Synthesis P. Dey et al. Paper

An Enantioselective Synthesis of (5*S*,6*R*,11*S*,14*R*)-Acremodiol

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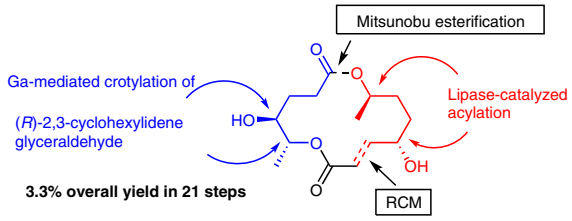


Received: 27.07.2017
Accepted after revision: 29.07.2017
Published online: 29.08.2017
DOI: 10.1055/s-0036-1588557; Art ID: ss-2017-n0303-op

Abstract An expeditious synthesis of the (5*S*,6*R*,11*S*,14*R*)-isomer of acremodiol was developed via a convergent route. One of the required building blocks was synthesized earlier via two sequential lipase-catalyzed secondary carbinol acetylations. The other unit was derived from (*R*)-2,3-cyclohexylideneglyceraldehyde as a chiral template. The bismacrolide skeleton was constructed by an intermolecular esterification reaction under Mitsunobu conditions followed by a ring-closing metathesis of the resultant α,ω-dialkenoic ester.

Keywords asymmetric synthesis, (*R*)-2,3-cyclohexylideneglyceraldehyde, macrodiolide, ring-closing metathesis, lipase-catalyzed transesterification

Macrolides are prevalent in various natural sources[1] and often show impressive medicinal and other biological profiles, besides providing synthetic challenges.[2] Amongst these, acremodiol is a 14-membered bismacrolide isolated from a soil sample of the Bermuda islands containing acremonium-like anamorphic fungus.[3a] Based on NMR, ESI-MS, and FAB-MS data, natural acremodiol was assigned the structure (5*R*,6*R*,11*R*,14*R*)-**1**. It showed inhibitory property against a series of Gram-positive bacteria and fungi,[3a] unlike another closely related bis-lactone, colletodiol.[3b] It was also active in cellular phagocytosis assay with dog PMNL cells and reduced the oxidative burst at concentrations ≥4 μg/mL. Sharma et al. developed the first synthesis of (5*R*,6*R*,11*R*,14*R*)-**1**, its 11-epimer, and acremonol.[3c] But the spectroscopic and chirooptical data of the synthetic compounds were not in agreement with the reported values for the natural sample.[3c] Accordingly, a revision of structure was suggested. Hence, there is a need to prepare isomers of acremodiol for biological evaluation/structural confirmation. Due to the presence of four stereogenic centers in it, 16 stereomers of acremodiol are possible. In this paper, we report an efficient synthesis of (5*S*,6*R*,11*S*,14*R*)-**1**, a stereomer of acremodiol that has not been synthesized so far. The chemical structures of the acremodiol stereomers, synthesized by Sharma et al. and in the present paper are shown in Figure 1.

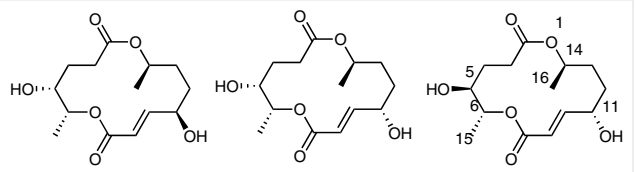
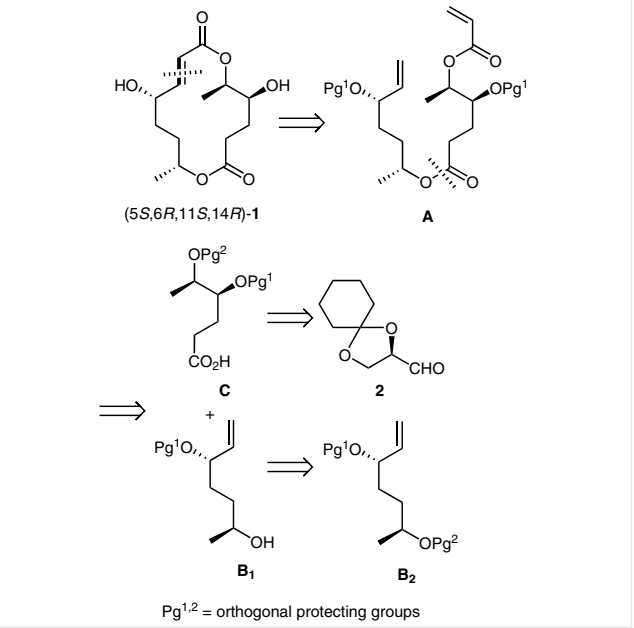


Figure 1 Various acremodiol stereomers that have been synthesized

Based on retrosynthesis, we envisioned that the synthesis of (5*S*,6*R*,11*S*,14*R*)-**1** (Scheme 1) could be achieved by a ring-closing metathesis (RCM) of the immediate precursor **A**-unit and global removal of the protecting group (Pg[1] = Bn). The **A**-unit, in turn, can be obtained by an esterification reaction between the hept-6-ene-2,5-diol derivative $\mathbf{B_1}$ and the 4,5-dihydroxyhexanoic acid derivative **C** under Mitsunobu conditions[4] followed by selective deprotection and acrylation. Regarding the required building blocks, the $\mathbf{B_1}$-unit was proposed to be derived easily from the $\mathbf{B_2}$-unit (Pg[2] = TBDPS) that was recently synthesized by us following a chemoenzymatic route.[5] The versatility of the $\mathbf{B_2}$-unit and its stereomers has already been adequately demonstrated via syntheses of several O-heterocycles by our group.[5] We planned to use (*R*)-2,3-cyclohexylideneglyceraldehyde (**2**) as the chiral template to synthesize the **C**-unit. Compound **2** is an ideal starting material in asymmetric synthesis due to the presence of diverse functionalities in it. Previously, we have employed it extensively for the enantiomeric syntheses of a wide range of biologically active natural

compounds, and as a chiral template for some asymmetric transformations.[6a–g,6j] Moreover, its *S*-enantiomer can also be easily obtained from inexpensive vitamin C.[7]

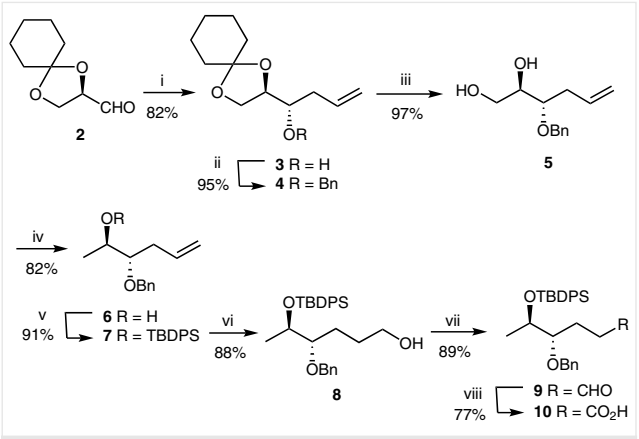


Scheme 1 Retrosynthesis of (5*S*,6*R*,11*S*,14*R*)-**1**

To realize the synthetic plan, the initial task was the preparation of the **C** unit from the aldehyde **2** and transformation of the $\mathbf{B_2}$-unit to the required $\mathbf{B_1}$-unit. These are sequentially described below.

