Stereoselective synthesis of the C15–C26 fragment of the antitumor agent (–)-dictyostatin†

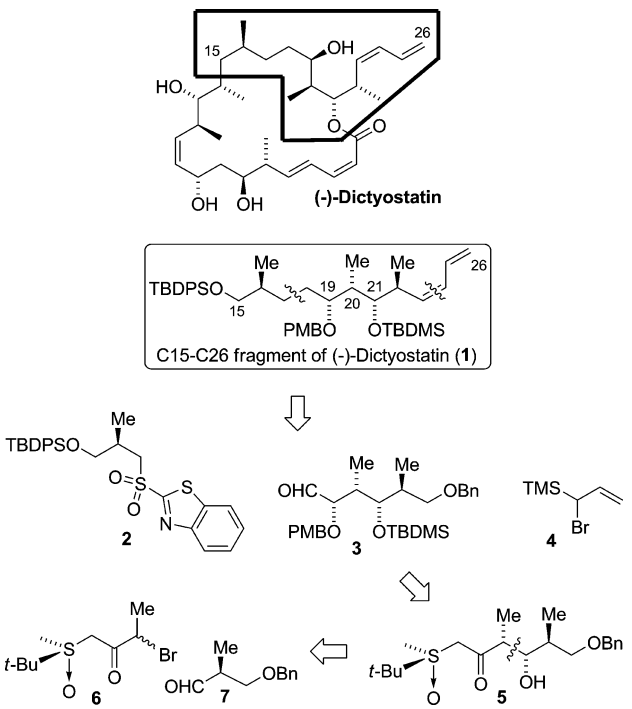
Leticia Ferreiro-Mederos,[a,b] Silvia Vila-Gisbert,[a] Antonio Urbano,*[a] M. Carmen Carreño*[a] and Françoise Colobert*[b]

Received 26th July 2010, Accepted 30th September 2010
DOI: 10.1039/c0ob00491j

The synthesis of the C15–C26 fragment of (–)-dictyostatin is reported in 10 steps and 28% overall yield. The key steps are the two stereoselective sulfoxide-directed processes: a Reformatsky-type reaction and a β-keto sulfoxide reduction.

Introduction

The marine-derived macrolactone (–)-dictyostatin (Scheme 1) was first isolated in small amounts by Pettit and coworkers from the Maldives sponge *Spongia sp.* in 1994[1] and more recently by Wright and coworkers from the Caribbean *Corallistidae* sponges in 2003.[2]



Scheme 1 Retrosynthesis of **1**, the C15–C26 fragment of (–)-Dictyostatin.

Dictyostatin comprises a 26-carbon polyketide backbone with 11 stereocentres, featuring a 22-membered macrolide (C1–C21), an (*E*,*Z*)-dienoate moiety (C1–C5), a (*Z*)-olefin (C10–C11) and a terminal (*Z*)-1,3-diene (C23–C26). Their relative stereochemistry was determined in 2004 by Paterson and coworkers based on a combination of extensive high field NMR studies and molecular modelling.[3] This assignment was later validated through the independent and concurrent total syntheses of (–)-dictyostatin by the Paterson and Curran groups.[4]

Dictyostatin displays low nanomolar cytotoxicity towards a range of human cancer cell lines including those with a multidrug-resistant phenotype.[5] Its significant therapeutic potential and relationship to discodermolide[6] has stimulated many synthetic efforts over the last few years[7] including several total syntheses of (–)-dictyostatin[8] and related hybrids[9] and analogs,[10] as well as the preparation of different fragments.[11]

In relation with a program devoted to asymmetric synthesis mediated by sulfoxides,[12] we have described a highly stereoselective Reformatsky-type reaction of chiral α-bromo-α′-sulfinyl ketones with aldehydes in the presence of SmI_2.[13] Herein, we report the synthesis of the C15–C26 unit of dictyostatin (**1** in Scheme 1), with five stereocenters and the terminal (*Z*)-1,3-diene moiety, using two sulfoxide-directed processes: a Reformatsky-type reaction and a β-keto sulfoxide reduction,[14] to generate the *syn-syn* stereotriad at C19–C21 of the final target with high levels of stereocontrol.

Results and discussion

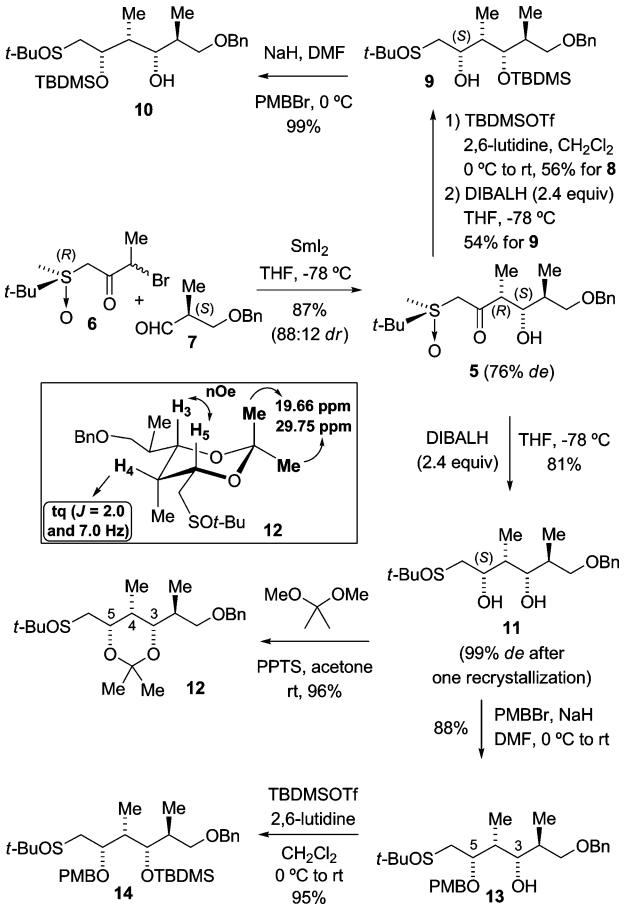
Our retrosynthetic analysis of the C15–C26 fragment of dictyostatin **1** is depicted in Scheme 1. The left part of the molecule would be accessible through a Julia reaction between the known sulfone **2**, derived from Roche ester, and the appropriately protected aldehyde intermediate **3**, whereas the formation of the right diene moiety of the synthetic target would be possible through a two-step Nozaki–Hiyama allylation/Peterson olefination process between the silyl bromide **4** and the aldehyde obtained after debenzylation and oxidation of a suitable intermediate derived from **3**. The key aldehyde **3** could be obtained after the well-established diastereoselective reduction of the β-ketosulfoxide moiety present in **5**, selective diol protection and Pummerer reaction.[15] Finally, derivative **5** would be formed using our Reformatsky-type reaction between the known α-bromo-α′-sulfinyl ketone **6** and the aldehyde **7**, also derived from Roche ester. The development of a methodology allowing the synthesis of some stereoisomers of the stereotriad is highly important. With our methodology, up to four diastereomers of the stereotriad could be easily accessible in a stereocontrolled manner depending on the absolute configuration

[a]*Departamento de Química Orgánica (Módulo 01), Universidad Autónoma de Madrid, 28049, Madrid, Spain. E-mail: antonio.urbano@uam.es, carmen.carrenno@uam.es*
[b]*Laboratoire de Stéréochimie, Université de Strasbourg, ECPM 25 rue Becquerel, 67087, Strasbourg Cedex 2, France*

† Electronic supplementary information (ESI) available: Experimental procedures for (*S*)-**7** and copies of ^{1}H- and ^{13}C-NMR spectra for all new compounds. See DOI: 10.1039/c0ob00491j

of the sulfoxide and/or the conditions chosen to effect the reduction step of the β-ketosulfoxide.

Thus, the synthesis of the C15–C26 fragment of dictyostatin started with the Reformatsky-type reaction between the α-bromo-α′-*tert*-butylsulfinyl ketone (S*R*)-**6**,[13a,b] as a mixture of epimers at the C stereocenter, and the known aldehyde (*S*)-**7** (Scheme 2).[16] Under the typical experimental conditions (SmI_2, THF, −78 °C), we could obtained the Reformatsky adduct *syn*-**5** with good diastereoselectivity (88 : 12 *dr*)[17] and yield (87%).



