An Expeditious Asymmetric Synthesis of Polyfunctional 1,7-Dioxaspiro[5.5]undecanes

Sandrine Gerber-Lemaire*[a] and Pierre Vogel[a]

Keywords: Bis(cyclohept-1-ene) derivatives / Ozonolysis / Polyfunctional spiroketals / Selective protection

Quick access to polyfunctional spiroketal (3*R*)-4-[(2*S*,6*R*,8*R*,10*S*)-4,4-bis(ethylthio)-10-hydroxy-8-(2-hydroxyethyl)-1,7-dioxaspiro[5.5]undec-2-yl]butane-1,3-diol [(+)-**19**] is now available through the stereoselective functionalization of enantiomerically pure protected tetrol (4*R*,4′*R*,6*R*,6′*R*)-1,1′-methylenebis[4-[(benzyloxy)methoxy]-6-[(triethylsilyl)oxy]cyclohept-1-ene [(−)-**9**], derived from 2,2′-methylenedifuran.

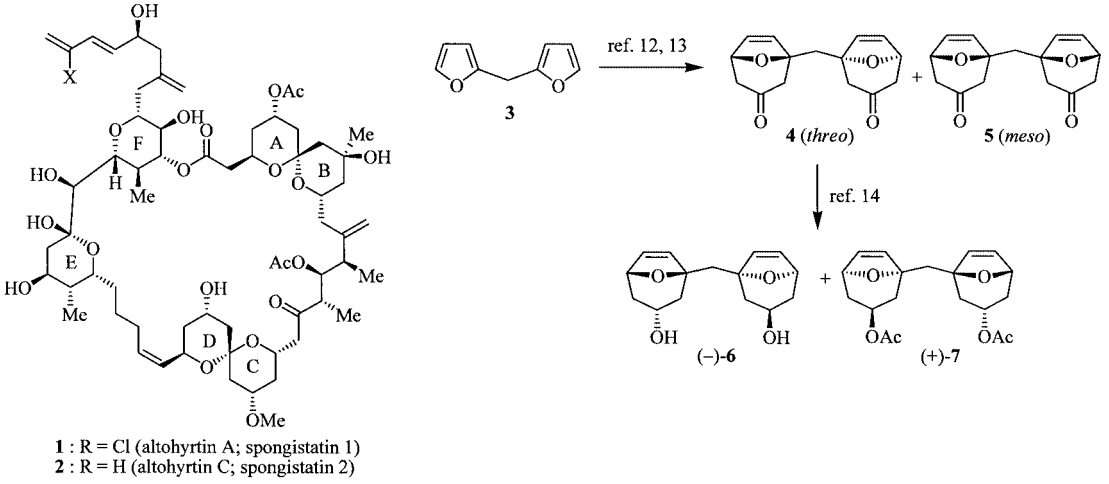
Introduction

A large variety of natural products of biological interest contain the 1,7-dioxaspiro[5.5]undecane (6,6-spiroketal) moiety.[1−4] Several synthetic approaches to spiroketals have been proposed,[5] and the focus during the last decade has been on the two AB and CD spiroketal units[6] of altohyrtins (spongistatins),[7] highly promising anti-tumor agents[8] isolated in minute amounts from rare marine sponges.[9−11]

Our group has developed a noniterative, asymmetric synthesis of C_{15} polyketides, starting from the readily available 2,2′-methylenedifuran (**3**). Double [4+3] cycloaddition of halogenated 2-oxyallyl cations to **3** generates, after reductive workup, a 55:45 mixture of diketones **4** and **5** (60%yield) that are readily separated (Scheme 1).[12] In theory, all possible pentadecan-1,3,5,7,9,11,13,15-octols can be prepared from *meso*-**5**.[13] We have reported that *threo*-**4** can be converted into the enantiomerically pure diacetate (+)-**7** and diol (−)-**6**,[14] and we have shown that they can be transformed in a few steps into enantiomerically pure, long-chain polyketides.[15] We report here that (+)-**7** can be converted into polyfunctional 1,7-dioxaspiro[5.5]undecanes related to the spiroketal moieties of spongistatins.

Results and Discussion

As already reported, (+)-**7** can be transformed into the semi-protected tetrol (−)-**8** in 68% yield (Scheme 2). Double silylation with Et_3SiCl/imidazole provided (−)-**9**

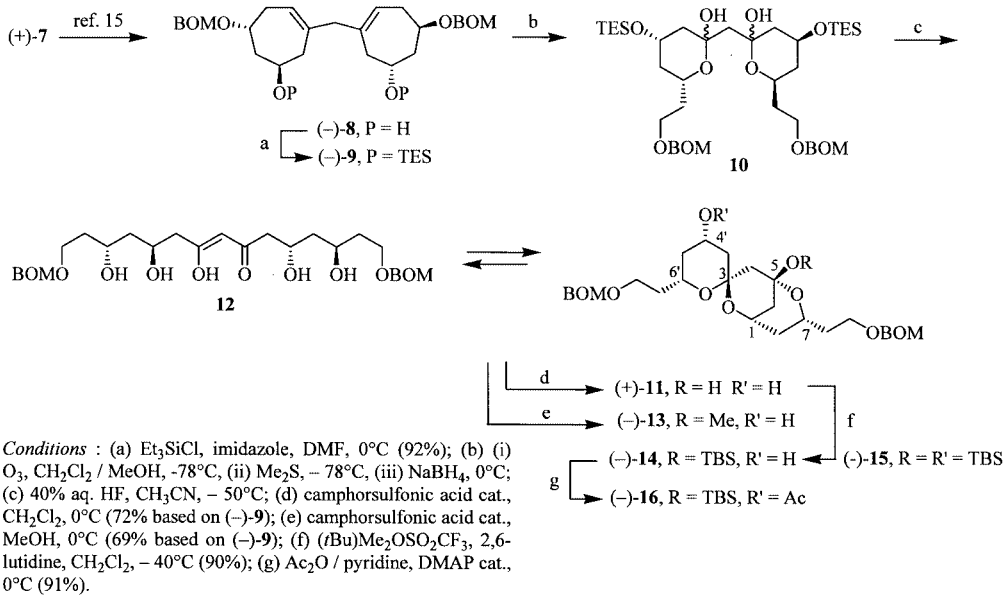


Scheme 1

(92%). Ozonolysis of (−)-**9** in an MeOH/CH_2Cl_2 (1:1) mixture (−78 °C), followed by reductive treatment first with Me_2S (−78 °C) and then with $NaBH_4$ at 0 °C, afforded a mixture of dihemiacetals **10** that was not isolated but was directly subjected to acidic treatment (40% aq. HF in

[a] Institute of Chemical Sciences and Engineering, Swiss Institute of Technology (EPFL),
BCH, 1015 Lausanne, Switzerland
Fax: (internat.) + 41-21-693-93-55
E-mail: Sandrine.Gerber@epfl.ch

  DOI: 10.1002/ejoc.200400514



Scheme 2. Synthesis of protected tricyclic spiroketals

CH_3CN, −50 °C). A mixture of tricyclic hemiacetal **11** and β-hydroxyenone **12** was formed (^{1}H NMR analysis of the crude product). When this mixture was treated with a catalytic amount of camphorsulfonic acid in MeOH at 0 °C, spiroketal (−)-**13** was obtained in 69% yield [based on (−)-**9**]. In the absence of MeOH, treatment of **11** and **12** under the same catalytic conditions in CH_2Cl_2 (0 °C) provided pure (+)-**11** in 72% yield. Silylation with 1 equiv. of (*t*Bu)-$Me_2SiOSO_2CF_3$ in the presence of 2,6-lutidine at low temperature (−40 °C) was highly selective and resulted in the formation of the semi-protected spiroketal (−)-**14** in 90% yield. The reasons for the faster silylation of the tertiary alcoholic moiety of the hemiacetal relative to the secondary alcohol group of (+)-**11** are not clear to us.[16] With the use of 2 equiv. of (*t*Bu)$Me_2SiOSO_2CF_3$, a mixture of the disilylated derivative (−)-**15** (60% yield) and (−)-**14** (23% yield) was observed.

Acetylation of alcohol (−)-**14** under standard conditions (Ac_2O/pyridine, DMAP cat., 0 °C) gave acetate (−)-**16** (91%), the structure of which was established by its spectroscopic data and especially its 2D-NOESY ^{1}H NMR spectrum (Figure 1). Proton signal assignments were carried out as follows. The most deshielded multiplet (δ_H = 5.69 ppm) was assigned to C(4′)-H. It showed cross-peaks with signals at δ_H = 2.24 and 1.99 ppm. These signals in turn did not present any cross-peak with other protons adjacent to oxygen atoms, and so were assigned to C(3′)-H_2. The multiplet at δ_H = 1.86−1.95 ppm showed cross-peaks with the signal of C(4′)-H and with a multiplet at δ_H = 4.00 ppm [C(6′)-H], and so was assigned to C(5′)-H_2. The other multiplet (δ_H = 4.26 ppm) presenting cross peaks with the signal of CH_2CH$_2$OBOM corresponds to C(7)-H, and the remaining signal of a proton adjacent to an oxygen atom (δ_H = 4.85 ppm) was thus assigned to C(1)-H. The signals of C(4)-H_2 at δ = 1.85 and 2.69 ppm and of C(9)-H_2 at δ = 1.79 ppm were then easily assigned from their multiplicities. The (*S*) absolute configuration at C(3) and the conformation of the spiroketal were established from the 2D-NOESY-^{1}H NMR spectrum of (−)-**16**. The most stable spiroketal (two axial oxygen atoms, double anomeric effect, *conformation B*) was not verified by the NOEs observed. In particular, two cross-peaks between the signals of C(4)-H_2 (δ_H = 1. 85 and 2.69 ppm) and C(3′)-H_2 (δ_H = 1.99 and 2.24 ppm) would be expected for this structure, and these were not observed in the 2D-NOESY-^{1}H NMR spectrum. On the contrary, diagnostic NOEs required for *conformation A* [C(6′)-H/C(4′)-H, C(4′)-H/C(1)-H, C(7)-H/C(9)-H, C(9)-H/C(3′)-H] were observed. This established the formation of the kinetic spiroketal (axial/equatorial arrangement), which was trapped by the formation of an additional hemiacetal at C(5). The structures of the (3*R*) enantiomer (kinetic or thermodynamic conformers) were not verified

