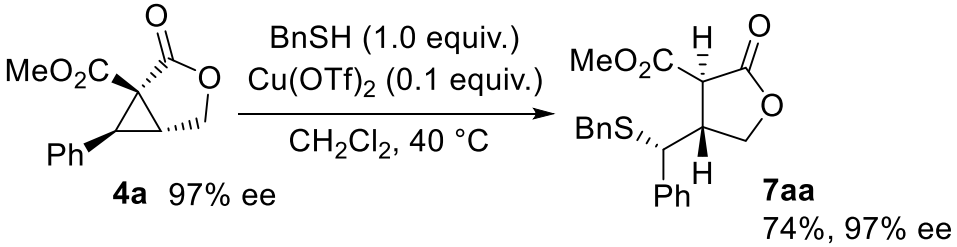
(d) Lewis acid: $Sc(OTf)_3$ (9 mg, 18 μmol), solvent: 1,2-dichloroethane, *T* = 70.

Reaction time = 3 h., x = 50, y = 72.

5g : colorless solid; mp = 118-120°C; $[\alpha]_D^{25}$ = 107.2 (*c* = 1.00, chloroform, λ = 589 nm); ^{1}H NMR (400MHz,$CDCl_3$) δ 3.28-3.36 (m, 1H), 3.48 (d, J = 9.4 Hz, 1H), 3.61 (s, 3H), 4.23 (d, J = 11.8 Hz, 1H), 4.26 (dd, J = 8.2, 8.4 Hz, 1H), 4.32 (dd, J = 8.2, 9.2 Hz, 1H), 4.51 (d, J = 6.1 Hz, 1H), 4.58 (d, J = 11.8 Hz, 1H), 7.22-7.26 (m, 2H), 7.33-7.41 (m, 3H), 7.52 (d, J = 8.6 Hz, 2H), 8.28 (d, J = 8.6 Hz, 2H) ; ^{13}C NMR (101 MHz, CDCl3) δ 46.5, 49.1, 53.5, 68.5, 71.7, 79.0, 124.6, 128.1, 128.5, 128.9, 129.2, 136.8, 146.0, 148.6, 167.5, 171.3; IR (KBr,neat) 2954, 2913, 1773, 1740, 1520, 1356, 1159, 1028, 1016, 750 cm^{-1} ; HRMS (ESI) calcd for $C_{20}H_{19}NO_7$ $(M+Na)^+$ 408.1054, found 408.1055. Based on the fixed absolute configuration at the β-position of lactone **4g** (94% ee), ee of **5g** was determined as 94% ee.

OHM reactions using thiols.

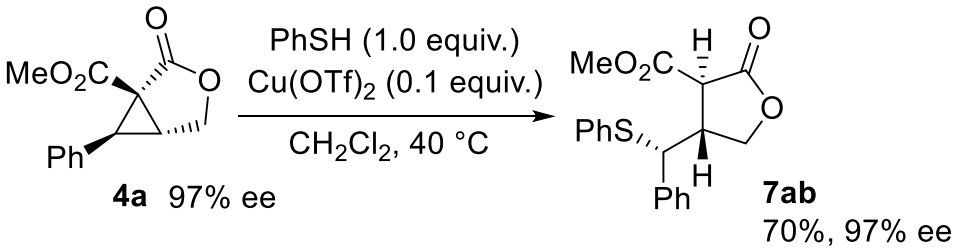
(α*S*, β*R*)-α-methoxycarbonyl-β-(*R*)-(benzylthio)(phenyl)methyl-γ-butyrolactone (7aa)



Benzyl mercaptan (25 μL, 0.215 mmol) was added to a solution of cyclopropane **4a** (50 mg, 0.215 mmol) in CH_2Cl_2 (2.2 mL) at 0°C under an Ar atmosphere. Additionally, $Cu(OTf)_2$ (8 mg, 22 μmol) was added to the mixture at the same temperature, followed by being stirred at 40°C for 5 h. The reaction mixture was cool down to 0°C, water (3 mL) was added to the mixture, which was extracted with $CHCl_3$ (2 mL x 3). The organic layers were washed with brine, dried (Na_2SO_4) and concentrated. The obtained crude was purified by column chromatography (SiO_2, hexane/AcOEt = 4/1) to give the product **7aa** (57 mg, 74 %).

7aa: yellow oil; $[\alpha]_D^{25}$ = 339.7 (*c* = 1.00, chloroform, λ = 589 nm); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.31-3.41 (m, 1H), 3.44 (d, *J* = 9.5 Hz, 1H) , 3.55 (s, 3H), 4.22 (d, *J* = 11.8 Hz, 1H), 4.28 (dd, *J* = 9.2, 8.3 Hz, 1H), 4.36 (d, *J* = 6.7 Hz, 1H), 4.41 (dd, *J* = 9.2, 8.0, 1H), 4.54 (d, *J* = 11.8, 1H), 7.23-7.25 (m, 1H), 7.29-7.43 (m, 9H) ; ^{13}C NMR (101 MHz, $CDCl_3$) δ 45.6, 48.0, 51.8, 68.1, 69.5, 79.0, 125.9, 126.9, 127.0, 127.6, 127.9, 136.4, 136.9, 147.9, 166.1, 170.5; IR (KBr, neat) 3350, 3063, 3030, 2872, 1780, 1741, 1496, 1454, 1207, 1022, 698 cm^{-1}; HRMS (ESI) calcd for $C_{20}H_{20}O_4S$ $(M+Na)^+$ 379.0980 , found 379.0975. Based on the fixed absolute configuration at the β-position of lactone **4a** (97% ee), ee of **7aa** was determined as 97% ee.

