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# A concise enantioselective synthesis of (+)-decarestrictine L via proline-catalyzed sequential α-aminooxylation and Horner–Wadsworth–Emmons olefination

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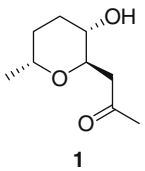
ABSTRACT

A short enantioselective synthesis of (+)-decarestrictine L, a cholesterol biosynthesis inhibitor metabolite, is described using a D-proline catalyzed sequential α-aminooxylation and a Horner–Wadsworth–Emmons olefination.



## 1. Introduction

The decarestrictines are secondary metabolites that were isolated from various *Penicillium* strains.[1] Several members of the decarestrictine family of natural products have been shown to inhibit the biosynthesis of cholesterol in both a HEP-G2 liver cells assay and in vivo.[2] While the majority of the decarestrictines contain a 10-membered lactone ring in their structure,[1–3] decarestrictine L **1** is unique in possessing a tetrahydropyranyl nucleus (Fig. 1).[2] Decarestrictine L **1** was isolated as a minor component from a culture broth of *Penicillium simplicissium* in 1992[1] and its absolute configuration (+)-(2*R*,3*S*,6*R*) was subsequently confirmed by total synthesis by Kibayashi et al.[4] Several other syntheses[5] of decarestrictine L **1** have been reported but many suffer from one or more disadvantages, which include the use of chiral building blocks, long reaction sequences, and low yields.[6] In recent years, proline and its derivatives have proven to be versatile organocatalysts.[7] Herein, we report an efficient synthesis of (+)-decarestrictine L **1** from the readily available raw materials via a D-proline-catalyzed sequential aminooxylation–olefination[8] reaction followed by intramolecular conjugate 1,4-addition as the key reactions (Scheme 4).




**1**

**Figure 1.**

## 2. Results and discussion

The retrosynthetic approach to (+)-decarestrictine L **1** is outlined in Scheme 1. Decarestrictine L **1** was envisioned to be obtained via intramolecular cyclization involving 1,4-conjugate addition of enone **2**. We envisaged a D-proline-catalyzed sequential aminooxylation–olefination of aldehyde **3** for the efficient construction of enone moiety **2**. Aldehyde **3**, a suitable intermediate, could be obtained by two routes: (i) Jacobsen's hydrolytic kinetic resolution (HKR)[9] of terminal epoxide (±)-**4** and (ii) Noyori's asymmetric reduction[10] of β-ketoester **7**.

Route 1 presents the synthesis of intermediate aldehyde **3** which commences with 5-hexene-1-ol **5**, protected as its benzyl ether **8**. The olefinic function in **8** was epoxidized smoothly {MCPBA, $CHCl_3$} to give racemic epoxide (±)-**4**, which was subjected to Jacobsen's HKR[9] {(*S*,*S*)-cobalt salen, $H_2O$} to give the corresponding enantiomerically pure epoxide (−)-**4** in 43% yield and 99% ee, {$[\alpha]_D^{25} = -5.1$ (*c* 2.0, $CHCl_3$)} along with the separable diol **9** in 47% yield. The chiral epoxide (−)-**4**, readily purified by column chromatography, was subjected to regioselective reductive ring opening with $LiAlH_4$ in THF at 0 °C to afford the secondary alcohol **10** as the exclusive product in 92% yield and 99% ee. The alcohol **10** was protected as its TBS ether (TBSCl, imid.) and the benzyl ether **11** were subsequently deprotected under hydrogenolysis conditions {10% Pd/C, $H_2$ (1 atm), $Et_3N$} to give the primary alcohol **12** in 97% yield. The oxidation of alcohol **12** (IBX, DMSO) produced the key intermediate aldehyde **3** in 98% yield {$[\alpha]_D^{25} = -12.0$ (*c* 3.0, $CHCl_3$)} (Scheme 2). Since the overall yield that could be realized for intermediate aldehyde **3** in HKR route was considerably lower (30%), we envisioned an alternate route for its synthesis.

Noyori's discovery of rhodium(I) and ruthenium(II) complexes of BINAP enantiomers has revolutionized stereoselective organic synthesis.[10a] In particular, stereo- and chemoselective reduction of β-ketoesters to the corresponding β-hydroxyesters can be