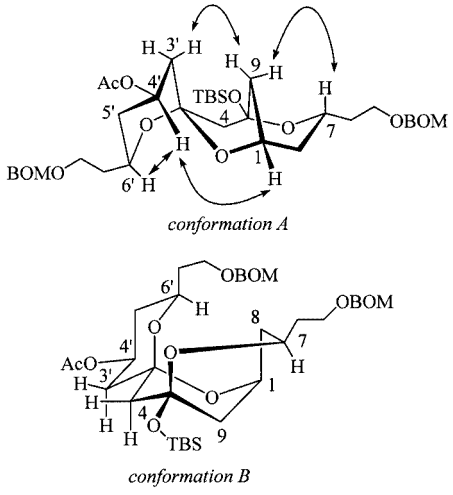
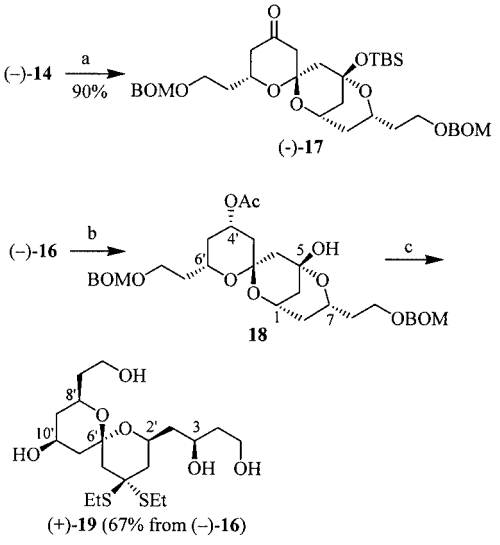


Figure 1. Representation of (−)-**16** with indication of the proton pairs presenting diagnostic NOEs in the 2D-NOESY ^{1}H NMR spectrum

by the cross-peaks observed. The 2D-NOESY-^{1}H NMR spectrum of (−)-**16** was thus consistent with a (3*S*)-configured spiroketal.

Attempts to oxidize the alcohol of (+)-**11** under Dess−Martin,[17] Swern,[18] and Ley's[19] conditions resulted in decomposition of the starting material. Under the same conditions, methyl acetal (−)-**13** also decomposed and the expected ketone could not be isolated in better yield than 10%. Fortunately, silyl acetal (−)-**14** was successfully oxidized under Ley's conditions (Pr_4NRuO_4 0.2 equiv., NMO, molecular sieves) to provide the desired ketone (−)-**17** in 90% yield.

If our methodology for the synthesis of 1,7-dioxaspiro[5.5]undecanes is to be applied to the formation of spongistatins, the tricyclic system will have to be opened (Scheme 3). This operation can be achieved in good yield by desilylation of (−)-**16** in the presence of aqueous HF at −40 °C (98% crude yield), followed by a subsequent thioacetalization step in a mixture of EtSH/CH_2Cl_2 (1:10) in the presence of BBr_3 (2 equiv., 0 °C). This acidic treatment induced the opening of the silyl acetal at the C(5) position, allowing protection of the resulting ketone as a dithioacetal and equilibration of the spiroketal to the most stable conformer (axial/axial arrangement). This sequence provided (+)-**19** in 67% yield [based on (−)-**16**]. Selective functionalization of each ring of these spiroketals should thus be possible through derivatization of the ketone at C(4′) position of (−)-**17** or at C(4′) position of (+)-**19**.



Conditions : (a) TPAP cat., NMO, MS 4A, CH_2Cl_2, 25°C; (b) 40% aq. HF, CH_3CN, – 40°C; (c) BBr_3, EtSH, CH_2Cl_2, 0°C

Scheme 3. Preparation of the polyfunctional spiroketal (+)-**19**

Conclusion

The chemistry disclosed in this report demonstrates the versatility of our noniterative approach to the preparation of C_{15} polyketides and to spiroketals derived from them. Quick access to polyfunctional 1,7-dioxaspiro[5.5]undecanes is now available. The formation of a tricyclic structure [hemiacetal at C(5)] allows the trapping of the less energetically favored kinetic spiroketal. Moreover, as various stereoisomers of the starting diolefin (−)-**9** can easily be obtained through the same methodology [*meso* and *threo* derivatives, C(6),C(6′)-*exo* and -*endo* diols], the transformations reported here can generate a high diversity of stereoisomeric spiroketals on gram scale amounts. Studies to obtain analogues of the spiroketals described here and intermediates useful for the synthesis of natural products of biological interest, including spongistatins, are underway in our laboratory.

Experimental Section

General: Commercial reagents (Fluka, Aldrich) were used without purification. Solvents were distilled prior to use: MeOH from Mg and I_2, DMF from P_2O_5, and CH_2Cl_2 from CaH_2. Light petroleum ether used refers to the fraction boiling at 40−60 °C. Solutions after reactions and extractions were concentrated in a rotary evaporator under reduced pressure. Liquid/solid flash chromatography (FC): columns of silica gel (0.040−0.63 mm, Merck No.9385 silica gel 60, 240−400 mesh). TLC for reaction monitoring: Merck silica gel $60F_{254}$ plates; detection by UV light; Pancaldi reagent [$(NH_4)_6MoO_4$, $Ce(SO_4)_2$, H_2SO_4, H_2O] or $KMnO_4$. IR spectra: Perkin−Elmer 1420 spectrometer. ^{1}H NMR spectra: Bruker ARX 400 spectrometer (400 MHz); δ(H) in ppm relative to the solvent's residual ^{1}H signal ($CHCl_3$: δ = 7.27 ppm; CH_3OD: δ = 3.34 ppm; C_6H_6: δ = 7.3 ppm) as internal reference; all ^{1}H assignments were confirmed by 2D-COSY-45 and 2D-NOESY spectra. ^{13}C NMR spectra: Same instrument as above (100.6 MHz); δ(C) in ppm relative to solvent's ^{13}C signal ($CDCl_3$: δ = 77.0 ppm; CD_3OD: δ = 48.5 ppm; C_6D_6: δ = 128.5 ppm) as internal reference; coupling constants *J* in Hz. MS: Nermag R-10-10C, chemical ionization (NH_3) mode *m*/*z* (amu) [% relative base peak (100%)]. MALDI-TOF mass spectra were obtained from the Swiss Institute of Technology Mass Spectral Facility. Elemental analyses: Ilse Beetz, 96301 Kronach, Germany.

(4*R*,4′*R*,6*R*,6′*R*)-4,4′-Bis(benzyloxy)methoxy-6,6′-bis(triethylsilyl)-oxy-1,1′-methylenebis(cyclohept-1-ene) [(−)-9]: Imidazole (5 equiv., 2.34 g, 34.41 mmol) and chlorotriethylsilane (3 equiv., 3.5 mL, 20 64 mmol) were added at 0 °C to a solution of (−)-**8**[15] (3.5 g, 6.881 mmol) in DMF (70 mL). After stirring at 0 °C for 45 min, the mixture was poured into H_2O (150 mL) and extracted with diethyl ether (100 mL, 3 times). The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (EtOAc/PE, 1:6) to afford (−)-**9** as a colorless oil (4.66 g, 92%). R_f = 0.55 (EtOAc/EP, 1:6). $[\alpha]_D^{20}$ = −38, $[\alpha]_{577}^{20}$ = −42, $[\alpha]_{546}^{20}$ = −46, $[\alpha]_{435}^{20}$ = −83, $[\alpha]_{405}^{20}$ = −105 (*c* = 0.66, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3030, 2955, 2910, 2875, 1740, 1500, 1455, 1415, 1375, 1240, 1165, 1080, 1040, 1030, 870, 745 cm^{-1}. UV (MeCN): $\lambda_{max.}$ (ε [dm^3·mol^{-1}·cm^{-1}]) = 218 (15230) nm. ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C): δ = 0.58, 0.60 [2 q, $^3J_{H,H}$ = 6.5, 6.7 Hz, 12 H, 6 CH_2 (TES)], 0.96 [m, 18 H, 6 CH_3 (TES)], 1.97 [ddd, $^2J_{H,H}$ = 13.5, $^3J_{H,H}$ = 8.4, 3.3 Hz, 2 H, C(5)-H, C(5′)-H], 2.07−2.10 [m, 2 H, C(5)-H, C(5′)-H], 2.15 [br. d, $^2J_{H,H}$ = 14.8 Hz, 2 H, C(7)-H, C(7′)-H], 2.28−2.40 [m, 4 H, C(3)-H_2, C(3′)-H_2], 2.72 [s, 2 H, C(8)-H_2], 3.91−4.00 [m, 4 H, C(4)-H, C(6)-H, C(4′)-H, C(6′)-H], 4.62 [s, 4 H, 2CH_2Ph], 4.78 [AB system, 4 H, 2

CH_2 (BOM)], 5.46 [t, $^3J_{H,H}$ = 6.2 Hz, 2 H, C(2)-H, C(2′)-H], 7.38−7.28 (m, 10 H, $H_{arom.}$) ppm. ^{13}C NMR ($CDCl_3$, 100.6 MHz, 25 °C): δ = 4.75 [t, $^1J_{C,H}$ = 117, 6 CH_2 (TES)], 6.9 [q, $^1J_{C,H}$ = 121, 6 CH_3 (TES)], 32.8 [t, $^1J_{C,H}$ = 128, C(7), C(7′)], 40.3 [t, $^1J_{C,H}$ = 129, C(3), C(3′)], 46.4 [t, $^1J_{C,H}$ = 125, C(5), C(5′)], 51.5 [t, $^1J_{C,H}$ = 125, C(8)], 66.0 [d, $^1J_{C,H}$ = 140, C(6), C(6′)], 69.3 [t, $^1J_{C,H}$ = 144, 2 CH_2Ph], 71.6 [d, $^1J_{C,H}$ = 146, C(4), C(4′)], 92.6 [t, $^1J_{C,H}$ = 162, 2 CH_2 (BOM)], 123.1 [d, $^1J_{C,H}$ = 156, C(2), C(2′)], 127.6, 127.8, 128.4 [3 d, $^1J_{C,H}$ = 160, 158, 161, 10 $C_{arom.}$], 138.0 (s, 2 $C_{arom.}$), 138.1 [s, C(1), C(1′)] ppm. CI-MS: *m*/*z* (%) = 754 (57) [M + NH_4^+], 600 (2), 467 (5), 377 (10), 245 (11), 132 (16), 91 (100) [$PhCH_2^+$]. $C_{43}H_{68}O_6Si_2$ (737.176): calcd. C 70.06, H 9.30; found C 70.01, H 9.16.

