DOI: 10.1002/ejoc.200901285

Synthetic Studies toward the CD Spiroketal of Spongistatins

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Keywords: Spiro compounds / Polyketides / Natural products / Desymmetrization / Alcoholysis

Starting from the readily available *meso*-1,1′-methylenebis(8-oxabicyclo[3.2.1]oct-6-en-3-one) (**1**), *meso*-1,1′-methylenebis[(4*R*,4′*S*,6*R*,6′*S*)-4,6-dioxycyclohept-1-en-1-yl]tetrasilyl ethers **7** and **8** were obtained and transformed into all-*syn* 1,3,5,11,13,15-hexahydroxypentadeca-7,9-dione derivatives **9** and **10**. The conversion of these intermediates into spiroketals was not successful. An alternative strategy based on the sequential and stereoselective functionalization of **1** afforded a 1-(2,4,6,8-tetrahydroxyoctyl)cyclohept-1-ene-4,6-diol derivative [(+)-**15**, 94 % *ee*]. Ozonolysis of the cycloheptene moiety of (+)-**19** provided the equatorial/axial spiroketal (+)-**21**. Pivaloylation of its primary alcohol moiety and Meerwein methylation of the remaining secondary alcohol unit furnished (–)-**24**, a potential precursor of the ketal isomer of the CD fragment found in spongistatins 1 and 2.

Introduction

Spiroketals and in particular their 6,6-congeners are key structural elements of a variety of natural products of biological interest, for example, marine macrolides, ionophores and polyether antibiotics.[1] The spiroketal fragments are often very important for the biological activity of the compounds containing them. In particular, spongistatins (altohyrtins), which were isolated from marine sponges of the genus *Spongia* by three research groups in 1993,[2] display two highly oxygenated 6,6-spiroketals in their macrolactone skeleton (Figure 1). These marine macrolides are potent cancer cell growth inhibitors and thus appear to represent promising leads for the development of new anti-cancer agents.[3] Nevertheless, their use in clinical evaluation is limited by their low natural abundance, which has stimulated organic chemists to develop efficient synthetic routes to address this supply issue.[4]

In addition to seminal reports by the groups of Evans,[5] Kishi,[6] Paterson,[7] Smith,[8] Crimmins,[9] Heathcock[10] and Ley[11] on the total syntheses of spongistatins 1 and 2, much effort has been devoted to the implementation of straightforward and high-yielding pathways towards the ABCD "northern" hemisphere[12] and the EF tetrahydropyran subunits.[13] Our group has been involved for several years in the development of innovative and non-iterative strategies towards the stereocontrolled synthesis of C_{15} polyketides and their analogues.[14] Following the recent reports on the synthesis of the polyol subunit of the polyene macrolide antibiotic RK-397[15] and on an advanced precursor of the AB spiroketal of spongistatins,[12j] we report

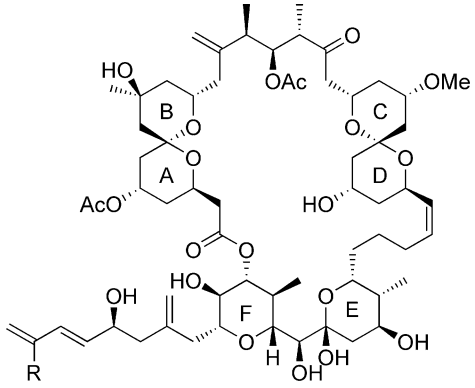

Figure 1. Representative members of the spongistatin (altohyrtins) family.

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Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.200901285.

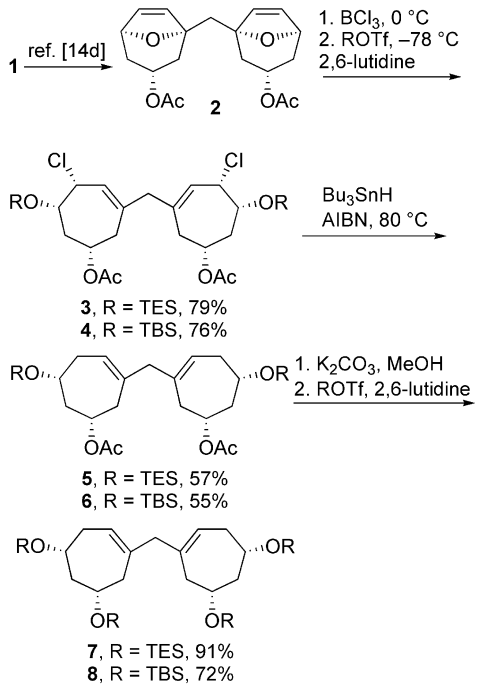
herein the application of this methodology to the preparation of potential intermediates of the CD spiroketal fragment.

Results and Discussion

The strategies envisaged for the synthesis of the CD spiroketal **A** (Scheme 1) involve the obtention of the keto polyol precursor **B** either from diketone **C** by desymmetrization (path A) or from functionalized cycloheptene **D** by oxidative cleavage of the olefin and selective reduction of the resulting aldehyde (path B). Intermediate **C** should arise from the simultaneous functionalization of the diolefin *meso*-**E**, whereas cycloheptene **D** should result from the stereoselective transformation of the *meso*-**E**, which can be produced from the readily accessible diketone **1**.[14c]

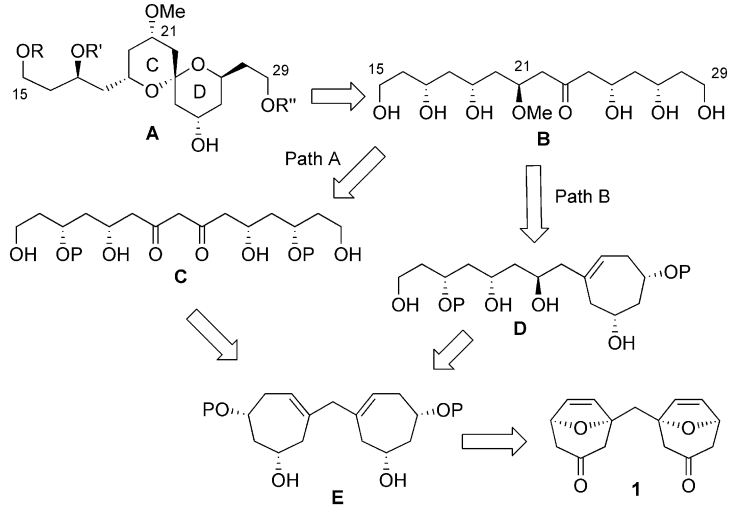
Diketone **1** was converted into the *exo*-diacetate **2** as previously reported.[14d] For the approach by path A, silyl ethers were envisaged as protecting moieties on the C_{15} skeleton. Boron trichloride mediated opening of the oxa bridges followed by treatment with silyl triflates afforded chlorinated cycloheptenes **3** and **4** in 79 and 76% yields, respectively (Scheme 2). A sequence of reductive dechlorination followed by replacement of the acetyl groups by *tert*-butyldimethyl or triethylsilyl moieties delivered fully protected tetrols **7** and **8**, respectively.

Diketone intermediates of type **C** were prepared by oxidative cleavage of both olefins followed by selective reduction of the aldehyde moieties in situ (Scheme 3). All our attempts at the dihydroxylation ($KMnO_4$ or OsO_4 cat./NMO) of dienes **7** and **8** led to decomposition of the starting diolefins. Ozonolysis at –78 °C followed by reductive treatment with dimethyl sulfide afforded intermediate dialdehydes, which were further reduced in situ to the corresponding 1,3-diketones **9** and **10**. Treatment with several hydrides such as $NaBH(OAc)_3$, $NaBH_4$, DIBAL-H or BH_3 was not successful, either giving back the starting material or leading to unselective reduction of both the aldehyde and



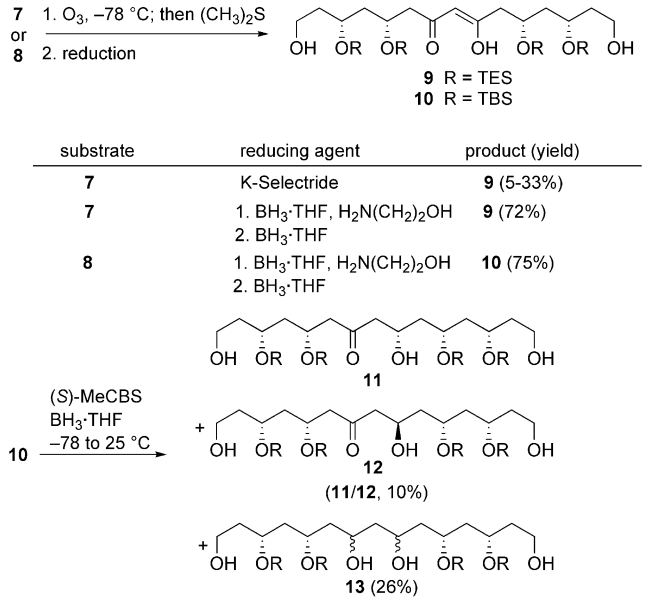
Scheme 2. Synthesis of the cycloheptene precursors (R = TES, TBS).

