A Stereoselective Total Synthesis of Decarestrictine I

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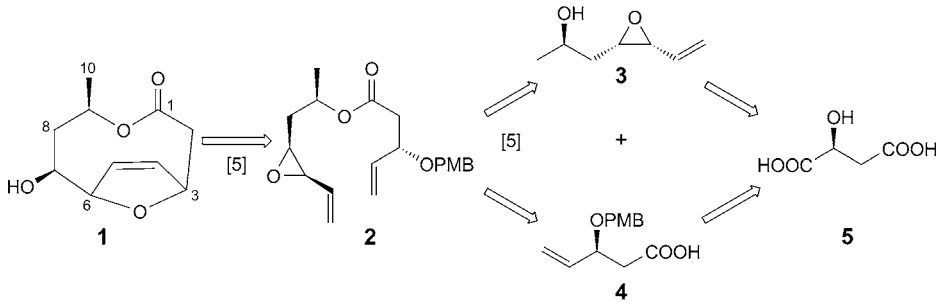
A convergent and stereoselective total synthesis of decarestrictine I, a polyketide natural product, is described. Both acid and alcohol fragments were prepared from the readily available L-malic acid *via Still–Gennari* olefination and *Sharpless* asymmetric epoxidation. The *Steglich* esterification and ring-closing metathesis (RCM) are employed to combine both acid and alcohol fragments.

Introduction. – Decanolides are a very important class of compounds in the decarestrictine family. The decarestrictines were isolated from various *Penicillium* strains [1] and identified as bioactive compounds by virtual screening. Several members of the decarestrictine family of natural products were found to inhibit the biosynthesis of cholesterol in HEP-G2 liver cells [2][3]. Among them, decarestrictine I (**1**) possesses unique structural features such as a ten-membered lactone fused with a dihydrofuran ring comprising a (*Z*)-configured C=C bond. Recent reports illustrated its total synthesis [4][5]. Due to its fascinating structural features and biological importance, we were interested to take up its total synthesis too. Our strategy relies on *Still–Gennari* olefination, *Sharpless* asymmetric epoxidation, *Steglich* esterification, ring-closing metathesis, and an intramolecular epoxide ring-opening sequence as key steps to accomplish the total synthesis of **1**.

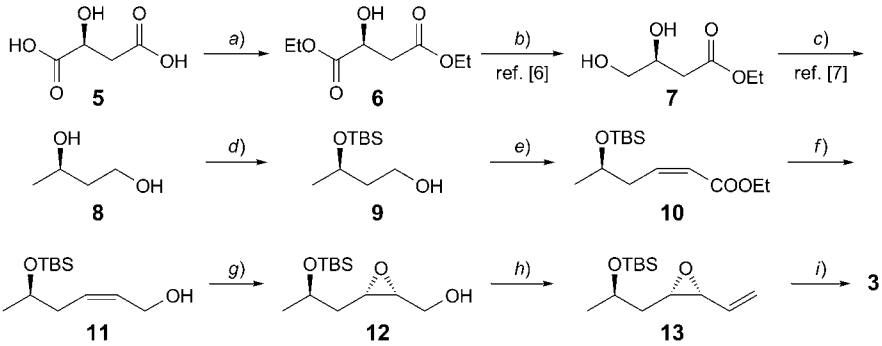
Results and Discussion. – The retrosynthetic analysis (*Scheme 1*) reveals that the target molecule **1** could be obtained by ring-closing metathesis of the diene **2** followed by epoxide ring opening. The diene ester **2** in turn could be prepared by esterification of acid **4** with alcohol **3**. Though our retrosynthetic analysis is analogous to the earlier approach [5], the key fragments **3** and **4** were prepared from a common precursor, L-malic acid, whereas, in the previous synthesis, both **3** and **4** were synthesized *via* the kinetic resolution of an epoxide, wherein half of the epoxide could not be used for the synthesis.

We initiated the synthesis of alcohol fragment **3** (*Scheme 2*) from commercially available L-malic acid (**5**). Accordingly, the esterification of **5**, followed by reduction of the diester **6** [6] with $NaBH_4$, $BH_3 \cdot SMe_2$ afforded the dihydroxy ester **7** in 74% yield over two steps. Chemoselective mono-tosylation of **7**, followed by reduction of the *p*-toluenesulfonate with $LiAlH_4$ afforded the 1,3-diol **8** [7] in 82% yield. (*tert*-Butyl)(dimethyl)silyl (TBS) protection of **8** with TBSCl and 1*H*-imidazole furnished the disilyl ether in 90% yield, which, upon selective removal of the primary silyl ether

Scheme 1. *Retrosynthetic Analysis of Decarestrictine I* (**1**)