(1*S*,3*S*,4′*S*,5*R*,6′*R*,7*R*)-6′,7-Bis{2-[(benzyloxy)methoxy]ethyl}-tetrahydrospiro[2,6-dioxabicyclo[3.3.1]nonane-3,2′-pyran]-4′,5-diol [(+)-11]: A stream of ozone was passed at −78 °C through a solution of (−)-**9** (1.5 g, 2.035 mmol) in CH_2Cl_2/MeOH (25 mL/25 mL) for 5 min. A stream of O_2 was passed through the mixture for 2 min, and Me_2S (4equiv., 645 μL, 8.139 mmol) was added dropwise. After the mixture had been stirred at −78 °C for 5 min, $NaBH_4$ (4 equiv., 308 mg, 8.139 mmol) was added and the mixture was warmed to 0 °C for 30 min. Acetic acid (500 μL) was added, and the solution was stirred at 0 °C for an additional 5 min. The mixture was poured into a satd. aq. solution of $NaHCO_3$ (80 mL) and extracted with EtOAc (80 mL, 3 times). The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo to afford a pale yellow oil (1.6 g, 98%). HF (40% in water, 4.5 mL) was added dropwise at −50 °C to a solution of the crude bis(hemiketals) **10** (1.6 g, 1.987 mmol) in MeCN (45 mL). After stirring at −50 °C for 20 min, the mixture was poured, with vigorous stirring, into a satd. aq. solution of $NaHCO_3$ (100 mL), cooled to 0 °C. After 5 min, solid $NaHCO_3$ was added to reach pH = 8 and the solution was extracted with EtOAc (80 mL, 3 times). The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. The residue (mixture of **11** and **12**) was taken up in CH_2Cl_2 (20 mL), cooled to 0 °C, and treated with camphorsulfonic acid (30 mg). After stirring at 0 °C for 30 min, the mixture was directly purified by flash chromatography on silica gel (CH_2Cl_2/MeOH, 15:1) to afford (+)-**11** as a colorless oil [818 mg, 72% from (−)-**9**].

Data for Intermediate (3*R*,5*S*,11*S*,13*R*)-1,15-Bis[(benzyloxy)methoxy]-3,5,9,11,13-pentahydroxypentadec-8-en-7-one (12): R_f = 0.3 (CH_2Cl_2/MeOH, 10:1). IR (film): $\tilde{\nu}$ = 3385, 2940, 1650, 1600, 1495, 1435, 1430, 1405, 1380, 1165, 1035 cm^{-1}. UV (MeCN): $\lambda_{max.}$ (ε [dm^3·mol^{-1}·cm^{-1}]) = 208 (10180), 197 (10150) nm. ^{1}H NMR ([D$_4$]MeOH, 400 MHz, 25 °C): δ = 1.68 [m, $^2J_{H,H}$ = 13.0 Hz, 1 H, C(4)-H], 1.72−1.89 [m, 6 H, C(2)-H_2, C(12)-H_2, C(14)-H_2], 2.04 [ddd, $^2J_{H,H}$ = 13.0, $^3J_{H,H}$ = 9.8, 3.2 Hz, 1 H, C(4)-H], 2.40 [m, 2 H, C(6)-H, C(10)-H], 2.49 [d, $^2J_{H,H}$ = 13.8 Hz, 1 H, C(10)-H], 2.52 [d, $^2J_{H,H}$ = 15.9, 1 H, C(6)-H], 3.69, 3.70 [2 t, $^3J_{H,H}$ = 6.6 Hz, 4 H, C(1)-H_2, C(15)-H_2], 4.04 [m, 1 H, C(3)-H], 4.13 [m, 2 H, C(11)-H, C(13)-H], 4.63, 4.64 [2 s, 4 H, 2CH_2Ph], 4.66 [m, 1 H, C(5)-H], 4.84, 4.85 [2 s, 4 H, 2 CH_2 (BOM)], 5.38 [s, 1 H, C(8)-H], 7.27−7.39 (m, 10 H, $H_{arom.}$) ppm. ^{13}C NMR ([D$_4$]MeOH, 100.6 MHz, 25 °C): δ = 40.1, 40.2 [2 t, C(2), C(14)], 42.2 [t, C(4)], 44.8 [t, C(12)], 42.8, 45.5 [2 t, C(6), C(10)], 60.1, 60.3 [2 t, C(1), C(15)], 67.6 [d, C(11)], 71.7, 71.9 [2 t, 2CH_2Ph], 74.6, 75.3 [2 d, C(3), C(13)], 78.5 [d, C(5)], 96.6, 96.7 [2 t, 2CH_2 (BOM)], 107.2 [d, C(8)], 129.6, 129.8, 130.3 (3 d, 10 $C_{arom.}$), 140.0, 140.1 (2 s, 2 $C_{arom.}$), 178.4 [s, C(9)], 196.7 [s, C(7)] ppm.

Data for (+)-11: R_f = 0.13 (CH_2Cl_2/MeOH, 15:1). $[\alpha]_D^{20}$ = +11, $[\alpha]_{577}^{20}$ = +12, $[\alpha]_{435}^{20}$ = +23, $[\alpha]_{405}^{20}$ = +26 (*c* = 0.36, CH_2Cl_2). IR (film): $\tilde{\nu}$ = 3445, 3030, 2945, 2895, 1655, 1635, 1555, 1455, 1375, 1325, 1210, 1165, 1040, 815, 740, 700 cm^{-1}. UV (MeCN): $\lambda_{max.}$ (ε [dm^3·mol^{-1}·cm^{-1}]) = 254 (18250), 198 (8790) nm. ^{1}H NMR ([D$_4$]MeOH, 400 MHz, 25 °C): δ = 1.61 [dd, $^2J_{H,H}$ = 9.6, $^3J_{H,H}$ = 3.4 Hz, 1 H, C(3′)-H], 1.62 [dd, $^2J_{H,H}$ = 10.9, $^3J_{H,H}$ = 3.4 Hz, 1 H, C(8)-H], 1.60−1.93 [m, 7 H, C(7)-CH_2, C(9)-H_2, C(3′)-H, C(6′)-CH_2], 1.94 [d, $^2J_{H,H}$ = 11.0 Hz, 1 H, C(4)-H], 1.99 [dm, $^3J_{H,H}$ = 10.9 Hz, 1 H, C(8)-H], 2.85 [dd, $^2J_{H,H}$ = 11.0, $^4J_{H,H}$ = 2.7 Hz, 1 H, C(4)-H], 3.69 [t, $^3J_{H,H}$ = 6.6 Hz, 4 H, 2 CH_2-OBOM], 3.99−4.14 [m, 3 H, C(7)-H, C(4′)-H, C(6′)-H], 4.48−4.55 [m, 1 H, C(1)-H], 4.66 (s, 2 H, CH_2Ph), 4.67, 4.72 (2 d, 2 H, $^2J_{H,H}$ = 12.0 Hz, CH_2Ph), 4.86 [s, 4 H, 2 CH_2 (BOM)], 7.28−7.40 (m, 10 H, $H_{arom.}$) ppm. ^{13}C NMR ([D$_4$]MeOH, 100.6 MHz, 25 °C): δ = 39.7, 40.2 [2 t, $^1J_{C,H}$ = 125, 126, C(7)-CH_2, C(6′)-CH_2], 43.6 [t, $^1J_{C,H}$ = 125, C(9)], 42.8 [t, $^1J_{C,H}$ = 127, C(8)], 44.3 [t, $^1J_{C,H}$ = 125, C(5′)], 45.4 [t, $^1J_{C,H}$ = 127, C(3′)], 45.6 [t, $^1J_{C,H}$ = 128, C(4)], 60.2, 60.3 [2 t, $^1J_{C,H}$ = 141, 2 CH_2-OBOM], 66.3 [d, $^1J_{C,H}$ = 144, C(1)], 69.9 [d, $^1J_{C,H}$ = 148, C(4′)], 71.6, 71.7 (2 t, $^1J_{C,H}$ = 142, 2 CH_2Ph), 74.2, 75.3 [2 d, $^1J_{C,H}$ = 140, 142, C(7), C(6′)], 96.0, 96.6 [2 t, $^1J_{C,H}$ = 159, 162, 2 CH_2 (BOM)], 110.8, 111.3 [2 s, C(3,2′), C(5)], 129.5, 129.8, 130.3 (3 d, $^1J_{C,H}$ = 160, 159, 160, 10 $C_{arom.}$), 141.9 (s, 2 $C_{arom.}$) ppm. CI-MS: *m*/*z* (%) = 576 (2) [M + NH_4^+], 516 (1), 391 (6), 312 (20), 205 (44), 91 (100) [$PhCH_2^+$]. $C_{31}H_{42}O_9$ (558.663): calcd. C 66.65, H 7.58; found C 66.34, H 7.57.