ketone functionalities or inducing decomposition of the starting materials. The use of K-selectride afforded the expected 1,3-diketone **9** in low yields. Gratifyingly, the reducing agent resulting from a mixture of BH_3 and 1-aminoethanol provided an efficient and selective reduction of the aldehyde moieties to deliver the 1,3-diketones **9** and **10** in 72 and 75% yields, respectively (two steps). Unfortunately, all our attempts to desymmetrize the 1,3-diketones **9** and **10** by enantioselective reduction of one oxo group[16] failed to produce the expected β-hydroxy ketone in reasonable yields. Typically, by using the Corey–Bakshi–Shibata (CBS) methodology,[17] a low conversion (63% yield of recovered starting material) led to a mixture of the diastereoisomeric



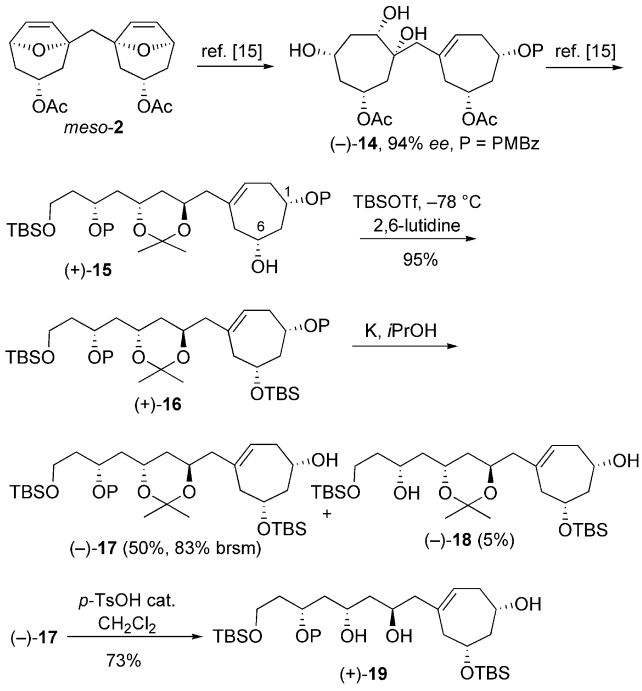
Scheme 1. Retrosynthetic scheme for the CD spiroketal of spongistatins.

alcohols **11** and **12** in yields of 10% along with diol **13** (26% yield). Variation of the solvent, the nature of the borane and the amount of hydride did not give satisfying results. The low yields did not allow conclusive measurement of the asymmetric induction by the Mosher ester methodology.[18] As an alternative, reduction of the double bond in the keto enols **9** and **10** was attempted, but the olefin could not be hydrogenated. As the desymmetrization of the linear diketones **9** and **10** was not successful, another approach based on the early-stage desymmetrization of cycloheptene derivatives of type *meso*-**E** (Scheme 1) was developed.



Scheme 3. Exploration of path A.

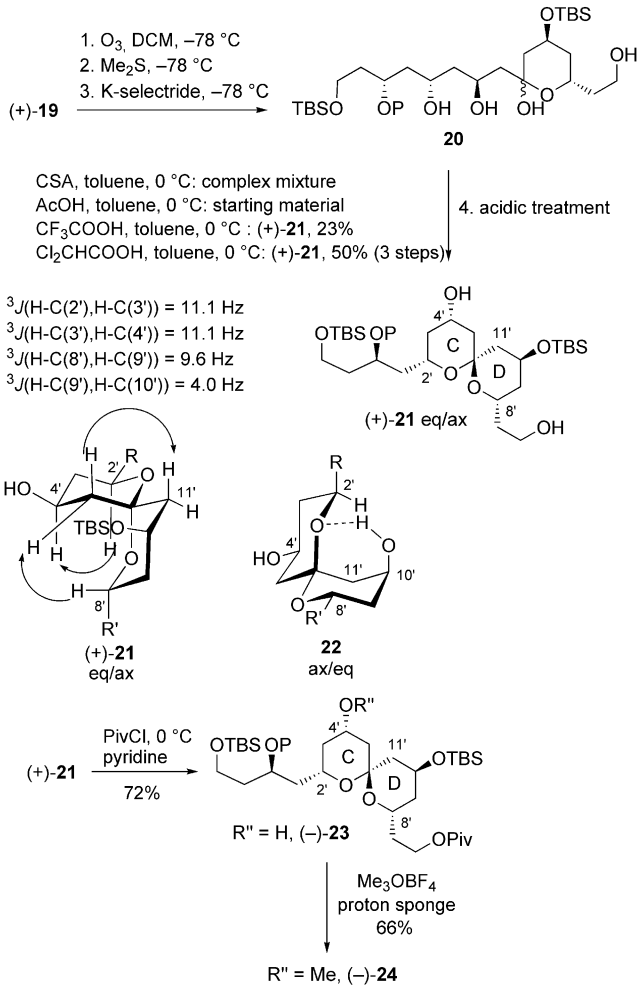
Following path B (Scheme 1) and our previous report,[16] diolefin *meso*-**2** was converted into the semi-protected hexol (+)-**15** (Scheme 4). The key reaction of this sequence was the Sharpless asymmetric dihydroxylation reaction for the desymmetrization of *meso*-**E** to give intermediate diol (–)-**14** with 94% *ee*. Etherification of the remaining secondary alcohol of (+)-**15** in the presence of PMBCl and sodium hydride led to an inseparable 1:1 mixture of the expected derivative and the product of migration of the *p*-methoxybenzoyl from the C-1 to the C-6 position of the cycloheptene. Other sources of the *p*-methoxybenzoyl group such as *p*-methoxybenzyl trichloroacetimidate (PMBTCA) in the presence of Ph_3CBF_4 did not prevent the migration of the ester moiety. Finally, the alcohol at the C-6 position was eventually protected as a *tert*-butyldimethylsilyl ether in high yield (95%). Discrimination between the two *p*-methoxybenzoyl moieties was achieved by alcoholysis in the presence of potassium isopropoxide generated in situ, which afforded alcohol (–)-**17** in 83% yield based on recovered starting material (50% yield). Careful monitoring of the reaction allowed the reaction to be stopped as soon as the diol (–)-**18** appeared. This was isolated in 5% yield and could easily be converted back into the starting material (+)-**16** by esterification. Although treatment of (–)-**17** with 10% of PPTS resulted in a very slow removal of the acetonide moiety, the use of a catalytic amount of *p*-TsOH in dichloromethane provided a rapid access to diol (+)-**19** in 73% yield and established the functionalities for the spirocyclization step.



Scheme 4. Stereoselective functionalization following path B.

Opening of the second cycloheptene was achieved by ozonolysis followed by reductive treatment of the intermediate ozonide first with dimethyl sulfide and then with K-Selectride to provide the intermediate hemiketal **20** as a mixture of two diastereoisomers (Scheme 5). The latter was not isolated but submitted directly to acidic treatment. The use of camphorsulfonic acid led to decomposition of the starting hemiketal. Milder acids such as acetic acid failed to induce spirocyclization. In the presence of trifluoroacetic acid, partial removal of the primary *tert*-butyldimethylsilyl ether resulted in only 23% yield of the expected spiroketal (+)-**21**. By tuning the strength of the acid, optimal conditions were achieved with dichloroacetic acid, which afforded (+)-**21** in 50% yield from triol (+)-**19** (three steps). The structure of the spiroketal was assigned on the basis of its 2D NOESY ^1H NMR spectrum. The $^3J_{H,H}$ coupling constants observed for protons 2′-H, 3′-H, 4′-H, 8′-H, 9′-H and 10′-H as well as diagnostic NOEs (2′-H/4′-H) established the chair conformation of the two rings with the *tert*-butyldimethylsilyl ether at C-10′ being in the axial position. Cross-peaks between the signals of 5′-H and 11′-H proved the axial orientation of the O-7′ atom, whereas NOEs between 5′-H/8′-H established the equatorial position of O-1′. The configuration of spiroketal (+)-**21** was thus assigned as equatorial/axial whereas the natural target presents an axial/equatorial configuration of the CD spiroketal. Apparently, the silyl ether moiety at C-10′ prevents the hydrogen bridge necessary for the stabilization of the naturally occur-

ring configuration, as depicted in the expected analogue **22**, which does not contain the silyl ether moiety.[4] The final functionalizations involved the selective protection of the primary alcohol as a pivaloate ester and methylation of the alcohol at C-4′ in the presence of the Meerwein salt to afford (–)-**24** (66% yield) as a potential highly advanced precursor of the CD spiroketal of spongistatins.



Scheme 5. Spiroketalization and final functionalizations.