Scheme 2

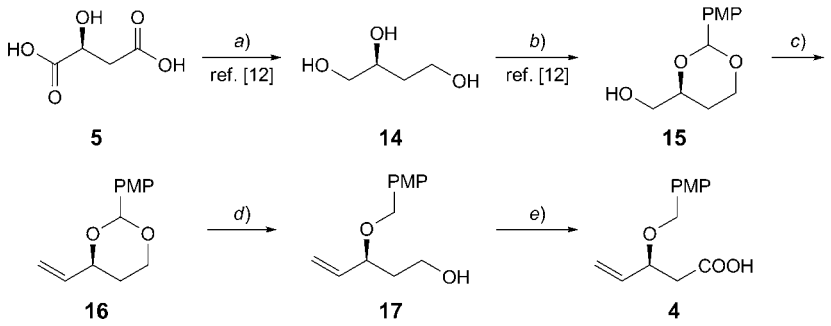


a) EtOH, cat. H_2SO_4, reflux, 18 h; 80%. *b*) $BH_3 \cdot SMe_2$, $NaBH_4$, THF, r.t., 90 min; 92%. *c*) 1. TsCl, Et_3N, CH_2Cl_2, 0° to r.t., 8 h; 2. $LiAlH_4$, THF, 0° to r.t., 8 h; 82%. *d*) 1. ^{t}BuMe$_2$SiCl (TBSCl), 1*H*-imidazole, CH_2Cl_2, 0° to r.t., 8 h; 90%; 2. cat. camphorsulfonic acid (CSA), CH_2Cl_2/MeOH 4:1, −10°, 30 min; 80%. *e*) 1. 2-Iodoxybenzoic acid (IBX), DMSO, CH_2Cl_2, 0° to r.t., 2 h; 2. $(CF_3CH_2O)_2POCH_2CO_2Et$, NaH, THF, −78°, 1 h; 75%. *f*) Diisobutylaluminium hydride (DIBAL-H), CH_2Cl_2, −78° to r.t., 2 h; 90%. *g*) (−)-Diethyl tartrate ((−)-DET), Ti(O^{i}Pr)$_4$, *t*-BuOOH (TBHP), CH_2Cl_2, −20°, 16 h; 85%. *h*) 1. IBX, DMSO, CH_2Cl_2, 0° to r.t., 2 h; 2. Ph_3PCH_3I, BuLi, THF, −10° to r.t., 2 h, 68%. *i*) Bu_4NF, THF, r.t., 4 h, 88%.

with camphorsulfonic acid (CSA) in CH_2Cl_2/MeOH, gave the alcohol **9**, which was subjected to oxidation with 2-iodoxybenzoic acid (IBX) in DMSO, followed by chain elongation with the *Still–Gennari* reagent [8], $(F_3CCH_2O)_2P(O)CH_2CO_2Et$, to furnish the corresponding (*Z*)-*α*,*β*-unsaturated ester **10** in 75% yield, along with a trace amount of the (*E*)-isomer, which was separated by column chromatography. Reduction of **10** with DIBAL-H afforded the corresponding allylic alcohol **11** in 90% yield. The *Sharpless* asymmetric epoxidation [9] of **11** with (−)-diethyl tartrate (DET)/Ti(O^{i}Pr)$_4$/*t*-BuOOH (TBHP) in CH_2Cl_2 gave the epoxide **12** in 85% yield with the required configuration. In analogy to [5], oxidation of **12** with IBX [10] in DMSO/CH_2Cl_2, followed by C_1 homologation [11] with $Ph_3P{=}CH_2$, gave the corresponding vinyl epoxide **13** in 68% yield over two steps. Deprotection of the silyl ether by treatment with TBAF in THF afforded the required alcohol **3** in 88% yield.

Next, we attempted the synthesis of acid fragment **4** from commercially available L-malic acid (**5**; *Scheme 3*). Accordingly, **5** was converted to the triol **14** in 90% yield using $BH_3 \cdot SMe_2$ and $B(OMe)_3$ [12]. Conversion of **14** to the acetal **15** was achieved by treatment with anisaldehyde dimethyl acetal using a catalytic amount of CSA [12]. Oxidation of **15** using IBX in $DMSO/CH_2Cl_2$ afforded the aldehyde, which was then subjected to *Wittig* olefination with (methylidene)(triphenyl)phosphorane to furnish the vinyl derivative **16** in 69% yield [13]. Regioselective reductive ring opening of the 4-methoxybenzylidene acetal using DIBAL-H at $-15°$ in CH_2Cl_2 gave the alcohol **17** in 88% yield [13][14]. Oxidation of the latter with IBX in dry $DMSO/CH_2Cl_2$ gave the aldehyde, which was further oxidized with $NaClO_2$ and NaH_2PO_4 in the presence of 2-methylbut-2-ene [15] in *t*-BuOH/H_2O to afford the desired acid **4** in 89% yield. Though the conversion of **17** to **4** was analogous to an earlier approach [5], a different oxidation protocol [10] was used to improve the yield.

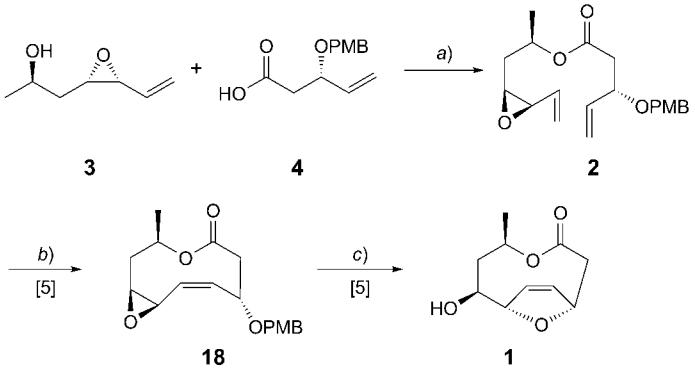
Scheme 3



a) $BH_3 \cdot SMe_2$, $B(OMe)_3$, THF, 0° to r.t., 24 h; 90%. *b*) 4-MeO–$C_6H_4CH(OMe)_2$ (PMP = 4-MeO–C_6H_4), 0° to r.t., CSA, CH_2Cl_2, 20 h; 82%. *c*) 1. IBX, DMSO, CH_2Cl_2, 0° to r.t., 2 h; 2. Ph_3PCH_3I, BuLi, THF, $-10°$ to r.t., 2 h; 69%. *d*) DIBAL-H, CH_2Cl_2, $-15°$, 2 h; 88%. *e*) 1. IBX, DMSO, CH_2Cl_2, 0° to r.t., 2 h; 2. $NaClO_2$, NaH_2PO_4, 2-methylbut-2-ene, *t*-BuOH, 6 h, 89%.

