Pergamon

SCIENCE DIRECT®

Tetrahedron 59 (2003) 2781–2791

TETRAHEDRON

New approach toward the total synthesis of (+)-aphidicolin by tandem transannular Diels–Alder/aldol strategy

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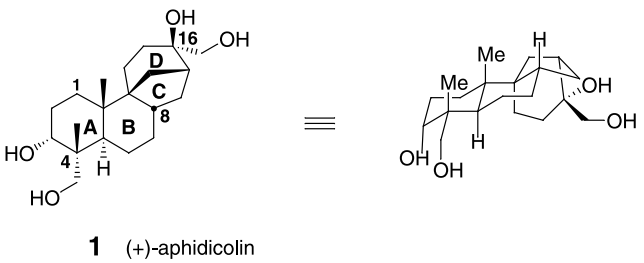
Received 16 January 2003; revised 10 March 2003; accepted 10 March 2003

Abstract—The synthesis of a 15-membered macrocyclic triene containing all the required substituents of ring A of (+)-aphidicolin (**1**) is reported. This compound underwent a thermal transannular cycloaddition followed by an intramolecular aldol reaction to yield tetracycle **32** containing 8 chiral centers which is considered a key intermediate for the synthesis of (+)-aphidicolin and related analogs.

1. Introduction

More than two decades ago, (+)-aphidicolin **1** (Fig. 1) was isolated from *Cephalosporium aphidicola*[1] and its structure was elucidated shortly thereafter.[2] This tetraolic compound is known to be active against *Herpes simplex* type 1 virus as well as being a DNA polymerase α-inhibitor in eucaryotic cells.[3,4] Besides these remarkable features, its unique molecular skeleton has attracted the synthetic chemists. Its synthesis has been the subject of intense research, having more than 10 groups achieving the total synthesis of **1**.[5] The hydroxymethyl group introduction at position 4 (Fig. 1) with good diastereoselectivity proved to be problematic in majority of previous work. This problem was finally tackled by Smith et al. in 1988, succeeding the transformation using a five-step process.[6]



1 (+)-aphidicolin

Figure 1. (+)-Aphidicolin in 2D and 3D.

2. Project review

The initial experiments conducted toward the total synthesis of (+)-aphidicolin employing the transannular Diels–Alder (TADA) strategy were carried out back in 1990.[7]

Model studies showed that *trans–cis–cis* (TCC) macrocyclic compound **2** (Scheme 1) only lead to decomposition when subjected to TADA conditions (thermal or Lewis acid catalyzed), the thermal version being limited by the fact that temperatures exceeding 200°C are causing *trans–cis* diene isomerization through [1,5]-H sigmatropic shift.[8] However, treatment of the corresponding *trans–trans–cis* (TTC) macrocycle **3** under basic conditions at 210°C furnished tetracyclic compound **4** after TADA/aldol reactions in tandem, with complete stereocontrol including the alcohol at position 11. Proper functionalization at C-16 was then performed by taking advantage of that feature.[7]

In the second generation, significant improvements were made to the general sequence and tetracyclic compound **4** was obtained, followed by appropriate functionalization at C-16 affording compound **5** (Scheme 2). The elaboration of ring A was then achieved in 10 steps. Unexpectedly, several problems were encountered, the major issue being the hydroxymethyl group introduction at C-4. Finally the synthesis of (11*R*)-(−)-8-epi-11-hydroxyaphidicolin **6** was completed.[9]

In order to circumvent the unexpected difficulty of introducing the C-4 hydroxymethyl group, it was decided to start with the advanced intermediate **10** (Scheme 3) that would give, after TADA/aldol reactions, the tetracyclic compound **7** having all the substituents of ring A. We thus like to report herein a new sequence that allowed the

Keywords: aphidicolin; transannular Diels–Alder; total synthesis; cycloaddition; diastereoselectivity.

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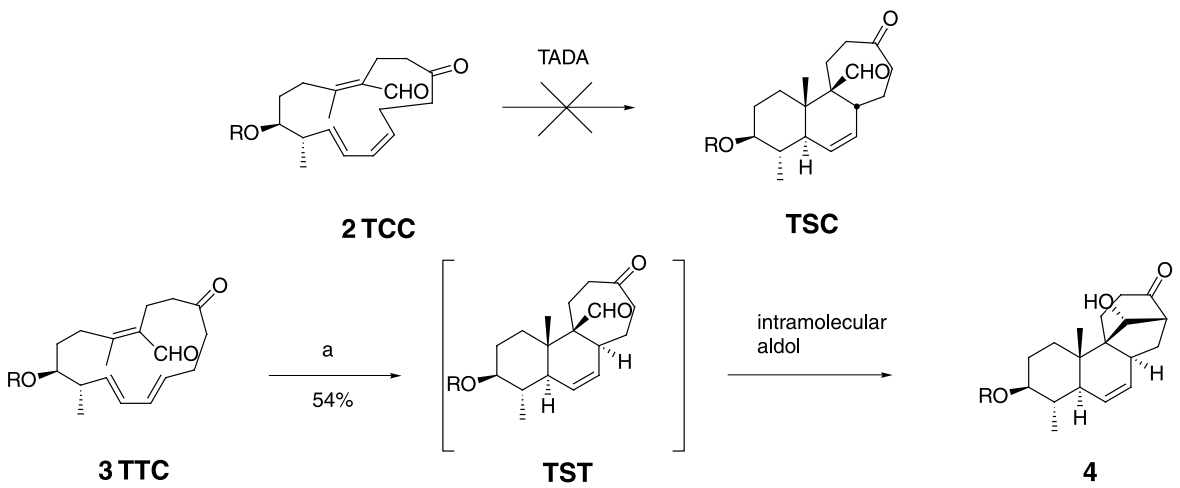
0040–4020/03/$ - see front matter
doi:10.1016/S0040-4020(03)00372-7

