A Chiral β,δ-Dioxo-ε-sulfinyl Ester in a Convergent Enantioselective Synthesis towards the C_1–C_{13} Polyol Fragment of Amphotericin B

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This paper describes an efficient stereocontrolled and convergent approach towards the C_1–C_{13} polyol fragment of amphotericin B. The strategy is based on the stereoselective reduction of a chiral β,γ-dioxo-ε-sulfinyl ester to obtain *anti*- or *syn*-1,3-diols.

The antibiotic macrolide Amphotericin B is a natural compound produced by *Streptomyces nodosus.* It is characterised by a rigid macrolactone ring bearing on one side a hydrophilic polyol, the C_1-C_{13} fragment, and on the other a hydrophobic heptaene, the $C_{20}-C_{33}$ part. The structure of Amphotericin B was established by X-ray crystallographic analysis.[1]

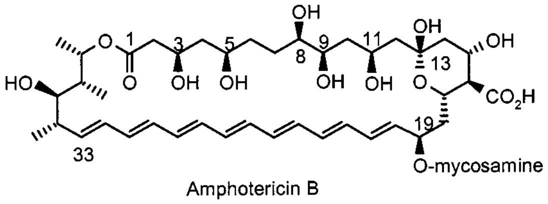


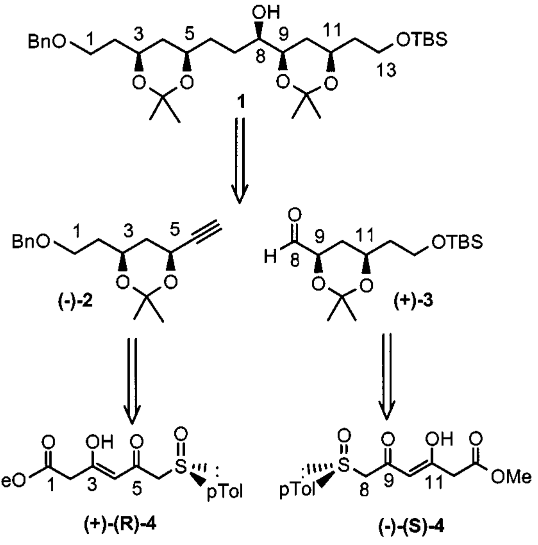
Figure 1

This antibiotic agent attracted considerable attention for its potent antifungal properties. Unfortunately its use in fungicide treatment has been attenuated by serious side-effects.[2] Some recent papers describe analogs of Amphotericin B with the same antimycotic action but a reduced toxicity.[3]

Several reports on the synthesis of Amphotericin B have been published including the first total synthesis by Nicolaou,[4] the formal synthesis of Masamune[5] and the approach of McGarvey using the oxazoline methodology.[6] Many other groups have described the synthesis of the polyol fragment of Amphotericin B starting from natural products such as amino acids (L-aspartic acid, L-glutamic acid)[6a,7] or modified sugars.[8] We also reported the synthesis of the different stereogenic centers of this polyol unit, using the chiral induction of sulfoxides.[9]

More recently, Carreira[10] reported the synthesis of the C_1-C_{13} fragment by asymmetric aldolisation of a dienolate on furfural induced by a chiral BINAP catalyst. This publication prompted us to report our own results and describe a novel and efficient stereocontrolled convergent approach towards the C_1-C_{13} polyol fragment **1** of Amphotericin B that involves similar intermediates.[11] Our strategy is based on the stereoselective reduction of a chiral β,δ-dioxo-ε-sulfinyl ester[12,13,15] to obtain *anti*-or *syn*-1,3-diols.

As shown in the retrosynthetic Scheme (Scheme 1), the polyol **1** can be obtained by condensation of the two *syn*-diols (−)-(3*S*, 5*S*)-**2** and (+)-(2*R*, 4*R*)-**3**, which can be prepared by reduction of the β,δ-dioxo-ε-sulfinyl esters (−)-(*S*)-**4** and (+)-(*R*)-**4** in a similar way to our previous work.[13−16]



Scheme 1

The sulfoxides (−)-**4** or (+)-**4** were readily obtained in one step from the corresponding dioxo ester **5**, prepared on a multigram scale from commercially available dehydroacetic acid.[17] The trianion of **5**, obtained at 0°C with NaH (1 equiv.) and *t*BuLi (2 equiv.) in THF, was added to the corresponding pure menthyl-*p*-toluenesulfinate (*R* or *S*) to give the compounds (−)-**4** or (+)-**4**, respectively (Scheme 2). As shown in our previous studies,[12,13,15] the δ-carbonyl in (−)-**4** or (+)-**4** is totally enolized (^{1}H-NMR spectroscopy showed enol signals at $\delta = 14.5$ and 5.6). Consequently, two equivalents of Dibal−H in THF at −78°C were required for the stereoselective reduction of the β-carbonyl; one to quench the δ-carbonyl enolate and one to reduce the β-carbonyl. Thus, the reduction of (−)-**4** or (+)-**4** (Scheme 3) was carried out without any protection of the δ-carbonyl

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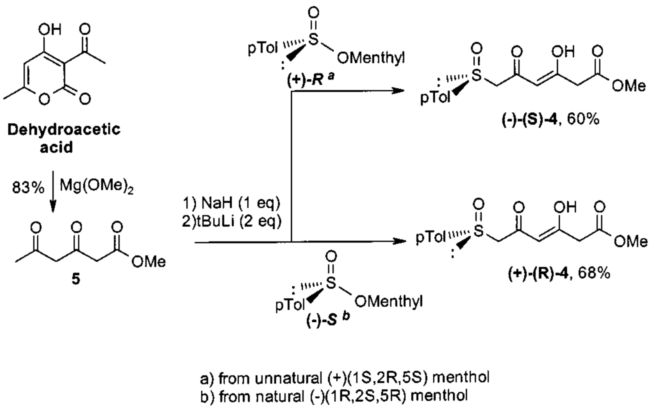
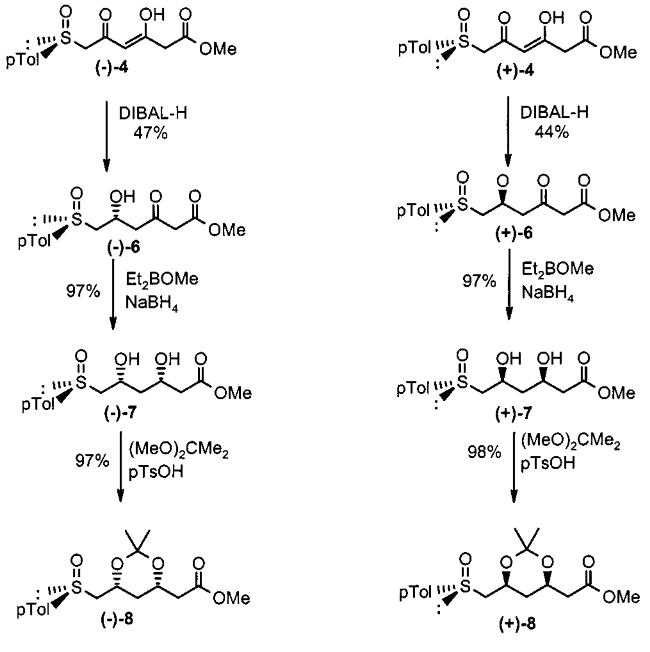
and with no significant reduction of the terminal ester function. As expected, the ^{1}H-NMR analysis of the crude material showed only one diastereomer (de > 95%). The resulting pure β-hydroxy-δ-oxo-ε-sulfinyl esters (−)-**6** and (+)-**6** were isolated after chromatography on metal-free silica gel.[18]