In the present strategy, the key fragments **3** and **4** were synthesized in 14.9 and 39.8% yield, respectively, whereas in the earlier approach they were prepared in 8 and 21.4% yield, respectively [5]. Finally, in contrast to the esterification described in [5], we attempted the coupling of the fragments **3** and **4** (*Scheme 4*) under *Steglich* conditions [16] using DCC/DMAP in CH_2Cl_2 to afford the diene **2** ester in 80% yield. Ring-closing metathesis of **2** according to [5] in the presence of *Grubbs*' second-generation catalyst [17] afforded the desired lactone (*Z*)-**18** in 65% yield as the major product. The (*Z*)-configuration in **18** was established by its spectroscopic data, wherein the signal of one of the olefinic H-atoms appeared at 5.64 ppm as *ddd* ($J = 1.8$, 8.3, 11.7). Deprotection of the PMB (4-MeO–$C_6H_4CH_2$) ether **18**, followed by an intramolecular ring opening of the epoxide in the presence of DDQ [18] in CH_2Cl_2, gave the target molecule, decarestrictine I (**1**), in 70% yield. The physical data of the synthetic decarestrictine I (**1**) were in agreement with those reported in [5].

Scheme 4



a) *N*,*N*′-Dicyclohexylcarbodiimide (DCC), 4-(dimethylamino)pyridine (DMAP), CH_2Cl_2, 0° to r.t., 10 h; 80%. *b*) *Grubbs*' *II* catalyst, CH_2Cl_2, reflux, 12 h; 65%. *c*) 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), CH_2Cl_2/H_2O, 0° to r.t., 1 h; 70%.

Conclusions. – In summary, a modified efficient strategy has been described for the total synthesis of decarestrictine I (**1**) in a convergent manner starting from the precursor L-malic acid (**5**). The target molecule was synthesized with an overall yield of 5.4%, whereas in earlier approach, the yield reported was 2.8%. The present synthesis involves *cis*-selective *Wittig* olefination, *Sharpless* asymmetric epoxidation, and ring-closing metathesis (RCM) as key steps.

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Experimental Part

General. All reactions were conducted under N_2 in anh. solvents such as CH_2Cl_2, THF, AcOEt, and Et_2O. Progress of the reaction was monitored by TLC using silica gel plates with fluorescent indicator (254 nm) and visualized with a UV lamp, anisaldehyde or β-naphthol soln., or alkaline $KMnO_4$ soln. All commercially available reagents were purchased and used as supplied. Optical rotations: at ambient temp. (25°) in $CHCl_3$ with a polarimeter using 2-ml capacity cell with 100-mm path length. IR Spectra: *PerkinElmer IR-683* spectrophotometer with NaCl optics; $\tilde{\nu}$ in cm^{-1}. ^1H- and ^{13}C-NMR spectra: *Fourier* transform mode at the field strength specified either on a *Bruker UXNMR FT-300* MHz (*Avance*) or a *Varian VXR-unity-500* MHz spectrometer; spectra were recorded in $CDCl_3$ in 5-mm diameter tubes; δ in ppm rel. to the residual signals of $CHCl_3$ (7.25 ppm or 77.0 ppm); coupling constants, *J* in Hz. MS: *Agilent Technologies 1100 Series* (Agilent ChemStation software); in *m*/*z*.

Diethyl (2S)-2-Hydroxybutanedioate (**6**) [18]. To a stirred soln. of L-*malic acid* (5.0 g, 37.31 mmol) in EtOH (60 ml) was added a cat. amount of H_2SO_4 (0.5 ml). The resulting mixture was then stirred under reflux for 18 h, and the solvent was removed *in vacuo*. After completion, the reaction was quenched with sat. $NaHCO_3$ soln. (50 ml), and the mixture was extracted with AcOEt (2 × 40 ml). The combined org. extracts were washed with brine (50 ml), dried (Na_2SO_4), and concentrated under reduced pressure. The crude residue was purified by column chromatography (CC) to afford pure **6** (5.6 g, 80%). Liquid. $[\alpha]_D^{25} = -5.2$ ($c = 0.9$, $CHCl_3$). IR (neat): 3492, 2985, 2933, 1735, 1468, 1393, 1269, 1105, 859. ^1H-NMR (500 MHz, $CDCl_3$): 4.50–4.46 (*m*, 1 H); 4.31–4.24 (*m*, 2 H); 4.18 (*q*, *J* = 7.1, 2 H); 2.88–2.76 (*m*, 2 H); 1.63 (br. *s*, 1 H); 1.31 (*t*, *J* = 7.1, 3 H); 1.27 (*t*, *J* = 7.0, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 173.2; 170.4; 67.2; 61.8; 60.8; 38.6; 14.0. ESI-MS: 213 ($[M + Na]^+$).

Ethyl (3S)-3,4-Dihydroxybutanoate (**7**) [6]. To a stirred soln. of **6** (4.0 g, 21.05 mmol) in THF (50 ml) was added $BH_3 \cdot SMe_2$ (10.8 ml, 21.68 mmol, 2M in THF) dropwise at r.t. The resulting soln. was stirred at r.t., until evolution of H_2 ceased (30 min). The flask was then cooled in an ice bath (10°), and stirring was continued for another 10 min. To this mixture was added $NaBH_4$ (39 mg, 5 mol-%) under vigorous stirring at the same temp. The mixture was stirred at r.t. until the disappearance of **6** (1 h; by TLC). To this mixture, EtOH (10 ml) and TsOH (200 mg, 5 mol-%) were added, and the resulting cloudy soln. was stirred for 30 min at r.t. Removal of the solvent resulted in the formation of a colorless gum, which was treated with benzene/EtOH 1:1 (50 ml), and the solvent was removed again *in vacuo*. This process was repeated thrice, and the resulting residue was purified by CC to afford **7** (2.9 g, 92%). Colorless viscous liquid. $[\alpha]_D^{25} = +6.22$ ($c = 1.22$, $CHCl_3$). IR (neat): 3419, 2966, 2926, 1771, 1467, 1372, 1177, 968. ^{1}H-NMR (300 MHz, $CDCl_3$): 4.28–4.14 (*m*, 1 H); 4.14 (*q*, $J = 7.1$, 2 H); 3.79 (br. *s*, 1 H); 3.68–3.42 (*m*, 2 H); 3.24 (br. *s*, 1 H); 2.60–2.38 (*m*, 2 H); 1.24 (*t*, $J = 7.2$, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 172.4; 68.5; 65.6; 60.7; 37.7; 14.0. ESI-MS: 171 ($[M+Na]^+$).