Synthesis of C-Unit

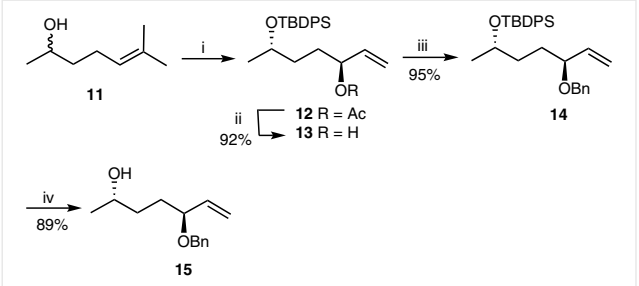
It commenced from the homoallylic alcohol **3**,[6h,i,k] which was conveniently prepared by a Ga-mediated allylation[6e] of **2** in the room temperature ionic liquid, 1-butyl-3-methylimidazolium bromide ([bmim][Br]). The reaction proceeded with 94:6 diastereoselectivity to yield the *anti*-isomer **3** as the major product, which was isolated by column chromatography as a pure enantiomer. It is worth mentioning that the designated allylation reaction can be carried out with near-stoichiometric amounts of the substrates and only 0.5 equivalent of Ga-metal, unlike most of the reported Barbier-type protocols. Benzylation of the alcohol **3** furnished **4**,[6c,8a] which on treatment with aqueous methanolic HCl[8b] afforded the diol **5**[9a] (Scheme 2). This was converted into the alcohol **6**[9b] by Martinelli monotosylation (Bu_2SnO, *p*-TsCl, Et_3N),[9c] followed by $LiAlH_4$ reduction. Its silylation with *tert*-butyldiphenylsilyl chloride (TBDPSCl), imidazole and 4-dimethylaminopyridine (DMAP) gave **7**, which was regioselectively hydroborated with $BH_3{\cdot}SMe_2$, and the intermediate trialkylborane oxidized with H_2O_2/NaOH to afford the alcohol **8**. Its PCC oxidation to the aldehyde **9**, followed by Pinnick oxidation furnished the acid **10** (**C**-unit equivalent).



Scheme 2 *Reagents and conditions*: (i) Ga, allyl bromide, [bmim][Br], 4 h; (ii) NaH, BnBr, Bu_4NI, THF, reflux, 4 h; (iii) aq 2 N HCl, MeOH, 25 °C, 4 h; (iv) 1) *p*-TsCl, Bu_2SnO, Et_3N, CH_2Cl_2, 25 °C, 6 h, 2) $LiAlH_4$, THF, reflux, 8 h; (v) TBDPSCl, imidazole, DMAP, CH_2Cl_2, 25 °C, 7 h; (vi) 1) $BH_3{\cdot}SMe_2$, THF, 0 °C, 3 h, 2) aq NaOH, H_2O_2, 0 °C, 3 h, then 25 °C, 12 h; (vii) PCC, NaOAc, CH_2Cl_2, 0–25 °C, 3 h; (viii) $NaClO_2$, $NaHPO_4{\cdot}2H_2O$, H_2O_2, aq MeCN, 0–15 °C, 6 h.

Synthesis of $\mathbf{B_1}$-Unit

Earlier we have synthesized all the stereomers of the **B1**-unit starting from (±)-sulcatol (**11**) using two highly enantioselective Novozym 435®-catalyzed acylation reactions[5] as the key steps. The acetate **12**, obtained during that course of the synthesis was ideally disposed to provide the $\mathbf{B_1}$-unit. Hence, it was converted into the corresponding allylic alcohol **13**, by treatment with K_2CO_3 in MeOH (Scheme 3). Its benzylation to **14** and subsequent desilylation gave the alcohol **15** ($\mathbf{B_1}$-unit equivalent).

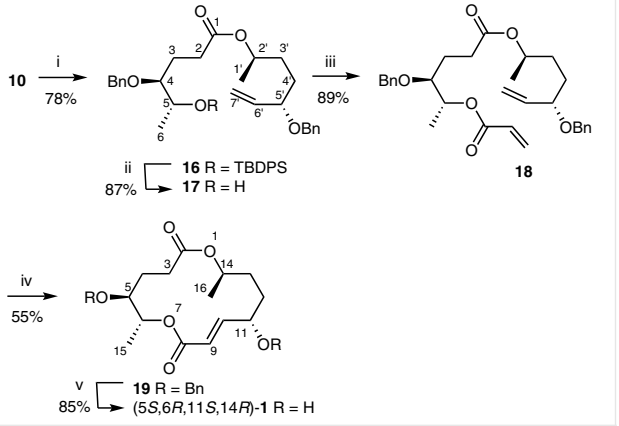


Scheme 3 *Reagents and conditions*: i) Ref. 5; ii) K_2CO_3, MeOH, 25 °C, 4 h; iii) NaH, BnBr, Bu_4NI, THF, reflux, 4 h; iv) Bu_4NF, THF, 0 °C, 7 h.

