Asymmetric Synthesis of Chiral Cycloalkenone Derivatives via Palladium Catalysis

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Electronic Supplementary Material (ESI) for Chemical Science
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1. Experimental Procedures

a) General Considerations. Unless otherwise indicated, all reactions were performed in oven- or flame-dried glassware with magnetic stirring under a nitrogen or argon atmosphere. Air- and moisture-sensitive liquids and solutions were transferred via oven-dried, stainless steel syringe or cannula and were introduced into the reaction vessel through rubber septa. Reactions performed below room temperature (23 °C) were cooled with ice/water baths (0 °C) or dry ice/isopropanol baths (−78 °C). Anhydrous PhMe, PhH, CH₂Cl₂ and THF were obtained from a Seca solvent purification system by Glass Contour. Hexamethyldisilazane (HMDS) and 1,2-dichloroethane (DCE) were distilled from CaH₂ under nitrogen. For use in Pd-AA reactions—except the oxidations of meso diesters, as noted below—anhydrous and deoxygenated THF was obtained from a Na/benzophenone ketyl still under argon. Unless otherwise indicated, yields are of isolated products. pH 7 buffer was prepared by dissolving K₂HPO₄ (99 g) and KH₂PO₄ (77 g) in DI water (1 L). Meso dibenzoates 13 and 15 were prepared by benzylation of the corresponding diols.¹ Pd₂dba₃·CHCl₃,² ligand L₁,³ and IBX (2-iodoxybenzoic acid)⁴ were prepared by literature procedures. (η³-C₅H₅)₂Pd₂Cl₂ was prepared by the literature procedure⁵ and then crystallized from CH₂Cl₂ / hexanes.

Analytical and preparative thin-layer chromatography was performed using pre-coated 250 µm layer thickness silica gel 60 F₂₅₄ plates (EMD Chemicals Inc.). Visualization was performed by ultraviolet light fluorescence quenching and/or by staining with aqueous potassium permanganate, aqueous ceric ammonium molybdate, or ethanolic para-anisaldehyde solutions followed by heating. Flash column chromatography was performed using 40-63 µm silica gel (Silicycle silica gel) using compressed air. The eluent employed for flash chromatography is reported using volume/volume ratios. Proton nuclear magnetic resonance (¹H NMR) spectra were acquired using a Varian Inova 600 MHz, Varian Inova 500 MHz, Varian Inova 300 MHz, or Varian Mercury 400 MHz spectrometer. Chemical shifts (δ) are reported in parts per million.

¹ See a) I. Erden, C. Gärtner, M. Saeed Azimi, *Org. Lett.*, **2009**, *11*, 3986; b) J. Lou, M. Hashimoto, N. Verova, K. Nakanishi, *Org. Lett.*, **1999**, *1*, 51; c) B. M. Trost, J. Richardson, K. Yong, *J. Am. Chem. Soc.*, **2006**, *128*, 2540.
² T. Ukai, H. Kawazura, Y. Ishii, J. J. Bonnet, J. A. Ibers, *J. Organomet. Chem.* **1974**, *65*, 253.
³ B. M. Trost, D. L. van Vranken, C. Bingel, *J. Am. Chem. Soc.* **1992**, *114*, 9327.
⁴ M. Frigerio, M. Santagostino, S. Sputore, *J. Org. Chem.*, **1999**, *64*, 4537.
⁵ N. Marion, O. Navarro, J. Mei, E. D. Stevens, N. M. Scott, S. P. Nolan, *J. Am. Chem. Soc.*, **2006**, *128*, 4101.
(ppm) and are calibrated to the residual solvent peak (CHCl₃, 7.26 ppm). Coupling constants (J) are reported in Hz. Multiplicities are reported using the following abbreviations: app = apparent, s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet (range of multiplet is given). Carbon nuclear magnetic resonance (¹³C NMR) spectra were recorded using a Varian Inova 150 MHz, Varian Inova 125 MHz, Varian Inova 75 MHz, or a Varian Mercury 100 MHz spectrometer. Chemical shifts (δ) are reported in parts per million (ppm) and are calibrated to the residual solvent peak (CHCl₃, 77.16 ppm).

Infrared spectroscopic data were recorded on a Thermo Scientific Nicolet IR100 FT-IR spectrometer, using thin films of the sample on NaCl plates. The absorbance frequencies are recorded in wavenumbers (cm⁻¹). Chiral HPLC analysis was performed using an Agilent Technologies 1200 Series HPLC equipped with a Daicel CHIRALPAK® chiral stationary phase column (IA [amylose tris(3,5-dimethylphenylcarbamate) immobilized on silica support], IB [cellulose tris(3,5-dimethylphenylcarbamate) immobilized on silica support], or IC [cellulose tris(3,5-dichlorophenylcarbamate) immobilized on silica support]) or using a SpectraSYSTEM™ P1000 pump equipped with a SpectraSERIES™ UV100 detector and a Daicel chiral stationary phase column (CHIRALCEL® OD-H [cellulose tris(3,5-dimethylphenylcarbamate) immobilized on silica support], CHIRALCEL® OJ-H [cellulose tris (4-methylbenzoate) immobilized on silica support]), or CHIRALPAK® AD-H ([amylose tris(3,5-dimethylphenylcarbamate) immobilized on silica support]). Retention times of enantioenriched products were determined either from admixtures of the two enantiomers, each independently prepared from the meso dibenzoate using (R,R) or (S,S)-L₁, or from racemic materials prepared from racemic γ-hydroxycycloalkenones.

Optical rotations were measured using a JASCO P2000 polarimeter using 5 cm glass cells with a sodium 589 nm filter and are reported as [α]D, concentration (g/100 mL), and solvent. Melting points were determined on a Thomas Hoover Capillary Melting Point Apparatus and are uncorrected. High-resolution mass spectra were acquired by the Vincent Coates Foundation Mass Spectrometry Laboratory, Stanford University (http://massspec.stanford.edu).
b) Synthesis of *meso* Dibenzoate 14.

![Chemical reaction diagram](image)

**14**: Based on the procedure of Bäckvall and co-workers. A 500 mL round-bottom flask was charged with PhCO$_2$H (37.0 g, 304 mmol, 7.6 equivalents), benzoquinone (8.85 g, 81.9 mmol, 2.05 equivalents), Pd(OAc)$_2$ (358 mg, 1.59 mmol, 0.04 equivalents), and acetone (250 mL). The resulting dark, heterogeneous reaction mixture was stirred for 15 minutes, and then 1,3-cyclohexadiene (**SI-1**, 3.8 mL, 3.2 g, 39.9 mmol, 1 equivalent) was added via syringe pump over 4 hours. The reaction mixture was stirred for 14 additional hours, concentrated to a black residue, dissolved in Et$_2$O (750 mL), and washed with 2 N NaOH (2 x 150 mL). As noted by Bäckvall and co-workers, the *cautious* addition of a small amount (≤ 500 mg) of NaBH$_4$ helped improve phase separation, and this was necessary on some occasions. The pooled aqueous phases were extracted with Et$_2$O (200 mL), and to the pooled organics was added *ca.* 10 g SiO$_2$. The pooled organics were dried over MgSO$_4$, filtered, and concentrated to an oil, which was passed through a column of SiO$_2$ eluting with 4:1 hexanes:Et$_2$O. Concentration to a white solid and recrystallization from heptane (100 mL) afforded 7.8 g of 14 as a white solid. The filtrate was concentrated and recrystallized from heptane (20 mL) to afford a second crop of 14 (0.48 g, 8.28 g total, 25.69 mmol, 64%).

**$^1$H NMR** (500MHz, CDCl$_3$): 8.09-8.08 (m, 4H), 7.59-7.56 (m, 2H), 7.47-7.44 (m, 4H), 6.09 (d, J = 1.3 Hz, 2H), 5.45 (d, J =1.5 Hz, 2H), 2.11-2.09 (m, 4H)

*Analytical data matched literature data.*

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6 J. E. Bäckvall, K. L. Granberg, R. B. Hopkins, *Acta Chem. Scand.* 1990, 44, 492.
c) **Synthesis of Oxidative Desymmetrization Products 16-18.**

![Chemical Structure](image)

**Representative procedure for oxidative desymmetrization: Synthesis of 17.**

A flame-dried 250 mL round-bottom flask equipped with a stir bar was charged with THF (*ca.* 200 mL, Seca solvent system), which was sparged with a vigorous N₂ flow (Schlenk line) for 30 min. A separate 250 mL round-bottom flask was charged with a large stir bar, sealed with a septum, and flame-dried under vacuum. The mass of this flask/stir bar/septum system was recorded. The septum was removed, the flask was tared, and KH (*ca.* 30% dispersion in mineral oil, 2.22 g) was added. The flask was sealed with the septum and then evacuated and backfilled with N₂. The KH dispersion in oil was washed with THF (3 x 10 mL), using a cannula to remove the washings. These washings, which contain trace amounts of KH, were cautiously quenched at 0 °C with, sequentially, isopropanol, methanol, and water. The flask was quickly flame-dried under vacuum to afford KH as a free-flowing gray powder (0.74 g, determined by difference in mass, 18.45 mmol, 2.05 equivalents). The flask was backfilled with N₂ and placed in a 0 °C bath, and then THF (37 mL) was added, followed by HMDS dropwise (4.25 mL, 3.27 g, 20.3 mmol, 2.26 equivalents, 1.1 equivalents relative to KH). The mixture was stirred at 0 °C for 15 min, and then the cooling bath was removed and the mixture was stirred 30 min at room temperature, to afford a slightly cloudy solution of KHMDS in THF. The mixture was cooled to 0 °C, and a solution of (2-methyl-1-nitropropyl)benzene (SI-2, 4.09 g, 18.9 mmol, 2.1 equivalents) in THF
(38 mL total, including rinses) was added via cannula. The mixture turned yellow during this time, and, after 1-2 min, a cream-colored heterogeneous mixture of nitronate 9 formed. The cooling bath was then removed, and the mixture was stirred for 30 min. During this time, the catalyst solution was prepared by combining \(\left(\eta^3-C_3H_5\right)_2\text{PdCl}_2\) (49.4 mg, 0.135 mmol, 0.015 equivalent, finely ground with a spatula) and \((R,R)-\text{L1}\) (280 mg, 0.405 mmol, 0.045 equivalent) in a flame-dried 3-dram vial equipped with a stir bar, which was evacuated and backfilled with N\(_2\) and then treated with THF (5 mL). The bright yellow, homogeneous catalyst solution was stirred for vigorously at least 10 min. A flame-dried 50 mL round-bottom flask equipped with a stir bar was charged with 14 (2.90 g, 9.0 mmol, 1.0 equivalent), sealed with a septum, evacuated, backfilled with N\(_2\), treated with THF (24 mL), and stirred to effect complete dissolution (< 5 min). The flask containing 9 was cooled to 0 °C, and the solution of 14 was transferred to the former via cannula, using additional THF (6 mL) to rinse the flask and cannula. The catalyst solution was then immediately transferred via cannula. Care was taken to maintain vigorous stirring throughout the additions. The cooling bath was removed after the additions, and the resulting yellow-orange, heterogeneous mixture was stirred vigorously for 30 min, at which point TLC analysis (3:1 hexanes:Et\(_2\)O) indicated complete consumption of 14. The reaction mixture was poured into a separatory funnel containing Et\(_2\)O (200 mL) and pH 7 phosphate buffer (150 mL), which was shaken thoroughly for 1-2 min. The phases were separated, and the aqueous phase was extracted with Et\(_2\)O (100 mL). The pooled organics were dried over MgSO\(_4\), filtered, and concentrated. The residue was purified by column chromatography (6:1→4:1→2:1 hexanes:Et\(_2\)O, crude material loaded using 6:1 hexanes:Et\(_2\)O and some CH\(_2\)Cl\(_2\)) to afford 17 (1.30 g, 6.01 mmol, 67%, 99% ee) as a light yellow, viscous oil that solidified to a white solid on standing in a refrigerator.