a) from unnatural (+)(1S,2R,5S) menthol
b) from natural (-)(1R,2S,5R) menthol

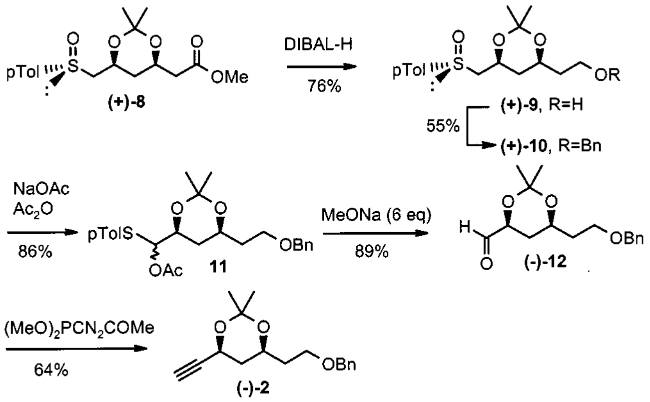
Scheme 2



Scheme 3

The δ-carbonyl in (−)-**6** was reduced with diethylmethoxyborane and borohydride[19] to obtain exclusively, and in nearly quantitative yield, the *syn*-diol (−)-**7** (*de* > 95%), which was finally transformed into the corresponding acetonide (−)-**8**. The same protocol applied to the compound (+)-**6** stereoselectively gave the *syn*-diol (+)-**7** (*de* > 95%) and then the acetonide (+)-**8**.[15] The large nonequivalence of the two methyl groups of the acetonide in the ^{13}C-NMR spectrum confirmed the relative configuration of the diols: $\delta = 20.0$ and 30.2 for the acetonide (+)-**8** and $\delta = 20.3$ and 30.4 for the acetonide (−)-**8**, which are characteristic of a *syn*-diol acetonide.[20] Typical values for the *anti*-diol acetonide methyl groups are $\delta = 24$ and 25.5.[20,13,16c]

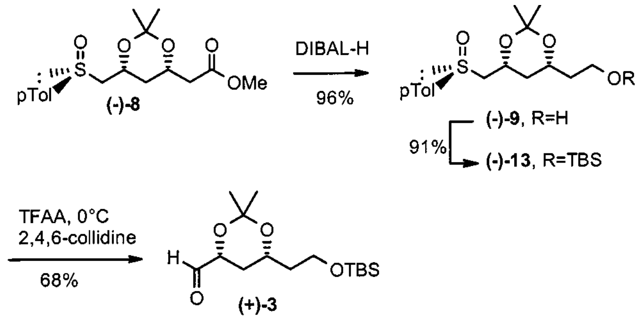
The synthesis of the alkyne (−)-**2** (Scheme 4) started with the reduction of the ester in the β,δ-dihydroxy-ε-sulfinyl ester (+)-**8** to the alcohol (+)-**9** (76%) in dilute conditions with Dibal−H (4.5 equiv.), followed by protection of the free hydroxyl with a benzyl group to give (+)-**10** (55%). A Pummerer rearrangement (NaOAc in boiling Ac_2O) gave, in 86%, the O,S-acetal **11** as a mixture of diastereomers. The aldehyde (−)-**12** was obtained in one step (89%) by adding, at 0°C, the O,S-acetal **11** to an excess of sodium methanolate (6 equiv.) in MeOH. This procedure does not give any isomerization of the chiral center α to the aldehyde because the six-membered acetonide derived from the *syn*-diol is thermodynamically more stable (equatorial aldehyde) than that made from the *anti*-diol. In the *anti* configuration it would have been necessary to use the following three steps for the transformation of the Pummerer intermediate into the aldehyde to avoid any racemization: desulfurization of the O,S-acetal (Raney Ni), acetate hydrolysis (MeONa) and oxidation of the alcohol to the aldehyde.[15,16a,b] Finally, the alkyne (−)-**2** was obtained in mild conditions from the aldehyde (−)-**12** following an improved one-pot procedure, developed by Bestmann,[21] using dimethyl diazomethylphosphonate generated *in situ* from the corresponding 1-acylphosphonate. Other attempts, like the Corey−Fuchs method, gave only poor results.[22]



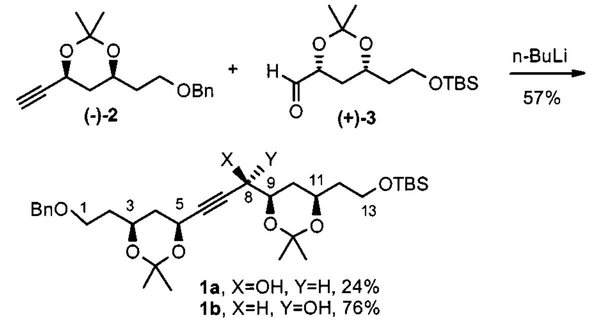
Scheme 4

The other aldehyde, (+)-**3** (Scheme 5), was obtained from the *syn*-β,δ-dihydroxy-ε-sulfinyl ester (−)-**8** by ester group reduction with Dibal−H (4 equiv.) in the same conditions as described above. The resulting alcohol, (−)-**9** (96% yield), was silylated and the protected product (−)-**13** was submitted to a Pummerer reaction with trifluoroacetic anhydride in acetonitrile.[23] This procedure allows a mild one-pot conversion of the sulfoxide to the aldehyde (+)-**3** in 68% yield.