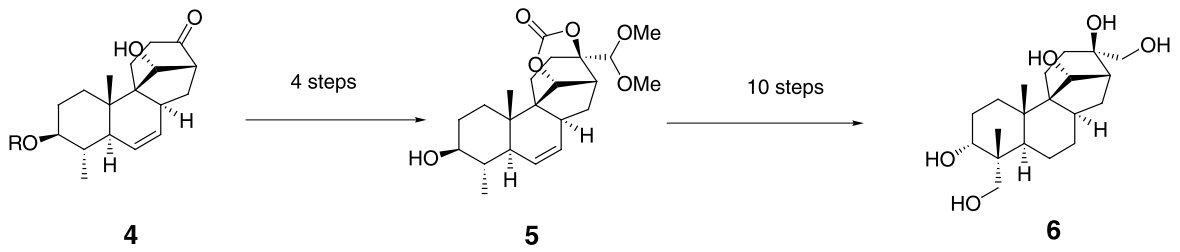


Scheme 1. (a) Toluene, Et_3N, sealed tube, 210°C, 18 h.

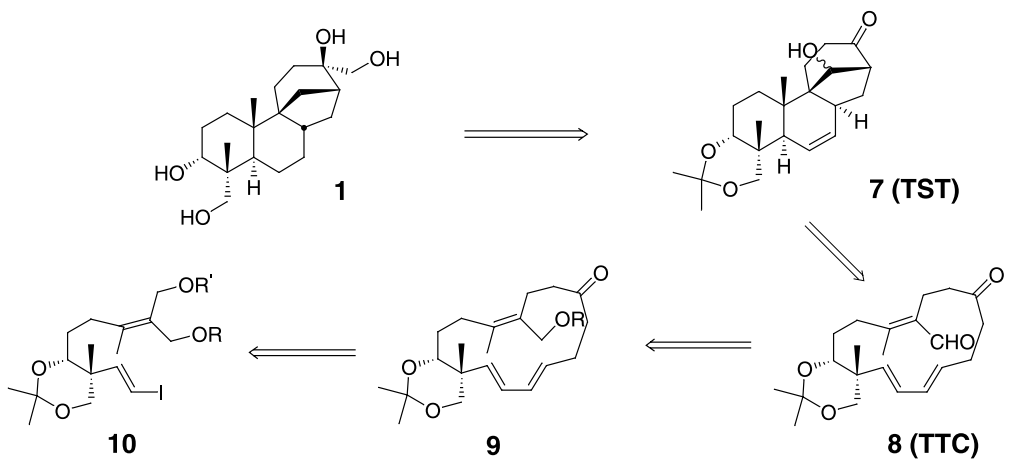
synthesis of this new tetracycle **7**, which can be viewed as a key intermediate for the total synthesis of (+)-aphidicolin and related analogs.

3. Results and discussion

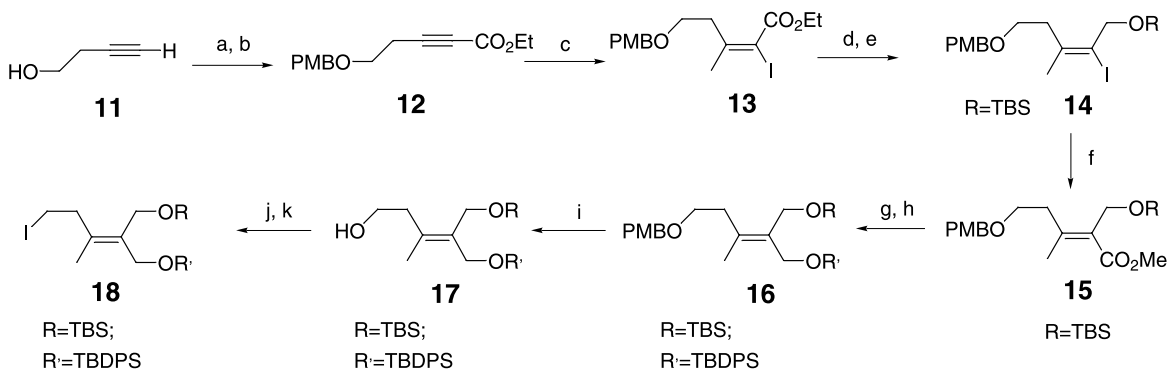
The strategy was started with the protection of 4-butynol as a PMB-ether using *p*-methoxybenzyl iodide,[10] followed by deprotonation at the alkyne position and quench with ethylchloroformate to afford compound **12** (Scheme 4). The latter was then submitted to an organocopper conjugate addition methodology reported previously by our group,[11] affording the vinylic iodide **13** in excellent yield. The ester function was then reduced and the resulting alcohol was protected to a TBDMS ether affording **14** in quantitative yield (2 steps). The vinylic iodide was then transformed to a methyl ester under palladium carbonylation conditions to give **15**.[12] The ester function was again reduced and the alcohol was protected as a TBDPS ether to afford **16**, allowing us to do selective deprotection later in the sequence. It should be noted that this sequence allowed us to obtain a well functionalized tetrasubstituted alkene with full control of the different substituents. The PMB ether was selectively cleaved to furnish the homo-allylic alcohol **17** that was protected as a mesylate which was in turn substituted under the Finkelstein conditions to give the desired iodide **18** with 72% yield (last 4 steps).