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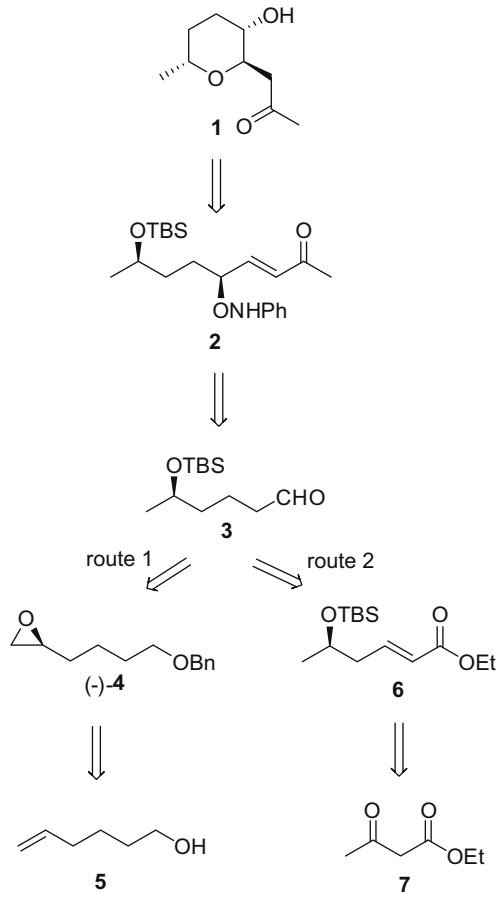
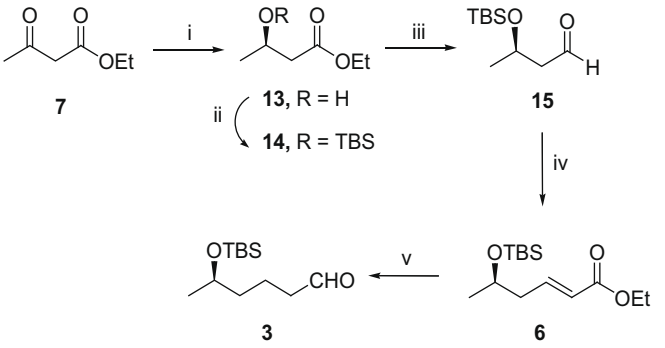



**Scheme 1.** Retrosynthetic route to decarestrictine L.

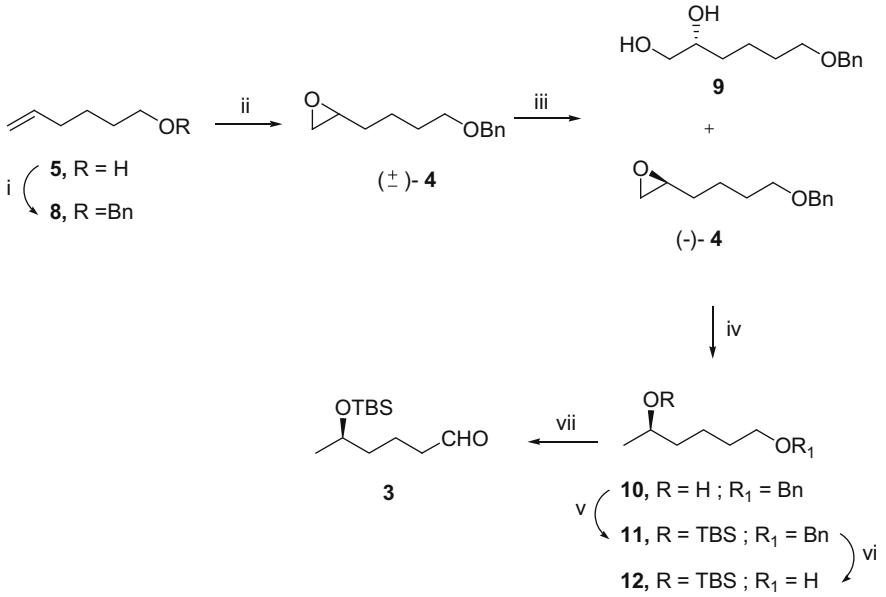
achieved in high yields and excellent enantioselectivity.[10b] Our second approach toward the synthesis of intermediate aldehyde **3** involves Ru-catalyzed asymmetric reduction[10c] {[(*R*)-Ru(BINAP)$Cl_2$]$_2$·$NEt_3$, 2 N HCl, $H_2$ (100 psi)} of ethyl acetoacetate **7** that



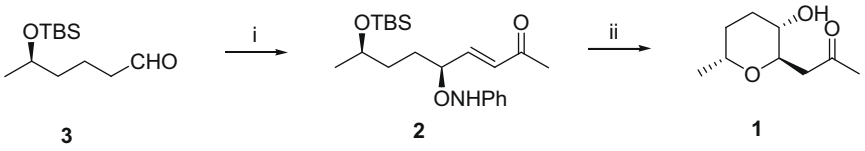

**Scheme 3.** Reagents and conditions: (i) [(R)-Ru(BINAP)$Cl_2$]$_2$·$NEt_3$ (0.1 mol %), 2 M HCl (0.1 mol %), MeOH, $H_2$ (100 psi), 50 °C, 16 h, 95%, 98% ee; (ii) TBSCl, imid., $CH_2Cl_2$, 0–25 °C, 2 h, 97%; (iii) DIBAL-H, toluene, −78 °C, 1 h, 85%; (iv) $Ph_3P{=}CHCO_2Et$, THF, 25 °C, 12 h, 93%; (v) (a) $H_2$ (1 atm), 10% Pd/C,$Et_3N$, MeOH, 12 h; (b) DIBAL-H, toluene, −78 °C, 1 h, 82% (for two steps).

