Organic & Biomolecular Chemistry

Cite this: *Org. Biomol. Chem.*, 2012, **10**, 8140

www.rsc.org/obc

PAPER

Asymmetric synthesis of a highly functionalized enantioenriched system close to thapsigargin framework†

Aurélien Tap,[a] Morgan Jouanneau,[b] Gilles Galvani,[a] Geoffroy Sorin,[a] Marie-Isabelle Lannou,[a] Jean-Pierre Férézou[b] and Janick Ardisson*[a]

Received 29th February 2012, Accepted 6th August 2012
DOI: 10.1039/c2ob26194d

A straightforward approach to a highly functionalized enantioenriched bicyclo[5.3.0]decadienone system close to the thapsigargin framework has been achieved. The developed synthetic route involves two main stages: installation of the chains on either side of the quaternary center at C7 starting from a central enantiopure epoxide and formation of the bicyclic octahydroazulene through subsequent Pauson–Khand annelation.

Introduction

In recent years, research on natural sesquiterpene lactones has fostered a renewed interest. These lactones are promising candidates in cancer drug discovery and their activities position them as lead compounds in clinical trials.[1]

Thapsigargin (Tg) **1** is a highly oxygenated sesquiterpene lactone belonging to the 6,12-guaianolide family, isolated from the Mediterranean plant species *Thapsia* (*Apiaceae*).[2] This compound presents a challenging complex chemical structure, including a polyoxygenated 5-7-5 tricyclic core possessing eight stereogenic centres and functionalized with five different ester groups (Fig. 1). Tg is a very potent inhibitor of the endo/sarcoplasmic calcium ATPase (SERCA).[3,4] Tg derivatives are currently under clinical trials for treatment of prostate cancer.

Two main challenges emerge for Tg total synthesis: (i) the construction of the 5,7-fused bicyclic core, (ii) the installation of

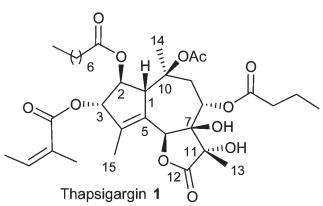
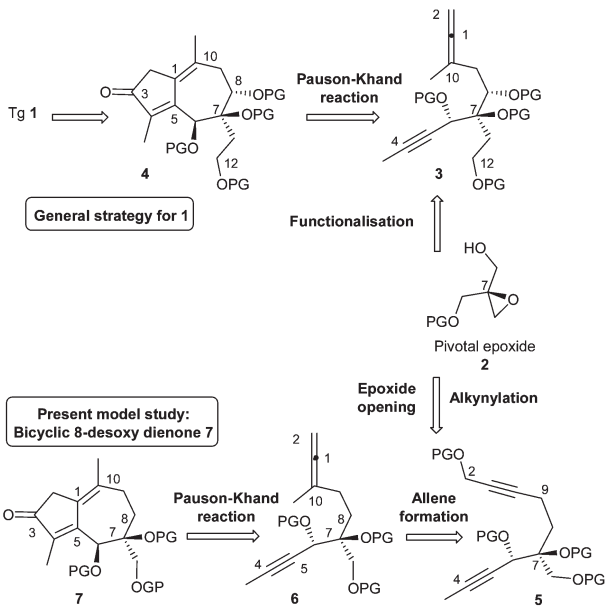


Fig. 1 Thapsigargin (Tg) **1**.



Scheme 1 Synthetic strategy to Tg **1** and 8-desoxy dienone **7**.

the dense array of functional groups present throughout the cyclic system. Remarkably, the Ley group succeeded in the first and unique total synthesis of Tg[5] as well as in the elaboration of a pivotal scaffold allowing access to unnatural analogues,[6] by means of a key diene ring closure metathesis step. A few other efforts have led to alternative interesting approaches, through either an efficient domino metathetic route (Kaliappan)[7] or a photochemical rearrangement (Massanet).[8]

Our general strategy for the synthesis of Tg **1** relies on two key points (Scheme 1). The stereocontrolled installation of the functionalities on either side of the C7 tertiary alcohol is envisioned at the beginning of the synthesis, through the addition of

[a]*Faculté de Pharmacie, CNRS UMR 8638, Université Paris Descartes, 4 avenue de l'Observatoire, 75270 Paris Cedex 06, France. E-mail: janick.ardisson@parisdescartes.fr; Tel: +33 (0) 1 53 73 97 54*
[b]*LCPSN, ICMMO, CNRS UMR 8182, Bâtiment 410, Université Paris-Sud-11, 15 rue Georges Clemenceau, F-91405 Orsay Cedex, France. Tel: +33 (0)1 69 1576 30*

†Electronic supplementary information (ESI) available: Experimental procedures, spectral data, copies of ^{1}H NMR and ^{13}C NMR spectra of new compounds. See DOI: 10.1039/c2ob26194d

side arms to the pivotal 7-centered (*R*)-epoxide **2**,[9] to deliver intermediate **3**. Then, Rh(I)-catalyzed allenic Pauson–Khand (A.P.K.) reaction, should allow the construction of bicyclo[5.3.0]-decadienone **4**, chosen as an advanced precursor of Tg **1**.[10,11]

To validate the above strategy, we decided to synthesize the enantioenriched 8-desoxy dienone **7**, structurally close to dienone **4**. As for Tg **1**, the synthetic route will start from (*R*)-epoxide **2**, however, with a reduced number of steps. Bicyclic dienone **7** should be accessible from regiocontrolled epoxide opening through propargylation,[12] followed by successive alkynylation[13] and A.P.K. reaction,[10,11] *via* intermediates **5** and **6**.

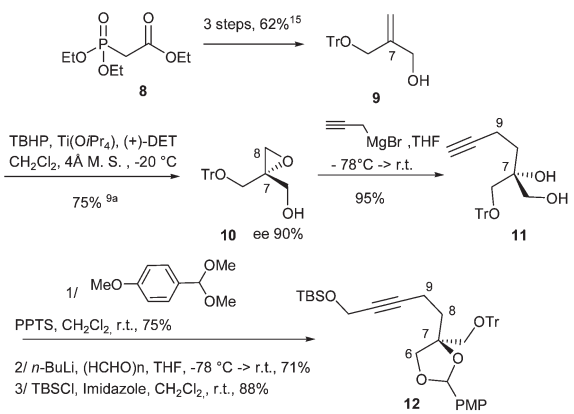
We report here the results of this chemical validation study.[14]

Results and discussion

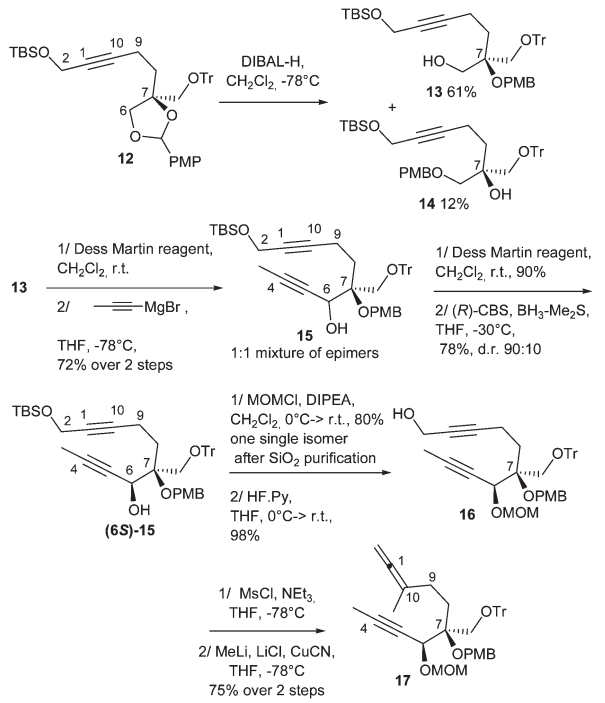
The synthesis began with the formation of the known (*R*)-epoxide **10** available by means of an asymmetric Sharpless epoxidation reaction of monoprotected allylic diol **9** with L-(+)-diethyl tartrate [L-(+)-DET], in 75% yield and up to 90% ee (Scheme 2).[9a] Trityl (Tr) ether **9** was readily prepared in three steps from commercial phosphonate **8**.[15,16]

The ensuing nucleophilic opening of the epoxide moiety with propargylmagnesium bromide proceeded in high yield to deliver the terminal alkyne **11**.[12,17,18] The latter was then converted into the corresponding PMB acetal before subsequent formylation of the triple bond and protection of the incipient primary hydroxyl group to give the fully protected intermediate **12** bearing orthogonally protected hydroxyl functions.