Scheme 2 Four-step stereoselective synthesis of advanced intermediate **14** from known compounds **6** and **7**.

Next, we performed the protection of the OH group of carbinol **5** as the corresponding OTBDMS ether **8** (TBDMSOTf, lutidine, CH_2Cl_2, 0 °C to rt, 56%) followed by the diastereoselective sulfoxide-directed DIBAL-H reduction (THF, −78 °C) of the carbonyl group, to afford carbinol **9** in 54% yield, after chromatographic purification. Nevertheless, all attempts to carry out the protection of alcohol **9**, for example as its PMB ether (NaH, PMBBr, DMF, 0 °C), led to migration of the silyl group at C-3 to yield quantitatively carbinol **10**, which, in our hands, proved to be unreactive to further alcohol protection.

With this result in hand, we decided to carry out the stereoselective reduction step on unprotected carbinol **5**. Thus, the treatment of the hydroxy ketone **5** (76% *de*) with 2.4 equiv of DIBALH in THF at −78 °C furnished the corresponding diol **11** (76% *de*). The minor component of the mixture could be removed after one recrystallization affording, in 81% yield, diastereoisomerically pure **11** containing the *syn-syn* stereotriad with the correct absolute configuration present in natural dictyostatin. The relative *syn* disposition of the diol moiety of **11** was demonstrated, after transformation into acetonide **12** (acetone dimethyl acetal, PPTS, acetone, rt, 96%), by applying the ^{13}C NMR criterion described by Rychnovsky[18] and Evans.[19] Compound **12** showed differentiated chemical shifts of the two geminal methyl groups of the dioxolane moiety in the ^{13}C NMR spectrum (19.66 and 29.75 ppm, respectively), as a consequence of the chair conformation adopted by the heterocyclic fragment, with bulkier substituents adopting an equatorial disposition. We could also confirm the relative stereochemistry on the basis of the observed NOESY correlations between protons H_3 and H_5 situated in a 1,3-diaxial disposition. This structural assignment also allowed us to establish the relative *syn* configuration of the methyl group at C-4 of compound **12** by measuring the two small coupling constants (J = 2.0 Hz) in the ^1H NMR spectrum between H_4 and H_3/H_5, which are only possible if H_4 adopts an equatorial disposition (Scheme 2).

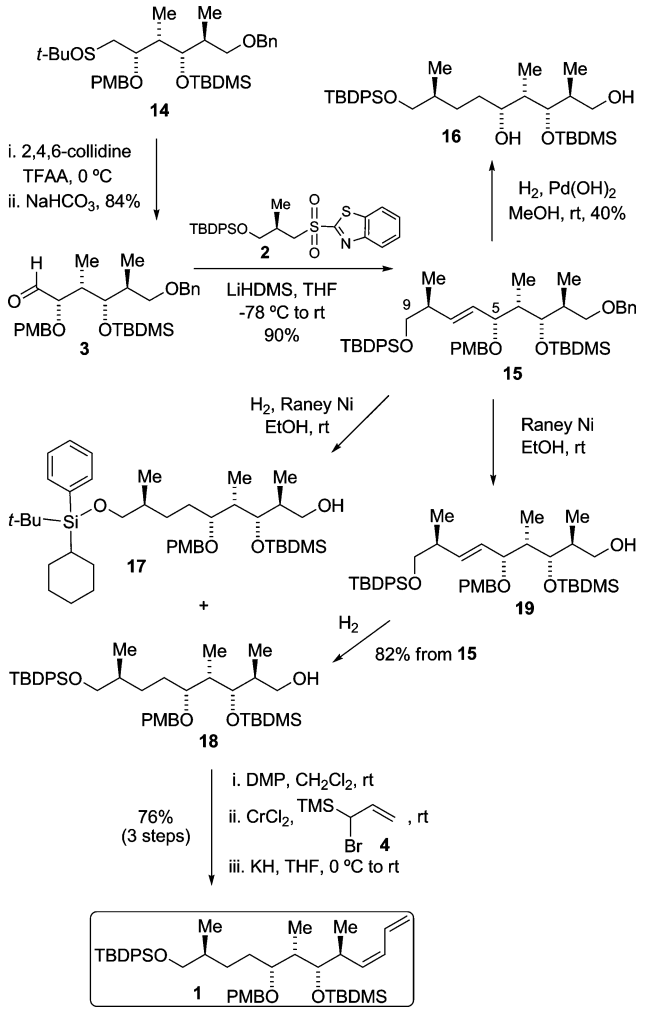
Once the *syn-syn* stereotriad at C19–C21 of the final target was installed, we turned our attention to the selective mono protection of the diol moiety of **11**. This task proved to be arduous and after much experimentation we found that the treatment of diol **11** with NaH in the presence of PMBBr (DMF, 0 °C to rt) gave rise to the exclusive protection of the hydroxyl group at C-5 affording the PMB ether derivative **13** in 88% yield.[20] The selective protection of the OH β to the sulfoxide in the presence of another γ-carbinol was unprecedented. The stabilization of the intermediate β-alkoxide by the proximal sulfinyl oxygen could be the origin of such a chemoselective reaction. The subsequent protection of the carbinol at C-3 of **13** was easily achieved by treatment with TBDMSOTf and 2,6-lutidine (CH_2Cl_2, 0 °C to rt), affording the differently protected triol **14** in 95% yield.

With **14** successfully synthesized, we undertook the transformation of the sulfoxide in order to install the left fragment of the C15–C26 unit of dictyostatin (Scheme 3).

Thus, after submitting sulfoxide **14** to the Pummerer reaction (i. 2,4,6-collidine, TFAA, 0 °C; ii. $NaHCO_3$), aldehyde **3** was obtained in 84% yield, after chromatographic purification. The modified Julia reaction[21] of compound **3** with known sulfone **2**,[22] (LiHMDS, THF, −78 °C to rt), furnished the differently protected tetraol derivative **15** with 90% yield.

At this point, it was interesting to perform simultaneously the reduction of the double bond and the deprotection of the benzyl alcohol at the right end of compound **15**. With this aim, we initially submitted derivative **15** to hydrogenation in the presence of $Pd(OH)_2$ (MeOH, rt). Under these conditions (Scheme 3), the double bond of **15** was hydrogenated and the benzyl group hydrogenolyzed, but the PMB protecting group at C-5 was also cleaved, giving rise to the corresponding diol **16**, in 40% yield.

Next, we tried to perform the required double reduction process by treatment of **15** with hydrogen in the presence of RANEY® Ni (EtOH, rt), as depicted in Scheme 3. In this case, we could observe the formation of the desired saturated primary alcohol **18** but always accompanied with variable amounts of a secondary product (depending on the experimental conditions), later identified as compound **17**, in which one of the aromatic rings of the OTBDPS protecting group at C-9 of **15**, had been also fully hydrogenated to the corresponding cyclohexane ring. Finally, we could successfully achieve the required goal by using a one-pot



Scheme 3 Completion of the synthesis of **1**, the C15–C26 unit of (–)-dictyostatin.

two-step procedure comprising first the treatment of compound **15** with RANEY® Ni (EtOH, rt) to afford the unsaturated alcohol **19** (which can be isolated), followed by *in situ* hydrogenation of the double bond of **19** giving rise to the saturated carbinol **18**, in 82% yield for the one-pot two-step process (Scheme 3).

With compound **18** in hand, we undertook the final steps of the synthesis to construct the right part of the C15–C26 unit of dictyostatin, the terminal (*Z*)-1,3-diene moiety. We chose the protocol used by Paterson in the total synthesis of discodermolide.[23] Thus, the Dess–Martin oxidation (DMP, CH_2Cl_2, rt) of alcohol **18** furnished the corresponding aldehyde, which, without further purification, was submitted to a Nozaki–Hiyama[24] allylation followed by a Peterson olefination protocol[25] (i. $CrCl_2$, silyl bromide **4**, THF, rt, 16 h; ii. KH, THF, 0 °C to rt), to afford diene **1**, the C15–C26 fragment of (–)-dictyostatin, with a 76% yield for the three last steps.