Scheme 2.



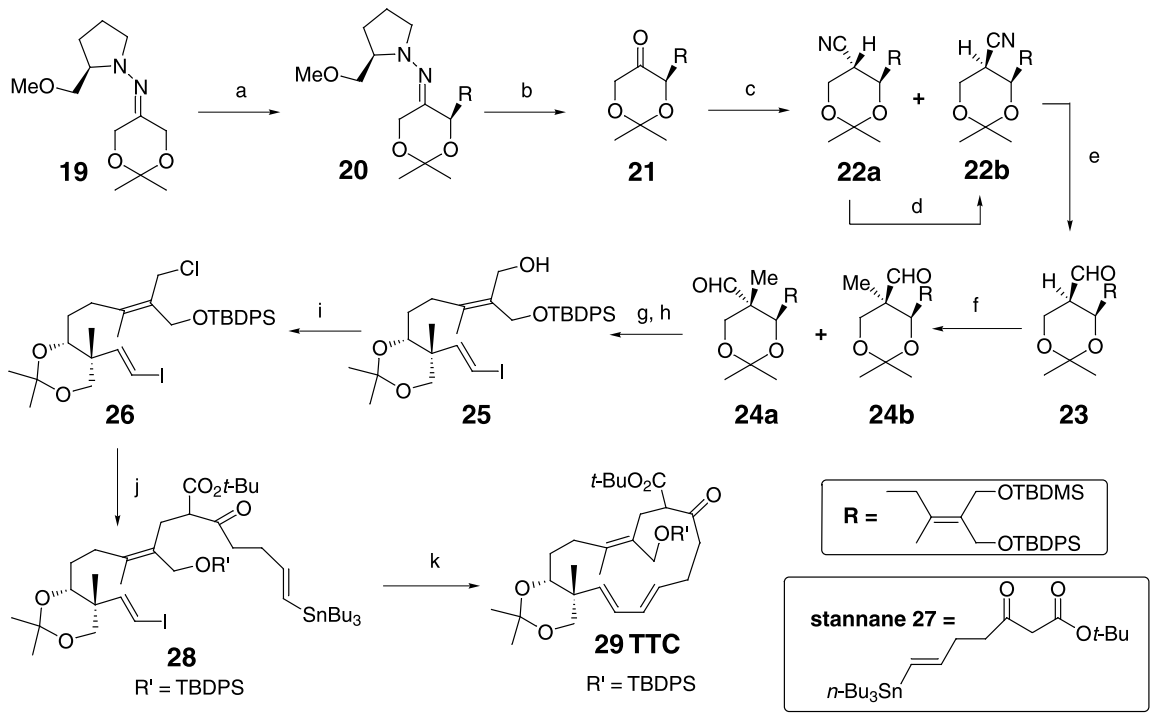
Scheme 3.