(1*S*,3*S*,4′*S*,5*R*,6′*R*,7*R*)-6′,7-Bis{2-[(benzyloxy)methoxy]ethyl}-5-methoxy-tetrahydrospiro[2,6-dioxabicyclo[3.3.1]nonane-3,2′-pyran]-4′-ol [(−)-13]: The same procedure as above was applied on (−)-**9** (500 mg, 0.678 mmol). The crude mixture of **11** and **12** was taken up in MeOH (8 mL) at 0 °C and treated with camphorsulfonic acid (5 mg). After stirring at 0 °C for 15 min, the solution was poured into a satd. aq. solution of $NaHCO_3$ (20 mL) and extracted with EtOAc (20 mL, 3 times). The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. Purification by flash chromatography on silica gel (CH_2Cl_2/MeOH, 20:1) afforded (−)-**13** as a pale yellow oil [268 mg, 69% from (−)-**9**]. R_f = 0.22 (CH_2Cl_2/MeOH, 15:1). $[\alpha]_D^{20}$ = −18, $[\alpha]_{435}^{20}$ = −30, $[\alpha]_{405}^{20}$ = −41 (*c* = 0.15, CH_2Cl_2). IR (film): $\tilde{\nu}$ = 3355, 3030, 2920, 1590, 1420, 1370, 1325, 1210, 1120, 1030, 770 cm^{-1}. UV (MeCN): $\lambda_{max.}$ (ε [dm^3·mol^{-1}·cm^{-1}]) = 197 (8670) nm. ^{1}H NMR (C_6D_6, 400 MHz, 25 °C): δ = 1.60 [dd, $^2J_{H,H}$ = 12.7, $^3J_{H,H}$ = 11.1 Hz, 1 H, C(8)-H], 1.72 [m, 2 H, C(9)-H_2], 1.73 [d, $^2J_{H,H}$ = 10.8 Hz, 1 H, C(4)-H], 1.80 [m, 2 H, C(5′)-H_2], 1.75−1.96 [m, 4 H, CH_2-C(7), CH_2-C(6′)], 1.91 [dd, $^2J_{H,H}$ = 12.9, $^3J_{H,H}$ = 2.8 Hz, 1 H, C(3′)-H], 2.10 [dd, $^2J_{H,H}$ = 12.9, $^3J_{H,H}$ = 8.9 Hz, 1 H, C(3′)-H], 2.11 [dm, $^2J_{H,H}$ = 12.7 Hz, 1 H, C(8)-H], 2.63 [dd, $^2J_{H,H}$ = 10.8, $^4J_{H,H}$ = 2.7 Hz, 1 H, C(4)-H], 3.30 [s, 3 H, OCH_3], 3.72−3.88 [m, 4 H, 2 CH_2-OBOM], 3.97 (s, O*H*), 4.27 [m, 1 H, C(7)-H], 4.36−4.38 [m, 2 H, C(4′)-H, C(6′)-H], 4.68, 4.71 (2 d, $^2J_{H,H}$ = 11.8 Hz, 2 H, CH_2Ph), 4.75, 4.79 (2 d, $^2J_{H,H}$ = 12.1 Hz, 2 H, CH_2Ph), 4.82−4.86 [m, 1 H, C(1)-H], 4.90, 4.93 [2 d, $^2J_{H,H}$ = 7.1 Hz, 2 H, CH_2 (BOM)], 4.95, 4.97 [2 d, $^2J_{H,H}$ = 6.8 Hz, 2 H, CH_2 (BOM)], 7.20−7.25 (m, 2 H, $H_{arom.}$), 7.35−7.30 (m, 4 H, $H_{arom.}$), 7.46, 7.51 (2 d, $^3J_{H,H}$ = 8.6, 7.4 Hz, 4 H, $H_{arom.}$) ppm. ^{13}C NMR (C_6D_6, 100.6 MHz, 25 °C): δ = 38.5, 39.0 [2 t, CH_2-C(7), CH_2-C(6′)], 41.6 [t, C(9)], 42.5 [t, C(8)], 43.4 [t, C(3′)], 43.9 [t, C(5′)], 44.6 [t, C(4)], 50.8 (q, OCH_3), 59.5, 59.6 (2 t, 2 CH_2-OBOM), 65.5 [d, C(4′)], 69.0 [d, C(1)], 70.4, 70.5 (2 t, 2CH_2Ph), 73.4 [d, C(7)], 74.8 [d, C(6′)], 95.0, 95.4 [2 t, 2 CH_2 (BOM)], 109.2, 110.2 [2 s, C(3,2′), C(5)], 128.3, 128.6, 129.1 (3 d, 10 $C_{arom.}$), 139.0 (s, 2 $C_{arom.}$) ppm. MALDI-TOF: *m*/*z* = 611 [M + K^+]. $C_{32}H_{44}O_9$ (572.691): calcd. C 67.11, H 7.74; found C 66.32, H 7.68.

(1*S*,3*S*,4′*S*,5*S*,6′*R*,7*R*)-6′,7-Bis{2-[(benzyloxy)methoxy]ethyl}-5-[(*tert*-butyldimethylsilyl)oxy]-tetrahydrospiro[2,6-dioxabicyclo-

[3.3.1]nonane-3,2′-pyran]-4′-ol [(−)-14]: 2,6-Lutidine (2.5 equiv., 115 μL, 0.984 mmol) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (0.1 M in CH_2Cl_2, 1 equiv., 3.94 mL, 0.394 mmol) were added to a solution of (+)-**11** (220 mg, 0.394 mmol) in anhydrous CH_2Cl_2 (1.2 mL), cooled to −40 °C. After stirring at −40 °C for 1 h, the mixture was poured into a satd. aq. solution of $NaHCO_3$ (20 mL) and extracted with $CHCl_3$ (20 mL, 3 times). The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. Purification by chromatography on silica gel (EtOAc/PE, 1:5) afforded (−)-**14** as a colorless oil (239 mg, 90%). R_f = 0.48 (EtOAc/petroleum ether, 1:4). $[\alpha]_D^{20}$ = −6, $[\alpha]_{577}^{20}$ = −7, $[\alpha]_{435}^{20}$ = −14, $[\alpha]_{405}^{20}$ = −17 (*c* = 0.25, CH_2Cl_2). IR (film): $\tilde{\nu}$ = 3485, 3045, 3030, 2925, 1495, 1470, 1385, 1255, 1095, 835, 775, 735, 695, 665 cm^{-1}. UV (MeCN): $\lambda_{max.}$ (ε [$dm^3 \cdot mol^{-1} \cdot cm^{-1}$]) = 207 (4600), 194 (10490) nm. ^1H NMR (C_6D_6, 400 MHz, 25 °C): δ = 0.20, 0.21 [2 s, 6 H, Si(CH_3)$_2$], 1.13 (s, 9 H, *t*Bu), 1.63 [dd, $^2J_{H,H}$ = 11.9, $^3J_{H,H}$ = 11.2 Hz, 1 H, C(8)-H], 1.69 [dd, $^2J_{H,H}$ = 12.1, $^3J_{H,H}$ = 3.2 Hz, 1 H, C(5′)-H], 1.74 [d, $^2J_{H,H}$ = 10.7 Hz, 1 H, C(4)-H], 1.77−1.84 [m, 3 H, C(9)-H_2, C(5′)-H], 1.87 [dd, $^2J_{H,H}$ = 12.9, $^3J_{H,H}$ = 2.1 Hz, C(3′)-H], 1.91−2.06 [m, 4 H, C(7)-CH_2, C(6′)-CH_2], 2.15 [dd, $^2J_{H,H}$ = 12.9, $^3J_{H,H}$ = 9.6 Hz, 1 H, C(3′)-H], 2.17 [dm, $^2J_{H,H}$ = 11.9 Hz, 1 H, C(8)-H], 2.73 [dd, $^2J_{H,H}$ = 10.7, $^4J_{H,H}$ = 2.7 Hz, 1 H, C(4)-H], 3.76−3.88 [m, 4 H, 2 CH_2-OBOM], 4.29 [m, 1 H, C(7)-H], 4.40−4.43 [m, 2 H, C(4′)-H, C(6′)-H], 4.79 [s, 2 H, CH_2Ph], 4.71, 4.88 [2 d, 2 H, $^2J_{H,H}$ = 12.3 Hz, CH_2Ph], 4.94 [m, 1 H, C(1)-H], 4.95, 4.98 [2 s, 4 H, 2CH_2 (BOM)], 7.20−7.26 (m, 2 H, $H_{arom.}$), 7.31−7.36 (m, 4 H, $H_{arom.}$), 7.47, 7.55 (2 d, $^3J_{H,H}$ = 7.4, 4 H, $H_{arom.}$) ppm. ^{13}C NMR (C_6D_6, 100.6 MHz, 25 °C): δ = −5.5 [q, Si(CH_3)$_2$], 18.2 [s, *C*(CH_3)$_3$], 25.9 (q, *t*Bu), 37.9, 38.8 [2 t, C(7)-*C*H_2, C(6′)-*C*H_2], 41.0 [t, C(3′)], 42.0 [t, C(5′)], 42.3 [t, C(9)], 43.5, 43.6 [2 t, C(4), C(8)], 59.6 [t, 2 *C*H_2-OBOM], 64.7 [d, C(4′)], 68.1 [d, C(1)], 69.4, 69.5 (2 t, 2 *C*H_2Ph), 71.9 [d, C(7)], 73.4 [d, C(6′)], 108.6, 109.6 [2 s, C(3,2′), C(5)], 127.3, 128.2, 128.3 (3 d, 10 $C_{arom.}$), 138.4, 138.7 (2 s, 2 $C_{arom.}$) ppm. MALDI-TOF: *m*/*z* = 673 [M + H^+]. $C_{37}H_{56}O_9Si$ (672.926): calcd. C 66.04, H 8.39, Si 4.17; found C 66.06, H 8.30, Si 4.12.