\(^1\text{H NMR}\) (500 MHz; CDCl\(_3\)): \(\delta\) 8.07-8.05 (m, 2H), 7.60 (tt, \(J = 7.5, 1.4\) Hz, 1H), 7.49-7.45 (m, 2H), 6.98 (ddd, \(J = 10.2, 2.7, 1.3\) Hz, 1H), 6.13-6.11 (m, 1H), 5.85-5.81 (m, 1H), 2.73-2.67 (m, 1H), 2.57-2.52 (m, 1H), 2.51-2.46 (m, 1H), 2.30-2.22 (m, 1H)

**Chiral HPLC:** OJ-H, 90:10 heptane:isopropanol, 0.50 mL/min, 254 nm, 29.48 min (R enantiomer), 34.32 min (S enantiomer)

\([\alpha]_D^{23} = +167^\circ\) (c = 0.85, CHCl\(_3\)), Lit.: \([\alpha]_D = +201\) (c = 0.85, CHCl\(_3\))\(^7\)

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\(^7\) L. Yu, R. Zhang, Z. Wang, *J. Chem. Soc., Perkin Trans. 1*, **2001**, 2958.
For (S)-17, prepared as described above with (S,S)-L1 in 98% ee, $[\alpha]_D^{23} = -178^\circ$ (c = 0.85, CHCl$_3$), Lit.: $[\alpha]_D = -197$ (c = 1.9, CH$_2$Cl$_2$)$^8$

**M.P.** = 32-33 °C

*Analytical data matched previously reported data.*$^1c$

Cycloalkenones 16 and 18 were prepared following the above procedure. Analytical data matched previously reported data and are partially reproduced below. For cyclopentenone 16, the reaction was quenched 10 min after the addition of the catalyst solution (13 consumed by TLC analysis). Compound 16 was obtained in 78% yield (0.859 mmol) and 99% ee (1.1 mmol reaction scale). For cycloheptenone 18, the reaction was quenched 3 h after the addition of the catalyst solution, at which point the reaction had reached 68% conversion based on 32% recovered 15 (0.395 mmol). Compound 18 was obtained in 50% isolated yield (0.621 mmol, 73% yield based on 68% conversion) and 99% ee (1.25 mmol reaction scale).

16:

$^1$H NMR (400 MHz; CDCl$_3$): $\delta$ 8.05-8.03 (m, 2H), 7.71 (dd, $J = 5.7$, 2.4 Hz, 1H), 7.62-7.58 (m, 1H), 7.49-7.44 (m, 2H), 6.41 (dd, $J = 5.7$, 1.3 Hz, 1H), 6.12 (dtd, $J = 6.4$, 2.3, 1.3 Hz, 1H), 2.96 (dd, $J = 18.8$, 6.4 Hz, 1H), 2.50 (dd, $J = 18.8$, 2.2 Hz, 1H)

**Chiral HPLC:** OJ-H, 90:10 heptane:isopropanol, 0.50 mL/min, 254 nm, 33.74 min ($R$ enantiomer), 37.56 min ($S$ enantiomer)

$[\alpha]_D^{25} = +184^\circ$ (c = 0.38, CHCl$_3$)

18:

$^1$H NMR (400 MHz; CDCl$_3$): $\delta$ 8.08-8.05 (m, 2H), 7.61-7.57 (m, 1H), 7.49-7.45 (m, 2H), 6.58 (ddd, $J = 12.5$, 3.3, 1.2 Hz, 1H), 6.09 (ddt, $J = 12.5$, 2.2, 0.6 Hz, 1H), 5.85 (dddd, $J = 9.5$, 4.6, 3.3, 2.2 Hz, 1H), 2.71-2.68 (m, 2H), 2.38-2.29 (m, 1H), 2.09-1.92 (m, 3H).

**Chiral HPLC:** OJ-H, 90:10 heptane:isopropanol, 0.50 mL/min, 254 nm, 32.14 min ($S$ enantiomer), 35.26 min ($R$ enantiomer)

$[\alpha]_D^{25} = +131^\circ$ (c = 0.41, CHCl$_3$)

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$^8$ R. J. Kazlauskas, A. N. E. Weissfloch, A. T. Rappaport, L. A. Cuccia, *J. Org. Chem.* **1991**, *56*, 2656.
d) Synthesis of Allylic Alkylation Products *ent*-2, 4, and 19-25.

4: A round-bottom Biotage® microwave vial (2.0 mL – 5.0 mL size) equipped with a large stir bar was charged with Pd$_2$dba$_3$·CHCl$_3$ (2.6 mg, 0.025 mmol, 0.025 equivalents), (S,S)-L1 (5.2 mg, 0.0075 mmol, 0.075 equivalents), and powdered NaOAc (24.6 mg, 0.3 mmol, 3 equivalents). The vial was sealed with a septum and evacuated and backfilled with N$_2$. Distilled THF (0.50 mL) was added, and the mixture was stirred for 10 minutes at room temperature to afford a heterogeneous, orange mixture. The vial was cooled to 0 °C, and solid 16 (20.2 mg, 0.0999 mmol, 1 equivalent) was added under N$_2$ flow. The reaction mixture was stirred for 3 h at 0 °C, at which point it was diluted with EtOAc (5 mL) and poured into saturated aqueous NaHCO$_3$ (5 mL). The phases were separated, and the aqueous phase was extracted with EtOAc (4 x 5 mL). The pooled organics were washed with saturated aqueous NaHCO$_3$ (5 mL), dried over MgSO$_4$, filtered, and concentrated. Purification of the residue by column chromatography (4:1→2:1 hexanes:EtOAc) afforded 4 (8.9 mg, 0.0635 mmol, 64%, 93% ee) as a clear, light yellow oil as well as recovered 16 (2.1 mg, 0.010 mmol, 10%, 79% ee).

$^1$H NMR (500 MHz; CDCl$_3$): 7.57 (dd, $J = 5.7, 2.4$ Hz, 1H), 6.34 (dd, $J = 5.7, 1.3$ Hz, 1H), 5.87-5.84 (m, 1H), 2.83 (dd, $J = 18.7, 6.4$ Hz, 1H), 2.33 (dd, $J = 18.7, 2.2$ Hz, 1H), 2.10 (s, 3H)

$^{13}$C NMR (125 MHz; CDCl$_3$): δ 205.1, 170.6, 159.1, 137.2, 72.1, 41.2, 21.0

Chiral HPLC: AD-H, 95:5 heptane:isopropanol, 0.80 mL/min, 220 nm, 11.15 min (R enantiomer), 12.17 min (S enantiomer)

$[\alpha]_D^{24} = +53.8^{\circ}$ (c = 0.81, CHCl$_3$), Lit: $+95^{\circ}$ (c = 0.1, CHCl$_3$)$^9$

Analytical data matched literature data.$^{10}$

$^9$ M. Le Liepvre, J. Ollivier, D. J. Atiken, *Eur. J. Org. Chem.*, 2009, 5953.

$^{10}$ K. Ulbrin, P. Kreitmeier, T. Vilaivan, O. Reiser, *J. Org. Chem.*, 2013, 78, 4202.
A round-bottom Biotage® microwave vial (2.0 mL – 5.0 mL size) equipped with a large stir bar was charged with 17 (40.7 mg, 0.188 mmol, 1 equivalent), (η³-C₃H₅)₂PdCl₂ (1.7 mg, 0.005 mmol, 0.025 equivalents), PPh₃ (7.8 mg, 0.03 mmol, 0.15 equivalents), and powdered NaOAc (82 mg, 1 mmol, 5 equivalents). The vial was sealed with a septum-lined cap and evacuated and backfilled with N₂. Distilled THF (1.0 mL) was added, the pierced septum cap was sealed thoroughly with electrical tape and Parafilm®, and the resulting heterogeneous, yellow mixture was stirred vigorously for 3 h. The reaction mixture was then diluted with EtOAc (5 mL) and poured into saturated aqueous NaHCO₃ (5 mL). The phases were separated, and the aqueous phase was extracted with EtOAc (4 x 5 mL). The pooled organics were washed with saturated aqueous NaHCO₃ (5 mL), dried over MgSO₄, filtered, and concentrated. Purification of the residue by column chromatography (4:1 → 2:1 hexanes:EtOAc) afforded 19 (21.7 mg, 0.141 mmol, 75%, 96% ee) as a clear, light yellow oil.

**1H NMR** (400 MHz; CDCl₃): δ 6.84 (ddd, J = 10.3, 2.8, 1.5 Hz, 1H), 6.05 (ddd, J = 10.3, 1.9, 0.9 Hz, 1H), 5.58-5.53 (m, 1H), 2.65-2.58 (m, 1H), 2.48-2.40 (m, 1H), 2.37-2.32 (m, 1H), 2.11 (s, 3H), 2.13-2.04 (m, 1H)

**13C NMR** (100 MHz; CDCl₃): δ 198.1, 170.5, 147.8, 131.0, 67.9, 35.1, 28.8, 21.2

**IR**: 2921, 1740, 1688, 1372, 1237, 1038, 895 cm⁻¹

**Chiral HPLC**: OJ-H, 95:5 heptane:isopropanol, 0.50 mL/min, 220 nm, 40.72 min (R enantiomer), 43.29 min (S enantiomer)

\[ [\alpha]D^{23} = +119.6° \text{ (c = 1.0, CHCl}_3\text{)}, \text{ Lit: } +113° \text{ (c = 1.48, CHCl}_3) \]

Analytical data matched literature data.¹¹

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¹¹ H. Suzuki, N. Yamazaki, C. Kibayashi, *J. Org. Chem.*, 2001, 66, 1494.
**ent-2**: A round-bottom Biotage® microwave vial (2.0 mL – 5.0 mL size) equipped with a stir bar was charged with 17 (21.8 mg, 0.101 mmol, 1 equivalent), (η^3-C_3H_5)_2PdCl_2 (0.9 mg, 0.0025 mmol, 0.025 equivalents), and PPh_3 (3.9 mg, 0.015 mmol, 0.15 equivalents). The vial was sealed with a septum-lined cap and evacuated and backfilled with N_2. Degassed (N_2 sparge) PhMe (0.50 mL) was added, followed immediately by 4-methoxybenzyl alcohol (62 µL, 0.50 mmol, 5 equivalents). The pierced septum cap was sealed thoroughly with electrical tape and Parafilm®, and the resulting homogeneous, yellow mixture was stirred for 10 h, during which time its appearance changed to homogeneous and yellow-green. The reaction mixture was then diluted with Et_2O (5 mL) and poured into saturated aqueous NaHCO_3 (5 mL). The phases were separated, and the aqueous phase was extracted with Et_2O (3 x 5 mL). The pooled organics were dried over MgSO_4, filtered, and concentrated. Purification of the residue by column chromatography (2:1 hexanes:EtOAc) afforded **ent-2** (14.5 mg, 0.0624 mmol, 62%, 91% ee) as a light yellow oil.

