Enantioselective Synthesis of (+)-(2*R*,3*S*,6*R*)-Decarestrictine L

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A convergent enantioselective synthesis of (+)-(2*R*,3*S*,6*R*)-decarestrictine L (**1**), a natural inhibitor of cholesterol biosynthesis, is described from commercially available (*S*)-malic acid and (*R*)-isobutyl lactate. The third chiral center was created by stereoselective reduction of a chiral α-hydroxy ketone, and an intramolecular S_N2-type reaction allowed the stereocontrolled formation of the tetrahydropyranyl ring.

Decarestrictine L, first isolated in 1992 in the research laboratories of Hoechst AG[1] from a culture of *Penicillium simplicissimum*, is a minor component of the decarestrictine family, a growing class of natural products with remarkable potential as new inhibitors of cholesterol biosynthesis.[2,3] Its biological activity as an inhibitor of the HMG-CoA reductase, involved in the first steps of the biosynthesis of cholesterol, was demonstrated by ^{13}C- and ^{18}O-labeling experiments.[3a,b] The major components of this family show a 10-membered lactone ring system, while decarestrictine L **1** has a tetrahydropyranic structure (Figure 1).[1,3,4] Some of these compounds share the common feature of a methyl carbinol moiety in the lactone or heterocyclic ring in the *R* configuration and different oxygenated chiral centers. The relative configuration of natural (+)-decarestrictine L was established by NMR,[1] and its absolute configuration (+)-(2*R*,3*S*,6*R*) was later confirmed by Kibayashi,[5] who reported the first total synthesis of the natural isomer.

The macrolactone derivatives of the decarestrictine family have been the subject of major synthetic efforts,[4,6] whereas decarestrictine L has received less attention. To our knowledge, only three total syntheses of this molecule have already been reported. One of them, due to Clark et al.,[7] corresponds to the racemic derivative, and the strategy used for the construction of the heterocyclic ring is based on a tandem intramolecular carbenoid insertion and ylide rearrangement reaction. The enantioselective synthesis reported by Kibayashi[5] stems from the previously known transformation of D-mannitol into 1,2:5,6-diepoxyhexane[8] and the stereoselective formation of the tetrahydropyranyl nucleus through an intramolecular 1,4-conjugate addition. A similar cyclization strategy was used by Nokami,[9] who introduced the methyl carbinol moiety from optically active propylene oxide. Both approaches suffer from low yields in the cyclization step.

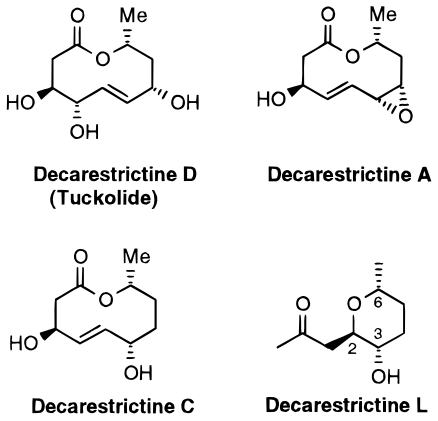

Figure 1.

In connection with our research devoted to asymmetric synthesis of polyhydroxylated natural products,[10] we focused on derivatives bearing a chiral tetrahydropyran moiety, with the aim of finding a general approach to efficiently create the heterocycle from a polyhydroxylated skeleton. We report in this paper an enantioselective and convergent synthesis of the natural isomer of decarestrictine L from commercially available (*S*)-malic acid and (*R*)-isobutyl lactate, using a stereocontrolled intramolecular substitution to generate the tetrahydropyran ring.

As shown in the retrosynthetic approach (Scheme 1), the polyhydroxylated derivative **12** can be considered as a suitable precursor of the tetrahydropyranyl ring by stereoselective intramolecular cyclization between the OH at C-7 and the mesylate at C-3. The synthesis of **12** could be achieved from **7** through a stereoselective

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(6) For a total synthesis of racemic derivatives see ref 4. For more recent asymmetric syntheses see: (a) Nagumo, S.; Suemune, H.; Sakai, K. *Tetrahedron* **1992**, *48*, 8667. (b) Jones, G. B.; Chapman, B. J.; Huber, R. S.; Beaty, R. *Tetrahedron: Asymmetry* **1994**, *5*, 1199. (c) Enders, D.; Plant, A.; Dreckel, K.; Prokopenko, O. F. *Liebigs Ann. Chem*. **1995**, 1127.
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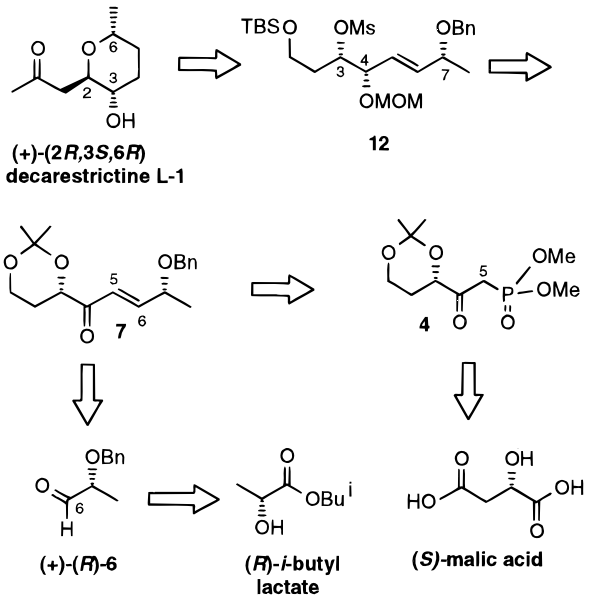
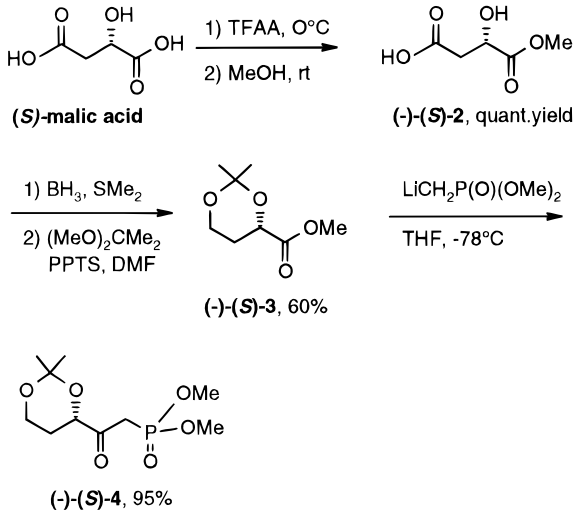
Scheme 1