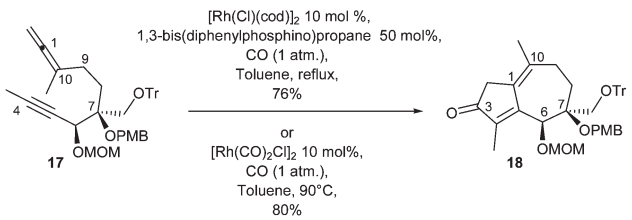
The synthesis was continued by installing the side chain at C4–C5 (Scheme 3). Reduction of acetal **12** with DIBAL-H in CH_2Cl_2 at low temperature provided the required primary alcohol **13** as the main product in 61% yield along with the corresponding regioisomeric tertiary alcohol **14** which was separated by flash chromatography (12% yield).[19] Then, the expected (6*S*) alcohol **15** was obtained through a four-step sequence. Oxidation of alcohol **13** to the corresponding aldehyde using Dess–Martin conditions[20] followed by nucleophilic addition of propynyl magnesium bromide afforded a 1 : 1 mixture of the two epimeric propargylic alcohols **15**. Successive oxidation reaction[20] and reduction of the resulting ynone with (*R*)-Corey–Bakshi–Shibata [(*R*)-CBS] reagent delivered the desired (6*S*) alcohol **15** in 78% yield and a d.r. of 90 : 10.[13b,c,21] The absolute



Scheme 2 Synthesis of silyl propargyl ether **12**.



Scheme 3 Synthesis of allenyne **17**.



Scheme 4 Synthesis of bicyclo[5.3.0]decadienone **18**.

configuration of the (*S*)-C6 centre of secondary alcohol **15** was confirmed through the synthesis of the corresponding (*R*)- and (*S*)-α-methoxyphenylacetic acid (MPA) esters.[18]

Subsequent protection of the C6 hydroxyl function of **(6*S*)-15** with a methoxymethyl (MOM) group and selective cleavage of the TBS ether at C2 allowed isolation of propargyl alcohol **16** as a single isomer after flash chromatography purification.

Finally, conversion of alcohol **16** into the allenyl precursor **17** of P.K.R. annelation was achieved in a two-step sequence: treatment with methanesulfonyl chloride and subsequent S_N2' reaction with methyl cyanocuprate.[10]

With allenyne **17** in hand, the feasibility of allene Pauson–Khand cyclocarbonylation[10,11] was then investigated under various conditions.[21] Allenyl compound **17** was first treated with *in situ* prepared $[Rh(CO)(dppp)_2Cl]$ – 10 mol% of $[Rh(Cl)(cod)]_2$ and 50 mol% of 1,3-bis(diphenylphosphino)propane – under CO atmosphere in refluxing toluene for 5 hours, to produce the bicyclo[5.3.0] derivative **18** in 76% yield (Scheme 4).[10] Conditions involving the use of 10 mol% of commercially available $[Rh(CO)_2Cl]_2$ in toluene at 90 °C for 5 hours under a CO atmosphere were also tested and led to **18** in 80% yield;[11] these latter conditions were preferred for simplicity's sake.

Conclusion

In summary, we report here preliminary studies towards a new approach of the synthesis of the highly functionalized bicyclo-[5.3.0]decadienone ring system of thapsigargin, starting from the C7-centered enantiopure epoxide **10** easily accessible by means of an asymmetric Sharpless epoxidation. Around the pivotal starting block **10** is then articulated the stereocontrolled implementation of the different substituents leading to the intermediate allenyne **17**, precursor of the P.K.R. double annelation reaction. The synthetic sequence used to prepare the desired 5-7 bicyclic dienone **18** allows high and reproducible yields and selectivities.

Application of the present approach to the total synthesis of thapsigargin **1** is currently in progress in our laboratories.

Experimental section

General remarks

All commercially available reagents and solvents (Fluka, Aldrich, Acros, Fisher) were used without further purification. For reactions requiring anhydrous conditions, commercial dry solvents were directly used (Fluka, Aldrich) or freshly distilled prior to use (THF and Et_2O over sodium/benzophenone system, DCM and DMSO over calcium hydride and MeOH and EtOH over magnesium). Unless otherwise noted, experiments were carried out under argon. Reactions were monitored by TLC (Merck silica gel 60 F_{254} plates) with detection by use of UV light (254 nm and 366 nm) or a phosphomolybdic acid solution in EtOH (5%) followed by heating at 100–110 °C. Purifications were performed by flash chromatography on silica gel (Merck silica gel 60, 40–63 μm). ^{1}H NMR spectra were recorded with Bruker AVANCE 300 and AVANCE 400 spectrometers at 300 and 400 MHz, respectively. Chemical shifts are given in ppm relative to the residual ^{1}H solvent signal ($CDCl_3$: δ = 7.26 ppm) as the internal reference. ^{1}H NMR assignments were confirmed by 2D COSY spectra. The given multiplicities reflect apparent signal patterns. ^{13}C NMR spectra were recorded with the same instruments as above at 100 MHz. Chemical shifts are given in ppm relative to the residual ^{13}C solvent signal ($CDCl_3$: δ = 77.0 ppm). ^{13}C NMR assignments were confirmed by 2D HSQC spectra. Coupling constants (J) are given in Hz for all NMR spectroscopic data. Melting points were measured with a Büchi 510 apparatus and are uncorrected. IR spectra were recorded with a Perkin Elmer Spectrum 65 FT-IR spectrometer. Mass spectra were recorded with the following instruments: ESI-MS: Waters ZQ 2000 spectrometer and ESI-TOF-HRMS: Waters LCT Premier spectrometer.

2-Triphenylmethoxymethyl-2-propenol **9** was synthesized according to a reported procedure, starting from ethyl 2-(triphenylmethoxymethyl)propenoate.[15]

(2*R*)-[2-(Triphenylmethoxymethyl)oxiran-2-yl]methan-1-ol (10). Sharpless epoxidation of **13** was carried out according to Kang procedure from 2-triphenylmethoxymethyl-2-propenol **9**.[9a] $[\alpha]_D^{22}$ −20.0 (*c* 1.5 in $CHCl_3$) (lit., −19.5 (*c* 1.5 in $CHCl_3$). Determination of ee *via* Mosher ester synthesis from (*R*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid [(+)-MTPA] or (*S*)-(−)-α-methoxy-α-(trifluoromethyl)phenyl acetic acid [(−)-MTPA], followed by ^{1}H NMR analysis (400 MHz; $CDCl_3$): ratio of integrals of CH_a doublets at δ 2.73 and 2.79 corresponds to up to 95 : 5.