Finally, the alkyne (−)-**2** was metallated with *n*BuLi at 0°C and added at −75°C to the aldehyde (+)-**3** to give, in 57% yield, a mixture of two C-8 isomers **1a**/**1b** in a 24:76 ratio as determined by ^{1}H-NMR spectroscopy (from the C_8 hydroxyl group signal), a similar result to the previous attempts to synthesize this fragment[7][10] (Scheme 6). We assigned the configuration of **1b** to the major isomer by comparison with the literature results.[7][10]



Scheme 5



Scheme 6

The natural configuration at C_8, as shown in **1a**, could be obtained from **1b** as described previously by a Mitsunobu reaction.[7] However, the $C_{11}-C_{13}$ fragment **1** of Amphotericin B could be obtained directly from the mixture **1a**/**1b** by reduction of the triple bond, oxidation of the carbinol at C_8 [10] and stereoselective reduction of the C_8 ketone by L-Selectride®.[4a,6a,10]

In conclusion, we have reported an efficient convergent synthesis of a known precursor of the $C_{11}-C_{13}$ polyol fragment of Amphotericin B from the chiral β,δ-dioxo-ε-sulfinyl ester. It has been demonstrated that this highly functionalized dioxo sulfoxide is a powerful tool for the stereoselective synthesis of natural products containing *syn*- or *anti*-1,3-diol and 1,2-diol units

Experimental Section

General: Melting points were determined with a Reichert microscope. − ^{1}H- and ^{13}C-NMR spectra were recorded at 200 and 50 MHz in $CDCl_3$ on a Bruker AC 200 SY spectrometer. Chemical shifts are reported in δ units (ppm). Peak multiplicities are abbreviated as: singlet, s; doublet, d; triplet, t; multiplet, m. − Optical rotations were recorded using a Perkin−Elmer 241MC polarimeter at 25°C (λ = 589 nm). − Thin layer chromatography (TLC) was performed using precoated sheets of silica gel 60 (230−400 mesh) from Merck. Eluting solvents are indicated in the text. Dry THF was distilled from sodium/benzophenone. Diisopropylamine was freshly distilled over potassium hydroxide. − Apparatus for all experiments carried out under an inert atmosphere was dried by flaming under pressure and was then filled with argon. Treated silica gel was prepared according to literature[18] by washing silica gel (1 kg) with two liters of dilute HCl (10%) and then rinsed several times with water until neutral pH. Finally, silica gel was filtered and dried for one week under air before use.

Methyl (−)-(*S*)-3,5-Dioxo-6-(*p*-tolylsulfinyl)hexanoate (4): To a suspension of NaH (2.2 g, 1.2 equiv.) in dry THF (250 mL) was added dropwise at 0°C a solution of methyl 3,5-dioxohexanoate (**5**)[17] (12.11 g, 0.0765 mol) in THF (25 mL). To the resulting thick, white mixture was added by cannula at 0°C, over a period of 15 min, *tert*-butyllithium (100 mL of a 1.5 M solution in pentane, 2.04 equiv.). The solution turned from yellow/orange to deep red during the addition. (+)-Menthyl (*R*)-*p*-tolylsulfinate (11.31 g, 0.5 equiv.) in THF (35 mL) was then added dropwise over 20 min. Stirring at 0°C was continued for an additional 40 min until all sulfinate was consumed (tlc). The reaction was quenched with saturated NH_4Cl (10 mL) and diluted with AcOEt (250 mL), and then acidified to pH 1 with 1 N HCl (170 mL) and conc. H_2SO_4. The aqueous layer was extracted with AcOEt (3 × 150 mL). The combined organic extracts were washed with brine (100 mL), dried over $MgSO_4$ and filtered before being concentrated. The crude oily residue was purified by rapid chromatography on treated silica gel[18] (hexane and CH_2Cl_2) to give (−)-**4** as an orange oil (7.85 g, 69%), which was used directly in the next step. An analytical sample was obtained by crystallization (CH_2Cl_2/diethyl ether). This product exists entirely in the enol form. $[\alpha]_D^{20}$ = −268 (*c* = 0.89, $CHCl_3$). m.p. 58°C. − ^{1}H NMR (200 MHz, $CDCl_3$): δ = 14.56 (br. s, 1 H, OH enol), 7.55 (A part of AA′BB′, 2 H, *p*Tol, J_{AB} = 8 Hz, Δν = 41 Hz), 7.34 (B part of AA′BB′, 2 H, *p*Tol, J_{AB} = 8 Hz, Δν = 41 Hz), 5.52 (s, 1 H, H enol), 3.75 (s, 3 H, OCH_3), 3.69 (A part of AB, 1 H, 6-CH_2, J_{AB} = 10 Hz, Δν = 20 Hz), 3.58 (B part of AB, 1 H, 6-$CH_{2,\ JAB}$ = 10 Hz, Δν = 20 Hz), 3.37 (s, 2 H, CH_2), 2.42 (s, 3 H, CH_3-Ar). − ^{13}C NMR ($CDCl_3$): δ (CO) = 189.6 (C=O), 180.2 (C=O enol form), 167.4 (CO_2CH_3); C 143.1, 139.6; CH 130.7, 124.7, 103.4 (enol); CH_2 65.5, 45.9; CH_3 53.2 (OCH_3), 22.2 ($ArCH_3$). − $C_{14}H_{16}O_5S$ (296.33): calcd. C 56.74, H 5.44; found C 56.93, H 5.48.

Methyl (−)-[5*R*,*S*(*S*)]-5-Hydroxy-3-oxo-6-(*p*-tolylsulfinyl)hexanoate (6): To a solution of (−)-**4** (6.0 g, 22.2 mmol) in THF (400 mL) was added dropwise (over 15 min) at − 78°C a solution of Dibal−H (45 mL 1 M in toluene, 2 equiv.). Stirring was continued for a further 15 min before adding MeOH (90 mL). After 1 h stirring the solution was kept for 0.5 h at room temperature and the solvent was evaporated to afford an orange powder, which was dissolved in AcOEt (300 mL) and treated with sat. disodium L-tartrate dihydrate (200 mL). This mixture was stirred overnight at room temperature and then acidified to pH 4 with conc. HCl. The aqueous layer was extracted with AcOEt (2 × 150 mL) and saturated with brine before extraction with AcOEt (150 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated to afford a solid residue. The crude product was purified by rapid chromatography on treated silica gel[18] (AcOEt/CH_2Cl_2, 1:1) and the resulting solid was recrystallized (CH_2Cl_2/diethyl ether) to give (−)-**6** as colorless crystals (3.10 g, 47%, *de* > 95%) containing 9% of enol. − $[\alpha]_D^{20}$ = −206 (*c* = 0.82, $CHCl_3$). − M.p. 123°C. − ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.53 (A part of AA′BB′, 2 H, *p*Tol, J_{AB} = 8 Hz, Δν = 33 Hz), 7.36 (B of AA′BB′), 2 H, *p*Tol, J_{AB} = 8 Hz, Δν = 33 Hz), 4.62 (m, 1 H, H_x of ABX), 4.11 (d, 1 H, OH, *J* = 3.4 Hz), 3.74 (s, 3 H, OCH_3), 3.48 (s, 2 H, CH_2CO_2Me), 2.92 (ABX, 2 H, 6-CH_2, J_{AB} = 13.4 Hz, J_{AX} = 9.5 Hz, J_{BX} = 3.8 Hz, Δν = 75 Hz), 2.80 (d, 2 H, 4-CH_2, *J* = 6 Hz), 2.42 (s, 3 H, CH_3-Ar). − ^{13}C NMR ($CDCl_3$): δ CO = 202.2 (CO), 167.9 (CO_2CH_3); C, 142.5, 139.8; CH 130.9, 124.7, 64.3 (CHOH); CH_2 60.8, 50.3, 49.7; CH_3 53.2 (OCH_3), 22.1 ($ArCH_3$). − $C_{14}H_{18}O_5S$ (298.34): calcd. C 56.36, H 6.08; found C 56.07, H, 6.03.

