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Synthesis of (+)-decarestrictine L

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Abstract—A synthesis of (+)-decarestrictine L **1**, a cholesterol biosynthesis inhibitory metabolite isolated from *Penicillium simplicissimum*, is described. Beginning from tri-*O*-acetyl-D-glucal, alkylation with trimethylaluminum introduced the axial methyl group at C-2 in a stereoselective fashion. Chain extension at the C-6 carbon was accomplished by generation of the primary tosylate, followed by displacement with cyanide anion. The synthesis of (+)-**1** was completed in 13 steps and 6.3% overall yield.
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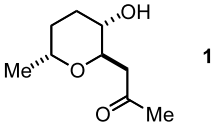
1. Introduction

The decarestrictines consist of a family of thirteen new metabolites isolated from *Penicillium simplicissimum* and *Penicillium corylophilum*.[1] The majority of the decarestrictines contain a 10-membered lactone ring in their structure. In contrast, decarestrictine L **1** possesses a tetrahydropyranyl ring. These metabolites exhibit an inhibitory effect on cholesterol biosynthesis. This beneficial effect was corroborated by in vivo studies with normolipidemic rats where it was found that cholesterol biosynthesis in HEP-G2 liver cells was significantly inhibited. Additionally, it appears that the decarestrictines are highly selective in that they exhibit no significant antibacterial, antifungal, anti-protozoal, or antiviral activity.

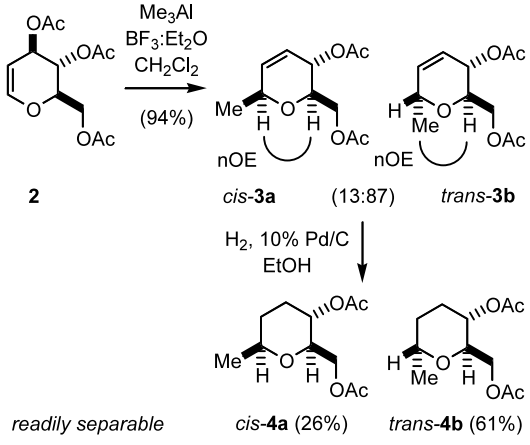


1

The structure of **1** was initially assigned on the basis of its mass spectral data and extensive 2D NMR analysis.[1a] The absolute configuration of **1** was established as (2*R*,3*S*,6*R*) as a result of the first total synthesis by Machinaga and Kibayashi [18 steps, 5%].[2] The cholesterol inhibitory activity of **1** along with its low abundance continues to make it an appealing synthetic target. Within the last decade, total syntheses by Clark [9 steps, 6% (racemic)],[3] Nokami [9 steps, 5%],[4] Solladie [19 steps, 13%],[5] and Hatakeyama [17 steps, 14%][6] have been reported. We report herein a synthesis of (+)-**1** using tri-*O*-acetyl-D-glucal as starting material.

2. Results and discussion

Under Lewis acidic conditions, the reaction of glycals with a variety of weak *C*-nucleophiles generates the corresponding *C*-glycosides.[7] Suitable nucleophiles include allyltrimethylsilane,[8] trimethylsilylcyanide,[9] and trialkylaluminum reagents.[10] Substituent factors contributing to the stereoselectivity of this reaction have been explored by Woerpel.[11] Reaction of tri-*O*-acetyl-D-glucal **2** with trimethylaluminum in the presence of boron trifluoride etherate gave a mixture of the known[12] *cis*-**3a** and *trans*-**3b** (94%, 17:83 ratio, Scheme 1). Complete separation of the two products was not



Scheme 1.