Experimental

General

Melting points were obtained in open capillary tubes and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ at 300 and 75 MHz, respectively. All reactions were monitored by thin layer chromatography that was performed on pre-coated sheets of silica gel 60, and flash column chromatography was done with silica gel 60 (230–400 mesh) from Merck. Eluting solvents are indicated in the text. The apparatus for inert atmosphere experiments was dried by flaming in a stream of dry argon. Diisopropylamine was used freshly distilled over KOH. NaH was washed before use with several portions of hexane. CH_2Cl_2 was pre-dried over $CaCl_2$, distilled over P_2O_5 and carefully kept under an argon atmosphere. Dry THF was distilled from sodium/benzophenone ketyl. All other reagent quality solvents were pre-dried over activated molecular sieves and kept under an argon atmosphere. For routine work-ups, hydrolysis was carried out with water, extractions with CH_2Cl_2, and solvent drying with $MgSO_4$.

(3*R*,4*S*,5*S*)-6-(Benzyloxy)-1-[(*R*)-*tert*-butylsulfinyl]-4-hydroxy-3,5-dimethylhexan-2-one (5)

A solution of SmI_2 was freshly prepared by a rapid addition of diiodomethane (184 μL, 2.3 mmol, 2.0 equiv.) in THF (25 mL) to samarium powder (376 mg, 2.5 mmol, 2.2 equiv.) at 10 °C, under an Ar atmosphere (do not use a N_2 atmosphere). The mixture was stirred at the same temperature for 1 h in the dark. The solution turned dark blue and was cooled to −78 °C. A solution of γ-bromo-β-ketosulfoxide **6**[13b] (290 mg, 1.1 mmol, 1 equiv.) in THF (3.1 mL) was slowly added and the mixture stirred for 10 min. Then, a solution of aldehyde (*S*)-**7**[26] (see ESI†) (263 mg, 1.4 mmol, 1.3 equiv.) in THF (3.1 mL) was added dropwise. The resulting mixture was stirred for 90 min at −78 °C and quenched by the successive addition of HCl 0.1 M (20 mL) and brine (20 mL). EtOAc (20 mL) was added and the aqueous phase was extracted with more EtOAc (4 × 20 mL). The organic phase was washed with saturated aqueous solution of $Na_2S_2O_3$ (2 × 40 mL) and brine (40 mL). After work-up and flash chromatography over demetalled silica gel[27] (EtOAc) without pressure, compound **5** was obtained, as a 88 : 12 mixture of diastereoisomers, as a yellow oil (349 mg, 87% yield): R_f 0.38 (MeOH–EtOAc–CH_2Cl_2 0.3 : 2 : 6); $[\alpha]_D^{20}$ = +145.7 (*c* 0.5, $CHCl_3$); ^{1}H NMR δ 7.35–7.26 (m, 5H), 4.53 (s, 2H), 4.07 (dd, *J* = 9.0 and 3.0 Hz, 1H), 3.66 and 3.52 (AB system, *J* = 13.5 Hz, 2H), 3.62 (dd, *J* = 9.0 and 4.8 Hz, 1H), 3.58 (dd, *J* = 9.0 and 6.3 Hz, 1H), 2.82 (dq, *J* = 6.9 and 3.0 Hz, 1H), 1.96 (m, 1H), 1.29 (s, 9H), 1.19 (d, *J* = 6.9 Hz, 3H), 0.93 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR δ 206.1, 138.0, 128.4, 127.7, 127.7; 74.5, 74.0, 73.5, 56.1, 54.3, 36.0, 22.8, 13.8, 8.0. HRMS (FAB+) calcd for $C_{19}H_{30}O_4S$ $[M + H]^+$ 355.1943, found 355.1943.

(3*R*,4*S*,5*S*)-6-(Benzyloxy)-4-(*tert*-butyldimethylsilyloxy)-1-[(*R*)-*tert*-butylsulfinyl]-3,5-dimethylhexan-2-one (8)

2,6-Lutidine (215 μL, 1.85 mmol, 4.0 equiv.) was added dropwise to a solution of Reformatsky adduct **5** (76% *de*) (217 mg, 0.46 mmol, 1.0 equiv.) in CH_2Cl_2 (3 mL) at 0 °C, followed by the addition of TBDMSOTf (160 μL, 0.69 mmol, 1.5 equiv.). The reaction mixture was stirred at room temperature for 48 h and hydrolyzed with an aqueous saturated solution of NH_4Cl (3 mL). After work-up and flash chromatography (hexane–EtOAc 3 : 2), compound **8** was obtained as a colourless oil (123 mg, 56% yield): R_f 0.75 (EtOAc); $[\alpha]_D^{20}$ = +45.5 (*c* 0.85, acetone); ^{1}H NMR δ

7.34–7.28 (m, 5H), 4.47 (s, 2H), 4.07 (t, J = 6.0 Hz, 1H), 3.6–3.5 (m, 1H), 3.55 (s, 2H), 3.37 (dd, J = 6.0 and 9.0 Hz, 1H), 3.15–3.05 (m, 1H), 2.0–1.9 (m, 1H), 1.18 (s, 9H), 1.19 (d, J = 6.9 Hz, 3H), 0.93 (d, J = 6.9 Hz, 3H), 0.88 (s, 9H), 0.02 (s, 3H), 0.00 (s, 3H); ^{13}C NMR δ 205.7, 138.5, 128.4, 127.6, 127.5, 74.1, 73.1, 72.1, 58.1, 54.1, 50.6, 38.9, 26.1, 22.7, 18.3, 14.6, 13.1, –3.9, –4.2; HRMS (FAB+) calcd for $C_{25}H_{45}O_4SSi$ [M + H]$^+$ 469.2808, found 469.2808.

(2*S*,3*S*,4*S*,5*S*)-6-(Benzyloxy)-4-(*tert*-butyldimethylsilyloxy)-1-[(*R*)-*tert*-butylsulfinyl]-3,5-dimethylhexan-2-ol (9)

A solution of DIBAL-H 1.5 M in toluene (120 µL, 0.18 mmol, 2.4 equiv.) was added dropwise to a solution of ketone **8** (35.5 mg, 0.075 mmol, 1 equiv.) in THF (1.5 mL) at –78 °C, and stirred under these conditions for 3 h. The reaction was hydrolyzed with methanol (4 mL) and a saturated solution of sodium and potassium tartrate (4 mL). After the addition of EtOAc (4 mL), the mixture was vigorously stirred for 2 h, the aqueous layer extracted with EtOAc (3 × 10 mL) and the organic layers washed with brine. After work-up and flash chromatography (hexane–EtOAc 2 : 3), carbinol **9** was obtained as a colourless oil (19.1 mg, 54% yield): R_f 0.34 (hexane–EtOAc 3 : 2); $[\alpha]_D^{20}$ = +18.0 (c 0.2, acetone); ^{1}H NMR δ 7.37–7.27 (m, 5H), 4.51 and 4.46 (AB system, J = 6.0 Hz, 2H); 4.36–4.32 (m, 1H), 3.89 (t, J = 3.0 Hz, 1H), 3.65 (broad s, 1H), 3.52 (dd, J = 6.0 and 9.0 Hz, 1H), 3.32 (dd, J = 6.0 and 9.0 Hz, 1H), 2.61 (dd, J = 9.0 and 12.0 Hz, 1H), 2.46 (dd, J = 3.0 and 12.0 Hz, 1H), 2.21–2.13 (m, 1H), 1.88–1.83 (m, 1H), 1.23 (s, 9H), 0.98 (d, J = 6.0 Hz, 3H), 0.95 (d, J = 6.0 Hz, 3H), 0.08 (s, 3H), 0.05 (s, 3H); ^{13}C NMR δ 138.5, 128.3, 127.7, 127.5, 77.2, 73.7, 72.9, 69.9, 53.7, 45.0, 44.1, 36.2, 26.1, 22.6, 18.4, 12.2, 11.7, –3.9, –4.3. HRMS (FAB+) calcd for $C_{25}H_{47}O_4SSi$ [M + H]$^+$ 471.2964, found 471.2968.