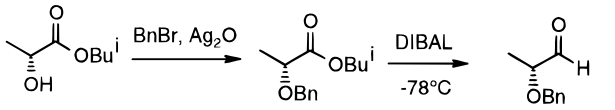
reduction of the α-hydroxy ketone moiety. Finally, the C_5-C_6 disconnection of the keto derivative **7** could give two fragments: the ketophosphonate **4** and the aldehyde **6** that could be assembled by a Horner−Wadsworth−Emmons olefination. The compound **4** could be synthesized from malic acid and the aldehyde **6** from the readily available isobutyl lactate.

Scheme 2



The synthesis of fragment **4** began with transformation of (*S*)-malic acid into the methyl ester **2** in quantitative yield by the known one-pot chemoselective monoesterification with MeOH via the corresponding anhydride made with trifluoroacetic anhydride[11,12] (Scheme 2). The carboxylic acid function was then reduced at low temperature (−15 °C) with borane dimethyl sulfide,[13,14] and

Scheme 3



the resulting crude diol was protected with dimethoxypropane in dimethylformamide.[15] The purification of the corresponding 1,3-acetonide **3** by chromatography on silica gel produced different degradated byproducts. We finally found that addition of Et_3N (1%) to the eluent prevented opening of the acetonide.[16] Under these conditions, compound **3** was isolated pure in 60% yield. Reaction of **3** with lithium dimethyl methylphosphonate[17,18] at −78 °C afforded the β-ketophosphonate **4** in 95% yield. All attempts to purify compound **4** by flash column chromatography were unsuccessful, probably due to the high polarity of this material. Therefore, **4** was employed in the next Horner−Wadsworth−Emmons step without further purification.

On the other hand, the aldehyde **6**, necessary for coupling with fragment **4**, was synthesized from (*R*)-isobutyl lactate, which was first benzylated with Ag_2O[19,20] to get the derivative **5** (85% yield) in enantiomerically pure form (Scheme 3). This benzylation procedure was used instead of the more conventional NaH/BnBr method to avoid the strong racemization that is known[20] to occur under these conditions. DIBAL reduction of the ester group in ether/pentane (1:9) afforded the aldehyde (+)-(*R*)-**6** in 96% isolated yield.

The phosphonate **4** was then coupled, in the presence of 1 equiv of NaH in THF, with the aldehyde **6**, giving **7** in 90% yield (Scheme 4). We noticed that this experimental procedure was very critical since the reaction temperature must be maintained at −40 °C during the addition of the aldehyde to the phosphonate anion, and a slow rate for the addition was required to achieve such excellent yield. Moreover, this reaction was difficult to scale up. After several experiments, we determined that optimal results were obtained when the amount of phosphonate was limited to ∼0.5 g to avoid byproducts and get high yield.

To obtain the *syn*-1,2-diol derivative **8**, a highly diastereoselective reduction of the carbonyl group in compound **7** was required. Treatment of **7** with a variety of reducing agents provided mixtures of *anti* and *syn* isomers. The *anti* derivative was preferentially formed by reducing the carbonyl group of **7** with DIBAL/$ZnBr_2$ (90% yield and 60% de). We finally found that L-Selectride (Aldrich) at −78 °C afforded the *syn* isomer **8**

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(14) The selective reduction of the carboxylic acid function could also be achieved with borane in THF at 0 °C to afford the free 1,3-diol as a colorless oil: $[\alpha]_D = -26$ (*c* 1.56, $CHCl_3$).[12]

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(16) The structure of the byproduct was tentatively assigned as the 2-*O*-(methoxyisopropyl)-2-hydroxy-γ-lactone on the base of its ^1H NMR spectrum.