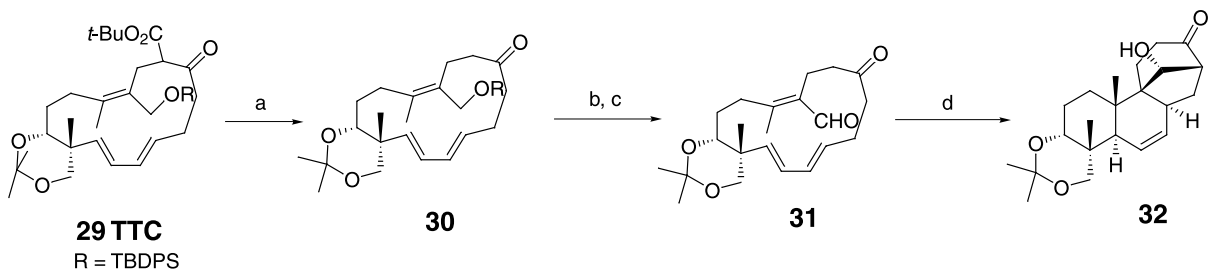
Scheme 4. (a) NaH, PMBI, room temperature, 15 h (68%); (b) *n*-BuLi, THF, $ClCO_2Et$, 2 h (81%); (c) CuI, MeLi, THF, −45°C, 1 h then I_2/THF, −45°C, 1 h and 0°C, 2 h (95%); (d) DIBAL/DCM, DCM:hexanes (2:1), −78°C, 2 h; (e) TBDMSCl, imidazole, DCM, room temperature, 15 h, quantitative (2 steps); (f) $PdCl_2(PPh_3)_2$, CO, MeOH, NMP, 70°C, 48 h (75%); (g) DIBAL/tol, toluene, −78°C, 1.5 h (66%); (h) TBDPSCl, imidazole, DCM, room temperature, 15 h; (i) DDQ, DCM/H_2O, 18:1, room temperature, 1 h; (j) MsCl, Et_3N, DCM, room temperature, 1.5 h; (k) NaI, acetone, reflux, 2.5 h (72%:4 steps).

In order to create chiral centers at position 3 and 4, we used the Enders' methodology[17] with iodide **18** as the electrophile. The anion of chiral hydrazone **19**[18] was generated by treatment with *t*-BuLi in THF at low temperature and reacted with iodide **18**, giving alkylated hydrazone **20** as the only diastereoisomer. Hydrolysis was then performed[13] to give chiral ketone **21**, which was treated with lithium cyanide[14] and diethylcyanophosphonate, yielding a mixture of cyanophosphonates. This mixture was then directly treated with samarium diiodide(II), affording an easily separable mixture of nitriles **22a** and **22b** with a ratio of 1:1.5, respectively.[15] Isomer **22a** was reconverted into **22b** by treatment under basic conditions. The nitrile **22b** was then reduced to the aldehyde **23** which was in turn methylated using conditions previously reported by our group;[16] treating product **23** with KH and then quenching with MeI at −16°C allowed us to get a clean mixture of the two alkylated products **24a** and **24b** with a ratio of 1:3.2, respectively.

The mixture was then directly submitted to Takaï homologation conditions[19] to afford the corresponding vinylic iodide. Selective TBDMS ether deprotection was then operated to furnish the pure allylic alcohol **25** after separation from its diastereoisomer. The alcohol was then transformed to corresponding chloride,[20] giving compound



Scheme 5. (a) *t*-BuLi, THF, −78°C, 2 h then −100°C, iodide **18**, 1 h then −78°C, 15 h (62% (98% corrected)); (b) sat'd oxalic acid solution/Et_2O (1:10), room temperature, 2.5 h (90%); (c) LiCN, $(Et_2O)POCN$, THF, room temperature, 1 h, then SmI_2, THF, room temperature, 2.5 h, 1.5:1 (**22b**:**22a**) (96%: combined yield); (d) MeONa/MeOH, room temperature, 3 days, 1:1.5 (**22b**:**22a**) (96%: combined yield); (e) (from **22b**), DIBAL/tol, toluene, −78°C, 1.5 h (89%); (f) KH, THF, 0°C, 5 min then −16°C, MeI, 2 h, 1:3.2 (**24a**:**24b**); (g) $CrCl_2$, CHI_3, 1,4-dioxane/THF (2:1), room temperature, 3 h; (h) PPTS, EtOH 95%, room temperature, 15 h (38%: 3 steps); (i) PPh_3, HCA, THF, −40°C (97%); (j) stannane **28**, acetone, Cs_2CO_3, CsI, 18-C-6, room temperature, 3 days (92%); (k) $PdCl_2(P(fur)_3)_2$, THF/DMF (1:1), DIPEA, 50°C, 3 h (56%) (conc.=2×10^{-3} M).



Scheme 6. (a) Toluene, Et_3N, 190°C, sealed tube, 15 h (68%); (b) TBAF, THF, room temperature, 24 h (77%); (c) Dess–Martin periodinane, DCM, room temperature, 1 h (80%); (d) toluene, Et_3N, 250°C, sealed tube, 48 h (77%).

26 which was transformed using classic β-ketoester alkylation with stannane **27**[21] to afford macrocyclic precursor **28**. Finally the macrocyclization was achieved using Stille coupling[22] to afford TTC macrocycle **29** (Scheme 5).