**1H NMR** (500 MHz; CDCl_3): δ 7.31-7.28 (m, 2H), 6.97 (ddd, J = 10.3, 2.4, 1.4 Hz, 1H), 6.92-6.89 (m, 2H), 5.99 (ddd, J = 10.3, 1.9, 1.0 Hz, 1H), 4.58 (q, J = 12.3 Hz, 2H), 4.25 (ddt, J = 9.3, 4.7, 2.3 Hz, 1H), 3.81 (s, 3H), 2.63-2.58 (m, 1H), 2.37-2.30 (m, 2H), 2.08-2.00 (m, 1H).

**13C NMR** (100 MHz; CDCl_3): δ 199.0, 159.6, 150.9, 129.9, 129.8, 129.5, 114.1, 72.3, 70.8, 55.4, 35.5, 29.3

**Chiral HPLC**: IC, 90:10 heptane:isopropanol, 0.80 mL/min, 220 nm, 33.96 min (S enantiomer), 35.95 min (R enantiomer)

[α]_D^23 = +69.4° (c = 1.0, CHCl_3), Lit (2): −89.2° (c = 1.01, CHCl_3)^12a

*Analytical data matched literature data.*^12

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^12 a) J. E. Audia, L. Boisvert, A. D. Patten, A. Villalobos, S. J. Danishefsky, *J. Org. Chem.*, 1989, 54, 3738; b) C. Spino, B. Hill, P. Dubé, S. Gingras, *Can. J. Chem.*, 2003, 81, 81.
20: A round-bottom Biotage® microwave vial (2.0 mL – 5.0 mL size) equipped with a stir bar was charged with 17 (22.3 mg, 0.103 mmol, 1 equivalent), (η⁴-C₃H₅)₂Pd₂Cl₂ (0.9 mg, 0.0025 mmol, 0.025 equivalents), PPh₃ (3.9 mg, 0.015 mmol, 0.15 equivalents), 4-methoxyphenol (24.8 mg, 0.20 mmol, 2 equivalents), and Cs₂CO₃ (65.2 mg, 0.20 mmol, 2 equivalents). The vial was sealed with a septum-lined cap and evacuated and backfilled with N₂. Degassed (N₂ sparge) CH₂Cl₂ (0.50 mL) was added, the pierced septum cap was sealed thoroughly with electrical tape and Parafilm®, and the resulting heterogeneous, yellow mixture was stirred vigorously for 30 min. The reaction mixture was then diluted with Et₂O (5 mL) and poured into saturated aqueous NaHCO₃ (5 mL). The phases were separated, and the aqueous phase was extracted with Et₂O (3 x 5 mL). The pooled organics were dried over MgSO₄, filtered, and concentrated. Purification of the residue by column chromatography (4:1→2:1→1:1 hexanes:Et₂O) afforded 20 (17.9 mg, 0.0820 mmol, 80%, 98% ee) as a yellow solid.

\[ R_f = 0.26 \text{ (1:1 hexanes:Et}_2\text{O)} \]

\( ^1\text{H NMR} \) (400 MHz; CDCl₃): \( \delta 7.03 \) (ddd, \( J = 10.3, 2.4, 1.5 \text{ Hz}, 1\text{H} \)), 6.92-6.83 (m, 4H), 6.06 (ddd, \( J = 10.3, 1.9, 1.0 \text{ Hz}, 1\text{H} \)), 4.96 (ddt, \( J = 9.3, 4.7, 2.3 \text{ Hz}, 1\text{H} \)), 3.78 (s, 3H), 2.70-2.62 (m, 1H), 2.47-2.38 (m, 2H), 2.27-2.14 (m, 1H)

\( ^{13}\text{C NMR} \) (100 MHz; CDCl₃): \( \delta 198.5, 154.8, 151.0, 149.2, 130.4, 117.7, 115.0, 72.6, 55.8, 35.3, 29.4 \)

IR: 3001, 2915, 2796, 1661, 1486, 1443, 1364, 1271, 1208, 1024, 930, 861, 816, 764 cm⁻¹

Chiral HPLC: IC, 90:10 heptane:isopropanol, 0.80 mL/min, 220 nm, 28.52 min (S enantiomer), 32.10 min (R enantiomer)

\( [\alpha]_D^{24} = +100.5^\circ \) (c = 1.0, CHCl₃)

M.P. = 48-50 °C

HRMS (ESI): Calculated for C₁₅H₁₁O₃ (M+H)⁺: 219.1016, found 291.1015
A round-bottom Biotage® microwave vial (2.0 mL – 5.0 mL size) equipped with a stir bar was charged with 17 (42.0 mg, 0.194 mmol, 1 equivalent), (η³-C₃H₅)₂PdCl₂ (1.8 mg, 0.005 mmol, 0.025 equivalents), PPh₃ (7.9 mg, 0.03 mmol, 0.15 equivalents), and Cs₂CO₃ (130.3 mg, 0.40 mmol, 2 equivalents). The vial was sealed with a septum-lined cap and evacuated and backfilled with N₂. Degassed (N₂ sparge) CH₂Cl₂ (1.0 mL) was added, followed by 2-bromophenol (47 µL, 0.40 mmol, 2 equivalents). The pierced septum cap was sealed thoroughly with electrical tape and Parafilm®, and the resulting heterogeneous, yellow mixture was stirred vigorously for 30 min. The reaction mixture was then diluted with Et₂O (5 mL) and poured into saturated aqueous NaHCO₃ (5 mL). The phases were separated, and the aqueous phase was extracted with Et₂O (3 x 5 mL). The pooled organics were dried over MgSO₄, filtered, and concentrated. Purification of the residue by column chromatography (4:1 → 2:1 hexanes:EtOAc) afforded 21 (34.3 mg, 0.128 mmol, 66%, 92% ee) as a viscous, yellow oil.

**Rf = 0.37 (2:1 hexanes:EtOAc)**

**¹H NMR** (400 MHz; CDCl₃): δ 7.58 (dd, J = 7.9, 1.6 Hz, 1H), 7.29 (ddd, J = 8.2, 7.4, 1.6 Hz, 1H), 7.07 (ddd, J = 10.3, 2.6, 1.4 Hz, 1H), 7.00 (dd, J = 8.3, 1.3 Hz, 1H), 6.92 (ddd, J = 7.9, 7.4, 1.4 Hz, 1H), 6.10 (ddd, J = 10.3, 1.8, 0.9 Hz, 1H), 5.10-5.05 (m, 1H), 2.78-2.71 (m, 1H), 2.49-2.40 (m, 2H), 2.36-2.27 (m, 1H).

**¹³C NMR** (100 MHz; CDCl₃): δ 198.2, 153.9, 148.1, 134.1, 130.8, 128.7, 123.6, 116.6, 114.3, 73.4, 35.2, 29.3

**IR:** 3301, 3021, 2916, 1662, 1562, 1454, 1422, 1363, 1258, 1225, 1188, 1037, 1017, 931, 861, 738 cm⁻¹

**Chiral HPLC:** IC, 97:3 heptane:isopropanol, 0.80 mL/min, 220 nm, 27.93 min (S enantiomer), 29.63 min (R enantiomer)

[α]b⁺ = + 111.1° (c = 0.46, CHCl₃)

**HRMS (ESI):** Calculated for C₁₂H₁₂BrO₂ (M+H)⁺: 267.0015, found 267.0019
22: A round-bottom Biotage® microwave vial (2.0 mL – 5.0 mL size) equipped with a stir bar was charged with 17 (42.6 mg, 0.197 mmol, 1 equivalent), ($\eta^3$-C$_3$H$_5$)$_2$PdCl$_2$ (1.8 mg, 0.005 mmol, 0.025 equivalents), PPh$_3$ (7.9 mg, 0.03 mmol, 0.15 equivalents), and potassium phthalimide (185.2 mg, 1.0 mmol, 5 equivalents). The vial was sealed with a septum-lined cap and evacuated and backfilled with N$_2$. Distilled THF (1.0 mL) was added, the pierced septum cap was sealed thoroughly with electrical tape and Parafilm®, and the resulting heterogeneous, cream-colored mixture was stirred for 20 h. The reaction mixture was then diluted with Et$_2$O (5 mL) and filtered through a large pipet plug of Florisil®, eluting with Et$_2$O (5 mL). The filtrate was concentrated, and purification of the residue by column chromatography (2:1→1:1 hexanes:EtOAc) afforded 22 (32.6 mg, 0.135 mmol, 69%, 99% ee) as a white solid.

$R_f$ = 0.34 (1:1 hexanes:EtOAc)

$^1$H NMR (500 MHz; CDCl$_3$): $\delta$ 7.89-7.85 (m, 2H), 7.78-7.74 (m, 2H), 6.88 (dt, $J$ = 10.3, 2.1 Hz, 1H), 6.16 (ddd, $J$ = 10.3, 2.9, 1.0 Hz, 1H), 5.22-5.17 (m, 1H), 2.71-2.63 (m, 2H), 2.60-2.51 (m, 1H), 2.23-2.18 (m, 1H)

$^{13}$C NMR (100 MHz; CDCl$_3$): $\delta$ 197.4, 167.7, 149.5, 134.5, 131.8, 130.5, 123.7, 47.2, 36.9, 28.3

IR: 3420, 2919, 2848, 1743, 1691, 1658, 1367, 1341, 1094, 1004, 839, 774, 713 cm$^{-1}$

Chiral HPLC: IA, 90:10 heptane:isopropanol, 0.80 mL/min, 220 nm, 28.47 min (S enantiomer), 31.83 min (R enantiomer)

$[\alpha]_D^{24} = +79.5^\circ$ (c = 0.76, CHCl$_3$)

M.P. = 123-124 °C

HRMS (ESI): Calculated for C$_{14}$H$_{12}$NO$_3$ (M+H)$^+$: 242.0812, found 242.0812
23: A round-bottom Biotage® microwave vial (2.0 mL – 5.0 mL size) equipped with a stir bar was charged with 17 (21.4 mg, 0.0990 mmol, 1 equivalent), (η³-C₃H₅)₂PdCl₂ (0.9 mg, 0.0025 mmol, 0.025 equivalents), and PPh₃ (3.9 mg, 0.015 mmol, 0.15 equivalents). The vial was sealed with a septum-lined cap and evacuated and backfilled with N₂. Degassed (N₂ sparge) CH₂Cl₂ (0.50 mL) was added followed by di-n-propylamine (41 µL, 0.30 mmol, 3 equivalents), and the pierced septum cap was sealed thoroughly with electrical tape and Parafilm®. The resulting homogeneous, yellow solution was stirred for 30 min. The reaction mixture was then diluted with Et₂O (5 mL) and poured into saturated aqueous NaHCO₃ (5 mL). The phases were separated, and the aqueous phase was extracted with Et₂O (3 x 5 mL). The pooled organics were dried over MgSO₄, filtered, and concentrated. Purification of the residue by column chromatography (2:1 – 1:1 hexanes:EtOAc) afforded 23 (13.3 mg, 0.0680 mmol, 69%, 99% ee) as a clear, yellow, viscous oil.