(α*S*, β*R*)-α-Methoxycarbonyl-β-(*R*)-(phenylthio)(phenyl)methyl-γ-butyrolactone (7ab)

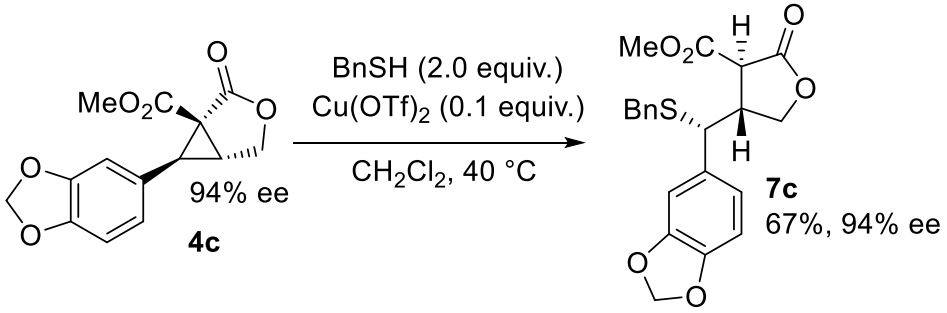


Benzenethiol (24 μL, 0.215 mmol) was added to a solution of cyclopropane **4a** (50 mg, 0.215 mmol)

in CH_2Cl_2 (2.2 mL) at 0°C under an Ar atmosphere. Additionally, $Cu(OTf)_2$ (8 mg, 22 μmol) was added to the mixture at the same temperature, followed by being stirred at 40°C for 1.5 h. The reaction mixture was cool down to 0°C, water (2.2 mL) was added to the mixture, which was extracted with $CHCl_3$ (2 mL x 3). The organic layers were washed with brine, dried (Na_2SO_4) and concentrated. The obtained crude was purified by column chromatography (SiO_2, hexane/AcOEt = 5/1) to give the product **7ab** (52 mg, 70 %).

7ab: colorless solid; mp = 79-82 °C; $[\alpha]_D^{25}$ = 234.9 (*c* = 1.00, chloroform, λ = 589 nm); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29-7.14 (m, 10H), 4.72 (dd, *J* = 9.3, 8.0 Hz, 1H), 4.29 (t, *J* = 9.0 Hz, 1H), 4.05 (d, *J* = 10.3 Hz, 1H), 3.64-3.55 (m, 1H), 3.42 (s, 3H), 3.34 (d, *J* = 9.6 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.3, 167.5, 138.9, 133.3, 132.9, 129.1, 128.8, 128.3, 128.3, 71.1, 57.3, 53.0, 51.7, 45.8; IR (KBr, neat) 2955, 2891, 1780, 1734, 1435, 1379, 1292, 1142, 1067, 1020, 746, 704, 691 cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{18}O_4S$ $(M+Na)^+$ 365.0823, found 365.0818. Based on the fixed absolute configuration at the β-position of lactone **4a** (97% ee), ee of **7ab** was determined as 97% ee.

(α*S*, β*R*)-α-Methoxycarbonyl-β-(*R*)-(benzylthio)(3,4-methylenedioxyphenyl)methyl -γ-butyrolactone (7c)

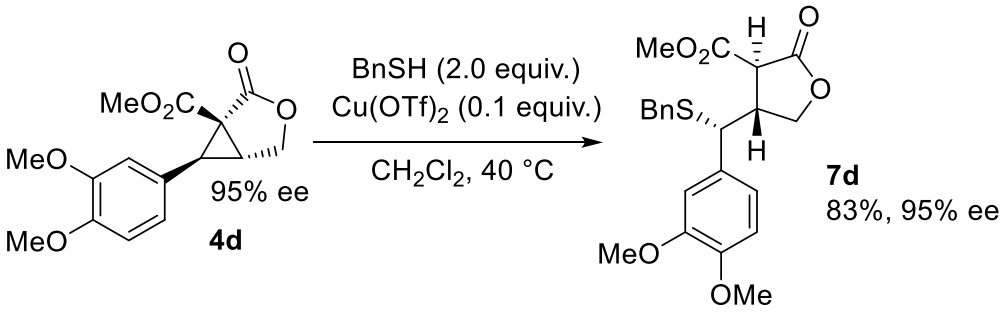


Benzyl mercaptan (50 μL, 0.430 mmol) was added to a solution of cyclopropane **4c** (59 mg, 0.215 mmol) in CH_2Cl_2 (2.2 mL) at 0°C under an Ar atmosphere. Additionally, $Cu(OTf)_2$ (8 mg, 22 μmol) was added to the mixture at the same temperature, followed by being stirred at 40°C for 30 min. The reaction mixture was cool down to 0°C, water (2.0 mL) was added to the mixture, which was extracted with $CHCl_3$ (2 mL x 3). The organic layers were washed with brine, dried (Na_2SO_4) and concentrated. The obtained crude was purified by column chromatography (SiO_2, hexane/AcOEt = 4/1) to give the product **7c** (58 mg, 67 %).