(3R)-Butane-1,3-diol (**8**) [7]. To a stirred soln. of **7** (1.0 g, 6.76 mmol) in CH_2Cl_2 (20 ml) was added Et_3N (2.82 ml, 20.27 mmol) at 0°. After 15 min, TsCl (1.29 g, 6.76 mmol) was added at r.t., and the mixture was stirred for 10 h. After completion, the mixture was treated with H_2O (20 ml) and extracted with CH_2Cl_2 (40 ml). The combined extracts were washed with brine (20 ml) and dried (Na_2SO_4). The solvent was evaporated under reduced pressure, and the resulting *p*-toluenesulfonate was directly used in the next step without further purification. To a stirred suspension of $LiAlH_4$ (0.51 g, 13.51 mmol) in THF (10 ml) at 0° was added a soln. of the *p*-toluenesulfonate in THF (10 ml) under N_2. The mixture was stirred at r.t. for 8 h, then cooled to 0°, treated with sat. aq. Na_2SO_4 soln. (10 ml), and filtered through *Celite*. The residue was washed with AcOEt (30 ml), and the filtrate was dried (Na_2SO_4). Removal of the solvent, followed by purification by CC (SiO_2; 50% AcOEt in hexane), gave **8** (0.50 g, 82%). Colorless oil. $[\alpha]_D^{25} = -10.2$ ($c = 1.04$, EtOH). IR (neat): 3350, 2969, 2935, 1377, 1053. ^{1}H-NMR (300 MHz, $CDCl_3$): 4.12–4.00 (*m*, 1 H); 3.92–3.75 (*m*, 2 H); 2.53 (br. *s*, 2 H); 1.73–1.64 (*m*, 2 H); 1.22 (*d*, $J = 6.2$, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 67.7; 61.1; 40.0; 23.5. EI-MS: 91 ($[M+H]^+$).

(5R)-2,2,3,3,5,9,9,10,10-Nonamethyl-4,8-dioxa-3,9-disilaundecane. To an ice-cold soln. of **8** (0.5 g, 5.55 mmol) and 1*H*-imidazole (2.26 g, 33.30 mmol) in anh. CH_2Cl_2 (10 ml) was added a soln. of TBSCl (2.5 g, 16.65 mmol) in CH_2Cl_2 (5 ml). The mixture was stirred at r.t. for 24 h, then diluted with H_2O (10 ml), and extracted with Et_2O (3 × 10 ml). The combined org. phases were washed with brine (10 ml) and dried (Na_2SO_4). Removal of the solvent, followed by purification by CC, gave the bis-TBS ether (1.59 g, 90%). Colorless oil. $[\alpha]_D^{25} = -10.2$ ($c = 0.7$, $CHCl_3$). IR (neat): 2958, 2931, 1472, 1256, 1095, 836. ^{1}H-NMR (300 MHz, $CDCl_3$): 4.01–3.89 (*m*, 1 H); 3.66 (*t*, $J = 6.6$, 2 H); 1.71–1.52 (*m*, 2 H); 1.13 (*d*, $J = 6.2$, 3 H); 0.89 (*s*, 9 H); 0.88 (*s*, 9 H); 0.05 (*s*, 6 H); 0.04 (*s*, 6 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 65.5; 60.0; 42.7; 25.9; 25.8; 25.6; 23.8; −4.4; −4.8. ESI-MS: 341 ($[M+Na]^+$).

*(3R)-3-{[(*tert*-Butyl)(dimethyl)silyl]oxy}butan-1-ol* (**9**). To an ice-bath cooled soln. of the bis-TBS ether (1.5 g, 4.71 mmol) in CH_2Cl_2/MeOH 4:1 (10 ml) was added a cat. amount of CSA. The resulting mixture was stirred at −10° for 30 min, and then the reaction was quenched with solid $NaHCO_3$ (1 g), followed by filtration through *Celite*. The filtrate was concentrated under reduced pressure, and the crude product was purified by CC to afford **9** (0.76 g, 80%). Colorless oil. $[\alpha]_D^{25} = +2.3$ ($c = 0.5$, $CHCl_3$). IR (neat): 3390, 2952, 1462, 1252, 1082, 834. ^{1}H-NMR (300 MHz, $CDCl_3$): 4.17–4.05 (*m*, 1 H); 3.91–3.78 (*m*, 1 H); 3.77–3.65 (*m*, 1 H); 1.85–1.72 (*m*, 1 H); 1.70–1.56 (*m*, 1 H); 1.19 (*d*, $J = 6.0$, 3 H); 0.89 (*s*, 9 H); 0.09 (*s*, 3 H); 0.08 (*s*, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 68.3; 60.4; 40.3; 25.7; 25.6; 23.3; −4.3; −4.9. ESI-MS: 227 ($[M+Na]^+$).