Synthesis of (5*S*,6*R*,11*S*,14*R*)-1

For the synthesis, the acid **10** was esterified with alcohol **15** under Mitsunobu conditions (Ph_3P, DIAD) to obtain the ester **16** (Scheme 4). Its desilylation turned out to be quite problematic. When attempted with Bu_4NF in THF, decomposition of the ester could not be avoided even at 0 °C, and the recovery of the generated **15** was also unsatisfactory (55% yield). Use of HF in MeCN also led to degradation of **16** to some unidentified products. Although use of

HF·pyridine in THF is seldom recommended for deprotection of secondary TBDPS ethers,[10a] we obtained the desired alcohol **17** in a modest (42%) yield under these conditions. Carrying out the reaction in THF and pyridine[10b] (1:1 v/v) as the solvent led to **17** in a markedly improved yield (87%) without any ester hydrolysis or decomposition. Its conversion into the acrylate **18** with acryloyl chloride/Hünig's base in CH_2Cl_2 proceeded uneventfully. An RCM[11] reaction between the terminal olefin moieties in **18** with Grubbs I catalyst in CH_2Cl_2 at 40 °C gave the macrodiolide **19** along with unreacted **18** (16% yield) under high dilution conditions (2 mM of **18** in CH_2Cl_2). The *E*-geometry of the incipient olefin was confirmed from the ^{1}H NMR olefinic resonances, namely at δ = 5.86 (d, *J* = 16.0 Hz, 1 H) and δ = 6.64 (dd, *J* = 16.0, 9.5 Hz, 1 H). Attempted debenzylation of **19** with DDQ in CH_2Cl_2/H_2O (4:1)[12] furnished an intractable mixture of products. Finally, the required debenzylation was accomplished with $TiCl_4$ in CH_2Cl_2[13] to afford the target compound in 85% yield. However, the spectral data, and the optical rotation {$[\alpha]_D^{26}$ –13.0 (*c* 0.89, MeOH)} of (5*S*,6*R*,11*S*,14*R*)-**1** were not in correspondence with the reported value {$[\alpha]_D^{25}$ +98 (*c* 0.3, MeOH)} of natural acremodiol.[3a] The ^{1}H and ^{13}C spectral data of all three isomers (shown in Figure 1) along with those reported for natural acremodiol have been provided in the Supporting Information to allow comparison of the changes.



Scheme 4 *Reagents and conditions*: i) **15**, Ph_3P, DIAD, THF, 0 to 25 °C, 18 h; ii) HF·Pyr, THF–pyridine (1:1 v/v), 25 °C, 6 h; iii) acryloyl chloride, DIPEA, CH_2Cl_2, 25 °C, 3 h; iv) Grubbs I catalyst, CH_2Cl_2, 40 °C, 48 h; v) $TiCl_4$, CH_2Cl_2, 0 to 25 °C, 0.5 h.

In summary, we have developed a convergent synthesis of (5*S*,6*R*,11*S*,14*R*)-**1**, which features our own chemoenzymatic route and a Ga-mediated carbonyl allylation, as the key steps. Synthesis of the target was achieved in 21 steps in an overall yield of 3.3% as compared to the only report of the synthesis of (5*R*,6*R*,11*R*,14*R*)-**1** (22 steps, 0.7% yield) and its C-11 epimer (26 steps, 0.6% yield), using a Sharpless epoxidation, a Sharpless dihydroxylation, and a Jacobsen resolution for installing the stereocenters. Though our synthesis did not furnish the natural acremodiol, our synthetic plan relies on use of inexpensive reagents/materials and operationally simple and selective reactions, making it more efficient and potentially scalable.

The chemicals were procured from Fluka or Sigma Aldrich and were used as received. Other reagents were of AR grade. Novozym 435® lipase was purchased from Sigma Aldrich. All anhydrous reactions were carried out under an argon atmosphere, using freshly dried solvents. All organic extracts were dried over anhyd Na_2SO_4. IR spectra were recorded as films with a JASCO model A-202 spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ (unless otherwise mentioned) with a Bruker AC-200 instrument or 500 MHz Varian NMR spectrometer. Optical rotations were recorded on a Jasco DIP-360 digital polarimeter. Elemental analyses were recorded on Elementar Vario micro cube. Melting points were recorded on Büchi M 560 instrument.

(2*R*,3*S*)-1,2-Cyclohexylidenedioxyhex-5-en-3-ol (3)

A mixture of Ga metal (0.820 g, 11.77 mmol) and allyl bromide (2.44 mL, 28.23 mmol) in [bmim][Br] (50 mL) was stirred at r.t. for 0.5 h, followed by addition of **2** (4.0 g, 23.53 mmol). After stirring at r.t. for 4 h, the mixture was extracted with Et_2O (2 × 30 mL), the combined organic extracts were evaporated in vacuo, and the residue purified by column chromatography (silica gel, 0–15% EtOAc/hexane) to obtain **3** (4.1 g, 82%) as a colorless oil; $[\alpha]_D^{24}$ +10.5 (*c* 1.24, $CHCl_3$) {Lit.[6k] $[\alpha]_D^{25}$ +10.2 (*c* 1.41, $CHCl_3$)}; R_f = 0.52 (20% EtOAc/hexane).

IR (thin film): 3453, 1642, 1101, 1044 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 5.93–5.72 (m, 1 H, H-5), 5.17–5.09 (m, 2 H, H-6), 4.02–3.89 (m, 3 H, H-2, H-3, H_B-1), 3.81–3.73 (m, 1 H, H_A-1), 2.38–2.10 (m, 2 H, H-4), 1.82 (br s, 1 H, OH), 1.64–1.49 (m, 8 H, 4 × ring CH_2), 1.47–1.24 (m, 2 H, ring CH_2).

(4*S*,5*R*)-4-Benzyloxy-5,6-cyclohexylidenedioxyhex-1-ene (4)

To a stirred suspension of hexane-washed NaH (1.81 g, 50% suspension in oil, 37.68 mmol) in THF (10 mL) was added **3** (4.00 g, 18.84 mmol) in THF (50 mL). After refluxing the mixture for 1 h, it was brought to r.t., BnBr (2.69 mL, 22.61 mmol) and Bu_4NI (10 mol %) were added, and the mixture refluxed until completion of the reaction (TLC, 4 h). The mixture was brought to r.t., extracted with Et_2O (3 × 25 mL), the combined organic extracts were washed with H_2O (2 × 10 mL) and brine (1 × 5 mL), and dried. Removal of solvent in vacuo, followed by column chromatography (silica gel, 0–10% EtOAc/hexane) of the residue afforded pure **4** (5.4 g, 95%) as a colorless oil $[\alpha]_D^{25}$ +27.5 (*c* 1.47, $CHCl_3$) {Lit.[8a] $[\alpha]_D^{25}$ +16.7 (*c* 1.15, $CHCl_3$)}; R_f = 0.91 (10% EtOAc/hexane).