(1*S*,3*S*,4′*S*,5*S*,6′*R*,7*R*)-6′,7-Bis{2-[(benzyloxy)methoxy]ethyl}-4′,5-[(*tert*-butyldimethylsilyl)oxy]-tetrahydrospiro[2,6-dioxabicyclo-[3.3.1]nonane-3,2′-pyran [(−)-15]: 2,6-Lutidine (3 equiv., 63 μL, 0.537 mmol) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (2 equiv., 82 μL, 0.358 mmol) were added at −30 °C to a solution of (+)-**11** (100 mg, 0.179 mmol) in anhydrous CH_2Cl_2 (4 mL). After stirring at −30 °C for 45 min, the mixture was poured into a satd. aq. solution of $NaHCO_3$ (10 mL) and extracted with $CHCl_3$ (10 mL, 3 times). The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. Purification by chromatography on silica gel (EtOAc/PE, 1:10 to 1:4) afforded (−)-**15** as a colorless oil (84 mg, 60%) and (−)-**14** as a colorless oil (28 mg, 23%).

Data for (−)-15: R_f = 0.50 (EtOAc/petroleum ether, 1:8). $[\alpha]_D^{20}$ = −26 (*c* = 0.38, CH_2Cl_2). IR (film): $\tilde{\nu}$ = 2955, 2930, 2885, 2855, 1470, 1460, 1385, 1360, 1330, 1255, 1170, 1100, 1045, 1005, 835, 775, 735, 700 cm^{-1}. UV (MeCN): $\lambda_{max.}$ (ε [$dm^3 \cdot mol^{-1} \cdot cm^{-1}$]) = 193 (17400) nm. ^1H NMR (C_6D_6, 400 MHz, 25 °C): δ = 0.32, 0.22 [2 s, 12 H, 2 Si(CH_3)$_2$], 1.13, 1.15 (2 s, 18 H, *t*Bu), 1.69 [dd, $^2J_{H,H}$ = 14.7, $^3J_{H,H}$ = 12.4 Hz, 1 H, C(8)-H], 1.89 [m, 2 H, C(9)-H_2], 1.90 [d, $^2J_{H,H}$ = 10.6 Hz, 1 H, C(4)-H], 1.97−2.01 [m, 2 H, C(5′)-H_2], 2.02−2.12 [m, 4 H, C(7)-CH_2, C(6′)-CH_2], 2.24 [dd, $^2J_{H,H}$ = 14.6, $^3J_{H,H}$ = 7.7 Hz, 1 H, C(3′)-H], 2.30 [ddd, $^2J_{H,H}$ = 14.7, $^3J_{H,H}$ = 4.7, 2.9 Hz, 1 H, C(8)-H], 2.36 [dd, $^2J_{H,H}$ = 14.6, $^3J_{H,H}$ = 3.8 Hz, 1 H, C(3′)-H], 2.84 [dd, $^2J_{H,H}$ = 10.6, $^4J_{H,H}$ = 2.5 Hz, 1 H, C(4)-H], 3.85−3.95 (m, 4 H, 2 CH_2-OBOM), 4.23 [m, 1 H, C(6′)-H], 4.32 [m, 1 H, C(7)-H], 4.48 [m, 1 H, C(4′)-H], 4.77 (m, 4 H, 2 CH_2Ph), 4.91 [m, 1 H, C(1)-H], 4.95, 5.00 [2 d, $^2J_{H,H}$ = 7.0 Hz, 2 H, CH_2 (BOM)], 4.99 [s, 2 H, CH_2 (BOM)], 7.22 (m, 2 H, $H_{arom.}$), 7.31 (m, 4 H, $H_{arom.}$), 7.51 (m, 4 H, $H_{arom.}$) ppm. ^{13}C NMR (C_6D_6, 100.6 MHz, 25 °C): δ = −5.5, −5.4, −4.3, −4.1 [4 q, 2 Si(*C*H_3)$_2$], 18.0 [s, *C*(CH_3)$_3$], 25.9 (q, *t*Bu), 38.6, 39.3 [2 t, C(7)-*C*H_2, C(6′)-*C*H_2], 41.6 [t, C(5′)], 42.0 [t, C(8)], 43.3 [t, C(3′)], 44.1 [t, C(9)], 44.4 [t, C(4)], 59.7 (t, 2 *C*H_2-OBOM), 66.5 [d, C(4′)], 68.1 [d, C(1)], 69.4, 69.5 (2 t, 2 *C*H_2Ph), 72.2 [d, C(7)], 73.9 [d, C(6′)], 94.1, 94.2 [2 t, 2 *C*H_2 (BOM)], 108.4, 108.5 [2 s, C(3,2′), C(5)], 127.0, 128.1, 128.6 (3 d, 10 $C_{arom.}$), 138.4, 138.6 (2 s, 2 $C_{arom.}$) ppm. $C_{43}H_{70}O_9Si_2$ (787.189): calcd. C 65.61, H 8.96, Si 7.14; found C 65.69, H 8.92, Si 7.17.

(1*S*,3*S*,4′*S*,5*S*,6′*R*,7*R*)-6′,7-Bis{2-[(benzyloxy)methoxy]ethyl}-5-[(*tert*-butyldimethylsilyl)oxy]-tetrahydrospiro[2,6-dioxabicyclo-[3.3.1]nonane-3,2′-pyran]-4′-yl Acetate [(−)-16]: 4-(Dimethylamino)pyridine (5 mg) was added at 0 °C to a solution of alcohol (−)-**14** (380 mg, 0.565 mmol) in pyridine/acetic anhydride (2.5 mL/2.5 mL). The mixture was stirred at 0 °C for 45 min and the solvents were evaporated in vacuo. Purification by flash chromatography on silica gel (EtOAc/PE, 1:5) afforded (−)-**16** as a pale yellow oil (367 mg, 91%). R_f = 0.56 (EtOAc/pentane, 1:4). $[\alpha]_D^{20}$ = −4, $[\alpha]_{577}^{20}$ = −5, $[\alpha]_{435}^{20}$ = −38 (*c* = 0.25, CH_2Cl_2). IR (film): $\tilde{\nu}$ = 3065, 3035, 2930, 1740, 1610, 1495, 1470, 1370, 1330, 1255, 1115, 835, 775, 735, 635, 665 cm^{-1}. UV (MeCN): $\lambda_{max.}$ (ε [$dm^3 \cdot mol^{-1} \cdot cm^{-1}$]) = 207 (9050) nm. ^1H NMR (C_6D_6, 400 MHz, 25 °C): δ = 0.10, 0.11 [2 s, 6 H, Si(CH_3)$_2$], 1.03 (s, 9 H, *t*Bu), 1.61 [dd, $^2J_{H,H}$ = 12.8, $^3J_{H,H}$ = 11.0 Hz, 1 H, C(8)-H], 1.79 [m, 2 H, C(9)-H_2], 1.85 [d, $^2J_{H,H}$ = 10.6 Hz, 1 H, C(4)-H], 1.86 (s, 3 H, OAc), 1.86−1.95 [m, 2 H, C(5′)-H_2], 1.99 [dd, $^2J_{H,H}$ = 14.8, $^3J_{H,H}$ = 4.8 Hz, 1 H, C(3′)-H], 1.70−2.00 [m, 4 H, C(7)-CH_2, C(6′)-CH_2], 2.13 [ddd, $^2J_{H,H}$ = 12.8, $^3J_{H,H}$ = 4.3, 2.8 Hz, 1 H, C(8)-H], 2.24 [dd, $^2J_{H,H}$ = 14.8, $^3J_{H,H}$ = 8.5 Hz, 1 H, C(3′)-H], 2.69 [dd, $^2J_{H,H}$ = 10.6, $^4J_{H,H}$ = 2.7 Hz, 1 H, C(4)-H], 3.66−3.81 (m, 2 H, CH_2-OBOM), 3.82 (tm, $^3J_{H,H}$ = 6.6 Hz, 2 H, CH_2-OBOM), 4.00 [m, 1 H, C(6′)-H], 4.26 [m, 1 H, C(7)-H], 4.67, 4.72 (2 d, $^2J_{H,H}$ = 12.1 Hz, 2 H, CH_2Ph), 4.73 (s, 2 H, CH_2Ph), 4.85 [m, 1 H, C(1)-H], 4.86, 4.92 [2 d, $^2J_{H,H}$ = 7.0 Hz, 2 H, CH_2 (BOM)], 4.92, 4.97 [2 d, $^2J_{H,H}$ = 7.0 Hz, 2 H, CH_2 (BOM)], 5.69 [m, 1 H, C(4′)-H], 7.13−7.17 (m, 2 H, $H_{arom.}$), 7.23−7.28 (m, 4 H, $H_{arom.}$), 7.42−7.48 (m, 4 H, $H_{arom.}$) ppm. ^{13}C NMR (C_6D_6, 100.6 MHz, 25 °C): δ = −5.5, −5.4 [2 q, $^1J_{C,H}$ = 118, Si(*C*H_3)$_2$], 18.2 [s, *C*(CH_3)$_3$], 20.8 (q, $^1J_{C,H}$ = 129, OAc), 25.9 (q, $^1J_{C,H}$ = 125, *t*Bu), 38.4, 38.7 [2 t, $^1J_{C,H}$ = 125, 127, C(7)-*C*H_2, C(6′)-*C*H_2], 40.1 [t, $^1J_{C,H}$ = 126, C(3′)], 41.0 [t, $^1J_{C,H}$ = 131, C(5′)], 41.7 [t, $^1J_{C,H}$ = 127, C(9)], 42.0 [t, $^1J_{C,H}$ = 129, C(8)], 43.2 [t, $^1J_{C,H}$ = 133, C(4)], 59.4, 59.7 [2 t, $^1J_{C,H}$ = 141, 140, 2 *C*H_2-OBOM], 67.1 [d, $^1J_{C,H}$ = 142, C(4′)], 68.1 [d, $^1J_{C,H}$ = 145, C(1)], 69.4, 69.5 [2 t, $^1J_{C,H}$ = 147, 2 *C*H_2Ph], 72.1 [d, $^1J_{C,H}$ = 141, C(7)], 72.7 [d, $^1J_{C,H}$ = 141, C(6′)], 94.3, 94.4 [2 t, $^1J_{C,H}$ = 159, 2 *C*H_2 (BOM)], 108.7 [s, C(3,2′), C(5)], 127.3, 128.3, 128.5 (3 d, masked, 10 $C_{arom.}$), 138.5, 138.7 (2 s, 2 $C_{arom.}$), 169.7 (s, C=O) ppm. MALDI-TOF: *m*/*z* = 898 [M +8 Na]. $C_{39}H_{58}O_{10}Si$ (714.963): calcd. C 65.51, H 8.18; found C 65.50, H 8.16.