produced (*R*)-ethyl 3-hydroxybutyrate[11] **13** in 95% yield with high enantiopurity (98% ee, Mosher ester). After protecting as its TBS ether, the resulting ester **14** was subjected to selective reduction with DIBAL-H at −78 °C that afforded the corresponding aldehyde **15** in 85% yield which was immediately reacted with the stabilized Wittig salt to give α,β-unsaturated ester **6** in 93% yield, {$[\alpha]_D^{25} = -15.8$ (*c* 2.4, $CHCl_3$)}. Exposure of the ester **6** to 10% Pd/C under $H_2$ (1 atm) followed by its selective reduction with DIBAL-H at −78 °C furnished aldehyde **3** in 60% overall yield (Scheme 3).

With the intermediate aldehyde **3** readily available, we carried out the sequential aminoxylation–olefination on aldehyde **3** catalyzed by D-proline at −20 °C, that resulted in the formation of the precursor aminooxy olefinic ketone **2** in 60% yield. The final step was the TBAF-mediated deprotection of TBS ether in **2**, which should result in simultaneous cyclization to produce tetrahydropyranyl skeleton **1**. Unfortunately, the desired 1,4-conjugate addition did not proceed to give the desired product even after the use of several Lewis acids (e.g., $BF_3{\cdot}OEt_2$, $Cu(OTf)_2$, CuI or $AuCl_3$). In turn, the reaction produced complex mixtures, which were difficult to separate. However, the removal of anilinoxy group in **2**, {$Cu(OAc)_2$, EtOH},[8f] followed by desilylation (TBAF, THF) of the




**Scheme 2.** Reagents and conditions: (i) BnBr, NaH, THF, 0–25 °C, 6 h, 97%; (ii) MCPBA, $CHCl_3$, 25 °C, 6 h, 85%; (iii) (*S,S*)-(−)-*N,N*-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediaminocobalt (0.5 mol %), $H_2O$ (0.55 equiv), 24 h, 43%, 99% ee; (iv) $LiAlH_4$, THF, 0 °C, 30 min, 92%, 99% ee; (v) TBSCl, Imid., $CH_2Cl_2$, 0–25 °C, 2 h, 98%; (vi) $H_2$ (1 atm), 10% Pd/C, $Et_3N$, MeOH, 12 h, 25 °C, 97%; (vii) IBX, DMSO, 25 °C. 2 h, 98%.




**Scheme 4.** Reagents and conditions: (i) PhNO (0.9 equiv), D-proline (20 mol %), −20 °C, 24 h then diethyl (2-oxopropyl)phosphonate (1.5 equiv), cesium carbonate (1.5 equiv), −20 to 0 °C, 2 h, 60%; (ii) (a) $Cu(OAc)_2$, EtOH, 25 °C, overnight; (b) TBAF, THF, 25 °C, 6 h, 60% (over two steps).

crude product induced an instantaneous intramolecular 1,4-conjugate addition[4,5a] to afford (+)-decarestrictine L **1** in 60% yield over two steps. The synthetic (+)-decarestrictine L **1** was identical in all respects to the natural product.

## 3. Conclusion

In conclusion, we have demonstrated the use of D-proline catalyzed sequential α-aminooxylation–olefination strategy for the concise synthesis of (+)-decarestrictine L **1** with an overall yield of 22% (route 2). Simple procedures, easy to use reagents, cheap, and readily available starting materials are some of the salient features of this approach.

## 4. Experimental section

### 4.1. General information

Solvents were purified and dried by standard procedures before use. Optical rotations were measured using sodium D line on a JASCO-181 digital polarimeter. $^1$H NMR and $^{13}$C NMR spectra were recorded on Brucker AC-200 spectrometer unless mentioned otherwise. Elemental analysis was carried out on a Carlo Erba CHNS-O analyzer. IR spectra were recorded on a Perkin–Elmer model 683 B and absorption is expressed in $cm^{-1}$. Purification was done using column chromatography (60–120 mesh).