IR (thin film): 3067, 3031, 1641, 998, 926 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.33–7.29 (m, 5 H, C_6H_5), 5.99–5.78 (m, 1 H, H-2), 5.18–5.05 (m, 2 H, H-1), 4.68–4.54 (m, 2 H, OCH_2Ph), 4.12–3.98 (m, 2 H, H-5, H-4), 3.92–3.83 (m, 1 H, H_B-6), 3.60–3.52 (m, 1 H, H_A-6), 2.44–2.34 (m, 2 H, H-3), 1.62–1.55 (m, 8 H, 4 × ring CH_2), 1.44–1.26 (m, 2 H, ring CH_2).

(2*R*,3*S*)-3-Benzyloxyhex-5-ene-l,2-diol (5)

A mixture of **4** (5.35 g, 17.69 mmol) and aq 2 N HCl (4–5 drops) in MeOH (10 mL) was stirred at 25 °C until completion of the reaction (TLC, 4 h). Cyclohexanone dimethyl ketal formed in the reaction was removed by washing with hexane (3 × 20 mL). The MeOH layer was

concentrated in vacuo, the residue diluted with H_2O (30 mL), and extracted with EtOAc (3 × 20 mL). The combined organic extracts were washed successively with H_2O (3 × 20 mL), aq 10% $NaHCO_3$ (2 × 10 mL), H_2O (2 × 20 mL), and brine (1 × 10 mL), and dried. Solvent removal followed by column chromatography (silica gel, 0–5% MeOH/$CHCl_3$) of the residue gave pure **5** (3.8 g, 97%) as a colorless oil; $[\alpha]_D^{26}$ +35.2 (*c* 1.05, $CHCl_3$) {Lit.[9a] $[\alpha]_D^{25}$ +33.9 (*c* 1.0, $CHCl_3$)}; R_f = 0.48 (5% MeOH/$CHCl_3$).

IR (thin film): 3386, 3068, 3010, 1641, 917 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 7.33–7.25 (m, 5 H, C_6H_5), 5.92–5.79 (m, 1 H, H-5), 5.20–5.12 (m, 2 H, H-6), 4.69–4.47 (m, 2 H, OCH_2Ph), 3.73–3.63 (m, 4 H, H-2, H-3, H-1), 2.54–2.25 (m, 2 H, H-4), 1.75 (br s, 2 H, OH).

(2*R*,3*S*)-3-Benzyloxyhex-5-en-2-ol (6)

To a cooled (0 °C) and stirred solution of **5** (3.83 g, 17.23 mmol) and Et_3N (2.88 mL, 20.68 mmol) in CH_2Cl_2 (50 mL) was added *p*-TsCl (3.61 g, 18.95 mmol) followed by Bu_2SnO (129 mg, 0.52 mmol). After stirring for 6 h at r.t., H_2O (15 mL) was added to the mixture, the organic layer separated, and the aqueous layer extracted with $CHCl_3$ (2 × 10 mL). The combined organic extracts were washed with H_2O (1 × 10 mL) and brine (1 × 5 mL), and dried. Solvent removal followed by column chromatography (silica gel, 0–15% EtOAc/hexane) of the residue gave the corresponding primary monotosylate (5.5 g, 85%) as a colorless oil; $[\alpha]_D^{25}$ +33.9 (*c* 1.06, $CHCl_3$); R_f = 0.33 (20% EtOAc/hexane).

IR (thin film): 3528, 3030, 1640, 1360, 1176, 974, 915 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 7.79–7.75 (d, *J* = 8.4 Hz, 2 H, C_6H_5), 7.33–7.24 (m, 7 H, C_6H_5), 5.92–5.71 (m, 1 H, H-5), 5.16–5.06 (m, 2 H, H-6), 4.59 (d, *J* = 11.2 Hz, 1 H, OCH_BPh), 4.41 (d, *J* = 11.2 Hz, 1 H, OCH_APh), 4.24–4.06 (m, 2 H, H-1), 3.88–3.81 (m, 1 H, H-2), 3.56–3.48 (m, 1 H, H-3), 2.42–2.36 [merged s (at δ = 2.42) and m, 5 H, CH_3, H-4], 1.85 (br s, 1 H, OH).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 144.8, 137.7, 133.6, 132.3, 129.7, 128.2, 127.8, 127.6, 117.8, 78.1, 71.9, 71.3, 70.3, 34.2, 21.4.

Anal. Calcd for $C_{20}H_{24}O_5S$: C, 63.81; H, 6.43. Found: C, 64.03; H, 6.82.

To a suspension of $LiAlH_4$ (424 mg, 11.16 mmol) in THF (30 mL) was added dropwise the above tosylate (4.20 g, 11.16 mmol) in THF (20 mL). The mixture was refluxed for 8 h, brought to r.t., and the excess hydride decomposed with sat. aq Na_2SO_4. The mixture was filtered, the filtrate concentrated in vacuo, and the residue purified by column chromatography (silica gel, 0–15% EtOAc/hexane) to obtain pure **6** (2.2 g, 96%) as a colorless oil; $[\alpha]_D^{26}$ +5.8 (*c* 1.01, $CHCl_3$) {Lit.[9b] $[\alpha]_D^{30}$ +3.8 (*c* 0.3, $CHCl_3$)}; R_f = 0.53 (10% EtOAc/hexane).

IR (thin film): 3440, 3068, 3009, 1641, 995, 916 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 7.35–7.31 (m, 5 H, C_6H_5), 5.95–5.77 (m, 1 H, H-5), 5.17–5.04 (m, 2 H, H-6), 4.69–4.52 (m, 2 H, OCH_2Ph), 3.97–3.87 (m, 1 H, H-3), 3.46–3.38 (m, 1 H, H-2), 2.46–2.23 (m, 2 H, H-4), 2.00 (br s, 1 H, OH), 1.18 (d, *J* = 6.4 Hz, 3 H, H-1).

(4*S*,5*R*)-4-Benzyloxy-5-*tert*-butyldiphenylsilyloxyhex-1-ene (7)

To a stirred solution of **6** (2.20 g, 10.67 mmol), imidazole (1.09 g, 16.00 mmol), and DMAP (catalytic) in CH_2Cl_2 (20 mL) was added dropwise TBDPSCl (3.32 mL, 12.80 mmol). After stirring the mixture for 7 h at r.t., it was poured into ice-cold H_2O (20 mL), the organic layer separated, and the aqueous portion extracted with $CHCl_3$ (3 × 10 mL). The combined organic extracts were washed with H_2O (2 × 10 mL) and brine (1 × 5 mL), and dried. Removal of solvent in vacuo followed by purification of the residue by column chromatography (silica gel, 0–5% EtOAc/hexane) afforded pure **7** (4.3 g, 91%) as a colorless oil; $[\alpha]_D^{26}$ –6.0 (*c* 1.24, $CHCl_3$); R_f = 0.70 (5% EtOAc/hexane).