(2*S*,3*S*,4*R*,5*S*)-1-(Benzyloxy)-5-(*tert*-butyldimethylsilyloxy)-6-[(*R*)-*tert*-butylsulfinyl]-2,4-dimethylhexan-3-ol (10)

To a solution of compound **9** (65.5 mg, 0.14 mmol, 1 equiv) in DMF (460 µL), NaH 60% in mineral oil (6 mg, 0.153 mmol, 1.1 equiv.) was added at 0 °C. Then, *p*-methoxybenzyl bromide (30.3 µL, 0.21 mmol, 1.5 equiv.) was added dropwise and the resulting mixture was stirred for 3 h at 0 °C and hydrolyzed with an aqueous saturated solution of NH_4Cl (0.5 mL). After work-up and flash chromatography (hexane–EtOAc 1 : 2), compound **10** was obtained as a colourless oil (65.0 mg, 99% yield): R_f 0.5 (EtOAc); $[\alpha]_D^{20}$ = +5.55 (c 0.63, $CHCl_3$); ^{1}H NMR δ 7.37–7.27 (m, 5H), 4.55 and 4.50 (AB system, J = 12.0 Hz, 2H), 4.19 (ddd, J = 1.0, 5.7 and 9.0 Hz, 1H), 3.90 (d, J = 8.7 Hz, 1H), 3.62 (dd, J = 3.0 and 9.0 Hz, 1H); 3.52 (dd, J = 6.0 and 9.0 Hz, 1H), 3.50 (br s, 1H), 2.80 (dd, J = 9.0 and 12.0 Hz, 1H), 2.60 (dd, J = 3.0 and 12.0 Hz, 1H), 1.88–1.83 (m, 1H), 1.23 (s, 9H), 0.91 (s, 9H), 0.92 (d, J = 6.0 Hz, 3H), 0.83 (d, J = 6.0 Hz, 3H), 0.20 (s, 3H), 0.10 (s, 3H); ^{13}C NMR δ 138.5, 128.5, 127.8, 127.7, 76.4, 73.9, 73.5, 70.2, 53.4, 52.3, 41.3, 36.6, 25.9, 23.0, 18.3, 14.2, 9.1, –4.1, –4.5. HRMS (ES+) calcd for $C_{25}H_{47}O_4SSi$ [M + H]$^+$ 471.2948, found 471.2956.

(2*S*,3*R*,4*S*,5*S*)-6-(Benzyloxy)-1-[(*R*)-*tert*-butylsulfinyl]-3,5-dimethylhexane-2,4-diol (11)

To a solution of ketone **5** (76% *de*) (1.98 g, 5.6 mmol, 1 equiv.) in THF (136 mL), a solution of DIBAL-H 1.5 M in toluene (9.04 mL, 13.4 mmol, 2.4 equiv.) was slowly added at –78 °C and stirred under these conditions for 3 h. The reaction was hydrolyzed with methanol (20 mL) and a saturated solution of sodium and potassium tartrate (60 mL). After the addition of EtOAc (20 mL), the mixture was vigorously stirred for 2 h, the aqueous layer was extracted with EtOAc (3 × 30 mL) and the organic layers washed with brine. After work-up and crystallisation in Et_2O (100 mL) and acetone (1 mL) at –20 °C over 2 days, diol **11** was obtained as a white solid (1.60 g, 81% yield): mp 106–107 °C; R_f 0.21 (EtOAc); $[\alpha]_D^{20}$ = +122.7 (c 1, $CHCl_3$); ^{1}H NMR δ 7.37–7.27 (m, 5H), 4.54 (s, 2H), 4.47 (d, J = 9.3 Hz, 1H), 4.50 (s, 1H), 4.18 (s, 1H), 3.84 (d, J = 9.0 Hz), 3.62 (dd, J = 3.8 and 13.6 Hz, 1H), 3.45 (dd, J = 9.6 and 13.6 Hz, 1H), 2.72 (dd, J = 9.9 and 12.6 Hz, 1H), 2.41 (dd, J = 2.7 and 12.6 Hz, 1H), 2.02 (m, 1H), 1.72 (dq, J = 1.7 and 6.7 Hz, 1H), 1.26 (s, 9H), 0.97 (d, J = 7.0 Hz, 3H), 0.72 (d, J = 6.9 Hz, 3H); ^{13}C NMR δ 137.2, 128.6, 128.0, 127.8, 82.4, 74.0, 71.0, 52.7, 51.6, 39.0, 35.8, 22.9, 12.8, 4.8. HMRS (FAB+) calcd for $C_{19}H_{32}O_4S$ [M + H]$^+$ 357.2100, found 357.2095.

(4*S*,5*R*,6*S*)-4-[(*S*)-1-(Benzyloxy)propan-2-yl]-6-[(*R*)-*tert*-butylsulfinylmethyl]-2,2,5-trimethyl-1,3-dioxane (12)

To a solution of diol **11** (0.47 g, 1.32 mmol, 1 equiv.) in acetone (8.25 mL), 2,2-dimethoxypropane (6.48 mL, 52.68 mmol, 40 equiv.) and *p*-toluenesulfonic acid (0.1 g, 0.39 mmol, 0.3 equiv.) were added. The reaction mixture was stirred overnight at room temperature and quenched with a saturated solution of Na_2CO_3. After extraction with EtOAc (5 × 20 ml) and work-up, compound **12** was obtained as a yellowish oil (0.501 g, 96% yield): R_f 0.74 (EtOAc–MeOH 9 : 1); $[\alpha]_D^{20}$ = +82.7 (c 1, $CHCl_3$); ^{1}H NMR δ 7.29–7.34 (m, 5H), 4.54 and 4.46 (AB system, J = 12.1 Hz, 2H); 4.5–4.4 (m, 1H), 3.81 (dd, J = 1.7 and 10.1 Hz, 1H), 3.57 (dd, J = 2.9 and 8.7 Hz, 1H), 3.44 (dd, J = 6.2 and 8.7 Hz, 1H), 2.64 (dd, J = 10.4 and 12.4 Hz, 1H), 2.37 (dd, J = 2.1 and 12.5 Hz, 1H), 1.86 (dtd, J = 3.0, 6.6 and 9.6 Hz, 1H), 1,57 (m, 1H), 1.44 (s, 3H), 1.39 (s, 3H), 1.27 (s, 9H), 0.93 (d, J = 7.0 Hz, 3H), 0.91 (d, J = 6.9 Hz, 3H); ^{13}C NMR δ 138.9, 128.3, 127.4, 127.3, 99.6, 73.9, 73.2, 72.1, 67.7, 52.6, 49.9, 35.3, 33.2, 29.8, 19.7, 22.8, 12.6, 5.1. HRMS (FAB+) calcd for $C_{22}H_{36}O_4S$ (M + H)$^+$ 397.2413, found 397.2411.

(2*S*,3*S*,4*R*,5*S*)-1-(Benzyloxy)-6-[(*R*)-*tert*-butylsulfinyl]-5-(4-methoxybenzyloxy)-2,4-dimethylhexan-3-ol (13)

To mineral oil-free NaH (124 mg, 3.12 mmol, 1.1 equiv.), a solution of diol **11** (1.01 g, 2.83 mmol, 1.0 equiv.) in DMF (9.4 mL) was added dropwise at 0 °C. After stirring for 15 min at 0 °C, PMBBr (611 µL, 4.24 mmol, 1.5 equiv.) was slowly added. The reaction mixture was stirred for 4 h at 0 °C and overnight at room temperature, and was quenched with NH_4Cl. After work-up and flash chromatography (hexane–EtOAc 3 : 1), carbinol **13** was obtained as a colourless oil (1.18 g, 88% yield); R_f 0.30 (MeOH–EtOAc 1 : 9); $[\alpha]_D^{20}$ = +72.5 (c 0.85, acetone); ^{1}H NMR δ 7.36–7.27 (m, 7H), 6.86 (d, J = 8.7 Hz, 2H), 4.62 and 4.52 (AB system, J = 12.0 Hz, 2H); 4.50 and 4.46 (AB system, J = 12.0 Hz, 2H), 4.03 (ddd, J = 3.0, 6.0 and 9.0 Hz, 1H), 3.80 (s, 1H), 3.77 (d, J = 12.0 Hz, 1H), 3.47 (m, 3H), 2.85 (dd, J = 9.0 and 13.2 Hz, 1H), 2.68 (dd, J = 3.0 and 13.2 Hz, 1H), 2.05–1.88 (m, 2H), 1.25 (s, 9H), 0.94 (d, J = 7.2 Hz, 3H), 0.80 (d, J = 7.2 Hz, 3H); ^{13}C NMR δ 159.3, 137.8, 130.4, 129.7, 128.4, 127.7, 113.8, 77.3, 75.9, 74.8, 73.8, 55.3,

53.4, 52.6, 49.5, 38.0, 36.4, 22.9, 13.9, 8.6. HRMS (FAB+) calcd for $C_{27}H_{40}O_5S$ [M + H]$^+$ 477.2667, found 477.2675.