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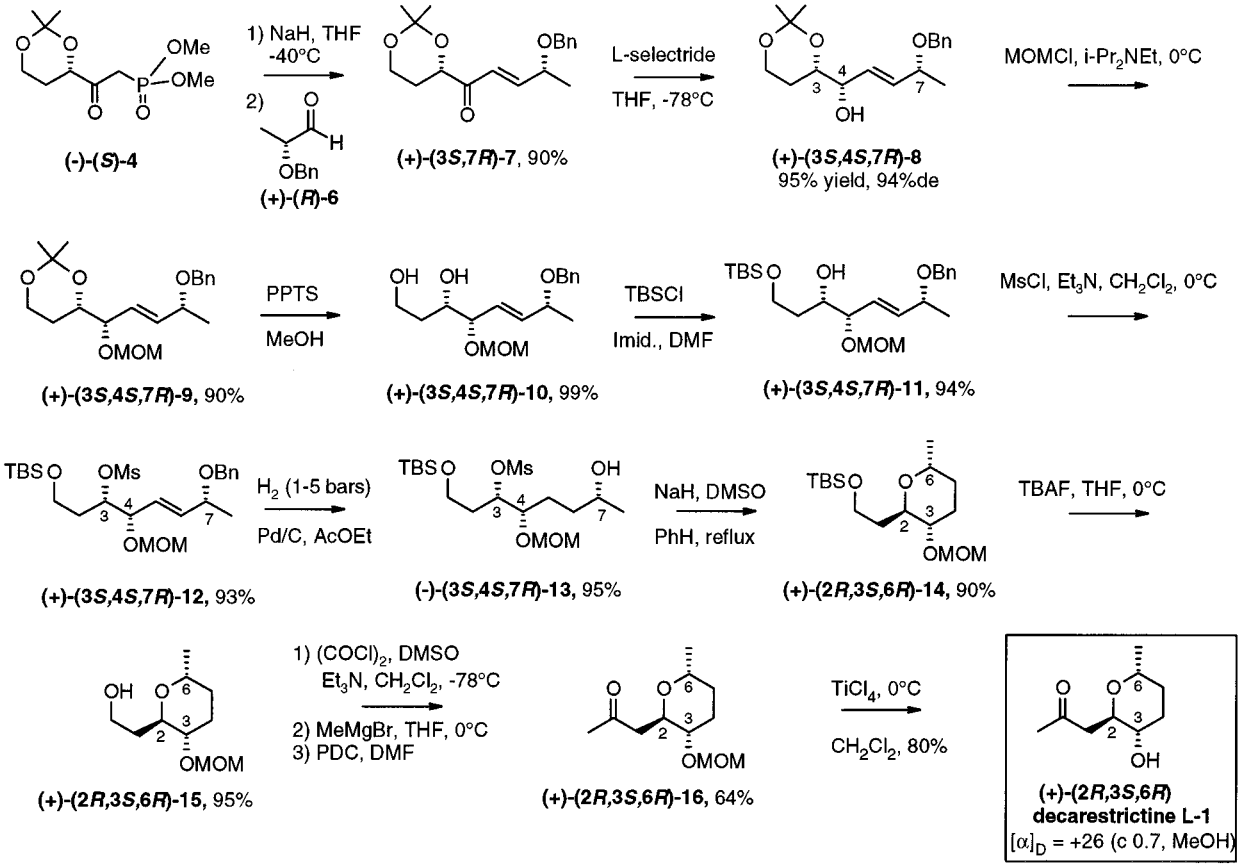
Scheme 4



in 95% yield in a highly diastereoslective manner (>97:3). A similar diastereoselectivity with this reagent was reported by Nicolaou in the synthesis of the polyhydroxylated chain of amphotericin B[18a] and in the synthesis of sphingosine.[18b] Our results could be explained on the basis of the Felkin−Anh model assuming a favored approach of the reducing agent from the less hindered face in a conformation of **7** in which the vicinal oxygen is perpendicular to the plane of the carbonyl group. The relative and absolute configurations of compound **8** were further confirmed by chemical correlation with natural decarestrictine L.

Once the stereogenic center at C-4 was generated, the next few steps for the transformation of compound **8** into the mesylate **13** (Scheme 4) involved the selective and differential protection of the hydroxy groups: protection of the OH at C-4 with MOMCl/*i*-Pr_2NEt, cleavage of the acetonide with PPTS/MeOH, selective protection of the primary terminal OH with TBDMSCl/imidazole, and finally mesylation of the OH at C-3 to introduce the adequate leaving group for the cyclization. These four steps occurred with an overall yield of 78%. Debenzylation and reduction of the double bond of **12** were accomplished in a single step by hydrogenation over palladium on charcoal (8 h at 1 bar to reduce the double bond and then 10 h at 5 bars for the debenzylation step) to obtain the compound **13** in 95% overall yield. This sequential procedure is critical; the debenzylation has to be done after reducing the double bond to avoid the formation of degradated products of the allylic alcohol in the reduction conditions.

The cyclization step to form the pyran ring was carried out under standard conditions[21] with NaH in refluxing benzene. This reaction gave compound **14** in 90% yield with complete inversion of configuration at C-3.

After deprotection of the silylated group in **14**, the primary hydroxy group of **15** was submitted to Swern oxidation to obtain the corresponding aldehyde that, without purification, was reacted with methylmagnesium bromide. The resulting secondary carbinol was oxidized with PDC in DMF to the methyl ketone **16** with an overall yield of 61% from **14**.

Deprotection of the MOM group was not as straightforward as we could expect due to the C-2 epimerization observed in the presence of HCl. After several experiments we could obtain (+)-(2*R*,3*S*,6*R*)-decarestrictine L (**1**) without epimerization by treating the MOM derivative **16** with $TiCl_4$ in CH_2Cl_2 at 0 °C.[22] The resulting decarestrictine L was isolated in 80% yield and was shown to have all the characteristics described in the literature for the natural product.[1] The fact that the natural enantiomer was obtained confirmed the configurational assignment of all the precursors and that of the compound **8** obtained by stereoselective reduction of the ketone **7**.

Conclusion

We have reported an alternative source of decarestrictine L (**1**) from readily available and inexpensive starting materials, (*S*)-malic acid and (*R*)-isobutyl lactate, in a 28% overall yield. An interesting stereochemical feature was the preparation of the intermediate (3*S*,4*S*,7*R*)-**8**

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using the highly diastereoselective L-Selectride reduction of the α-hydroxy ketone **7**.

