A Concise, Enantioselective Synthesis of (+)-Decarestrictine L from Tri-*O*-acetyl-D-glucal

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Abstract: We describe a new and efficient approach to the enantioselective synthesis of (+)-(2*R*,3*S*,6*R*)-decarestrictine L from commercially available tri-*O*-acetyl-D-glucal, based on a stereoselective Michael addition.

Key words: Michael addition, Wolf–Kishner reaction, Wacker oxidation

Decarestrictine L is a minor component of the decarestrictine family and was first isolated in 1992[1] from a culture of *Penicillium simplicissimus*. Whereas the major components of the decarestrictine family show a 10-membered lactone ring system, decarestrictine L is unique in possessing a tetrahydropyranyl nucleus (Figure 1).

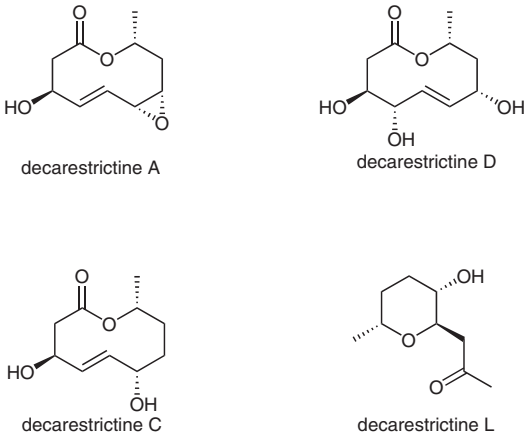
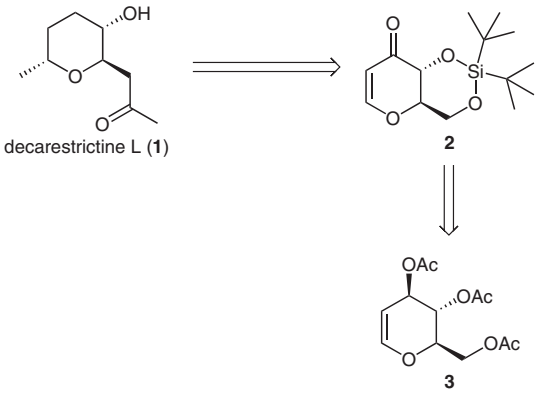


Figure 1 Representative members of the decarestrictine family

Decarestrictine L has been shown to inhibit HMG-CoA reductase, which is involved in the first steps of the biosynthesis of cholesterol.[2] The interesting biological properties of this molecule, coupled with the extreme scarcity of the natural material, make it an appealing synthetic target. Some good total syntheses of decarestrictine L can be found in the literature.[3] However, most of these syntheses suffer from one or more drawbacks with regard to the number of steps, stereoselectivity, overall chemical yield or the availability of the starting materials.[4] We previously published an enantioselective synthesis of (+)-decarestrictine L from the relatively inexpensive and readily available chiral pool material ethyl (*R*)-3-hydroxybutyrate by using our furan approach.[3g] We obtained (+)-decarestrictine L in 17 steps and 12% overall yield. Although the overall yield of our synthesis compared favourably with those reported in the literature,[4] we still felt that the number of steps needed to be shortened. We now wish to report a short (11 steps) enantioselective synthesis of (+)-decarestrictine L that uses the relatively inexpensive and commercially available tri-*O*-acetyl-D-glucal. Our synthesis is outlined retrosynthetically in Scheme 1.



Scheme 1 Retrosynthetic analysis of decarestrictine L (**1**)

We anticipated that stereoselective Michael addition of dimethylcuprate on enone **2**, followed by a Wolf–Kishner reaction, removal of the protecting group and side-chain elaboration, would lead to our target compound.

Accordingly, compound **4** was prepared in two steps from **3**[5] in 91% yield, following the procedure described by Mori and Hayashi[6] (Scheme 2). Pyridinium dichromate (PDC) oxidation of **4** afforded α,β-unsaturated ketone **2** in 97% yield, which underwent a stereoselective Michael addition with dimethyl cuprate to give diastereoisomers **5** and **6** in 10 and 70% yield, respectively. With ketone **6** in hand, the stage was set for the Wolf–Kishner reaction,[7] which afforded compound **7** in 47% overall yield (2 steps). Removal of the silyl protecting group of **7** with HF in acetonitrile afforded diol **8** in 99% yield. Diol **8** was uneventfully converted into nitrile **10** in 60% overall yield by selective tosylation of its primary alcohol followed by tosylate displacement with sodium cyanide. Reduction of nitrile **10** with diisobutylaluminium hydride (DIBAL-H)[8] gave aldehyde **11**, which was subjected to a Wittig reaction to obtain alkene **12** in 30% yield. Alkene **12** under-