Methyl (−)-[3*S*,5*R*,*S*(*S*)]-*syn*-3,5-Dihydroxy-6-(*p*-tolylsulfinyl)hexanoate (7): A solution of (−)-**6** (3.04 g, 10 mmol) in THF/MeOH

(100 mL/20 mL, 5:1) was cooled at −78 °C. After rapid addition (2 min) of a solution of Et_2BOMe (1 M in THF, 11.2 mL, 1.1 equiv.) a white precipitate was formed. Stirring was continued during 20 min before adding $NaBH_4$ (0.5 g, 1.3 equiv.) in one portion, which led to a homogeneous solution. After 4 h at −78 °C, AcOH (20 mL) and then sat. $NaHCO_3$ (100 mL) were added at room temperature until pH 7 was reached. The aqueous layer was extracted with AcOEt (3 × 150 mL) and the combined organic extracts were dried ($MgSO_4$) and concentrated. The yellow oil was then azeotropically distilled with MeOH (3 × 50 mL). The product was purified by rapid chromatography on treated silica gel[18] (AcOEt) to afford the light yellow oil (−)-**7**, which crystallized at low temperature (4 °C) (2.9 g, 97%, *de* > 95%). − $[\alpha]_D^{20} = -198$ ($c = 1.15$, $CHCl_3$). − M.p. 91 °C. − ^1H NMR (200 MHz, $CDCl_3$): $\delta = 7.50$ (A of AA′BB′, 2 H, *p*Tol, $J_{AB} = 8$ Hz, $\Delta\nu = 37$ Hz), 7.31 (B of AA′BB′, 2 H, *p*Tol, $J_{AB} = 8$ Hz, $\Delta\nu = 37$ Hz), 4.96 (br. s, 1 H, OH), 4.47 (m, 1 H, H^x of ABX), 4.29 (m, 1 H, H^x of ABX), 4.17 (br. s, 1 H, OH), 3.65 (s, 3 H, OCH_3), 2.86 (ABX, 2 H, 6-CH_2, $J_{AB} = 13.2$ Hz, $J_{AX} = 9.8$ Hz, $J_{BX} = 2.4$ Hz, $\Delta\nu = 49$ Hz), 2.47 (m, ABX type, 2 H, CH_2CO_2Me), 2.39 (s, 3 H, CH_3−Ar), 1.80−1.53 (m, 2 H, 4-CH_2). − ^{13}C NMR ($CDCl_3$): δ = CO 173.1 (CO_2CH_3); C 142.3, 140.2; CH 130.7, 124.6, 68.2 (CHOH), 66.7 (CHOH); CH_2 63.9, 42.7, 42.1; CH_3 54.1 (OCH_3), 22.0 ($ArCH_3$).

Methyl (−)-[3*S*,5*R*,*S*(*S*)]-*syn*-3,5-(Isopropylidenedioxy)-6-(*p*-tolylsulfinyl)hexanoate (8): The dihydrosulfoxide (−)-**7** (1.3 g, 4.33 mmol) and a catalytic amount of *p*TsOH (65 mg) were dissolved in acetone (65 mL) and 2,2-dimethoxypropane (6.5 mL). Stirring at room temperature (3 h) was maintained until starting material had disappeared (tlc). The solvents were removed and the crude product was then diluted in CH_2Cl_2 (100 mL) and sat. $NaHCO_3$ (10 mL) was added. The mixture was stirred for 15 min at room temperature and diluted with water (50 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL) and the combined organic extracts were washed with water (100 mL), dried ($MgSO_4$) and concentrated to afford (−)-**8** as sharp, colorless needles (1.43 g, 97%). $[\alpha]_D^{20} = -172$ ($c = 0.97$, $CHCl_3$). − M.p. 92−95 °C. − ^1H NMR (200 MHz, $CDCl_3$): $\delta = 7.46$ (A of AA′BB′, 2 H, *p*Tol, $J_{AB} = 8$ Hz, $\Delta\nu = 41$ Hz), 7.25 (B of AA′BB′, 2 H, *p*Tol, $J_{AB} = 8$ Hz, $\Delta\nu = 41$ Hz), 4.6−4.4 (m, 1 H), 4.35−4.26 (m, 1 H), 3.61 (s, 3 H, OCH_3), 2.70 (m, ABX type, 2 H, 6-CH_2), 2.40 (ABX, 2 H, CH_2CO_2Me, $J_{AB} = 15.0$ Hz, $J_{AX} = 7$ Hz, $J_{BX} = 6.8$ Hz, $\Delta\nu = 38$ Hz), 2.34 (s, 3 H, CH_3−Ar), 1.56 (dt, 1 H, 4-H_{eq}, $J_{gem} = 14$ Hz, $J_3 = 2.4$ Hz), 1.48 [s, 3 H, $C(Me)_2$], 1.35 [s, 3 H, $C(Me)_2$], 1.29−1.12 (m, 1 H, 4-H_{ax}). − ^{13}C NMR ($CDCl_3$): δ CO = 171.5 (CO_2CH_3); C 142.0, 141.9, 100.1 [$C(Me)_2$]; CH 130.5, 124.3, 66.2 (CHOH), 63.9 (CHOH); CH_2 65.3, 41.5, 36.4; CH_3 52.2 (OCH_3), 30.4 (CH_3), 21.9 ($ArCH_3$), 20.3(CH_3). − $C_{17}H_{24}O_5S$ (340.42): calcd. C 59.98, H 7.11; found C 60.06, H 6.89.