Conclusions

We have described the synthesis of an advanced precursor of the CD spiroketal of spongistatins 1 and 2 in 3% overall yield from the previously reported *meso* diketone **1** in 21 steps requiring the isolation of only 12 intermediates. A sequence of highly stereoselective transformations allowed the installation of the functionalities of the natural target on the starting bicyclic template. The presence of a protecting group at C-10′ prevented the direct formation of the natural axial/equatorial configuration at the spiro centre and the thermodynamically favoured axial/axial isomer was never observed. Removal of the silyl ethers and equilibration in the presence of metal cations such as Mg^{2+},[5a] Zn^{2+},[10b] Ca^{2+}[8a] or Hg^{2+}[11d] should promote the formation of the natural axial/equatorial configuration. This synthetic route and the previous preparation of a precursor of the AB spiroketal illustrate the high versatility of bicyclic templates of type **E** for the asymmetric synthesis of natural polyketides and their analogues.

Experimental Section

General: All commercially available reagents and solvents (Fluka, Aldrich, Acros) were used without further purification. For reactions requiring anhydrous conditions, dry solvents were bought (Fluka, Aldrich). Unless otherwise noted, experiments were carried out under argon. Reactions were monitored by TLC (Merck silica gel $60F_{254}$ plates) with detection by UV light, $KMnO_4$ or Pancaldi reagents [$(NH_4)_6MoO_4$, $Ce(SO_4)$, H_2SO_4, H_2O]. Purifications were performed by flash chromatography on silica gel (Merck no. 9385 silica gel 60, 240–400 mesh).

^{1}H NMR spectra were recorded with the Bruker ARX-400 and DPX-400 spectrometers at 400 MHz and the Bruker AVII-800 spectrometers at 800 MHz. Chemical shifts are given in ppm relative to the residual ^{1}H solvent signal (MeOD: δ = 3.34 ppm; $CDCl_3$: δ = 7.27 ppm; C_6D_6: δ = 7.30 ppm) as the internal reference. ^{1}H NMR assignments were confirmed by 2D COSY spectra. The multiplicities given reflect apparent signal patterns. ^{13}C NMR spectra were recorded with the same instrument as above at 101 MHz. Chemical shifts are given in ppm relative to the residual ^{13}C solvent signal (MeOD: δ = 49 ppm; $CDCl_3$: δ = 77 ppm; C_6D_6: δ = 128.5 ppm). ^{13}C NMR assignments were confirmed by 2D HSQC spectra. Coupling constants J are given in Hz for all NMR data.

IR spectra were recorded with a Perkin–Elmer Paragon 1000 FT-IR spectrometer. Mass spectra were recorded with the following instruments: MALDI-TOF: Axima-CFR$^+$ spectrometer, Kratos; ESI-Q: Finnigan SSQ 710C spectrometer, Thermoquest; ESI-HRMS: Q-Tof Ultima spectrometer, Micromass. Elemental analyses were performed at Ilse Beetz, 96301, Kronach, Germany using an EPFL-ISIC-LCS instrument. Optical Rotations were determined at 25 °C with a Jasco P-1020 polarimeter; [α] values are given in units of 10^{-1} deg cm^2 g^{-1}.

Methylenebis[(1*R*,1′*S*,5*S*,5′*R*,6*R*,6′*S*)-5-chloro-6-(triethylsilyloxy)cyclohept-3-ene-1,3-diyl] Diacetate (3): A 1.0 M solution of BCl_3 in DCM (8.6 mL, 3 equiv.) was added dropwise to a stirred solution of **2** (1 g, 2.9 mmol) in anhydrous DCM (28 mL) at 0 °C. After stirring at 0 °C for 4 h, a saturated aqueous solution of $NaHCO_3$ (2 × 30 mL) was added slowly under vigorous stirring and the aqueous layer was extracted with DCM (3 × 20 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. The residue was taken up in anhydrous DCM (28 mL) and cooled to –78 °C. 2,6-Lutidine (2.5 mL, 21.5 mmol 7.5 equiv.) and TESOTf (2 mL, 8.6 mmol, 3 equiv.) were added. After stirring at –78 °C for 1 h, the mixture was poured into a saturated aqueous solution of $NaHCO_3$ (25 mL) and extracted with DCM (3 × 20 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. Purification by chromatography on silica gel (Et_2O/PE, 1:9) afforded **3** as a colourless oil (1.46 g, 79%). R_f = 0.3 (Et_2O/PE, 1:9). IR (film): $\tilde{\nu}$ = 2955, 2915, 1730, 1370, 1245, 1100, 1025, 830, 770 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.75 (d, $^3J_{H,H}$ = 8.3 Hz, 2 H, 4-H, 4′-H), 4.60 (dddd, $^3J_{H,H}$ = 11.4, $^3J_{H,H}$ = 11.4, $^3J_{H,H}$ = 2.8, $^3J_{H,H}$ = 2.8 Hz, 2 H, 1-H, 1′-H), 4.46 (dd, $^3J_{H,H}$ = 2.8, $^3J_{H,H}$ = 8.3 Hz, 2 H, 5-H, 5′-H), 3.94 (dt, $^3J_{H,H}$ = 11.4, $^3J_{H,H}$ = 2.8, $^3J_{H,H}$ = 2.8 Hz, 2 H, 6-H, 6′-H), 2.78 (m, 2 H, 2-H, 2′-H), 2.76 (s, 2 H, 8-H_2), 2.47 (q, $^2J_{H,H}$ = 11.4, $^3J_{H,H}$ = 11.4, $^3J_{H,H}$ = 11.4 Hz,

2 H, 7-H, 7′-H), 2.04 (m, 4 H, 7-H, 7′-H, 2-H, 2′-H), 2.03 (s, 6 H, 2 OAc), 0.96 [t, $^3J_{H,H}$ = 7.8 Hz, 18 H, CH_3 (TES)], 0.61 [q, $^3J_{H,H}$ = 7.8 Hz, 12 H, CH_2 (TES)] ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 170.1, 141.1, 125.5, 69.3, 69.1, 63.5, 51.0, 40.4, 36.5, 21.3, 6.8, 4.7 ppm. HRMS (ESI): calcd. for $C_{31}H_{54}Cl_2O_6Si_2Na$ [M + Na]$^+$ 671.2734; found 671.2724.

Methylenebis{(1*R*,1′*S*,5*S*,5′*R*,6*R*,6′*S*)-5-chloro-6-[(*tert*-butyl)(dimethyl)silyloxy]cyclohept-3-ene-1,3-diyl} Diacetate (4): A 1.0 M solution of BCl_3 in DCM (5.7 mL, 5 equiv.) was added dropwise to a stirred solution of **2** (400 mg, 1.15 mmol) in anhydrous DCM (11 mL) at 0 °C. After stirring at 0 °C for 4 h, a saturated aqueous solution of $NaHCO_3$ (2 × 30 mL) was added slowly under vigorous stirring. The aqueous layer was extracted with DCM (3 × 20 mL) and the combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. The residue was taken up in anhydrous DCM (11 mL) and cooled to –78 °C. 2,6-Lutidine (0.9 mL, 8 mmol 7 equiv.) and TBSOTf (0.8 mL, 3.4 mmol, 3 equiv.) were added. After stirring at –78 °C for 1 h, the mixture was poured into a saturated aqueous solution of $NaHCO_3$ (25 mL) and extracted with DCM (3 × 20 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. Purification by chromatography on silica gel (Et_2O/PE, 1:10) afforded **4** as a colourless oil (569 mg, 76%). R_f = 0.37 (Et_2O/PE, 1:9). IR (film): $\tilde{\nu}$ = 3440 (H_2O), 2930, 2855, 1737, 1240, 1105, 1025, 840 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.73 (d, $^3J_{H,H}$ = 8.3 Hz, 2 H, 4-H, 4′-H), 4.61 (dddd, $^3J_{H,H}$ = 11.4, $^3J_{H,H}$ = 11.4, $^3J_{H,H}$ = 2.7, $^3J_{H,H}$ = 2.7 Hz, 2 H, 1-H, 1′-H), 4.45 (d, $^3J_{H,H}$ = 2.7, $^3J_{H,H}$ = 8.3 Hz, 2 H, 5-H, 5′-H), 3.94 (dt, $^3J_{H,H}$ = 11.4, $^3J_{H,H}$ = 2.7, $^3J_{H,H}$ = 2.7 Hz, 2 H, 6-H, 6′-H), 2.76 (m, 4 H, 2-H, 2′-H, 8-H_2), 2.45 (q, $^2J_{H,H}$ = 11.4, $^3J_{H,H}$ = 11.4, $^3J_{H,H}$ = 11.4 Hz, 2 H, 7-H, 7′-H), 2.04 (m, 10 H, 7-H, 7′-H, 2-H, 2′-H, 2 OAc), 0.89 [s, 18 H, (CH_3)$_3$CSi], 0.08 [s, 12 H, (CH_3)$_2$Si] ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 170.1, 141.0, 125.6, 69.4, 69.0, 63.3, 51.0, 40.3, 36.6, 25.7, 21.3, 18.0, –4.6, –4.9 ppm. HRMS (ESI): calcd. for $C_{31}H_{54}Cl_2O_6Si_2Na$ [M + Na]$^+$ 671.2734; found 671.2731.