(2*S*)-2-(Trityloxymethyl)hex-5-yne-1,2-diol (11). A mixture of magnesium turnings (4.74 g, 195 mmol), mercury(II) chloride (269 mg, 0.99 mmol) and a single crystal of iodide in freshly distilled diethyl ether (100 mL) was carefully treated with propargyl bromide (80% in toluene, 10.5 mL, 97.4 mmol) dissolved in freshly distilled diethyl ether (40 mL). After the reaction had started, the mixture was cooled to 0 °C and the rest of the propargyl bromide solution was added within 1 hour. After being cooled at 0 °C for an additional hour the reaction mixture was warmed to room temperature and stirred for another hour. Epoxide **10** (3.75 g, 10.8 mmol) was dissolved in anhydrous THF and cooled to −78 °C. Under vigorous stirring, this solution was treated with freshly prepared propargylmagnesium bromide (84 mL, 10.84 mmol) very slowly within 1 hour and the mixture was slowly warmed to room temperature. After 3 hours the reaction was quenched with saturated aqueous NH_4Cl. The solution was extracted with diethyl ether (3×). The combined extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The crude residue was purified by flash chromatography on silica gel (pentane/ethyl acetate 80 : 20 to 75 : 25) to yield the expected diol **11** (4 g, 95%) as a colorless oil. $[\alpha]_D^{22}$ −9.6 (*c* 1.5 in $CHCl_3$); ν_{max}/cm^{-1} 3418, 3296, 3061, 2929, 1491, 1449, 1224, 1074, 766, 708; δ_H (400 MHz; $CDCl_3$): 7.28–7.44 (15 H, m), 3.61 (1 H, d, J = 11.5 Hz), 3.50 (1 H, d, J = 11.5 Hz), 3.20 (1 H, d, J = 9.3 Hz), 3.12 (1 H, d, J = 9.3 Hz), 2.66 (1 H, s), 2.22–2.15 (2 H, m), 1.92 (1 H, t, J = 2.6 Hz), 1.81–1.76 (2 H, m), 1.56 (1 H, s); δ_C (100 MHz; $CDCl_3$): 143.4, 128.6, 128.0, 127.3, 87.0, 84.6, 73.6, 68.5, 66.5, 66.2, 33.3, 12.4; *m*/*z* 409.1770 (MNa^+, $C_{26}H_{26}NaO_3$ requires 409.1779).

(4*S*)-*tert*-Butyl{5-[2-(4-methoxyphenyl)-4-(trityloxymethyl)-1,3-dioxolan-4-yl)pent-2-ynyloxy}dimethylsilane (12). Diol **11** (4.31 g, 11.2 mmol) was dissolved in dry CH_2Cl_2 (8 mL) before addition, at room temperature, of *p*-anisaldehyde dimethylacetal (3.8 mL, 22.3 mmol) and PPTS (280 mg, 1.12 mmol). The mixture was stirred at room temperature for 2 hours and the solvent removed under reduced pressure. The crude product was dissolved in CH_2Cl_2 before addition of a small quantity of PPTS and a drop of water. The mixture was stirred for 30 min then quenched with an aqueous saturated solution of $NaHCO_3$ and extracted with CH_2Cl_2 (3×), the organic layers were combined, washed with brine, dried over $MgSO_4$ and the solvent removed under reduced pressure. The crude residue was dissolved in an anhydrous mixture of THF/MeOH (50 : 2.5 mL). Sodium borohydride (633 mg, 16.7 mmol) was added at 0 °C. The mixture was stirred 30 min at 0 °C, quenched with an aqueous saturated solution of NH_4Cl and extracted with CH_2Cl_2 (3×); the organic layers were combined, washed with brine, dried over $MgSO_4$ and the solvent removed under reduced pressure. The crude residue was purified by flash chromatography on silica gel (pentane/ethyl acetate 90 : 10) to afford (4*S*)-4-(but-3-ynyl)-2-(4-methoxyphenyl)-4-(trityloxymethyl)-1,3-dioxolanes, (4.2 g, 75%, unseparated 1.3 : 1 mixture of diastereomers) as a colorless oil. ν_{max}/cm^{-1} 3292, 2934, 2293, 1615, 1517, 1448, 1375, 1250, 1072, 1033, 918, 834, 748, 704; *m*/*z* 527.2205 (MNa^+,

$C_{34}H_{32}NaO_4$ requires 527.2198). Major diastereomer: δ_H (400 MHz; $CDCl_3$): 7.55–7.28 (17 H, m), 6.96 (2 H, d, J = 8.6), 5.88 (1 H, s), 4.07 (1 H, d, J = 8.5), 3.98 (1H, d, J = 8.5 Hz), 3.84 (3 H, s), 3.32 (1 H, d, J = 9.6 Hz), 3.26 (1 H, d, J = 9.6 Hz), 2.31–2.27 (1 H, m), 2.19–2.06 (3 H, m), 1.95 (2 H, t, J = 2.7 Hz); δ_C (100 MHz; $CDCl_3$): 160.5, 143.6, 128.7, 128.1, 128.0, 127.8, 127.1, 113.8, 103.9, 86.8, 84.2, 81.9, 72.0, 68.3, 65.7, 55.2, 34.9, 13.0. Minor diastereomer: δ_H (400 MHz; $CDCl_3$): 7.55–7.28 (17 H, m), 6.99 (2 H, d, J = 8.6 Hz), 5.86 (1 H, s), 4.20 (1 H, d, J = 8.6 Hz), 3.88 (1H, d, J = 8.6 Hz), 3.82 (3 H, s), 3.23 (2 H, s), 2.31–2.27 (1 H, m), 2.19–2.06 (3 H, m), 1.98 (2 H, t, J = 2.7 Hz); δ_C (100 MHz; $CDCl_3$): 160.4, 143.5, 128.7, 128.1, 128.0, 127.8, 127.1, 113.6, 103.8, 86.6, 84.2, 81.9, 72.8, 68.4, 65.5, 55.2, 33.9, 13.0.

A solution of *n*-BuLi (1.6 M in hexane, 1.1 mL, 1.75 mmol) was added slowly to a stirred solution of the precedent 1.3 : 1 mixture of (4*S*)-4-(but-3-ynyl)-2-(4-methoxyphenyl)-4-(trityloxymethyl)-1,3-dioxolanes (680 mg, 1.35 mmol) in anhydrous THF (3 mL), at −78 °C. The reaction mixture was stirred for 1 hour at −78 °C before addition of depolymerized paraformaldehyde (obtained by heating the polymer) (400 mg, 13.5 mmol). The reaction mixture was stirred for 10 min at −78 °C and then 30 min at room temperature. The mixture was quenched with an aqueous saturated solution of NH_4Cl and extracted with Et_2O (3×); the organic layers were combined, washed with brine, dried over $MgSO_4$; then the solvent was removed under reduced pressure. The crude oil was purified by flash chromatography on silica gel (pentane/ethyl acetate 80 : 20 to 70 : 30) to afford the expected primary alcohol, (4*S*)-5-[2-(4-methoxyphenyl)-4-(trityloxymethyl)-1,3-dioxolan-4-yl]pent-2-yn-1-ol, (513 mg, 71%, 1.3 : 1 mixture of diastereomers), as a colorless oil. ν_{max}/cm^{-1} 3519, 2943, 2253, 1615, 1518, 1448, 1375, 1250, 1072, 1034, 918, 834, 749, 710; *m/z* 557.2310 (MNa^+, $C_{35}H_{34}NaO_5$ requires 557.2304). Major diastereomer: δ_H (400 MHz; $CDCl_3$): 7.50–7.23 (17 H, m), 6.93 (2 H, d, J = 8.7 Hz), 5.83 (1 H, s), 4.20 (2 H, s), 4.03 (1 H, d, J = 8.5 Hz), 3.93 (1 H, d, J = 8.5 Hz), 3.82 (s, 3H), 3.24 (1 H, d, J = 9.6 Hz), 3.20 (1 H, d, J = 9.6 Hz), 2.32–2.19 (2 H, m), 2.12–1.93 (3 H, m); δ_C (100 MHz; $CDCl_3$): 160.5, 143.6, 128.7, 128.2, 128.1, 127.9, 127.1, 113.8, 103.9, 86.8, 86.1, 82.0, 78.4, 72.1, 65.7, 55.3, 51.4, 35.0, 13.3. Minor diastereomer: δ_H (400 MHz; $CDCl_3$): 7.50–7.23 (17 H, m), 6.85 (2 H, d, J = 8.7 Hz), 5.80 (1 H, s), 4.22 (2 H, s), 4.16 (1 H, d, J = 8.6 Hz), 3.82 (1 H, d, J = 8.6 Hz), 3.80 (3 H, s), 3.16 (2 H, s), 2.32–2.19 (2 H, m), 2.12–1.93 (3 H, m); δ_C (100 MHz; $CDCl_3$): 160.5, 143.6, 128.7, 128.2, 128.1, 127.9, 127.1, 113.7, 103.8, 86.8, 86.1, 82.0, 78.4, 72.9, 65.5, 55.3, 51.4, 34.0, 13.3.