(−)-[2*R*,4*R*,*S*(*S*)]-6-Hydroxy-*syn*-2,4-(isopropylidenedioxy)-1-(*p*-tolylsulfinyl)hexane (9): The ester (−)-**8** (25 mg, 0.07 mmol) was dissolved in dry THF (6 mL) at −78 °C. A solution of Dibal−H (1 M in toluene, 0.3 mL, 0.3 mmol, 4 equiv.) was added dropwise and the evolution of the reaction was monitored by tlc and the temperature rose slowly. After 7 h the reaction was hydrolyzed by adding sat. NH_4Cl (6 mL). Water (6 mL) and AcOEt (6 mL) were added and the aqueous layer was acidified with 5% aqueous H_2SO_4 and was then extracted with AcOEt (3 × 10 mL). The combined organic extracts were washed with brine (20 mL) and dried ($MgSO_4$). Evaporation of the solvent afforded a pale yellow oil, which was purified by column chromatography on silica gel (AcOEt; AcOEt/MeOH, 9:1) to give (−)-**9** as a light yellow oil (22 mg, 96%). − $[\alpha]_D^{20} = -152$ ($c = 0.55$, $CHCl_3$). − ^1H NMR (200 MHz, $CDCl_3$): $\delta = 7.48$ (A of AA′BB′, 2 H, *p*Tol, $J_{AB} = 8$ Hz, $\Delta\nu = 21$ Hz), 7.32 (B of AA′BB′, 2 H, *p*Tol, $J_{AB} = 8$ Hz, $\Delta\nu = 21$ Hz), 4.48 (m, 1 H, H-2), 4.15 (m, 1 H, H-4), 3.71 (t, 2 H, H-6, $J = 4.8$ Hz), 2.74 (m, 2 H, H-1), 2.38 (s, 3 H, CH_3−Ar), 1.69 (q, 2 H, H-5, $J = 4.8$ Hz), 1.52 (s, 3 H, CH_3, acetonide), 1.43 (dt, 1 H, H_{eq}-3, $J_{gem} = 23.4$ Hz, $^3J = 2.9$ Hz), 1.41 (s, 3 H, CH_3, acetonide), 1.28 (m, 1 H, H_{ax}-3). − ^{13}C NMR ($CDCl_3$): δ = 142.1 (C arom.), 141.8 (C arom.), 130.6 (CH arom.), 124.4 (CH arom.), 100.0 (C, acetonide), 69.1 (CH-2), 65.4 (CH_2-6), 64.1 (CH-4), 60.8 (CH_2-1), 38.8 (CH_2-3), 36.9 (CH_2-5), 30.6 (CH_3, acetonide), 22.0 (CH_3, *p*Tol), 20.5 (CH_3, acetonide). − $C_{16}H_{24}O_4S$ (312.43): calcd. C 61.50, H 7.74; found C 61.42, H 7.80.

(−)-[2*R*,4*R*,*S*(*S*)]-6-(*tert*-Butyldimethylsilyloxy)-*syn*-2,4-(isopropylidenedioxy)-1-(*p*-tolylsulfinyl)hexane (13): The alcohol (−)-**9** (483 mg, 1.55 mmol) was dissolved at 0 °C under argon in dry DMF (15 mL). Imidazole (274 mg, 4.02 mmol, 2.6 equiv.) and then *tert*-butyldimethylsilyl chloride (350 mg, 2.32 mmol, 1.5 equiv.) were successively added. After 15 h at room temperature the reaction was hydrolyzed with water (20 mL) and diluted with ether (15 mL). Stirring was continued until clear separation of the layers was observed. The aqueous layer was extracted with ether (3 × 15 mL) and the combined organic extracts were successively washed with water (5 × 15 mL) and brine (20 mL) before being dried over $MgSO_4$. Evaporation of the solvent gave a crude oil, which was purified by rapid chromatography on silica gel to obtain (−)-**13** as a yellow oil (597 mg, 91%). − $[\alpha]_D^{20} = -123$ ($c = 1.29$, $CHCl_3$). − ^1H NMR (200 MHz, $CDCl_3$): $\delta = 7.51$ (A of AA′BB′, 2 H, *p*Tol, $J_{AB} = 8$ Hz, $\Delta\nu = 44$ Hz), 7.29 (B of AA′BB′, 2 H, *p*Tol, $J_{AB} = 8$ Hz, $\Delta\nu = 44$ Hz), 4.51−4.41 (m, 1 H, H-2), 4.14−4.03 (m, 1 H, H-4), 3.76−3.55 (m, 2 H, H-6), 2.74 (m, 2 H, H-1), 2.38 (s, 3 H, CH_3−Ar), 1.65−1.54 (m, 2 H, H-5), 1.51 (s, 3 H, CH_3, acetonide), 1.49 (dt, 1 H, H_{eq}-3, $J_{gem} = 10.0$ Hz, $^3J = 2.5$ Hz), 1.41 (s, 3 H, CH_3, acetonide), 1.31−1.13 (m, 1 H, H_{ax}-3), 0.86 (s, 9 H, Si*t*Bu), 0.13 (s, 6 H, $SiMe_2$). − ^{13}C NMR ($CDCl_3$): δ = 142.1 (C, arom.), 141.9 (C, arom.), 130.6 (CH, arom.), 124.4 (CH, arom.), 99.9 (C, acetonide), 66.1 (CH-2), 65.6 (CH_2-6), 64.1 (CH-4), 59.2 (CH_2-1), 39.9 (CH_2-3), 37.3 (CH_2-5), 30.7 (CH_3, acetonide), 26.5 (CH_3, *t*Bu), 22.0 (CH_3, *p*Tol), 20.5 (CH_3, acetonide), 18.9 (C, Si*t*Bu), −4.8 (CH_3, $SiMe_2$). − $C_{22}H_{38}O_4SiS$ (426.69): calcd. C 61.93, H 8.98; found C 61.72, H 8.87.

(+)-(2*R*,4*R*)-6-(*tert*-Butyldimethylsilyloxy)-*syn*-2,4-(isopropylidenedioxy)hexanal (3): To a cooled (0 °C) solution of the sulfoxide (−)-**13** (122 mg, 0.29 mmol) in dry acetonitrile (3 mL) were added 2,4,6-collidine (76 µL, 0.57 mmol, 2 equiv.) and then trifluoroacetic anhydride (81 µL, 0.57 mmol, 2 equiv.). When no more starting material was detected (0.5 h, tlc), the reaction was quenched at 0 °C with aqueous $NaHCO_3$ (150 mg, 1.75 mmol, 6 equiv in 3 mL H_2O). The mixture was stirred for a further 2 h at room temperature before being diluted with ether (5 mL) and water (5 mL). The aqueous layer was extracted with ether (2 × 5 mL) and the combined organic extracts were successively washed with 1 N HCl (5 mL), sat. $NaHCO_3$ (5 mL) and then with water (3 × 5 mL) before being dried over $MgSO_4$. The crude product obtained after removal of the solvent was purified by chromatography on silica gel to give the pure aldehyde (+)-**3** as a colorless oil (59 mg, 68%). − $[\alpha]_D^{20} = +55$ ($c = 1.30$, $CHCl_3$). − ^1H NMR (200 MHz, $CDCl_3$): $\delta = 9.58$ (s, 1 H, CHO), 4.31 (dd, 1 H, H-2, $J = 12.2$ Hz, $J = 2.9$ Hz), 4.18−4.05 (m, 1 H, H-4), 3.79−3.59 (m, 2 H, H-6), 1.75 (dt, 1 H, H_{eq}-3, $J_{gem} = 12.9$ Hz, $^3J = 2.8$ Hz), 1.69−1.60 (m, 2 H, H-5), 1.46 (s, 6 H, CH_3, acetonide), 1.42−1.24 (m, 1 H, H_{ax}-3), 0.89 (s, 9 H, Si*t*Bu), 0.04 (s, 6 H, $SiMe_2$). − ^{13}C NMR ($CDCl_3$): δ = 202.0 (CHO), 99.8 (C, acetonide), 74.8 (CH-2), 65.7 (CH-4), 59.2 (CH_2-6), 39.9 (CH_2-3), 31.9 (CH_2-5), 30.5 (CH_3, acetonide), 26.6 (CH_3, *t*Bu), 20.2 (CH_3, acetonide), 19.0 (C, *t*Bu), −4.7 (CH_3, $SiMe_2$). −

$C_{15}H_{30}O_4Si$ (302.49): calcd. C 59.56, H 10.00; found C 59.60, H 10.13.