Rf = 0.41 (1:1 hexanes:EtOAc)

¹H NMR (500 MHz; CDCl₃): δ 6.98 (dt, J = 10.3, 2.0 Hz, 1H), 6.02 (ddd, J = 10.3, 2.8, 1.3 Hz, 1H), 3.68-3.64 (m, 1H), 2.57-2.52 (m, 1H), 2.46-2.30 (m, 5H), 2.15-2.11 (m, 1H), 1.92-1.86 (m, 1H), 1.49-1.42 (m, 4H), 0.88 (t, J = 7.4 Hz, 6H)

¹³C NMR (125 MHz; CDCl₃): δ 199.6, 156.1, 130.6, 57.7, 53.2, 37.4, 24.6, 22.3, 11.9

IR: 2917, 2892, 2832, 2775, 1773, 1444, 1360, 1189, 1063 cm⁻¹

Chiral HPLC: AD-H, 99:1 heptane:isopropanol, 0.50 mL/min, 220 nm, 16.00 min (R enantiomer), 18.61 min (S enantiomer)

[α]D²³ = +131.3° (c = 1.33, CHCl₃)

HRMS (ESI): Calculated for C₁₂H₂₂NO (M+H)⁺: 196.1696, found 196.1697

Note: Although spectroscopic data could be obtained in CDCl₃/CHCl₃, following its concentration from these solvents and upon standing, 23 underwent darkening to a purple oil. Passage of an ethereal solution of this material through a pipet plug of Florisil® returned it to a clear, yellow oil, which was stable after prolonged storage under N₂ in a refrigerator.
A round-bottom Biotage® microwave vial (2.0 mL – 5.0 mL size) equipped with a stir bar was charged with 17 (21.1 mg, 0.0976 mmol, 1 equivalent), (η³-C₃H₅)₂PdCl₂ (0.9 mg, 0.0025 mmol, 0.025 equivalents), and PPh₃ (3.9 mg, 0.015 mmol, 0.15 equivalents). The vial was sealed with a septum-lined cap and evacuated and backfilled with N₂. Degassed (N₂ sparge) CH₂Cl₂ (0.50 mL) was added followed by N-benzyl-2-((tert-butyldimethylsilyl)oxy)ethan-1-amine¹³ (SI-3, vide supra, 79.6 mg, 0.30 mmol, 3 equivalents, via tared 100 µL syringe). The pierced septum cap was sealed thoroughly with electrical tape and Parafilm®. The resulting homogeneous, yellow solution was stirred for 30 min. The reaction mixture was then diluted with Et₂O (5 mL) and poured into saturated aqueous NaHCO₃ (5 mL). The phases were separated, and the aqueous phase was extracted with Et₂O (3 x 5 mL). The pooled organics were dried over MgSO₄, filtered, and concentrated. Purification of the residue by column chromatography (4:1 hexanes:EtOAc) afforded 24 (29.8 mg, 0.0829 mmol, 85%, 87% ee) as a clear, yellow, viscous oil.

Rₓ = 0.32 (2:1 hexanes:EtOAc)

¹H NMR (500 MHz; CDCl₃): δ 7.38-7.30 (m, 4H), 7.27-7.24 (m, 1H), 7.03 (dt, J = 10.3, 2.0 Hz, 1H), 6.04 (ddd, J = 10.3, 2.7, 1.3 Hz, 1H), 3.81-3.66 (m, 3H), 3.62 (td, J = 6.3, 1.4 Hz, 2H), 2.67 (t, J = 6.4 Hz, 2H), 2.54 (ddd, J = 16.4, 4.0, 2.9, 1.2 Hz, 1H), 2.33-2.21 (m, 2H), 1.98-1.90 (m, 1H), 0.87 (s, 9H), 0.02 (s, 6H)

¹³C NMR (125 MHz; CDCl₃): δ 199.4, 155.6, 140.0, 130.9, 128.51, 128.48, 127.2, 63.2, 57.7, 56.1, 52.9, 37.2, 26.0, 24.8, 18.4, -5.23, -5.24

IR: 2986, 2912, 2888, 2816, 1662, 1450, 1362, 1236, 1085, 925, 825, 766, 720, 688 cm⁻¹

Chiral HPLC: AD-H, 98:2 heptane:isopropanol, 0.30 mL/min, 220 nm, 13.49 min (R enantiomer), 14.55 min (S enantiomer)

¹³D. McKerrecher, K. G. Pike, M. J. Waring, “Heteroaryl benzamide derivatives for use as GLK activations in the treatment of diabetes.” U.S. Patent US 2009/0105214 A1, April 23, 2009.
$[\alpha]_D^{24} = +41.4^\circ$ (c = 0.49, CHCl$_3$)

**HRMS (ESI):** Calculated for C$_{21}$H$_{34}$NO$_2$Si (M+H)$^+$: 360.2353, found 360.2351

Note: 24 was obtained containing a small amount (ca. 6%, $^1$H NMR) of an unidentified, possibly aromatic impurity.

25: A round-bottom Biotage® microwave vial (2.0 mL – 5.0 mL size) equipped with a stir bar was charged with 18 (23.0 mg, 0.0999 mmol, 1 equivalent), ($\eta^3$-C$_3$H$_5$)$_2$PdCl$_2$ (0.9 mg, 0.0025 mmol, 0.025 equivalents), dppf (1,1'-bis(diphenylphosphino)ferrocene, 4.2 mg, 0.0075 mmol, 0.075 equivalents), and potassium phthalimide (92.6 mg, 0.5 mmol, 5 equivalents). The vial was sealed with a septum-lined cap and evacuated and backfilled with N$_2$. Distilled THF (0.5 mL) was added, the pierced septum cap was sealed thoroughly with electrical tape and Parafilm®, and the resulting heterogeneous, golden yellow mixture was stirred for 3 h. The reaction mixture was then diluted with Et$_2$O (5 mL) and filtered through a large pipet plug of Florisil®, eluting with Et$_2$O (5 mL). The filtrate was concentrated, and purification of the residue by column chromatography (4:1→2:1 hexanes:EtOAc) afforded 25 (16.1 mg, 0.0631 mmol, 63%, 94% ee) as a white solid.

$R_f = 0.36$ (1:1 hexanes:EtOAc)

$^1$H NMR (400 MHz; CDCl$_3$): $\delta$ 7.89-7.84 (m, 2H), 7.78-7.73 (m, 2H), 6.47 (ddd, $J = 12.5$, 3.2, 1.3 Hz, 1H), 6.09 (dd, $J = 12.5$, 2.9 Hz, 1H), 5.16 (ddt, $J = 11.3$, 4.8, 3.1 Hz, 1H), 2.74-2.68 (m, 2H), 2.52-2.43 (m, 1H), 2.10-1.93 (m, 3H).

$^{13}$C NMR (100 MHz; CDCl$_3$): $\delta$ 202.7, 167.6, 144.2, 134.5, 131.8, 131.6, 123.7, 50.7, 43.1, 31.7, 20.2

IR: 2891, 1745, 1682, 1646, 1450, 1368, 1154, 1091, 883, 791, 711 cm$^{-1}$

Chiral HPLC: IA, 90:10 heptane:isopropanol, 0.80 mL/min, 220 nm, 32.73 min ($S$ enantiomer), 42.0 min ($R$ enantiomer)

$[\alpha]_D^{23} = +47.5^\circ$ (c = 1.2, CHCl$_3$)
M.P. = 147-148 °C

HRMS (ESI): Calculated for C_{13}H_{14}NO_3 (M+H)^+: 256.0968, found 256.0971

e) **Synthesis of Compound 26.**

![Image of reaction scheme]

26: To a ½-dram vial equipped with a small stir bar was added TBAF·3H_2O (101.8 mg, 0.32 mmol, 4 equivalents), THF (0.80 mL), and AcOH (4.6 µL, 0.08 mmol, 1 equivalent). The mixture was cooled to 0 °C and stirred for 5 min, at which point it was transferred *via* syringe to a pre-cooled (0 °C) 3-dram vial containing neat 24 (29.0 mg, 0.0806 mmol, 1 equivalent, 87% ee) and a stir bar. The homogeneous, yellow solution was stirred for 1 h at this temperature, by which time its appearance had turned to brown and homogeneous. The reaction mixture was warmed to 23 °C and stirred for 1 h, by which time its appearance had turned to purple and homogeneous. The reaction mixture was then diluted with Et_2O (5 mL) and poured into saturated aqueous NaHCO_3 (5 mL), using some water (*ca.* 5 mL) to transfer. The phases were separated, and the aqueous phase was extracted with Et_2O (3 x 5 mL). The pooled organics were dried over MgSO_4, filtered, and concentrated. Purification of the residue by column chromatography (2:1→1:1 hexanes:EtOAc) afforded 26 (15.2 mg, 0.0620 mmol, 77%, 85% ee) as a clear, yellow, viscous oil and as a single diastereomer (NMR).

R_f = 0.21 (2:1 hexanes:EtOAc)

^1H NMR (400 MHz; CDCl_3): δ 7.38-7.25 (m, 5H), 4.09-4.06 (br s, 1H), 3.87 (ddd, J = 11.3, 3.6, 2.3 Hz, 1H), 3.71-3.62 (m, 3H), 3.02-2.99 (m, 1H), 2.73-2.18 (m, 7H), 1.92-1.85 (m, 1H).

^13C NMR (100 MHz; CD_3CN): δ 209.7, 140.0, 129.7, 129.2, 127.9, 78.3, 67.7, 59.3, 57.4, 46.6, 46.4, 39.1, 17.3 (Not all carbons could be resolved in CDCl_3; as a result, the spectrum was acquired in CD_3CN)

IR: 2916, 2864, 2819, 1695, 1432, 1333, 1149, 1116, 1092, 1075, 1049, 735, 690 cm^{-1}

Chiral HPLC: AD-H, 95:5 heptane:isopropanol, 0.80 mL/min, 220 nm, 15.66 min (26), 20.37 min (*ent*-26)
\[ \alpha_d^{23} = -30.4^\circ (c = 1.0, \text{CHCl}_3) \]

**HRMS (ESI):** Calculated for C_{15}H_{20}NO_2 (M+H)^+: 246.1489, found 246.1484

Note: The product is assigned as the *cis* diastereomer on the basis of a presumed pseudoaxial attack of oxygen, in accordance with literature precedent.

### f) Synthesis of γ-Hydroxycycloalkenones 1, 5, and 27.

![Reaction Scheme]

1: A round-bottom Biotage® microwave vial (2.0 mL – 5.0 mL size) equipped with a stir bar was charged with 17 (41.7 mg, 0.193 mmol, 1 equivalent) and Me_3SnOH (72.3 mg, 0.40 mmol, 2.1 equivalents). The vial was sealed with a septum-lined cap, and then it was evacuated and backfilled with N_2. Freshly distilled 1,2-dichloroethane (0.50 mL) was added, and the pierced septum cap was sealed thoroughly with electrical tape and Parafilm®. The vessel was heated to 80 °C for 14 h, at which point it was cooled to room temperature, diluted with EtOAc (5 mL), and applied to a column of Florisil® (8 cm x 3 cm). The column was eluted with EtOAc (50 mL), and the solution was concentrated. Preparative thin-layer chromatography (1:2 hexanes:EtOAc) afforded recovered 17 (11.3 mg, 0.0522 mmol, 27% recovery) and 1 (9.2 mg, 0.082 mmol, 43%, 58% based on 73% conversion) as a clear, colorless oil. Chiral HPLC analysis of recovered 17 indicated 99% ee.