TBDMSCl (558 mg, 3.71 mmol) and imidazole (526 mg, 7.73 mmol) were successively added to a stirred solution of the precedent mixture of alcohols (1.65 g, 3.09 mmol) in anhydrous CH_2Cl_2 (20 mL), at room temperature. The mixture was stirred for 1 hour at room temperature, quenched with an aqueous saturated solution of NH_4Cl and extracted with CH_2Cl_2 (3×); the organic layers were combined, washed with brine, dried over $MgSO_4$ and the solvent removed under reduced pressure. The crude residue was purified by flash chromatography on silica gel (pentane/ethyl acetate 98 : 2 to 95 : 5) to yield the expected ether **12** (1.9 g, 95%, 1.3 : 1 mixture of diastereomers), as a colorless oil. ν_{max}/cm^{-1} 2928, 2856, 1615, 1517, 1448, 1249, 1071, 834, 777, 703; *m/z* 671 (MNa^+); *m/z* 671.3188 (MNa^+, $C_{41}H_{48}NaO_5Si$ requires 671.3169). Major diastereomer: δ_H (400 MHz; $CDCl_3$): 7.49–7.25 (17 H, m), 6.91 (2 H, d, J = 8.7 Hz), 5.81 (1H s,), 4.27 (2 H, s), 4.01 (1 H, d, J = 8.5 Hz), 3.90 (1 H, d, J = 8.5 Hz), 3.82 (3 H, s), 3.22 (1 H, d, J = 9.6 Hz), 3.15 (1 H, d, J = 9.6 Hz), 2.30–2.20 (2 H, m), 2.09–2.00 (2 H, m), 0.91 (9 H, s), 0.11 (6 H, s); δ_C (100 MHz; $CDCl_3$): 160.5, 143.6, 128.7, 128.2, 128.1, 127.9, 127.1, 113.8, 103.9, 86.8, 84.9, 82.0, 78.8, 72.1, 65.7, 55.3, 51.9, 35.1, 34.0, 25.9 13.4, −5.1. Minor diastereomer: δ_H (400 MHz; $CDCl_3$): 7.49–7.25 (17 H, m), 6.85 (2 H, d, J = 8.6 Hz), 5.80 (1 H, s), 4.29 (2 H, s), 4.13 (1 H, d, J = 8.6 Hz), 3.83 (1 H, d, J = 8.6 Hz), 3.80 (3 H, s), 3.16 (2 H, s), 2.30–2.20 (2 H, m), 2.09–2.00 (2 H, m), 0.92 (9 H, s), 0.12 (6 H, s); δ_C (100 MHz; $CDCl_3$): 160.5, 143.6, 128.7, 128.2, 128.1, 127.9, 127.1, 113.7, 103.9, 86.8, 84.9, 82.0, 78.8, 72.8, 65.6, 55.3, 51.9, 35.1, 34.0, 25.9 13.4, −5.1.

(2*R*)-7-(*tert*-Butyldimethylsilyloxy)-2-(4-methoxybenzyloxy)-2-(trityloxymethyl)hept-5-yn-1-ol (13) and (2*R*)-7-(*tert*-butyldimethylsilyloxy)-1-(4-methoxybenzyloxy)-2-(trityloxymethyl)hept-5-yn-2-ol (14). DIBAL-H (1.1 M in cyclohexane, 4.2 mL, 4.67 mmol) was added at −78 °C over 3.5 h to a stirred solution of the PMP acetal **12** (605 mg, 0.934 mmol) in anhydrous CH_2Cl_2 (10 mL). The mixture was stirred for 1 hour at −78 °C, quenched with an aqueous solution of NaOH 4 M and extracted with CH_2Cl_2 (3×); the organic layers were combined, washed with brine, dried over $MgSO_4$ and the solvent removed under reduced pressure. The crude residue was purified by flash chromatography on silica gel (pentane/ethyl acetate 98 : 2 to 95 : 5) to yield in order of elution the required primary alcohol **13**, (370 mg, 61%) and the secondary alcohol **14** (73 mg, 12%) as colorless oils. **13**: $[\alpha]_D^{22}$ −5.9 (*c* 1.0 in $CHCl_3$); ν_{max}/cm^{-1} 3476, 2929, 2857, 1613, 1514, 1249, 1076, 836, 777, 707; δ_H (400 MHz; $CDCl_3$): 7.46–7.17 (17 H, m), 6.82 (2 H, d, J = 8.7 Hz), 4.36 (1 H, d, J = 10.5 Hz), 4.32 (1 H, d, J = 10.5 Hz), 4.27 (2 H, s), 3.79 (3 H, s), 3.74 (2 H, d, J = 6.9 Hz), 3.31 (1 H, d, J = 9.6 Hz), 3.07 (1 H, d, J = 9.6 Hz), 2.21–2.18 (1 H, m), 2.09–1.92 (3 H, m), 1.87 (1 H, t, J = 6.9 Hz), 0.91 (9 H, s), 0.11 (6 H, s); δ_C (100 MHz; $CDCl_3$): 159.1, 143.5, 130.6, 129.1, 128.7, 127.9, 127.1, 113.8, 86.8, 85.2, 78.7, 78.6, 63.9, 63.7, 63.6, 55.3, 51.9, 29.9, 25.9, 12.4, −5.1; *m/z* 673.3318 (MNa^+, $C_{41}H_{50}NaO_5Si$ requires 673.3325). **14**: $[\alpha]_D^{22}$ +1.9 (*c* 0.62 in $CHCl_3$); ν_{max}/cm^{-1} 3554, 2928, 1514, 1449, 1249, 835, 775; δ_H (400 MHz; $CDCl_3$): 7.42–7.18 (17 H, m), 6.86 (2 H, d, J = 8.6 Hz), 4.47 (2 H, s), 4.25 (2 H, s), 3.81 (3 H, s), 3.58 (1 H, d, J = 9.0 Hz), 3.47 (1H, d, J = 9.0 Hz), 3.14 (1 H, d, J = 8.8 Hz), 3.04 (1 H, d, J = 8.8 Hz), 2.47 (1H, s), 2.19–2.05 (2 H, m), 1.84 (1H, d, J = 8.3 Hz), 1.81 (1H, d, J = 8.3 Hz), 0.90 (9 H, s), 0.10 (6 H, s); *m/z* 673.3337 (MNa^+, $C_{41}H_{50}NaO_5Si$ requires 673.3325).