(+)-[2*S*,4*S*,*S*(*R*)]-6-Hydroxy-*syn*-2,4-(isopropylidenedioxy)-1-(*p*-tolylsulfinyl)hexane (9): Dibal−H in toluene (10 mmol, 4.5 equiv.) was added dropwise to a solution at −78°C of the ester (+)-**8**[15] (760 mg, 2.23 mmol) in dry THF (150 mL). After stirring for 4 h (monitored by tlc) the reaction was quenched with sat. NH_4Cl (10 mL) and then diluted with AcOEt (30 mL) and water (40 mL). The aqueous layer was acidified with 5% H_2SO_4 and extracted with AcOEt (2 × 50 mL). The combined organic extracts were washed with brine (50 mL), dried ($MgSO_4$), filtered and evaporated. The resulting crude product was purified by column chromatography on silia gel (AcOEt; AcOEt/MeOH, 9:1) to afford the alcohol (+)-**9** as a light yellow oil (530 mg, 76%). − $[\alpha]_D^{20} = +165$ ($c = 1.73$, $CHCl_3$). − ^1H NMR (200 MHz, $CDCl_3$): $\delta = 7.51$ (A of AA′BB′, 2 H, *p*Tol, $J_{AB} = 8$ Hz, $\Delta\nu = 42$ Hz), 7.30 (B of AA′BB′, 2 H, *p*Tol, $J_{AB} = 8$ Hz, $\Delta\nu = 42$ Hz), 4.56−4.43 (m, 1 H, H-2), 4.22−4.04 (m, 1 H, H-4), 3.73 (t, 2 H, H-6, $J = 5.6$ Hz), 2.81−2.65 (m, 2 H, H-1), 2.38 (s, 3 H, CH_3-Ar), 1.74−1.66 (m, 2 H, H-5), 1.53 (s, 3 H, CH_3, acetonide), 1.48−1.19 (m, 2 H, H-3), 1.41 (s, 3 H, CH_3, acetonide). − ^{13}C NMR ($CDCl_3$): $\delta = 142.1$ (C arom.), 141.9 (C arom.), 130.6 (CH arom.), 124.4 (CH arom.), 100.0 (C, acetonide), 69.2 (CH-2), 65.5 (CH_2-6), 64.1 (CH-4), 60.9 (CH_2-1), 38.8 (CH_2-3), 36.9 (CH_2-5), 30.6 (CH_3, acetonide), 22.0 (CH_3, *p*Tol), 20.5 (CH_3, acetonide). − $C_{16}H_{24}O_4S$ (312.43): calcd. C 61.50, H 7.74; found C 62.10, H 7.69.

(+)-[2*S*,4*S*,*S*(*R*)]-6-Benzyloxy-*syn*-2,4-(isopropylidenedioxy)-1-(*p*-tolylsulfinyl)hexane (10): Sodium hydride (9 mg, 0.36 mmol, 1.3 equiv.) was added to a solution of the alcohol (+)-**9** (87 mg, 0.28 mmol) at 0°C in dry THF (3 mL). The suspension was stirred for 30 min before adding tetrabutylammonium iodide (15 mg, 0.04 mmol, 0.15 equiv.) and benzyl bromide (66 μL, 0.56 mmol, 2 equiv.). After stirring overnight at room temperature, water (5 mL) and then CH_2Cl_2 (10 mL) were added to the reaction mixture. The aqueous layer was extracted with CH_2Cl_2 (2 × 5 mL). The combined organic extracts were washed with water (5 × 10 mL), brine (100 mL) and dried over $MgSO_4$ before being filtered and concentrated. The crude oily residue was purified by rapid chromatography on silica gel to give the protected alcohol (+)-**10** as a yellow oil (55%). − $[\alpha]_D^{20} = +141$ ($c = 0.99$, $CHCl_3$). − ^1H NMR (200 MHz, $CDCl_3$): $\delta = 7.53$ (A of AA′BB′, 2 H, *p*Tol, $J_{AB} = 8.2$ Hz, $\Delta\nu = 46$ Hz), 7.30 (B of AA′BB′, 2 H, *p*Tol, $J_{AB} = 8.2$ Hz, $\Delta\nu = 46$ Hz), 7.38−7.21 (m, 5 H, Ph), 4.55−4.41 (m, 1 H, H-2), 4.47 (d, 2 H, OCH_2Ph, $J = 0.86$ Hz), 4.17−4.04 (m, 1 H, H-4), 3.63−3.45 (m, 2 H, H-6), 2.80−2.65 (m, 2 H, H-1), 2.39 (s, 3 H, CH_3-Ar), 1.79−1.68 (m, 2 H, H-5), 1.51 (s, 3 H, CH_3, acetonide), 1.50 (dt, 1 H, H-3_{eq}, $J_{gem} = 12.6$ Hz, $^3J = 2.6$ Hz), 1.41 (s, 3 H, CH_3, acetonide), 1.31−1.14 (m, 2 H, H-3_{ax}). − ^1H NMR (200 MHz, C_6D_6): $\delta = 7.75$ (A of AA′BB′, 2 H, *p*Tol, $J_{AB} = 8$ Hz, $\Delta\nu = 11$ Hz), 7.38−7.12 (m, 5 H, Ph), 6.64 (B of AA′BB′, 2 H, *p*Tol, $J_{AB} = 8$ Hz, $\Delta\nu = 11$ Hz), 4.62−4.49 (m, 1 H, H-2), 4.44−4.31 (m, 2 H, OCH_2Ph), 3.99−3.86 (m, 1 H, H-4), 3.60−3.39 (m, 2 H, H-6), 2.66−2.48 (m, 2 H, H-1), 2.02 (s, 3 H, CH_3-Ar), 1.87−1.66 (m, 2 H, H-5), 1.59 (s, 3 H, CH_3, acetonide), 1.45 (s, 3 H, CH_3, acetonide), 1.56−0.95 (m, 2 H, H-3). − ^{13}C NMR ($CDCl_3$): $\delta = 142.1$ (C arom.), 141.9 (C arom.), 139.0 (C arom.), 130.6 (CH arom.), 129.0 (CH arom.), 128.2 (CH arom.), 124.4 (CH arom.), 99.9 (C, acetonide), 73.6 (OCH_2Ph), 66.6 (CH_2-6), 66.5 (CH-2), 65.6 (CH_2-1), 64.1 (CH-4), 37.2 (CH_2-3), 37.1 (CH_2-5), 30.6 (CH_3, acetonide), 22.0 (CH_3, *p*Tol), 20.5 (CH_3, acetonide). − ^{13}C NMR (C_6D_6): $\delta = 143.8$ (C arom.), 140.5 (C arom.), 139.4 (C arom.), 130.0 (CH arom.), 123.9 (CH arom.), 99.4 (C, acetonide), 73.1 (OCH_2Ph), 66.4 (CH_2-6), 66.3 (CH-2), 65.8 (CH_2-1), 63.9 (CH-4), 37.1 (CH_2-3), 37.0 (CH_2-5), 30.4 (CH_3, acetonide), 21.1 (CH_3, *p*Tol), 20.0 (CH_3, acetonide). − $C_{23}H_{30}O_4S$ (402.55): calcd. C 68.63, H 7.51; found C 65.76, H 7.04.