(2*S*,3*S*,4*S*,5*S*)-1-(Benzyloxy)-3-(*tert*-butyldimethylsilyloxy)-6-[(*R*)-*tert*-butylsulfinyl]-5-(4-methoxybenzyloxy)-2,4-dimethylhexane (14)

To a solution of carbinol **13** (1.18 g, 2.47 mmol, 1.0 equiv.) in DMF (13 mL), 2,6-lutidine (1.15 mL, 9.88 mmol, 4.0 equiv.) and TBDMSOTf (880 µL, 3.84 mmol, 1.5 equiv.) were successively added at 0 °C. The reaction mixture was stirred overnight at room temperature and more TBDMSOTf (283 µL, 1.23 mmol, 0.5 equiv.) was added. After stirring for 12 h, more TBDMSOTf (283 µL, 1.23 mmol, 0.5 equiv.) was added and the reaction was continued for 6 h. After hydrolysis with NH_4Cl, work-up and flash chromatography (hexane, then hexane–EtOAc 2 : 1, then hexane–EtOAc 1 : 2), compound **14** was obtained as a colourless oil (1.39 g, 95% yield): R_f 0.66 (EtOAc); $[\alpha]_D^{20}$ = +43.5 (*c* 1.2, acetone); ^{1}H NMR δ 7.35–7.23 (m, 7H), 6.84 (d, *J* = 12.0 Hz, 2H), 4.65 and 4.50 (AB system, *J* = 10.8 Hz, 2H), 4.44 (s, 2H), 4.03 (ddd, *J* = 2.2, 5.8 and 8.4 Hz, 1H), 3.84 (t, *J* = 3.8 Hz, 1H), 3.78 (s, 3H), 3.45 (dd, *J* = 6.6 and 9.4 Hz, 1H), 3.29 (dd, *J* = 7.2 and 9.4 Hz, 1H), 2.68 (dd, *J* = 2.8 and 13.2 Hz, 1H), 2.6–2.5 (m, 1H), 2.16–1.97 (m, 2H), 1.22 (s, 9H), 1.01 (d, *J* = 7.1 Hz, 3H), 0.80 (d, *J* = 6.9 Hz, 3H), 0.89 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H); ^{13}C NMR δ 159.3, 138.7, 130.5, 129.7, 128.3, 127.4, 113.8, 46.1, 73.4, 73.0, 72.8, 55.3, 52.6, 50.4, 40.3, 39.3, 26.1, 22.9, 18.4, 13.9, 12.0, –3.7, –3.9. HRMS (FAB+) calcd for $C_{33}H_{54}O_5SSi$ [M + H]$^+$ 591.3562, found 591.3540.

(2*S*,3*S*,4*S*,5*S*)-6-(Benzyloxy)-4-(*tert*-butyldimethylsilyloxy)-2-(4-methoxybenzyloxy)-3,5-dimethylhexanal (3)

To a solution of sulfoxide **14** (600 mg, 1.01 mmol, 1 equiv.) in CH_3CN (12 mL), 2,4,6-collidine (403 µL, 3.05 mmol, 3.0 equiv.) and trifluoroacetic anhydride (702 µL, 5.05 mmol, 5.0 equiv.) were successively added at 0 °C. The reaction mixture was stirred for 15 min at 0 °C, quenched with an aqueous saturated solution of $NaHCO_3$ (15 mL) and the resulting solution was stirred for 2 h at room temperature. After extraction with EtOAc (4 × 15 mL), work-up and flash chromatography (hexane–EtOAc 3 : 1), aldehyde **3** was obtained as a colourless wax (425 mg, 84%): $[\alpha]_D^{20}$ = +80.6 (*c* 0.63, acetone); ^{1}H NMR δ 9.54 (d, *J* = 4.7 Hz, 1H), 7.39–7.26 (m, 7H), 6.90 (d, *J* = 8.7 Hz, 2H), 4.62 and 4.48 (AB system, *J* = 11.9 Hz, 2H), 4.47 (s, 2H), 3.83 (s, 3H), 3.79 (dd, *J* = 3.1 and 6.4 Hz, 1H), 3.70 (t, *J* = 4.6 Hz, 1H), 3.55 (dd, *J* = 5.9 and 9.1 Hz, 1H), 3.25 (dd, *J* = 6.9 and 9.1 Hz, 1H), 2.27–3.17 (m, 1H), 2.04–1.94 (m, 1H), 0.99 (d, *J* = 7.0 Hz, 3H), 0.95 (d, *J* = 7.0 Hz, 3H), 0.90 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H); ^{13}C NMR δ 203.5, 159.5, 138.6, 129.8, 129.5, 129.2, 128.3, 127.6 113.9 84.2, 74.2, 73.1, 72.3, 55.3, 37.8, 26.2, 18.4, 15.1, 14.2, 11.3, –3.8, –4.0. HRMS (ES) calcd for $C_{29}H_{44}O_5Si$ [M + H]$^+$ 501.3010, found 501.3030.

(6*S*,9*R*,10*S*,11*S*,7*E*)-11-[(*S*)-1-(Benzyloxy)propan-2-yl]-9-(4-methoxybenzyloxy)-2,2,6,10,13,13,14,14-octamethyl-3,3-diphenyl-4,12-dioxa-3,13-disilapentadec-7-ene (15)

To a well-stirred solution of sulfone **2**[22] (509.7 mg, 1.00 mmol, 2.5 equiv.) in THF (10.0 mL) at –78 °C, a solution of lithium bis(trimethylsilyl)amide (TMS_2NLi) 1.0 M in THF (960 µL, 0.96 mmol, 2.4 equiv.) was slowly added *via* a syringe. The resulting solution turned dark orange and was stirred for 30 min at –78 °C and 30 min at 0 °C. To this mixture, cooled at –78 °C, a solution of aldehyde **3** (205 mg, 0.40 mmol, 1 equiv.) in THF (666 µL) was added *via* a cannula. After additional stirring for 12 h at –78 °C, the reaction was allowed to warm to room temperature for 10 h. The mixture was quenched with a saturated aqueous solution of NH_4Cl and extracted with EtOAc and CH_2Cl_2. After work-up and flash chromatography (hexane, then hexane–EtOAc 1 : 99), olefin **15** was obtained as a colourless wax (285 mg, 90% yield): R_f 0.68 (hexane–EtOAc 5 : 1); $[\alpha]_D^{20}$ = +30.0 (*c* 0.56, acetone); ^{1}H NMR δ 7.70 (d, *J* = 7.7 Hz, 2H), 7.68 (d, *J* = 7.7 Hz, 2H), 7.36 (m, 11 H), 7.17 (d, *J* = 8.6 Hz, 2H), 6.81 (d, *J* = 9.0 Hz, 2H), 5.59 (dd, *J* = 7.5 and 15.6 Hz, 1H), 5.29 (dd, *J* = 8.5 and 15.9 Hz, 1H), 4.46 (d, *J* = 11.5 Hz, 1H), 4.41 (s, 2H), 4.17 (d, *J* = 11.5 Hz, 1H), 3.78 (s, 3H), 3.69 (dd, *J* = 3.2 and 4.7 Hz, 1H), 3.53 (m, 4H), 3.22 (dd, *J* = 7.6 and 9.1 Hz, 1H), 2.41 (qd, *J* = 6.8 and 13.4 Hz, 1H), 1.95 (ddd, *J* = 5.2, 7.0 and 12.3 Hz, 1H), 1.73 (m, 1H), 1.07 (s, 9H), 1.01 (d, 3H, *J* = 6.8 Hz), 0.96 (d, 3H, *J* = 6.8 Hz), 0.92 (d, 3H, *J* = 7.0 Hz), 0.84 (s, 9H), 0.02 (s, 3H), –0.03 (s, 3H); ^{13}C NMR δ 159.3, 139.1, 138.3, 135.9, 134.3, 134.2, 131.4, 129.9, 129.8, 128.6, 128.0, 127.8, 127.7, 114.0, 81.9, 76.9, 74.2, 73.3, 73.3, 69.7, 69.1, 55.6, 41.5, 39.9, 39.5, 27.3, 26.5, 19.7, 18.8, 17.5, 14.9, 11.6, –3.4, –3.6; HRMS (ES) calcd for $C_{49}H_{70}O_5Si_2$ [M + Na]$^+$ 817.4654, found 817.4634.