(4*S*,5*S*)-10-(*tert*-Butyldimethylsilyloxy)-5-(4-methoxybenzyloxy)-5-(trityloxymethyl)deca-2,8-diyn-4-ol (6*S*-15). Dess–Martin reagent (509 mg, 1.2 mmol) was added to a stirred solution of **13** (520 mg, 0.8 mmol) in anhydrous CH_2Cl_2 (13 mL) at room temperature. The mixture was stirred for 45 min at room temperature and quenched with an aqueous solution of $Na_2S_2O_3$ and extracted with CH_2Cl_2 (3×); the organic layers were combined, washed with brine, dried over $MgSO_4$ and the solvent removed

under reduced pressure. A solution of propynyl magnesium bromide (0.5 M in THF, 8.0 mmol, 16 mL) was added to a stirred solution of the precedent crude aldehyde in anhydrous THF (1 mL) at −78 °C. The mixture was warmed to room temperature and stirred for 2 hours. The reaction was quenched with an aqueous solution of NH_4Cl and extracted with Et_2O (3×); the organic layers were combined, washed with brine, dried over $MgSO_4$ and the solvent removed under reduced pressure. The crude residue was purified by flash chromatography on silica gel (pentane/ethyl acetate 90 : 10) to afford the secondary alcohol **15** as a 1 : 1 mixture of epimers (396 mg, 72%, yellow oil). Dess–Martin reagent (492 mg, 1.16 mmol) was then added to a stirred solution of the latter alcohol (396 mg, 0.58 mmol) in anhydrous CH_2Cl_2 (10 mL) at room temperature. The mixture was stirred for 1 hour at room temperature, then quenched with an aqueous solution of $Na_2S_2O_3$ and extracted with CH_2Cl_2 (3×); the organic layers were combined, washed with brine, dried over $MgSO_4$ and the solvent removed under reduced pressure. The crude residue was purified by flash chromatography on silica gel (pentane/ethyl acetate 98 : 2 to 95 : 5) to afford pure (5*S*)-10-(*tert*-butyldimethylsilyloxy)-5-(4-methoxybenzyloxy)-5-(trityloxymethyl)deca-2,8-diyn-4-one, (360 mg, 90%) as a yellow oil. $[\alpha]_D^{22}$ −8.7 (*c* 1.0 in $CHCl_3$); ν_{max}/cm^{-1} 2929, 2857, 2218, 1675, 1515, 1250, 1079, 837, 707; δ_H (400 MHz; $CDCl_3$): 7.44–7.22 (17 H, m), 6.83 (2 H, d, *J* = 8.7 Hz), 4.34 (1 H, d, *J* = 10.2 Hz), 4.27 (2 H, s), 4.20 (1 H, d, *J* = 10.2 Hz), 3.79 (3 H, s), 3.52 (1 H, d, *J* = 9.5 Hz), 3.25 (d, 1H, *J* = 9.5 Hz), 2.35–2.13 (2 H, m), 2.01 (3H, s), 1.86–1.92 (2 H, m), 0.91 (9 H, s), 0.11 (6 H, s); δ_C (100 MHz; $CDCl_3$): 189.5, 159.1, 143.1, 130.0, 129.1, 128.8, 127.8, 127.1, 113.7, 92.8, 86.7, 85.0, 84.5, 79.0, 78.9, 66.0, 63.2, 55.3, 51.9, 29.5, 25.9, 12.3, 4.38, −5.09; *m*/*z* 709.3333 (MNa^+, $C_{44}H_{50}NaO_5Si$ requires 709.3325).

BH_3–Me_2S (221 μL, 2.33 mmol) and (*R*)-Corey–Bakshi–Shibata [(*R*)-CBS)] reagent (1 M in toluene, 0.93 mL, 0.93 mmol) were successively added to a stirred solution of the preceding ketone (320 mg, 0.466 mmol) in anhydrous THF (4 mL) at −30 °C. The mixture was stirred at −30 °C for 1 hour and quenched slowly with EtOH and then with water. The aqueous layer was extracted with Et_2O (3×). The organic layers were combined, washed with brine, dried over $MgSO_4$ and the solvent removed under reduced pressure. The crude residue was purified by flash chromatography on silica gel (pentane–ethyl acetate 90 : 10) to give **(6*S*)-15** (250 mg, 78%, d.r. 90 : 10), as a colorless oil. ν_{max}/cm^{-1} 3529, 2928, 1613, 1514, 1449, 1249, 1075, 836, 777, 746, 707; δ_H (400 MHz; $CDCl_3$): 7.48–7.16 (17 H, m), 6.83 (2 H, d, *J* = 8.6 Hz), 4.81 (1 H, dq, *J* = 5.8, 2.0 Hz), 4.41 (1 H, d, *J* = 10.5 Hz), 4.30 (1 H, d, *J* = 10.5 Hz), 4.29 (2 H, s), 3.79 (3 H, s), 3.41 (1 H, d, *J* = 9.8 Hz), 3.22 (1 H, d, *J* = 9.8 Hz), 2.90 (1 H, d, *J* = 5.8 Hz), 2.35–2.06 (4 H, m), 1.86 (3 H, d, *J* = 2 Hz), 0.93 (9 H, s), 0.13 (6 H, s); δ_C (100 MHz; $CDCl_3$): 159.1, 143.2, 130.5, 129.2, 128.8, 127.9, 127.2, 113.7, 87.2, 85.4, 83.2, 79.5, 78.6, 77.2, 65.9, 64.6, 63.7, 55.3, 52.0, 30.0, 25.9, 12.9, 3.8, −5.1; *m*/*z* 711.3490 (MNa^+, $C_{44}H_{52}NaO_5Si$ requires 711.3482).

(6*S*,7*S*)-6-(4-Methoxybenzyloxy)-7-(methoxymethoxy)-6-(trityloxymethyl)deca-2,8-diyn-1-ol (16). DIPEA (50 μL, 0.64 mmol) and MOMCl (130 μL, 0.728 mmol) were successively added to a solution of alcohol **(6*S*)-15** (200 mg, 0.291 mmol) in anhydrous CH_2Cl_2 (2 mL) at 0 °C. The mixture was stirred at room temperature for 4 hours and quenched with water. The aqueous layers were extracted with CH_2Cl_2 (3×). The organic layers were combined, washed with brine, dried over $MgSO_4$ and the solvent removed under reduced pressure. The crude residue was purified by flash chromatography on silica gel (pentane/ethyl acetate 90 : 10) to yield the required pure MOM ether, (5*S*,6*S*)-6-(4-methoxybenzyloxy)-13,13,14,14-tetramethyl-5-(prop-1-ynyl)-6-(trityloxymethyl)-2,4,12-trioxa-13-silapentadec-9-yne, (170 mg, 80%, single diastereomer) as a colorless oil. $[\alpha]_D^{22}$ +33.4 (*c* 1.0 in $CHCl_3$); ν_{max}/cm^{-1} 2931, 1810, 1071, 905, 727, 648; δ_H (400 MHz; $CDCl_3$): 7.48–7.18 (17 H, m), 6.82 (2 H, d, *J* = 8.6 Hz), 4.93 (1 H, d, *J* = 6.6 Hz), 4.73 (1 H, q, *J* = 2.0 Hz), 4.59 (1 H, d, *J* = 6.6 Hz), 4.48 (2 H, s), 4.28 (2 H, s), 3.79 (3 H, s), 3.41 (1 H, d, *J* = 9.9 Hz), 3.35 (3 H, s), 3.33 (1 H, d, *J* = 9.9 Hz), 2.31–2.06 (4 H, m), 1.82 (3 H, d, *J* = 2 Hz), 0.91 (9 H, s), 0.12 (6 H, s); δ_C (100 MHz; $CDCl_3$): 158.7, 143.6, 131.6, 128.9, 128.6, 127.7, 127.0, 113.5, 94.6, 88.0, 85.7, 83.9, 79.8, 78.3, 75.3, 69.2, 65.0, 63.9, 56.1, 55.3, 52.0, 31.0, 25.9, 12.9, 3.7, −5.1; *m*/*z* 755.3753 (MNa^+, $C_{46}H_{56}NaO_6Si$ requires 755.3744).