(2*S*,4*S*)-1-Acetoxy-6-benzyloxy-*syn*-2,4-(isopropylidenedioxy)-1-(*p*-tolylthio)hexane (11): Anhydrous sodium acetate (200 mg, 10 equiv.) followed by acetic anhydride (6 mL) were added to the sulfoxide (+)-**10** (98 mg, 0.24 mmol). The mixture was refluxed for 10 h at 135°C then stirred for 2 h at room temperature. The brown heterogeneous solution was filtered through Celite and washed with CH_2Cl_2. The solvents were removed by azeotropic distillation with toluene (4 × 5 mL). The resulting crude product was purified by chromatography on silica gel (AcOEt/hexane) to give the pure product **11** as a yellow oil (93 mg, 86%) along with a 70/30 mixture of diastereomers at C-1. − ^1H NMR (200 MHz, $CDCl_3$): $\delta = 7.40$ (A of AA′BB′, 2 H, *p*Tol, $J_{AB} = 8$ Hz, $\Delta\nu = 57$ Hz), 7.33 (m, 5 H, Ph), 7.11 (B of AA′BB′, 2 H, ITol, $J_{AB} = 8$ Hz, $\Delta\nu = 57$ Hz), 6.06 (d, 0.7 H, H-1, $J = 5.6$ Hz, major isomer), 5.94 (d, 0.3 H, H-1, $J = 5.6$ Hz, minor isomer), 4.52 [A of AB, 1 H, CH_2 (OBn), $J_{AB} = 12.1$ Hz, $\Delta\nu = 6$ Hz], 4.49 [B of AB, 1 H, CH_2 (OBn), $J_{AB} = 12.1$ Hz, $\Delta\nu = 6$ Hz], 4.17−3.99 (m, 2 H, H-2 + H-4), 3.66−3.48 (m, 2 H, H-6), 2.33 (s, 3 H, CH_3-Ar), 2.05 (s, 3 H, OAc), 1.82−1.72 (m, 2 H, H-5), 1.61 (dt, 1 H, H-3_{eq}, $J_{gem} = 15.3$ Hz, $^3J = 2.4$ Hz), 1.50−1.21 (m, 1 H, H-3_{ax}), 1.40 (s, 3 H, CH_3, acetonide), 1.37 (s, 3 H, CH_3, acetonide). − ^{13}C NMR ($CDCl_3$): $\delta = 170.4$ (CO), 170.3 (CO), 139.1 (C arom.), 134.9 (CH arom.), 134.4 (CH arom.), 130.4 (CH arom.), 130.3 (CH arom.), 129.0 (CH arom.), 128.6 (C arom.), 128.3 (C arom.), 99.8 (C, acetonide), 83.7 (CH-1), 83.5 (CH-1), 73.7 (CH_2, OBn), 71.2 (CH-2), 70.6 (CH-2), 66.6 (CH_2-6), 66.3 (CH-4), 37.1 (CH_2-5), 33.8 (CH_2-3), 33.2 (CH_2-3), 30.6 (CH_3, acetonide), 21.9 (CH_3, OAc), 21.6 (CH_3, *p*Tol), 20.3 (CH_3, acetonide). − $C_{25}H_{32}O_5S$ (444.59): calcd. C 67.54, H 7.25; found C 67.50, H 7.10.

(−)-(2*S*,4*S*)-6-Benzyloxy-*syn*-2,4-(isopropylidenedioxy)hexanal (12): Sodium methanolate (53 mg, 0.99 mmol, 6 equiv.) was added to a solution at 0°C of the O,S-acetal **11** (73 mg, 0.16 mmol) in MeOH (5 mL). The reaction was stirred at 0°C until no more starting material was detected by tlc (3 h). The reaction was then quenched with sat. NH_4Cl (3 mL) and water (3 mL). After dilution with CH_2Cl_2 (5 mL) the aqueous layer was acidified to pH 5 with a few drops of 10% HCl and then extracted with CH_2Cl_2 (3 × 5 mL). The combined organic extracts were washed with water (10 mL), brine (10 mL) and dried over $MgSO_4$. The solvent was removed and the crude product was purified by chromatography on silica gel to afford aldehyde (−)-**12** as a pale yellow oil (40 mg, 89%). − $[\alpha]_D^{20} = -38$ ($c = 1.02$, $CHCl_3$). − ^1H NMR (200 MHz, $CDCl_3$): $\delta = 9.58$ (d, 1 H, H-1, $^4J = 0.5$ Hz), 7.40−7.28 (m, 5 H, Ph), 4.52 [A of AB, 1 H, CH_2 (OBn), $J_{AB} = 12.1$ Hz, $\Delta\nu = 5$ Hz], 4.49 [B of AB, 1 H, CH_2 (OBn), $J_{AB} = 12.1$ Hz, $\Delta\nu = 5$ Hz], 4.30 (ddd, 1 H, H-2, $^3J = 12.2$ Hz, $^3J = 3.1$ Hz, $^4J = 0.5$ Hz), 4.15−4.06 (m, 1 H, H-4), 3.66−3.50 (m, 2 H, H-6), 1.83−1.70 (m, 3 H, H-5 + H-3_{eq}), 1.46 (s, 6 H, CH_3, acetonide), 1.41−1.23 (m, 1 H, H-3_{ax}). − ^{13}C NMR ($CDCl_3$): $\delta = 201.9$ (CHO), 139.2 (C arom.), 129.1 (CH arom.), 128.3 (CH arom.), 99.8 (C, acetonide), 74.7 (CH_2, OBn), 73.7 (CH-2), 66.4 (CH_2-6), 66.1 (CH-4), 37.1 (CH_2-2), 31.7 (CH_2-5), 30.5 (CH_3, acetonide), 20.2 (CH_3, acetonide). − $C_{16}H_{22}O_4$ (278.35): calcd. C 69.04, H 7.97; found C 67.59, H 7.82.