Methylenebis[(1*R*,1′*S*,6*R*,6′*S*)-6-(triethylsilyloxy)cyclohept-3-ene-1,3-diyl] Diacetate (5): Bu_3SnH (1.5 mL, 5.8 mmol, 3 equiv.) and AIBN (32 mg, 0.19 mmol, 0.1 equiv.) were added to a solution of **3** in toluene (7 mL) and the mixture was warmed to 80 °C. After stirring at 80 °C for 3 h, the mixture was concentrated in vacuo. Purification by chromatography on silica gel (Et_2O/PE, 1:9) afforded **5** as a colourless oil (609 mg, 57%). R_f = 0.72 (Et_2O/PE, 1:9). IR (film): $\tilde{\nu}$ = 2955, 2925, 1730, 1370, 1265, 1245, 1020, 770 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.51 (m, 2 H, 4-H, 4′-H), 4.49 (t, $^3J_{H,H}$ = 11.4 Hz, 2 H, 1-H, 1′-H), 3.53 (t, $^3J_{H,H}$ = 11.4 Hz, 2 H, 6-H, 6′-H), 2.69 (d, $^2J_{H,H}$ = 14.5 Hz, 1 H, 8-H_2), 2.67 (d, $^2J_{H,H}$ = 14.5 Hz, 1 H, 8-H_2), 2.35 (m, 2 H, 2-H, 2′-H), 2.24 (m, 6 H, 5-H_2, 5′-H_2, 7-H, 7′-H), 2.07 (m, 2 H, 2-H, 2′-H), 2.02 (s, 6 H, 2 OAc), 1.80 (q, $^2J_{H,H}$ = 11.4, $^3J_{H,H}$ = 11.4, $^3J_{H,H}$ = 11.4 Hz, 2 H, 7-H, 7′-H), 0.95 [t, $^3J_{H,H}$ = 8.0 Hz, 18 H, CH_3 (TES)], 0.60 [q, $^3J_{H,H}$ = 8.0 Hz, 12 H, CH_2 (TES)] ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 170.0, 136.9, 124.6, 69.3, 67.7, 49.6, 47.9, 37.6, 36.9, 21.4, 6.8, 4.7 ppm. HRMS (ESI): calcd. for $C_{31}H_{56}O_6Si_2Na$ [M + Na]$^+$ 603.3513; found 603.3505.

Methylenebis{(1*R*,1′*S*,6*R*,6′*S*)-6-[(*tert*-butyl)(dimethyl)silyloxy]cyclohept-3-ene-1,3-diyl} Diacetate (6): Bu_3SnH (0.9 mL, 3.5 mmol, 4 equiv.) and AIBN (14 mg, 0.09 mmol, 0.1 equiv.) were added to a solution of **4** in toluene (4 mL) and the mixture was warmed to 80 °C. After stirring at 80 °C for 5 h, the mixture was concentrated in vacuo. Purification by chromatography on silica gel (Et_2O/PE, 1:13 to 1:10) afforded **6** as a colourless oil (279 mg, 55%). R_f = 0.70 (Et_2O/PE, 1:9). IR (film): $\tilde{\nu}$ = 3220, 2915, 2850, 1730, 1470, 1265, 1180, 740 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.51 (m, 2 H, 4-H, 4′-H), 4.49 (tt, $^3J_{H,H}$ = 11.4, $^3J_{H,H}$ = 2.5 Hz, 2 H, 1-H, 1′-H); 3.53 (tt, $^3J_{H,H}$ = 10.5, $^3J_{H,H}$ = 3.1 Hz, 2 H, 6-H, 6′H), 2.70 (d, $^2J_{H,H}$ = 14.2 Hz, 1 H, 8-H_2), 2.64 (d, $^2J_{H,H}$ = 14.2 Hz, 1 H, 8-H_2), 2.37 (dd, $^2J_{H,H}$ = 12.3, $^3J_{H,H}$ = 12.3 Hz, 2 H, 2-H, 2′-H), 2.26–2.21 (m, 6 H, 5-H_2, 5′-H_2, 7-H, 7′-H), 2.05 (d, $^2J_{H,H}$ = 12.3 Hz, 2 H, 2-H, 2′-H), 2.02 (s, 6 H, 2 OAc), 1.78 (q, $^2J_{H,H}$ = 11.4, $^3J_{H,H}$ = 11.4, $^3J_{H,H}$ = 11.4 Hz, 2 H, 7-H, 7′-H), 0.88 [s, 18 H, (CH_3)$_3$CSi], 0.06, 0.05 [2 s, 12 H, (CH_3)$_2$Si] ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 170.0, 136.9, 124.6, 69.3, 68.0, 49.6, 47.8, 37.5, 36.9, 25.9, 21.4, 18.1, –4.8 ppm. HRMS (ESI): calcd. for $C_{31}H_{57}O_6Si_2$ [M + H]$^+$ 581.3694; found 581.3688.

1,1′-Methylenebis[(4*R*,4′*S*,6*R*,6′*S*)-4,6-bis(triethylsilyloxy)cyclohept-1-ene] (7): K_2CO_3 (380 mg, 2.75 mmol, 4 equiv.) was added to a solution of **5** (400 mg, 0.69 mmol) in MeOH (7 mL). After stirring at 25 °C for 2 h, the mixture was poured into a saturated aqueous solution of $NaHCO_3$ (30 mL) and extracted with EtOAc (3 × 30 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated in vacuo. The residue was taken up in anhydrous DCM (7 mL) and cooled to –78 °C. 2,6-Lutidine (0.15 mL, 1.27 mmol, 7.5 equiv.) and TESOTf (0.12 mL, 0.51 mmol, 3 equiv.) were added dropwise. After stirring at –78 °C for 1 h, the mixture was poured into a saturated aqueous solution of $NaHCO_3$ (30 mL) and extracted with DCM (3 × 30 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. Purification by chromatography on silica gel (Et_2O/PE, 1:25) afforded **7** as a colourless oil (493 mg, 91%). R_f = 0.33 (Et_2O/PE, 1:25). IR (film): $\tilde{\nu}$ = 2950, 2875, 1455, 1240, 1060, 1005, 740 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.53 (m, 2 H, 2-H, 2′-H), 4.45 (t, $^3J_{H,H}$ = 10.8, $^3J_{H,H}$ = 10.8 Hz, 2 H, 4-H, 4′-H), 3.32 (t, $^3J_{H,H}$ = 10.8, $^3J_{H,H}$ = 10.8 Hz, 2 H, 6-H, 6′-H), 2.60 (s, 2 H, 8-H_2), 2.30–2.19 (m, 8 H, 3-H_2, 3′-H_2, 5-H, 5′-H, 7-H, 7′-H), 2.07 (d, $^2J_{H,H}$ = 13.3 Hz, 2 H, 7-H, 7′-H), 1.80 (q, $^2J_{H,H}$ = 10.8, $^3J_{H,H}$ = 10.8, $^3J_{H,H}$ = 10.8 Hz, 2 H, 5-H, 5′-H), 0.96 [t, $^3J_{H,H}$ = 8.0 Hz, 18 H, CH_3 (TES)], 0.94 [t, $^3J_{H,H}$ = 8.9 Hz, 18 H, CH_3 (TES)], 0.59 [q, $^3J_{H,H}$ = 8.0 Hz, 12 H, CH_2 (TES)], 0.52 [q, $^3J_{H,H}$ = 8.9 Hz, 12 H, CH_2 (TES)] ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 137.6, 124.6, 68.2, 67.7, 52.9, 50.8, 40.3, 37.8, 6.8, 6.4, 4.7, 4.6 ppm. HRMS (ESI): calcd. for $C_{39}H_{80}O_4Si_4Na$ [M + Na]$^+$ 747.5031; found 747.5056.

1,1′-Methylenebis{(4*R*,4′*S*,6*R*,6′*S*)-4,6-bis[(*tert*-butyl)(dimethyl)silyloxy]cyclohept-1-ene} (8): K_2CO_3 (216 mg, 1.56 mmol, 4 equiv.) was added to a solution of **6** (227 mg, 0.39 mmol) in MeOH (4 mL). After stirring at 25 °C for 2 h, the mixture was poured into a saturated solution of $NaHCO_3$ (10 mL) and extracted with EtOAc (10 mL, 3 times). The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated in vacuo. The residue was taken up in anhydrous DCM (4 mL) and cooled to –78 °C. 2,6-Lutidine (0.3 mL, 2.7 mmol, 7 equiv.) and TBSOTf (0.27 mL, 1.17 mmol, 3 equiv.) were added dropwise. After stirring at –78 °C for 1 h, the mixture was poured into a saturated aqueous solution of $NaHCO_3$ (10 mL) and extracted with DCM (3 × 10 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. Purification by chromatography on silica gel (Et_2O/PE, 1:50) afforded **8** as a colourless oil (204 mg, 72%). R_f = 0.37 (Et_2O/PE, 1:75). IR (film): $\tilde{\nu}$ = 3300 (H_2O), 2915, 2850, 1470, 1265, 1180, 1050, 735 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.52 (m, 2 H, 2-H, 2′-H), 3.45 (t, $^3J_{H,H}$ = 10.7, $^3J_{H,H}$ = 10.7 Hz, 2 H, 4-H, 4′-H), 3.34 (t, $^3J_{H,H}$ = 10.7, $^3J_{H,H}$ = 10.7 Hz, 2 H, 6-H, 6′-H), 2.59 (s, 2 H, 8-H_2), 2.27–2.18 (m, 8 H, 3-H_2, 3′-H_2, 5-H, 5′-H, 7-H, 7′-H), 2.05 (m, 2 H, 7-H, 7′-H), 1.75 (q, $^2J_{H,H}$ = 10.7, $^3J_{H,H}$ = 10.7, $^3J_{H,H}$ = 10.7 Hz, 2 H, 5-H, 5′-H), 0.89 [s, 36 H, (CH_3)$_3$CSi], 0.61 [s, 24 H, (CH_3)$_2$Si] ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 137.6, 124.6,

68.5, 68.0, 52.7, 50.7, 40.2, 37.8, 25.9, 18.3, –4.7, –4.8 ppm. HRMS (ESI): calcd. for $C_{39}H_{81}O_4Si_4$ [M + H]$^+$ 725.5212; found 725.5253.