A molar solution of HF.Py (1.65 mL, 1.64 mmol) was added to a solution of the preceding silyl ether (60 mg, 0.082 mmol) in anhydrous THF (0.6 mL) at 0 °C. The mixture was stirred at 0 °C for 10 min, warmed to room temperature, then stirred for 1 hour. The reaction was quenched with an aqueous solution of $NaHCO_3$ and extracted with Et_2O (3×). The organic layers were combined, washed with brine, dried over $MgSO_4$ and the solvent removed under reduced pressure. The crude residue was purified by flash chromatography on silica gel (pentane–ethyl acetate 90 : 10) to afford pure **16** (47 mg, 93%) as a colorless oil. $[\alpha]_D^{22}$ +34.9 (*c* 1.0 in $CHCl_3$); ν_{max}/cm^{-1} 2950, 1510, 1451, 1247, 1033, 755, 706; δ_H (400 MHz; $CDCl_3$): 7.49–7.18 (17 H, m), 6.81 (2 H, d, *J* = 8.6 Hz), 4.93 (1 H, d, *J* = 6.6 Hz), 4.79 (1 H, q, *J* = 2.1 Hz), 4.58 (1 H, d, *J* = 6.6 Hz), 4.49 (2 H, s), 4.19 (2 H, s), 3.79 (3 H, s), 3.38 (1 H, d, *J* = 8.8 Hz), 3.33 (3 H, s), 3.33 (1 H, d, *J* = 8.8 Hz), 2.33–2.02 (5 H, m), 1.82 (3 H, d, *J* = 2.1 Hz); δ_C (100 MHz; $CDCl_3$): 158.7, 143.6, 131.5, 128.9, 128.5, 127.7, 127.0, 113.5, 94.5, 85.7, 83.9, 79.8, 78.3, 75.3, 69.2, 65.0, 63.9, 56.1, 55.3, 52.0, 31.0, 25.9, 12.9, 3.7, −5.1; *m*/*z* 641.2868 (MNa^+, $C_{40}H_{42}NaO_6$ requires 641.2879).

(((*S*)-2-(4-Methoxybenzyloxy)-2-((*S*)-1-(methoxymethoxy)but-2-ynyl)-5-methylhepta-5,6-dienyloxy)methanetriyl)tribenzene (17). NEt_3 (11.6 μL, 0.084 mmol) and MsCl (6.5 μL, 0.084 mmol) were successively added to a solution of the primary alcohol **16** (47 mg, 0.076 mmol) in anhydrous CH_2Cl_2 (0.5 mL), at 0 °C, then the solution was stirred for 1 hour at room temperature. The mixture was quenched with an aqueous solution of NH_4Cl and extracted with CH_2Cl_2 (3×). The organic layers were combined, washed with brine, dried over $MgSO_4$ and the solvent removed under reduced pressure. The residue was passed through a short pad of silica gel to afford crude mesylate. To a solution of CuCN (27 mg, 0.304 mmol) and anhydrous LiCl (26 mg, 0.608 mmol) in THF (0.3 mL) was gradually added MeLi (1.6 M in Et_2O, 0.2 mL, 0.304 mmol) at −78 °C. Then the reaction mixture was warmed to −20 °C, and the solids dissolved at this temperature. The reaction mixture was cooled to −78 °C again, and the crude mesylate was added to the reaction mixture which was further

stirred for 1h30 at this temperature. The reaction mixture was quenched by addition of saturated aqueous NH_4Cl and extracted with Et_2O (5×). The organic layers were combined, washed with brine, dried over $MgSO_4$ and the solvent removed under reduced pressure. The crude residue was purified by flash chromatography on silica gel (pentane/ethyl acetate 98 : 2) to afford pure allene **17** (35 mg, 75% over 2 steps) as a colorless oil. $[\alpha]_D^{22}$ +50.9 (*c* 1.0 in $CHCl_3$); ν_{max}/cm^{-1} 2931, 1514, 1248, 1096, 1033, 704; δ_H (400 MHz; $CDCl_3$): 7.49–7.21 (17 H, m), 6.81 (2 H, d, *J* = 8.6 Hz), 4.93 (1 H, d, *J* = 6.6 Hz), 4.71 (1 H, q, *J* = 2.1 Hz), 4.60 (2 H, m), 4.58 (1 H, d, *J* = 6.6 Hz), 4.51 (2 H, s), 3.79 (3 H, s), 3.37 (1 H, d, *J* = 9.9 Hz), 3.36 (1 H, d, *J* = 9.9 Hz), 3.32 (3 H, s), 2.14–1.94 (3 H, m), 1.82 (3 H, d, *J* = 2.1 Hz), 1.77–1.72 (1 H, m), 1.64 (3 H, t, *J* = 3.0 Hz); δ_C (100 MHz; $CDCl_3$): 205.8, 158.7, 143.9, 131.9, 129.2, 129.0, 128.8, 127.7, 127.0, 113.6, 99.0, 94.6, 86.7, 83.7, 80.5, 75.6, 74.7, 69.7, 65.1, 64.0, 56.2, 55.3, 29.5, 26.6, 19.2, 3.9; *m*/*z* 639.3110 (MNa^+, $C_{41}H_{44}NaO_5$ requires 639.3086).

(4*S*,5*S*)-5-(4-Methoxybenzyloxy)-4-(methoxymethoxy)-3,8-dimethyl-5-(trityloxymethyl)-4,5,6,7-tetrahydroazulen-2(1*H*)-one (18). Protocol 1: Allene **17** (17 mg, 0.028 mmol) was dissolved in anhydrous toluene (0.3 mL) and the solution was evacuated and charged with Ar three times and with CO three times; then $[RhCl(cod)]_2$ (1.4 mg, 0.0028 mmol) and 1,3-bis(diphenylphosphino)propane (5.8 mg, 0.014 mmol) were added. The mixture was refluxed under CO balloon (1 atm) for 5 h. Most of the solvent was evaporated *in vacuo* and the resulting concentrated mixture was filtered through a pad of celite (washings with ether). The combined filtrates were evaporated *in vacuo*. The crude residue was purified by flash chromatography on silica gel (pentane/ethyl acetate 80 : 20) to yield the title ketone **18** (13.7 mg, 76%) as a colorless oil.

Protocol 2: Allene **17** (13 mg, 0.021 mmol) was dissolved in anhydrous toluene (0.3 mL) and the solution was evacuated and charged with argon three times, then with CO three times before addition of $[Rh(CO)_2Cl]_2$ (0.8 mg, 0.002 mmol). The mixture was heated at 90 °C under CO balloon (1 atm) for 5 h. Most of the solvent was evaporated *in vacuo* and the concentrated mixture filtered through a pad of celite (washings with ether). The combined filtrates were evaporated *in vacuo* and the crude residue purified by flash chromatography on silica gel (pentane–ethyl acetate 80 : 20) to yield **18** (10.3 mg, 80%) as a colorless oil. $[\alpha]_D^{22}$ +36.8 (*c* 1.0 in $CHCl_3$); ν_{max}/cm^{-1} 2924, 2852, 1694, 1611, 1513, 1449, 1247, 1149, 1097, 1033, 706; δ_H (400 MHz; $CDCl_3$): 7.48–7.20 (17 H, m), 6.87 (2 H, d, *J* = 8.7), 5.18 (1 H, s), 4.79 (1 H, d, *J* = 6.7 Hz), 4.60 (1 H, d, *J* = 11.2 Hz), 4.58 (1 H, d, *J* = 11.2 Hz), 4.55 (1 H, d, *J* = 6.7 Hz), 3.81 (3 H, s), 3.30 (1 H, d, *J* = 10.3 Hz), 3.26 (3 H, s), 3.06 (1 H, d, *J* = 10.3 Hz), 2.86–2.79 (1 H, d, *J* = 20.8 Hz), 2.63–2.56 (1 H, d, *J* = 20.8 Hz), 2.38–2.29 (1 H, m), 2.05–1.93 (1 H, m), 1.88–1.78 (2 H, m), 1.78 (3 H, s), 1.67 (3 H, s); δ_C (100 MHz; $CDCl_3$): 205.4, 160.4, 158.7, 143.2, 141.7, 135.1, 131.7, 129.1, 128.7, 128.2, 127.7, 127.0, 113.6, 95.9, 86.7, 80.4, 75.6, 64.9, 55.3, 40.3, 31.2, 30.3, 23.9, 8.71; *m*/*z* 667.3030 (MNa^+, $C_{42}H_{44}NaO_6$ requires 667.3036).