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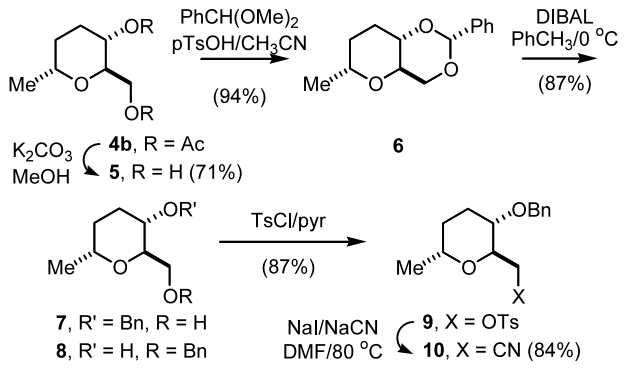
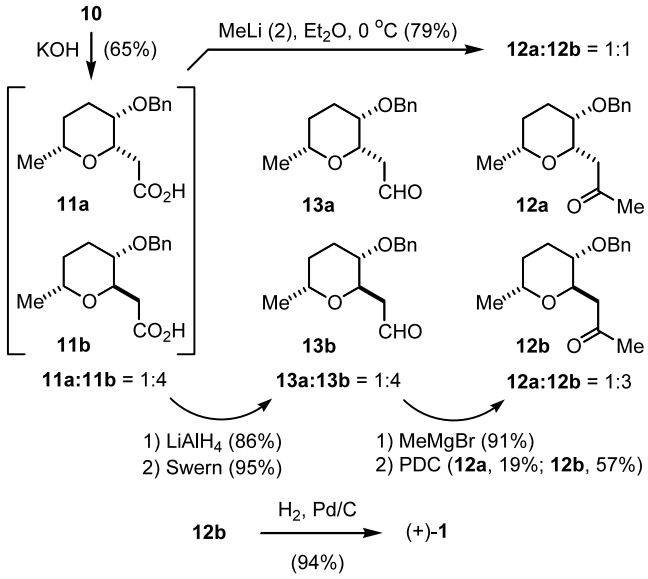
possible by column chromatography, however the leading and trailing fractions contained pure **3a** and **3b**, respectively. The structural assignments are based on NMR spectral data. In particular, the NOESY NMR spectra of *cis*-**3a** evidences a cross peak due to a nonbonding ^1H–^1H interaction between the C-2 methine proton (δ 4.31 ppm) and the C-6 methine proton (δ 3.74 ppm), while the NOESY NMR spectra of *trans*-**3b** shows an interaction between the methyl group (δ 1.28 ppm) and the C-6 methine proton (δ 3.98 ppm). Catalytic hydrogenation of the mixture of **3a**/**b** (13:87 ratio) gave a *readily separable* mixture of *cis*-**4a** and *trans*-**4b** (ca. 25:75 ratio, Scheme 1). The increase in the ratio of **4a**:**4b** compared to the starting ratio of **3a**:**3b** is attributed to olefin isomerization of **3** prior to reduction. The structural assignments of *cis*-**4a** and *trans*-**4b** are based on their NMR spectral data. In particular, the signal for the C-2 methine proton of *cis*-**4a** appears at δ 3.48 ppm, while the signal for the corresponding proton of *trans*-**4b** appears at δ 3.94 ppm. The chemical shift for an equatorial proton of a rigid six-membered ring is generally found downfield by 0.1–0.7 ppm compared to that of an axial proton.[13] Additionally, the ^{13}C NMR signal for the methyl group of *cis*-**4a** appears at δ 21.7 ppm, while the corresponding signal for *trans*-**4b** appears at δ 19.9 ppm. It has been observed that ^{13}C NMR signals for axial methyl groups in noninverting cyclohexane rings are shielded by 5–7 ppm as compared to equatorial methyl groups.[14]

Hydrolysis of *trans*-**4b** gave the diol **5**, which upon reaction with benzaldehyde dimethyl acetal gave the benzylidine acetal **6** (Scheme 2). Reductive cleavage of the benzylidene acetal was accomplished using DIBAL-H in toluene to afford a mixture of the primary alcohol **7** and the secondary alcohol **8** (7:1 ratio as determined by ^1H NMR spectroscopy). While chromatographic separation of **7** and **8** was not possible, the following step resulted in selective reaction at the primary hydroxyl group, thus allowing purification. Reaction of the mixture of **7**/**8** with tosyl chloride gave only the corresponding primary tosylate **9** as a crystalline solid, whilst tosylation of the secondary alcohol **8** is relatively slow. Nucleophilic substitution of the tosylate **9** with sodium cyanide (in the presence of NaI) then gave the nitrile **10**.



Scheme 2.



Scheme 3.

With nitrile **10** in hand, introduction of the methyl ketone functionality was explored. Unfortunately, reaction of **10** with methylmagnesium iodide, followed by hydrolysis did not produce the methyl ketone **12b**; instead the product was tentatively assigned as an unsaturated nitrile resulting from intramolecular elimination. Basic hydrolysis of **10** gave a mixture of two isomeric carboxylic acids *cis*-**11a** and *trans*-**11b** (1:4 ratio, Scheme 3). Reaction of the crude mixture of **11a**/**11b** with methyllithium in dry ether gave a mixture of isomeric methyl ketones *cis*-**12a** and the known[6] *trans*-**12b** (1:1 ratio). Presumably, epimerization of the C-6 center is due to elimination with subsequent readdition. The increase in the ratio of **12a**:**12b** (compared to the starting ratio of **11a**:**11b**) is attributed to epimerization at C-6 via elimination/readdition. Due to this epimerization, an alternative (albeit longer) route to **12b** was explored.[15] Hydrolysis of nitrile **10**, followed by $LiAlH_4$ reduction and Swern oxidation gave an inseparable mixture of aldehydes **13a** and **13b** (1:4 ratio). Addition of methylmagnesium bromide to **13a**/**b**, followed by oxidation then afforded a mixture of **12a**/**12b** (1:3 ratio), which were separable by preparative TLC.