**1H NMR** (500 MHz; CDCl_3): \( \delta \) 6.93 (ddd, \( J = 10.2, 2.4, 1.7 \) Hz, 1H), 5.98 (ddd, \( J = 10.2, 2.0, 1.1 \) Hz, 1H), 4.59 (m, 1H), 2.62-2.56 (m, 1H), 2.42-2.33 (m, 2H), 2.04-1.96 (m, 2H)

**13C NMR** (125 MHz; CDCl_3): 199.0, 153.0, 129.4, 66.5, 35.5, 32.6

\[ \alpha_d^{25} = +102.6^\circ (c = 0.92, \text{CHCl}_3) \], Lit: +110° (c = 0.2, CHCl_3)

*Analytical data matched literature data.*

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14. E. Vásquez, A. Galindo, D. Gnecco, S. Bernès, J. L. Terán, R. G. Enríquez, *Tetrahedron: Asymmetry, 2001*, 12, 3209.
15. A. S. Demir, O. Sesenoglu, *Org. Lett.*, 2002, 4, 2021.
16. G. Dickmeiss, V. De Sio, J. Udmark, T. B. Poulsen, V. Marcos, K. A. Jørgensen, *Angew. Chem. Int. Ed.*, 2009, 48, 6650.
To determine the ee of 1, a portion of the material obtained was converted to 17 as follows: to a solution of 1 (3.9 mg, 0.035 mmol, 1 equivalent) in CH$_2$Cl$_2$ (0.35 mL) at 0 °C was added pyridine (28 µL, 0.35 mmol, 10 equivalents) and benzoyl chloride (20 µL, 0.17 mmol, 5 equivalents). The solution was stirred for 5 min, and then it was warmed to 23 °C. After 1 h 30 min, the reaction mixture was diluted with Et$_2$O (1 mL) and water (1 mL) and transferred to a test tube containing pH 7 buffer (1 mL). The phases were separated, and the aqueous phase was extracted with Et$_2$O (3 x 1 mL). The pooled organics were dried over MgSO$_4$, filtered, and concentrated. Purification of the residue by preparative thin-layer chromatography (2:1 hexanes:EtOAc) delivered 17 (4.4 mg, 0.020 mmol, 59%) as a clear, colorless oil. Analytical data (1H NMR) matched that reported, and chiral HPLC analysis indicated 99% ee.

5: A round-bottom Biotage® microwave vial (2.0 mL – 5.0 mL size) equipped with a stir bar was charged with 18 (46.8 mg, 0.203 mmol, 1 equivalent) and Me$_3$SnOH (72.3 mg, 0.40 mmol, 2.0 equivalents). The vial was sealed with a septum-lined cap, and then it was evacuated and backfilled with N$_2$. Freshly distilled 1,2-dichloroethane (0.50 mL) was added, and the pierced septum cap was sealed thoroughly with electrical tape and Parafilm®. The vessel was heated to 80 °C for 14 h, at which point it was cooled to room temperature, diluted with EtOAc (5 mL), and applied to a column of Florisil® (8 cm x 3 cm). The column was eluted with EtOAc (50 mL), and the solution was concentrated. Preparative thin-layer chromatography (1:2 hexanes:EtOAc) afforded recovered 18 (16.1 mg, 0.0699 mmol, 34% recovery) and 5 (13.3 mg, 0.105 mmol, 52%, 79% based on 66% conversion) as a clear, colorless oil. Chiral HPLC analysis of recovered 18 indicated 99% ee.

1H NMR (500 MHz; CDCl$_3$): δ 6.57 (ddd, J = 12.5, 3.0, 1.1 Hz, 1H), 5.95 (ddd, J = 12.5, 2.2, 0.8 Hz, 1H), 4.59-4.55 (m, 1H), 2.63-2.53 (m, 2H), 2.23-2.10 (m, 2H), 1.87-1.79 (m, 3H).

13C NMR (125 MHz; CDCl$_3$): 203.4, 149.3, 130.0, 70.6, 43.2, 35.3, 18.4
\[\alpha\]_D^{24} = + 119.2^\circ \text{ (c = 0.67, CHCl}_3\text{), Lit: } + 113.9^\circ \text{ (c = 0.54, CHCl}_3\text{)}^{17}

Analytical data matched literature data.\(^{17}\)

To determine the ee of 5, a portion (4.4 mg, 0.035 mmol) was benzyolated in the same manner as 1. Purification by preparative thin-layer chromatography (2:1 hexanes:EtOAc) delivered 18 (3.9 mg, 0.017 mmol, 49%), and chiral HPLC analysis indicated 99% ee.

![Chemical Structure](image)

27: A round-bottom Biotage\(^{\circledR}\) microwave vial (2.0 mL – 5.0 mL size) equipped with a stir bar was charged with 16 (40.4 mg, 0.200 mmol, 1 equivalent) and Me\(_3\)SnOH (54.2 mg, 0.30 mmol, 1.5 equivalents). The vial was sealed with a septum-lined cap, and then it was evacuated and backfilled with N\(_2\). Freshly distilled 1,2-dichloroethane (0.50 mL) was added, and the pierced septum cap was sealed thoroughly with electrical tape and Parafilm\(^{\circledR}\). The vessel was heated to 80 °C for 14 h, at which point it was cooled to room temperature, diluted with EtOAc (5 mL), and applied to a column of Florisil\(^{\circledR}\) (8 cm x 3 cm). The column was eluted with EtOAc (50 mL), and the solution was concentrated. Preparative thin-layer chromatography (1:2 hexanes:EtOAc) afforded recovered 16 (14.3 mg, 0.0707 mmol, 35% recovery) and 27 (8.7 mg, 0.089 mmol, 44%, 69% based on 65% conversion) as a clear, colorless oil. Chiral HPLC analysis of recovered 16 indicated 99% ee.

\(^{1}\)H NMR (500 MHz; CDCl\(_3\)): \(\delta\) 7.57 (dd, \(J = 5.7, 2.3\) Hz, 1H), 6.23 (dd, \(J = 5.7, 1.3\) Hz, 1H), 5.07-5.05 (m, 1H), 2.78 (dd, \(J = 18.5, 6.1\) Hz, 1H), 2.36-2.19 (br s, 1H), 2.28 (dd, \(J = 18.5, 2.2\) Hz, 1H).

\(^{13}\)C NMR (125 MHz; CDCl\(_3\)): 206.7, 163.3, 135.4, 70.6, 44.4

\[\alpha\]_D^{24} = + 51.8^\circ \text{ (c = 0.87, CHCl}_3\text{), Lit: } + 57^\circ \text{ (c = 1, CHCl}_3\text{)}^{16}

Analytical data matched literature data.\(^{16}\)

\(^{17}\) M. Kawasumi, N. Kanoh, Y. Iwabuchi, Org. Lett., 2011, 13, 3620.
To determine the ee of 27, a portion (3.4 mg, 0.035 mmol) was benzyolated in the same manner as 1. Purification by preparative thin-layer chromatography (2:1 hexanes:EtOAc) delivered 16 (4.4 mg, 0.022 mmol, 62%), and chiral HPLC analysis (vide supra) indicated 95% ee.

g) Total Synthesis of (+)-Tricholomenyn A (28).

\[ \begin{align*}
O & \quad \text{OBz} \\
\text{17} & \quad 99\% \text{ ee} \\
\text{OBz} & \quad \text{38} \\
\text{38} & \quad >19:1 \text{ dr} \\
\text{38} & \quad 99\% \text{ ee}
\end{align*} \]

\[ \text{17} \rightarrow \text{38} \]

38: Based on the procedure of Kitahara and co-worker.\(^\text{18}\) To a solution of 17 (783 mg, 3.62 mmol, 1 equivalent) in THF (4.8 mL) at 0 °C was added hydrogen peroxide (1.12 mL of a ca. 30% aqueous solution, 10.86 mmol, 3 equivalents) followed by Triton B (benzytrimethylammonium hydroxide, 0.14 mL of a 40% aqueous solution, 0.36 mmol, 0.10 equivalent). The resulting light yellow reaction mixture was stirred at 0 °C for 1 h, and then it was diluted with saturated aqueous NaHCO\(_3\) (5 mL) and Et\(_2\)O (10 mL). The phases were separated, and the aqueous phase was extracted with Et\(_2\)O (3 x 10 mL). The pooled organics were dried over MgSO\(_4\), filtered, and concentrated. The residue was purified by column chromatography (4:1 hexanes:EtOAc) to afford 38 (665 mg, 2.86 mmol, 79% yield) as a colorless oil.

\[ R_f = 0.36 \text{ (4:1 hexanes:EtOAc)} \]

\(^1\)H NMR (400 MHz; CDCl\(_3\)): \( \delta \) 8.02-8.00 (m, 2H), 7.59 (t, \( J = 7.4 \text{ Hz}, 1H \)), 7.47-7.43 (m, 2H), 5.76 (q, \( J = 3.3 \text{ Hz}, 1H \)), 3.81 (ddd, \( J = 3.8, 2.9, 0.9 \text{ Hz}, 1H \)), 3.39 (d, \( J = 3.8 \text{ Hz}, 1H \)), 2.57-2.27 (m, 3H), 2.07-2.00 (m, 1H).

\(^13\)C NMR (100 MHz, CDCl\(_3\)): 203.9, 165.7, 133.7, 129.8, 129.4, 128.7, 67.6, 55.4, 55.2, 32.0, 22.3.

IR: 3064, 2951, 1716, 1585, 1585, 1492, 1452, 1408, 1317, 1267, 1178, 1108, 1070, 1028, 923, 847, 791, 764 cm\(^{-1}\)

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\(^\text{18}\) T. Tachihara, T. Kitahara, *Tetrahedron*, 2003, 59, 1773.
**Chiral HPLC:** Chiracel OJ-H, 90:10 heptane:isopropanol, 0.80 mL/min, 220 nm, 11.07 min (38), 11.94 min (ent-38)

$[\alpha]_b^{23} = -4.5^\circ$ (c = 0.75, CHCl$_3$). For ent-38, $[\alpha]_b^{23} = +3.6^\circ$ (c = 0.75, CHCl$_3$)

**HRMS (ESI):** Calculated for C$_{13}$H$_{12}$NaO$_4$ (M+Na)$^+$: 255.0628, found 255.0629

Note: On some occasions, a second addition of Triton B (0.10 equiv) was necessary to initiate the reaction.

37: A solution of 38 (656 mg, 2.82 mmol, 1 equivalent) in MeOH (22 mL) was cooled to 0 °C and treated with a freshly prepared, pre-cooled (0 °C) solution of LiOH·H$_2$O (178 mg, 4.24 mmol, 1.5 equivalents) in MeOH (6 mL). The reaction mixture was stirred at 0 °C for 1 h before it was quenched by the addition of pH 7 buffer (25 mL) and poured into Et$_2$O (50 mL). The phases were separated, and the aqueous phase was extracted with Et$_2$O (3 x 50 mL). The pooled organics were dried over MgSO$_4$, filtered, and concentrated, and the residue was purified by column chromatography (4:1→1:1 hexanes:EtOAc) to afford 37 (302 mg, 2.36 mmol, 83%) as a clear, colorless oil.