7c: colorless amorphous; $[\alpha]_D^{22}$ = 232.4 (*c* = 1.00, chloroform, λ = 589 nm); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.23 (m, 3H), 7.21 – 7.15 (m, 2H), 6.83 (d, *J* = 1.7 Hz, 1H), 6.74 (d, *J* = 7.9 Hz, 1H),

6.64 (dd, *J* = 7.9, 1.8 Hz, 1H), 5.97 (s, 2H), 4.55 (dd, *J* = 9.4, 7.7 Hz, 1H), 4.00 – 3.94 (m, 1H), 3.57 (d, *J* = 13.7 Hz, 1H), 3.50 (s, 3H), 3.47 – 3.29 (m, 3H), 3.23 (d, *J* = 9.6 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.3, 167.3, 148.3, 147.6, 137.4, 132.7, 129.0, 128.7, 127.5, 122.3, 108.3, 108.1, 101.4, 70.9, 52.9, 51.6, 51.4, 45.8, 35.2; IR (KBr, neat) 2995, 2957, 2907, 2839, 1775, 1738, 1589, 1508, 1456, 1327, 1246, 1126, 1002 cm^{-1}; HRMS (ESI) calcd for $C_{21}H_{20}O_6S$ $(M+Na)^+$ 423.0878, found 423.0873. Based on the fixed absolute configuration at the β-position of lactone **4c** (94% ee), ee of **7c** was determined as 94% ee.

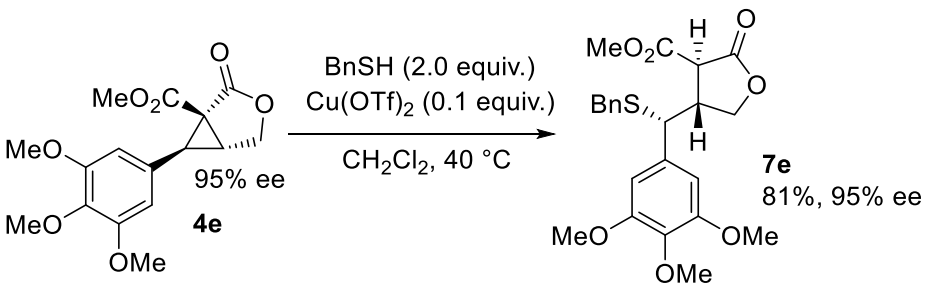
(α*S*, β*R*)-α-Methoxycarbonyl-β-(*R*)-(benzylthio)(3,4-dimethoxyphenyl)methyl -γ-butyrolactone (6d)



Benzyl mercaptan (65 μL, 0.554 mmol) was added to a solution of cyclopropane **4d** (81 mg, 0.277 mmol) in CH_2Cl_2 (2.8 mL) at 0°C under an Ar atmosphere. Additionally, $Cu(OTf)_2$ (10 mg, 28 μmol) was added to the mixture at the same temperature, followed by being stirred at 40°C for 30 min. The reaction mixture was cool down to 0°C, water (2.5 mL) was added to the mixture, which was extracted with $CHCl_3$ (2 mL x 3). The organic layers were washed with brine, dried (Na_2SO_4) and concentrated. The obtained crude was purified by column chromatography (SiO_2, hexane/AcOEt = 4/1) to give the product **7d** (95 mg, 83 %).

7d: colorless solid; mp = 94-97 °C; $[\alpha]_D^{26}$ = 312.4 (*c* = 1.00, chloroform, λ = 589 nm); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.23 (d, J = 9.1 Hz, 1H), 3.38-3.48 (m, 3H), 3.43 (s, 3H), 3.56 (d, J = 13.6 Hz, 1H), 3.88 (s, 3H), 3.89 (s, 3H), 3.99 (dd, J = 8.5 Hz, 1H), 4.58 (dd, J = 7.5, 7.7 Hz, 1H), 6.73 (dd, J = 2.0, 8.2 Hz, 1H), 6.80-6.83 (m, 2H), 7.17-7.19 (m, 2H), 7.23-7.32 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 35.1, 45.6, 51.5, 51.6, 52.8, 56.0, 56.1, 71.0, 110.8, 110.9, 121.2, 127.4, 128.6, 129.0, 131.0, 137.5, 148.9, 149.0, 167.5, 171.3; IR (KBr, neat) 3001, 2947, 2835, 1782, 1732, 1514, 1261,1144,1026 cm^{-1}; HRMS (ESI) calcd for $C_{22}H_{24}O_6S$ $(M+Na)^+$ 439.1191, found 439.1186. Based on the fixed absolute configuration at the β-position of lactone **4d** (95% ee), ee of **7d** was determined as 95% ee.