(2*S*,3*S*,4*S*,5*R*,8*S*)-3-(*tert*-Butyldimethylsilyloxy)-9-(*tert*-butyldiphenylsilyloxy)-2,4,8-trimethylnonane-1,5-diol (16)

To a solution of olefin **15** (20 mg, 0.025 mmol, 1 equiv.) in MeOH (3 mL), $Pd(OH)_2$ (9 mg, 0.025 mmol, 1 equiv.) was added. Then, H_2 was bubbled into the solution with a balloon and stirred under H_2 atmosphere overnight. The reaction mixture was filtered over celite, rinsed several times with EtOAc. After evaporation of the solvent and flash chromatography (hexane–EtOAc 1 : 1), diol **16** was obtained as a colourless wax (5.8 mg, 40% yield); R_f 0.53 (hexane–EtOAc 1 : 1); $[\alpha]_D^{20}$ = –5.6 (*c* 0.58, $CHCl_3$); ^{1}H NMR δ 7.68 (d, *J* = 7.5 Hz, 2H), 7.68 (d, *J* = 7.5 Hz, 2H), 7.53–7.32 (m, 6H), 3.81–3.77 (m, 1H), 3.72–3.69 (m, 1H), 3.60 (d, *J* = 9.0 Hz, 2H), 3.50 (m, 2H), 2.49 (br s, 2H), 2.21–2.12 (m, 1H); 1.73–1.27 (m, 6H), 1.06 (s, 9H), 0.95–0.91 (m, 9H), 0.92 (s, 9H), 0.11 (s, 3H), 0.07 (s, 3H); ^{13}C NMR δ 135.6, 134.0, 129.5, 127.6, 78.2, 72.6, 68.8, 65.8, 41.7, 37.7, 35.9, 32.5, 29.8, 26.9, 26.0, 19.3, 18.2, 16.9, 15.6, 9.5, –3.9, –4.2. HRMS (ES) calcd for $C_{34}H_{58}O_4Si_2$ [M + Na]$^+$ 609.3765, found 609.3782.

(2*S*,3*S*,4*S*,5*R*,8*S*)-9-(*tert*-Butyl(cyclohexyl)(phenyl)silyloxy)-3-(*tert*-butyldimethylsilyloxy)-5-(4-methoxybenzyloxy)-2,4,8-trimethylnonan-1-ol (17)

To a solution of olefin **15** (75 mg, 0.094 mmol, 1 equiv.) in EtOH (10 mL), activated RANEY® Ni was added at room temperature, followed by bubbling H_2 into the solution with a balloon and stirred for 7 days at atmospheric pressure. The reaction mixture was carefully filtered over celite, which must never dry, and rinsed several times with EtOAc. After evaporation of the solvent alcohol **17** was obtained as a colourless wax (50.8 mg, 75% yield): R_f 0.23 (hexane–EtOAc 5 : 1); $[\alpha]_D^{20}$ = –7.1 (*c* 1.9, acetone); ^{1}H NMR δ 7.57 (d, *J* = 8.0 Hz, 2H), 7.36–7.34 (m, 3H), 7.15 (d, *J* = 8.0 Hz, 2H); 6.75 (d, *J* = 8.0 Hz, 2H), 4.43 and 4.28 (AB system, *J* = 12.0 Hz, 2H), 3.79 (s, 3H), 3.76–3.66 (m, 1H), 3.68–3.62 (m, 3H),

3.50–3.48 (m, 1H), 3.32–3.30 (m, 1H), 2.55 (br s, 1H), 1.94–1.61 (m, 7H), 1.34–1.25 (m, 11H), 0.97 (s, 9H), 0.97–0.87 (m, 9H), 0.92 (s, 9H), 0.13 (s, 3H), 0.11 (s, 3H); ^{13}C NMR δ 159.2, 135.5, 134.8, 130.7, 129.5, 128.9, 127.4, 113.8, 81.0, 76.3, 71.4, 69.1, 65.3, 55.3, 39.4, 38.9, 36.5, 29.7, 28.4, 27.4, 27.0, 26.2, 25.0, 19.3, 18.3, 16.9, 14.6, 11.6, –3.5, –3.9. HRMS (ES) calcd for $C_{42}H_{73}O_5Si_2$ [M + H]$^+$ 713.4986, found 713.4995.

(2*S*,3*S*,4*S*,5*R*,8*S*,6*E*)-3-(*tert*-Butyldimethylsilyloxy)-9-(*tert*-butyldiphenylsilyloxy)-5-(4-methoxybenzyloxy)-2,4,8-trimethylnon-6-en-1-ol (19)

To a solution of olefin **15** (168 mg, 0.23 mmol, 1 equiv.) in EtOH (18 mL), activated RANEY® Ni was added at room temperature. The reaction mixture was stirred until complete consumption of all starting material by TLC. The reaction mixture was carefully filtered over celite, which must never dry, and rinsed several times with EtOAc. After evaporation of the solvent and flash chromatography, alcohol **19** was obtained as a colourless wax (83 mg, 52% yield): R_f 0.24 (hexane–EtOAc 5 : 1); $[\alpha]_D^{20} = -21.3$ (*c* 0.6, acetone); ^{1}H NMR δ 7.68 (d, *J* = 7.7 Hz, 2H), 7.66 (d, *J* = 7.7 Hz, 2H), 7.40 (m, 6H), 7.15 (d, *J* = 7.7 Hz, 2H), 6.72 (d, *J* = 7.7 Hz, 2H), 5.62 (dd, *J* = 7.5 and 15.6 Hz, 1H), 5.34 (dd, *J* = 8.5 and 15.9 Hz, 1H), 4.48 and 4.19 (AB system, *J* = 12.0 Hz, 2H), 3.86 (t, *J* = 3.9 Hz, 1H), 3.79 (s, 3H), 3.66–3.44 (m, 5H), 2.68 (t, *J* = 3.0 Hz, 1H), 2.41 (qd, *J* = 6.8 and 13.4 Hz, 1H), 1.95 (m, 1H), 1.73 (m, 1H), 1.03 (s, 9H), 1.01 (d, *J* = 6.8 Hz, 3H), 0.96 (d, *J* = 6.8 Hz, 3H); 0.92 (d, *J* = 7.0 Hz, 3H), 0.84 (s, 9H), 0.11 (s, 3H), 0.07 (s, 3H); ^{13}C NMR δ 159.3, 137.6, 134.3, 134.2, 132.8, 129.9, 128.6, 128.0, 127.8, 112.7, 80.9, 74.7, 73.3, 69.3, 68.7, 65.4, 55.2, 40.7, 40.3, 39.5, 26.9, 26.0, 18.3, 17.3, 17.0, 13.5, 12.1, –3.8, –4.0. HRMS (ES) calcd for $C_{42}H_{64}O_5Si_2$ [M + Na]$^+$ 727.4184, found 727.4183.