Experimental Section

Methyl (−)-(*S*)-2,4-*O*-Isopropylidene-2,4-dihydroxybutanoate (3). BH_3·Me_2S 97% (6.42 mL, 67.8 mmol) was added dropwise to a solution of (−)-(*S*)-methyl malate[11,12] **2** (5 g, 33.9 mmol) in 100 mL of dry THF at −15 °C under argon. The mixture was allowed to warm to room temperature and stirred for 24 h. The reaction was cautiously hydrolyzed by dropwise addition of 20 mL of H_2O and concentrated. The residue was diluted with AcOEt and filtered. The solid was washed with AcOEt, and the organic phases were combined and concentrated in vacuo to give the diol precursor of **3**, which was used in the next step without further purification: ^{1}H NMR ($CDCl_3$) δ 4.66 (dd, J = 6.7, 4.5 Hz, 1H), 4.03 (t, J = 5.6 Hz, 2H), 3.80 (s, 3H), 2.24 (m, 1H), 2.04 (m, 1H).

The crude diol (4.5 g, 33.9 mmol) was dissolved in 50 mL of dry DMF and 150 mL of 2,2-dimethoxypropane, and PPTS (375 mg, 1.5 mmol) was added. The mixture was stirred for 24 h at room temperature and washed with saturated aqueous $NaHCO_3$, extracted with $CHCl_3$, dried over $MgSO_4$, and evaporated. The excess of DMF was eliminated by azeotropic distillation with diethyl ether. Chromatography (hexane/AcOEt 75:25 + 1% Et_3N) yielded, after washing with saturated NH_4Cl, 3.9 g (60%) of **3** as a yellow oil: $[\alpha]^{20}_D$ = −17.0 (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 4.52 (m, 1H), 3.95 (m, 2H), 3.76 (s, 3H), 2.03−1.74 (m, 2H), 1.48 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 171.0, 98.7, 68.3, 59.1, 51.9, 29.2, 27.2, 19.7; IR ($CHCl_3$) 3150, 2940, 2860, 2300, 1730, 1635. Anal. Calcd for $C_8H_{14}O_4$: C, 55.16; H, 8.10. Found: C, 55.54; H, 7.88.

(−)-(*S*)-3,5-*O*-Isopropylidene-1-(dimethoxyphosphonyl)-3,5-dihydroxypentan-2-one (4). A solution of *n*-BuLi (1.6 M in hexane, 13.1 mL, 21 mmol) was added to dimethyl methylphosphonate (2.27 mL, 21 mmol) dissolved in 40 mL of dry THF and stirred at −78 °C for 15 min. A solution of **3** (1.75 g, 10 mmol) in 30 mL of dry THF was added dropwise and stirred for 3 h at −78 °C. The mixture was quenched with saturated aqueous NH_4Cl, extracted with AcOEt, washed with saturated aqueous NaCl, and dried over $MgSO_4$, and the solvent was evaporated to give 2.53 g (95%) of **4** as a yellow oil. The product was used without further purification: $[\alpha]^{20}_D$ = −50.0 (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 4.37 (m, 1H), 3.90 (m, 2H), 3.77 (d, J_{H-P} = 11.4 Hz, 6H), 3.47 (dd, J = 22.7 and 14.2 Hz, 1H), 3.15 (dd, J = 22.0 and 14.2 Hz, 1H), 1.73 (m, 2H), 1.46 (s, 3H), 1.43 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 201.8, 99.0, 73.9, 59.4, 52.9, 52.7, 35.4, 29.5, 26.4, 18.8; IR ($CHCl_3$) 3000, 2950, 2870, 2850, 1725, 1390. Anal. Calcd for $C_{10}H_{19}O_6P$: C, 45.11; H, 7.19. Found: C, 44.88; H, 7.08.

Isobutyl (+)-(*R*)-2-(Benzyloxy)propionate (5). Ag_2O (11.6 g, 50 mmol) was added to a mixture of (*R*)-isobutyl lactate (7.5 mL, 50 mmol) and BnBr (6.6 mL, 55 mmol) in 75 mL of dry Et_2O. The suspension was refluxed overnight, filtered, and concentrated. The crude product was purified by chromatography (hexane/Et_2O 90:10) to give 8.8 g (85%) of **5** as a colorless oil: $[\alpha]^{20}_D$ = +84.5 (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.35 (m, 5H), 4.72 and 4.45 (AB syst, J = 11.5 Hz, $\Delta\nu$ = 52 Hz, 2H), 4.07 (q, J = 6.8 Hz, 1H), 3.95 (dd, J = 6.7 and 2.4 Hz, 2H), 1.97 (m, 1H), 1.45 (d, J = 6.8 Hz, 3H), 0.95 (d, J = 6.7 Hz, 6H); ^{13}C NMR ($CDCl_3$) δ 173.4, 136.7, 128.4 × 2, 127.9 × 2, 127.8, 74.0, 71.9, 70.8, 27.7, 19.0, 18.8; IR ($CHCl_3$) 3000, 1740, 1520, 1425. Anal. Calcd for $C_{14}H_{20}O_3$: C, 71.14; H, 8.54. Found: C, 71.04; H, 8.46.