Decarboxylation occurred under thermal conditions (sealed tube, toluene, Et_3N, 190°C) to give compound **30** (Scheme 6). The TBDPS group was then cleaved and the corresponding alcohol was oxidized to desired aldehyde **31**, in order to test our TADA methodology. Interestingly, heating the macrocycle **31** at 250°C for 48 h led to the desired tetracyclic compound **32** with a 77% yield. The structure of compound **32** having the TST stereochemistry for the ABC tricyclic skeleton has been proven by X-ray analysis (Fig. 2).[23]

4. Conclusion

The enantioselective synthesis of tetracycle **32** was completed in 14 steps from **18** and **19**. X-Ray analysis of **32** shows that the two chiral centers introduced initially on the macrocycle (at pro C-3 and C-4) are perfectly controlling the creation of six new centers and three new rings. This spectacular transformation is of course due to the high degree of control at the transannular Diels–Alder cycloaddition followed by the intramolecular aldol reaction, the residual alcohol being also obtained in a diastereoselective manner. The tetracyclic compound **32** is featuring 8 chiral centers, all contiguous; from those three are quaternary centers, two being contiguous. We believe that this highly functionalized tetracyclic compound is an excellent key intermediate for the completion of (+)-aphidicolin synthesis and for the preparation of analogs. These results shows the versatility of the TADA methodology since we were able to use it with a well-functionalized macrocycle containing all the desired substituents of ring A. This again demonstrates the efficiency of the TADA methodology.[24]

5. Experimental

5.1. General

All the reactions were performed under N_2 atmosphere with flame dried glassware when necessary. Solvents were distilled and dried according to standard procedures. Analytical TLC were performed on pre-coated glass plates (0.25 mm) with silica gel 60F-250 (Merck). Flash chromatography was performed with 230–400 mesh gel 60 (Merck). ^1H and ^{13}C NMR spectra were recorded on a Brüker AC-300 and are referenced with respect to the residual signals of the solvent; they are described using standard abbreviations. IR spectra were recorded on a Perkin–Elmer 1600 FT-IR. Mass spectra were recorded on a ZAB-1F micromass spectrometer.

5.1.1. (*E*)-5-[(*p*-Methoxy)benzyloxy]-2-iodo-3-methyl-pent-2-ethylenoate (12). To a stirred suspension of sodium hydride (60 wt%/mineral oil, 2.09 g, 86.9 mmol) in tetrahydrofuran (200 mL) at 0°C was added a solution of 4-butynol **11** (4.7 mL, 62.1 mmol) in tetrahydrofuran

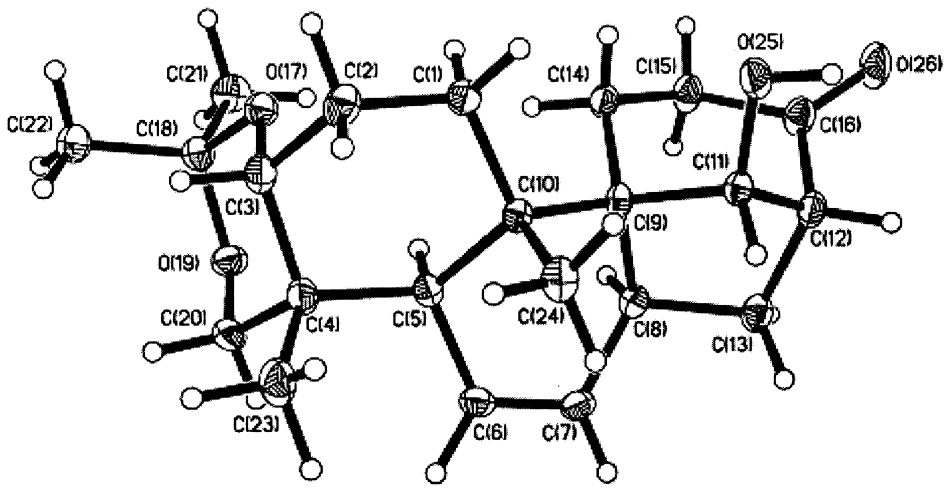


Figure 2. X-Ray structure of tetracycle **32**.

(50 mL) over a 5 min period. The reaction was stirred at room temperature for 3 h after which a solution of PMBI freshly prepared (13.9 g, 55.9 mmol) was added. The resulting mixture was stirred for 18 h at room temperature after that water (50 mL) was added. After being stirred for 1 h the mixture was extracted with diethyl ether (3×150 mL) and the combined organic phases were washed with brine, dried over magnesium sulfate, filtered and concentrated. The residue was purified by flash chromatography (10% ethyl acetate in hexanes) to give the protected alcohol (7.2 g, 68%, clear oil). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.27 (2H, d, J=8.5 Hz) and 6.88 (2H, d, J=8.5 Hz, Ph), 4.47 (2H, s, $PhCH_2O-$), 3.77 (3H, s, MeOPh−), 3.56 (2H, t, J=7.0 Hz, $BnOCH_2-$), 2.48 (2H, td, J=7.0, 2.5 Hz, CH_2CCH), 2.02 (1H, t, J=2.5 Hz, CH). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 159.3, 129.4, 129.3, 113.8, 81.4, 72.6, 69.5, 67.9, 55.2, 19.9. IR (film) ν 3292, 2934, 2863, 1613, 1513, 1248, 823. MS (EI): 190 $(M)^+$. HRMS $(M)^+$ calcd for $C_{12}H_{14}O_2$: 190.0944; found: 190.0989±0.0005.