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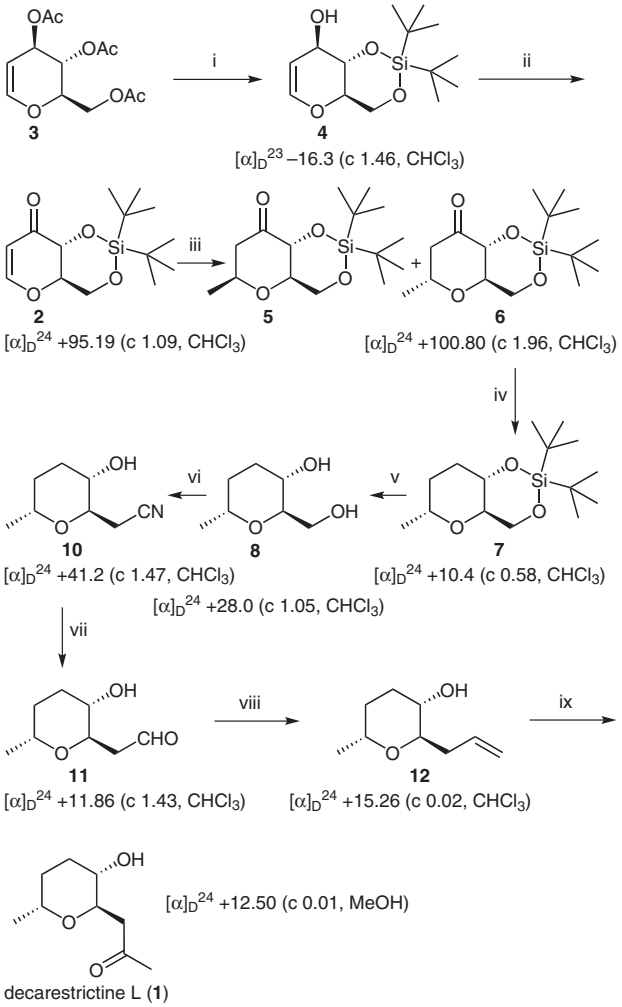

Scheme 2 *Reagents and conditions*: (i) (a) K_2CO_3, MeOH; (b) *t*-$Bu_2Si(OTf)_2$, DMF, Py, –30 °C (91%, 2 steps); (ii) PDC, DMF (97%); (iii) MeLi, CuLi, TMSCl, Et_2O, –78 °C (10% for **5** and 71% for **6**); (iv) (a) NH_2NHTs, PTSA, MS, MeOH (75%); (b) $NaBH_3CN$, PTSA, DMF–sulfolane (1:1), 100 °C (62%); (v) HF, MeCN (99%); (vi) (a) *p*-TsCl, Py, CH_2Cl_2 (84% of corresponding tosylate **9**); (b) NaCN, DMSO, 70 °C (72%); (vii) DIBAL-H, toluene, –78 °C (99%); (viii) Ph_3PCH_2Br, *n*-BuLi (30%); (ix) $PdCl_2$, CuCl, DMF, H_2O (92%).

went a Wacker oxidation,[9] affording (+)-decarestrictine L (**1**) almost quantitatively.

In conclusion, an enantioselective synthesis of (+)-decarestrictine L from relatively cheap and commercially available tri-*O*-acetyl-D-glucal was completed in 11 steps and an overall yield of 4.8%. This overall yield might be improved once the Wittig reaction used to obtain alkene **12** has been optimised. Nevertheless, this new synthesis of (+)-decarestrictine L competes favourably with those reported in the literature.[4] Moreover, this new method will allow the synthesis of decarestrictine L analogues through the use of different alkyl cuprates in the Michael addition step. The design of those analogues is being carried out by means of QSAR studies.[10]

Solvents were purified and dried by standard procedures before use. Melting points are uncorrected. ^1H and ^{13}C NMR spectra were recorded with a Bruker ARX-400 spectrometer (^1H: 400 MHz, ^{13}C: 100.61 MHz) using TMS as internal standard (chemical shifts in δ values, *J* in Hz). Mass spectrometry was carried out with a Hewlett–Packard 5988A spectrometer. Flash chromatography (FC) was performed on silica gel (Merck 60, 230–400 mesh); analytical TLC was performed on plates precoated with silica gel (Merck 60 F254, 0.25 mm).