### 4.2. 1-Benzyloxy-hex-5-ene, 8

To a stirred suspension of activated NaH (2.88 g, 119.81 mmol) in dry THF (100 mL) a solution of 5-hexen-1-ol **5** (10.0 g, 99.84 mmol) in dry THF (100 mL) was added dropwise at 0 °C followed by the addition of benzyl bromide (20.49 g, 119.81 mmol). The reaction mixture was then stirred at 25 °C for 6 h. After the completion of reaction (monitored by TLC), it was quenched with saturated solution of ammonium chloride and the product was extracted with diethyl ether. The combined organic layer was then washed with water, brine, and dried over anhydrous $Na_2SO_4$. Removal of solvent under reduced pressure and column chromatographic purification with petroleum ether/ethyl acetate (49:1 v/v) gave the benzyl ether **8** as a colorless liquid. Yield: 18.43 g, 97% yield; IR ($CHCl_3$, $cm^{-1}$) 3065, 3030, 2976, 2857, 1640, 1496, 1454; $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 7.29–7.32 (m, 5H), 5.78–5.86 (m, 1H), 4.97–5.10 (m, 2H), 4.54 (s, 2H), 3.51 (t, $J$ = 6.2 Hz, 2H), 2.00 (q, $J$ = 7.1 Hz, 2H), 1.38–1.70 (m, 4H); $^{13}$C NMR (50 MHz, $CDCl_3$): $\delta$ 138.8, 138.6, 128.4, 127.6, 127.5, 114.7, 72.9, 70.3, 33.7, 29.4, and 25.6. Anal. Calcd for $C_{13}H_{18}O$: C, 82.06; H, 9.53. Found: C, 82.08; H, 9.55.

### 4.3. 2-[4-(Benzyloxy)butyl]oxirane (±)-4

To a stirred solution of olefin **8** (18.0 g, 94.60 mmol) in dry $CHCl_3$ (350 mL) was added *m*-chloroperbenzoic acid (48.97 g, 283.80 mmol) and the mixture was stirred at 25 °C for 6 h. After completion of reaction (monitored by TLC), the solvent was removed under reduced pressure and the residue was extracted with ethylacetate. The organic layer was washed with saturated $NaHCO_3$ solution, brine, and dried over anhydrous $Na_2SO_4$. The solvent was removed under reduced pressure to afford the crude product which was subjected to column chromatographic purification with petroleum ether/ethyl acetate (19:1 v/v) to give the racemic epoxide (±)-**4** as a colorless liquid. Yield: 16.59 g, 85% yield; IR ($CHCl_3$, $cm^{-1}$) 3032, 2859, 1637, 1496, 1454, 1410, 1362; $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 7.26–7.33 (m, 5H), 4.48 (s, 2H), 3.46 (t, $J$ = 6.0 Hz, 2H), 2.86–2.88 (m, 1H), 2.69 (dd, $J$ = 4.0, 5.1 Hz, 1H), 2.43 (dd, $J$ = 2.8, 5.2 Hz, 1H), 1.51–1.66 (m, 6H); $^{13}$C NMR (50 MHz, $CDCl_3$): $\delta$ 138.6, 128.3, 127.6, 127.5, 72.9, 70.1, 52.1, 46.9, 32.3, 29.6, 22.8. Anal. Calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80. Found: C, 75.67; H, 8.80.

### 4.4. (*S*)-2-[4-(Benzyloxy)butyl]oxirane, (−)-4

To a suspension of (*S*,*S*)-(−)-*N*,*N*-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexane-diaminocobalt (190 mg, 0.5 mol%) in toluene (2 mL) was added acetic acid (0.026 mL, 0.1 mol %) and the mixture was stirred while open to air for 1 h at 25 °C. The solvent was then removed under reduced pressure and the brown residue was dried under vacuum. The racemic epoxide (±)-**4** (13.0 g, 63.10 mmol) was added in one portion and the reaction mixture was then cooled in an ice bath. Water (0.55 equiv 0.64 mL) was added slowly, followed by stirring at 25 °C for 24 h. After completion of reaction (monitored by TLC), the reaction mixture was subjected to column chromatographic purification with petroleum ether/ethyl acetate (19:1 v/v) to afford the (*S*)-epoxide (−)-**4** in 43% yield (5.60 g); $[\alpha]_D^{25} = -5.1$ (*c* 2.0, $CHCl_3$); 99% ee (HPLC). HPLC analysis: Column: Lichrocart® (250 × 4.6 mm), Merck 5 μm, mobile phase: isopropylalcohol/*n*-hexane (2/98), wavelength: 254 nm, flow rate: 1.0 mL/min, retention time: 2.65 min (−)-isomer, 3.23 min (+)-isomer.