To a solution of the previous alkyne (7.2 g, 37.9 mmol) in tetrahydrofuran (180 mL) at −78°C was added a solution of *n*-butyllithium (19 mL, 45.5 mmol, 2.39 M in hexanes). After stirring for 2 h a solution of freshly distilled ethylchloroformate (10.9 mL, 113.7 mmol) in tetrahydrofuran (20 mL, pre-cooled to −78°C) was added. The reaction solution was then stirred for another 2 h at −78°C after which a saturated aqueous ammonium chloride solution (50 mL) was added. The resulting mixture was extracted with diethyl ether (3×150 mL) and the combined organic phases were washed with brine, dried over magnesium sulfate, filtered and concentrated. The residue was purified by flash chromatography (10% ethyl acetate in hexanes) to give compound **12** (8.0 g, 81%, clear oil). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.21 (2H, d, J=8.5 Hz) and 6.82 (2H, d, J=8.5 Hz, Ph), 4.40 (2H, s, $PhCH_2O$), 4.14 (2H, q, J=6.7 Hz, $CO_2CH_2CH_3$), 3.77 (3H, s, MeOPh), 3.55 (2H, t, J=6.8 Hz, $BnOCH_2$), 2.54 (2H, t, J=6.8 Hz, CH_2C), 1.23 (3H, t, J=6.7 Hz, $CO_2CH_2CH_3$). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 158.9, 153.3, 129.3, 128.9, 113.4, 87.3, 74.5, 67.3, 62.4, 55.0, 20.2, 13.7. IR (film) ν 2993, 2240, 1710, 1251, 823. MS (EI): 262 $(M)^+$. HRMS $(M)^+$ calcd for $C_{15}H_{18}O_4$: 262.1205; found: 262.1201±0.0008.

5.1.2. (*E*)-5-[(*p*-Methoxy)benzyloxy]-2-iodo-3-methylpent-2-ethylenoate (13). To a suspension of copper(I) iodide (99.99%, 10.8 g, 56.8 mmol) in tetrahydrofuran (150 mL) at 0°C was added a solution of methyllithium (71 mL, 113.6 mmol, 1.6 M in Et_2O). After complete dissolution of the precipitate, the solution was cooled down to −45°C and then a cooled (−78°C) solution of acetylenic ester **12** (7.45 g, 28.4 mmol) in tetrahydrofuran (50 mL) was added. The reaction mixture was stirred for 1 h after which a cooled (−78°C) solution of iodine (21.6 g, 85.2 mmol) in tetrahydrofuran (50 mL) was slowly added. The resulting mixture was then stirred for 1 h at this temperature before being warmed-up to 0°C and stirred again for another 2 h. Excess reagents were quenched by the addition of a saturated aqueous ammonium chloride solution (50 mL) and a 10% ammonium hydroxide solution (50 mL). Extraction was performed using diethyl ether (3×200 mL) and ethyl acetate (1×150 mL) and the combined organic phases were washed with brine, dried over magnesium sulfate, filtered and concentrated. The residue was purified by flash chromatography (20% ethyl acetate in hexanes) to give compound **13** (10.9 g, 95%, yellowish oil). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.25 (2H, d, J=8.7 Hz) and 6.88 (2H, d, J=8.7 Hz, Ph), 4.42 (2H, s, $PhCH_2O$), 4.21 (2H, q, J=7.1 Hz, $CO_2CH_2CH_3$), 3.80 (3H, s, MeOPh), 3.57 (2H, t, J=6.8 Hz, $BnOCH_2$), 2.79 (2H, t, J=6.8 Hz, $CH_2C(CH_3)$=), 2.09 (3H, s, $C(CH_3)$=), 1.29 (3H, t, J=7.1 Hz, $CO_2CH_2CH_3$). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 166.2, 159.1, 151.7, 130.3, 129.2, 113.8, 87.1, 72.5, 68.1, 61.9, 55.3, 36.6, 30.2, 14.0. IR (film) ν 2941, 2862, 1713, 1610, 1512, 1462, 1364, 1246, 1094, 818. MS (EI): 405 $(MH)^+$. HRMS $(MH)^+$ calcd for $C_{16}H_{22}IO_4$: 405.0563; found: 405.0554±0.0012.