(+)-(*R*)-2-(Benzyloxy)propanal (6). A solution of DIBAL (1 M in hexane, 67 mL, 67 mmol) was dropwise added to ester **5** (11.8 g, 50 mmol) dissolved in 300 mL of a mixture of Et_2O/pentane 1/9 at −78 °C. After the solution was stirred for 30 min, 30 mL of MeOH and 150 mL of saturated aqueous sodium tartrate were added, and the organic phase was diluted with 150 mL of AcOEt. The mixture was stirred for 30−40 min at 0 °C and evaporated. The residue was dissolved in AcOEt, and saturated aqueous sodium tartrate was added. The mixture was stirred for 30 min, extracted with AcOEt, dried over $MgSO_4$, and concentrated in vacuo. The crude product was purified by chromatography (hexane/Et_2O 80:20) to give 7.88 g (96%) of **6** as a colorless oil: $[\alpha]^{20}_D$ = +38.5 (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 9.67 (d, J = 1.8 Hz, 1H), 7.34 (m, 5H), 4.67 and 4.59 (AB syst, J = 12.0 Hz, $\Delta\nu$ = 10 Hz, 2H), 3.89 (dq, J = 7.0, 1.8 Hz, 1H), 1.34 (d, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 200.0, 137.0, 128.5 × 2, 128.0 × 3, 75.5, 72.0, 15.0; IR ($CHCl_3$) 1720. Anal. Calcd for $C_{10}H_{12}O_2$: C, 73.14; H, 7.36. Found: C, 72.87; H, 7.64.

(+)-(3*S*,7*R*)-7-*O*-Benzyl 1,3-*O*-Isopropylidene-1,3,7-trihydroxy-5-octen-4-one (7). A solution of phosphonate **4** (583 mg, 2.19 mmol) in 30 mL of dry THF was added to a suspension of NaH (53 mg, 2.19 mmol) in 30 mL of dry THF at −40 °C, and the mixture was stirred for 40 min. A solution of aldehyde **6** (300 mg, 1.83 mmol) in 50 mL of dry THF was added dropwise for 1 h, and the temperature was allowed to rise to room temperature. After the mixture was stirred for 20 h, 30 mL of saturated aqueous NH_4Cl was added, the resulting mixture was extracted with Et_2O, washed with saturated aqueous NaCl, and dried over $MgSO_4$, and the solvent was evaporated. The product was purified by chromatography (hexane/Et_2O 75:25) to give 500 mg (90%) of **7** as a colorless liquid: $[\alpha]^{20}_D$ = +7.0 (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.32 (m, 5H), 6.95 (dd, J = 15.8, 5.6 Hz, 1H), 6.74 (dd, J = 15.8, 1.0 Hz, 1H), 4.50 (m, 3H), 4.20−3.86 (m, 3H), 1.75 (m, 2H), 1.49 (s, 3H), 1.48 (s, 3H), 1.33 (d, J = 6.5 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 197.9, 149.1, 138.1, 128.3 × 2, 127.6 × 3, 123.4, 98.6, 74.2, 73.9, 70.7, 59.4, 29.5, 27.1, 20.5, 19.0; IR ($CHCl_3$) 3020, 1675, 1620, 1210.

(+)-(3*S*,4*S*,7*R*)-7-*O*-Benzyl-1,3-*O*-isopropylidene-1,3,4,7-tetrol-5-octene (8). To a solution of **7** (3 g, 10 mmol) in 150 mL of dry THF was added a suspension of L-Selectride (1 M in THF, 19.8 mL, 19.8 mmol) at −78 °C. The mixture was stirred for 1 h, quenched with saturated aqueous NH_4Cl (150 mL), and extracted with Et_2O and the solvent evaporated. The residue was dissolved in AcOEt and washed with a 5% solution of H_2O_2 for 2 h. The organic phase was washed with H_2O and dried over $MgSO_4$ and the solvent evaporated to give 2.88 g (95%) of **8** as a colorless liquid. The product was used without further purification, but a sample was purified by chromatography (Et_2O/hexane 50:50) for analysis: $[\alpha]^{20}_D$ = +32.0 (*c* 1, $CHCl_3$); ^{1}H NMR (C_6D_6) δ 7.37−7.05 (m, 5H), 5.80 (dd, J = 15.7, 7.0 Hz, 1H), 5.57 (dd, J = 15.7, 7.0 Hz, 1H), 4.54 and 4.33 (AB syst, J = 12.0 Hz, $\Delta\nu$ = 42 Hz, 2H), 3.92 (t, J = 6.0 Hz, 1H), 3.83 (qn, J = 6.5 Hz, 1H), 3.53 (m, 3H), 2.65 (br s, 1H), 1.40 (s, 3H), 1.24 (d, J = 6.5 Hz, 3H), 1.20 (s, 3H), 0.90 (m, 2H); ^{13}C NMR (C_6D_6) δ 139.8, 135.3, 130.2, 127.8 × 5, 98.7, 75.2 × 2, 72.5, 70.1, 59.2, 30.0, 27.2, 21.8, 19.3; IR ($CHCl_3$) 3560, 2950, 2870, 1715, 1515. Anal. Calcd for $C_{18}H_{26}O_4$: C, 70.56; H, 8.55. Found: C, 70.20; H, 8.34.

(+)-(3*S*,4*S*,7*R*)-7-*O*-Benzyl-1,3-*O*-Isopropylidene-4-*O*-(methoxymethyl)-1,3,4,7-tetrol-5-octene (9). To a solution of **8** (1.53 g, 5 mmol) in 75 mL of dry CH_2Cl_2 at 0 °C were added *i*-Pr_2NEt (8.6 mL, 50 mmol) and MOMCl (2.5 mL, 50 mmol). After the mixture was stirred at room temperature for 10 h, a saturated aqueous $NaHCO_3$ solution was added. The resulting mixture was extracted with CH_2Cl_2, washed with saturated aqueous NaCl, and dried over $MgSO_4$ and the solvent evaporated. Chromatography (hexane/Et_2O 65:35) gave 1.58 g (90%) of **9** as a colorless oil: $[\alpha]^{20}_D$ = +61.0 (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.31 (m, 5H), 5.72 (dd, J = 15.8, 6.8 Hz, 1H), 5.57 (dd, J = 15.8, 6.6 Hz, 1H), 4.72 and 4.64 (AB syst, J = 6.7 Hz, $\Delta\nu$ = 13 Hz, 2H), 4.57 and 4.38 (AB syst, J = 12.0 Hz, $\Delta\nu$= 36 Hz, 2H), 4.04−3.83 (m, 5H), 3.40 (s, 3H), 1.70 (m, 2H), 1.46 (s, 3H), 1.39 (s, 3H), 1.28 (d, J = 6.5 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 138.6, 136.8, 128.3, 127.7, 127.6 × 2, 127.4 × 2, 98.3, 94.3, 78.5, 75.0, 71.0, 70.0, 59.6, 55.3, 29.8, 27.0, 21.6, 19.2; IR ($CHCl_3$) 2990, 2400, 1720, 1450, 1385, 1375. Anal. Calcd for $C_{20}H_{30}O_5$: C, 68.54; H, 8.62. Found: C, 68.26; H, 8.42.