IR (thin film): 3071, 1641, 998, 914 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 7.71–7.66 (m, 4 H, C_6H_5), 7.39–7.31 (m, 11 H, C_6H_5), 5.79–5.61 (m, 1 H, H-2), 5.04–4.95 (m, 2 H, H-1), 4.73 (d, *J* = 11.6 Hz, 1 H, OCH_BPh), 4.55 (d, *J* = 11.6 Hz, 1 H, OCH_APh), 3.94–3.89 (m, 1 H, H-4), 3.43–3.39 (m, 1 H, H-5), 2.33–2.18 (m, 2 H, H-3), 1.07 [merged s (at δ = 1.07) and d, *J* = 6.2 Hz, 12 H, H-6, *t*-C_4H_9].

^{13}C NMR (50 MHz, $CDCl_3$): δ = 139.1, 136.0, 135.5, 134.5, 133.9, 129.6, 129.5, 128.2, 127.6, 127.5, 127.4, 127.3, 116.5, 83.5, 72.7, 71.4, 35.8, 27.0, 19.2, 18.3.

Anal. Calcd for $C_{29}H_{36}O_2Si$: C, 78.33; H, 8.16. Found: C, 78.62; H, 7.93.

(4*S*,5*R*)-4-Benzyloxy-5-*tert*-butyldiphenylsilyloxyhexan-1-ol (8)

To a stirred and cooled (0 °C) solution of **7** (4.30 g, 9.67 mmol) in THF (20 mL) was added $BH_3{\cdot}SMe_2$ (644 µL, 95% purity, 6.45 mmol), and the mixture stirred for 3 h at the same temperature. Aq 3 N NaOH (3.87 mL) was added to the mixture at 0 °C, followed by aq 30% H_2O_2 (3.87 mL). After stirring for 3 h at 0 °C and 12 h at 25 °C, the mixture was extracted with EtOAc (3 × 15 mL). The combined organic extracts were washed with H_2O (2 × 10 mL), aq 10% HCl (1 × 10 mL), H_2O (2 × 10 mL), and brine (1 × 5 mL), and dried. Solvent removal followed by column chromatography (silica gel, 0–15% EtOAc/hexane) of the residue furnished pure **8** (3.9 g, 88%) as a colorless oil; $[\alpha]_D^{25}$ –4.0 (*c* 1.01, $CHCl_3$); R_f = 0.52 (15% EtOAc/hexane).

IR (thin film): 3405, 3070, 3010, 1642, 998 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 7.71–7.64 (m, 4 H, C_6H_5), 7.38–7.29 (m, 11 H, C_6H_5), 4.81 (d, *J* = 11.6 Hz, 1 H, OCH_BPh), 4.47 (d, *J* = 11.6 Hz, 1 H, OCH_APh), 3.93–3.89 (m, 1 H, H-4), 3.54–3.48 (m, 2 H, H-1), 3.38–3.34 (m, 1 H, H-5), 1.55–1.49 (m, 5 H, H-3, H-2, OH), 1.06 [merged s (at δ = 1.06) and d, *J* = 6.2 Hz, 12 H, H-6, *t*-C_4H_9].

^{13}C NMR (50 MHz, $CDCl_3$): δ = 138.8, 136.0, 134.5, 133.9, 129.6, 128.3, 127.8, 127.6, 127.5, 83.7, 72.8, 71.9, 62.8, 29.2, 27.4, 27.0, 19.2, 18.4.

Anal. Calcd for $C_{29}H_{38}O_3Si$: C, 75.28; H, 8.28. Found: C, 75.57; H, 8.11.

(4*S*,5*R*)-4-Benzyloxy-5-*tert*-butyldiphenylsilyloxyhexanal (9)

To a cooled (0 °C) and stirred suspension of PCC (2.54 g, 11.77 mmol) and NaOAc (10 mol%) in CH_2Cl_2 (30 mL) was added the alcohol **8** (3.63 g, 7.85 mmol) in one lot. After stirring for 3 h at 25 °C, the reaction mixture was diluted with Et_2O (30 mL) and the supernatant passed through a column of silica gel. Removal of solvent in vacuo followed by column chromatography of the residue (silica gel, 0–10% EtOAc/hexane) furnished pure **9** (3.2 g, 89%) as a colorless oil; $[\alpha]_D^{26}$ –8.4 (*c* 1.30, $CHCl_3$); R_f = 0.59 (15% EtOAc/hexane).

IR (thin film): 3071, 3014, 2725, 1722 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 9.64 (t, *J* = 1.6 Hz, 1 H, H-1), 7.70–7.68 (m, 4 H, C_6H_5), 7.39–7.27 (m, 11 H, C_6H_5), 4.78–4.61 (m, 1 H, OCH_BPh), 4.49–4.32 (m, 1 H, OCH_APh), 3.96–3.89 (m, 1 H, H-4), 3.37–3.31 (m, 1 H, H-5), 2.38 (dt, *J* = 7.2, 1.6 Hz, 2 H, H-2), 1.84–1.76 (m, 2 H, H-3), 1.08–1.06 (m, 12 H, H-6, *t*-C_4H_9).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 18.7, 19.2, 23.1, 27.0, 40.3, 71.1, 72.4, 82.6, 127.5, 127.6, 127.7, 127.8, 128.2, 129.6, 129.7, 133.6, 134.3, 135.9, 138.5, 202.5.

Anal. Calcd for $C_{29}H_{36}O_3Si$: C, 75.61; H, 7.88. Found: C, 75.97; H, 7.50.

(4*S*,5*R*)-4-Benzyloxy-5-*tert*-butyldiphenylsilyloxyhexanoic Acid (10)

To a stirred solution of **9** (3.00 g, 6.51 mmol) in MeCN (10 mL) was added $NaH_2PO_4·2H_2O$ (203 mg, 1.30 mmol) in H_2O (1 mL) and aq 30% H_2O_2 (810 µL, 7.16 mmol). The mixture was cooled to 0 °C, $NaClO_2$ (1.18 g, 13.02 mmol) in H_2O (1 mL) added dropwise over 0.5 h and stirred at 15 °C until completion of the reaction (6 h, monitored by gas evolution). After the addition of $NaHSO_3$ (250 mg), the mixture was extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with H_2O (2 × 15 mL) and brine (1 × 10 mL), and concentrated in vacuo to get a residue, which on column chromatography (silica gel, 0–10% EtOAc/hexane) furnished pure **10** (2.4 g, 77%) as a viscous colorless oil; $[\alpha]_D^{26}$ –8.3 (*c* 1.10, $CHCl_3$); R_f = 0.47 (25% EtOAc/hexane).