### 4.5. (*R*)-6-(Benzyloxy)hexan-2-ol, 10

To a suspension of $LiAlH_4$ (1.01 g, 26.66 mmol) in dry THF (30 mL), a solution of epoxide (−)-**4** (5.0 g, 24.24 mmol) in THF (50 mL) was added dropwise at 0 °C. The reaction mixture was stirred at this temperature for 30 min. After completion of reaction (monitored by TLC), it was quenched with aq 20% solution of sodium hydroxide (2 mL) at 0 °C. The reaction mixture was filtered through sintered funnel, dried over anhydrous $Na_2SO_4$ and concentrated. Purification by column chromatography with petroleum ether/ethyl acetate (9:1 v/v) gave the secondary alcohol **10** as a colorless liquid. Yield: 4.65 g (92%); $[\alpha]_D^{25} = -7.9$ (*c* 2.0, $CHCl_3$); 99% ee (HPLC); IR (neat, $cm^{-1}$): 3354, 2935, 1657, 1460, 1416, 1375, 1300; $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 7.29–7.33 (m, 5H), 4.48 (s, 2H), 3.70–3.79 (m, 1H), 3.46 (t, $J$ = 6.2 Hz, 2H), 2.0 (br s, 1H), 1.41–1.70 (m, 6H), 1.15 (d, $J$ = 6.2 Hz, 3H); $^{13}$C NMR (50 MHz, $CDCl_3$): $\delta$ 138.5, 128.3, 127.6, 127.5, 72.9, 70.3, 67.6, 39.0, 29.7, 23.5, 22.4. Anal. Calcd for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68. Found: C, 75.75; H, 9.66. HPLC analysis: Column: Lichrocart® (250 × 4.6 mm), Merck 5 μm, mobile phase: isopropylalcohol/*n*-hexane (1/99), wavelength: 254 nm, flow rate:

1.0 mL/min, retention time: 2.94 min (+)-isomer, 5.63 min (−)-isomer.

### 4.6. (*R*)-[6-(Benzyloxy)hexan-2-yloxy]-*tert*-butyldimethylsilane, 11

To a solution of alcohol **10** (4.50 g, 21.60 mmol) in dry $CH_2Cl_2$ (80 mL) at 0 °C were added imidazole (2.94 g, 43.20 mmol) and *tert*-butyldimethylsilyl chloride (4.88 g, 32.40 mmol). The reaction mixture was then stirred at 25 °C for 2 h. After completion of reaction (monitored by TLC), it was diluted with $CH_2Cl_2$, washed with water, brine, and dried over anhydrous $Na_2SO_4$. Removal of the solvent under reduced pressure gave the crude product which was then purified by column chromatography with pure petroleum ether to give **11** as a colorless liquid. Yield: 6.83 g (98%); $[\alpha]_D^{25} = -10.0$ (*c* 1.0, $CHCl_3$); IR (neat, $cm^{-1}$): 2929, 2856, 1471, 1462, 1455, 1373, 1361; $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ 7.31–7.33 (m, 5H), 4.48 (s, 2H), 3.72–3.81 (m, 1H), 3.45 (t, *J* = 6.4 Hz, 2H), 1.33–1.63 (m, 6H), 1.12 (d, *J* = 6.1 Hz, 3H), 0.88 (s, 9H), 0.04 (s, 6H); $^{13}C$ NMR (50 MHz, $CDCl_3$): $\delta$ 138.7, 128.2, 127.5, 127.3, 72.8, 70.3, 68.4, 39.5, 29.8, 25.9, 23.8, 22.4, 18.1, −4.4, −4.7. Anal. Calcd for $C_{19}H_{34}O_2Si$: C, 70.75; H, 10.62. Found: C, 70.78; H, 10.77.

### 4.7. (*R*)-5-(*tert*-Butyldimethylsilyloxy)hexan-1-ol, 12

A mixture of benzyl ether **11** (6 g, 18.60 mmol), 10% Pd/C, and catalytic amount of triethylamine (2 drops) was stirred under $H_2$ (1 atm) at 25 °C. After completion of reaction (monitored by TLC), it was filtered through Celite (MeOH eluent) and the solvent evaporated under reduced pressure to afford the title compound as a slightly yellow colored oil. Yield: 4.19 g (97%); $[\alpha]_D^{25} = -13.8$ (*c* 1.6, $CHCl_3$); IR (neat, $cm^{-1}$): 3438.4, 2930.4, 2857.9, 1225.6, 1099.5, 1050.13; $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ 3.70–3.78 (m, 1H), 3.59 (t, *J* = 6.3, 2H), 1.62 (br s, 1H), 1.32–1.55 (m, 6H), 1.09 (d, *J* = 6.1 Hz, 3H), 0.84 (s, 9H), 0.04 (s, 6H); $^{13}C$ NMR (50 MHz, $CDCl_3$): $\delta$ 68.5, 62.6, 39.4, 32.7, 25.9, 23.7, 21.7, 18.1, −4.41, −4.71. Anal. Calcd for $C_{12}H_{28}O_2Si$: C, 62.01; H, 12.14. Found: C, 62.07; H, 12.14.