(+)-(3*S*,4*S*,7*R*)-7-*O*-Benzyl-4-*O*-(methoxymethyl)-1,3,4,7-tetrol-5-octene (10). To a solution of **9** (1.76 g, 5 mmol) in 300 mL of dry MeOH was added PPTS (630 mg, 2.53 mmol). The solution was stirred at room temperature for 3 h and neutralized with saturated aqueous $NaHCO_3$ and the solvent

evaporated. The residue was dissolved in CH_2Cl_2 (100 mL) and H_2O (100 mL), extracted with CH_2Cl_2, and dried over $MgSO_4$ and the solvent evaporated to give 1.53 g (99%) of **10** as a colorless oil. The product was used without further purification, but a sample was purified by chromatography (hexane/Et_2O 8:92) for analysis: $[\alpha]^{20}_D = +72.0$ (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.30 (m, 5H), 5.73 (dd, J = 15.8 and 7.0 Hz, 1H), 5.51 (dd, J = 15.8 and 7.6 Hz, 1H), 4.74 and 4.60 (AB syst, J = 6.7 Hz, $\Delta\nu$ = 27 Hz, 2H), 4.54 and 4.38 (AB syst, J = 11.8 Hz, $\Delta\nu$ = 31 Hz, 2H), 3.88 (m, 5H), 3.38 (s, 3H), 3.10 (br s, 2H), 1.68 (m, 2H), 1.27 (d, J = 6.4 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 138.3, 138.0, 128.3, 127.7, 127.5 × 2, 127.4 × 2, 94.0, 80.4, 74.8, 73.1, 70.1, 60.7, 55.6, 34.3, 21.3; IR ($CHCl_3$) 2990, 2880, 1710, 1520, 1420. Anal. Calcd for $C_{17}H_{26}O_5$: C, 65.78; H, 8.44. Found: C, 65.33; H, 8.57.

(+)-(3*S*,4*S*,7*R*)-7-*O*-Benzyl-1-*O*-(*tert*-butyldimethylsilyl)-4-*O*-(methoxymethyl)-1,3,4,7-tetrol-5-octene (11). To a solution of **10** (1.56 g, 5 mmol) in 50 mL of dry DMF were added TBDMSCl (910 mg, 6 mmol) and imidazole (823 mg, 12 mmol). After being stirred at room temperature for 4 h, the mixture was quenched with H_2O (30 mL) and Et_2O (75 mL), extracted with Et_2O, washed with saturated aqueous NH_4Cl and saturated aqueous NaCl, and dried over $MgSO_4$ and the solvent evaporated. Chromatography (hexane/Et_2O 60:40) yielded 2.0 g (94%) of **11** as a colorless oil: $[\alpha]^{20}_D = +63.0$ (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.31 (m, 5H), 5.65 (ddd, J = 15.7, 7.2, 6.8 Hz, 2H), 4.76 and 4.62 (AB syst, J = 6.6 Hz, $\Delta\nu$ = 28 Hz, 2H), 4.57 and 4.38 (AB syst, J = 11.8 Hz, $\Delta\nu$ = 36 Hz, 2H), 3.89 (m, 5H), 3.40 (s, 3H), 3.18 (br s, 1H), 1.68 (m, 2H), 1.28 (d, J = 6.5 Hz, 3H), 0.89 (s, 9H), 0.07 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 138.6, 137.4, 128.4, 128.3, 127.6 × 2, 127.4 × 2, 94.0, 80.0, 75.0, 72.3, 70.1, 61.1, 55.6, 35.0, 25.9 × 3, 21.5, 18.2, −5.5 × 2; IR ($CHCl_3$) 3590, 3480, 3000, 2950, 1720, 1610. Anal. Calcd for $C_{23}H_{40}O_5Si$: C, 65.05; H, 9.49. Found: C, 65.20; H, 9.42.