Structural assignments for *cis*-**12a** and *trans*-**12b** are based on their ^1H NMR spectral data. The signal for the C-2 methine proton of *cis*-**12a** appears at δ 3.96 ppm while that for *trans*-**12b** appears at δ 3.51 ppm. Additionally, the ^{13}C NMR signal for the methyl group of *cis*-**12a** appears δ 22.5 ppm, while the corresponding signal for *trans*-**12b** appears at δ 18.9 ppm. The structural assignment of **12b** was further corroborated by reductive deprotection of the benzyl ether to give (+)-**1**. The ^1H and ^{13}C NMR spectral data for **1** obtained by the above route are consistent with the literature values.[1a,5]

In summary, (+)-decarestrictine L was prepared in 13 steps and 6.3% overall yield from commercially available tri-*O*-acetyl-D-glucal. This route is competitive with the other reported syntheses of **1**.

3. Experimental

3.1. General data

Spectrograde solvents were used without purification with the exception of dry ether and dry THF which were distilled from sodium benzophenone ketyl. Anhydrous methylene chloride, anhydrous *N*,*N*-dimethylformamide (DMF), anhydrous acetonitrile, and anhydrous dimethyl sulfoxide (DMSO) were purchased from Aldrich. Column chromatography was performed on silica gel 60 (60–200 mesh, Aldrich). Melting points were obtained on a Mel-Temp melting point apparatus and are uncorrected. All ^{1}H and ^{13}C NMR spectra were recorded at 300 and 75 MHz respectively. Elemental analyses were obtained from Midwest Microlabs, Indianapolis, IN and high resolution mass spectra were obtained from the Washington University Resource for Biomedical and Bioorganic Mass Spectrometry.

3.2. 2,6-Anhydro-1,3,4-trideoxy-D-ribo-hept-3-enitol diacetate, 3a and 2,6-anhydro-1,3,4-trideoxy-D-arabino-hept-3-enitol diacetate, 3b

Into a flame-dried flask under N_2 at −40°C was added a solution of tri-*O*-acetyl-D-glucal (1.02 g, 3.75 mmol) in anhydrous CH_2Cl_2 (25 mL), followed by a solution of trimethylaluminum (2.0 M solution in hexanes, 3.64 mL, 7.5 mmol), and finally boron trifluoride diethyl etherate (0.48 mL, 3.8 mmol). The reaction mixture was stirred at −40°C for 1.5 h and at 0°C for 3.5 h. The rose-colored reaction mixture was slowly quenched with saturated aqueous $NaHCO_3$ (50 mL), (CAUTION: vigorous effervescence) during which time the solution became lime green in color. The layers were separated and the organic layer was washed with water (2×25 mL) and brine (2×25 mL). The aqueous layers were extracted with methylene chloride (4×25 mL), and the combined organic layers were dried ($MgSO_4$) and concentrated. The residue was purified by chromatography (SiO_2, hexanes–ethyl acetate = 3:1) to give a nearly inseparable mixture of the known[12] *cis*-**3a** and *trans*-**3b** (1:5.3 by GC) as a colorless oil (0.80 g, 94%). However, the first eluting fraction from the column contained only the *cis* isomer, whilst the trailing fraction contained only the *trans* isomer.

***cis*-3a**: $[\alpha]_D^{23}$ +109 (*c* 0.216, $CHCl_3$); IR (neat, cm^{-1}) 2977, 2935, 2874, 1748, 1455, 1372, 1239, 1103, 1050, 975, 908, 788, 722; ^{1}H NMR ($CDCl_3$) δ 5.78 (td, J = 1.5, 10.3 Hz, 1H), 5.66 (td, J = 2.1, 10.3 Hz, 1H), 5.26 (tdd, J = 1.9, 2.7, 9.1 Hz, 1H), 4.36–4.27 (m, 1H), 4.24 (dd, J = 2.6, 12.0 Hz, 1H), 4.15 (dd, J = 5.9, 12.0 Hz, 1H), 3.74 (ddd, J = 2.7, 6.2, 8.8 Hz, 1H), 2.12 (s, 3H), 2.10 (s, 3H), 1.28 (d, J = 6.8 Hz, 3H); ^{13}C NMR (C_6D_6) δ 169.9, 169.4, 134.2, 124.8, 75.5, 71.8, 66.3, 64.5, 22.1, 21.5, 21.3.

***trans*-3b**: $[\alpha]_D^{23}$ +71.2 (*c* 0.332, $CHCl_3$); IR (neat, cm^{-1}) 2977, 2935, 1739, 1448, 1371, 1232, 1194, 1049, 971, 907, 729; ^{1}H NMR ($CDCl_3$) δ 5.86 (ddd, J = 1.5, 2.4, 10.3 Hz, 1H), 5.72 (ddd, J = 2.1, 2.9, 10.3 Hz, 1H), 5.08 (dddd, J = 1.5, 2.1, 2.9, 6.1 Hz, 1H), 4.31–4.45 (m, 1H), 4.21 (dd, J = 6.2, 11.7 Hz, 1H), 4.12 (dd, J = 3.5, 11.7 Hz, 1H), 3.98 (dt, J = 3.5, 6.2 Hz, 1H), 2.18 (s, 3H), 2.16 (s, 3H), 1.29 (d, J = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 170.7, 170.3, 134.5, 122.8, 69.5, 67.9, 64.9, 62.8, 21.2, 20.9, 19.2.