*Ethyl (2Z,5R)-5-{[(*tert*-Butyl)(dimethyl)silyl]oxy}hex-2-enoate* (**10**). To a stirred soln. of IBX (2.05 g, 7.35 mmol) in DMSO (6 ml) at 25° was added a soln. of **9** (1.0 g, 4.90 mmol) in CH_2Cl_2 (12 ml). The mixture was stirred at 25° for 2 h, and the resulting solid was filtered and then washed with Et_2O (10 ml). The filtrate was extracted with Et_2O, washed with H_2O, followed by brine, and dried (Na_2SO_4), and then concentrated under reduced pressure to afford the crude aldehyde, which was immediately used for the next reaction without further purification. To a stirred soln. of bis(trifluoroethyl)(ethoxycarbonyl)methylphosphonate (2.11 g, 6.37 mmol) in dry THF (20 ml) at 0° was added NaH (0.235 g, 9.8 mmol), and the mixture was stirred for 30 min at 0°. To this mixture was added a soln. of aldehyde in dry THF (5 ml) and stirred for 30 min at −78°. The reaction was quenched with sat. aq. NH_4Cl soln. (5 ml), and

the mixture was stirred at r.t. for another 10 min. The layers were separated, and the aq. layer was extracted with AcOEt (2 × 10 ml). The combined org. layers were washed with brine (2 × 15 ml), dried (Na_2SO_4), and concentrated *in vacuo*. The resulting residue was purified by CC to afford **10** (0.95 g, 75%). Viscous oil. $[\alpha]_D^{25} = -10.2$ ($c = 1.8$, $CHCl_3$). IR (neat): 2931, 2851, 1721, 1219, 772. ^{1}H-NMR (300 MHz, $CDCl_3$): 6.41–6.30 (*m*, 1 H); 5.87–5.81 (*m*, 1 H); 4.17 (*q*, *J* = 6.7, 2 H); 4.01–3.91 (*m*, 1 H); 2.89–2.70 (*m*, 2 H); 1.29 (*t*, *J* = 6.7, 3 H); 1.16 (*d*, *J* = 6.0, 3 H); 0.88 (*s*, 9 H); 0.06 (*s*, 3 H); 0.05 (*s*, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 166.3; 146.7; 120.7; 67.9; 59.7; 38.6; 25.8; 23.6; 18.0; 14.2; −4.4; −4.7. ESI-MS: 295 ($[M + Na]^+$).

*(2Z,5*R*)-5-[[(*tert*-Butyl)(dimethyl)silyl]oxy}hex-2-en-1-ol* (**11**) [19]. To a stirred soln. of **10** (1.8 g, 6.61 mmol) in dry CH_2Cl_2 was added DIBAL-H (13.1 ml, 13.22 mmol,1.0M in toluene) dropwise at 0°. The resulting mixture was stirred for 1 h at r.t. After completion, the reaction was quenched with sat. sodium potassium tartarate soln., and the mixture was filtered through *Celite* and washed with CH_2Cl_2. The org. layer was separated, and the aq. layer was extracted with CH_2Cl_2. The combined org. layers were dried (Na_2SO_4), and concentrated *in vacuo*. The residue was purified by CC (SiO_2; 25% AcOEt/hexane) to afford pure **11** (1.36 g, 90%). Colorless liquid. $[\alpha]_D^{25} = +0.5$ ($c = 1.6$, $CHCl_3$). IR (neat): 3346, 2956, 2930, 1219, 1004, 772. ^{1}H-NMR (300 MHz, $CDCl_3$): 5.84–5.52 (*m*, 2 H); 4.25–4.08 (*m*, 2 H); 3.94–3.77 (*m*, 1 H); 2.38–2.12 (*m*, 2 H); 1.62 (br. *s*, 1 H); 1.15 (*d*, *J* = 6.0, 3 H); 0.89 (*s*, 9 H); 0.06 (*s*, 3 H); 0.05 (*s*, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 130.3; 129.4; 68.1;58.3; 37.4; 32.7; 25.8; 23.5; −4.6. ESI-MS: 253 ($[M + Na]^+$).

*4,5-Anhydro-2-*O*-[(*tert*-butyl)(dimethyl)silyl]-1,3-dideoxy-*D*-arabino-hexitol* (**12**). To a stirred mixture of molecular sieves (4 Å, 3.0 g) and $Ti(O^iPr)_4$ (0.46 ml, 1.56 mmol) in CH_2Cl_2 (10 ml) at −20° was added (−)-diethyl tartrate (DET) in CH_2Cl_2 (0.26 ml, 1.56 mmol), and the mixture was stirred at −20° for 10 min. To this mixture, a soln. of **11** (1.2 g, 5.21 mmol) in CH_2Cl_2 (10 ml) and 3.3M soln. of *t*-BuOOH (TBHP; 3.1 ml, 10.42 mmol) were added successively. The resulting mixture was stirred at −20° for 16 h, and the reaction was quenched with H_2O (0.46 ml) and 30% NaOH (0.26 ml). After 30 min, the mixture was filtered through *Celite*, and the aq. layer was extracted with CH_2Cl_2 (2 × 10 ml). The combined org. extracts were washed with brine, dried (Na_2SO_4), and concentrated *in vacuo*. The residual oil was purified by CC (SiO_2; 15% AcOEt in hexane) to give **12** (1.09 g, 85%). Colorless oil. $[\alpha]_D^{25} = -18.3$ (c = 1.8, $CHCl_3$). IR (neat): 3419, 2957, 2931, 1465, 1255, 1039. ^{1}H-NMR (300 MHz, $CDCl_3$): 4.13–4.00 (*m*, 1 H); 3.88–3.64 (*m*, 2 H); 3.25–3.16 (*m*, 1 H); 3.14–3.05 (*m*, 1 H); 1.85–1.74 (*m*, 1 H); 1.70–1.58 (*m*, 1 H); 1.22 (*d*, *J* = 6.0, 3 H); 0.90 (*s*, 9 H); 0.10 (*s*, 6 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 66.8; 60.8; 56.2; 54.7; 37.4; 25.8; 24.4; −4.6. ESI-MS: 269 ($[M + Na]^+$).