(*R*)-((*S*)-2-Hydroxy-2-(trityloxymethyl)pent-4-ynyl) 2-methoxy-2-phenylacetate. (*R*)-(–)-α-Methoxyphenylacetic acid (23 mg, 0.140 mmol), DMAP (4.0 mg, 0.035 mmol) and DCC (29 mg, 0.140 mmol) were successively added to a solution of diol **11** (45 mg, 0.116 mmol in anhydrous CH_2Cl_2 (1.5 mL), at room temperature. The mixture was stirred for 20 min and was filtered over a pad of celite. The solvent was removed under reduced pressure.[18] δ_H (400 MHz; $CDCl_3$): 7.40–7.25 (20 H, m), 4.72 (1 H, s), 4.26 (1 H, d, *J* = 11.2 Hz), 4.19 (1 H, d, *J* = 11.2 Hz), 3.38 (3 H, s), 3.06 (1 H, d, *J* = 9.2 Hz), 2.99 (1 H, d, *J* = 9.2 Hz), 2.06–1.97 (2 H, m), 1.86 (1 H, t, *J* = 2.6 Hz), 1.75–1.65 (2 H, m).

(*S*)-((*S*)-2-Hydroxy-2-(trityloxymethyl)pent-4-ynyl) 2-methoxy-2-phenylacetate. (*S*)-(+)-α-Methoxyphenylacetic acid (29 mg, 0.178 mmol), DMAP (5.0 mg, 0.044 mmol) and DCC (37 mg, 0.178 mmol) were successively added to a solution of diol **11** (57 mg, 0.148 mmol) in anhydrous CH_2Cl_2 (1.5 mL), at room temperature. The mixture was stirred for 20 min and was filtered over a pad of celite. The solvent was removed under reduced pressure.[18] δ_H (400 MHz; $CDCl_3$): 7.41–7.24 (20 H, m), 4.67 (1 H, s), 4.20 (2 H, s), 3.38 (3 H, s), 3.03 (3H, s), 1.99–1.91 (2 H, m), 1.83 (1 H, t, *J* = 2.6 Hz), 1.63–1.47 (2 H, m).

(*R*)-((4*S*,5*S*)-10-(*tert*-Butyldimethylsilyloxy)-5-(4-methoxybenzyloxy)-5-(trityloxymethyl)deca-2,8-diyn-4-yl) 2-methoxy-2-phenylacetate. (*R*)-(–)-α-Methoxyphenylacetic acid (5.6 mg, 0.034 mmol), DMAP (1.0 mg, 0.0083 mmol) and DCC (7 mg, 0.034 mmol) were successively added to a solution of alcohol **(6*S*)-15** (19 mg, 0.028 mmol) in anhydrous CH_2Cl_2 (1 mL), at room temperature. The mixture was stirred for 20 min and was filtered over a pad of celite. The solvent was removed under reduced pressure.[18] δ_H (400 MHz; $CDCl_3$): 7.48–7.14 (22 H, m), 6.76 (2 H, d, *J* = 8.7 Hz), 6.00 (1 H, q, *J* = 2.2 Hz), 4.65 (1 H, s), 4.26 (2 H, s), 4.21 (2 H, s), 3.78 (3 H, s), 3.34 (3 H, s), 3.30 (1 H, d, *J* = 9.9 Hz), 3.18 (1 H, d, *J* = 9.9 Hz), 2.17–1.96 (4 H, m), 1.70 (3 H, d, *J* = 2.2 Hz), 0.90 (9 H, s), 0.11 (6 H, s).

(*S*)-((4*S*,5*S*)-10-(*tert*-Butyldimethylsilyloxy)-5-(4-methoxybenzyloxy)-5-(trityloxymethyl)deca-2,8-diyn-4-yl) 2-methoxy-2-phenylacetate. (*S*)-(+)-α-Methoxyphenylacetic acid (5.7 mg, 0.035 mmol), DMAP (1.0 mg, 0.0087 mmol) and DCC (7 mg, 0.035 mmol) were successively added to a solution of alcohol **(6*S*)-15** (20 mg, 0.029 mmol) in anhydrous CH_2Cl_2 (1 mL), at room temperature. The mixture was stirred for 20 min and was filtered over a pad of celite. The solvent was removed under reduced pressure.[18] δ_H (400 MHz; $CDCl_3$): 7.48–7.14 (22 H, m), 6.76 (2 H, d, *J* = 8.7 Hz), 6.04 (1 H, q, *J* = 2.2 Hz), 4.79 (1 H, s), 4.25 (2 H, s), 4.09 (2 H, s), 3.78 (3 H, s), 3.35 (3 H, s), 3.20 (2 H, s), 2.21–2.02 (4 H, m), 1.78 (3 H, d, *J* = 2.2 Hz), 0.91 (9 H, s), 0.11 (6 H, s).

Acknowledgements

A. T. and M. J. thank ANR for doctoral fellowships (ANR Thaser 2010). We thank Elise Prost for assistance with NMR experiments.

Notes and references

1 A. Ghantous, H. Gali-Muhtasib, H. Vuorela, N. A. Saliba and N. Darwiche, *Drug Discovery Today*, 2010, **15**, 668.

2 (*a*) U. S. B. Rasmussen, S. B. Christensen and F. Sandberg, *Acta Pharm. Suec.*, 1978, **15**, 133; (*b*) G. Falsone, H. Haddad and D. Wendisch, *Arch. Pharm.*, 1986, **319**, 372; (*c*) A. Andersen, C. Cornett, A. Lauridsen, C. E. Olsen and S. B. Christensen, *Acta Chem. Scand.*, 1994, **48**, 340; (*d*) S. B. Christensen, A. Andersen and U. W. Smitt, *Prog. Chem. Nat. Prod.*, 1997, **71**, 129; (*e*) H. Liu, K. G. Jensen, L. M. Tran, M. Chen, L. Zhai, C. E. Olsen, H. Sohoel, S. R. Denmeade, J. T. Isaacs and S. B. Christensen, *Phytochemistry*, 2006, **67**, 2651; (*f*) A. Pagani, F. Pollastro, S. Spera, M. Ballero, O. Sterner and G. Appendino, *Nat. Prod. Commun.*, 2007, **2**, 637; (*g*) M. Lambert, J. L. Wolfender, D. Stærk, S. B. Christensen, K. Hostettmann and J. W. Jaroszewski, *Anal. Chem.*, 2007, **79**, 727. X-ray crystallography: (*h*) C. Toyoshima, M. Nakasako, H. Nomura and H. Ogawa, *Nature*, 2000, **405**, 647; (*i*) C. Toyoshima and H. Nomura, *Nature*, 2002, **418**, 605.

3 (*a*) Y. Furuya, P. Lundmo, A. D. Short, D. L. Gill and J. T. Isaacs, *Cancer Res.*, 1994, **54**, 6167; (*b*) Y. Gong, L. J. Blok, J. E. Perry, J. K. Lindzey and D. J. Tindall, *Endocrinology*, 1995, **136**, 2172.

4 (*a*) S. B. Christensen, A. Andersen, H. Kromann, M. Treiman, B. Tombal, S. Denmeade and J. T. Isaacs, *Bioorg. Med. Chem.*, 1999, **7**, 1273; (*b*) D. J. V. Grien, L. Antony, S. L. Dalrymple, Y. Xu, S. B. Christensen, S. R. Denmeade and J. T. Isaacs, *Mol. Cancer Ther.*, 2009, **8**, 1340; (*c*) J.-K. Huang, C.-T. Chou, H.-T. Chang, S.-S. Shu, C.-C. Kuo, J.-Y. Tsai, W.-C. Liao, J.-L. Wang, K.-L. Lin, Y.-C. Lu, I.-S. Chen, S.-I. Liu, C.-M. Ho and C.-R. Jan, *J. Recept. Signal Transduction*, 2011, **31**, 247; (*d*) M. Greiner, B. Kreutzer, S. Lang, V. Jung, A. Cavalié, G. Unteregger, R. Zimmermann and B. Wullich, *Prostate*, 2011, **71**, 1074.