$R_f = 0.19$ (1:1 hexanes:EtOAc)

$^1$H NMR (400MHz, CDCl$_3$): 4.57-4.54 (m, 1H), 3.60-3.58 (m, 1H), 3.31 (d, 3.8 Hz, 1H), 2.42-2.39 (m, 2H), 2.23-2.14 (m, 1H), 1.84-1.77 (m, 1H)

$^{13}$C NMR (125MHz, CDCl$_3$): 205.2, 64.6, 58.0, 55.0, 31.6, 25.7

IR (film): 3418 (br), 2944, 1714, 1427, 1338, 1257, 1228, 1187, 1060, 985, 941, 871, 804, 785, 769 cm$^{-1}$

$[\alpha]_b^{23} = -102.6$ (c = 0.29, CHCl$_3$). For ent-37, $[\alpha]_b^{23} = +104.6$ (c = 0.29, CHCl$_3$)

**HRMS (ESI):** Calculated for C$_6$H$_9$O$_3$ (M+H)$^+$: 126.0546, found 126.0545
39: Based on the procedure of Figueredo, Bayón, and co-workers.\textsuperscript{19} To a solution of 37 (123 mg, 0.960 mmol, 1 equivalent) in MeCN (4.8 mL) at 0 °C was added DMAP (129 mg, 1.06 mmol, 1.1 equivalents) followed immediately by Ac\textsubscript{2}O (0.36 mL, 3.84 mmol, 4 equivalents). The reaction mixture was stirred for 1-2 min at 0 °C, and then the cooling bath was removed and the reaction mixture stirred for 10 min. It was then poured into a mixture of Et\textsubscript{2}O (10 mL) and saturated aqueous NaHCO\textsubscript{3} (10 mL), diluting this mixture with a small amount of water. The phases were separated, and the aqueous phase was extracted with Et\textsubscript{2}O (2 x 10 mL). The pooled organics were dried over MgSO\textsubscript{4}, filtered, and concentrated. The residue was purified by column chromatography (2:1 hexanes:EtOAc) to afford 39 (144 mg, 0.846 mmol, 88%) as a clear, light yellow oil.

$R_f$ = 0.35 (2:1 hexanes:EtOAc)

\textsuperscript{1}H NMR (500 MHz; CDCl\textsubscript{3}): $\delta$ 5.50-5.47 (m, 1H), 3.67-3.64 (m, 1H), 3.31 (d, $J$ = 3.8 Hz, 1H), 2.47-2.41 (m, 1H), 2.37-2.30 (m, 1H), 2.25-2.18 (m, 1H), 2.09 (s, 3H), 1.90-1.84 (m, 1H)

\textsuperscript{13}C NMR (125 MHz; CDCl\textsubscript{3}): $\delta$ 203.9, 170.3, 67.1, 55.2, 55.0, 31.8, 22.1, 21.1

IR: 2952, 1716, 1442, 1373, 1233, 1130, 1040, 964, 863, 796, 762 cm\textsuperscript{-1}

$[\alpha]$\textsubscript{D}\textsuperscript{22} = $-55.0^\circ$ (c = 0.40, CHCl\textsubscript{3})

HRMS (ESI): Calculated for C\textsubscript{8}H\textsubscript{10}NaO\textsubscript{4} (M+Na)$^+$: 193.0471, found 193.0466

\textsuperscript{19} Toribio, G., Marjanet, G., Alibés, R., de March, P., Font, J., Bayón, P., Figueredo, M. Eur. J. Org. Chem. 2011, 1534.
Preparation of Mukaiyama reagent 40: The synthesis of \( N,N \)-dichloro-\textit{tert}-butylamine (SI-5) was adapted from the literature procedure for \textit{tert}-butyl hypochlorite.\(^{20}\) To a 250 mL Erlenmeyer flask equipped with a stir bar was added commercial, household bleach (\textit{ca.} 5-10\% NaOCl, 100 mL). The flask was cooled to 0 °C, and the fume hood lights were turned off. AcOH (4.9 mL, 86 mmol, 2.2 equivalents) was added dropwise, followed by \textit{tert}-butylamine (SI-4, 4.1 mL, 39 mmol, 1 equivalent, \textit{added cautiously}). The reaction mixture was stirred for 5 min, and then it was poured into a separatory funnel containing CH\(_2\)Cl\(_2\) (100 mL). At this point, the fume hood lights were turned on. The aqueous phase was discarded, and the organic phase was washed with saturated aqueous NaHCO\(_3\) (50 mL) then water (50 mL), dried over MgSO\(_4\), filtered, and concentrated to provide the volatile SI-5 (2.23 g, 15.7 mmol, 40\%) as a light yellow oil. SI-5 was used immediately in the next step, which was adapted from the literature.\(^{21}\) SI-5 (2.23 g, 15.7 mmol, 1.2 equivalents) was dissolved in PhH (13 mL), and \textit{S}-phenyl thioacetate (SI-6, 1.77 mL, 13.1 mmol, 1 equivalent) was added. The flask was heated to 80 °C and then sealed with a plastic cap. After 1 h 15 min, TLC (5:1 hexanes:Et\(_2\)O) indicated complete consumption of SI-6. The flask was cooled to room temperature and concentrated. Volatile material was removed azeotropically with PhH (2 x 20 mL). The residue was dissolved in CH\(_2\)Cl\(_2\), filtered through a large pipet column of sand, and concentrated to deliver crude 40 (3.18 g, 14.7 mmol, >100\%), which was used without further purification.

\(^{20}\) M. J. Mintz, C. Walling, \textit{Org. Synth.} 1969, 49, 9.

\(^{21}\) T. Mukaiyama, J.-i. Matsuo, M. Yanagisawa, \textit{Chem. Lett.}, 2000, 1072.
The procedure was adapted from the literature.\textsuperscript{22} Ketone 39 (42.5 mg, 0.250 mmol, 1 equivalent) was dried by azeotropic removal of water with PhH (2 x 2 mL), and then it was dissolved in freshly distilled THF (2.5 mL). The solution was cooled to \(-78\) °C. Freshly prepared LiHMDS (0.70 mL of a solution prepared by adding nBuLi [0.43 mL of a 2.36 M solution in hexanes] to freshly distilled HMDS [0.23 mL] in THF [2.0 mL] at \(-78\) °C, stirring for 30 min, then warming to 23 °C and using immediately, corresponds to 0.263 mmol, 1.05 equivalents) was added, and the clear, colorless enolate solution was stirred at \(-78\) °C for 30 min. A solution of reagent 40 (162 mg, 0.75 mmol, 3 equivalents) in THF (2 x 300 µL) was added \textit{via} syringe, affording a neon green/yellow reaction mixture. After stirring for 30 min at \(-78\) °C, the reaction mixture was poured into a mixture of pH 7 buffer (10 mL) and Et$_2$O (10 mL). The phases were separated, and the aqueous phase was extracted with Et$_2$O (2 x 10 mL). The pooled organics were washed with water (10 mL) then brine (10 mL), dried over MgSO$_4$, filtered, and concentrated. The residue was purified by column chromatography (4:1 hexanes:EtOAc) to afford 41 (24.5 mg, 0.145 mmol, 58%) as a viscous yellow oil that partially solidified over time.

$R_f = 0.35$ (2:1 hexanes:EtOAc)

$^{1}$H NMR (500 MHz; CDCl$_3$): $\delta$ 6.60 (ddd, $J = 10.6, 4.7, 2.5$ Hz, 1H), 6.10 (dt, $J = 10.6, 1.5$ Hz, 1H), 5.76 (dq, $J = 4.7, 1.1$ Hz, 1H), 3.74 (ddd, $J = 3.6, 2.5, 1.2$ Hz, 1H), 3.51-3.49 (m, 1H), 2.15 (s, 3H)

$^{13}$C NMR (125 MHz; CDCl$_3$): $\delta$ 192.7, 169.9, 139.5, 129.1, 64.0, 55.4, 53.0, 20.8

IR: 2919, 2850, 1739, 1689, 1372, 1220, 1024, 794 cm$^{-1}$

$[\alpha]_b^{22} = -377.3^\circ$ (c = 0.80, CHCl$_3$)

M.P. = 85-86 °C (solid material obtained \textit{via} IBX oxidation)

MS (ESI): Calculated for C$_8$H$_7$O$_4$: 168.04, found 167.15 (M-H)$^-$

Notes:

1) Ketone 39 and enone 41 could not be separated from each other by chromatography, and 41 was obtained in this manner containing a small amount ($ca.~3\%$, $^1$H NMR) of unreacted 39. The material also contained minor amounts of apparent byproducts from reagent 40 ($ca.~10\%$, $^1$H NMR).

\textsuperscript{22} T. Mukaiyama, J.-i. Matsuo, H. Kitagawa, \textit{Chem. Lett.}, \textbf{2000}, 1250.
2) The oxidation $39 \rightarrow 41$ could also be performed with IBX and catalytic $p$-TsOH·H$_2$O (0.35 equivalents) in DMSO, although this required an excess of IBX (6-7 equivalents) and extended heating (65 °C, 24 h) to obtain high conversion. These conditions delivered $39$ and $41$ as the only isolable products but in highly variable yields (25-66%), a result that led us to favor the above procedure.

$42$: Based on literature procedures. A ½-dram vial equipped with a small stir bar was charged with I$_2$ (43 mg, 0.17 mmol, 1.3 equivalents), Phl(OOCOCF$_3$)$_2$ (72 mg, 0.17 mmol, 1.3 equivalents), CH$_2$Cl$_2$ (250 µL), and pyridine (27 µL, 0.34 mmol, 2.6 equivalents), and this mixture was stirred for 15 min. Meanwhile, to a solution of $41$ (21.7 mg, 0.129 mmol, 1 equivalent) in CH$_2$Cl$_2$ (300 µL) was added BHT (butylated hydroxytoluene, 0.7 mg, 0.003 mmol, 0.065 equivalents). The former solution was transferred to the latter via 100 µL syringe, using additional CH$_2$Cl$_2$ (100 µL) to rinse the vial and syringe. The latter vial was capped, sealed well with Parafilm®, and wrapped in aluminum foil. After stirring for 24 h, the reaction mixture was diluted with Et$_2$O (5 mL) and poured into aqueous Na$_2$S$_2$O$_3$ (10 mL). The phases were separated, the aqueous phase was extracted with Et$_2$O (2 x 5 mL), and the pooled organics were dried over MgSO$_4$, filtered, and concentrated. The residue was purified by column chromatography (4:1→2:1 hexanes:EtOAc) to deliver $42$ (18.7 mg, 0.0636 mmol, 49%) as a viscous, yellow oil that partially solidified over time.