5.1.3. (*E*)-5-[(*p*-Methoxy)benzyloxy]-1-(*tert*-butyl) dimethyl silyloxy-2-iodo-3-methylpent-2-ene (14). To a solution of vinylic ester **13** (10.9 g, 26.9 mmol) in a mixture of dichloromethane/hexanes (2:1, 300 mL total) at −78°C was added slowly a solution of DIBAL-H (81 mL, 80.7 mmol, 1.0 M in DCM). The solution has been stirred for 2 h then quenched with ethyl acetate (20 mL) and then using an aqueous solution (1 M, 40 mL) of sodium and potassium tartrate (Rochelle salts). It was then warmed-up to room temperature and stirred for 4 h before extraction with diethyl ether (3×200 mL). The combined organic phases were washed with brine, dried over magnesium sulfate, filtered and concentrated. The crude product (9.7 g, quantitative, clear oil) was used as is for the next step. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.23 (2H, d, J=8.7 Hz) and 6.89 (2H, d, J=8.7 Hz, Ph), 4.44 (2H, s, $PhCH_2O$), 4.40 (2H, d, J=6.7 Hz, CH_2OH), 3.81 (3H, s, MeOPh), 3.48 (2H, t, J=5.7 Hz, $BnOCH_2$), 2.95 (1H, t, J=6.7 Hz, OH), 2.59 (2H, t, J=5.7 Hz, $CH_2C(CH_3)$=), 1.93 (3H, s, $-C(CH_3)$=). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 159.4, 141.4, 129.6, 129.2, 113.9, 104.0, 72.9, 69.2, 66.3, 55.3, 34.2, 29.8. IR (film) ν 3425, 2906, 2863, 1613, 1586, 1514, 1464, 1361, 1248, 823. MS (EI): 362 $(M)^+$. HRMS $(M)^+$ calcd for $C_{14}H_{19}IO_3$: 362.0379; found: 362.0369±0.0011.

To a stirred solution of the previous alcohol (9.7 g, 26.9 mmol) in dichloromethane (125 mL) at room temperature were successively added imidazole (2.2 g, 32.3 mmol) and *t*-butyldimethylchlorosilane (4.9 g, 32.3 mmol). The resulting mixture was stirred at room temperature for 15 h after which a saturated aqueous sodium bicarbonate was added (40 mL). Extraction was then performed using diethyl ether (3×75 mL) and the combined organic phases were washed with brine, dried over magnesium sulfate, filtered and concentrated. The residue was purified by flash chromatography (15% ethyl acetate in hexanes) to give compound **14** (12.8 g, quantitative, clear oil). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.24 (2H, d, J=8.7 Hz) and 6.88 (2H, d, J=8.7 Hz, Ph), 4.42 (2H, s, $PhCH_2O$), 4.37 (2H, s, $CH_2OTBDMS$), 3.81 (3H, s, MeOPh), 3.48 (2H, t, J=7.0 Hz, $BnOCH_2$), 2.60 (2H, t, J=7.0 Hz, $CH_2C(CH_3)$=), 1.98 (3H, s, $C(CH_3)$=), 0.92 (9H, s, $SiC(CH_3)_3$), 0.11 (6H, s, $Si(CH_3)_2$). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 159.1, 139.9, 130.3, 129.2, 113.8, 105.7, 72.6, 68.0, 67.7, 55.3, 34.7, 30.3, 26.0, 26.0, −5.0. IR (film) ν 2929, 2856, 1613, 1514, 1464, 1361, 1249, 1086, 837. MS (EI): 419 $(M^+-C_4H_9)$. HRMS $(M^+-C_4H_9)$ calcd for $C_{16}H_{24}ISiO_3$: 419.0539; found: 419.0534±0.0013.

5.1.4. (*E*)-5-[(*p*-Methoxy)benzyloxy]-1-(*tert*-butyl) dimethylsilyloxy-3-methylpent-2-methylenoate (15). To a solution of vinylic iodide **14** (6.4 g, 13.5 mmol) in NMP (50 mL) was added Et_3N (7.5 mL, 53.8 mmol) and methanol (16.3 mL, 403.5 mmol). The resulting solution was stirred with carbon monoxide bubbling for 15 min before the bis(triphenylphospine)palladium(II) dichloride (283 mg, 0.40 mmol) addition, after which some carbon monoxide was again bubbled through solution for 5 min. The flask was then transferred into a pressure vessel where a 300 psi carbon monoxide pressure was applied. The vessel was then heated to 70°C (temperature monitored using a probe inside the vessel) for 44 h, after which it was cooled down and gas was evacuated. The mixture was then quenched with the addition of a saturated aqueous ammonium chloride solution (50 mL) and extracted with diethyl ether/hexanes (1:1, 4×250 mL). The combined organic phases were washed with brine, dried over magnesium sulfate, filtered and concentrated. The residue was purified by flash chromatography (15% ethyl acetate in hexanes) to give compound **15** (4.1 g, 75%, yellowish oil). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.25 (2H, d, J=8.9 Hz) and 6.88 (2H, d, J=8.9 Hz, Ph), 4.43 (2H, s, $PhCH_2O$), 4.38 (2H, s, $CH_2OTBDMS$), 3.81 (3H, s, MeOPh), 3.73 (3H, s, CO_2CH_3), 3.52 (2H, t, J=7.1 Hz, $BnOCH_2$), 2.52 (2H, t, J=7.1 Hz, $CH_2C(CH_3)$=), 1.97 (3H, s, $C(CH_3)$=), 0.87 (9H, s, $SiC(CH_3)_3$), 0.04 (6H, s, $Si(CH_3)_2$). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 169.2, 159.1, 144.4, 130.3, 130.2, 129.2, 113.8, 113.8, 72.6, 68.12, 59.9, 55.3, 51.2, 35.8, 25.9, 21.5, −5.4. IR (film) ν 2952, 2856, 1721, 1613, 1514, 1464, 1361, 1302, 1249, 1214, 1094, 838. MS (EI): 351 ($M^+-C_4H_9$). HRMS ($M^+-C_4H_9$) calcd for $C_{18}H_{27}SiO_5$: 351.1628; found: 351.1620±0.0010.