IR (thin film): 3500–2500, 3070, 1709 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 7.72–7.65 (m, 4 H, C_6H_5), 7.41–7.29 (m, 11 H, C_6H_5), 4.75 (d, *J* = 11.6 Hz, 1 H, OCH_BPh), 4.43 (d, *J* = 11.6 Hz, 1 H, OCH_APh), 3.98–3.87 (m, 1 H, H-4), 3.43–3.35 (m, 1 H, H-5), 2.42–2.33 (m, 2 H, H-2), 1.91–1.70 (m, 2 H, H-3), 1.06 [merged s (at δ = 1.07) and d, *J* = 5.0 Hz, 12 H, H-6, *t*-C_4H_9].

^{13}C NMR (50 MHz, $CDCl_3$): δ = 179.8, 138.7, 135.9, 134.4, 133.7, 129.7, 129.6, 128.3, 127.7, 127.6, 127.5, 82.6, 72.6, 71.2, 30.4, 27.0, 25.5, 19.2, 18.6.

Anal. Calcd for $C_{29}H_{36}O_4Si$: C, 73.07; H, 7.61. Found: C, 72.93; H, 7.26.

(3*S*,6*S*)-6-*tert*-Butyldiphenylsilyloxyhept-1-en-3-ol (13)

A mixture of **12** (3.43 g, 8.35 mmol) and K_2CO_3 (1.38 g, 10.02 mmol) in MeOH (20 mL) was stirred at 25 °for 4 h. After filtration, the residue was concentrated in vacuo, dissolved in Et_2O (150 mL), and washed with H_2O (2 × 30 mL) and brine (1 × 10 mL), and dried. Removal of solvent in vacuo followed by column chromatography (silica gel, 0–5% EtOAc/hexane) of the residue afforded pure **13** (2.84 g, 92%) as a colorless liquid; $[\alpha]_D^{24}$ –9.6 (*c* 1.06, $CHCl_3$) {Lit.[5] $[\alpha]_D^{24}$ –10.1 (*c* 1.06, $CHCl_3$)}; R_f = 0.53 (10% EtOAc/hexane).

IR (thin film): 3420, 3050, 997 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 7.70–7.65 (m, 4 H, C_6H_5), 7.42–7.31 (m, 6 H, C_6H_5), 5.87–5.70 (m, 1 H, H-2), 5.20–5.02 (m, 2 H, H-1), 4.00–3.87 (m, 2 H, H-3, H-6), 1.71 (br s, 1 H, OH), 1.55–1.52 (m, 4 H, H-4, H-5), 1.06 [merged s (at δ = 1.06) and d, *J* = 5.6 Hz, 12 H, H-7, *t*-C_4H_9].

(3*S*,6*S*)-3-Benzyloxy-6-*tert*-butyldiphenylsilyloxyhept-1-ene (14)

Benzylation of **13** (2.61 g, 7.09 mmol) with hexane-washed NaH (0.680 g, 14.16 mmol, 50% suspension in oil), BnBr (1.01 mL, 8.51 mmol), and Bu_4NI (10 mol%) in THF (40 mL), followed by workup and column chromatography (silica gel, 0–5% EtOAc/hexane) afforded pure **14** (3.09 g, 95%) as a colorless oil; $[\alpha]_D^{31}$ –24.2 (*c* 1.24, $CHCl_3$) {Lit.[5] $[\alpha]_D^{23}$ –25.0 (*c* 1.20, $CHCl_3$)}; R_f = 0.56 (5% EtOAc/hexane).

IR (thin film): 3070, 1642 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.68–7.62 (m, 4 H, C_6H_5), 7.43–7.27 (m, 11 H, C_6H_5), 5.72-5.65 (m, 1 H, H-2), 5.21–5.09 (m, 2 H, H-1), 4.55 (d, *J* = 12.0 Hz, 1 H, OCH_BPh), 4.29 (d, *J* = 12.0 Hz, 1 H, OCH_APh), 3.88–3.83 (m, 1 H, H-3), 3.67–3.60 (m, 1 H, H-6), 1.69–1.43 (m, 4 H, H-4, H-5), 1.05 [merged s (at δ = 1.06) and d, *J* = 5.5 Hz, 12 H, H-7, *t*-C_4H_9].

(2*S*,5*S*)-5-Benzyloxyhept-6-en-2-ol (15)

To a cooled (0 °C) and stirred solution of **14** (2.95 g, 6.44 mmol) in THF (20 mL) was added Bu_4NF (9.66 mL, 9.66 mmol, 1 M in THF). After stirring for 7 h, the reaction mixture was poured into ice-cold H_2O (15 mL) and extracted with EtOAc (3 × 20 mL). The combined organic extracts were washed with H_2O (2 × 20 mL) and brine (1 × 5 mL), and dried. Removal of solvent followed by column chromatography of the residue (silica gel, 0–10% EtOAc/hexane) furnished **15** (1.26 g, 89%) as a colorless oil; $[\alpha]_D^{32}$ –19.8 (*c* 1.03, $CHCl_3$) {Lit.[5] $[\alpha]_D^{25}$ –20.6 (*c* 1.06, $CHCl_3$)}; R_f = 0.49 (20% EtOAc/hexane).

IR (thin film): 3405, 3065, 3030, 1643 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.38–7.28 (m, 5 H, C_6H_5), 5.80–5.73 (m, 1 H, H-6), 5.26–5.21 (m, 2 H, H-7), 4.60 (d, *J* = 11.5 Hz, 1 H, OCH_BPh), 4.36 (d, *J* = 11.5 Hz, 1 H, OCH_APh), 3.80–3.78 (m, 2 H, H-5, H-2), 1.72–1.50 (m, 5 H, H-4, H-3, OH), 1.18 (d, *J* = 6.5 Hz, 3 H, H-1).