5 (*a*) M. Ball, S. P. Andrews, F. Wierschem, E. Cleator, M. D. Smith and S. V. Ley, *Org. Lett.*, 2007, **9**, 663; (*b*) S. V. Ley, A. Antonello, E. P. Balskus, D. T. Booth, S. B. Christensen, E. Cleator, H. Gold, K. Hogenauer, U. Hunger, R. M. Myers, S. F. Oliver, O. Simic, M. D. Smith, H. Sohoel and A. J. Woolford, *Proc. Natl. Acad. Sci. U. S. A.*, 2004, **101**, 12073.

6 (*a*) S. F. Oliver, K. Högenauer, O. Simic, A. Antonello, M. D. Smith and S. V. Ley, *Angew. Chem., Int. Ed.*, 2003, **42**, 5996; (*b*) H. Sohoel, T. Liljefors, S. V. Ley, S. F. Oliver, A. Antonello, M. D. Smith, C. E. Olsen, J. T. Isaacs and S. B. Christensen, *J. Med. Chem.*, 2005, **48**, 7005; (*c*) S. P. Andrews, M. M. Tait, M. Balland and S. V. Ley, *Org. Biomol. Chem.*, 2007, **5**, 1427.

7 K. P. Kaliappan and R. S. Nandurdikar, *Org. Biomol. Chem.*, 2005, **3**, 3613.

8 F. L. Manzano, F. M. Guerra, F. J. Moreno-Dorado, Z. D. Jorge and G. M. Massanet, *Org. Lett.*, 2006, **8**, 2879.

9 (*a*) J.-H. Kang, M. A. Siddiqui, D. M. Sigano, K. Krajewski, N. E. Lewin, Y. Pu, P. M. Blumber, J. Lee and V. E. Marquez, *Org. Lett.*, 2004, **6**, 2413; (*b*) K.-i. Takao, Y. Kojima, T. Miyashita, Y. Kentaro, T. Yamada and K.-i. Tadano, *Heterocycles*, 2009, **77**, 167.

10 For Mukai's synthesis of various guaianolide skeletons through A.P.K. reactions see: (*a*) C. Mukai, I. Nomura, K. Hyamanishi and M. Hanaoka, *Org. Lett.*, 2002, **4**, 1755; (*b*) C. Mukai, I. Nomura and S. Kitagaki, *J. Org. Chem.*, 2003, **68**, 1376; (*c*) C. Mukai, F. Inagaki, T. Yoshida, K. Yoshitani, Y. Hara and S. Kitagaki, *J. Org. Chem.*, 2005, **70**, 7159; (*d*) T. Hirose, N. Miyakoshi and C. Mukai, *J. Org. Chem.*, 2008, **73**, 1061; (*e*) F. Inagaki, S. Narita, T. Hasegawa, S. Kitagaki and C. Mukai, *Angew. Chem., Int. Ed.*, 2009, **48**, 2007; (*f*) T. Kawamura, F. Inagaki, S. Narita, Y. Takahashi, S. Hirata, S. Kitagaki and C. Mukai, *Chem.–Eur. J.*, 2010, **16**, 5173; (*g*) Y. Hayashi, K. Ogawa, F. Inagaki and C. Mukai, *Org. Biomol. Chem.*, 2012, **10**, 4747.

11 For Brummond's synthesis of various guaianolide skeletons through A.P.K. reactions see: (*a*) K. M. Brummond, H. Chen, K. D. Fischer, A. D. Kerekes, B. Rickards, P. C. Still and S. J. Geib, *Org. Lett.*, 2002, **4**, 1931; (*b*) K. M. Brummond and D. Gao, *Org. Lett.*, 2003, **5**, 3491; (*c*) K. M. Brummond and D. Chen, *Org. Lett.*, 2008, **10**, 705; (*d*) F. Grillet, C. Huang and K. M. Brummond, *Org. Lett.*, 2011, **13**, 6304.

12 J. Ramharter and J. Mulzer, *Org. Lett.*, 2009, **11**, 1151.

13 For a direct asymmetric alkynylation, see for instance: (*a*) D. Boyall, D. E. Frantz and E. M. Carreira, *Org. Lett.*, 2002, **4**, 2605; for asymmetric reduction of α,β-ynones, see for instance: (*b*) E. J. Corey, R. K. Bakshi and S. Shibata, *J. Am. Chem. Soc.*, 1987, **109**, 5551; (*c*) E. J. Corey and C. J. Helal, *Angew. Chem., Int. Ed.*, 1998, **37**, 1986; (*d*) B. M. Trost, J. L. Gunzner, O. Dirat and Y. H. Rhee, *J. Am. Chem. Soc.*, 2002, **124**, 10396.

14 For clarity, thapsigargin carbon numeration has been maintained all over the theoretical part of the paper.

15 (*a*) J. Villieras and M. Rambaud, *Synthesis*, 1982, 924; (*b*) M. Honma, T. Sawada, Y. Fujisawa, M. Utsugi, H. Watanabe, A. Umino, T. Matsumura, T. Hagihara, M. Takno and M. Nakada, *J. Am. Chem. Soc.*, 2003, **125**, 2860.

16 In an initial approach, trityl ether was not the optimal protecting group in terms of orthogonality. Various ethers corresponding to 9 were prepared; however, among them, PMB (*p*-methoxybenzyl) and TBS (*tert*-butyldimethylsilyl) ethers have proved unstable when they are purified by flash chromatography and TBDPS (*tert*-butyldiphenylsilyl) ether led to significant lower yields than trityl ether (45% *versus* 75%) when subjected to Sharpless epoxidation.

17 The ee (90%) and absolute configuration of 11 have been confirmed again through the synthesis of the corresponding (*R*)- and (*S*)-α-methoxyphenylacetic acid (MPA) esters, proving the absence of Payne rearrangement.

18 Synthesis of (*R*)- and (*S*)-α-methoxyphenylacetic acid (MPA) esters: (*a*) B. M. Trost, D. O. O'Krongly and J. L. Belletire, *J. Am. Chem. Soc.*, 1980, **102**, 7595; (*b*) B. M. Trost and D. P. Curran, *Tetrahedron Lett.*, 1981, **22**, 4929; (*c*) B. M. Trost, J. L. Belletire, P. G. Goldleski, P. G. McDougal, J. M. Balkovec, J. J. Baldwin, M. Christy, G. S. Ponticello, S. L. Varga and J. P. Springer, *J. Org. Chem.*, 1986, **51**, 2370.

19 This modest regioselectivity is surprising but consistent with several literature results. Comparable (or even worse) regioselectivities were reported when the primary alcohol function of similar acetal core was protected by a sterically bulky group (for instance TBDPS). (*a*) K. J. Hale and J. Cai, *Tetrahedron Lett.*, 1996, **37**, 4233; (*b*) J. Xie and D. A. Hale, *Tetrahedron Lett.*, 2009, **50**, 4485; (*c*) J. Xie, Y. Ma and D. A. Horne, *Org. Lett.*, 2009, **11**, 5082; (*d*) J. Xie and D. A. Horne, *Tetrahedron Lett.*, 2009, **50**, 4485; (*e*) J. Xie, Y. Ma and D. A. Horne, *Tetrahedron*, 2011, **67**, 7485; (*f*) P. D. O'Connor, C. K. Knight, D. Friedrich, X. Peng and L. A. Paquette, *J. Org. Chem.*, 2007, **72**, 1747; (*g*) S. Raghavan and T. Sreekanth, *Tetrahedron Lett.*, 2007, **48**, 9090.

20 D. B. Dess and J. C. Martin, *J. Org. Chem.*, 1983, **48**, 4155.

21 Recently, at the time when the present study was in progress in our laboratories, Brummond described the synthesis of racemic 6,12-guaianolide systems relatively close to our targets using an A.P.K. strategy[11d].