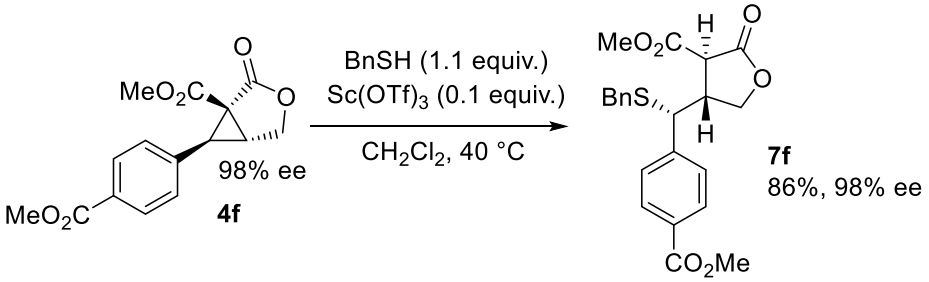
(α*S*, β*R*)-α-Methoxycarbonyl-β-(*R*)-(benzylthio)(3,4,5-trimethoxyphenyl)methyl -γ-butyrolactone (6e)



Benzyl mercaptan (64 μL, 0.516 mmol) was added to a solution of cyclopropane **4e** (83 mg, 0.258 mmol) in CH_2Cl_2 (2.6 mL) at 0°C under an Ar atmosphere. Additionally, $Cu(OTf)_2$ (9 mg, 26 μmol) was added to the mixture at the same temperature, followed by being stirred at 40°C for 30 min. The reaction mixture was cool down to 0°C, water (2.2 mL) was added to the mixture, which was extracted with $CHCl_3$ (2 mL x 3). The organic layers were washed with brine, dried (Na_2SO_4) and concentrated. The obtained crude was purified by column chromatography (SiO_2, hexane/AcOEt = 2/1) to give the product **7e** (93 mg, 81 %).

7e: colorless solid; mp = 114-116 ℃; $[\alpha]_D^{25}$ = 247.1 (*c* =1.00, chloroform, l = 589 nm); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.22-3.29 (m, 1H), 3.40-3.47 (m, 3H), 3.46 (s, 3H), 3.60 (d, J = 13.9 Hz, 1H), 3.85 (s, 9H), 3.97-4.03 (m, 1H), 4.57-4.61 (m, 1H), 6.44 (s, 2H) 7.19-7.20 (m, 2H), 7.24-7.32 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 35.3, 45.6, 51.6, 52.1, 52.9, 56.2, 60.9, 71.0, 105.4, 127.5, 128.6, 129.0, 134.3, 137.4, 137.7, 153.4, 167.6, 171.3 ; IR (KBr, neat) 2995, 2957, 2907, 2839, 1775, 1738, 1589, 1508, 1456, 1327, 1246, 1126, 1002 cm^{-1}; HRMS (ESI) calcd for $C_{23}H_{26}O_7S$ $(M+Na)^+$ 469.1297, found 469.1291. Based on the fixed absolute configuration at the β-position of lactone **4e** (95% ee), ee of **7e** was determined as 95% ee.

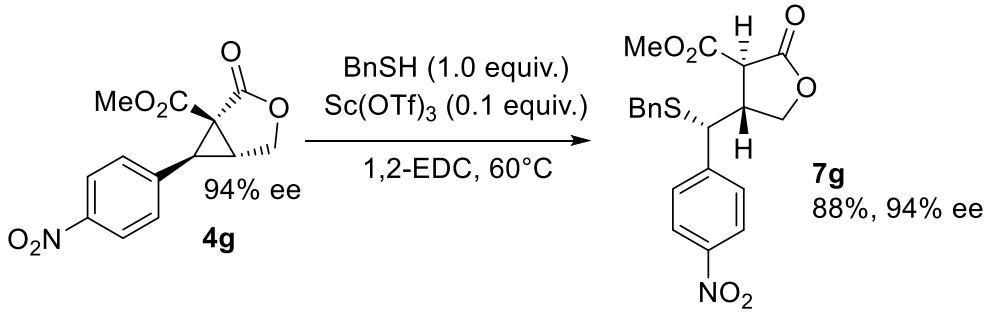
(α*S*, β*R*)-α-Methoxycarbonyl-β-(*R*)-(benzylthio)(4-methoxycarbonylphenyl)methyl -γ-butyrolactone (7f)



Benzylmercaptan (18 μL, 0.152 mmol) was added to a solution of cyclopropane **4f** (40 mg, 0.138 mmol) in CH_2Cl_2 (1.5 mL) at 0°C under an Ar atmosphere. Additionally, $Sc(OTf)_3$ (7 mg, 14 μmol) was added to the mixture at the same temperature, followed by being stirred at 40°C for 2 h. The reaction mixture was cool down to 0°C, water (2.0 mL) was added to the mixture, which was extracted with $CHCl_3$ (2 mL x 3). The organic layers were washed with brine, dried (Na_2SO_4) and concentrated. The obtained crude was purified by column chromatography (SiO_2, hexane/AcOEt = 3/1) to give the product **7f** (49 mg, 86 %).

7f : colorless solid; mp = 105-108 ℃; $[\alpha]_D^{26}$= 351.6 (*c* = 1.00, chloroform, λ = 589 nm); ^{1}H NMR (400MHz,$CDCl_3$) δ 3.22 (d, J = 9.9 Hz, 1H), 3.35 (d, J = 9.4 Hz, 1H), 3.37 (s, 3H), 3.37-3.47 (m, 1H), 3.54-3.59 (m, 2H), 3.93 (s, 3H), 4.00 (dd, J = 9.1 Hz, 1H), 4.59 (dd, J = 7.9, 9.5 Hz, 1H), 7.14-7.18 (m, 2H), 7.23-7.33 (m, 3H), 7.36 (d, J = 8.4 Hz, 2H), 8.02 (d, J = 8.4 Hz, 2H) ; ^{13}C NMR (101 MHz, $CDCl_3$) δ 35.2, 45.2, 51.2, 51.5, 52.4, 52.9, 70.7, 127.6, 128.6, 128.8, 129.0, 130.2, 137.0, 144.1, 166.5, 167.2, 171.0; IR (NaCl, neat) 3030, 2953, 2907, 1784, 1732, 1717, 1608, 1435, 1283, 1020, 704 cm^{-1} ; HRMS (ESI) calcd for $C_{22}H_{22}O_6S$ $(M+Na)^+$ 437.1035, found 437.1029. Based on the fixed absolute configuration at the β-position of lactone **4f** (98% ee), ee of **7f** was determined as 98% ee.