(4*S*,5*R*)-[(2*R*,5*S*)-5-Benzyloxyhept-6-en-2-yl]-4-benzyloxy-5-*tert*-butyldiphenylsilyloxy hexanoate (16)

A solution of **10** (2.22 g, 4.66 mmol), **15** (1.03 g, 4.66 mmol), and PPh_3 (1.83 g, 6.99 mmol), in THF (20 mL) was stirred, cooled to 0 °C and treated with DIAD (1.38 mL, 6.99 mmol). The mixture was stirred for 18 h at r.t., diluted with H_2O, and extracted with EtOAc (2 × 15 mL). The combined organic extracts were washed with H_2O (2 × 10 mL) and brine (1 × 5 mL), and dried. After concentrating in vacuo, the residue was subjected to column chromatography (silica gel, 0–20% EtOAc/hexane) to give pure **16** (2.5 g, 78%) as a colorless oil; $[\alpha]_D^{26}$ –17.1 (*c* 1.01, $CHCl_3$); R_f = 0.69 (10% EtOAc/hexane).

IR (thin film): 3070, 3031, 1730, 998, 928 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 7.70–7.64 (m, 4 H, C_6H_5), 7.39–7.28 (m, 16 H, C_6H_5), 5.77–5.60 (m, 1 H, H-6′), 5.23–5.14 (m, 2 H, H-7′), 4.89–4.80 (m, 1 H, H-2′), 4.72 (d, *J* = 11.4 Hz, 1 H, OCH_BPh), 4.56 (d, *J* = 11.8 Hz, 1 H, OCH_APh), 4.42 (d, *J* = 11.4 Hz, 1 H, OCH_BPh), 4.31 (d, *J* = 12.0 Hz, 1 H, OCH_APh), 3.92–3.87 (m, 1 H, H-5′), 3.74–3.64 (m, 1 H, H-4), 3.40–3.32 (m, 1 H, H-5), 2.37–2.18 (m, 2 H, H-2), 1.62–1.52 (m, 6 H, H-3, H-3′, H-4′), 1.14 (d, *J* = 6.4 Hz, 3 H, H-1′), 1.03 [merged s (at δ = 1.05) and d, *J* = 7.0 Hz, 12 H, H-6, *t*-C_4H_9].

^{13}C NMR (50 MHz, $CDCl_3$): δ = 173.3, 138.9, 138.7, 136.0, 135.9, 134.5, 133.7, 129.6, 129.5, 128.3, 128.2, 127.7, 127.6, 127.4, 117.4, 82.9, 80.0, 72.7, 71.4, 70.5, 70.0, 31.5, 31.2, 30.9, 27.0, 26.0, 19.9, 19.2, 18.6.

Anal. Calcd for $C_{43}H_{54}O_5Si$: C, 76.07; H, 8.02. Found: C, 76.21; H, 8.10.

(4*S*,5*R*)-[(2*R*,5*S*)-5-Benzyloxyhept-6-en-2-yl]-4-benzyloxy-5-hydroxyhexanoate (17)

To a mixture of **16** (1.40 g, 2.06 mmol) and pyridine/THF (1:1, 20 mL) in a Teflon vessel was added HF·pyridine (70:30, 2 mL). After stirring at r.t. for 6 h, the mixture was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with H_2O (2 × 10 mL) and brine (1 × 10 mL) and concentrated in vacuo. The residue was column chromatographed (silica gel, 0–25% EtOAc/hexane) to afford pure **17** (790 mg, 87%) as a colorless oil; $[\alpha]_D^{27}$ –11.3 (*c* 1.03, $CHCl_3$); R_f = 0.43 (15% EtOAc/hexane).

IR (thin film): 3406, 3067, 1720, 1642, 994, 927 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.36–7.27 (m, 10 H, 2 × C_6H_5), 5.72–5.67 (m, 1 H, H-6′), 5.25–5.20 (m, 2 H, H-7′), 4.91–4.87 (m, 1 H, H-2′), 4.59 (d, *J* = 12.5 Hz, 1 H, OCH_BPh), 4.57 (d, *J* = 11.5 Hz, 1 H, OCH_APh), 4.54 (d, *J* = 11.0 Hz, 1 H, OCH_BPh), 4.33 (d, *J* = 11.5 Hz, 1 H, OCH_APh), 3.98–3.93 (m, 1 H, H-5′), 3.74–3.70 (m, 1 H, H-4), 3.36–3.35 (m, 1 H, H-5), 2.51–2.44 (m, 1 H, H_B-2), 2.39–2.32 (m, 1 H, H_A-2), 1.95–1.81 (m, 3 H, H-3, OH), 1.73–1.64 (m, 2 H, H-3′), 1.53–1.48 (m, 2 H, H-4′), 1.19 (two overlapping d, *J* = 7.0, 6.0 Hz, 6 H, H-1′, H-6).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 173.5, 138.7, 138.6, 138.2, 128.5, 128.3, 127.9, 127.8, 127.7, 127.5, 117.5, 81.9, 80.0, 72.1, 70.8, 70.1, 67.4, 31.6, 31.3, 30.3, 23.6, 20.0, 18.0.

Anal. Calcd for $C_{27}H_{36}O_5$: C, 73.61; H, 8.24. Found: C, 73.95; H, 8.62.

(4*S*,5*R*)-[(2*R*,5*S*)-5-Benzyloxyhept-6-en-2-yl]-5-acryloyloxy-4-benzyloxyhexanoate (18)

To a cooled (0 °C) solution of **17** (790 mg, 1.79 mmol) in CH_2Cl_2 (15 mL) were added DIPEA (0.60 mL, 3.59 mmol) and acryloyl chloride (0.29 mL, 3.59 mmol). After stirring at r.t. for 3 h, the mixture was poured into ice-cold H_2O (20 mL), the organic layer separated, and the aqueous portion extracted with $CHCl_3$ (3 × 10 mL). The combined organic extracts were washed with H_2O (2 × 10 mL) and brine (1 × 5 mL), and dried. Removal of solvent in vacuo followed by purification of the residue by column chromatography (silica gel, 0–20% EtOAc/hexane) afforded pure **18** (790 mg, 89%) as a colorless oil; $[\alpha]_D^{26}$ –26.1 (*c* 1.22, $CHCl_3$); R_f = 0.51 (10% EtOAc/hexane).