3.3. 2,6-Anhydro-1,3,4-trideoxy-D-ribo-heptitol diacetate, 4a and 2,6-anhydro-1,3,4-trideoxy-D-arabino-heptitol diacetate, 4b

In a Parr apparatus, a solution of the mixture of **3a**/**3b** (4.02 g, 17.6 mmol) in absolute ethanol (75 mL) containing 10% Pd/C (60 mg) was stirred vigorously under H_2 (51 psi) for 4 h. The catalyst was removed via filtration through a bed of Celite and the filter bed was washed with CH_2Cl_2. The combined organic layers were evaporated under reduced pressure to give a yellow oil, which was purified by column chromatography (SiO_2, hexanes–ethyl acetate = 4:1) to give the *cis* isomer **4a** (1.33 g, 26%) followed by the *trans* isomer **4b** (2.39 g, 61%), both as colorless oils.

***cis*-4a**: $[\alpha]_D^{23}$ +50 (*c* 0.29, $CHCl_3$); IR (neat, cm^{-1}) 2973, 2940, 2869, 1743, 1444, 1375, 1247, 1093, 1042, 998, 878; ^{1}H NMR ($CDCl_3$) δ 4.67 (dt, J = 5.0, 10.3 Hz, 1H), 4.21 (dd, J = 5.3, 12.0 Hz, 1H), 4.14 (dd, J = 2.4, 12.0 Hz, 1H), 3.56 (ddd, J = 2.4, 5.3, 9.7 Hz, 1H), 3.56–3.48 (m, 1H), 2.28–2.16 (m, 1H), 2.11 (s, 3H), 2.06 (s, 3H), 1.78–1.67 (m, 1H), 1.65–1.55 (m, 1H), 1.55–1.37 (m, 1H), 1.24 (d, J = 6.2, 3H); ^{13}C NMR ($CDCl_3$) δ 170.4, 169.4, 77.4, 74.2, 68.4, 64.1, 32.7, 29.9, 22.0, 21.9, 21.7. FAB-HRMS m/z 231.1230 (calcd for $C_{11}H_{18}O_5H$ [M+H$^+$] m/z 231.1233).

***trans*-4b**: $[\alpha]_D^{23}$ +32 (*c* 0.26, $CHCl_3$); IR (neat, cm^{-1}) 2966, 2940, 2875, 1747, 1448, 1371, 1244, 1120, 1040, 977, 861; ^{1}H NMR ($CDCl_3$) δ 4.74 (ddd, J = 3.8, 5.6, 6.5 Hz, 1H), 4.34 (dd, J = 6.5, 11.5 Hz, 1H), 4.11 (dd, J = 4.4, 11.5 Hz, 1H), 4.00 (dpent, J = 4.1, 6.5 Hz, 1H), 3.94 (dt, J = 3.6, 6.2 Hz, 1H), 2.11 (s, 3H), 2.10 (s, 3H), 2.02–1.89 (m, 1H), 1.89–1.80 (m, 1H), 1.80–1.68 (m, 1H), 1.66–1.54 (m, 1H), 1.25 (d, J = 6.5 Hz, 3H); ^{13}C NMR (C_6D_6) δ 169.8, 169.3, 72.8, 68.2, 67.7, 63.0, 29.0, 25.3, 21.7, 21.4, 20.6. Anal. calcd for $C_{11}H_{18}O_5$: C, 57.38; H, 7.88. Found: C, 57.09; H, 7.85%.

3.4. 2,6-Anhydro-1,3,4-trideoxy-D-arabino-heptitol, 5

A solution of **4b** (3.21 g, 14.1 mmol) in saturated methanolic K_2CO_3 (20 mL) was stirred at room temperature for 3 h. The reaction mixture was neutralized with 1% by volume aqueous HCl (~100 mL), and extracted with ethyl acetate (6×40 mL). The combined organic layers were dried ($MgSO_4$) and concentrated. The residue was purified by chromatography (SiO_2, CH_2Cl_2–MeOH = 12:1) to give **5** as a colorless oil (1.45 g, 71%): **5**: $[\alpha]_D^{23}$ +43 (*c* 0.26, $CHCl_3$); IR (neat, cm^{-1}) 3392, 2937, 1650, 1453, 1379, 1224, 1136, 1059, 1001,

939, 893; ^{1}H NMR ($CDCl_3$) δ 4.07 (m, 1H), 3.82 (dd, J=5.3, 11.2 Hz, 1H), 3.73 (dd, J=3.5, 11.2 Hz, 1H), 3.64–3.56 (m, 2H), 2.25–2.05 (m, 2H), 1.92–1.54 (m, 4H), 1.27 (d, J=6.8, 3H); ^{13}C NMR ($CDCl_3$) δ 75.0, 68.1, 66.7, 62.6, 29.0, 27.4, 18.3. Anal. calcd for $C_7H_{14}O_3 \cdot 0.2H_2O$: C, 56.13; H, 9.69. Found: C, 56.29; H, 9.69%.

