Supporting Information

Enantio- and Diastereocontrolled conversion of chiral epoxide to trans-cyclopropane carboxylate: Application to the synthesis of Cascarillic acid, Grenadamide and L-(-)-CCG-II

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Experimental Section

General information

All reactions requiring anhydrous conditions were performed under a positive pressure of argon using oven-dried glassware (110 °C), which was cooled under argon. Solvents for anhydrous reactions were dried according to Perrin et al. Solvents used for chromatography were distilled at respective boiling points using known procedures. Progress of the reactions was monitored by TLC using precoated aluminium plates (Merck silica gel 60 F254). Column chromatographies were performed on silica gel 60-120/100-200/230-400 mesh obtained from S. D. Fine Chemical Co. India or Spectrochem India. IR spectra were recorded on a Perkin–Elmer infrared spectrometer model 599-B and model 1620 FTIR. $^1$H NMR spectra were recorded on Bruker AC-200, Bruker AV-400 and Bruker DRX–500 instruments using deuterated solvent. Chemical shifts are reported in ppm. Proton coupling constants (J) are reported as absolute values in Hz and multiplicity (brs, broad; s, singlet; d, doublet; t, triplet; m, multiplet). $^{13}$C NMR spectra were recorded on Bruker AC-200, Bruker AV-400 and Bruker DRX-500 instruments operating at 50 MHz, 100 MHz, and 125 MHz, respectively. $^{13}$C NMR chemical shifts are reported in ppm relative to the central line of CDCl$_3$ ($\delta$ 77.0). Microanalytical data were obtained using a Carlo–Erba CHNS-0 EA 1108 elemental analyzer. All the melting points were recorded on a Büchi B-540 electrothermal melting point apparatus. Yields refer to chromatographically and spectroscopically pure compounds. Enantiomeric excess was determined using Mosher analysis.

**(1R,2R)-2-Hexylcyclopropyl)methanol (7):** To a stirred suspension of LiAlH$_4$ (765 mg, 20.17 mmol) in dry THF (100 mL) at -10 °C was added ester 3a (5 g, 25.21 mmol) over 20 min under argon atmosphere. After stirring for 20 min, the reaction was quenched by adding 10% aqueous NaOH at 0 °C. The mixture was filtered with pad of celite, and washed with EtOAc. The organic layer was dried (Na$_2$SO$_4$), and concentrated. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (9:1) as eluent gave 7 (3.15 g, 80% yield) as a colorless syrupy liquid. [α]$_D^{25}$ -22.2 (c 1.0, CHCl$_3$); IR (neat, cm$^{-1}$): $\nu$$_{max}$ 3350, 2854, 1466, 1216, 1033; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 0.26-0.41 (2H, m), 0.55-0.67 (1H, m), 0.76-0.91 (4H, m), 1.15-1.47 (10H, m), 1.70 (1H, brs), 3.44 (2H, dd, J 1.9, 7.0 Hz.), $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 9.8, 14.0, 17.1, 21.0, 23.0, 29.0, 29.5, 31.8, 33.5, 67.0; MS (ESI): m/z 178.96 (M+Na$^+$); Elemental analysis (%) calcd. for (C$_{10}$H$_{20}$O): C, 76.86; H, 12.90 %; Found: C, 76.65; H, 12.72%.

**(1R,2R)-Ethyl 2-heptylcyclopropanecarboxylate (3b):** To a suspension of sodium hydride (4.25 g, 106.35 mmol, 60% in mineral oil) in toluene (100 ml) at 0 °C was added triethylphosphonoacetate (27.78 ml, 140.06 mmol) dropwise over 15 min. After stirring for 10 min, epoxide 1b (5 g, 35.15 mmol) was added dropwise over 15 min, followed by heating at 80 °C for 8 h, then temperature increased to 110 °C and stirred for 6 h. The reaction mixture was cooled to room temperature, diluted with EtOAc (100 ml), and then washed with saturated aqueous ammonium chloride (100 ml). The organic phase was separated and the aqueous phase extracted with Et$_2$O (3 x 50 mL). The combined organic phases were washed with brine, dried over Na$_2$SO$_4$ and concentrated under reduced pressure.
The crude material was purified by flash chromatography using petroleum ether/EtOAc (99:1) to give cyclopropane 3b (6.34 g, 85% yield) as a thick colorless oil. [α]_D^25 -56.7 (c 1.0, CHCl3); [lit.2 [α]_D^20 +57.9 (c 0.96, CHCl3) for ent-3b] IR (neat, cm⁻¹): ν_max 2933, 2855, 1730; ¹H NMR (400 MHz, CDCl₃): δ 0.31-0.36 (2H, m), 0.53-0.66 (1H, m), 0.76-0.8 (1H, m), 0.89 (3H, t, J 6.1 Hz), 1.21-1.39 (15H, m), 4.10 (2H, q, J 7.2, 14.3); ¹³C NMR (100 MHz, CDCl₃): δ 11.6, 13.9, 14.1, 18.7, 22.8, 29.3, 29.4, 29.5, 29.6, 31.9, 33.8, 60.6, 179.9