*(1*R*)-1,2-Anhydro-4-*O*-[(*tert*-butyl)(dimethyl)silyl]-3,5-dideoxy-1-ethenyl-*D*-threo-pentitol* (**13**). To a stirred soln. of IBX (1.4 g, 4.87 mmol) in DMSO (4.2 ml) under N_2 was added **12** (1.0 g, 4.06 mmol) in anh. CH_2Cl_2 (10 ml) at r.t., and the mixture was stirred for 2 h. The mixture was then diluted with Et_2O (10 ml) and filtered through *Celite*. The filtrate was washed with sat. aq. $NaHCO_3$ (15 ml), dried (Na_2SO_4), and concentrated *in vacuo*. The crude aldehyde was immediately used for the next reaction without further purification.

To a soln. of (methyl)(triphenyl)phosphonium iodide (4.93 g, 12.27 mmol) in anh. THF (50 ml) at −10° was added BuLi (4.8 ml, 12.22 mmol, 2.5M in hexane) dropwise. The resulting mixture was stirred at 25° for 1 h and then cooled to −10°. To this mixture, a soln. of aldehyde in anh. THF (10 ml) was added. After 2 h, the reaction was quenched with sat. aq. NH_4Cl (20 ml), and the mixture was extracted with Et_2O (50 ml) and then washed sequentially with H_2O (30 ml), followed by brine (30 ml) soln. The org. layers were dried (Na_2SO_4) and concentrated *in vacuo*. Purification of the resulting residue by flash CC (SiO_2; 5% AcOEt in hexane) gave **13** (670 mg, 68%). Colorless oil. $[\alpha]_D^{25} = +13.2$ ($c = 0.85$, $CHCl_3$). IR (neat): 2926, 2950, 1463, 1219, 773. ^{1}H-NMR (300 MHz, $CDCl_3$): 5.79–5.65 (*m*, 1 H); 5.52–5.32 (*m*, 2 H); 4.08–3.97 (*m*, 1 H); 3.47–3.41 (*m*, 1 H); 3.27–3.19 (*m*, 1 H); 1.74–1.63 (*m*, 1 H); 1.62–1.52 (*m*, 1 H); 1.19 (*d*, *J* = 6.0, 3 H); 0.89 (*s*, 9 H); 0.08 (*s*, 6 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 132.7; 120.2; 66.5; 57.2; 56.2; 37.5; 25.8; 24.2; −4.5; −4.8. ESI-MS:265 ($[M + Na]^+$).

*(1*R*)-1,2-Anhydro-3,5-dideoxy-1-ethenyl-*D*-threo-pentitol* (**3**) [5]. To a stirred soln. of **13** (0.6 g, 2.47 mmol) in anh. THF (5 ml) was added TBAF (4.9 ml, 4.94 mmol, 1.0M soln. in THF) at 0°. The resulting soln. was stirred at r.t. for 4 h. After completion, the reaction was quenched with Et_2O/H_2O 1:1 (10 ml). The org. layers were washed with brine, dried (Na_2SO_4), and concentrated *in vacuo*. The residue

was purified by flash CC (SiO_2; 20% AcOEt in hexane) to yield pure **3** (280 mg, 88%). Colorless oil. $[\alpha]_D^{25} = -25.3$ ($c = 1.6$, $CHCl_3$). IR (neat): 3404, 2923, 2853, 1459, 1375, 1219, 772. ^{1}H-NMR (300 MHz, $CDCl_3$): 5.80–5.67 (*m*, 1 H); 5.54–5.35 (*m*, 2 H); 4.15–4.01 (*m*, 1 H); 3.52–3.44 (*m*, 1 H); 3.34–3.26 (*m*, 1 H); 1.80–1.55 (*m*, 2 H); 1.29 (*d*, $J = 6.7$, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 132.3; 120.5; 66.0; 56.9; 55.9; 36.6; 23.7. LC/MS: 151 ($[M + Na]^+$).

*(−)-(2*S*)-Butane-1,2,4-triol* (**14**) [12]. To a soln. of $BH_3 \cdot SMe_2$ (11.4 ml, 120 mmol) at 0° was added $B(OMe)_3$ (12.5 ml, 110 mmol) in 25 ml of dry THF. The mixture was stirred at the same temp. for 15 min, and then **5** (5.00 g, 37.3 mmol) was added. After stirring for 23 h at r.t., the reaction was quenched with MeOH at 0°. The solvent was removed under reduced pressure, and the residue was filtered through a short pad of SiO_2 eluting with MeOH/CH_2Cl_2 1:4. Evaporation of the solvent gave **14** (3.84 g, 97%). Colorless oil. The crude product was instantly used in the next reaction without further purification.

*[(4*S*)-2-(4-Methoxyphenyl)-1,3-dioxan-4-yl]methanol* (**15**) [12]. To a soln. of **14** (3.64 g, 34.3 mmol) and 1-(dimethoxymethyl)-4-methoxybenzene (11.6 ml, 68.1 mmol) in CH_2Cl_2 (36.4 ml) at r.t. was added a cat. amount of CSA (799 mg, 3.44 mmol). After stirring for 19 h at r.t., the reaction was quenched with Et_3N, and the mixture was concentrated under reduced pressure. The crude product was purified by CC (AcOEt/hexane 1:1) to afford **15** (6.25 g, 81%). Colorless oil. $[\alpha]_D^{25} = +5.8$ ($c = 1.5$, $CHCl_3$). IR (neat): 3387, 2923, 2852, 1459, 1516, 1246, 772. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.46–7.39 (*m*, 2 H); 6.93–6.87 (*m*, 2 H); 5.51 (*s*, 1 H); 4.33–4.25 (*m*, 1 H); 4.06–3.92 (*m*, 2 H); 3.81 (*s*, 3 H); 3.75–3.61 (*m*, 2 H); 2.09–1.84 (*m*, 2 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 160.0; 130.9; 127.3; 113.5; 101.1; 66.5; 65.6; 55.2; 26.7. ESI-MS: 247 ($[M + Na]^+$).