IR (thin film): 3066, 3029, 1725, 1639, 1620, 987, 928 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.34–7.26 (m, 10 H, 2 × C_6H_5), 6.41 (d, *J* = 17.5, Hz, 1 H, olefinic), 6.13 (dd, *J* = 17.5, 10.5 Hz, 1 H, olefinic), 5.83 (d, *J* = 10.5 Hz, 1 H, olefinic), 5.76–5.68 (m, 1 H, H-6′), 5.25–5.16 (m, 3 H, H-7′, H-5), 4.91–4.87 (m, 1 H, H-2′), 4.71 (d, *J* = 11.5 Hz, 1 H, OCH_BPh), 4.59 (d, *J* = 12.0 Hz, 1 H, OCH_APh), 4.48 (d, *J* = 11.0 Hz, 1 H, OCH_BPh), 4.34 (d, *J* = 11.5 Hz, 1 H, OCH_APh), 3.75–3.70 (m, 1 H, H-5′), 3.55–3.51 (m, 1 H, H-4), 2.48–2.43 (m, 1 H, H_B-2), 2.39–2.33 (m, 1 H, H_A-2), 1.89–1.82 (m, 2 H, H-3), 1.71–1.64 (m, 2 H, H-3′), 1.55–1.49 (m, 2 H, H-4′), 1.31 (d, *J* = 6.0 Hz, 3 H, H-6), 1.18 (d, *J* = 6.5 Hz, 3 H, H-1′).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 173.0, 165.5, 138.7, 138.6, 138.2, 128.7, 128.4, 128.3, 127.9, 127.7, 127.4, 117.4, 80.0, 79.8, 72.6, 71.7, 70.7, 70.1, 31.6, 31.2, 30.7, 25.8, 19.9, 15.0.

Anal. Calcd for $C_{30}H_{38}O_6$: C, 72.85; H, 7.74. Found: C, 72.46; H, 7.62.

(9*E*,5*S*,6*R*,11*S*,14*R*)-5,11-Dibenzyloxy-6,14-dimethyl-1,7-dioxacyclotetradec-9-ene-2,8-dione (19)

A mixture of **18** (300 mg, 0.61 mmol) and Grubbs I catalyst (150 mg, 0.18 mmol) in degassed CH_2Cl_2 (300 mL) was stirred at 40 °C for 48 h. After concentrating the mixture in vacuo, the residue was subjected to purification by preparative TLC (silica gel, 10% EtOAc/hexane) to furnish pure **19** (130 mg, 55% based on conversion) and recovered **18** (50 mg) as a white solid; mp 91–93 °C; $[\alpha]_D^{28}$ –45.3 (*c* 1.11, $CHCl_3$); R_f = 0.42 (10% EtOAc/hexane).

IR (thin film deposited from $CHCl_3$ solution): 3019, 1720, 1648, 1029, 985 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.37–7.27 (m, 10 H, 2 × C_6H_5), 6.64 (dd, *J* = 16.0, 9.5 Hz, 1 H, H-10), 5.86 (d, *J* = 16.0 Hz, 1 H, H-9), 5.21–5.15 (m, 1 H, H-6), 4.76–4.73 (m, 1 H, H-14), 4.57 (d, *J* = 11.5 Hz, 1 H, OCH_BPh), 4.53 (d, *J* = 10.5 Hz, 1 H, OCH_APh), 4.49 (d, *J* = 10.5 Hz, 1 H, OCH_BPh), 4.37 (d, *J* = 12.0 Hz, 1 H, OCH_APh), 3.78–3.73 (m, 1 H, H-11), 3.34–3.30 (m, 1 H, H-5), 2.41–2.32 (m, 2 H, H-3), 2.10–1.99 (m, 2 H, H-4), 1.89–1.82 (m, 2 H, H-13), 1.70–1.66 (m, 1 H, H-12), 1.58–1.51 (m, 1 H, H-12), 1.34 (d, *J* = 6.0 Hz, 3 H, H-15), 1.13 (d, *J* = 6.5 Hz, 3 H, H-16).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.3, 164.8, 147.9, 137.9, 137.8, 128.5, 128.2, 127.7, 125.0, 81.7, 78.4, 72.0, 71.3, 70.5, 69.1, 31.7, 28.6, 28.1, 24.4, 18.8, 17.6.

Anal. Calcd for $C_{28}H_{34}O_6$: C, 72.08; H, 7.35. Found: C, 72.38; H, 7.25.

(5*S*,6*R*,11*S*,14*R*)-1

To a stirred and cooled (0 °C) solution of **19** (25 mg, 0.05 mmol) in CH_2Cl_2 (2 mL) was added $TiCl_4$ (11.8 µL, 0.11 mmol) and the mixture stirred at r.t. until the completion of the reaction (TLC, 0.5 h). After concentration in vacuo, the residue was purified by preparative TLC (silica gel, 5% MeOH/$CHCl_3$) to get pure (5*S*,6*R*,11*S*,14*R*)-**1** (13 mg, 85%) as a white solid; mp 133–135 °C (Lit.[3a] mp 110–112 °C for natural **1**); $[\alpha]_D^{26}$ –13.0 (*c* 0.89, MeOH) {Lit.[3a] $[\alpha]_D^{25}$ +98 (*c* 0.3, MeOH) for natural **1**)}; R_f = 0.43 (5% MeOH/$CHCl_3$).

IR (thin film deposited from a $CHCl_3$ solution): 3405, 1723, 1653, 1648, 985 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 6.56 (dd, 16.5, 8.5 Hz, 1 H, H-10), 5.92 (d, *J* = 16.0 Hz, 1 H, H-9), 5.27–5.22 (m, 1 H, H-6), 4.90–4.87 (m, 1 H, H-14), 4.39 (br s, 1 H, OH-5), 4.17–4.11 (m, 1 H, H-11), 3.72–3.76 (m, 1 H, H-5), 2.92–2.86 (m, 1 H, H_B-3), 2.61–2.56 (m, 1 H, H_A-3), 2.17–2.11 (m, 1 H, H_B-4), 2.00–1.94 (m, 1 H, H_A-4), 1.89–1.84 (m, 1 H, H_B-13), 1.79–1.74 (m, 3 H, H_A-13, H_B-12, OH-11), 1.69–1.60 (m, 1 H, H_A-12), 1.27 (d, *J* = 7.0 Hz, 3 H, H-15), 1.20 (d, *J* = 6.5 Hz, 3 H, H-16).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 175.1, 164.9, 147.8, 123.2, 74.1, 72.6, 71.5, 70.4, 31.9, 29.7, 28.8, 26.2, 19.2, 16.6.

Anal. Calcd for $C_{14}H_{22}O_6$: C, 58.73; H, 7.74. Found: C, 59.07; H, 7.68.

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1588557.

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