(+)-(3*S*,4*S*,7*R*)-7-*O*-Benzyl-1-*O*-(*tert*-butyldimethylsilyl)-3-*O*-(methanesulfonyl)-4-*O*-(methoxymethyl)-1,3,4,7-tetrol-5-octene (12). Triethylamine (13.8 mL, 100 mmol) was added to a solution of **11** (2.13 g, 5 mmol) in 100 mL of dry CH_2Cl_2 at 0 °C. After 15 min, MsCl (3.88 mL, 50 mmol) was added. The mixture was stirred for 40 min at 0 °C, quenched with saturated aqueous NH_4Cl (75 mL), extracted with CH_2Cl_2, washed with saturated aqueous NaCl, and dried over $MgSO_4$ and the solvent evaporated. Chromatography (hexane/Et_2O 65:35) yielded 2.34 g (93%) of **12** as a colorless oil: $[\alpha]^{20}_D = +30.0$ (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.32 (m, 5H), 5.87−5.52 (m, 2H), 4.85 (m, 1H), 4.73 and 4.61 (AB syst, J = 6.6 Hz, $\Delta\nu$ = 22 Hz, 2H), 4.56 and 4.39 (AB syst, J = 11.8 Hz, $\Delta\nu$ = 32 Hz, 2H), 4.32 (t, J = 6.8 Hz, 1H), 4.00 (qn, J = 6.5 Hz, 1H), 3.75 (m, 2H), 3.39 (s, 3H), 3.06 (s, 3H), 2.09−1.76 (m, 2H), 1.29 (d, J = 6.5 Hz, 3H), 0.89 (s, 9H), 0.06 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 138.5 × 2, 128.3 × 2, 127.5 × 2, 127.4, 126.3, 94.1, 80.7, 76.5, 74.7, 70.1, 58.2, 55.7, 38.1, 33.5, 25.7 × 3, 21.3, 18.1, −5.5 × 2; IR ($CHCl_3$) 3000, 2950, 2400, 1715, 1440, 1360. Anal. Calcd for $C_{24}H_{42}O_7SSi$: C, 57.34; H, 8.42. Found: C, 57.58; H, 8.34.

(−)-(3*S*,4*S*,7*R*)-1-*O*-(*tert*-Butyldimethylsilyl)-3-*O*-(methanesulfonyl)-4-*O*-(methoxymethyl)-1,3,4,7-tetrahydroxyoctane (13). To a solution of **12** (620 mg, 1.2 mmol) in 30 mL of AcOEt was added Pd/C 10% (10% weight), and the mixture was stirred for 8 h under 1−2 bars of hydrogen pressure and then overnight under 5 bars. The suspension was filtered on Celite and washed with AcOEt and the solvent evaporated. Chromatography (hexane/Et_2O 40:60) yielded 475 mg (95%) of **13** as a colorless oil: $[\alpha]^{20}_D = -30.0$ (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 4.92 (m, 1H), 4.69 and 4.65 (AB syst, J = 6.9 Hz, $\Delta\nu$ = 6 Hz, 2H), 3.76 (m, 4H), 3.38 (s, 3H), 3.04 (s, 3H), 2.05−1.48 (m, 6H), 1.18 (d, J = 6.2 Hz, 3H), 0.88 (s, 9H), 0.05 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 96.9, 79.7, 78.1, 67.4, 58.3, 56.0, 38.0, 34.5, 32.2, 25.8 × 3, 25.4, 23.5, 18.1, −5.5 × 2; IR ($CHCl_3$) 3680, 3620, 2940, 2920, 2390, 1460. Anal. Calcd for $C_{17}H_{38}O_7SSi$: C, 49.24; H, 9.24. Found: C, 49.37; H, 9.04.

(+)-(2*R*,3*S*,6*R*)-3-*O*-[(Methoxymethyl)oxy]-6-methyl-2-[2-*O*-(*tert*-butyldimethylsilyl)-2-hydroxyethyl]tetrahydropyran (14). To a solution of **13** (500 mg, 1.2 mmol) in 60 mL of benzene were added NaH (50 mg) and dry DMSO (5−6 drops). After the mixture was stirred at reflux overnight, saturated aqueous NH_4Cl (15 mL) was added. The mixture was extracted with Et_2O, washed with saturated aqueous NaCl, dried over $MgSO_4$, and concentrated in vacuo to give 344 mg (90%) of **14** as a colorless oil. The product was used without further purification, but a sample was purified by chromatography (hexane/Et_2O 85:15) for analysis: $[\alpha]^{20}_D = +25.0$ (*c* 1, $CHCl_3$); ^{1}H NMR (C_6D_6) δ 4.58 and 4.53 (AB syst, J = 6.9 Hz, $\Delta\nu$ = 6 Hz, 2H), 4.03 (dt, J = 9.1, 4.8 Hz, 1H), 3.80 (m, 2H), 3.68 (ddq, J = 10.4, 6.4, 4.1 Hz, 1H), 3.32 (q, J = 5.0 Hz, 1H), 3.20 (s, 3H), 1.82 (m, 2H), 1.68−1.29 (m, 4H), 1.10 (d, J = 6.4 Hz, 3H), 1.00 (s, 9H), 0.11 (s, 3H), 0.10 (s, 3H); ^{13}C NMR (C_6D_6) δ 95.1, 74.5, 70.9, 66.1, 60.1, 55.1, 34.4, 28.6, 26.2 × 3, 25.0, 19.7, 18.6, −5.2 × 2; IR ($CHCl_3$) 3000, 2950, 2930, 2860, 1515, 1470. Anal. Calcd for $C_{16}H_{34}O_4Si$: C, 60.33; H, 10.76. Found: C, 60.19; H, 10.77.