3-((1R,2R)-2-Heptylcyclopropyl)propanoic acid (12): To the ester 11 (400 mg, 1.66 mmol) dissolved in MeOH (10 mL) and H₂O (6.67 mL) was added LiOH.H₂O (208 mg, 4.98 mmol) and stirred at 0 °C to room temperature for 5 h. The reaction mixture was further diluted with H₂O (5 mL) and stirred for 30 min then concentrated by rotary evaporator to quarter of its volume. The mixture was acidified (upto pH 5) with 1 M HCl and the reaction mixture was extracted with EtOAc (3 x 10 mL). The combined organic layer was washed with brine (2 x 10 mL) and dried over anhydrous Na₂SO₄, concentrated and the crude product was purified by column chromatography eluting with petroleum ether/EtOAc (9:1) to give 12 (371 mg, 82% yield) as a pale yellow color syrupy liquid. [α]_D^25 -13.99 (c 1, CHCl3); [lit.19d [α]_D^25 +13.5 (c 1, CHCl3) for ent-12]; IR (neat, cm⁻¹): ν_max 3420, 2855, 1711, 1458, 1216, 759, 668; ¹H NMR (400 MHz, CDCl₃): δ 0.32-0.35 (2H, m), 0.54-0.59 (1H, m), 0.78-0.82 (1H, m), 0.89 (3H, t, J 6.1 Hz), 1.27-1.39 (12H, m), 1.53-1.68 (2H, m), 2.26-2.28 (2H, m); ¹³C NMR (100 MHz, CDCl₃): δ 11.9, 13.9, 14.1, 18.7, 22.8, 29.3, 29.6, 31.9, 33.8, 38.9, 179.9; MS (ESI): m/z 235.33 (M+Na)+; Elemental analysis (%) calcd. for C₁₃H₂₄O₂: C, 73.54; H, 11.39 %; Found: C, 73.70; H, 11.44%.

(2S,3S)-2,3-Dihydroxy-3-phenylpropyl 4-methylbenzenesulfonate (18): To a mixture of triol 17 (4.0 g, 23.66 mmol), in dry CH₂Cl₂ (40 mL) was added dibutyltin oxide (0.292 mg, 0.2 mol %) followed by the addition of p-toluenesulfonyl chloride (4.94 g, 26.0 mmol) and Et₃N (3.62 mL, 26.0 mmol) and reaction was stirred at room temperature under nitrogen. The reaction was monitored by TLC, after completion of reaction (6 h) the mixture was quenched by adding water. The solution was extracted with dichloromethane (3 x 100 mL) and then combined organic phase was washed with water, dried (Na₂SO₄) and concentrated. Silica gel column chromatography of crude product using petroleum ether:EtOAc (7:3) as eluent afforded monotosyl compound 18 (6.8 g, 89% yield) as a viscous liquid. [α]_D^25 +15.4 (c 1.2, CHCl3); IR (CHCl3, cm⁻¹): ν_max 3503, 1729, 1493, 1359, 1189, 1175, 1096, 973, 758, 665; ¹H NMR (200 MHz, CDCl₃): δ 2.37 (3H, s), 2.83 (2H, brs), 3.77-3.82 (2H, m), 3.91-3.98 (1H, m), 4.55 (1H, d, J 6.1 Hz), 7.19-7.27 (7H, m), 7.67 (2H, d, J 8.3 Hz); ¹³C NMR (50 MHz, CDCl₃): δ 21.5, 70.4, 73.4, 73.5, 126.5, 127.8, 128.1, 128.5, 129.8, 132.2, 139.7, 145; Elemental analysis (%) calcd. for C₁₆H₁₈O₅S: C, 59.61; H, 5.63; S, 9.95%; Found: C, 59.75; H, 5.49; S, 9.74%.