### 4.8. (*R*)-5-(*tert*-Butyldimethylsilyloxy)hexanal, 3

To a well-stirred solution of alcohol **12** (4.00 g, 17.21 mmol) in DMSO (30 mL), 2-iodoxybenzoic acid (9.64 g, 34.42 mmol) was added in one portion. The reaction mixture was then stirred for 1 h at 25 °C. After the completion of reaction (monitored by TLC), it was diluted with water and diethyl ether. Subsequent filtration (diethyl ether eluent) and washing the filtrate with water, brine followed by drying over anhydrous $Na_2SO_4$ and removal of solvent under reduced pressure gave crude product which on chromatographic separation with petroleum ether/ethyl acetate (19:1 v/v) gave the intermediate aldehyde **3** as a light yellow colored liquid. Yield: 3.89 g (98%); $[\alpha]_D^{25} = -12.0$ (*c* 3.0, $CHCl_3$); IR (neat, $cm^{-1}$): 3020, 2930, 2857, 1722, 1572, 1472, 1215; $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ 9.71 (t, *J* = 1.8 Hz, 1H), 3.71–3.83 (m, 1H), 2.33–2.39 (dt, *J* = 7.1, 8.8 Hz, 2H), 1.54–1.70 (m, 2H), 1.35–1.43(m, 2H), 1.09 (d, *J* = 6.0 Hz, 3H), 0.84 (s, 9H), 0.05 (s, 6H); $^{13}C$ NMR (50 MHz, $CDCl_3$): $\delta$ 202.0, 67.6, 43.4, 38.46, 25.40, 23.26, 17.85, 17.59, −4.84, −5.23. Anal. Calcd for $C_{12}H_{26}O_2Si$: C, 62.55; H, 11.37. Found: C, 62.65; H, 11.77.

### 4.9. (*R*)-Ethyl (−)-3-hydroxybutyrate, 13

Ethyl acetoacetate **7** (7.50 g, 57.69 mmol) and dry methanol (25 mL) were mixed and deoxygenated with flowing nitrogen for 5 min. The catalyst $[(R)\text{-Ru(BINAP)Cl}_2]_2{\cdot}NEt_3$ (50 mg, 0.1 mol %) was added along with 2 N HCl (0.05 mL, 0.1 mol %). The mixture was transferred to a standard Parr reactor apparatus and flushed by evacuating and refilling with hydrogen several times. The apparatus was heated at 50 °C with stirring under 100 psi of hydrogen for 16 h. After completion of reaction (monitored by TLC) the reaction was cooled and concentrated under reduced pressure. The residue was subjected to column chromatographic purification with petroleum ether/ethyl acetate (9:1 v/v) to get pure (*R*)-alcohol **13** as a colorless liquid. Yield: 7.23 g, (95%); $[\alpha]_D^{25} = -46.0$ (*c* 1.0, $CHCl_3$); lit.[11] $[\alpha]_D^{25} = -46.0$ (*c* 1.0, $CHCl_3$); 98% ee (Mosher ester); IR ($CHCl_3$, $cm^{-1}$) 3441.7, 2978.6, 2935.7, 1734.0, 1636.1, 1458.1; $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ 4.12–4.22 (m, 3H), 3.20 (d, *J* = 3.8 Hz, 1H), 2.42–2.45 (m, 2H), 1.21–1.31 (m, 6H); $^{13}C$ NMR (50 MHz, $CDCl_3$): $\delta$ 172.5, 64.2, 60.5, 43.2, 22.6, 14.1. Anal. Calcd for $C_6H_{12}O_3$: C, 54.53; H, 9.15. Found: C, 54.56; H, 9.35.

### 4.10. (*R*)-(−)-Ethyl (*tert*-butyldimethyl silyloxy)butyrate, 14

To a solution of ethyl (*R*)-(−)-3-hydroxybutyrate **13** (7.0 g, 52.97 mmol) in dry $CH_2Cl_2$ (300 mL) at 0 °C were added imidazole (7.21 g, 105.94 mmol) and *tert*-butyldimethylsilyl chloride (11.98 g, 79.46 mmol). The reaction mixture was then stirred at 25 °C for 2 h. After completion of reaction (monitored by TLC), it was diluted with $CH_2Cl_2$, washed with water, brine, and dried over anhydrous $Na_2SO_4$. Concentration and purification by column chromatography with petroleum ether/ethyl acetate (49:1 v/v) gave aldehyde **14** as a colorless liquid. Yield: 12.66 g, (97%); $[\alpha]_D^{25} = -26.0$ (*c* 1.0, $CH_2Cl_2$); lit.[12] $[\alpha]_D^{25} = -25.5$ (*c* 1.0, $CH_2Cl_2$); IR ($CHCl_3$ $cm^{-1}$) 2958, 2931, 2897, 2857, 1739, 1473, 1447; $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ 4.19–4.28 (m, 1H), 4.13 (q, *J* = 7.2 Hz, 2H), 2.44 (dd, *J* = 7.4, 14.5 Hz, 1H), 2.32 (dd, *J* = 5.4, 14.5 Hz, 1H), 1.22 (t, *J* = 7.2 Hz, 3H), 1.17 (d, *J* = 6.1 Hz, 3H), 0.82 (s, 9H), $\delta$ 0.05 (s, 3H), $\delta$ 0.04 (s, 3H); $^{13}C$ NMR (50 MHz, $CDCl_3$): $\delta$ 171.2, 65.8, 59.9, 44.8, 25.7, 23.9, 17.9, 14.2, −4.5, −5.0. Anal. Calcd for $C_{12}H_{26}O_3Si$: C, 58.49; H, 10.63. Found: C, 58.54; H, 10.56.