(α*S*, β*R*)-α-Methoxycarbonyl-β-(*R*)-(benzylthio)(4-nitrophenyl)methyl-γ-butyrolactone (7g)



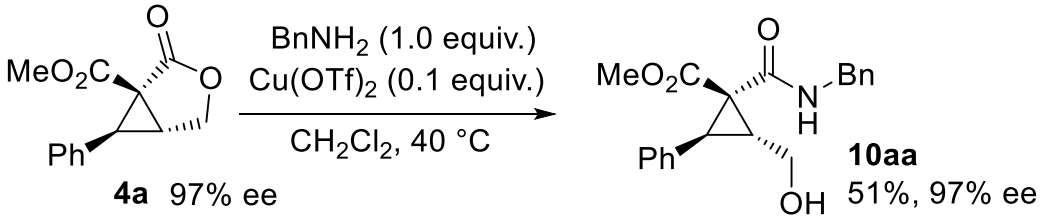
Benzyl mercaptan (42 μL, 0.361 mmol) was added to a solution of cyclopropane **4g** (100 mg, 0.361 mmol) in 1,2-dichloroethane (3.6 mL) at 0°C under an Ar atmosphere. Additionally, $Sc(OTf)_3$ (18 mg, 36 μmol) was added to the mixture at the same temperature, followed by being stirred at 40°C for 2 h. The reaction mixture was cool down to 0°C, water (5.0 mL) was added to the mixture, which was extracted with $CHCl_3$ (5 mL x 3). The organic layers were washed with brine, dried (Na_2SO_4) and concentrated. The obtained crude was purified by column chromatography (SiO_2, hexane/AcOEt =5/1) to give the product **7g** (126 mg, 88 %).

7g : yellow amorphous; $[\alpha]_D^{25}$ = 335.9 (*c* = 1.00, chloroform, λ = 589 nm); ^{1}H NMR (400 MHz, $CDCl_3$)

δ 3.21 (d, J = 9.8 Hz, 1H), 3.37 (d, J = 13.9 Hz, 1H), 3.38-3.47 (m, 1H), 3.42 (s, 3H), 3.53-3.65 (m, 2H), 4.02 (dd, J = 8.9 Hz, 1H), 4.60 (dd, J = 7.9, 9.5 Hz, 1H), 7.15-7.17 (m, 2H), 7.27-7.33 (m, 3H), 7.43 (d, J = 8.8 Hz, 2H), 8.20 (d, J = 8.8 Hz, 2H) ; ^{13}C NMR (101 MHz, CDCl3) δ 35.4, 45.0, 50.8, 51.3, 53.0, 70.5, 124.0, 127.8, 128.8, 128.9, 129.5, 136.6, 146.7, 147.6, 167.0 170.7; IR (NaCl, neat) 3030, 2953, 1782, 1738, 1605, 1520, 1348, 1148, 1024 cm^{-1} ; HRMS (APCI) calcd for $C_{20}H_{19}NO_6S$ $(M+Na)^+$ 424.0831, found 424.0825. Based on the fixed absolute configuration at the β-position of lactone **4g** (94% ee), ee of **7g** was determined as 94% ee.

OHM reactions using amines.

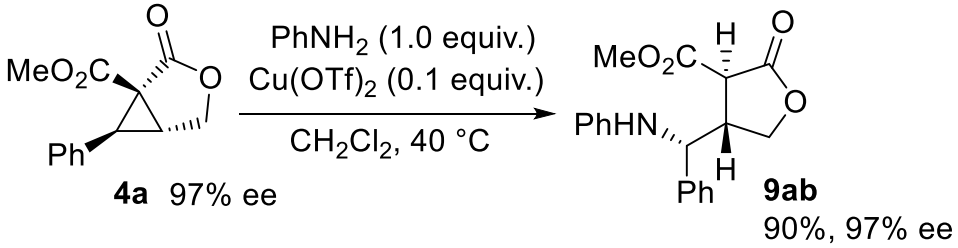
methyl (1*R*,2*R*,3*S*)-1-(benzylcarbamoyl)-2-(hydroxymethyl)-3-phenylcyclopropane -1-carboxylate (10aa)



Benzylamine (24 μL, 0.215 mmol) was added to a solution of cyclopropane **4a** (50 mg, 0.215 mmol) in CH_2Cl_2 (2.2 mL) at 0°C under an Ar atmosphere. Additionally, $Cu(OTf)_2$ (8 mg, 22 μmol) was added to the mixture at the same temperature, followed by being stirred at 40°C for 24 h. The reaction mixture was cool down to 0°C, water (2.2 mL) was added to the mixture, which was extracted with $CHCl_3$ (2 mL x 3). The organic layers were washed with brine, dried (Na_2SO_4) and concentrated. The obtained crude was purified by column chromatography (SiO_2, hexane/AcOEt = 1/1) to give the product **10aa** (37 mg, 51 %). (Conversion = 55%)