(3*S*,5*S*,8*Z*,11*R*,13*R*)-1,9,15-Trihydroxy-3,5,11,13-tetrakis(triethylsilyloxy)pentadec-8-en-7-one (9): After degassing the solution using O_2, a stream of ozone was passed at –78 °C through a solution of **7** (25 mg, 0.035 mmol) in DCM (0.5 mL) for 1 min. A stream of O_2 was again passed through the mixture for 1 min and Me_2S (0.01 mL, 0.138 mmol, 4 equiv.) was then added dropwise. After stirring at –78 °C for 5 min, a solution of 1-aminoethanol (0.002 mL, 0.034 mmol, 1 equiv.) in BH_3·THF (1 M in THF, 0.075 mL, 2.2 equiv.) was added dropwise. After stirring at –78 °C for 1 h, the solution was allowed to warm up to 0 °C. After an additional hour, methanol (10 mL) was added and the solvents were removed under reduced pressure. The residue was purified by flash chromatography on silica gel (DCM/MeOH, 99:1) to afford **9** as a colourless oil (19 mg, 72%). R_f = 0.50 (DCM/MeOH, 98:2). IR (film): $\tilde{\nu}$ = 2950, 2915, 1600, 1455, 1375, 1265, 1070, 1000, 745 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.52 (s, 1 H, 8-H), 4.16 (t, $^3J_{H,H}$ = 5.6 Hz, 3-H, 13-H), 4.10 (t, $^3J_{H,H}$ = 5.2 Hz, 2 H, 5-H, 11-H), 3.82 (m, 2 H, 1-H, 15-H), 3.73 (m, 2 H, 1-H, 15-H), 2.45 (m, 4 H, 6-H_2, 10-H_2), 1.89 (m, 2 H, 2-H, 14-H), 1.74–1.61 (m, 6 H, 4-H_2, 12-H_2, 2-H, 14-H), 0.98 [t, $^3J_{H,H}$ = 7.7 Hz, 18 H, CH_3 (TES)], 0.96 [t, $^3J_{H,H}$ = 7.7 Hz, 18 H, CH_3 (TES)], 0.61 [m, 24 H, CH_2 (TES)] ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 191.3, 102.4, 68.9, 66.9, 60.1, 46.9, 44.5, 37.7, 6.8, 5.0 ppm. MS (ESI): *m*/*z* = 794 [M + H]$^+$. HRMS (ESI): calcd. for $C_{39}H_{85}O_8Si_4$ [M + H]$^+$ 793.5322; found 793.5334.

(3*S*,5*S*,8*Z*,11*R*,13*R*)-1,9,15-Trihydroxy-3,5,11,13-tetrakis[(*tert*-butyl)(dimethyl)silyloxy]pentadec-8-en-7-one (10): After degassing the solution using O_2, a stream of ozone was passed at –78 °C through a solution of **8** (25 mg, 0.035 mmol) in DCM (0.5 mL) for 1 min. A stream of O_2 was again passed through the mixture for 1 min and Me_2S (0.01 mL, 0.138 mmol, 4 equiv.) was then added dropwise. After stirring at –78 °C for 5 min, a solution of 1-aminoethanol (0.002 mL, 0.034 mmol, 1 equiv.) in BH_3·THF (1 M in THF, 0.075 mL, 2.2 equiv.) was added dropwise. After stirring at –78 °C for 1 h, the solution was allowed to warm to 0 °C. After an additional hour, methanol (10 mL) was added and the solvents were removed under reduced pressure. The residue was purified by flash chromatography on silica gel (DCM/MeOH, 99:1) to afford **10** as a colourless oil (20 mg, 75%). R_f = 0.48 (DCM/MeOH, 98:2). IR (film): $\tilde{\nu}$ = 2930, 2855, 1715, 1600, 1462, 1360, 1250, 1070, 1005, 830, 770 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.53 (s, 1 H, 8-H), 4.14 (t, $^3J_{H,H}$ = 6.4 Hz, 2 H, 3-H, 13-H), 4.07 (t, $^3J_{H,H}$ = 5.6 Hz, 2 H, 5-H, 11-H), 3.81 (m, 2 H, 1-H, 15-H), 3.73 (m, 2 H, 1-H, 15-H), 2.43 (d, $^2J_{H,H}$ = 6.0 Hz, 4 H, 6-H_2, 10-H_2), 1.87 (m, 2 H, 2-H, 14-H), 1.74 (t, $^3J_{H,H}$ = 6.4 Hz, 4 H, 4-H_2, 12-H_2), 1.72–1.65 (m, 2 H, 2-H, 14-H), 0.90 [s, 18 H, $(CH_3)_3CSi$], 0.88 [s, 18 H, $(CH_3)_3CSi$], 0.10 [s, 12 H, $(CH_3)_2Si$], 0.06 [s, 6 H, $(CH_3)_2Si$], 0.04 [s, 6 H, $(CH_3)_2Si$] ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 191.3, 102.6, 68.6, 67.0, 59.8, 46.6, 44.4, 37.8, 25.8, 17.9, 4.4, –4.6, –4.7 ppm. HRMS (ESI): calcd. for $C_{39}H_{85}O_8Si_4$ [M + H]$^+$ 793.5322; found 793.5349.

(+)-(1*S*,6*R*)-6-[(*tert*-Butyl)(dimethyl)silyloxy]-4-[((4*R*,6*S*)-6-{(2*R*)-4-[(*tert*-butyl)(dimethyl)silyloxy]-2-(4-methoxybenzoyloxy)butyl}-2,2-dimethyl-1,3-dioxan-4-yl)methyl]cyclohept-3-en-1-yl 4-Methoxybenzoate [(+)-16]: 2,6-Lutidine (0.5 mL, 4.11 mmol, 3 equiv.) and TBSOTf (0.47 mL, 2.06 mmol, 1.5 equiv.) were added dropwise at –78 °C to a solution of (+)-**15** (1 g, 1.37 mmol) in DCM (14 mL). After stirring at –78 °C for 30 min, the mixture was poured into a saturated aqueous solution of $NaHCO_3$ (50 mL) and extracted with DCM (3 × 50 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (EtOAct/PE, 1:10 to 1:6) to afford (+)-**16** as a colourless oil (1.1 g, 95%). R_f = 0.27 (EtOAc/PE, 1:8). IR (film): $\tilde{\nu}$ = 2930, 2855, 1710, 1605, 1510, 1255, 1165, 1100, 835, 770 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.99 (d, $^3J_{H,H}$ = 8.9 Hz, 4 H, $COC_6H_4OCH_3$), 6.92 (d, $^3J_{H,H}$ = 8.9 Hz, 4 H, $COC_6H_4OCH_3$), 5.54 (t, $^3J_{H,H}$ = 6.8 Hz, 1 H, 3-H), 5.35 (m, 1 H, 2‴-H), 4.81 (m, 1 H, 1-H), 3.98 (m, 1 H, 6″-H), 3.90 (m, 1 H, 4″-H), 3.87 (s, 6 H, 2 $COC_6H_4OCH_3$), 3.70 (t, $^3J_{H,H}$ = 6.5 Hz, 2 H, 4‴-H_2), 3.62 (br. t, $^3J_{H,H}$ = 10.2, $^3J_{H,H}$ = 10.2 Hz, 1 H, 6-H_2), 2.47–2.34 (m, 4 H, 5-H, 7-H, 2-H_2), 2.28 (dd, $^2J_{H,H}$ = 14.1, $^3J_{H,H}$ = 7.1 Hz, 1 H, 1′-H), 2.18 (d, $^2J_{H,H}$ = 13.9 Hz, 5-H), 2.05 (dd, $^2J_{H,H}$ = 14.1, $^3J_{H,H}$ = 5.9 Hz, 1 H, 1′-H), 2.01–1.90 (m, 4 H, 1‴-H, 3‴-H_2, 7-H), 1.82 (ddd, $^2J_{H,H}$ = 14.5, $^3J_{H,H}$ = 5.2, $^3J_{H,H}$ = 5.2 Hz, 1 H, 1‴-H), 1.64–1.55 (m, 2 H, 5″-H_2), 1.29 [s, 3 H, $(CH_3)_2C(2'')$], 1.26 [s, 3 H, $(CH_3)_2C(2'')$], 0.88 [s, 9 H, $(CH_3)_3CSi$], 0.87 [2s, 9 H, $(CH_3)_3CSi$], 0.08 [s, 3 H, $(CH_3)_2Si$], 0.07 [s, 3 H, $(CH_3)_2Si$], 0.02 [s, 6 H, $(CH_3)_2Si$] ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 165.7, 165.4, 163.3, 137.6, 131.5, 123.0, 122.7, 113.5, 100.3, 69.8, 69.4, 67.6, 65.0, 63.9, 59.6, 55.4, 47.8, 45.9, 42.2, 40.4, 38.5, 37.4, 33.5, 25.9, 25.8, 24.8, 24.7, 18.3, 18.1, –4.7, –5.4 ppm. HRMS (ESI): calcd. for $C_{46}H_{73}O_{10}Si_2$ [M + H]$^+$ 841.4742; found 841.4756. $C_{46}H_{72}O_{10}Si_2$ (841.2): C 65.68, H 8.63; found C 65.90, H 8.37. $[\alpha]_{589}^{25}$ = +3, $[\alpha]_{577}^{25}$ = +7, $[\alpha]_{435}^{25}$ = +13, $[\alpha]_{405}^{25}$ = +17 (*c* = 0.15, DCM).