3.5. 2,6-Anhydro-1,3,4-trideoxy-4,6-*O*-(phenylmethylene)-D-arabino-heptitol, 6

To a solution of **5** (1.60 g, 11.0 mmol) dissolved in anhydrous acetonitrile (40 mL), at room temperature under N_2, was added benzaldehyde dimethyl acetal (16.4 mL, 0.110 mol) and *p*-toluenesulfonic acid (0.22 g, 10 mol%, as a solution in anhydrous acetonitrile ~2 mL). The reaction mixture immediately turned bright yellow and was stirred for 4 h. The mixture was neutralized with triethylamine (~1 mL) and washed with saturated aqueous $NaHCO_3$ (2×50 mL), followed by water (1×50 mL), and brine (2×50 mL). The aqueous layers were extracted with ethyl acetate (4×50 mL) and the combined organic layers were dried ($MgSO_4$) and concentrated. Purification of the residue by chromatography (SiO_2, hexanes–ethyl acetate=10:1) afforded 6 as a colorless crystalline solid (2.40 g, 94%). **6**: mp 67–68°C; $[\alpha]_D^{23}$ +29 (*c* 0.20, $CHCl_3$); IR (KBr, cm^{-1}) 2974, 2951, 2927, 2876, 1458, 1386, 1332, 1291, 1214, 1144, 1130, 1101, 1070, 1001, 769, 700; ^{1}H NMR ($CDCl_3$) δ 7.52–7.32 (m, 5H), 5.57 (s, 1H), 4.26–4.16 (m, 2H), 3.76–3.62 (m, 2H), 3.62–3.48 (m, 1H), 2.14–1.81 (m, 3H), 1.68 (td, J=3.2, 13.2 Hz, 1H), 1.37 (d, J=6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 137.3, 128.7, 128.0, 125.8, 101.8, 79.5, 70.3, 69.4, 66.1, 29.7, 24.6, 17.6. Anal. calcd for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found: C, 71.64; H, 7.80%.

3.6. 2,6-Anhydro-1,3,4-trideoxy-4-*O*-(phenylmethyl)-D-arabino-heptitol, 7

To a solution of **6** (2.76 g, 11.8 mmol) in toluene (75 mL) at 0°C, was added dropwise a solution of DIBAL (1.0 M in toluene, 30.0 mL, 30 mmol). After addition was complete the ice bath was removed and the reaction mixture was stirred at room temperature for 24 h. Methanol (20 mL) was slowly added to destroy the excess DIBAL and 10% aqueous NaOH (~5 ml) was added to neutralize the reaction mixture. The mixture was extracted with ethyl acetate (4×50 mL) and the organic layers were washed with brine (3×20 mL), dried ($MgSO_4$), and concentrated. Purification of the residue by chromatography (SiO_2, hexanes–ethyl acetate=1:1) afforded a colorless oil (2.43 g, 87%). The oil consisted of a mixture of **7** and **8**, in a 7:1 ratio as determined by integration of the benzylic proton signals of each. **7**: IR (neat, cm^{-1}) 3440, 3030, 2966, 2935, 2872, 1497, 1454, 1378, 1227, 1208, 1096, 736, 698; ^{1}H NMR ($CDCl_3$) δ 7.40–7.28 (m, 5H), 4.65 (d, J=11.7 Hz, 1H), 4.50 (d, J=11.7 Hz, 1H), 4.14–4.02 (m, 1H), 3.76–3.65 (m, 3H), 3.35 (m, 1H), 2.10 (br s, 1H), 2.04–1.95 (m, 1H), 1.81–1.59 (m, 3H), 1.28 (d, J=6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 137.9, 128.2, 127.6, 127.5, 73.9, 73.1, 70.9, 68.2, 63.0, 29.0, 24.6, 18.4. Anal. calcd for $C_{14}H_{20}O_3 \cdot 0.5H_2O$: C, 68.54; H, 8.63. Found: C, 68.25; H, 8.31%.