(1*S*,3*S*,5*S*,6′*R*,7*R*)-6′,7-Bis{2-[(benzyloxy)methoxy]ethyl}-5-[(*tert*-butyldimethylsilyl)oxy]-dihydrospiro[2,6-dioxabicyclo[3.3.1]nonane-3,2′-pyran]-4′(3′*H*)-one [(−)-17]: Activated molecular sieves (4 Å, 45 mg, 500 mg/mmol), *N*-methylmorpholine *N*-oxide (2.5 equiv., 30 mg, 0.224 mmol), and TPAP (0.2 equiv., 6.3 mg, $1.790.10^{-5}$ mol) were added to a solution of (−)-**14** (50 mg, $8.950.10^{-5}$ mol) in anhydrous CH_2Cl_2 (1.5 mL). The mixture was stirred at 25 °C for 50 min and filtered through a pad of silica gel (EtOAc, 50 mL). The filtrate was concentrated in vacuo. Purification by flash chromatog-

raphy on silica gel (EtOAc/PE, 1:5) afforded (−)-**17** as a colorless oil (45 mg, 90%). R_f = 0.43 (EtOAc/petroleum ether, 1:6). $[\alpha]_D^{20}$ = −15, $[\alpha]_{577}^{20}$ = −15, $[\alpha]_{435}^{20}$ = −30, $[\alpha]_{405}^{20}$ = −35 (c = 0.4, CH_2Cl_2). IR (film): $\tilde{\nu}$ = 3030, 2930, 2855, 1715, 1500, 1470, 1385, 1255, 1095, 1045, 835, 775, 735 cm^{-1}. UV (MeCN): $\lambda_{max.}$ (ε [$dm^3 \cdot mol^{-1} \cdot cm^{-1}$]) = 206 (6830), 200 (6860) nm. ^1H NMR (C_6D_6, 400 MHz, 25 °C): δ = 0.12, 0.13 [2 s, 6 H, Si(CH_3)$_2$], 1.05 (s, 9 H, *t*Bu), 1.57 [dd, $^2J_{H,H}$ = 12.3, $^3J_{H,H}$ = 11.3 Hz, 1 H, C(8)-H], 1.73 [m, 2 H, C(9)-H_2], 1.79−1.92 [m, 4 H, C(7)-CH_2, C(6′)-CH_2], 2.00 [d, $^2J_{H,H}$ = 10.9 Hz, C(4)-H], 2.08 [dm, $^2J_{H,H}$ = 12.3 Hz, 1 H, C(8)-H], 2.56 [dd, $^2J_{H,H}$ = 15.8, $^3J_{H,H}$ = 4.9, 1 H, C(5′)-H], 2.73 [dd, $^2J_{H,H}$ = 10.9, $^3J_{H,H}$ = 2.7 Hz, 1 H, C(4)-H], 2.53, 2.79 [2 d, $^2J_{H,H}$ = 14.4 Hz, 2 H, C(3′)-H_2], 2.82 [dd, $^2J_{H,H}$ = 15.8, $^3J_{H,H}$ = 7.1 Hz, 1 H, C(5′)-H], 3.76 (m, 4 H, 2 CH_2-OBOM), 4.22 [m, 1 H, C(7)-H], 4.50 [m, 1 H, C(6′)-H], 4.57, 4.62 [2 d, $^2J_{H,H}$ = 12.1 Hz, 2 H, CH_2Ph], 4.67, 4.78 [2 d, $^2J_{H,H}$ = 12.3 Hz, 2 H, CH_2Ph], 4.81 [m, 1 H, C(1)-H], 4.79, 4.82 [2 d, $^2J_{H,H}$ = 6.7 Hz, 2 H, CH_2 (BOM)], 4.85, 4.88 [2 d, $^2J_{H,H}$ = 7.0 Hz, 2 H, CH_2 (BOM)], 7.13−7.39 (m, 6 H, $H_{arom.}$), 7.41, 7.47 [2 d, $^2J_{H,H}$ = 7.5 Hz, 4 H, $H_{arom.}$] ppm. ^{13}C NMR (C_6D_6, 100.6 MHz, 25 °C): δ = −4.7 [q, $^1J_{C,H}$ = 118, Si(CH_3)$_2$], 18.9 [s, C(CH_3)$_3$], 26.6 [q, $^1J_{C,H}$ = 125, *t*Bu], 38.9, 39.0 [2 t, $^1J_{C,H}$ = 126, CH_2-C(7), CH_2-C(6′)], 42.0 [t, $^1J_{C,H}$ = 129, C(9)], 42.7 [t, $^1J_{C,H}$ = 127, C(8)], 43.7 [t, $^1J_{C,H}$ = 130, C(4)], 48.1 [t, $^1J_{C,H}$ = 129, C(3′)], 50.7 [t, $^1J_{C,H}$ = 128, C(5′)], 60.2, 60.3 [2 t, $^1J_{C,H}$ = 142, 140, 2 CH_2-OBOM], 69.0 [d, $^1J_{C,H}$ = 145, C(1)], 70.1, 70.2 (2 t, $^1J_{C,H}$ = 146, 2 CH_2Ph), 72.0 [d, $^1J_{C,H}$ = 141, C(7)], 72.2 [d, $^1J_{C,H}$ = 142, C(6′)], 94.4, 95.0 [2 t, $^1J_{C,H}$ = 158, 2 CH_2 (BOM)], 108.2, 109.5 [2 s, C(3,2′), C(5)], 127.9 (d, $^1J_{C,H}$ = 160, $C_{arom.}$), 129.1, 129.7 (2 d, masked, $C_{arom.}$), 139.1, 139.4 (2 s, 2 $C_{arom.}$), 203.3 [s, C(4′)] ppm. MALDI-TOF: m/z = 671 [M + H^+], 613 [M − *t*Bu]$^+$. $C_{37}H_{54}O_9Si$ (670.911): calcd. C 66.24, H 8.11; found C 66.23, H 8.09.

(3*R*)-4-[(2*S*,6*S*,8*R*,10*S*)-4,4-Bis(ethylthio)-10-hydroxy-8-(2-hydroxyethyl)-1,7-dioxaspiro[5.5]undec-2-yl]butane-1,3-diol [(+)-19]: HF (40% in water, 0.5 mL) was added dropwise at −40 °C to a solution of (−)-**16** (87 mg, 0.122 mmol) in acetonitrile (3.5 mL). After stirring at −40 °C for 30 min, the mixture was poured with vigorous stirring into a satd. aq. solution of $NaHCO_3$ (15 mL), cooled to 0 °C. After 5 min, solid $NaHCO_3$ was added to reach pH = 8 and the solution was extracted with EtOAc (15 mL, 3 times). The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. The residue was taken up in CH_2Cl_2/ethanethiol (2 mL/0.2 mL) and cooled to 0 °C. BBr_3 (2 equiv., 1 M in CH_2Cl_2, 0.244 mmol, 244 μL) was added dropwise. The solution was stirred at 0 °C for 15 min and poured into a satd. aq. solution of $NaHCO_3$ (15 mL), cooled to 0 °C. After the mixture had been stirred for 2 min, the aqueous layer was extracted with CH_2Cl_2 (15 mL, 3 times). The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo at −20 °C. Purification by flash chromatography on silica gel (CH_2Cl_2/MeOH, 15:1) afforded (+)-**19** as a pale yellow oil (34 mg, 67%).

Data for Intermediate (1*S*,3*S*,4′*S*,5*S*,6′*R*,7*R*)-6′,7-Bis{2-[(benzyloxy)methoxy]ethyl}-5-hydroxy-tetrahydrospiro[2,6-dioxabicyclo[3.3.1]nonane-3,2′-pyran]-4′-yl Acetate (18): IR (film): $\tilde{\nu}$ = 3440, 3060, 3035, 2935, 1740, 1610, 1490, 1375, 1320, 1250, 1110, 830, 785, 660 cm^{-1}. UV (MeCN): $\lambda_{max.}$ (ε [$dm^3 \cdot mol^{-1} \cdot cm^{-1}$]) = 205 (10040) nm. ^1H NMR (C_6D_6, 400 MHz, 25 °C): δ = 1.61 [dd, $^2J_{H,H}$ = 13.7, $^3J_{H,H}$ = 11.4 Hz, 1 H, C(8)-H], 1.89 [m, 2 H, C(9)-H_2], 1.83 [d, $^2J_{H,H}$ = 12.4 Hz, 1 H, C(4)-H], 1.87 (s, 3 H, OAc), 1.88 [m, 2 H, C(5′)-H_2], 2.01 [dd, $^2J_{H,H}$ = 14.7, $^3J_{H,H}$ = 7.9 Hz, 1 H, C(3′)-H], 1.80−2.12 [m, 4 H, C(7)-CH_2, C(6′)-CH_2], 2.15 [ddd, $^2J_{H,H}$ = 13.7, $^3J_{H,H}$ = 4.1, 2.6 Hz, 1 H, C(8)-H], 2.24 [dd, $^2J_{H,H}$ = 14.7, $^3J_{H,H}$ = 4.3 Hz, 1 H, C(3′)-H], 2.69 [dd, $^2J_{H,H}$ = 12.4, $^4J_{H,H}$ = 2.6 Hz, 1 H, C(4)-H], 3.55−3.82 (m, 4 H, 2 CH_2-OBOM), 4.01 [m, 1 H, C(6′)-H], 4.22 [m, 1 H, C(7)-H], 4.68, 4.74 [2 d, $^2J_{H,H}$ = 12.4 Hz, 2 H, CH_2Ph], 4.74 (s, 2 H, CH_2Ph), 4.83 [m, 1 H, C(1)-H], 4.87, 4.91 [2 d, $^2J_{H,H}$ = 7.1 Hz, 2 H, CH_2 (BOM)], 4.90 [s, 2 H, CH_2 (BOM)], 5.65 [m, 1 H, C(4′)-H], 7.12−7.16 (m, 2 H, $H_{arom.}$), 7.25 (m, 4 H, $H_{arom.}$), 7.44−7.49 (m, 4 H, $H_{arom.}$) ppm. MALDI-TOF: m/z = 601 [M + H^+].