### 4.11. (*R*)-(−)-Ethyl (*tert*-butyldimethylsilyloxy)butanal, 15

To a stirred solution of ester **14** (11.50 g, 46.69 mmol) in dry toluene (250 mL), a solution of diisobutylaluminium hydride (46.8 mL, 1 M in cyclohexane) was added dropwise at −78 °C and stirred at this temperature for 1 h. After completion of reaction (monitored by TLC), it was diluted with a saturated solution of Rochelle salt and stirred for further 3 h. The organic phase was separated and the aqueous phase was extracted twice with $CH_2Cl_2$. The combined organic phase was then washed with water, brine, and dried over anhydrous $Na_2SO_4$. Removal of solvent under reduced pressure and column chromatographic purification with petroleum ether/ethyl acetate (19:1 v/v) gave aldehyde **15** as a colorless liquid. Yield: 8.03 g, 85%; $[\alpha]_D^{25} = -13.6$ (*c* 1.6, $CH_2Cl_2$); lit.[12] $[\alpha]_D^{25} = -11.3$ (*c* 1.0, $CH_2Cl_2$); IR ($CHCl_3$, $cm^{-1}$) 2957, 2930, 2896, 2858, 1729, 1473, 1463, 1377, 1362; $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ 9.76 (dd, *J* = 2.1, 2.7 1H), 4.25–4.40 (m, 1H), 2.40–2.59 (m, 2H), 1.19 (d, *J* = 6.2 Hz, 3H), 0.84 (s, 9H), 0.08 (s, 3H), 0.06 (s, 3H); $^{13}C$ NMR (50 MHz, $CDCl_3$): $\delta$ 202.0, 64.5, 52.9, 25.7, 24.1, 17.9, −4.4, −5.0. Anal. Calcd for $C_{10}H_{22}O_2Si$: C, 59.35; H, 10.96. Found: C, 59.38; H, 10.97.

### 4.12. (*R*)-(−)-Ethyl 5-*tert*-butyldimethylsiloxyhex-2-enoate, 6

To a solution of aldehyde **15** (7.00 g, 34.59 mmol) in dry THF (200 mL) at 25 °C was added $Ph_3P{=}CHCOOEt$ (18.08 g, 51.89 mmol) and the reaction mixture was stirred for 12 h. After completion of reaction (monitored by TLC), the solvent was distilled off under reduced pressure and the crude mass on column chromatographic purification with petroleum ether/ethyl acetate (19:1 v/v) gave the α,β-unsaturated ester **6** as a slightly yellow colored liquid. Yield: 8.76 g, (93%); $[\alpha]_D^{25} = -15.8$ (*c* 2.4, $CHCl_3$, $cm^{-1}$);

IR ($CHCl_3$) 2930, 2857, 1724, 1655, 1463, 1376; $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 6.83–6.94 (m, 1H), 5.82 (d, $J$ = 15.5 Hz, 1H), 4.2 (q, $J$ = 7.1 Hz, 2H), 2.31 (m, 2H), 1.29 (t, $J$ = 7.2 Hz, 3H), 1.18 (d, $J$ = 6.1 Hz, 3H), 0.88 (s, 9H), 0.04 (s, 6H); $^{13}$C NMR (50 MHz, $CDCl_3$): $\delta$ 170.7, 146.7, 128.2, 67.9, 59.9, 42.4, 25.7, 23.7, 18.0, 14.2, −4.58, −4.88. Anal. Calcd for $C_{14}H_{28}O_3Si$: C, 61.72; H, 10.36. Found: C, 61.90; H, 11.86.

### 4.13. (*R*)-(−)-Ethyl (*tert*-butyldimethylsilyloxy)hexanal, 3

A mixture of α,β-unsaturated ester **6** (8 g, 29.36 mmol), 10% Pd/C, and catalytic amount of triethylamine (2 drops) in MeOH (40 mL) was stirred under $H_2$ (1 atm) at 25 °C for 12 h. After completion of reaction (monitored by TLC), it was filtered over Celite plug (MeOH eluent) and the solvent evaporated under reduced pressure to give the corresponding saturated ester. To a stirred solution of the saturated ester in dry toluene (150 mL), a solution of diisobutylaluminium hydride (29.4 mL, 1 M in cyclohexane) was added dropwise at −78 °C and was stirred at this temperature for 1 h. After completion of reaction (monitored by TLC) the reaction mixture was diluted with a saturated solution of Rochelle salt and was stirred for further 3 h. The organic phase was separated and the aqueous phase extracted twice with $CH_2Cl_2$. The combined organic phase was then washed with water, brine, and dried over anhydrous $Na_2SO_4$. Removal of solvent under reduced pressure and column chromatographic purification with petroleum ether/ethyl acetate (19:1 v/v) gave aldehyde **3** as a colorless liquid. Yield: 5.55 g, (82%) (over two steps); $[\alpha]_D^{25} = -12.0$ ($c$ 3.0, $CHCl_3$); IR ($CHCl_3$, $cm^{-1}$) 3019, 2930, 2956, 2857, 1722, 1572, 1472, 1439; $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 9.76 (t, $J$ = 1.8 Hz, 1H), 3.68–3.83 (m, 1H), 2.34–2.41 (dt, $J$ = 7.1, 8.8 Hz, 2H), 1.58–1.70 (m, 2H), 1.35–1.43 (m, 2H), 1.10 (d, $J$ = 6.1 Hz, 3H), 0.84 (s, 9H), 0.04 (s, 6H); $^{13}$C NMR (50 MHz, $CDCl_3$): $\delta$ 202.0, 67.6, 43.4, 38.5, 25.4, 23.3, 17.8, 17.6, −4.84. −5.23. Anal. Calcd for $C_{12}H_{26}O_2Si$: C, 62.55; H, 11.37. Found: C, 62.65; H, 11.38.