(4a*R*,8*R*,8a*S*)-2,2-Di-*tert*-butyl-4,4a,8,8a-tetrahydropyrano[3,2-*d*][1,3,2]dioxasilin-8-ol (4)

To a solution of **3** (14 g, 51.4 mmol) in MeOH was added K_2CO_3 (100 mg), and the mixture was stirred at r.t. for 12 h. The MeOH was removed and the crude material was dissolved in $CHCl_3$ and concentrated. The solid obtained was dissolved in DMF (40 mL), pyridine (20 mL, 257.1 mmol) was added, and the mixture was cooled to –40 °C. *t*-$Bu_2Si(OTf)_2$ (18.3 mL, 56.6 mmol) was added slowly and the resulting mixture was stirred at r.t. for 1.5 h. EtOAc (30 mL) was added and the organic phase was washed with a 10% aq $CuSO_4$ (2 × 30 mL), H_2O (3 × 30 mL) and finally with brine (3 × 30 mL). The organic phase was dried over Na_2SO_4 and the solvent evaporated under reduced pressure. The residue was purified by chromatography on silica gel (EtOAc–hexane, 5%), affording **4**.

Yield: 13.4 g (91%); white solid; mp 84–85 °C; R_f = 0.71 (EtOAc); $[\alpha]_D^{23}$ –16.3 (*c* 1.46, $CHCl_3$).

IR (NaCl): 3440, 3074, 2939, 2889, 2862, 1647 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 6.25 (dd, *J* = 6.1, 1.8 Hz, 1 H, CH-8), 4.74 (dd, *J* = 6.1, 1.9 Hz, 1 H, CH-9), 4.31–4.26 (m, 1 H, CH-10), 4.16 (dd, *J* = 10.2, 4.9 Hz, 1 H, CH_2-5), 3.98–3.88 (m, 2 H, CH_2-5, CH-1), 3.85–3.78 (m, 1 H, CH-6), 2.66 (s, 1 H, OH), 1.05 [s, 9 H, $C(CH_3)_3$], 0.98 [s, 9 H, $C(CH_3)_3$].

^{13}C NMR ($CDCl_3$): δ = 143.49 (CH-8), 103.07 (CH-9), 77.27 (CH-1), 72.20 (CH-6), 70.01 (CH-10), 65.63 (CH_2-5), 27.36 [$C(CH_3)_3$], 26.84 [$C(CH_3)_3$], 22.65 [$C(CH_3)_3$], 19.75 [$C(CH_3)_3$].

MS (FAB^+): *m*/*z* (%) = 287 (7) $[M + 1]^+$, 286 (12) $[M]^+$, 285 (18) $[M – 1]^+$, 269 (100) $[M – OH]^+$, 229 (43) $[M – t\text{-}Bu]^+$.

HRMS (FAB^+): *m*/*z* calcd for $C_{14}H_{26}O_4Si$: 286.1632; found: 286.1647.

(4a*R*,8a*R*)-2,2-Di-*tert*-butyl-4,4a-dihydropyrano[3,2-*d*][1,3,2]dioxasilin-8(8a*H*)-one (2)

To a solution of **4** (1 g, 3.5 mmol) in DMF (33 mL), was added PDC (5.1 g, 13.9 mmol) and the mixture was stirred at r.t. for 1 h, quenched with sat. $NaHCO_3$ (10 mL) and extracted with EtOAc (30 mL). The organic phase was washed with H_2O (3 × 30 mL) and brine (3 × 30 mL). After drying with Na_2SO_4 and solvent evaporation, the residue was purified by chromatography on silica (EtOAc–hexane, 15%), affording **2**.

Yield: 960 mg (97%); colourless oil; R_f = 0.37 (EtOAc–hexane, 30%); $[\alpha]_D^{24}$ +95.19 (*c* 1.09, $CHCl_3$).

IR (NaCl): δ = 2964, 2937, 2889, 2860, 1703 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 7.18 (d, *J* = 5.8 Hz, 1 H, CH-8), 5.30 (d, *J* = 5.8 Hz, 1 H, CH-9), 4.49 (m, 1 H, CH-1), 4.20 (m, 2 H, CH_2-5), 4.10 (m, 1 H, CH-6), 0.98 [s, 9 H, $C(CH_3)_3$], 0.91 [s, 9 H, $C(CH_3)_3$].

^{13}C NMR ($CDCl_3$): δ = 191.08 (CO-10), 160.84 (CH-8), 105.75 (CH-9), 77.36 (CH-1), 74.68 (CH-6), 65.45 (CH_2-5), 27.32 [$C(CH_3)_3$], 26.85 [$C(CH_3)_3$], 22.78 [$C(CH_3)_3$], 20.02 [$C(CH_3)_3$].

MS (ESI): *m*/*z* (%) = 285 (100) $[M + 1]^+$, 331 (71).

HRMS (ESI): *m*/*z* calcd for $C_{14}H_{25}O_4Si$: 285.1444; found: 285.1517.