(–)-(2*R*)-4-[(*tert*-Butyl)(dimethyl)silyloxy]-1-[(4*S*,6*R*)-6-({(4*S*,6*R*)-6-[(*tert*-butyl)(dimethyl)silyloxy]-4-hydroxycyclohept-1-en-1-yl}methyl)-2,2-dimethyl-1,3-dioxan-4-yl]but-2-yl 4-Methoxybenzoate [(–)-17] and (–)-(1*S*,6*R*)-6-[(*tert*-Butyl)(dimethyl)silyloxy]-4-[((4*R*,6*R*)-6-{(2*R*)-4-[(*tert*-butyl)(dimethyl)silyloxy]-2-hydroxybutyl}-2,2-dimethyl-1,3-dioxan-4-yl)methyl]cyclohept-3-en-1-ol [(–)-18]: Potassium (300 mg, 7.7 mmol, 5 equiv.) was added to a solution of (+)-**16** (1.2 g, 1.54 mmol) in 2-propanol (15 mL) at 0 °C. The reaction was carefully monitored by TLC and poured into a saturated aqueous solution of $NaHCO_3$ (80 mL) as traces of diol (–)-**18** [R_f = 0.3 (EtOAc/PE, 1:4)] appeared. After extraction with DCM (3 × 80 mL) the combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (EtOAc/PE, 1:8 to 2:1) to afford (+)-**15** [480 mg, 39%; R_f = 0.84 (EtOAc/PE, 1:4)], the desired free alcohol (–)-**17** as a colourless oil [504 mg, 50%; R_f = 0.46 (EtOAc/PE, 1:4)] and diol (–)-**18** [41 mg, 5%; R_f = 0.3 (EtOAc/PE, 1:4)].

Data for (–)-17: IR (film): $\tilde{\nu}$ = 2930, 2855, 1710, 1605, 1510, 1255, 1165, 1095, 835, 770 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.98 (d, $^3J_{H,H}$ = 8.9 Hz, 2 H, $COC_6H_4OCH_3$), 6.92 (d, $^3J_{H,H}$ = 8.9 Hz, 2 H, $COC_6H_4OCH_3$), 5.50 (t, $^3J_{H,H}$ = 6.7 Hz, 1 H, 2‴-H), 5.35 (m, 1 H, 2-H), 3.96 (m, 1 H, 4′-H), 3.90 (m, 1 H, 6′-H), 3.87 (s, 3 H, $COC_6H_4OCH_3$), 3.73 (m, 1 H, 6‴-H), 3.70 (t, $^3J_{H,H}$ = 6.7 Hz, 2 H, 4-H_2), 3.66 (m, 1 H, 4‴-H), 2.38 (dd, $^2J_{H,H}$ = 14.2, $^3J_{H,H}$ = 9.3 Hz, 1 H, 7‴-H), 2.32–2.20 (m, 4 H, 3‴-H_2, 1″-H, 7‴-H), 2.15 (br. d, $^2J_{H,H}$ = 12.9 Hz, 1 H, 5‴-H), 2.05 (dd, $^2J_{H,H}$ = 13.9, $^3J_{H,H}$ = 5.9 Hz, 1 H, 1″-H), 1.99–1.88 (m, 4 H, 1-H, 3-H_2, 5‴-H), 1.82 (ddd, $^2J_{H,H}$ = 14.2, $^3J_{H,H}$ = 5.1, $^3J_{H,H}$ = 5.1 Hz, 1 H, 1-H), 1.67–1.55 (m, 2 H, 5′-H_2), 1.26 [s, 3 H, $(CH_3)_2C(2')$], 1.27 [s, 3 H, $(CH_3)_2C(2')$], 0.89 [s, 9 H, $(CH_3)_3CSi$], 0.87 [2 s, 9 H, $(CH_3)_3CSi$], 0.07 [s, 6 H, $(CH_3)_2Si$], 0.01 [s, 6 H, $(CH_3)_2Si$] ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 165.6, 163.2, 137.1, 131.5, 123.4, 123.1, 113.5, 100.2, 69.4, 67.9, 67.6, 64.9, 63.9, 59.5, 55.4, 49.2, 46.1, 41.2, 40.4, 38.5, 37.4, 36.4, 25.9, 25.8, 24.8, 24.7, 18.2, 18.0, –4.7, –4.8, –5.4, –5.5 ppm. HRMS (ESI): calcd. for $C_{38}H_{66}O_8Si_2Na$ [M + Na]$^+$ 729.4194; found 729.4168. $C_{38}H_{66}O_8Si_2$ (707.1): C 64.55, H 9.41; found C 64.75, H 9.28. $[\alpha]_{589}^{25}$ = –3, $[\alpha]_{577}^{25}$ = +3 (*c* = 0.15, DCM).

Data for (–)-18: IR (film): $\tilde{\nu}$ = 2930, 2855, 1470, 1380, 1255, 1095, 835, 775 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.51 (t, $^3J_{H,H}$ =

6.4 Hz, 1 H, 3-H), 4.05 (m, 1 H, 6′′-H), 3.94–3.87 (m, 2 H, 2′′′-H, 4′′-H), 3.79 (m, 1 H, 4′′′-H), 3.71 (m, 1 H, 6-H), 3.66 (m, 1 H, 1-H), 3.66 (m, 1 H, 4′′-H), 2.39 (dd, $^2J_{H,H}$ = 14.7, $^3J_{H,H}$ = 9.6 Hz, 1 H, 5-H), 2.32–2.22 (m, 4 H, 2-H_2, 1′-H, 5-H), 2.14 (br. d, $^2J_{H,H}$ = 13.1 Hz, 1 H, 7-H), 2.07 (dd, $^2J_{H,H}$ = 14.4, $^3J_{H,H}$ = 6.4 Hz, 1 H, 1′-H), 1.91 (m, 1 H, 7-H), 1.69–1.56 (m, 6 H, 1′′′-H_2, 3′′′-H_2, 5′′-H_2), 1.36 [s, 3 H, (CH_3)$_2$C(2′)], 1.34 [s, 3 H, (CH_3)$_2$C(2′)], 0.89 [s, 18 H, (CH_3)$_3$CSi], 0.07 [s, 6 H, (CH_3)$_2$Si], 0.06 [s, 6 H, (CH_3)$_2$Si] ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 136.9, 123.6, 100.4, 69.3, 67.9, 67.6, 66.7, 64.9, 61.1, 49.2, 46.2, 42.8, 41.2, 39.4, 38.4, 36.4, 25.8, 24.8, 18.2, 18.0, –4.8, –5.4 ppm. HRMS (ESI): calcd. for $C_{30}H_{61}O_6Si_2$ [M + H]$^+$ 573.4007; found 573.3983. $[\alpha]_{589}^{25}$ = –16, $[\alpha]_{577}^{25}$ = –51 (*c* = 0.1, DCM).