(2*S*,3*S*,4*S*,5*R*,8*S*)-3-(*tert*-Butyldimethylsilyloxy)-9-(*tert*-butyldiphenylsilyloxy)-5-(4-methoxybenzyloxy)-2,4,8-trimethylnonan-1-ol (18)

To a solution of olefin **15** (327 mg, 0.41 mmol, 1 equiv.) in EtOH (40 mL), activated RANEY® Ni was added at room temperature. The reaction mixture was stirred until complete consumption of all starting material by TLC. Then, H_2 was bubbled into the solution with a balloon and stirred for 20 min at atmospheric pressure. The reaction mixture was carefully filtered over celite, which must never dry, and rinsed several times with EtOAc. After evaporation of the solvent and flash chromatography (hexane–EtOAc 4 : 1), alcohol **18** was obtained as a colourless wax (242 mg, 82% yield): R_f 0.23 (hexane–EtOAc 5 : 1); $[\alpha]_D^{20} = +13.2$ (*c* 0.46, $CHCl_3$); ^{1}H NMR δ 7.68 (d, *J* = 8.0 Hz, 2H), 7.66 (d, *J* = 8.0 Hz, 2H), 7.44–7.34 (m, 6H), 7.21 (d, *J* = 8.4 Hz, 2H), 6.84 (d, *J* = 8.8 Hz, 2H), 4.40 and 4.25 (AB system, *J* = 11.1 Hz, 2H), 3.79 (s, 3H), 3.74 (t, *J* = 4.9 Hz, 1H), 3.66 (m, 1H), 3.55–3.42 (m, 3H), 3.30–3.25 (m, 1H), 2.52 (broad s, 1H), 1.94–1.77 (m, 2H), 1.69–1.49 (m, 5H), 1.06 (s, 9H), 0.97–0.87 (m, 18H), 0.06 (d, *J* = 10.7 Hz, 6H);^{13}C NMR δ 159.2, 135.6, 134.0, 130.7, 129.5, 129.5, 127.6, 113.8, 80.9, 76.3, 71.3, 68.8, 65.3, 55.3, 39.4, 38.9, 36.1, 29.5, 28.4, 26.9, 26.2, 19.3, 18.3, 16.8, 14.7, 11.6, –3.6, –3.9; HRMS (ES) calcd for $C_{42}H_{66}O_5Si_2$ [M + H]$^+$ 707.4529, found 707.4521.

(5*S*,6*S*,7*R*,10*S*)-5-[(*S*,*Z*)-Hexa-3,5-dien-2-yl)-7-(4-methoxybenzyloxy)-2,2,3,3,6,10,14,14-octamethyl-13,13-diphenyl-4,12-dioxa-3,13-disilapentadecane (1)

To a solution of alcohol **18** (242 mg, 0.34 mmol, 1.0 equiv.) in CH_2Cl_2 (3.5 mL), Dess–Martin periodinane (320 mg, 0.75 mmol, 2.2 equiv.) was added. After stirring for 30 min, hexane (1 mL) was added and the resulting white suspension was purified directly by flash chromatography (hexane, then hexane–EtOAc 95 : 5) to obtain the corresponding aldehyde, which was re-dissolved in THF (10 mL) along with bromo allyl silane **4** (335 mg, 1.74 mmol, 5.8 equiv.). The resulting solution was added *via* a cannula to a suspension of $CrCl_2$ (402 mg, 3.30 mmol, 11.0 equiv.) in THF (2.2 mL). The reaction mixture was stirred overnight at room temperature and the resulting suspension was partitioned between a pH 7 buffer (8 mL) and extracted with EtOAc (3 × 15 mL). After work-up, the resulting residue was dissolved in THF (4.2 mL) and added *via* a cannula to a well-stirred suspension of KH, pre-washed with hexane, (160 mg, 1.2 mmol, 4.0 equiv.) in THF (4.2 mL) at 0 °C. The reaction mixture was stirred for 2 h at room temperature and the resulting brown suspension was transferred *via* a cannula into H_2O (5 mL) and extracted with Et_2O (3 × 10 mL). After work-up and flash chromatography (hexane–EtOAc 95 : 5), diene **1** was obtained as a colourless wax (190 mg, 76% yield over three steps): R_f 0.8 (hexane–EtOAc 6 : 1); $[\alpha]_D^{20} = +13.2$ (*c* 0.46, $CHCl_3$); ^{1}H NMR δ 7.56 (d, *J* = 8.6 Hz, 2H), 7.54 (d, *J* = 7.6 Hz, 2H), (m, 2H), 7.35–7.33 (m, 6H), 7.21 (d, *J* = 7.6 Hz, 2H), 6.87 (d, *J* = 8.6 Hz, 2H), 6.47–6.33 (m, 1H), 5.95 (t, *J* = 11.0 Hz, 1H), 5.50 (t, *J* = 10.4 Hz, 1H), 5.12 (d, *J* = 16.6 Hz, 1H), 5.03 (d, *J* = 9.9 Hz, 1H), 4.45 and 4.25 (AB system, *J* = 11.4 Hz, 2H), 3.80 (s, 3H), 3.70–3.57 (m, 3H), 3.27 (dd, *J* = 10.3 and 5.9 Hz, 1H), 2.70 (m, 1H), 1.98–1.26 (m, 7H), 0.98–0.90 (m, 9H), 0.96 (s, 9H), 0.90 (s, 9H), 0.05 (s, 6H); ^{13}C NMR δ 159.1, 135.6, 134.7, 134.1, 132.5, 131.1, 129.5, 128.9, 127.6, 117.1, 113.7, 79.3, 76.8, 70.8, 68.9, 55.3, 40.0, 36.3, 35.9, 28.9, 28.3, 26.9, 26.3, 19.3, 18.9, 18.5, 16.8, 10.8, –3.3, –3.4. HRMS (ESI+) calcd for $C_{45}H_{69}O_4Si_2$ [M + H]$^+$ 729.4716, found 729.4728.

Conclusion

We have successfully achieved a short and highly stereoselective preparation of the C15–C26 fragment of the antitumor agent (–)-dictyostatin in only 10 steps and 28% overall yield, starting from the known bromo keto sulfoxide **6** and aldehyde **7**. Our synthesis of the natural product fragment, with five stereocenters and the terminal (*Z*)-1,3-diene moiety, features two enantiopure sulfoxide-directed processes, a Reformatsky-type reaction followed by a ketone reduction, as the key steps to efficiently generate the *syn-syn* stereotriad at C19–C21 of the final target, with high levels of stereocontrol. Although this exact fragment had not been previously prepared, our synthesis occurred in an overall yield similar to other approaches of different northern fragments obtained from Roche's ester reported in the literature.[4a,b,8e,11b,c,i] With respect to the stereoselectivity, our asymmetric reduction step took place in a highly diastereoselective manner, whereas the diastereoselectivity of the Reformatsky-type reaction is slightly lower than those resulting from aldol reactions[4a,b,11b,c,i] used by other authors.

Acknowledgements

We thank *Ministerio de Ciencia e Innovación* of Spain (Grant CTQ2008-04691) and CNRS and Ministère de la Recherche (France) for financial support. L.F.-M and S.V. thank *Comunidad Autónoma de Madrid* (Spain) for fellowships.