(4a*R*,6*S*,8a*R*)-2,2-Di-*tert*-butyl-6-methyltetrahydropyrano[3,2-*d*][1,3,2]dioxasilin-8(8a*H*)-one (5) and (4a*R*,6*R*,8a*R*)-2,2-Di-*tert*-butyl-6-methyltetrahydropyrano[3,2-*d*][1,3,2]dioxasilin-8(8a*H*)-one (6)

To a solution of CuI (4.6 g, 24.27 mmol) in Et_2O (30 mL) cooled to –20 °C, was slowly added a solution of MeLi (1.5 M in THF, 32.36 mL, 48.54 mmol). TMSCl (2.6 g, 24.27 mmol) was added to the last mixture cooled to –78 °C and stirred for 10 min. A solution of **2** (2.3 g, 8.09 mmol) in Et_2O (30 mL) was added using a cannula and the mixture was stirred for 1 h, quenched with sat. NH_4Cl (50 mL) and extracted with EtOAc (3 × 30 mL). The combined organic phases were washed with H_2O (3 × 50 mL) and brine (3 × 50 mL), dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. The residue was purified by chromatography on silica gel (EtOAc–hexane, 1%), affording **5** and **6**.

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Yield: 3.1 g (71%); colourless oil; R_f = 0.42 (EtOAc–hexane, 30%); $[\alpha]_D^{24}$ +100.80 (*c* 1.96, $CHCl_3$).

IR (NaCl): 2968, 2935, 2889, 2860, 1722 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 4.51 (q, *J* = 6.8 Hz, 1 H, CH-8), 4.40 (d, *J* = 9.5 Hz, 1 H, CH-1), 4.09 (dd, *J* = 9.7, 4.2 Hz, 1 H, CH_2-5), 3.93 (t, *J* = 9.8 Hz, 1 H, CH_2-5), 3.77 (td, *J* = 9.6, 4.3 Hz, 1 H, CH-6), 2.85 (dd, *J* = 13, 6.8 Hz, 1 H, CH_2-9), 2.28 (d, *J* = 13.6 Hz, 1 H, CH_2-9), 1.20 (d, *J* = 6.8 Hz, 3 H, CH_3-8), 1.00 [s, 9 H, $C(CH_3)_3$], 0.97 [s, 9 H, $C(CH_3)_3$].

^{13}C NMR ($CDCl_3$): δ = 202.87 (CO-10), 80.31 (CH-1), 71.73 (CH-6), 71.24 (CH-8), 67.32 (CH_2-5), 46.36 (CH_2-9), 27.24 [$C(CH_3)_3$], 26.89 [$C(CH_3)_3$], 22.65 [$C(CH_3)_3$], 20.01 [$C(CH_3)_3$], 18.32 (CH_3-8).

MS (ESI): *m*/*z* (%) = 285 (14) $[M + 1 – O]^+$, 301 (100) $[M + 1]^+$.

HRMS (ESI): *m*/*z* calcd for $C_{15}H_{29}O_4Si$: 301.1757; found: 301.1829.

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Yield: 435 mg (10%); colourless oil; R_f = 0.50 (EtOAc–hexane, 30%); $[\alpha]_D^{24}$ +1.2 (*c* 0.32, $CHCl_3$).

IR (NaCl): 2968, 2935, 2889, 2860, 1722 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 4.43 (d, *J* = 9.3 Hz, 1 H, CH-1), 4.24 (dd, *J* = 10.0, 4.7 Hz, 1 H, CH_2-5), 3.99 (t, *J* = 9.8 Hz, 1 H, CH_2-5), 3.88 (m, 1 H, CH-8), 3.57 (td, *J* = 10.1, 4.5 Hz, 1 H, CH-6), 2.51 (m, 1 H, CH_2-5), 2.42 (m, 1 H, CH_2-5), 1.30 (d, *J* = 5.9 Hz, 1 H, CH_3-8), 1.04 [s, 9 H, $C(CH_3)_3$], 1.00 [s, 9 H, $C(CH_3)_3$].

^{13}C NMR ($CDCl_3$): δ = 202.62 (CO-10), 79.95 (CH-1), 77.13 (CH-6), 74.99 (CH-8), 66.87 (CH_2-5), 48.99 (CH_2-9), 27.35 [$C(CH_3)_3$], 26.98 [$C(CH_3)_3$], 22.73 [$C(CH_3)_3$], 21.67 [$C(CH_3)_3$], 20.13 (CH_3-8).

MS (ESI): *m*/*z* (%) = 285 (14) $[M + 1 – O]^+$, 301 (100) $[M + 1]^+$.

HRMS (ESI): *m*/*z* calcd for $C_{15}H_{29}O_4Si$: 301.1757; found: 301.1829.