(+)-(3*R*,5*S*,7*R*)-1-[(*tert*-Butyl)(dimethyl)silyloxy]-8-{(4*S*,6*R*)-6-[(*tert*-butyl)(dimethyl)silyloxy]-4-hydroxycyclohept-1-en-1-yl}-5,7-dihydroxyoct-3-yl 4-Methoxybenzoate [(+)-19]: *p*TsOH (11 mg, 0.06 mmol, 0.05 equiv.) was added to a solution of (–)-**17** (814 mg, 1.15 mmol) in DCM (24 mL) at 0 °C. After 8 h, the reaction was poured into a saturated aqueous solution of $NaHCO_3$ (50 mL) and extracted with EtOAc (3 × 50 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (DCM/MeOH, 99:1 to 98:2) to afford (+)-**19** as a colourless oil (560 mg, 73%). R_f = 0.48 (DCM/MeOH, 98:2). IR (film): $\tilde{\nu}$ = 3385, 2925, 2855, 1705, 1605, 1510, 1255, 1165, 1100, 1030, 835 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.98 (d, $^3J_{H,H}$ = 8.9 Hz, 2 H, $COC_6H_4OCH_3$), 6.92 (d, $^3J_{H,H}$ = 8.9 Hz, 2 H, $COC_6H_4OCH_3$), 5.60 (t, $^3J_{H,H}$ = 6.8 Hz, 1 H, 2′-H), 5.32 (m, 1 H, 3-H), 4.11 (m, 1 H, 5-H), 3.99 (m, 1 H, 7-H), 3.86 (s, 3 H, $COC_6H_4OCH_3$), 3.84 (m, 1 H, 4′-H), 3.73 (m, 3 H, 1-H_2, 6′-H), 3.13, 2.49 [d, 2 H, C(O*H*)], 2.44–2.35 (m, 2 H, 7′-H, 3′-H), 2.29 (m, 2 H, 7′-H, 3′-H), 2.18 (br. d, $^2J_{H,H}$ = 6.5 Hz, 2 H, 8-H_2), 2.04–1.97 (m, 5 H, 4-H, 2-H_2, 5′-H_2), 1.87 (dt, $^2J_{H,H}$ = 14.2, $^3J_{H,H}$ = 4.9, $^3J_{H,H}$ = 4.9 Hz, 1 H, 4-H), 1.66 (m, 2 H, 6-H_2), 0.87 [s, 18 H, (CH_3)$_3$CSi], 0.07 [s, 3 H, (CH_3)$_2$Si], 0.06 [s, 3 H, (CH_3)$_2$Si], 0.01 [s, 6 H, (CH_3)$_2$Si] ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 166.1, 63.4, 137.7, 131.6, 125.0, 122.7, 113.6, 70.2, 68.1, 67.5, 66.7, 66.3, 59.6, 55.4, 48.5, 48.1, 42.5, 42.3, 40.7, 37.6, 36.1, 25.9, 25.7, 18.2, 17.9, –4.8, –5.0, –5.4, –5.5 ppm. HRMS (ESI): calcd. for $C_{35}H_{63}O_8Si_2$ [M + H]$^+$ 667.4061; found 667.4039. $C_{35}H_{62}O_8Si_2$ (667.0): C 63.02, H 9.37; found C 63.18, H 9.40. $[\alpha]_{589}^{25}$ = +10, $[\alpha]_{577}^{25}$ = +14, $[\alpha]_{435}^{25}$ = +23, $[\alpha]_{405}^{25}$ = +30 (*c* = 0.2, DCM).

(+)-(2*R*)-4-[(*tert*-Butyl)(dimethyl)silyloxy]-1-{(2*S*,4*S*,6*R*,8*S*,10*S*)-10-[(*tert*-butyl)(dimethyl)silyloxy]-4-hydroxy-8-(2-hydroxyethyl)-1,7-dioxaspiro[5.5]undec-2-yl}but-2-yl 4-Methoxybenzoate [(+)-21]: A stream of ozone was passed at –78 °C through a solution of (+)-**19** (120 mg, 0.18 mmol) in DCM (6 mL) for 2 min. A stream of O_2 was passed through the mixture for 2 min and Me_2S (0.03 mL, 0.36 mmol, 2 equiv.) was then added dropwise. After stirring at –78 °C for 5 min the solvents were evaporated under reduced pressure at –35 °C. The residue was dissolved in THF (6 mL) and cooled to –78 °C. At –78 °C, K-selectride (1 M in THF, 0.2 mL, 0.2 mmol, 1.1 equiv.) was added dropwise. After stirring at –78 °C for 1 h, semi-saturated NH_4Cl in MeOH was added and the solvents were removed in vacuo. The residue was filtered through a pad of silica gel (DCM/MeOH, 97:3) to afford a mixture of hemiketals **20**. Dichloroacetic acid (1.5 μL, 0.018 mmol, 0.1 equiv.) was added to a solution of the crude hemiketals in toluene (2.4 mL) at 0 °C. After 5 min the solution was warmed to 25 °C. After 20 min the reaction mixture was poured into a saturated solution of $NaHCO_3$ (20 mL) and extracted with EtOAc (3 × 20 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (DCM/MeOH, 98:2) to afford (+)-**21** as a colourless oil [60 mg, 50%, four steps starting from the triol (+)-**19**]. R_f = 0.34 (AcOEt/EP, 1:1). IR (film): $\tilde{\nu}$ = 2955, 2930, 2855, 1710, 1605, 1255, 110, 835, 775 cm^{-1}. ^{1}H NMR (400 MHz, C_6D_6): δ = 8.38 (d, $^3J_{H,H}$ = 8.9 Hz, 2 H, $COC_6H_4OCH_3$), 6.86 (d, $^3J_{H,H}$ = 8.6 Hz, 2 H, $COC_6H_4OCH_3$), 5.90 (dddd, $^3J_{H,H}$ = 6.4, $^3J_{H,H}$ = 6.4, $^3J_{H,H}$ = 12.0, $^3J_{H,H}$ = 12.0 Hz, 1 H, 2-H), 4.40 (ddd, $^3J_{H,H}$ = 11.1, $^3J_{H,H}$ = 5.5, $^3J_{H,H}$ = 5.5 Hz, 1 H, 2′-H), 4.27 (dddd, $^3J_{H,H}$ = 9.6, $^3J_{H,H}$ = 9.6, $^3J_{H,H}$ = 4.0, $^3J_{H,H}$ = 4.0 Hz, 1 H, 8′-H), 4.15 (br. t, $^3J_{H,H}$ = 4.0 Hz, 1 H, 10′-H), 4.09 (dddd, $^3J_{H,H}$ = 11.1, $^3J_{H,H}$ = 11.1, $^3J_{H,H}$ = 5.5, $^3J_{H,H}$ = 5.5 Hz, 1 H, 4′-H), 3.88 (t, $^3J_{H,H}$ = 6.4 Hz, 2 H, 4-H_2), 3.79 (m, 2 H, 2′′-H_2), 3.30 (s, 3 H, CO-$C_6H_4OCH_3$), 3.01 (dd, $^2J_{H,H}$ = 13.8, $^3J_{H,H}$ = 3.7 Hz, 1 H, 5′-H), 2.29 (ddd, $^3J_{H,H}$ = 13.8, $^3J_{H,H}$ = 6.9, $^3J_{H,H}$ = 6.9 Hz, 1 H, 1-H), 2.17 (ddd, $^2J_{H,H}$ = 6.5, $^3J_{H,H}$ = 6.5, $^3J_{H,H}$ = 6.5 Hz, 2 H, 3-H_2), 2.07 (br. dd, $^2J_{H,H}$ = 11.1 Hz, 1 H, 3′-H), 1.93 (m, 1 H, 1-H), 1.90 (m, 2 H, 11′-H_2), 1.83, 1.65 (2 m, 2 H, 1′′-H_2), 1.58 (ddd, $^2J_{H,H}$ = 9.6, $^3J_{H,H}$ = 9.6, $^3J_{H,H}$ = 4.0 Hz, 1 H, 9′-H), 1.49 (m, 1 H, 9′-H), 1.36 (m, 1 H, 5′-H), 1.13 (m, $^2J_{H,H}$ = 11.1, $^3J_{H,H}$ = 11.1, $^3J_{H,H}$ = 11.1 Hz, 1 H, 3′-H), 1.14 [s, 9 H, (CH_3)$_3$CSi], 1.08 [s, 9 H, (CH_3)$_3$CSi], 0.21 [s, 3 H, (CH_3)$_2$Si], 0.19 [s, 3 H, (CH_3)$_2$Si], 0.13 [s, 3 H, (CH_3)$_2$Si], 0.12 [s, 3 H, (CH_3)$_2$Si] ppm. ^{13}C NMR (101 MHz, C_6D_6): δ = 166.3, 164.1, 132.6, 124.4, 114.4, 99.9, 69.8, 68.5, 66.9, 65.6, 64.9, 61.1, 60.3, 55.3, 44.1, 42.8, 41.9, 41.7, 39.5, 39.2, 38.3, 26.7, 26.5, 19.0, 17.8, –5.0, –5.1, –5.2, –5.6 ppm. HRMS (ESI): calcd. for $C_{35}H_{62}O_9Si_2Na$ [M + Na]$^+$ 705.3830; found 705.3859. $[\alpha]_{589}^{25}$ = +3, $[\alpha]_{577}^{25}$ = –22 (*c* = 0.12, DCM).