*(4*S*)-4-Ethenyl-2-(4-methoxyphenyl)-1,3-dioxane* (**16**) [13]. Compound **15** (1.5 g, 6.69 mmol) was subjected to IBX oxidation as described for the synthesis of **13**. The crude aldehyde thus formed was immediately converted to **16** as described for the synthesis of **13**. Purification by CC (SiO_2; 10% AcOEt in hexane) afforded **16** (1.01 g, 69%). Colorless oil. $[\alpha]_D^{25} = -22.7$ ($c = 1.5$, $CHCl_3$). IR (neat): 2958, 2837, 1610, 1515, 1247. ^{1}H-NMR (500 MHz, $CDCl_3$): 7.43 (*d*, $J = 8.8$, 2 H); 6.88 (*d*, $J = 7.7$, 2 H); 5.99–5.90 (*m*, 1 H); 5.53 (*s*, 1 H); 5.33 (*d*, $J = 17.6$, 1 H); 5.17 (*d*, $J = 11.0$, 1 H); 4.38–4.32 (*m*, 1 H); 4.27 (*dd*, $J = 11.0$, 5.5, 1 H); 3.98 (*td*, $J = 12.1$, 2.2, 1 H); 3.79 (*s*, 3 H); 1.92 (*qt*, $J = 12.1$, 4.4, 1 H); 1.62–1.57 (*m*, 1 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 159.8; 137.8; 131.1; 127.3; 115.5; 113.5; 101.0; 77.5; 66.8; 55.2; 31.0. ESI-MS: 243 ($[M + Na]^+$).

*(3*S*)-3-[(4-Methoxybenzyl)oxy]pent-4-en-1-ol* (**17**) [13]. To a stirred soln. of **16** (0.5 g, 2.27 mmol) in dry CH_2Cl_2 (10 ml) was added DIBAL-H (6.8 ml, 6.81 mmol, 1.0M in toluene) dropwise at −15°. The resulting mixture was stirred for 1 h at −15° After completion, the reaction was quenched with sat. sodium potassium tartarate soln., and the mixture was filtered through *Celite*. The residue was washed with CH_2Cl_2, and the aq. layer was extracted with CH_2Cl_2 (2 × 10 ml). The combined org. layers were dried (Na_2SO_4), and concentrated *in vacuo*. Purification of the resulting residue by CC (SiO_2; 25% AcOEt in hexane) gave **17** (443 mg, 88%). Colorless liquid. $[\alpha]_D^{25} = -38.5$ ($c = 1.1$, $CHCl_3$). IR (neat): 3374, 2923, 2853, 1512, 1245, 1033. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.30–7.22 (*m*, 2 H); 6.93–6.85 (*m*, 2 H); 5.86–5.73 (*m*, 1 H); 5.31–5.22 (*m*, 2 H); 4.60–4.53 (*m*, 1 H); 4.33–4.26 (*m*, 1 H); 4.05–3.96 (*m*, 1 H); 3.80 (*s*, 3 H); 3.79–3.66 (*m*, 2 H); 1.93–1.71 (*m*, 2 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 159.1; 138.1; 129.4; 117.4; 113.8; 79.6; 69.8; 60.6; 55.2; 37.6. ESI-MS: 245 ($[M + Na]^+$).

*(3*S*)-3-[(4-Methoxybenzyl)oxy]pent-4-enoic Acid* (**4**) [5][10]. Compound **17** (400 mg, 1.80 mmol) was subjected to IBX oxidation as described for the synthesis of **13**. To a stirred soln. of the crude aldehyde and 2-methylbut-2-ene (2.5 ml) in *t*-BuOH (5 ml) at r.t. were added a soln. of $NaClO_2$ (0.330 g, 3.62 mmol) and NaH_2PO_4 (0.435 g, 3.62 mmol) in H_2O (4 ml) in two portions. The resulting mixture was stirred at r.t. for 6 h, before dilution with sat. aq. NH_4Cl soln. (10 ml). The resulting carboxylic acid was extracted with AcOEt (3 × 5 ml), dried (Na_2SO_4), and concentrated *in vacuo*. The residue was purified by flash CC (SiO_2, 25% AcOEt in hexane) to yield pure **4** (378 mg, 89%). Pale-yellow oil. $[\alpha]_D^{25} = -11.3$ ($c = 0.85$, $CHCl_3$). IR (neat): 3404, 2924, 2853, 1712, 1513, 1248, 1035. ^{1}H-NMR (500 MHz, $CDCl_3$): 7.24 (*d*, $J = 7.9$, 2 H); 6.87 (*d*, $J = 7.9$, 2 H); 5.84–5.74 (*m*, 1 H); 5.38–5.23 (*m*, 2 H); 4.59–4.54 (*m*, 1 H); 4.38–4.33 (*m*, 1 H); 4.27–4.21 (*m*, 1 H); 3.79 (*s*, 3 H); 2.73–2.66 (*m*, 1 H); 2.60–2.54 (*m*, 1 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 175.6; 159.2; 136.7; 129.8; 129.4; 118.4; 113.8; 76.2; 70.2; 55.2; 40.7. ESI-MS: 259 ($[M + Na]^+$).