(4a*R*,6*R*,8a*S*)-2,2-Di-*tert*-butyl-6-methylhexahydropyrano[3,2-*d*][1,3,2]dioxasiline (7)

To a solution of **6** (318 mg, 1.06 mmol) in MeOH (10 mL) was added *p*-toluenesulfonylhydrazine (217 mg, 1.16 mmol), PTSA (120 mg, 64 mmol) and 4Å MS (90 mg). The mixture was stirred at r.t. for 18 h, then the MeOH was evaporated under reduced pressure and the residue was dissolved in CH_2Cl_2 (15 mL). The organic phase was washed with H_2O (3 × 15 mL) and brine (3 × 15 mL), then the organic phase was dried over Na_2SO_4. Filtration and solvent evaporation afforded a residue that was purified by chromatography on silica gel (EtOAc–hexane, 20%), affording a mixture of *p*-tosylhydrazones [373 mg, 75%, yellow oil, R_f = 0.33 and 0.26 (30% EtOAc)].

The mixture of *p*-tosylhydrazones (373 mg, 0.79 mmol) was dissolved in DMF–sulfolane (1:1; 10 mL), and $NaBH_3CN$ (200 mg, 3.2 mmol) and PTSA (42 mg, 0.22 mmol) were added. The mixture was heated at 140 °C for 6 h, then cooled to r.t. and dissolved in EtOAc (20 mL). The organic phase was washed with H_2O (3 × 20 mL) and brine (3 × 20 mL), then the organic layer was dried over Na_2SO_4, filtered and evaporated. The crude material was purified by flash chromatography (EtOAc–hexane, 2%), affording **7**.

Yield: 141 mg (62%); colourless liquid; R_f = 0.68 (EtOAc–hexane, 30%); $[\alpha]_D^{24}$ +10.4 (*c* 0.58, $CHCl_3$).

IR (NaCl): 2966, 2935, 2881, 2860 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 4.12 (q, *J* = 6.5 Hz, 1 H, CH-8), 3.99 (dd, *J* = 9.8, 4.5 Hz, 1 H, CH_2-5), 3.77 (t, *J* = 9.8 Hz, 1 H, CH_2-5), 3.71 (m, 1 H, CH-1), 3.56 (td, *J* = 9.5, 4.7 Hz, 1 H, CH-6), 1.93 (m, 2 H, CH_2-9), 1.62 (m, 2 H, CH_2-10), 1.29 (d, *J* = 6.3 Hz, 3 H, CH_3-8), 1.04 [s, 9 H, $C(CH_3)_3$], 1.00 [s, 9 H, $C(CH_3)_3$].

^{13}C NMR ($CDCl_3$): δ = 74.72 (CH-6), 69.57 (CH-1), 68.72 (CH-8), 67.80 (CH_2-5), 28.97 (CH_2-9), 27.50 [$C(CH_3)_3$], 27.40 (CH_2-10), 27.13 [$C(CH_3)_3$], 22.65 [$C(CH_3)_3$], 19.92 [$C(CH_3)_3$], 16.49 (CH_3-8).

MS (ESI): *m*/*z* (%) = 285 (68), 286 (22) $[M]^+$, 287 (39), 307 (100), 309 (58) $[M + Na]^+$.

HRMS (ESI): *m*/*z* calcd for $C_{15}H_{31}O_3Si$: 287.1964; found: 287.2037.

(2*R*,3*S*,6*R*)-2-(Hydroxymethyl)-6-methyltetrahydro-2*H*-pyran-3-ol (8)

To a solution of **7** (55 mg, 0.19 mmol) in MeCN (2 mL), was added, dropwise, HF (48% in H_2O) until the reaction was complete. Sat. $NaHCO_3$ was added and the mixture was extracted with EtOAc. The organic layer was dried over Na_2SO_4, filtered and evaporated. The crude material was purified by flash chromatography (EtOAc–hexane, 50%), to afford **8**.

Yield: 29 mg (99%); yellow oil; R_f = 0.13 (EtOAc); $[\alpha]_D^{24}$ +28.0 (*c* 1.05, $CHCl_3$).

IR (NaCl): 3390, 2924, 2852 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 4.04 (m, 1 H, CH_2-1′), 3.74 (m, 2 H, CH-2,4), 3.56 (m, 2 H, CH_2-1′, CH-1), 1.85 (m, 1 H, CH_2-6), 1.74 (m, 2 H, CH_2-5,6), 1.57 (m, 1 H, CH_2-5), 1.25 (d, *J* = 6.2 Hz, 3 H, CH_3-4).

^{13}C NMR ($CDCl_3$): δ = 74.59 (CH-2), 67.69 (CH-4), 67.38 (CH-C1), 62.84 (CH_2-1′), 28.38 (CH_2-6), 27.20 (CH_2-5), 17.80 (CH_3-4).

MS (ESI): *m*/*z* (%) = 129 (11) $[M – OH]^+$, 169 (100) $[M + Na]^+$.