$R_f = 0.35$ (2:1 hexanes:EtOAc)

$^1$H NMR (400 MHz; CDCl$_3$): δ 7.38 (dd, $J = 5.2, 2.3$ Hz, 1H), 5.64 (dt, $J = 5.2, 1.2$ Hz, 1H), 3.78 (ddd, $J = 3.5, 2.3, 1.3$ Hz, 1H), 3.67 (dd, $J = 3.5, 1.2$ Hz, 1H), 2.15 (s, 3H)

$^{13}$C NMR (100 MHz; CDCl$_3$): δ 187.4, 169.6, 147.7, 104.9, 66.0, 55.2, 51.4, 20.7

IR: 2919, 1738, 1694, 1601, 1369, 1330, 1214, 1025, 963, 936, 904, 874, 781 cm$^{-1}$

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23 K. C. Nicolaou, T. Montagnon, P. S. Baran, Y.-L. Zhong, *J. Am. Chem. Soc.*, 2002, 124, 2245.
24 a) R. Benhida, P. Blanchard, J.-L. Fourrey, *Tetrahedron Lett.*, 1998, 39, 6849; b) M. Shoji, H. Imai, M. Mukaida, K. Sakai, H. Kakeya, H. Osada, Y. Hayashi, *J. Org. Chem.*, 2005, 70, 79.
\[ \alpha_D^{24} = -178.9^\circ \text{ (c = 0.50, CHCl}_3\text{), Lit: } -204.4^\circ \text{ (c = 0.50, CHCl}_3\text{)} \]  

Notes:

1) As with 41, compound 42 prepared in this manner contained a small amount of inseparable, unreacted 39 (ca. 3%, \textsuperscript{1}H NMR) as well as minor byproducts from reagent 40 (ca. 10%, \textsuperscript{1}H NMR).

2) Yields ranging from 49-66% were obtained, using 41 obtained from the Mukaiyama protocol or from IBX oxidation.

*Analytical data matched literature data.*\textsuperscript{25}

\[ \text{43: To a solution of compound SI-7 (40.3 mg, 0.30 mmol, 1.0 equivalent, prepared according to the procedure of Wulff and co-workers\textsuperscript{26}) in freshly distilled THF (1.0 mL) at } -78^\circ \text{C was added freshly titrated } n\text{BuLi (0.125 mL, 2.39 M in hexanes, 0.30 mmol, 1.0 equivalent) dropwise. The solution was stirred at } -78^\circ \text{C for 15 min, at which point it was warmed to } 0^\circ \text{C by replacing the cooling bath with an ice/water bath. After 15 min, the solution was re-cooled to } -78^\circ \text{C, and freshly distilled } Bu_3SnCl \text{ (81.4 } \mu\text{L, 0.30 mmol, 1.0 equivalent) was added dropwise. The cooling bath was removed, and the solution was stirred at room temperature for 30 min. It was then diluted with Et}_2O \text{ (5 mL) and quickly vacuum filtered through a fritted funnel containing a thin pad of SiO}_2 \text{, into a flame-dried 100 mL flask. The pad was washed with additional Et}_2O \text{ (15 mL). The filtrate was concentrated, the residue was dissolved in Et}_2O \text{, and the solution was filtered through a pipet plug of Celite® into a flame-dried 2-dram vial. The filtrate was concentrated to afford 43 (117 mg, 0.276 mmol, 92%) as a light yellow, clear oil, which was used without further purification.}

Note: In our hands, attempts to purify 43 using column chromatography on SiO\textsubscript{2} (hexanes eluent, no deactivation) led to complete destannylation, returning terminal alkyne SI-7. However, this could be avoided by purifying 43 using the quick filtration described.*

\textsuperscript{25} a) X. Ma, J. C. Jury, M. G. Banwell, *Tetrahedron Lett.* **2011**, 52, 2192; b) D. M. Pinkerton, M. G. Banwell, A. C. Willis, *Aust. J. Chem.* **2009**, 62, 1639.

\textsuperscript{26} W. Jiang, M. J. Fuertes, W. D. Wulff, *Tetrahedron*, **2000**, 56, 2183.
(--)-Tricholomenyn A (28): The procedure of Banwell and co-workers was adapted.\textsuperscript{25b} To a solution of 42 (17.5 mg, 0.0595 mmol, 1 equivalent) in distilled THF (1.0 mL) in a 2-dram vial at 0 °C was added 43 (50.4 mg, 0.12 mmol, 2 equivalents) via tared 100 µL syringe, yielding a golden yellow, homogeneous solution. To this was added Pd(OAc)\textsubscript{2} (1.3 mg, 0.006 mmol, 0.10 equivalent), CuI (1.1 mg, 0.006 mmol, 0.10 equivalent), and AsPh\textsubscript{3} (3.7 mg, 0.012 mmol, 0.20 equivalent) all at once under N\textsubscript{2} flow. The reaction mixture was stirred at 0 °C for 1 h 30 min, during which time its appearance changed to olive green and homogeneous. The reaction mixture was then poured into a mixture of Et\textsubscript{2}O (20 mL) and pH 7 buffer (5 mL), the phases were separated, and the aqueous phase was extracted with Et\textsubscript{2}O (2 x 5 mL). The pooled organics were washed with saturated aqueous NH\textsubscript{4}F (2 x 10 mL), then water (10 mL), then brine (10 mL), dried over MgSO\textsubscript{4}, filtered, and concentrated. The residue was purified by column chromatography (4:1 hexanes:EtOAc) followed by preparative thin-layer chromatography (20:1 CH\textsubscript{2}Cl\textsubscript{2}:PhH) to deliver 28 (9.9 mg, 0.0330 mmol, 55%, free of the impurities derived from 40 and residual ketone 39) as a clear, light yellow, viscous oil.

\[ \mathbf{R_f} = 0.31 \ (4:1 \ \text{hexanes}:\text{EtOAc}) \]

\[ \begin{align*} \text{\textsuperscript{1}H NMR} & \ (600 \ \text{MHz; CDCl}_3): \ \delta \ 6.75 \ (dd, \ J = 5.2, \ 2.5 \ Hz, \ 1H), \ 5.82 \ (dt, \ J = 5.2, \ 1.2 \ Hz, \ 1H), \\
& \ 5.45 \ (d, \ J = 1.6 \ Hz, \ 1H), \ 5.35 \ (d, \ J = 1.4 \ Hz, \ 1H), \ 5.11-5.09 \ (m, \ 1H), \ 3.74 \ (ddd, \ J = 3.7, \ 2.4, \ 1.4 \ Hz, \ 1H), \ 3.60 \ (dd, \ J = 3.6, \ 1.0 \ Hz, \ 1H), \ 2.27-2.20 \ (m, \ 4H), \ 2.14 \ (s, \ 3H), \ 1.68 \ (s, \ 3H), \ 1.62 \ (s, \ 3H) \end{align*} \]

\[ \begin{align*} \text{\textsuperscript{13}C NMR} & \ (125 \ \text{MHz; CDCl}_3): \ \delta \ 189.6, \ 169.8, \ 140.5, \ 132.6, \ 130.7, \ 125.2, \ 123.7, \ 123.2, \ 96.1, \\
& \ 82.0, \ 64.3, \ 54.9, \ 53.1, \ 37.1, \ 26.8, \ 25.8, \ 20.8, \ 17.9 \end{align*} \]

\[ \text{IR: \ 2922, \ 2205, \ 1742, \ 1702, \ 1617, \ 1443, \ 1372, \ 1299, \ 1219, \ 1116, \ 1025, \ 987, \ 909, \ 829, \ 779 \ \text{cm}^{-1} \]
$[\alpha]_D^{23} = -234.6^\circ$ (c = 0.96, CH$_2$Cl$_2$), Lit: $-241.3^\circ$ (c = 1.35, CH$_2$Cl$_2$), $^{23} -228^\circ$ (c = 0.1, CH$_2$Cl$_2$), $^{25} -235.7^\circ$ (c = 1.47, CH$_2$Cl$_2$), $^{27} -237$ (c = 0.6, CH$_2$Cl$_2$), $^{28} -148.1^\circ$ (c = 0.35, CH$_2$Cl$_2$) $^{30}$

HRMS (ESI): Calculated for C$_{18}$H$_{20}$NaO$_4$ (M+Na)$^+$: 323.1254, found 323.1255

Analytical data matched literature data $^{25b, 27-30}$

Note: Yields ranging from 55-60% were obtained using 42 prepared using either the Mukaiyama protocol or IBX oxidation, followed by iodination.

**h) Synthesis of Epoxyquinoid Precursors 44 and 45.**

44: To a solution of ent-37 (43.0 mg, 0.336 mmol, 1 equivalent, prepared as detailed above for 37, 98% ee) in CH$_2$Cl$_2$ (1.3 mL) was added TBSCl (65.8 mg, 0.44 mmol, 1.3 equivalents) and imidazole (35.4 mg, 0.52 mmol, 1.55 equivalents). The reaction mixture was stirred for 16 h, and then it was loaded directly onto an SiO$_2$ column and eluted with 10:1 hexanes:Et$_2$O to provide 44 (71.2 mg, 0.294 mmol, 88%) as a clear, colorless oil.

$R_f = 0.59$ (4:1 hexanes:EtOAc)

$^1$H NMR (400 MHz; CDCl$_3$): $\delta$ 4.44 (dd, $J = 4.0$, 2.8 Hz, 1H), 3.45 (app t, $J = 3.1$ Hz, 1H), 3.25 (d, $J = 3.9$ Hz, 1H), 2.42-2.28 (m, 2H), 2.12-2.03 (m, 1H), 1.72-1.66 (m, 1H), 0.88 (s, 9H), 0.11 (s, 3H), 0.09 (s, 3H).

$^{13}$C NMR (100 MHz; CDCl$_3$): $\delta$ 205.0, 65.3, 58.1, 55.0, 31.7, 25.9, 25.6, 18.2, -4.6, -4.7

IR: 2955, 2889, 2859, 1719, 1472, 1444, 1405, 1362, 1336, 1254, 1228, 1187, 1092, 1035, 982, 687, 839, 778 cm$^{-1}$

$[\alpha]_D^{23} = +58.2^\circ$ (c = 1.92, CHCl$_3$), Lit: $+57.3^\circ$ (c = 1.96, CHCl$_3$) $^{18}$

Analytical data matched literature data $^{18, 31}$

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$^{27}$ J. Li, S. Park, R. L. Miller, D. Lee, *Org. Lett.* 2009, 11, 571.
$^{28}$ T. Kamikubo, K. Ogasawara, *Chem. Commun.*, 1996, 1679.
$^{29}$ M. W. Miller, C. R. Johnson, *J. Org. Chem.* 1997, 62, 1582.
$^{30}$ L. Garlaschelli, E. Magistrali, G. Vidari, O. Zuffardi, *Tetrahedron Lett.* 1995, 36, 5633.
To a solution of 44 (26.3 mg, 0.109 mmol, 1 equivalent) at –78 °C was added freshly prepared LiHMDS (0.15 mL of a solution prepared by adding nBuLi [0.45 mL of a 2.20 M solution in hexanes] to freshly distilled HMDS [0.23 mL] in THF [0.50 mL] at –78 °C, stirring for 30 min, then warming to 23 °C and using immediately, corresponds to 0.13 mmol, 1.2 equivalents). The solution was stirred at –78 °C for 30 min, at which point a solution of 40 (70 mg, 0.33 mmol, 3 equivalents) in THF (200 µL) was added via cannula. Additional THF (2 x 100 µL) was used to rinse the vial containing 40 and the cannula. The reaction mixture was stirred at –78 °C for 1 h, at which point it was poured into a mixture of pH 7 buffer (3 mL) and Et₂O (5 mL). The phases were separated, and the aqueous phase was extracted with Et₂O (2 x 5 mL). The pooled organics were dried over MgSO₄, filtered, and concentrated, and the residue was purified by column chromatography (20:1 hexanes:EtOAc) to afford 45 (17.1 mg, 0.0711 mmol, 66%) as a clear, light yellow oil.