(5S)-(5S)-Oxiran-2-yl)(phenyl)methanol (19): To a solution of compound 18 (1.0 g, 3.1 mmol) in methanol (10 mL) at 0 °C was added solid K₂CO₃ (0.85g, 6.2 mmol) in one portion and continued the stirring at 0 °C for 15 min. After consumption of starting material (15 min), solvent was evaporated under reduced pressure. Residue was diluted with water (5 mL), extracted with ethyl acetate (2 x 15 mL). Organic layer was washed with water, brine, dried over Na₂SO₄. Solvent was evaporated under reduced pressure to give crude epoxide, which was further purified by column chromatography using petroleum ether:EtOAc (8:2) as eluent to afford epoxide 19 (0.367 g, 79% yield) as a viscous liquid. [α]_D^25 +7.89 (c 2.74, CHCl₃);
IR (CHCl₃, cm⁻¹): ν max 3460, 3019, 2896, 1612, 1513, 1454, 1215, 1043, 755, 700, 668; ¹H NMR (200 MHz, CDCl₃): δ 2.71-2.79 (2H, m), 3.10-3.17 (1H, m), 4.36 (1H, d, J 5.7 Hz), 7.26-7.36 (5H, m); ¹³C NMR (125 MHz, CDCl₃): δ 45.3, 56.0, 74.4, 126.2, 128.0, 128.4, 140; HRMS, (EI/DIP) for (M⁺): calc. 150.06018, Found: 150.05492.

(1R,2R)-Ethyl 2-(((S)-azido(phenyl)methyl)cyclopropanecarboxylate (15): To a solution of 20 (700 mg, 3.17 mmol) in dry CH₂Cl₂ (20 mL) at 0°C was added methanesulfonyl chloride (0.37 mL, 4.76 mmol), Et₃N (0.66 mL, 4.76) and DMAP (cat). After consumption of starting material (8 h), the reaction mixture was poured into Et₂O-H₂O mixture. The organic phase was separated and the aqueous phase extracted with Et₂O (3 x 20 mL). The combined organic phases were washed with water, brine, dried (Na₂SO₄) and concentrated to a yellow syrupy liquid, which was used as such in the next step.

To the solution of above mesylate in dry DMF (20 mL) was added NaN₃ (824 mg, 12.88 mmol) and the reaction mixture stirred at 70 °C for 8 h. It was cooled and poured into water and extracted with Et₂O (4 x 20 mL). The organic extracts were washed with water, brine, dried (Na₂SO₄) and concentrated. Column chromatography on silica gel column using petroleum ether:EtOAc (9:1) eluent gave 15 (662 mg, 85% yield) as a pale yellow color liquid. [α]D²⁵ 25° -27.9 (c 1.0, CHCl₃); IR (neat, cm⁻¹): ν max 2924, 2892, 2097, 1726, 1615, 1463, 1372, 1181, 1074, 1029, 761; ¹H NMR (200 MHz, CDCl₃): δ 0.81-0.93 (1H, m), 0.96-1.25 (4H, m), 1.52-1.84 (2H, m), 4.08 (2H, q, J 7.2, 14.2 Hz), 4.17 (2H, d, J 6.5 Hz), 7.14-7.32 (5H, m); ¹³C NMR (50 MHz, CDCl₃): δ 12.2, 12.9, 14, 25.8, 55.1, 66.2, 126.9, 128.7, 129.6, 138.2, 173; Elemental analysis (%) calcd. for C₁₃H₁₅N₃O₂: C, 75.75; H, 12.71; N, 7.62%; Found: C, 75.87; H, 12.48; N, 7.91%.

References:
\(^1\)H NMR (CDCl\(_3\), 400MHz) of compound (1\(_R\),2\(_R\))-Ethyl 2-hexylcyclopropanecarboxylate (3a)

\(^13\)C NMR (CDCl\(_3\), 100MHz) of compound (1\(_R\),2\(_R\))-Ethyl 2-hexylcyclopropanecarboxylate (3a)
$^1$H NMR (CDCl$_3$, 400MHz) of compound (1$R$,2$R$)-2-Hexylcyclopropyl)methanol (7)

$^{13}$C NMR (CDCl$_3$, 100MHz) of compound (1$R$,2$R$)-2-Hexylcyclopropyl)methanol (7)
$^1$H NMR (CDCl$_3$, 200MHz) of compound 2-((1S,2R)-2-Hexylcyclopropyl)acetonitrile (8)

$^{13}$C NMR (CDCl$_3$, 50MHz) of compound 2-((1S,2R)-2-Hexylcyclopropyl)acetonitrile (8)
$^1$H NMR (CDCl$_3$, 400MHz) of compound 2-((1$S,2R$)-2-Hexylcyclopropyl)acetic acid (9)

$^{13}$C NMR (CDCl$_3$, 100MHz) of compound 2-((1$S,2R$)-2-Hexylcyclopropyl)acetic acid
**1H spectra (CDCl₃, 500 MHz) of compound ethyl 2-((1S,2R)-2-heptylcyclopropyl)acetate (10)**

![1H NMR spectrum]