10aa : colorless oil; $[\alpha]^{25}_D$= -71.6 (*c* = 1.00, chloroform, λ = 589 nm); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (brs, 1H), 7.40 – 7.20 (m, 10H), 4.59 (dd, *J* = 15.0, 5.8 Hz, 1H), 4.52 (dd, *J* = 14.9, 5.6 Hz, 1H), 4.15 (dd, *J* = 12.3, 3.7 Hz, 1H), 3.93 – 3.81 (m, 1H), 3.49 (brs, 1H), 3.42 (d, *J* = 8.4 Hz, 1H), 3.24 (s, 3H), 3.01 (td, *J* = 8.3, 4.0 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.9, 168.3, 138.0, 135.0, 129.0, 128.9, 128.3, 127.7, 127.6, 127.5, 60.2, 52.0, 44.2, 41.0, 38.3, 34.8; IR (NaCl, neat) 3316 (broad peak), 3063, 3030, 2951, 1734, 1647, 1541, 1435, 1296, 1211, 1140, 1030, 741, 698 cm^{-1}; HRMS (ESI) calcd for $C_{20}H_{21}NO_4$ $(M+Na)^+$ 362.1361, found 362.1363. Based on the fixed absolute configuration of lactone **4a** (97% ee), ee of **10aa** was determined as 97% ee.

(α*S*, β*R*)-α-Methoxycarbonyl-β-(*R*)-(phenylamino)(phenyl)methyl-γ-butyrolactone (9ab)

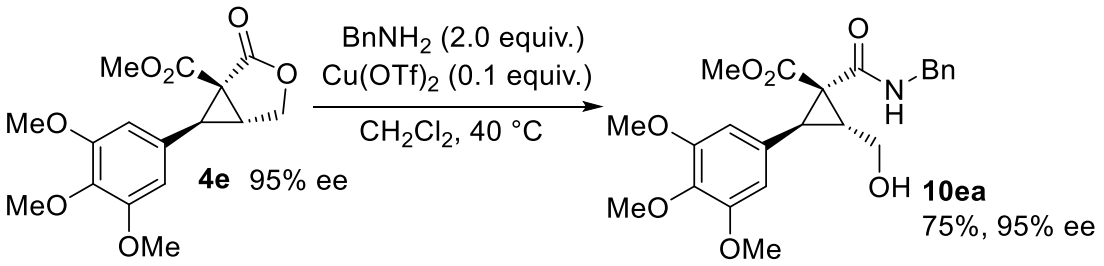


Aniline (20 μL, 0.215 mmol) was added to a solution of cyclopropane **4a** (50 mg, 0.215 mmol) in CH_2Cl_2 (2.2 mL) at 0°C under an Ar atmosphere. Additionally, $Cu(OTf)_2$ (8 mg, 22 μmol) was added to the mixture at the same temperature, followed by being stirred at 40°C for 24 h. The reaction mixture was cool down to 0°C, water (2.2 mL) was added to the mixture, which was extracted with $CHCl_3$ (2 mL x 3). The organic layers were washed with brine, dried (Na_2SO_4) and concentrated. The obtained crude was purified by column chromatography (SiO_2, hexane/AcOEt = 3/1) to give the product **9ab** (63 mg, 90 %).

9ab : colorless solid; mp = 139-141°C; $[\alpha]^{25}_D$= 122.9 (*c* = 1.00, chloroform, λ = 589 nm); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.20 (m, 5H), 7.11-7.08 (m, 2H), 6.69 (t, *J* = 7.3 Hz, 1H), 6.59 – 6.52 (m, 2H), 4.65 – 4.56 (m, 1H), 4.43 (brs, 1H), 4.28 (brs, 1H), 4.25 – 4.18 (m, 1H), 3.50 (s, 3H), 3.47-3.45 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.5, 167.7, 146.2, 139.5, 129.4, 129.1, 128.3, 127.0, 118.7, 114.2, 70.3, 59.9, 53.1, 50.1, 46.4; IR (NaCl, neat) 3412, 3024, 2961, 2893, 2359, 1794, 1717, 1601, 1514, 1445, 1296, 1179, 1043, 1013, 745, 700 cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{19}NO_4$ $(M+Na)^+$ 348.1212, found 348.1206. Based on the fixed absolute configuration at the β-position of lactone **4a** (97% ee), ee of **9ab** was determined as 97% ee.

methyl (1*R*,2*R*,3*S*)-1-(benzylcarbamoyl)-2-(hydroxymethyl)

-3-(3,4,5-trimethoxyphenyl)cyclopropane-1-carboxylate (10ea)