3.7. 2,6-Anhydro-1,3,4-trideoxy-4-*O*-(phenylmethyl)-6-methylbenzenesulfonate-D-arabino-heptitol, 9

To a solution of **7**/**8** (1.87 g, 7.93 mmol) in anhydrous CH_2Cl_2 under N_2 was added NEt_3 (3.30 mL, 23.7 mmol), DMAP (0.26 g, 2.1 mmol), and *p*-toluenesulfonyl chloride (4.52 g, 23.8 mol). After addition was complete, a condenser was attached and the reaction mixture was heated at reflux for 40 h. The reaction mixture was cooled to rt, washed with 1 M HCl (1×30 mL), followed by saturated aqueous $NaHCO_3$ (1×30 mL), and brine (1×30 mL). The aqueous washings were extracted with CH_2Cl_2 (3×50 mL). The combined organic layers were dried ($MgSO_4$) and concentrated. The residue was purified by chromatography (SiO_2, hexanes–ethyl acetate=5:1) to afford recovered starting material **8** (0.18 g) and **9** as a colorless crystalline solid (2.70 g, 87%). **9**: mp 45–46°C; $[\alpha]_D^{23}$ +45 (*c* 0.28, $CHCl_3$); IR (KBr, cm^{-1}) 3031, 2938, 2872, 1598, 1453, 1360, 1178, 1097, 967, 814, 665; ^{1}H NMR ($CDCl_3$)δ 7.79 (d, J=8.5 Hz, 2H), 7.38–7.24 (m, 7H), 4.57 (d, J=11.5 Hz, 1H), 4.41 (d, J=11.5 Hz, 1H), 4.27 (dd, J=5.0, 10.3 Hz, 1H), 4.16 (dd, J=3.2, 10.3 Hz, 1H), 4.03–3.91 (m, 1H), 3.77 (ddd, J=3.3, 5.0, 7.6 Hz, 1H), 3.35 (dt, J=4.4, 8.0 Hz, 1H), 2.44 (s, 3H), 2.03–1.90 (m, 1H), 1.80–1.65 (m, 2H), 1.65–1.52 (m, 1H), 1.19 (d, J=6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 144.2, 137.6, 132.7, 129.4, 128.1, 127.7, 127.5, 127.4, 72.5, 71.2, 70.8, 69.7, 68.4, 28.6, 24.4, 23.3, 18.2. Anal. calcd for $C_{21}H_{26}O_5S$: C, 64.59; H, 6.71. Found: C, 64.31; H, 6.69%.

3.8. 6-Methyl-3-(phenylmethoxy)-tetrahydro-2*H*-pyran-2-acetonitrile, 10

To a solution of **9** (3.57 g, 9.15 mmol) in anhydrous DMF (60 mL) under N_2 was added NaI (4.14 g, 27.6 mmol) and NaCN (1.40 g, 28.6 mmol). After addition was complete, a condenser was attached and the reaction mixture was heated to 80°C for 14 h. The reaction mixture was cooled to room temperature and was partitioned between ethyl acetate (100 mL) and H_2O (100 mL). The layers were separated and the organic layer was washed with H_2O (3×100 mL) and the aqueous layers were extracted with ethyl acetate (6×100 mL). The combined organic layers were dried ($MgSO_4$) and concentrated. The dark orange residue was purified by chromatography (SiO_2, hexanes–ethyl acetate=5:1) to give **10** as a nearly colorless thin oil (1.89 g, 84%). **10**: $[\alpha]_D^{23}$ +91 (*c* 0.32, $CHCl_3$); IR (neat, cm^{-1}) 2974, 2939, 2876, 2252, 1497, 1454, 1378, 1226, 1097, 1029, 738, 700; ^{1}H NMR ($CDCl_3$) δ 7.41–7.27 (m, 5H), 4.67 (d, J=11.5 Hz, 1H), 4.48 (d, J=11.5 Hz, 1H), 4.14 (ddq, J=2.3, 5.3, 6.8 Hz, 1H), 3.80 (ddd, J=4.4, 5.6, 8.2 Hz, 1H), 3.30 (ddd, J=4.1, 8.2, 9.1 Hz, 1H), 2.70 (dd, J=4.4, 16.7 Hz, 1H), 2.65 (dd, J=5.9, 16.7 Hz, 1H), 2.15–2.04 (m, 1H), 1.94–1.80 (m, 1H), 1.78–1.68 (m, 1H), 1.67–1.58 (m, 1H), 1.29 (d, J=6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 137.4, 128.2, 127.6, 127.5, 117.4, 76.0, 70.8, 68.9, 68.8, 28.7, 24.1, 22.1, 17.6. Anal. calcd for $C_{15}H_{19}O_2N$: C, 73.44; H, 7.81; N, 5.71%. Found: C, 73.28; H, 7.75; N, 5.78%.