Data for (+)-19: R_f = 0.27 (CH_2Cl_2/MeOH, 15:1). $[\alpha]_D^{20}$ = +28, $[\alpha]_{577}^{20}$ = +30, $[\alpha]_{435}^{20}$ = +59, $[\alpha]_{405}^{20}$ = +73 (c = 0.2, MeOH). IR (film): $\tilde{\nu}$ = 3375, 3030, 2945, 1660, 1460, 1435, 1115, 1025, 780, 665 cm^{-1}. UV (MeCN): $\lambda_{max.}$ (ε [$dm^3 \cdot mol^{-1} \cdot cm^{-1}$]) = 207 (11900) nm. ^1H NMR (C_6D_6, 400 MHz, 25 °C): δ = 1.27 [m, 6 H, 2 CH_3 (SEt)], 1.55−1.82 [m, 4 H, C(2)-H_2, CH_2-C(8′)], 2.08−2.20 [m, 6 H, C(4)-H_2, C(9′)-H_2, C(11′)-H_2], 1.99 [dd, $^2J_{H,H}$ = 10.8, $^3J_{H,H}$ = 2.6 Hz, 1 H, C(3′)-H], 2.07, 2.15 [2 d, $^2J_{H,H}$ = 10.8 Hz, 2 H, C(5′)-H_2], 2.28 [dd, $^2J_{H,H}$ = 10.8, $^3J_{H,H}$ = 2.1 Hz, 1 H, C(3′)-H], 2.63 [q, $^3J_{H,H}$ = 7.5 Hz, 2 H, CH_2 (SEt)], 2.79 [q, $^3J_{H,H}$ = 7.3 Hz, 2 H, CH_2 (SEt)], 3.66 [t, $^3J_{H,H}$ = 6.5 Hz, 2 H, C(1)-H_2], 3.69−3.77 [m, 2 H, CH_2-OH], 4.03 [m, 1 H, C(8′)-H], 4.08−4.13 [m, 2 H, C(2′)-H, C(10′)-H], 4.17 [m, 1 H, C(3)-H] ppm. ^{13}C NMR ([D_4]MeOH, 100.6 MHz, 25 °C): δ = 13.4, 15.0 [2 q, 2 CH_3 (SEt)], 24.0, 24.5 [2 t, 2 CH_2 (SEt)], 35.7, 36.6 [2 t, C(2), CH_2-C(8′)], 38.8, 39.4 [2 t, C(2′), C(5′)], 41.1, 42.6 [2 t, C(9′), C(11′)], 43.4 [t, C(4)], 49.1 [s, C(4′)], 59.0, 59.7 [2 t, C(1), CH_2-OH], 66.3 [d, C(10′)], 69.0, 69.1 [2 d, C(2′), C(8′)], 70.4 [d, C(3)], 98.1 [s, C(6′)] ppm. MALDI-TOF: m/z = 406 [M − H_2O]$^+$. $C_{19}H_{36}O_6S_2$ (424.619): calcd. C 53.75, H 8.55; found C 53.64, H 8.51.

Acknowledgments

This work was supported by the Swiss National Science Foundation. We thank Mr. Martial Rey, Mr. Francisco Sepùlveda, and Dr. Alain Razaname for technical help.

[1] For reviews, see, for example: [1a] T. L. B. Boivin, *Tetrahedron* **1987**, *43*, 3309. [1b] F. Perron, K. F. Albizati, *Chem. Rev.* **1989**, *89*, 1617. [1c] V. Vaillancourt, N. E. Pratt, F. Perron, K. F. Albizati, *Total Synth. Nat. Prod.* **1992**, 533. [1d] N. Haddad, Z. Abramovich, I. Ruhman, *Recent Res. Dev. Org. Chem.* **1997**, *1*, 35.

[2] For examples of insect pheromones, see: [2a] R. Baker, R. H. Herbert, *Nat. Prod. Rep.* **1984**, *1*, 299. [2b] W. M. Kitching, J. A. Lewis, M. T. Fletcher, R. A. I. Drew, C. J. Moore, W. Francke, *J. Chem. Soc., Chem. Commun.* **1986**, 853 and references cited therein. [2c] Y. Q. Tu, C. J. Moore, W. Kitching, *Tetrahedron: Asymmetry* **1995**, *6*, 397.

[3] For components of glandular secretions of higher insects, see, for example: J. R. Aldrich, G. K. Waite, S. Schutz, W. Francke, *J. Org. Chem.* **1994**, *59*, 6136.

[4] For polyether ionophores, see, for example: [4a] H. Mishima, M. Kurabayashi, C. Tamura, *Tetrahedron Lett.* **1975**, *10*, 711. [4b] R. W. Burg, B. M. Miller, J. Birnbaum, S. A. Currie, R. Hartman, Y. L. Wong, R. L. Monaghan, G. Olson, L. Putter, J. B. Tunac, H. Wallick, E. O. Stapley, R. Oiwa, S. Omura, *Antimicrob. Agents Chemother.* **1979**, *15*, 361. [4c] H. Mrozik, P. Eskola, M. H. Fisher, *Tetrahedron. Lett.* **1982**, *23*, 2377. [4d] S. M. Kupchan, E. J. La Voie, A. R. Branfman, B. Y. Fei, W. M. Bright, R. F. Bryan, *J. Am. Chem. Soc.* **1977**, *99*, 3199.

[5] [5a] P. Deslongchamps, D. D. Rowan, N. Pothier, T. Sauve, J. Saunders, *Can. J. Chem.* **1981**, *59*, 1105. [5b] P. Deslongchamps, D. D. Rowan, N. Pothier, J. Saunders, *Can. J. Chem.* **1981**, *59*, 1122. [5c] D. A. Evans, H. P. Ng, D. L. Rieger, *J. Am. Chem. Soc.* **1993**, *115*, 11446. [5d] D. A. Evans, S. W. Kaldor, T. K. Jones, J. Clardy, T. J. Stout, *J. Am. Chem. Soc.* **1990**, *112*, 7001. [5e] J. D. White, G. L. Bolton, A. P. Dantanarayana, C. M. J.

Fox, R. N. Hiner, R. W. Jackson, K. Sakuma, U. S. Warrier, *J. Am. Chem. Soc.* **1995**, *117*, 1908. [5f] M. T. Crimmins, R. O'Mahony, *J. Org. Chem.* **1989**, *54*, 1157. [5g] R. E. Ireland, J. P. Daub, *J. Org. Chem.* **1983**, *48*, 1303. [5h] R. E. Ireland, J. P. Daub, G. S. Mandel, N. S. Mandel, *J. Org. Chem.* **1983**, *48*, 1312. [5i] S. L. Schreiber, Z. Wang, *J. Am. Chem. Soc.* **1985**, *107*, 5303. [5j] N. L. Totah, S. L. Schreiber, *J. Org. Chem.* **1991**, *56*, 6255. [5k] B. Bernet, P. M. Bishop, M. Caron, T. Kawamata, B. L. Roy, L. Ruest, G. Sauve, P. Soucy, P. Deslongchamps, *Can. J. Chem.* **1985**, *63*, 2818. [5l] M. T. Crimmins, R. O′Mahony, *J. Org. Chem.* **1990**, *55*, 5894. [5m] Y. Zhao, N. E. Pratt, M. J. Heeg, K. F. Albizati, *J. Org. Chem.* **1993**, *58*, 1300. [5n] M. T. Crimmins, R. O′Mahony, *J. Org. Chem.* **1989**, *54*, 1157. [5o] M. T. Crimmins, D. M. Bankaitis-Davis, W. G. Hollis Jr., *J. Org. Chem.* **1988**, *53*, 652. [5p] M. F. Jacobs, B. D. Sothers, A. Huebener, W. Kitching, *J. Chem. Soc., Perkin Trans. 1* **1995**, 901. [5q] M. T. Crimmins, R. S. Al-awar, I. M. Vallin, R. O′Mahony, W. G. Hollis Jr., D. M. Bankaitis-Davis, J. G. Lever, *J. Am. Chem. Soc.* **1996**, *119*, 7513. [5r] M. T. Crimmins, D.G. Washburn, J. D. Katz, F. J. Zawacki, *Tetrahedron Lett.* **1998**, *39*, 3439. [5s] H. Huang, C. Mao, S. T. Jan, F. M. Uckun, *Tetrahedron Lett.* **2000**, *41*, 1699. [5t] A. G. M. Barrett, D. C. Braddock, C. D. de Koning, A. J. P. White, D. J. Williams, *J. Org. Chem.* **2000**, *65*, 375. [5u] R. Zemribo, K. T. Mead, *Tetrahedron Lett.* **1998**, *39*, 3891. [5v] G. Solladié, N. Huser, *Tetrahedron: Asymmetry* **1994**, *5*, 255. [5w] A. M. Doherty, S. V. Ley, B. Lygo, D. J. Williams, *J. Chem. Soc., Perkin Trans. 1* **1984**, 1371. [5x] S. Sauret, A. Cuer, J. G. Gouray, G. Jeminet, *Tetrahedron: Asymmetry* **1995**, *6*, 1995. [5y] H. Nakamura, K. Sato, A. Murai, *Tetrahedron Lett.* **1996**, *37*, 7267. [5z] K. T. Mead, B. N. Brewer, *Curr. Org. Chem.* **2003**, *7*, 227.