(−)-(3*S*,5*S*)-1-Benzyloxy-*syn*-3,5-(isopropylidenedioxy)hept-6-yne (2): The aldehyde (−)-**12** (92 mg, 0.33 mmol) was diluted with dry MeOH (1.5 mL). Successively, potassium carbonate (91 mg, 0.66 mmol, 2 equiv.) and a solution of dimethyl diazo-1-oxo-2-propylphosphonate (88 mg, 0.46 mmol, 1.4 equiv.) in dry MeOH (1 mL) were added. The reaction was stirred during 3 h at room temperature and then diluted with ether (5 mL) before being quenched with sat. $NaHCO_3$. This mixture was stirred at room temperature for 1 h and then diluted with water (5 mL). The aqueous layer was acidified to pH 1 with 20% HCl and then extracted with AcOEt (2 × 5 mL). The combined organic extracts were washed with brine (15 mL), dried ($MgSO_4$), filtered and evaporated. The crude residue was purified by chromatography on silica gel (AcOEt/hexane, 2:8) to obtain the alkyne (−)-**2** as a colorless oil (58 mg, 64%). − $[\alpha]_D^{20} = -19$ (c = 1.16, $CHCl_3$). − ^1H NMR (200 MHz, $CDCl_3$): δ = 7.37−7.28 (m, 5 H, Ph), 4.66 (dt, 1 H, H-5, ^3J = 11.1 Hz, ^4J = 2.7 Hz), 4.50 [d, 2 H, CH_2 (OBn), J = 1.6 Hz], 4.12−3.99 (m, 1 H, H-3), 3.66−3.47 (m, 2 H, H-1), 2.46 (d, 1 H, H-7, J = 2.1 Hz), 1.81−1.60 (m, 4 H, H-2 + H-4), 1.45 (s, 3 H, CH_3, acetonide), 1.43 (s, 3 H, CH_3, acetonide). − ^1H NMR (200 MHz, C_6D_6): δ = 7.29−7.06 (m, 5 H, Ph), 4.36 (dt, 1 H, H-5, ^3J = 11.7 Hz, ^4J = 2.4 Hz), 4.27 [d, 2 H, CH_2 (OBn), J = 3.3 Hz], 4.20−3.69 (m, 1 H, H-3), 3.50−3.24 (m, 2 H, H-1), 2.04 (d, 1 H, H-7, J = 2.1 Hz), 1.77−1.48 (m, 3 H, H-2 + H-4_{ax}), 1.46 (s, 3 H, CH_3, acetonide), 1.34 (dt, 1 H, H-4_{eq}, J = 12.9 Hz, ^3J = 2.7 Hz), 1.33 (s, 3 H, CH_3, acetonide). − ^{13}C NMR ($CDCl_3$): δ = 139.1 (C arom.), 129.1 (C arom.), 128.3 (CH arom.), 99.9 (C, acetonide), 83.3 (C-6), 75.3 (CH_2, OBn), 73.7 (CH-7), 66.5 (CH_2-1), 66.2 (CH-5), 60.9 (CH-3), 37.9 (CH_2-4), 36.9 (CH_2-2), 30.8 (CH_3, acetonide), 20.1 (CH_3, acetonide). − $C_{17}H_{22}O_3$ (274.36): calcd. C 74.42, H 8.08; found C 72.86, H 7.87.

(3*S*,5*S*,9*R*,11*R*)-1-Benzyloxy-13-(*tert*-butyldimethylsilyloxy)-8-hydroxy-*syn*-3,5:9,11-(diisopropylidenedioxy)tridec-6-yne (1a and 1b): BuLi (36 μmol, 1.05 equiv.) was added to a solution of the alkyne (−)-**2** (9.5 mg, 35 μmol) at −75°C in dry THF (0.5 mL). The reaction was stirred for 1 h at 0°C and then cooled to −75°C again before adding the aldehyde (+)-**3** (10 mg, 35 μmol) in solution in THF (0.5 mL). The reaction was left overnight and the temperature allowed to reach room temperature slowly. The solution was diluted with ether (3 mL) and the reaction was quenched by adding sat. NH_4Cl (3 mL). The aqueous layer was extracted with ether (3 × 5 mL) and the combined organic extracts were dried ($MgSO_4$) and concentrated to give a crude colorless oil (21 mg), which was purified by tlc to separate the mixture **1a**/**1b** (57%) from the unchanged aldehyde (+)-**3** and alkyne (−)-**2**. The mixture (24/76) of the two isomers **1a** (the desired 8*R* isomer) and **1b** (the 8*S* isomer) was purified by tlc (triple migration) to afford a pure analytic sample of the **1b** isomer {$[\alpha]_D^{20} = +10$ (c = 0.19, $CHCl_3$)}. **Mixture of two diastereomers:** ^1H NMR (200 MHz, $CDCl_3$): δ = 7.34 (m, 5 H, Ph), 4.70 (m, 1 H, H-9), 4.52 [A of AB, 1 H, CH_2 (OBn), J_{AB} = 12.3 Hz, $\Delta\nu$ = 7 Hz], 4.49 [B of AB, 1 H, CH_2 (OBn), J_{AB} = 12.3 Hz, $\Delta\nu$ = 7 Hz], 4.25−3.90 (m, 3 H, H-3 + H-5 + H-11), 3.80−3.46 (m, 4 H, H-1 + H-13), 2.66 (d, 0.76 H, OH of isomer 8*S*, J = 3.5 Hz), 2.38 (d, 0.24 H, OH of isomer 8*R*, J = 4.4 Hz), 1.80−1.65 (m, 8 H, H-2 + H-4 + H-10 + H-12), 1.58 (s, 3 H, CH_3, acetonide), 1.44 (s, 3 H, CH_3, acetonide), 1.42 (s, 3 H, CH_3, acetonide), 1.40 (s, 3 H, CH_3, acetonide), 0.90 (s, 9 H, Si*t*Bu), 0.06 (s, 6 H, $SiMe_2$). − ^{13}C NMR ($CDCl_3$): δ = 138.5 (C arom.), 128.5 (CH arom.), 127.8 (CH arom.), 99.3 (C, acetonide), 99.1 (C, acetonide), 85.2 (C-7), 81.4 (C-8), 73.2 (CH_2, OBn), 71.5 (CH-6), 65.9 (CH_2-13), 66.7 (CH-9), 65.3 (CH-3), 64.8 (CH-5), 60.5 (CH-11), 58.8 (CH_2-1), 39.5 (CH_2-2), 37.5 (CH_2-4), 36.3 (CH_2-10), 30.2 (CH_3, acetonide), 30.1 (CH_3, acetonide), 30.0 (CH_2-12), 26.0 (CH_3, Si*t*Bu), 20.1 (CH_3, acetonide), 19.5 (CH_3, acetonide), 18.4 (C, Si*t*Bu), −5.3 ($SiCH_3$). − $C_{32}H_{53}O_7Si$ (577.84): calcd. C 66.51, H 9.24; found C 66.38, H 9.19.

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