3.9. 1-[(3*S*,6*R*)-Tetrahydro-6-methyl-3-(phenylmethoxy)-2*H*-pyran-2-yl]-2-propanone, 12a/12b

A solution of **10** (0.21 g, 0.86 mmol) in aqueous KOH (1.36 g, 25.8 mmol, in 10 mL H_2O) was heated to reflux for 4 h. The reaction mixture was cooled to rt, acidified with 1 M HCl (~10 mL) and extracted with ether. The ethereal layers were dried ($MgSO_4$) and concentrated to give a colorless oil (0.15 g, 65%). This oil consisted of a mixture of isomeric carboxylic acids **11a** and **11b** (1:4) as indicated by NMR spectroscopy. Separation of the two isomers was not possible. ^{13}C NMR ($CDCl_3$) δ 175.4, 137.7, 128.1, 127.9, 127.5, 75.9, 70.7, 70.1, 68.4, 37.8, 28.9, 24.3, 18.6. To a flame-dried flask under N_2 at 0°C, was added a solution of **11a**/**11b** (0.080 g, 0.30 mmol) in dry ether (~6 mL) followed by a solution of methyllithium (1.6 M in ether, 0.40 mL, 0.66 mmol). After addition was complete, the ice bath was removed and the reaction mixture was allowed to stir at room temperature for 2 h. Chlorotrimethylsilane (0.17 mL) was added and the reaction was stirred for 30 min. The reaction mixture was quenched by the addition of 1 M HCl (4 mL), and after an additional 30 min of stirring, the layers were separated. The aqueous layer was extracted with ether (5×3 mL), the combined ethereal layers were dried ($MgSO_4$) and concentrated to give a brown oil (0.073 g, 79%). This was determined to be a mixture of **12a** and **12b** (1:1) by NMR spectroscopy. Preparative thin-layer chromatography (SiO_2, hexanes–ethyl acetate = 15:1) gave pure **12a** and pure **12b**.

Methyl ketone *cis*-12a: $[\alpha]_D^{23}$ +25.1 (*c* 0.432, $CHCl_3$); IR (neat, cm^{-1}) 2925, 2855, 1716, 1455, 1374, 1208, 1081, 1028, 740, 697; ^1H NMR ($CDCl_3$) δ 7.35–7.27 (m, 5H), 4.64 (d, J = 12.0 Hz, 1H), 4.34 (d, J = 12.0 Hz, 1H), 3.84 (ddd, J = 1.5, 5.9, 7.1 Hz, 1H), 3.58–3.45 (m, 1H), 3.37–3.32 (m, 1H), 2.84 (dd, J = 7.1, 16.4 Hz, 1H), 2.54 (dd, J = 5.9, 16.4 Hz, 1H), 2.10 (s, 3H), 1.71–1.38 (m, 4H), 1.20 (d, J = 6.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 206.9, 138.0, 128.0, 127.9, 127.4, 75.8, 74.4, 71.6, 70.8, 46.2, 31.7, 28.2, 26.7, 22.5. FAB-HRMS *m*/*z* 269.1727 (calcd for $C_{16}H_{22}O_3Li$ [M+Li$^+$] *m*/*z* 269.1729).

Methyl ketone *trans*-12b: $[\alpha]_D^{23}$ +43.3 (*c* 0.448, $CHCl_3$); IR (neat, cm^{-1}) 2971, 2935, 2871, 1714, 1454, 1358, 1134, 1095, 1070, 1028, 738, 699; ^1H NMR ($CDCl_3$)δ 7.38–7.27 (m, 5H), 4.63 (d, J = 11.7 Hz, 1H), 4.49 (d, J = 11.7 Hz, 1H), 4.19 (ddd, J = 4.7, 6.5, 8.5 Hz, 1H), 4.02–3.91 (m, 1H), 3.21–3.13 (m, 1H), 2.77 (dd, J = 4.7, 15.3 Hz, 1H), 2.61 (dd, J = 8.8, 15.3 Hz, 1H), 2.18 (s, 3H), 2.03–1.90 (m, 1H), 1.85–1.55 (m, 3H), 1.26 (d, J = 6.7 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 206.2, 137.9, 128.1, 127.5, 127.4, 76.1, 70.7, 70.2, 67.9, 46.9, 30.9, 28.9, 24.4, 18.9. FAB-HRMS *m*/*z* 269.1726 (calcd for $C_{16}H_{22}O_3Li$ [M+Li$^+$] *m*/*z* 269.1729).

3.10. 6-Methyl-3-(phenylmethoxy)-tetrahydro-2*H*-pyran-2-acetaldehyde

To a flame-dried flask, under N_2, was added a solution of the crude mixture of acids **11a**/**11b** (200 mg, 0.758 mmol) in dry THF (15 mL). The reaction mixture was cooled to 0°C and solid $LiAlH_4$ (140 mg, 7.58 mmol) was cautiously added. The reaction mixture was stirred at 0°C for 10 min, at room temperature for 20 min, and at reflux for 1 h. The reaction mixture was then cooled to room temperature and quenched by the slow dropwise addition of saturated aqueous sodium potassium tartrate (50 mL). The layers were separated and the aqueous layer was extracted with ether (4×30 mL). The ethereal layers were dried ($MgSO_4$) and concentrated to give a yellow oil (163 mg, 86%) which was identified as a mixture of alcohols (1:4) by NMR spectroscopy. ^{13}C NMR ($CDCl_3$) δ 137.8, 128.0, 127.3, 127.4, 76.1, 73.7, 70.6, 67.4, 61.5, 33.6, 28.7, 24.1, 19.2. To a flame-dried flask cooled to −78°C under N_2, was added oxalyl chloride (0.13 mL, 1.50 mmol), anhydrous CH_2Cl_2 (8 mL) and anhydrous DMSO (0.20 mL, 2.7 mmol). The reaction mixture was stirred for 1.5 h at −78°C and then a solution of the crude alcohols (150 mg, 0.60 mmol) in anhydrous CH_2Cl_2 (6 mL) was added. After stirring for 3 h at −78°C, NEt_3 (0.55 mL, 3.9 mmol) was added. The reaction mixture was warmed to room temperature and quenched with saturated aqueous NH_4Cl (10 mL) and neutralized with 10% HCl (~2 mL). The layers were separated and the organic layer was washed with brine (3×30 mL). The aqueous layers were extracted with CH_2Cl_2 (3×40 mL). The combined organic layers were dried ($MgSO_4$) and concentrated. The residue was purified by chromatography to give a mixture of **13a**/**13b** (1:4) as a yellow oil (141 mg, 95%).