*(1*R*)-1,2-Anhydro-3,5-dideoxy-1-ethenyl-4-*O*-{(3*S*)-3-[(4-methoxybenzyl)oxy]pent-4-enoyl}-*D*-threo-pentitol* (**2**) [5][16a]. To a stirred soln. of **3** (100 mg, 0.78 mmol) in CH_2Cl_2 (10 ml) were added DCC (402 mg, 1.95 mmol) and DMAP (190 mg, 1.56 mmol) at 0°. The mixture was stirred for 30 min, and then **4** (221 mg, 0.93 mmol) was added. The mixture was stirred for 10 h, and then the volatiles were evaporated under reduced pressure.The resulting crude product was adsorbed on silica gel and purified by flash CC (SiO_2, 6% AcOEt in hexane) to give **2** (216 mg, 80%). Colorless oil. $[\alpha]_D^{25} = -15.0$ ($c = 0.5$, $CHCl_3$). IR (neat): 2923, 2853, 1733, 1462, 1219, 772. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.22 (*d*, *J* = 8.6, 2 H); 6.85 (*d*, *J* = 8.6, 2 H); 5.84–5.61 (*m*, 2 H); 5.52–5.21 (*m*, 4 H); 5.17–5.03 (*m*, 1 H); 4.50 (*d*, *J* = 11.1, 1 H); 4.31 (*d*, *J* = 11.3, 1 H); 4.27–4.19 (*m*, 1 H); 3.79 (*s*, 3 H); 3.45–3.38 (*m*, 1 H); 3.20–3.08 (*m*, 1 H); 2.68–2.56 (*m*, 1 H); 2.51–2.41 (*m*, 1 H); 1.85–1.66 (*m*, 2 H); 1.30 (*d*, *J* = 6.4, 3 H).^{13}C-NMR (75 MHz, $CDCl_3$): 170.2; 159.1; 137.3; 132.2; 129.3; 120.4; 117.9; 113.7; 76.8; 70.2; 68.9; 56.7; 55.4; 55.2; 41.3; 34.2; 20.2. ESI-MS: 369 ($[M + Na]^+$).

*(1*S*,3*R*,7*S*,8*Z*,10*R*)-7-[(4-Methoxybenzyl)oxy]-3-methyl-4,11-dioxabicyclo[8.1.0]undec-8-en-5-one* (**18**) [5]. To a stirred soln. of **2** (0.12 g, 0.35 mmol) in CH_2Cl_2 (100 ml) was added 10 mol-% *Grubbs II* catalyst. The resulting mixture was stirred at reflux for 12 h under N_2. The solvent was then distilled off, and the residual soln. was stirred at r.t. for 2 h under air bubbling in order to decompose the catalyst. The remaining solvent was evaporated to dryness to give the brown-colored residue which was purified by CC (SiO_2; 5% AcOEt in hexane) to give **18** (71 mg, 65%). $[\alpha]_D^{25} = -63.0$ ($c = 0.3$, $CHCl_3$). IR (neat): 3450, 2925, 2854, 1731, 1513, 1248. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.14 (*d*, *J* = 8.4, 2 H); 6.77 (*d*, *J* = 8.7, 2 H); 5.64 (*ddd*, *J* = 1.8, 8.3, 11.7, 1 H); 5.49–5.42 (*m*, 1 H); 5.19 (*ddq*, *J* = 1.8, 8.3, 11.7, 1 H); 4.49 (*d*, *J* = 11.3, 1 H); 4.40–4.31 (*m*, 2 H); 3.75–3.69 (*m*, 4 H); 3.24 (*m*, 1 H); 2.83 (*dt*, *J* = 3.3, 10.5, 1 H); 2.60 (*dd*, *J* = 3.3, 10.3, 1 H); 2.28 (*t*, *J* = 10.5, 1 H); 2.11–2.05 (*m*, 1 H); 1.23 (*d*, *J* = 6.7, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 169.2; 159.2; 133.6; 130.0; 129.7; 114.2; 76.9; 71.9; 70.0; 66.8; 55.4; 54.4; 53.9; 41.2; 32.9. LC/MS: 341 ($[M + Na]^+$).

Decarestrictine I (= *(1*S*,5*R*,7*S*,8*S*)-7-Hydroxy-5-methyl-4,11-dioxabicyclo[6.2.1]undec-9-en-3-one*; **1**) [5]. To a stirred soln. of **2** (0.07 g, 0.2 mmol) in CH_2Cl_2/H_2O (2 ml, 19:1) was added DDQ (0.042 g, 0.33 mmol). The mixture was stirred at r.t. for 1 h. After completion, the reaction was quenched with sat. aq. $NaHCO_3$ soln. (2 ml), and the mixture was filtered through *Celite* and then washed with CH_2Cl_2 (20 ml). The filtrate was washed again with H_2O (15 ml), followed by brine (5 ml), and dried (Na_2SO_4). Removal of the solvent under reduced pressure followed by purification by CC (SiO_2; 15% AcOEt and hexane), gave **1** (0.030 g, 70%). $[\alpha]_D^{25} = -129.1$ ($c = 0.3$, MeOH). IR (neat): 3405.5, 2956.3, 2854, 1710, 1431.2, 1385, 1070. ^{1}H-NMR (300 MHz, $CDCl_3$): 5.95–5.82 (*m*, 2 H); 5.10–4.95 (*m*, 2 H); 4.92–4.85 (*m*, 1 H); 3.90 (*dt*, *J* = 4.6, 10.9, 1 H); 2.76–2.54 (*m*, 1 H); 2.01 (*dd*, *J* = 2.3, 3.1, 2 H); 1.68–1.60 (*m*, 1 H); 1.40–1.37 (*m*, 1 H); 1.25 (*d*, *J* = 6.2, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 171.5; 132.2; 127.5; 92.6; 81.6; 73.7; 71.2; 42.5; 39.9; 21.9. LC/MS: 221 ($[M + Na]^+$).

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