HRMS (ESI): *m*/*z* calcd for$C_7H_{14}NaO_3$: 169.0841; found: 169.0835.

[(2*R*,3*S*,6*R*)-3-Hydroxy-6-methyltetrahydro-2*H*-pyran-2-yl]methyl-4-methylbenzenesulfonate (9)

To a solution of **8** (50 mg, 0.34 mmol) in THF (3 mL) at 0 °C, was added, dropwise, pyridine (1 mL) and the solution was stirred for 10 min. *p*-TsCl (72 mg, 0.37 mmol) was added and the solution was stirred at 0 °C for 4 h. Sat. $NaHCO_3$ (10 mL) was added and the mixture was extracted with EtOAc (10 mL). The organic layer was washed with H_2O (3 × 10 mL) and brine (3 × 10 mL), then the organic layer was dried over Na_2SO_4, filtered and evaporated. The crude material was purified by flash chromatography (EtOAc–hexane, 30%) to afford **9**.

Yield: 86 mg (84%); colourless oil; R_f = 0.53 (EtOAc); $[\alpha]_D^{21}$ +21.71 (*c* 0.91, $CHCl_3$).

IR (NaCl): δ = 3433, 3033, 2972, 2937, 2871, 1599, 1358 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 7.80 (d, *J* = 8.4 Hz, 2 H, CH_o-Ts), 7.34 (d, *J* = 8.2 Hz, 2 H, CH_p-Ts), 4.30 (dd, *J* = 10.3, 4.7 Hz, 1 H, CH_2-1′), 4.14 (dd, *J* = 10.3, 2.9 Hz, 1 H, CH_2-1′), 3.96 (m, 1 H, CH-2), 3.64 (m, 1 H, CH-6), 3.57 (m, 1 H, CH-3), 2.44 (s, 1 H, CH_3-Ts), 1.84

(m, 1 H, CH_2-4), 1.72 (m, 2 H, CH_2-3,4), 1.54 (m, 1 H, CH_2-3), 1.17 (d, J = 6.3 Hz, 3 H, CH_3-6).

^{13}C NMR ($CDCl_3$): δ = 144.94 (C-Ts), 132.88 (C-Ts), 129.86 (CH_p-Ts), 127.96 (CH_o-Ts), 73.13 (CH-2), 69.48 (CH_2-2), 68.10 (CH-6), 65.62 (CH-3), 28.15 (CH_2-4), 26.85 (CH_2-5), 21.64 (CH_3-Ts), 17.60 (CH_3-6).

MS (ESI): m/z (%) = 301 (100) $[M]^+$, 323 (48).

HRMS (ESI): m/z calcd for $C_{14}H_{21}O_5S$: 301.1031; found: 301.1104.

2-[(2*R*,3*S*,6*R*)-3-Hydroxy-6-methyltetrahydro-2*H*-pyran-2-yl]acetonitrile (10)

To a solution of tosylate **9** (80 mg, 0.27 mmol) in DMSO (3 mL), was added NaCN (40 mg, 0.81 mmol), and the mixture was heated at 70 °C for 6 h. The reaction was quenched with H_2O (6 mL) and extracted with EtOAc (10 mL), the organic layer was washed with H_2O (3 × 8 mL) and brine (3 × 8 mL). After drying with Na_2SO_4 and solvent evaporation, the residue was purified by chromatography on silica (EtOAc–hexane, 20%) to afford **10**.

Yield: 30 mg (72%); colourless oil; R_f = 0.48 (EtOAc); $[\alpha]_D^{22}$ +41.22 (*c* 1.47, $CHCl_3$).

IR (NaCl): 3440, 2974, 2939, 2875, 2254 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 4.09 (m, 1 H, CH-6), 3.69 (m, 1 H, CH-2), 3.47 (m, 1 H, CH-3), 2.69 (m, 2 H, CH_2-1′), 1.88 (m, 2 H, CH_2-4,5), 1.71 (m, 1 H, CH_2-5), 1.58 (m, 1 H, CH_2-4), 1.25 (d, J = 6.2 Hz, 3 H, CH_3-6).

^{13}C NMR ($CDCl_3$): δ = 117.57 (CN), 70.55 (CH-2), 68.95 (CH-6), 68.34 (CH-3), 28.26 (CH_2-5), 27.19 (CH_2-4), 21.13 (CH_3-2), 17.20 (CH_2-2).

MS (ESI): m/z (%) = 139 (100) $[M + 1 - OH]^+$, 143 (13), 178 (9) $[M + Na]^+$.

HRMS (ESI): m/z calcd for $C_8H_{13}NNaO_2$: 178.0844; found: 178.0838.