### 4.14. Aminoxy olefinic ketone, 2

To a stirred solution of nitrosobenzene (0.88 g, 8.20 mmol) and D-proline (210 mg, 20 mol%) in $CH_3CN$ (40 mL) was added precursor aldehyde **3** (2.11 g, 9.11 mmol) at −20 °C. The reaction mixture was stirred at the same temperature for 24 h followed by the addition of diethyl(2-oxopropyl)phosphonate (2.65 g, 13.67 mmol) and $Cs_2CO_3$ (4.45 g, 13.67 mmol). After stirring for 2 h at 0 °C, reaction was quenched with saturated $NH_4Cl$ and extracted with ethylacetate (3 × 60 mL). The combined organic phase was dried over anhydrous $Na_2SO_4$ and concentrated under reduced pressure. Purification by column chromatography with petroleum ether/ethyl acetate (9:1 v/v) afforded aminooxy olefinic ketone **2** as a yellow oily liquid. Yield: 2.06 g (60%); $[\alpha]_D^{25} = -12.5$ ($c$ 4.0, $CHCl_3$); IR (neat, $cm^{-1}$): 3155, 2956, 2930, 2857, 1677, 1472, 1377; $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 7.24–7.16 (m, 2H), 6.93–6.82 (m, 3H), 6.74–6.63 (dd, $J$ = 6.6, 16.2 Hz, 1H), 6.23 (d, $J$ = 16.2 Hz, 1H), 4.38–4.28 (m, 1H), 3.86–3.73 (m, 1H), 2.23 (s, 3H), 1.96–1.44 (m, 4H), 1.09 (d, $J$ = 6.1 Hz, 3H), 0.84 (s, 9H), 0.04 (s, 6H); $^{13}$C NMR (50 MHz, $CDCl_3$)): $\delta$ 197.9, 148.4, 145.9, 131.7, 128.9, 122.1, 114.3, 83.2, 68.1, 34.8, 29.3, 27.3, 25.9, 23.8, 18.1, −4.27, −4.7. Anal. Calcd for $C_{21}H_{35}NO_3Si$: C, 66.80; H, 9.34; N, 3.71. Found: C, 66.85; H, 9.38; N, 3.91.

### 4.15. Decarestrictine L, 1

To a well-stirred solution of aminooxy olefinic ketone **2** (500 mg, 1.23 mmol) in ethanol was added copper acetate (750 mg, 30 mol %). The reaction mixture was then stirred overnight at 25 °C. After completion of reaction (monitored by TLC), the solvent was removed under reduced pressure and the residue was dissolved in dry THF. To this, a solution of 1 M tetrabutylammonium fluoride (2.55 mL, 2 equiv) was added at 25 °C. The reaction mixture was stirred at this temperature for 6 h after which the solvent was removed under reduced pressure and the residue was subjected to column chromatography with petroleum ether/ethyl acetate (17:3 v/v) to afford decarestrictine L **1** as an oily liquid.

Yield: 127 mg (60%); $[\alpha]_D^{25} = +28.6$ ($c$ 0.5, $CHCl_3$) lit.[4] $[\alpha]_D^{25} = +28.8$ ($c$ 0.49, $CHCl_3$); IR (neat, $cm^{-1}$): 3415, 2965, 2853, 1712, 1598, 1440; $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ 4.03 (q, $J$ = 6.5 Hz, 1H), 3.97–3.94 (m, 1H), 3.43–3.39 (m, 1H), 2.73 (d, $J$ = 6.5 Hz, 2H), 2.21 (s, 2H), 2.04 (br s, 1H), 1.90–1.57 (m, 4H), 1.22 (d, $J$ = 6.5 Hz, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ 207.7, 72.0, 69.4, 67.4, 46.3, 30.5, 28.2, 27.0, 18.4. Anal. Calcd for $C_9H_{16}O_3$: C, 62.77; H, 9.36. Found: C, 62.68; H, 9.38.

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