[6] [6a] M. M. Claffey, C. H. Heathcock, *J. Org. Chem.* **1996**, *61*, 7646. [6b] I. Paterson, R. M. Oballa, R. D. Norcross, *Tetrahedron Lett.* **1996**, *37*, 8581. [6c] L. A. Paquette, A. Braun, *Tetrahedron Lett.* **1997**, *38*, 5119. [6d] C. J. Hayes, C. H. Heathcock, *J. Org. Chem.* **1997**, *62*, 2678. [6e] I. Paterson, R. M. Oballa, *Tetrahedron Lett.* **1997**, *38*, 8241. [6f] A. B. Smith III, L. Zhuang, C. S. Brook, Q. Lin, W. H. Moser, R. E. L. Trout, A. M. Boldi, *Tetrahedron Lett.* **1997**, *38*, 8671. [6g] A. B. Smith III, Q. Lin, K. Nakayama, A. M. Boldi, C. S. Brook, M. D. McBriar, W. H. Moser, M. Sobukawa, L. Zhuang, *Tetrahedron Lett.* **1997**, *38*, 8675. [6h] I. Paterson, D. J. Wallace, K. R. Gibson, *Tetrahedron Lett.* **1997**, *38*, 8911. [6i] T. Terauchi, M. Nakata, *Tetrahedron Lett.* **1998**, *39*, 3795. [6j] M. T. Crimmins, D. G. Washburn, *Tetrahedron Lett.* **1998**, *39*, 7487. [6k] I. Paterson, D. J. Wallace, R. M. Oballa, *Tetrahedron Lett.* **1998**, *39*, 8545. [6l] M. M. Claffey, C. J. Hayes, C. H. Heathcock, *J. Org. Chem.* **1999**, *64*, 8267. [6m] D. Zuev, L. A. Paquette, *Org. Lett.* **2000**, *2*, 679. [6n] M. T. Crimmins, J. D. Katz, *Org. Lett.* **2000**, *2*, 957. [6o] T. Terauchi, T. Terauchi, I. Sato, T. Tsukada, N. Kanoh, M. Nakata, *Tetrahedron Lett.* **2000**, *41*, 2649. [6p] A. B. Smith III, V. A. Doughty, C. Stouggatakis, C. S. Bennett, J. Koyanagi, M. Takeuchi, *Org. Lett.* **2002**, *4*, 783. [6q] I. Paterson, M. J. Coster, *Tetrahedron Lett.* **2002**, *43*, 3285. [6r] E. B. Hulson, W. R. Roush, *Org. Lett.* **2002**, *4*, 3719. [6s] M. J. Gaunt, D. F. Hook, H. R. Tanner, S. V. Ley, *Org. Lett.* **2003**, *5*, 4815. [6t] M. J. Gaunt, A. S. Jessiman, P. Orsini, H. R. Tanner, D. F. Hook, S. V. Ley, *Org. Lett.* **2003**, *5*, 4819.

[7] For total syntheses of spongistatins: [7a] D. A. Evans, P. J. Coleman, L. C. Dias, *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2738. [7b] D. A. Evans, B. W. Trotter, B. Côté, P. J. Coleman, *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2741. [7c] D. A. Evans, B. W. Trotter, B. Côté, P. J. Coleman, L. C. Dias, A. N. Tyler, *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2744. [7d] D. A. Evans, B. W. Trotter, P. J. Coleman, B. Côté, L. C. Dias, H. A. Rajapakse, A. N. Tyler, *Tetrahedron* **1999**, *55*, 8671. [7e] J. Guo, K. J. Duffy, K. L. Stevens, P. I. Dalko, R. M. Roth, M. M. Hayward, Y. Kishi, *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 187. [7f] M. M. Hayward, R. M. Roth, K. J. Duffy, P. I. Dalko, K. L. Stevens, J. Guo, Y. Kishi, *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 187. [7g] A. B. Smith III, V. A. Doughty, A. Lin, L. Zhuang, M. D. McBriar, A. M. Boldi, W. H. Moser, N. Murase, K. Nakayama, M. Sobukawa, *Angew. Chem. Int. Ed.* **2001**, *40*, 191. [7h] A. B. Smith III, Q. Lin, V. A. Doughty, L. Zhuang, M. D. McBriar, J. K. Kerns, C. S. Brook, N. Murase, K. Nakayama, *Angew. Chem. Int. Ed.* **2001**, *40*, 196. [7i] A. B. Smith III, V. A. Doughty, C. Sfouggatakis, C. S. Bennett, J. Koyanagi, M. Takeuchi, *Org. Lett.* **2002**, *4*, 783. [7j] A. B. Smith III, W. Zhu, S. Shirakami, C. Sfouggatakis, V. A. Doughty, C. S. Bennett, Y. Sakamoto, *Org. Lett.* **2003**, *5*, 761. [7k] I. Paterson, D. Y. K. Chen, M. J. Coster, J. L. Aceña, J. Bach, K. R. Gibson, L. E. Keown, R. M. Oballa, T. Trieselmann, D. J. Wallace, A. P. Hodgson, R. D. Norcross, *Angew. Chem. Int. Ed.* **2001**, *40*, 4055. [7l] M. T. Crimmins, J. D. Katz, L. C. McAtee, E. A. Tabet, S. J. Kirincich, *Org. Lett.* **2001**, *3*, 949. [7m] M. T. Crimmins, J. D. Katz, D. G. Washburn, S. P. Allwein, L. F. McAtee, *J. Am. Chem. Soc.* **2002**, *124*, 5661. [7n] C. H. Heathcock, M. McLaughlin, J. Medina, J. L. Hubbs, G. A. Wallace, R. Scott, M. M. Claffey, C. J. Hayes, G. R. Ott, *J. Am. Chem. Soc.* **2003**, *125*, 12844. [7o] J. L. Hubbs, C. H. Heathcock, *J. Am. Chem. Soc.* **2003**, *125*, 12836. [7p] T. Terauchi, T. Tanaka, T. Terauchi, M. Morita, K. Kimijima, I. Sato, W. Shoji, Y. Nakamura, T. Tsukada, T. Tsunoda, C. Hayashi, N. Kanoh, M. Nakata, *Tetrahedron Lett.* **2003**, *44*, 7747. [7q] T. Terauchi, T. Terauchi, I. Sato, W. Shoji, T. Tsukada, T. Tsunoda, N. Kanoh, M. Nakata, *Tetrahedron Lett.* **2003**, *44*, 7741.

[8] G. R. Pettit, *J. Nat. Prod.* **1996**, *59*, 812.

[9] [9a] G. R. Pettit, Z. A. Cichacz, C. L. Herald, F. Gao, M. R. Boyd, J. M. Schmidt, E. Hamel, R. Bai, *J. Chem. Soc., Chem. Commun.* **1994**, 1605. [9b] G. R. Pettit, C. L. Herald, Z. A. Cichacz, F. Gao, M. R. Boyd, N. D. Christie, J. M. Schmidt, *Nat. Prod. Lett.* **1993**, *3*, 239. [9c] G. R. Pettit, C. L. Herald, Z. A. Cichacz, F. Gao, J. M. Schmidt, M. R. Boyd, N. D. Christie, F. E. Boettner, *J. Chem. Soc., Chem. Commun.* **1993**, 1805. [9d] G. R. Pettit, Z. A. Cichacz, F. Gao, C. L. Herald, M. R. Boyd, *J. Chem. Soc., Chem. Commun.* **1993**, 1166. [9e] G. R. Pettit, Z. A. Cichacz, F. Gao, C. L. Herald, M. R. Boyd, J. M. Schmidt, J. N. A. Hooper, *J. Org. Chem.* **1993**, *58*, 1302.

[10] N. Fusetani, K. Shinoda, S. Matsunaga, *J. Am. Chem. Soc.* **1993**, *115*, 3977.

[11] [11a] M. Kobayashi, S. Aoki, I. Kitagawa, *Tetrahedron Lett.* **1994**, *35*, 1243. [11b] M. Kobayashi, S. Aoki, H. Sakai, K. Kawazoe, N. Kihara, T. Sasaki, I. Kitagawa, *Tetrahedron Lett.* **1993**, *34*, 2795.

[12] [12a] M. E. Schwenter, P. Vogel, *Chem. Eur. J.* **2000**, *6*, 195. [12b] K. T. Meilert, M. E. Schwenter, Y. Shatz, R. Dubbaka, P. Vogel, *J. Org. Chem.* **2003**, *68*, 2964.

[13] M. E. Schwenter, P. Vogel, *J. Org. Chem.* **2001**, *66*, 7869.

[14] A. G. Csákÿ, P. Vogel, *Tetrahedron: Asymmetry* **2000**, *11*, 4935.

[15] S. Gerber-Lemaire, P. Vogel, *Eur. J. Org. Chem.* **2003**, 2959.

[16] Steric crowding about the equatorial alcohol at C(4′) is probably responsible for the faster silylation of the tertiary hydroxy group of (+)-**11** at low temperature.

[17] [17a] D. B. Dess, J. C. Martin, *J. Org. Chem.* **1983**, *48*, 4155. [17b] R. E. Ireland, L. Lin, *J. Org. Chem.* **1993**, *58*, 2899.

[18] [18a] A. J. Mancuso, S. L. Huang, D. Swern, *J. Org. Chem.* **1978**, *43*, 2480. [18b] T. T. Tidwell, *Org. React.* **1990**, *39*, 287.

[19] S. V. Ley, J. Norman, W. P. Griffith, S. P. Marsden, *Synthesis* **1994**, 639.

Received July 22, 2004