2-[(2*R*,3*S*,6*R*)-3-Hydroxy-6-methyltetrahydro-2*H*-pyran-2-yl]acetaldehyde (11)

To a solution of **10** (30 mg, 0.19 mmol) in toluene (3 mL) cooled to –78 °C, was added a solution of DIBAL-H (1.0 M in hexane, 0.76 mL, 0.76 mmol) and the mixture was stirred for 2 h. To the solution were added some drops of sat. NH_4Cl and the product was extracted with CH_2Cl_2 (10 mL). The organic layer was dried over Na_2SO_4 and the solvent was evaporated. The residue was purified by chromatography on silica (EtOAc–hexane, 40%), to afford **11**.

Yield: 30 mg (99%); R_f = 0.32 (EtOAc); $[\alpha]_D^{22}$ +11.86 (*c* 1.43, $CHCl_3$).

IR (NaCl): 3421, 2933, 2860, 1724 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 9.77 (m, 1 H, CHO), 4.12 (m, 1 H, CH-2), 3.95 (m, 1 H, CH-6), 3.44 (m, 1 H, CH-3), 2.71 (m, 2 H, CH_2-1′), 1.87 (m, 1 H, CH_2-4), 1.73 (m, 2 H, CH_2-4,5), 1.59 (m, 1 H, CH_2-5), 1.23 (d, J = 6.3 Hz, 3 H, CH_3-6).

^{13}C NMR ($CDCl_3$): δ = 201.08 (COH), 71.03 (CH-2), 69.16 (CH-6), 67.40 (CH-3), 45.81 (CH_2-2), 28.15 (CH_2-5), 27.10 (CH_2-4), 18.45 (CH_3-6).

MS (ESI): m/z (%) = 141 (23), 159 (3) $[M + 1]^+$, 279 (100).

HRMS (ESI): m/z calcd for $C_8H_{15}O_3$: 159.0943; found: 159.1238.

(2*R*,3*S*,6*R*)-2-Allyl-6-methyltetrahydro-2*H*-pyran-3-ol (12)

To a solution of dried phosphonium salt (204 mg, 0.57 mmol) in THF (3 mL) cooled to 0 °C was added, dropwise, *n*-BuLi (2.65 M in hexane, 215 μL, 0.57 mmol) and the solution was stirred for 30 min. To the orange solution was added, dropwise, compound **11** (30 mg, 0.19 mmol) dissolved in THF (3 mL). The mixture was stirred under the same conditions for 1 h, then sat. NH_4Cl (15 mL) was added and the mixture was extracted with EtOAc (3 × 10 mL). The combined organic phases were washed with H_2O (2 × 10 mL) and brine (2 × 10 mL), dried over Na_2SO_4 and the solvent evaporated under reduced pressure. The residue was purified by chromatography on silica gel (EtOAc–hexane, 5%) affording **12**.

Yield: 9 mg (30%); yellow oil; R_f = 0.21 (EtOAc); $[\alpha]_D^{22}$ +15.26 (*c* 0.02, CH_2Cl_2).

IR (NaCl): 3611, 2975, 2938, 1642 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 5.84 (m, 1 H, CH-2′), 5.09 (m, 2 H, CH_2-3′), 3.89 (m, 1 H, CH-4), 3.69 (m, 1 H, CH-2), 3.52 (m, 1 H, CH-1), 2.40 (m, 2 H, CH_2-1′), 1.86 (m, 1 H, CH_2-6), 1.64 (m, 3 H, CH_2-6, CH_2-5), 1.34 (d, J = 6.12 Hz, 3 H, CH_3-4).

^{13}C NMR ($CDCl_3$): δ = 134.76 (CH_2-3′), 116.91 (CH-2′), 76.69 (CH_2-1′), 67.89 (CH_2-6), 66.25 (CH_2-5), 35.32 (CH-2), 29.69 (CH-1), 27.91 (CH-4), 26.34 (CH_3-4).

MS (EI+): m/z (%) = 157 (11) $[M + 1]^+$, 156 (11) $[M]^+$, 83 (56), 81 (61), 71 (57), 69 (100).

HRMS (EI+): m/z calcd for $C_9H_{16}O_2$: 156.1150; found: 156.1166.

1-[(2*R*,3*S*,6*R*)-3-Hydroxy-6-methyltetrahydro-2*H*-pyran-2-yl]propan-2-one (1)

To a solution of **12** (13 mg, 0.08 mmol) in DMF (1.5 mL) and H_2O (125 μL) was added $PdCl_2$ (3 mg, 0.016 mmol) and CuCl (8 mg, 0.08 mmol), and the resulting mixture was stirred at r.t. under an O_2 atmosphere, for 1.5 h. To the solution was added brine (3 mL) and the mixture was extracted with CH_2Cl_2 (3 × 3 mL). The combined organic phases were dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. The residue was purified by chromatography on silica gel (EtOAc–hexane, 10%) affording **1**.