13b: IR (neat, cm^{-1}) 2919, 2853, 1726, 1448, 1368, 1255, 1202, 1090, 731, 698; ^1H NMR ($CDCl_3$) δ 9.71 (dd, J = 0.9, 2.1 Hz, 1H), 7.36–7.25 (m, 5H), 4.62 (d, J = 11.5 Hz, 1H), 4.47 (d, J = 11.5 Hz, 1H), 4.28–4.17 (m, 1H), 4.06–3.96 (m, 1H), 3.18 (dt, J = 4.7, 7.6 Hz, 1H), 2.90–1.50 (m, 6H), 1.27 (d, J = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 200.2, 137.6, 128.2, 127.6, 127.5, 76.3, 70.7, 68.9, 68.1, 46.8, 28.9, 24.4, 18.5. This product was used in the next step without further characterization.

3.11. 1-[(3*S*,6*R*)-Tetrahydro-6-methyl-3-(phenylmethoxy)-2*H*-pyran-2-yl]-2-propanone, 12a/12b

To a flame-dried flask under N_2 was added a solution of **13a**/**13b** (130 mg, 0.524 mmol) in dry THF (12 mL). The reaction mixture was cooled to 0°C and a solution of methylmagnesium bromide (3.0 M in Et_2O, 0.35 mL, 1.0 mmol) was added. The ice bath was removed and the reaction was stirred for 4 h at room temperature. The reaction mixture was quenched by the addition of saturated aqueous NH_4Cl (10 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (4×40 mL). The organic layers were dried ($MgSO_4$) and concentrated to give as a nearly colorless solid (126 mg, 91%). To a solution of the solid (28.0 mg, 0.106 mmol) in DMF (10 mL) was added pyridium dichromate (0.16 g, 0.42 mmol) and the reaction mixture was stirred at room temperature for 4 h. The reaction mixture was quenched by the addition of Et_2O (10 mL) and brine (10 mL). The layers were separated and the aqueous layer was extracted with ether (4×20 mL). The combined ethereal layers were dried ($MgSO_4$) and concentrated to give a mixture of **12a** and **12b** (1:3) by NMR spectroscopy. Purification of the crude

product by preparative thin-layer chromatography (SiO_2, hexanes–ethyl acetate = 10:1) gave pure **12a** (5.4 mg, 19%) and pure **12b** (16.0 mg, 57%).

3.12. 1-[(2*R*,3*S*,6*R*)-Tetrahydro-3-hydroxy-6-methyl-2*H*-pyran-2-yl]-2-propanone ((+)-decarestrictine L), 1

In a Parr apparatus, a solution of **12b** (0.041 g, 0.16 mmol) and 10% Pd/C (60 mg) in $CHCl_3$–MeOH (100:1, 12 mL) was stirred vigorously under a H_2 (49.5–42.0 psi) for 5 h. The catalyst was removed via filtration through a bed of Celite and the filter bed was washed with CH_2Cl_2 (2×50 mL). The combined organic layers were evaporated under reduced pressure to give (+)-**1** as a yellow oil (25.2 mg, 94%). (+)-**1**: $[\alpha]_D^{23}$ +21.1 (*c* 0.452, $CHCl_3$) [lit.[2] $[\alpha]_D^{23}$ +28.8 (*c* 0.49, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 4.01 (q, J = 6.5 Hz, 1H), 3.95 (m, 1H), 3.40 (m, 1H), 2.76 (dd, J = 5.6, 15.6 Hz, 1H), 2.70 (dd, J = 7.3, 15.6 Hz, 1H), 2.21 (s, 3H), 1.92–1.40 (m, 4H), 1.22 (d, J = 6.5 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 206.9, 72.2, 69.5, 67.7, 46.7, 31.2, 28.9, 27.7, 19.1. FAB-HRMS m/z 179.1264 (calcd for $C_9H_{16}O_3Li$ [M+Li$^+$] m/z 179.1260).

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