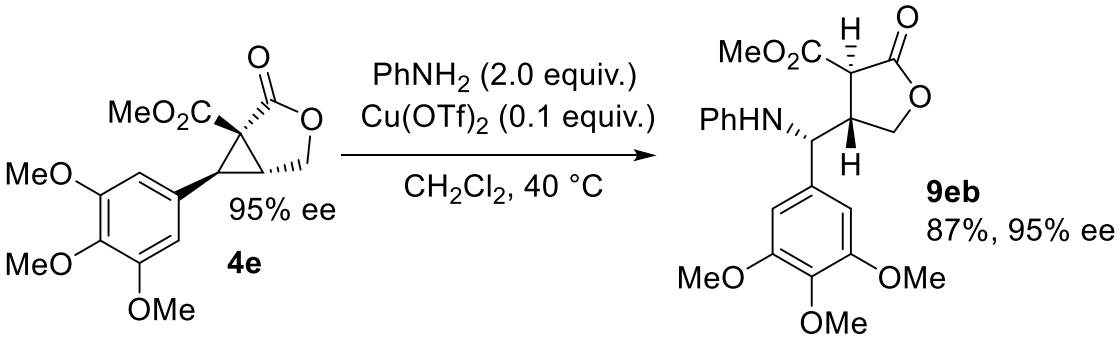


Following the procedure for the preparation of **10aa**, the reaction of bicyclolactone **4e** (69 mg, 0.215

mmol) with benzyl amine (44 μL, 0.43 mmol) in the presence of $Cu(OTf)_2$ (8 mg, 22 μmol) gave the product **10ea** (69 mg, 75%). (Reaction time = 24 h)

10ea : colorless oil; $[\alpha]^{28}_D$= -45.1 (*c* = 1.00, chloroform, λ = 589 nm); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (brs, 1H), 7.39 – 7.24 (m, 5H), 6.44 (s, 2H), 4.59 (dd, *J* = 14.9, 5.8 Hz, 1H), 4.50 (dd, *J* = 14.9, 5.5 Hz, 1H), 4.15 – 4.06 (m, 1H), 3.82 (s, 6H), 3.86-3.78 (m, 1H), 3.81 (s, 3H), 3.39 (d, *J* = 8.4 Hz, 1H), 3.34 (s, 3H), 2.95 (td, *J* = 8.3, 4.0 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.8, 167.9, 153.0, 138.0, 137.4, 130.8, 128.8, 127.6, 127.6, 106.0, 60.9, 60.0, 56.2, 52.2, 44.2, 41.3, 37.9, 34.9; IR (NaCl, neat) 3350 (broad peak), 3001, 2941, 2839, 1734, 1653, 1589, 1508, 1456, 1292, 1238, 1126, 1007, 912, 837, 731 cm^{-1}; HRMS (ESI) calcd for $C_{23}H_{27}NO_7$ $(M+Na)^+$ 452.1685, found 452.1680. Based on the fixed absolute configuration of lactone **4e** (95% ee), ee of **10ea** was determined as 95% ee.

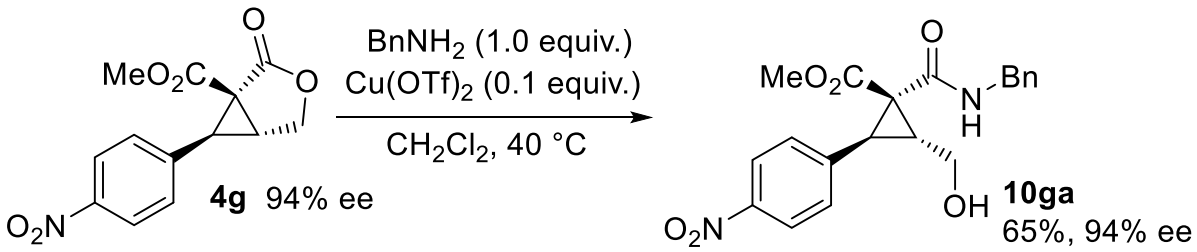
(α*S*, β*R*)-α-Methoxycarbonyl-β-(*R*)-(phenylamino)(3,4,5-trimethoxyphenyl)methyl -γ-butyrolactone (9eb)



Following the procedure for the preparation of **9ab**, the reaction of bicyclolactone **4e** (69 mg, 0.215 mmol) with aniline (39 μL, 0.43 mmol) in the presence of $Cu(OTf)_2$ (8 mg, 22 μmol) gave the product **9eb** (78 mg, 87%). (Reaction time = 30 min)

9eb: yellow solid; $[\alpha]^{26}_D$ = 69.0 (*c* = 1.00, chloroform, λ = 589 nm); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15-7.11 (m, 2H), 6.74 (t, *J* = 7.4 Hz, 1H), 6.60-6.58 (m, 2H), 6.47 (s, 2H), 4.67 – 4.59 (m, 1H), 4.35 (brs, 1H), 4.28 – 4.21 (m, 1H), 4.08 (brs, 1H), 3.84 (s, 6H), 3.81 (s, 3H), 3.61 (s, 3H), 3.48-3.45 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.3, 167.7, 153.8, 146.3, 137.8, 135.2, 129.5, 119.0, 114.3, 103.9, 70.3, 60.9, 60.4, 56.3, 53.2, 50.2, 46.4; IR (KBr, neat) 3391, 2992, 2945, 2843, 1775, 1740, 1597, 1508, 1466, 1325, 1250, 1125, 1011, 760, 696 cm^{-1}; HRMS (ESI) calcd for $C_{22}H_{25}NO_7$ $(M+Na)^+$ 438.1529 , found 438.1523. Based on the fixed absolute configuration at the β-position of lactone **4e** (95% ee), ee of **9eb** was determined as 95% ee.