(–)-(2*R*)-4-[(*tert*-Butyl)(dimethyl)silyloxy]-1-{(2*S*,4*S*,6*R*,8*S*,10*S*)-10-[(*tert*-butyl)(dimethyl)silyloxy]-8-[2-(2,2-dimethylpropanoyloxy)-ethyl]-4-hydroxy-1,7-dioxaspiro[5.5]undec-2-yl}but-2-yl 4-Methoxybenzoate [(–)-23]: A solution of pivaloyl chloride (5 μL, 0.04 mmol, 1.5 equiv.) in DCM/Py (0.15 mL, 1:3) was added dropwise to a solution of (+)-**21** (16 mg, 0.023 mmol) in DCM/Py (0.15 mL, 1:3) at 0 °C. The mixture was stirred at 0 °C for 5 h. The reaction was poured into a saturated aqueous solution of $NaHCO_3$ (10 mL) and extracted with DCM (3 × 10 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (AcOEt/EP, 1:4) to afford (–)-**23** as a colourless oil (13 mg, 72%), R_f = 0.38 (AcOEt/EP, 1:4). IR (film): $\tilde{\nu}$ = 2925, 2855, 1715, 1605, 1510, 1465, 1255, 1165, 1100, 835, 770 cm^{-1}. ^{1}H NMR (400 MHz, C_6D_6): δ = 8.37 (d, $^3J_{H,H}$ = 8.6 Hz, 2 H, $COC_6H_4OCH_3$), 6.86 (d, $^3J_{H,H}$ = 8.6 Hz, 2 H, $COC_6H_4OCH_3$), 5.92 (dddd, $^3J_{H,H}$ = 6.1, $^3J_{H,H}$ = 6.1, $^3J_{H,H}$ = 12.3, $^3J_{H,H}$ = 12.3 Hz, 1 H, 2-H), 4.41 (m, 1 H, 2′-H), 4.38 (m, 2 H, 2′′-H_2), 4.23 (m, 1 H, 8′-H), 4.13 (m, 1 H, 10′-H), 4.03 (m, 1 H, 4′-H), 3.89 (t, $^3J_{H,H}$ = 6.2 Hz, 2 H, 4-H_2), 3.31 (s, 3 H, CO-$C_6H_4OCH_3$), 3.01 (dd, $^2J_{H,H}$ = 13.3, $^3J_{H,H}$ = 4.0 Hz, 1 H, 5′-H), 2.30 (ddd, $^3J_{H,H}$ = 13.8, $^3J_{H,H}$ = 6.9, $^3J_{H,H}$ = 6.9 Hz, 1 H, 1-H), 2.19 (m, 2 H, 3-H_2), 2.02 (br. dd, $^2J_{H,H}$ = 12.2 Hz, 1 H, 3′-H), 1.92 (m, 1 H, 1-H), 1.89 (m, 2 H, 11′-H_2), 1.84 (m, 2 H, 1′′-H_2), 1.48 (m, 2 H, 9′-H_2), 1.37 [s, 9 H, COC(CH_3)$_3$], 1.33 (m, 1 H, 5′-H), 1.27 (m, 1 H, 3′-H), 1.14 [s, 9 H, (CH_3)$_3$CSi], 1.08 [s, 9 H, (CH_3)$_3$CSi], 0.21 [s, 3 H, (CH_3)$_2$Si], 0.19 [s, 3 H, (CH_3)$_2$Si], 0.13 [s, 3 H, (CH_3)$_2$Si], 0.12 [s, 3 H, (CH_3)$_2$Si] ppm. ^{13}C NMR (101 MHz, C_6D_6): δ = 178.2, 166.1, 164.1, 132.5, 124.4, 114.4, 99.6, 69.8, 66.6, 65.9, 65.4, 65.0, 61.4, 60.4, 55.3, 44.1, 42.7, 42.0, 41.6, 39.4, 38.3, 36.0, 27.9, 26.6, 26.5, 23.6, 18.9, 17.4, –4.4, –4.5, –4.8 ppm. HRMS (ESI): calcd. for $C_{40}H_{70}O_{10}Si_2Na$ [M + Na]$^+$ 789.4405; found 789.4376. $[\alpha]_{589}^{25}$ = –5, $[\alpha]_{577}^{25}$ = +13 (*c* = 0.1, DCM).

(–)-(2*R*)-4-[(*tert*-Butyl)(dimethyl)silyloxy]-1-{(2*S*,4*S*,6*R*,8*S*,10*S*)-10-[(*tert*-butyl)(dimethyl)silyloxy]-8-[2-(2,2-dimethylpropanoyloxy)-ethyl]-4-methoxy-1,7-dioxaspiro[5.5]undec-2-yl}but-2-yl 4-Methoxybenzoate [(–)-24]: Me_3OBF_4 (20 mg, 0.14 mmol, 9 equiv.) was

added to a solution of (–)-**23** (12 mg, 0.015 mmol) and a proton sponge (37 mg, 0.17 mmol, 11 equiv.) in DCM (0.3 mL) at 0 °C. The mixture was stirred at 0 °C for 30 min. The reaction was poured into a saturated aqueous solution of $NaHCO_3$ (10 mL) and extracted with DCM (3 × 10 mL). The combined organic extracts were washed with citric acid (10 mL, 10% w/w), dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (AcOEt/EP, 1:8) to afford (–)-**24** as a colourless oil (8 mg, 66%). R_f = 0.31 (AcOEt/EP, 1:8). IR (film): $\tilde{\nu}$ = 2955, 2925, 2885, 1730, 1715, 1605, 1510, 1460, 1255, 1165, 1095, 835 cm^{-1}. ^1H NMR (400 MHz, C_6D_6): δ = 8.37 (d, $^3J_{H,H}$ = 8.5 Hz, 2 H, $COC_6H_4OCH_3$), 6.85 (d, $^3J_{H,H}$ = 8.5 Hz, 2 H, $COC_6H_4OCH_3$), 5.95 (dddd, $^3J_{H,H}$ = 6.2, $^3J_{H,H}$ = 6.2, $^3J_{H,H}$ = 12.0, $^3J_{H,H}$ = 12.0 Hz, 1 H, 2-H), 4.45 (m, 1 H, 2′-H), 4.40 (t, $^3J_{H,H}$ = 5.5 Hz, 2 H, 2′′-H_2), 4.24 (dddd, $^3J_{H,H}$ = 6.2, $^3J_{H,H}$ = 6.2, $^3J_{H,H}$ = 12.0, $^3J_{H,H}$ = 12.0 Hz, 1 H, 8′-H), 4.12 (m, 1 H, 10′-H), 3.90 (t, $^3J_{H,H}$ = 6.3 Hz, 2 H, 4-H_2), 3.78 (m, 1 H, 4′-H), 3.40 [s, 3 H, C(4′)OCH_3], 3.31 (s, 3 H, $COC_6H_4OCH_3$), 3.18 (dd, $^2J_{H,H}$ = 13.6, $^3J_{H,H}$ = 3.5 Hz, 1 H, 5′-H), 2.33 (m, 1 H, 3′-H), 2.30 (m, 1 H, 1-H), 2.20 (ddd, $^2J_{H,H}$ = 6.5, $^3J_{H,H}$ = 6.5, $^3J_{H,H}$ = 6.5 Hz, 1 H, 3-H_2), 1.96 (m, 1 H, 1-H), 1.89 (m, 4 H, 11′-H_2, 1′′-H_2), 1.47 (m, 3 H, 5′-H, 9′-H_2), 1.40 (m, 1 H, 3′-H), 1.36 [s, 9 H, $COC(CH_3)_3$], 1.13 [s, 9 H, $(CH_3)_3CSi$], 1.07 [s, 9 H, $(CH_3)_3CSi$], 0.21 [s, 3 H, $(CH_3)_2Si$], 0.19 [s, 3 H, $(CH_3)_2Si$], 0.11 [s, 3 H, $(CH_3)_2Si$], 0.09 [s, 3 H, $(CH_3)_2$-Si] ppm. ^{13}C NMR (101 MHz, C_6D_6): δ = 178.1, 166.1, 164.1, 132.5, 124.4, 114.4, 99.6, 73.9, 69.9, 66.7, 65.9, 65.5, 61.5, 60.4, 55.5, 55.3, 44.2, 41.7, 39.8, 39.4, 38.2, 36.2, 27.8, 26.6, 26.4, 23.6, 8.9, 18.5, –4.2, –4.4, –4.6 ppm. HRMS (ESI): calcd. for $C_{41}H_{72}O_{10}Si_2Na$ $[M + Na]^+$ 803.4562; found 803.4549. $C_{41}H_{72}O_{10}Si_2$ (781.2): C 63.04, H 9.29; found C 63.11, H 9.32. $[\alpha]_{589}^{25}$ = –11, $[\alpha]_{577}^{25}$ = –16, $[\alpha]_{435}^{25}$ = –29, $[\alpha]_{405}^{25}$ = –36 (*c* = 0.14, DCM).

Supporting Information (see also the footnote on the first page of this article): Experimental procedures and full analytical data (including ^1H, ^{13}C and 2D spectra) for compounds **3–10**, (+)-**16**, (–)-**17**, (–)-**18**, (+)-**19**, (+)-**21**, (–)-**23** and (–)-**24**.

Acknowledgments

We thank the Swiss National Science Foundation for its generous financial support. We are grateful to Mr. Martial Rey (NMR spectrometry service, ISIC, EPFL), Dr. Laure Menin and Mr. Francisco Sepulveda (MS service, ISIC, EPFL) for technical help.

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Received: November 9, 2009
Published Online: February 15, 2010