Notes and references

1 G. R. Pettit, Z. A. Cichacz, F. Gao, M. R. Boyd and J. M. Schmidt, *J. Chem. Soc., Chem. Commun.*, 1994, 1111–1112.
2 R. A. Isbrucker, J. Cummins, S. A. Pomponi, R. E. Longley and A. E. Wright, *Biochem. Pharmacol.*, 2003, **66**, 75–82.
3 I. Paterson, R. Britton, O. Delgado and A. Wright, *Chem. Commun.*, 2004, 632–633.
4 (*a*) I. Paterson, R. Britton, O. Delgado, A. Meyer and K. G. Poullennec, *Angew. Chem., Int. Ed.*, 2004, **43**, 4629–4633; (*b*) Y. Shin, J. Fournier, Y. Fukui, A. M. Bruckner and D. P. Curran, *Angew. Chem., Int. Ed.*, 2004, **43**, 4634–4637.
5 (*a*) A. Canales, R. Matesanz, N. M. Gardner, J. M. Andreu, I. Paterson, J. F. Díaz and J. Jímenez-Barbero, *Chem.–Eur. J.*, 2008, **14**, 7557–7569; (*b*) C. Madiraju, M. C. Edler, E. Hamel, B. S. Raccor, G. Zhu, A. Vogt, Y. Shin, J. Fournier, Y. Fukui, A. M. Bruckner, D. P. Curran and B. W. Day, *Biochemistry*, 2005, **44**, 15053–15063.
6 I. Paterson and G. J. Florence, *Topics in Current Chemistry*, 2009, **286**, 73–119.
7 (*a*) B. Pfeiffer, C. N. Kuzniewski, C. Wullschleger and K.-H. Altmann, *Topics in Current Chemistry*, 2009, **286**, 1–72; (*b*) G. J. Florence, N. M. Gardner and I. Paterson, *Nat. Prod. Rep.*, 2008, **25**, 342–375.
8 See reference 4 and the following: (*a*) I. Paterson, R. Britton, O. Delgado, N. M. Gardner, A. Meyer, G. J. Naylor and K. G. Poullennec, *Tetrahedron*, 2010, **66**, 6534–6545; (*b*) W. Zhu, M. Jimenez, W.-H. Jung, D. P. Camarco, R. Balachandran, A. Vogt, B. W. Day and D. P. Curran, *J. Am. Chem. Soc.*, 2010, **132**, 9175–9187; (*c*) Y. Shin, J.-H. Fournier, A. Brueckner, Ch. Madiraju, R. Balachandran, B. S. Raccor, M. C. Edler, E. Hamel, R. P. Sikorski, A. Vogt, B. W. Day and D. P. Curran, *Tetrahedron*, 2007, **63**, 8537–8562; (*d*) P. V. Ramachandran, A. Srivastava and D. Hazra, *Org. Lett.*, 2007, **9**, 157–160; (*e*) G. W. O'Neil and A. Phillips, *J. Am. Chem. Soc.*, 2006, **128**, 5340–5341.
9 I. Paterson, N. M. Gardner and G. J. Naylor, *Pure Appl. Chem.*, 2009, **81**, 169–180 and references cited therein.
10 See reference 9 and the following: (*a*) I. Paterson, N. M. Gardner, E. Guzman and A. E. Wright, *Bioorg. Med. Chem.*, 2009, **17**, 2282–2289; (*b*) J. L. Eiseman, L. Bai, W.-H. Jung, G. Moura-Letts, B. W. Day and D. P. Curran, *J. Med. Chem.*, 2008, **51**, 6650–6653; (*c*) W.-H. Jung, C. Harrison, Y. Shin, J.-H. Fournier, R. Balachandran, B. S. Raccor, R. P. Sikorski, A. Vogt, D. P. Curran and B. W. Day, *J. Med. Chem.*, 2007, **50**, 2951–2966; (*d*) Y. Fukui, A. M. Bruckner, Y. Shin, R. Balachandran, B. W. Day and D. P. Curran, *Org. Lett.*, 2006, **8**, 301–304.
11 (*a*) J. S. Yadav and V. Rajender, *Eur. J. Org. Chem.*, 2010, 2148–2156; (*b*) H. L. Shimp and G. C. Micalizio, *Tetrahedron*, 2009, **65**, 5908–5915; (*c*) L. C. Dias, D. J. P. Lima, C. C. S. Goncalves and A. D. Andricopulo, *Eur. J. Org. Chem.*, 2009, 1491–1494; (*d*) P. V. Ramachandran and D. Pratihar, *Org. Lett.*, 2009, **11**, 1467–1470; (*e*) Ch. Zanato, L. Pignataro, Z. Hao and C. Gennari, *Synthesis*, 2008, 2158–2162; (*f*) A. K. Dilger, V. Gopalsamuthiram and S. D. Burke, *J. Am. Chem. Soc.*, 2007, **129**, 16273–16277; (*g*) V. Saibaba, A. Sampath, K. Mukkanti, J. Iqbal and P. Das, *Synthesis*, 2007, 2797–2802; (*h*) Ch. Monti, O. Sharon and C. Gennari, *Chem. Commun.*, 2007, 4271–4273; (*i*) O. Sharon, Ch. Monti and C. Gennari, *Tetrahedron*, 2007, **63**, 5873–5878; (*j*) G. Moura-Letts and D. P. Curran, *Org. Lett.*, 2007, **9**, 5–8; (*k*) J. Jaegel and M. E. Maier, *Synlett*, 2006, 693–696; (*l*) E. Prusov, H. Roehm and M. E. Maier, *Org. Lett.*, 2006, **8**, 1025–1028.
12 Review: (*a*) M. C. Carreño, G. Hernández-Torres, M. Ribagorda and A. Urbano, *Chem. Commun.*, 2009, 6129–6144; (*b*) Recent references: M. Lecea, G. Hernández-Torres, A. Urbano, M. C. Carreño and F. Colobert, *Org. Lett.*, 2010, **12**, 580–583; (*c*) M. Barbarotto, J. Geist, S. Choppin and F. Colobert, *Tetrahedron: Asymmetry*, 2009, **20**, 2780–2787; (*d*) A. Latorre, A. Urbano and M. C. Carreño, *Chem. Commun.*, 2009, 6652–6654; (*e*) F. Colobert, V. Valdivia, S. Choppin, F. Leroux, I. Fernández, E. Álvarez and N. Khiar, *Org. Lett.*, 2009, **11**, 5130–5133; (*f*) G. Hernández-Torres, A. Urbano, M. C. Carreño and F. Colobert, *Org. Lett.*, 2009, **11**, 4930–4933; (*g*) M. Obringer, M. Barbarotto, S. Choppin and F. Colobert, *Org. Lett.*, 2009, **11**, 3542–3545.
13 (*a*) M. Obringer, F. Colobert, B. Neugnot and G. Solladié, *Org. Lett.*, 2003, **5**, 629–632; (*b*) M. Obringer, F. Colobert and G. Solladié, *Eur. J. Org. Chem.*, 2006, 1455–1467; (*c*) F. Colobert, S. Choppin, L. Ferreiro-Mederos, M. Obringer, S. Luengo-Arratta, A. Urbano and M. C. Carreño, *Org. Lett.*, 2007, **9**, 4451–4454.
14 (*a*) N. Kunieda, J. Nokami and M. Kinoshita, *Chem. Lett.*, 1974, 369–372; (*b*) R. Annunziata, M. Cinquini and F. Cozzi, *J. Chem. Soc., Perkin Trans. 1*, 1979, 1687–1690; (*c*) M. C. Carreño, J. L. García Ruano, A. M. Martín, C. Pedregal, J. H. Rodríguez, A. Rubio and J. Sánchez, *J. Org. Chem.*, 1990, **55**, 2120–2128.
15 S. Akai and Y. Kita, *Topics in Current Chemistry*, 2007, **274**, 35–76.
16 Aldehyde (*S*)-**7** was obtained from commercially available (*S*) Roche ester in 3 steps and 85% overall yield (see ESI).
17 Determined by proton NMR analysis of the product. The minor component (12%) was a mixture of at least two diastereomers but we could not integrate the doublets corresponding to the methyl groups due to overlapping.
18 (*a*) S. D. Rychnovsky, B. N. Rogers and T. I. Richardson, *Acc. Chem. Res.*, 1998, **31**, 9–17; (*b*) S. D. Rychnovsky and D. J. Skalitzky, *Tetrahedron Lett.*, 1990, **31**, 945–948.
19 D. A. Evans, D. L. Rieger and J. R. Gage, *Tetrahedron Lett.*, 1990, **31**, 7099–7100.
20 The correct structure of compound **13** was deduced from COSY, HMQC and HMBC NMR spectra (see ESI).
21 Ch. Aissa, *European Journal of Organic Chemistry*, 2009, **2009**, 1831–1844.
22 M. T. Crimmins and A. C. DeBaillie, *J. Am. Chem. Soc.*, 2006, **128**, 4936–4937.
23 (*a*) I. Paterson, O. Delgado, G. J. Florence, I. Lyothier, M. O'Brien, J. P. Scott and N. Sereinig, *J. Org. Chem.*, 2005, **70**, 150–160; (*b*) I. Paterson and A. Schlapbach, *Synlett*, 1995, 498–500.
24 P. Cintas, *Synthesis*, 1992, 248–257.
25 L. F. van Staden, D. Gravestock and D. J. Ager, *Chem. Soc. Rev.*, 2002, **31**, 195–200.
26 C. H. Heathcock, S. D. Young, J. P. Hagen, P. Pilli and U. Badertscherad, *J. Org. Chem.*, 1985, **50**, 2095–2105.
27 J. S. Hubbard and T. M. Harris, *J. Org. Chem.*, 1981, **46**, 2566–2570.