(+)-(2*R*,3*S*,6*R*)-3-*O*-[(Methoxymethyl)oxy]-6-methyl-2-(2-hydroxyethyl)tetrahydropyran (15). To a solution of **14** (375 mg, 1.2 mmol) in 30 mL of dry THF at 0 °C under argon was added TBAF 1 M in THF (1.8 mL, 1.8 mmol), and the reaction was stirred at 0 °C for 4 h. SiO_2 (1 g) was added, and the mixture was stirred for 30 min. The solvent was removed and the product adsorbed on silica gel was chromatographed (hexane/Et_2O 20:80) to give 235 mg (95%) of **15** as a yellow oil: $[\alpha]^{20}_D = +44.5$ (*c* 1, $CHCl_3$); ^{1}H NMR (C_6D_6) δ 4.54 and 4.48 (AB syst, J = 6.8 Hz, $\Delta\nu$ = 10 Hz, 2H), 3.91 (ddd, J = 9.1, 5.1, 4.4 Hz, 1H), 3.76 (m, 2H), 3.63 (ddq, J = 10.7, 6.4, 4.6 Hz, 1H), 3.24 (dt, J = 5.6, 5.1 Hz, 1H), 3.17 (s, 3H), 3.13 (br s, 1H), 1.75 (m, 2H), 1.57 (m, 2H), 1.33 (m, 2H), 1.02 (d, J = 6.4 Hz, 3H); ^{13}C NMR (C_6D_6) δ 95.0, 74.4, 73.2, 66.6, 60.5, 55.2, 33.6, 28.4, 24.8, 19.2; IR ($CHCl_3$) 3620, 3490, 2940, 2400, 1525, 1425. Anal. Calcd for $C_{10}H_{20}O_4$: C, 58.80; H, 9.87. Found: C, 58.45; H, 9.56.

(+)-(2*R*,3*S*,6*R*)-3-[(Methoxymethyl)oxy]-6-methyl-2-(2-oxopropyl)tetrahydropyran (16). To a solution of oxalyl chloride (210 μL, 2.45 mmol) in 8 mL of dry CH_2Cl_2 at −78 °C under argon was added DMSO (315 μL, 4.40 mmol). The mixture was stirred for 1 h at −78 °C, and a solution of **15** (200 mg, 0.98 mmol) in 6 mL of dry CH_2Cl_2 was cannulated. After 3 h at −78 °C, Et_3N (890 mL, 6.36 mmol) was added, and the reaction was allowed to warm to room temperature. The mixture was quenched with saturated aqueous NH_4Cl (10 mL), neutralized with HCl 10% until pH = 6, extracted with CH_2Cl_2, washed with saturated aqueous NaCl, dried over $MgSO_4$, and concentrated in vacuo. The residue was triturated with Et_2O and filtered to give 200 mg (100%) of the corresponding aldehyde as a yellow oil. The product was used without further purification: ^{1}H NMR (C_6D_6) δ 9.53 (dd, J = 3.1, 1.9 Hz, 1H), 4.47 and 4.38 (AB syst, J = 6.8 Hz, $\Delta\nu$ = 10 Hz, 2H), 4.08 (ddd, J = 8.3, 6.6, 5.0 Hz, 1H), 3.64 (m, 1H), 3.12 (s, 3H), 3.06 (m, 1H), 2.43−2.17 (m, 2H), 1.60−1.18 (m, 4H), 0.97 (d, J = 6.5 Hz, 3H); ^{13}C NMR (C_6D_6) δ 199.6, 95.0, 74.5, 69.3, 67.2, 55.2, 46.0, 28.4, 24.7, 18.2. To a solution of this aldehyde (0.98 mmol) in 8 mL of dry THF at 0 °C under argon was added MeMgBr (3 M in Et_2O, 590 μL, 1.76 mmol). After the mixture was stirred for 4 h, saturated aqueous NH_4Cl (8 mL) was added, extracted with CH_2Cl_2, dried over $MgSO_4$, and concentrated in vacuo. The residue was dissolved in 15 mL of DMF, and PDC (1.84 g, 4.89 mmol) was added at room temperature. After 5 h, the mixture was quenched with Et_2O (20 mL) and H_2O (15 mL). The aqueous layer was saturated with NaCl before extraction with Et_2O. The combined organic layers were dried over $MgSO_4$ and evaporated. Chromatography (hexane/Et_2O 50:50) yielded 135 mg (64%) of **16** as a colorless oil: $[\alpha]^{20}_D = +43.0$ (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 4.72 and 4.63 (AB syst, J = 6.8 Hz, $\Delta\nu$ = 15 Hz, 2H), 4.16 (dt, J = 7.7, 5.9 Hz, 1H), 3.85 (m, 1H), 3.37 (s, 3H), 3.34 (m, 1H), 2.68 (m, 2H), 2.19 (s, 3H), 1.96−1.51 (m, 4H) and 1.21 (d, J = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 206.8, 94.7, 73.5, 70.5, 67.2, 55.4, 45.8, 30.1, 28.0, 24.1, 18.6; IR ($CHCl_3$) 3010, 2970, 2940, 2400, 1720, 1525, 1425.

(+)-(2*R*,3*S*,6*R*)-6-Methyl-2-(2-oxopropyl)tetrahydropyran-3-ol [Decarestrictine L (1)]. To a solution of **16** (100 mg, 0.46 mmol) in 15 mL of dry CH_2Cl_2 under argon at 0 °C

was added $TiCl_4$ (1 M in CH_2Cl_2, 2.8 mL, 2.77 mmol). The mixture was stirred for 30 min, hydrolyzed with saturated aqueous $NaHCO_3$ (8 mL) until pH = 7, extracted with CH_2Cl_2, and dried over $MgSO_4$. Evaporation and chromatography ($CHCl_3$/MeOH 92:8) yielded 64 mg (80%) of **1** as a colorless oil: $[\alpha]^{20}_D = +26.0$ (*c* 0.7, MeOH) [lit.[1] $[\alpha]^{20}_D = +21.8$ (*c* 0.5, MeOH)]; ^{1}H NMR ($CDCl_3$) δ 4.01 (q, $J = 6.5$ Hz, 1H), 3.95 (m, 1H), 3.40 (m, 1H), 2.73 (d, $J = 6.5$ Hz, 2H), 2.21 (s, 3H), 2.12 (br s, 1H), 1.92−1.50 (m, 4H), 1.22 (d, $J = 6.5$ Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 207.6, 72.0, 69.3, 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, 62.69; H, 9.38.

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