Yield: 13 mg (92%); colourless oil; R_f = 0.66 (EtOAc); $[\alpha]_D^{23}$ +12.50 (*c* 0.01, MeOH).

IR (NaCl): 3627, 3477, 2943, 2838, 1712, 1602 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 3.50 (m, 1 H, CH-2), 3.41 (m, 1 H, CH-6), 3.21 (m, 1 H, CH-3), 2.82 (dd, J = 15.3, 4.4 Hz, 1 H, CH_2-1′), 2.58 (dd, J = 15.5, 7.5 Hz, 1 H, CH_2-1′), 2.17 (s, 3 H, CH_3-3′), 2.03 (m, 1 H, OH), 1.65 (m, 1 H, CH_2-4), 1.25 (m, 3 H, CH_2-5, CH_2-4), 1.08 (d, J = 6.17 Hz, 3 H, CH_3-6).

^{13}C NMR ($CDCl_3$): δ = 208.95 (CO), 78.33 (CH-2), 73.55 (CH-3), 70.23 (CH-6), 47.13 (CH_2-1′), 32.96 (CH_2-5), 32.77 (CH_2-4), 31.00 (CH_3-3′), 21.19 (CH_3-6).

MS (EI+): m/z (%) = 156 (28) $[M - OH]^+$, 143 (100), 105 (66).

HRMS (EI+): m/z calcd for $C_9H_{16}O_2$: 156.0837; found: 156.0841.

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References

(1) Grabley, S.; Hammann, P.; Huetter, K.; Kirsch, R.; Kluge, H.; Thiericke, R.; Mayer, M.; Zeeck, A. *J. Antibiot.* **1992**, *45*, 1176.

(2) (a) Göhrt, A.; Zeeck, A.; Hüetter, K.; Kirsch, R.; Kluge, H.; Thiericke, R. *J. Antibiot.* **1992**, *45*, 66. (b) Mayer, M.; Thiericke, R. *J. Antibiot.* **1993**, *46*, 1372.

(3) (a) Machinaga, N.; Kibayashi, C. *Tetrahedron Lett.* **1993**, *34*, 5739. (b) Clark, J. S.; Whitlock, G. A. *Tetrahedron Lett.* **1994**, *35*, 6381. (c) Nokami, J.; Taniguchi, T.; Ogawa, Y. *Chem. Lett.* **1995**, 43. (d) Solladié, G.; Arce, E.; Bauder, C.; Carreño, M. C. *J. Org. Chem.* **1998**, *63*, 2332. (e) Esumi, T.; Kimura, R.; Mori, M.; Iwabuchi, Y.; Irie, H.; Hatakeyama, S. *Heterocycles* **2000**, *52*, 525. (f) Lukesh, J. M.; Donaldson, W. A. *Tetrahedron: Asymmetry* **2003**, *14*, 757. (g) García, I.; Gómez, G.; Teijeira, M.; Terán, C.; Fall, Y. *Tetrahedron Lett.* **2006**, *47*, 1333. (h) Clark, J. S.; Fessard, T. C.; Whitlock, G. A. *Tetrahedron* **2006**, *62*, 73.

(4) For a recent review on biological and synthetic studies on the decarestrictine family during the last fifteen years, see: Riatto, V. B.; Pilli, R. A.; Victor, M. M. *Tetrahedron* **2008**, *64*, 2279.

(5) Although D-glucal is commercially available, tri-*O*-acetyl-D-glucal is much cheaper and can be used for large-scale synthesis.

(6) Mori, Y.; Hayashi, H. *J. Org. Chem.* **2001**, *66*, 8666.

(7) (a) Hutchins, R. O.; Milewski, C. A.; Maryanoff, B. E. *J. Am. Chem. Soc.* **1973**, *95*, 3662. (b) Davies, M. J.; Moody, C. J. *J. Chem. Soc., Perkin Trans. 1* **1991**, *1*, 9.

(8) Marshall, J. A.; Crooks, S. L.; DeHoff, B. S. *J. Org. Chem.* **1988**, *53*, 1616.

(9) (a) Tsuji, J.; Shiizu, I.; Yamamoto, K. *Tetrahedron Lett.* **1976**, *34*, 2975. (b) Clark, J. S.; Fessard, T. C.; Whitlock, G. A. *Tetrahedron* **2006**, *62*, 73.

(10) For our preliminary results of QSAR studies on decarestrictine L, see: García, I.; Munteanu, C. R.; Fall, Y.; Gómez, G.; Uriarte, E.; Gonzalez-Diaz, H. *Bioorg. Med. Chem.* **2009**, *17*, 165.