Rf = 0.59 (4:1 hexanes:EtOAc)

1H NMR (400 MHz; CDCl₃): δ 6.52 (ddd, J = 10.5, 4.5, 2.6 Hz, 1H), 5.96 (ddd, J = 10.5, 1.8, 1.2 Hz, 1H), 4.66 (dq, J = 4.5, 1.1 Hz, 1H), 3.65 (ddd, J = 3.6, 2.5, 1.1 Hz, 1H), 3.46 (ddd, J = 3.6, 1.8, 1.1 Hz, 1H), 0.92 (s, 9H), 0.18 (s, 3H), 0.16 (s, 3H).

13C NMR (100 MHz; CDCl₃): δ 193.3, 144.5, 126.4, 63.8, 58.5, 53.5, 25.8, 18.3, -4.3, -4.8

IR: 2956, 2931, 2888, 2859, 1692, 1472, 1259, 1090, 876, 856, 839, 824, 806, 779 cm⁻¹

Analytical data matched literature data.¹⁸,³²

¹⁸ V. Rodeschini, P. Van de Weghe, E. Salomon, C. Tarnus, J. Eustache, J. Org. Chem., 2005, 70, 2409.
³² M. T. Barros, C. D. Maycock, M. R. Ventura, Chem. Eur. J., 2000, 6, 3991.
(-)-Tricholomeryn A (28)
| # | RetTime | Type | Width | Area | Height | %   |
|---|---------|------|-------|------|--------|-----|
| 1 | 33.955  | VV   | 0.5937| 1.47540e4 | 386.68399 | 40.1158 |
| 2 | 35.948  | VB   | 0.6394| 2.20245e4 | 536.22058  | 59.8842  |

**Totals:**

| Width | Area | Height | Total Area |
|-------|------|--------|------------|
| 3.67785e4 | 922.90457 | 3.67785e4 | 922.90457 |

**Area Percent Report**

| Sorted By | Signal |
|-----------|--------|
| Multiplier: | 1.0000 |
| Dilution: | 1.0000 |

Use Multiplier & Dilution Factor with ISTDs

**Signal 1: VWD1 A, Wavelength=220 nm**

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***End of Report***
Area Percent Report

Sorted By: Signal
Multiplier: 1.0000
Dilution: 1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 1: VWD1 A, Wavelength=220 nm

| Peak RetTime | Type | Width [min] | Area [mAU] | Height [s] | Area [mAU] | %     |
|--------------|------|-------------|------------|------------|------------|-------|
| 1            | VV   | 0.5897      | 5886.30420 | 154.62854  | 4.3601     |
| 2            | VB   | 0.7159      | 1.29117e5  | 2790.92456 | 95.6399    |

Totals: 1.35003e5 2945.55310

*** End of Report ***
## Area Percent Report

**Sorted By** : Signal  
**Multiplier:** : 1.0000  
**Dilution:** : 1.0000  
Use Multiplier & Dilution Factor with ISTDs

**Signal 1: VWD1 A, Wavelength=220 nm**

| # | RetTime [min] | Type | Width [min] | Area [mAU *s] | Height [mAU] | Area [%] |
|---|---------------|------|-------------|---------------|--------------|---------|
| 1 | 34.055        | BV   | 0.6033      | 2.49449e4     | 644.00079    | 93.7573 |
| 2 | 36.197        | VB   | 0.6539      | 1660.93286    | 39.24398     | 6.2427  |

**Totals** : 2.66058e4 683.24478

*** End of Report ***
Admixture (R) + (S)
Method       Method completed                               20:07:09 08/20/13
=====================================================================  

VWD1 A, Wavelength=220 nm (JIM/DEF_LC 2013-08-20 19-20-27/JTM-20-53-RAC-IC-90-10.D)

20 - Admixture (R) + (S)

=====================================================================  

Area Percent Report
=====================================================================  

Sorted By : Signal  
Multiplier: : 1.0000  
Dilution: : 1.0000  
Use Multiplier & Dilution Factor with ISTDs  

Signal 1: VWD1 A, Wavelength=220 nm

| #   | RetTime | Type | Width | Area        | Height | Area  | Height | Area  |
|-----|---------|------|-------|-------------|--------|-------|--------|-------|
| 1   | 28.030  | VB   | 0.4926| 2.47872e4   | 780.87238| 47.2756|
| 2   | 31.389  | BB   | 0.5549| 2.76441e4   | 771.46741| 52.7244|

Totals : 5.24314e4 1552.33978

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*** End of Report ***

Electronic Supplementary Material (ESI) for Chemical Science
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**Area Percent Report**

Sorted By : Signal
Multiplier: : 1.0000
Dilution: : 1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 1: VWD1 A, Wavelength=220 nm

| # | RetTime | Type | Width | Area       | Height     | Area % |
|---|---------|------|-------|------------|------------|--------|
| 1 | 28.677  | VV   | 0.5317| 491.20615  | 14.09659   | 1.2235 |
| 2 | 32.096  | VB   | 0.5698| 3.96559e4  | 1083.23499 | 98.7765|

Totals: 4.01471e4 1097.33157

*** End of Report ***
Method       Method completed                               21:40:31 08/20/13
=====================================================================  

| #  | RetTime [min] | Width [min] | Area [mAU] | Height [mAU] | Area % |
|----|--------------|-------------|------------|--------------|-------|
| 1  | 28.522 MM    | 0.5407      | 4.68005e4  | 1442.52966   | 98.2562 |
| 2  | 32.081 MM    | 0.5856      | 830.59882  | 23.63828     | 1.7438  |

Totals :                      4.76311e4  1466.16794

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*** End of Report ***
Method stopped by user 12:50:50 09/02/13

![Graph showing peak retention times and areas] (VWD1 A, Wavelength=220 nm (JIM/DEF_LC 2013-09-02 12-14-59/JTM-20-85-RAC-IC-97-3.D))

**Area Percent Report**

| Sorted By | Signal | Multiplier: 1.0000 | Dilution: 1.0000 |
|-----------|--------|---------------------|------------------|

Use Multiplier & Dilution Factor with ISTDs

**Signal 1: VWD1 A, Wavelength=220 nm**

| Peak Ret | Type | Width | Area     | Height | Area   | %     |
|----------|------|-------|----------|--------|--------|-------|
| #        | [min]| [min]| mAU      | *s     | [mAU]  | %     |
|---------|-----|------|---------|--------|--------|-------|
| 1       | 27.988 | VV | 0.4945  | 1.77155e4 | 551.05151 | 43.2881 |
| 2       | 29.717 | VV | 0.5230  | 2.32091e4 | 685.66119 | 56.7119 |

Totals: 4.09245e4 1236.71271

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**End of Report***
Method       Method completed                               20:42:35 09/16/13
===================================================================== 

Area Percent Report
===================================================================== 

Sorted By : Signal
Multiplier:      : 1.0000
Dilution:      : 1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 1: VWD1 A, Wavelength=220 nm

| #  | RetTime | Type | Width | Area   | Height | Area   | %    |
|----|---------|------|-------|--------|--------|--------|------|
| 1  | 26.212  | VV   | 0.4557| 1706.60278 | 58.19334 | 3.9701 |
| 2  | 27.571  | VV   | 0.4844| 4.12799e4  | 1329.99402 | 96.0299 |

Totals :  4.29865e4  1388.18736

===================================================================== 

*** End of Report *** 

Data File C:\CHEM32\1\DATA\JIM\DEF_LC 2013-09-16 18-39-01\JTM-20-96-2BR.D 
Sample Name: jtm-20-96-2br 

Electronic Supplementary Material (ESI) for Chemical Science 
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Area Percent Report

Sorted By : Signal
Multiplier:  : 1.0000
Dilution:  : 1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 1: VWD1 A, Wavelength=220 nm

Peak RetTime Type  Width     Area      Height     Area
#   [min]        [min]  mAU   *s   [mAU   ]       %
----|-------|----|-------|----------|----------|--------|
1   27.930 MM    0.5126 1.55156e4   504.45609  96.3207
2   29.712 MM    0.5590  592.67914   17.67150   3.6793
Totals :                  1.61083e4   522.12758

*** End of Report ***
### Area Percent Report

**Sorted By** : Signal  
**Multiplier:**  : 1.0000  
**Dilution:**  : 1.0000  
Use Multiplier & Dilution Factor with ISTDs

**Signal 1: VWD1 A, Wavelength=220 nm**

| #  | RetTime Type | Width [min] | Area [mAU] | *s | Height [mAU] | Area (%) |
|----|--------------|-------------|------------|----|--------------|---------|
| 1  | 28.593 VV    | 0.6977      | 276.30225  | 28.593 | 1.33518e4   | 44.1793 |
| 2  | 32.076 VB    | 0.8098      | 298.92535  | 32.076 | 1.68700e4   | 55.8207 |

**Totals:**  
3.02218e4  575.22760

*** End of Report ***
Area Percent Report

Sorted By : Signal
Multiplier: : 1.0000
Dilution: : 1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 1: VWD1 A, Wavelength=220 nm

| # | RetTime | Type | Width | Area   | Height | Area\Framework
|---|---------|------|-------|--------|--------|------
| 1 | 31.826  | VV   | 0.8156| 3.75540e4| 656.75989| 100.0000 |

Totals : 3.75540e4 656.75989

*** End of Report ***
### Area Percent Report

Sorted By : Signal  
Multiplier: 1.0000  
Dilution: 1.0000  
Use Multiplier & Dilution Factor with ISTDs

**Signal 1: VWD1 A, Wavelength=220 nm**

| # | RetTime [min] | Width [min] | Area mAU | Height *s | Area mAU % |
|---|--------------|-------------|---------|----------|-----------|
| 1 | 28.467 VB    | 0.6937      | 1.71254e4 | 356.93121 | 100.0000  |

**Totals:** 1.71254e4 356.93121

*** End of Report ***

---

**Data File**: C:\CHEM32\1\DATA\JIM\DEF_LC 2013-08-16 14-58-35\JTM-20-50-CHIRAL.D

**Sample Name**: jtm-20-50-chiral-S

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**Instrument 1**: 9/17/2013 5:09:28 PM Jim

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23 - Admixture (R) + (S)
Area Percent Report

Sorted By : Signal
Multiplier: : 1.0000
Dilution: : 1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 1: VWD1 A, Wavelength=220 nm

| #  | RetTime [min] | Type | Width [min] | Area [mAU] | Height [s] | Area [%]  |
|----|--------------|------|-------------|-----------|----------|-----------|
| 1  | 32.733       | VB   | 0.7858      | 4.33353e4 | 791.51624| 49.8124   |
| 2  | 41.994       | VV   | 1.0552      | 4.36618e4 | 588.27252| 50.1876   |

Totals : 8.69971e4 1379.78876

*** End of Report ***
Method stopped by user 17:28:08 10/21/13

Area Percent Report

Sorted By: Signal
Multiplier: 1.0000
Dilution: 1.0000

Use Multiplier & Dilution Factor with ISTDs

Signal 1: VWD1 A, Wavelength=220 nm

| # | RetTime | Type | Width | Area   | Height | Area    | %    |
|---|---------|------|-------|--------|--------|---------|------|
| 1 | 32.773  | MM   | 1.1269| 4673.79688 | 69.12724 | 3.0381 |
| 2 | 41.323  | MM   | 1.5156| 1.49166e5  | 1640.31873| 96.9619 |

Totals: 1.53840e5 1709.44596

*** End of Report ***
26 - Admixture (26 + en-26)