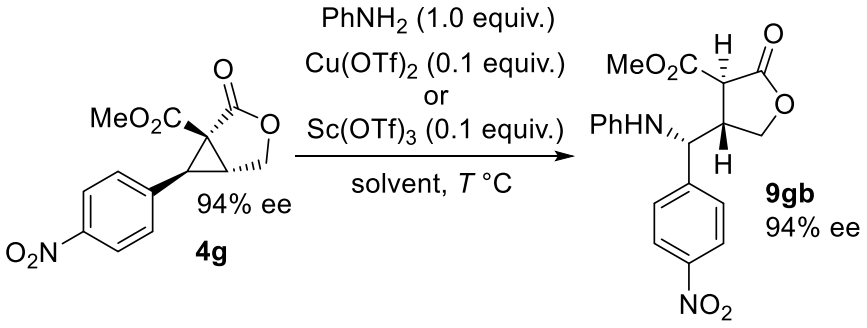
methyl (1*R*,2*R*,3*S*)-1-(benzylcarbamoyl)-2-(hydroxymethyl)-3-(4-nitrophenyl)cyclopropane -1-carboxylate (10ga)



Following the procedure for the preparation of **10aa**, the reaction of bicyclolactone **4g** (50 mg, 0.180 mmol) with benzyl amine (20 μL, 0.180 mmol) in the presence of $Cu(OTf)_2$ (8 mg, 22 μmol) gave the product **10ga** (45 mg, 65%). (Reaction time = 24 h)

10ga : colorless oil; $[\alpha]^{27}_D$= -66.3°(c 1.00, chloroform, λ = 589 nm); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (d, *J* = 8.8 Hz, 2H), 8.02 (brs, 1H), 7.41 (d, *J* = 8.3 Hz, 2H), 7.37 – 7.24 (m, 5H), 4.59 (dd, *J* = 14.9, 5.8 Hz, 1H), 4.53 (dd, *J* = 14.9, 5.6 Hz, 1H), 4.13 (dd, *J* = 12.3, 4.1 Hz, 1H), 3.84 (dd, *J* = 12.2, 8.3 Hz, 1H), 3.51 (d, *J* = 8.4 Hz, 1H), 3.32 (s, 3H), 2.98 (td, *J* = 8.3, 4.1 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.3, 167.1, 147.2, 143.0, 137.8, 130.0, 128.9, 127.8, 127.7, 123.5, 59.8, 52.4, 44.3, 41.4, 36.6, 35.2; IR (NaCl, neat) 3315 (broad peak), 3080, 2953, 2880, 1732, 1649, 1603, 1520, 1435, 1348, 1292, 1142, 1016, 854, 741, 698 cm^{-1}; HRMS (ESI) calcd for $C_{20}H_{20}N_2O_6$ $(M+Na)^+$ 407.1219, found 407.1214. Based on the fixed absolute configuration of lactone **4g** (94% ee), ee of **10ga** was determined as 94% ee.

(α*S*, β*R*)-α-Methoxycarbonyl-β-(*R*)-(phenylamino)(4-nitrophenyl)methyl -γ-butyrolactone (9gb)



Aniline (20 μL, 0.180 mmol) was added to a solution of cyclopropane **4g** (50 mg, 0.180 mmol) in solvent (2.2 mL) at 0°C under an Ar atmosphere. Additionally, Lewis acid (22 μmol) was added to the

mixture at the same temperature, followed by being stirred at *T* °C. The reaction mixture was cool down to 0°C, water (2.2 mL) was added to the mixture, which was extracted with $CHCl_3$ (2 mL x 3). The organic layers were washed with brine, dried (Na_2SO_4) and concentrated. The obtained crude was purified by column chromatography (SiO_2, hexane/AcOEt = 3/2) to give the product **9gb** (x mg, y %).

(a) Lewis acid: $Cu(OTf)_2$, solvent: CH_2Cl_2, *T* = 40.

Reaction time = 24 h, x = 7, y = 10.

(b) Lewis acid: $Sc(OTf)_3$, solvent: 1,2-dichloroethane, *T* = 70.

Reaction time = 8 h, x = 47, y = 70.

9gb: yellow amorphous; $[\alpha]^{26}_D$ = 70.1 (*c* = 1.00, chloroform, λ = 589 nm); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (d, *J* = 8.7 Hz, 2H), 7.50 (d, *J* = 8.7 Hz, 2H), 7.11 (t, *J* = 7.9 Hz, 2H), 6.73 (t, *J* = 7.4 Hz, 1H), 6.53 (d, *J* = 7.8 Hz, 2H), 4.68 – 4.56 (m, 2H), 4.36 – 4.22 (m, 2H), 3.56 (s, 3H), 3.54 – 3.45 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.9, 167.3, 147.9, 147.2, 145.3, 129.6, 128.0, 124.4, 119.5, 114.2, 69.7, 59.4, 53.4, 49.8, 45.7; IR (KBr, neat) 3383, 3026, 2953, 2922, 2853, 1778, 1740, 1603, 1522, 1437, 1350, 1265, 1152, 1020, 858, 754, 694 cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{18}N_2O_6$ $(M+Na)^+$ 393.1063 , found 393.1057. Based on the fixed absolute configuration at the β-position of lactone **4g** (94% ee), ee of **9gb** was determined as 94% ee.