**13C spectra (CDCl₃, 125 MHz) of compound ethyl 2-((1S,2R)-2-heptylcyclopropyl)acetate**

![13C NMR spectrum]
$^1$H spectra (CDCl$_3$, 400 MHz) of compound ethyl 3-((1R,2R)-2-heptylcyclopropyl)propanoate (11)

$^{13}$C spectra (CDCl$_3$, 100 MHz) of compound ethyl 3-((1R,2R)-2-heptylcyclopropyl)propanoate
$^1$H spectra (CDCl$_3$, 400 MHz) of compound 3-((1R,2R)-2-heptylcyclopropyl)-N-phenethylpropanamide (13)
$^{13}$C spectra (CDCl$_3$, 100 MHz) of compound 3-((1$R$,2$R$)-2-heptylcyclopropyl)-N-phenethylpropanamide (13)
$^1$H NMR (CDCl$_3$, 400MHz) of (1S,2S)-1-Phenylpropane-1,2,3-triol (17)

\[
\begin{array}{c}
\text{Chloroform-d} \\
2.7 \text{ ppm} \\
4.02 \text{ ppm} \\
5.00 \text{ ppm} \\
7.24 \text{ ppm} \\
\end{array}
\]

$^13$C NMR (CDCl$_3$, 100MHz) of (1S,2S)-1-Phenylpropane-1,2,3-triol

\[
\begin{array}{c}
\text{Chloroform-d} \\
40.53 \text{ ppm} \\
75.84 \text{ ppm} \\
77.58 \text{ ppm} \\
128.41 \text{ ppm} \\
\end{array}
\]
$^1$H NMR (CDCl$_3$, 200MHz) of (2S,3S)-2,3-Dihydroxy-3-phenylpropyl-4-methylbenzenesulfonate (18)

$^{13}$C NMR (CDCl$_3$, 50MHz) of (2S,3S)-2,3-Dihydroxy-3-phenylpropyl 4-methylbenzenesulfonate
$^1$H NMR (CDCl$_3$, 200MHz) of (S)-(S)-Oxiran-2-yl)(phenyl)methanol (19)

$^{13}$C NMR (CDCl$_3$, 50MHz) of (S)-(S)-Oxiran-2-yl)(phenyl)methanol
$^1$H NMR (CDCl$_3$, 400MHz) of (S)-2-((S)-(4-Methoxybenzyloxy)(phenyl)methyl)oxirane (1c)

![Hydrogen NMR Spectrum](image)

13C NMR (CDCl$_3$, 100MHz) of (S)-2-((S)-(4-Methoxybenzyloxy)(phenyl)methyl)oxirane

![Carbon NMR Spectrum](image)
$^1$H NMR (CDCl$_3$, 400MHz) of (1R,2R)-Ethyl 2-((R)-(4-methoxybenzyloxy)(phenyl)methyl)cyclopropanecarboxylate (3c)
$^{13}$C NMR (CDCl$_3$, 100MHz) of (1$R$,2$R$)-Ethyl 2-((R)-(4-methoxybenzyloxy) (phenyl) methyl)cyclopropanecarboxylate (3c)

DEPT (CDCl$_3$, 100 MHz) spectrum (3c)
\[^{1}\text{H NMR (CDCl}_3, 200\text{ MHz)}\] spectrum of (1R,2R)-Ethyl 2-((R)-hydroxy(phenyl)methyl)cyclopropanecarboxylate (20)

\[^{13}\text{C NMR (CDCl}_3, 50\text{ MHz)}\] spectrum of (1R,2R)-Ethyl 2-((R)-hydroxy(phenyl)methyl)cyclopropanecarboxylate
$^1$H NMR (CDCl$_3$, 200 MHz) spectrum of (1$R,2R$)-Ethyl 2-((S)-azido(phenyl)methyl) cyclopropanecarboxylate (15)

$^{13}$C NMR (CDCl$_3$, 50 MHz) spectrum of (1$R,2R$)-Ethyl 2-((S)-azido(phenyl)methyl) cyclopropanecarboxylate
$^1$H NMR (CDCl$_3$, 400 MHz) spectrum of (1$R,2R$)-2-((S)-Azido(phenyl)methyl)cyclopropanecarboxylic acid (21)

$^{13}$C NMR (CDCl$_3$, 100 MHz) spectrum of (1$R,2R$)-2-((S)-Azido(phenyl)methyl)cyclopropanecarboxylic acid
$^1$H NMR (D$_2$O, 500 MHz) spectrum of (1R,2R)-2-((S)-amino(carboxy)methyl)cyclopropanecarboxylic acid (14)
$^{13}$C NMR (D$_2$O, 125 MHz) spectrum of (1R,2R)-2-((S)-amino(carboxy)methyl)cyclopropanecarboxylic acid (14)

DEPT (D$_2$O, 500 MHz) spectrum (14)