5.1.5. (*E*)-5-[(*p*-Methoxy)benzyloxy]-1-methoxy(*tert*-butyl)diphenylsilyl-2-(*tert*-butyl)dimethylsilyloxy methylpent-2-ene (16). To a solution of vinylic ester **15** (6.8 g, 16.6 mmol) in toluene (100 mL) at −78°C was added slowly a solution of DIBAL-H (22.2 mL, 33.3 mmol, 1.5 M in toluene). The solution was stirred for 1.5 h and quenched with ethyl acetate (20 mL). The reaction mixture was then poured into an aqueous solution (1 M, 80 mL) of sodium and potassium tartrate (Rochelle salts). It was warmed-up to room temperature and stirred for 4 h before extraction with diethyl ether (3×200 mL). The combined organic phases were washed with brine, dried over magnesium sulfate, filtered and concentrated. The residue was purified by flash chromatography (20% ethyl acetate in hexanes) to give the corresponding alcohol (4.2 g, 66%, yellowish oil). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.24 (2H, d, J=8.7 Hz) and 6.88 (2H, d, J=8.7 Hz, Ph), 4.42 (2H, s, $PhCH_2O$), 4.34 (2H, s, $CH_2OTBDMS$), 4.23 (2H, s, CH_2OH), 3.80 (3H, s, MeOPh), 3.45 (2H, t, J=7.3 Hz, $BnOCH_2$), 2.39 (2H, t, J=7.3 Hz, $CH_2C(CH_3)$=), 1.79 (3H, s, $-C(CH_3)$=), 0.90 (9H, s, $SiC(CH_3)_3$), 0.08 (6H, s, $Si(CH_3)_2$). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 159.1, 133.0, 131.8, 130.4, 129.1, 129.1, 113.7, 72.6, 68.4, 61.8, 55.2, 34.8, 25.9, 18.9, 18.2, −5.4. IR (film) ν 3450, 2954, 2857, 1613, 1514, 1464, 1361, 1250, 1173, 1039, 836. MS (EI): 381 $(MH)^+$. HRMS $(MH)^+$ calcd for $C_{21}H_{37}SiO_4$: 381.2461; found: 381.2454±0.0011.

To a stirred solution of the previous alcohol (4.45 g, 11.7 mmol) in dichloromethane (100 mL) at 0°C were successively added imidazole (876 mg, 12.9 mmol) and *t*-butyldiphenylchlorosilane (3.34 mL, 12.9 mmol). The resulting mixture was stirred at room temperature for 15 h after which a saturated aqueous sodium bicarbonate was added (40 mL). Extraction was then performed using diethyl ether (3×100 mL) and the combined organic phases were washed with brine, dried over magnesium sulfate, filtered and concentrated. Compound **16** (7.24 g, quantitative, clear oil) was used as is for the next step but a small fraction was purified by flash chromatography (15% ethyl acetate in hexanes to give a clear oil). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.68 (4H, m) and 7.38 (6H, m) (2×Ph (TBDPS)), 7.26 (2H, d, J=8.7 Hz) and 6.87 (2H, d, J=8.7 Hz, Ph), 4.44 (2H, s, $PhCH_2O$), 4.29 (2H, s, $CH_2OTBDMS$), 4.26 (2H, s, $CH_2OTBDPS$), 3.80 (3H, s, MeOPh), 3.46 (2H, t, J=7.5 Hz, $BnOCH_2$), 2.43 (2H, t, J=7.5 Hz, $CH_2C(CH_3)$=), 1.50 (3H, s, $C(CH_3)$=), 1.02 (9H, s, $SiC(CH_3)_3$ (TBDPS)), 0.88 (9H, s, $SiC(CH_3)_3$ (TBDMS)), 0.05 (6H, s, $Si(CH_3)_2$). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 159.1, 135.7, 134.0, 133.8, 132.3, 130.6, 129.5, 129.2, 127.6, 127.5, 113.8, 72.6, 69.0, 60.7, 59.4, 55.3, 35.0, 26.9, 26.1, 19.3, 19.0, −5.2. IR (film) ν 3071, 2929, 2855, 1614, 1514, 1472, 1361, 1248, 1053, 836. MS (EI): 561 ($M^+-C_4H_9$). HRMS ($M^+-C_4H_9$) calcd for $C_{33}H_{45}Si_2O_4$: 561.2856; found: 561.2864±0.0017.

5.1.6. (*E*)-5-Hydroxy-1-methoxy(*tert*-butyl)diphenylsilyl-2-(*tert*-butyl)dimethylsilyloxy-3-methylpent-2-ene (17). To a solution of compound **16** (7.06 g, 11.4 mmol) in a mixture of dichloromethane/water (18:1, 190 mL) at room temperature was added in portions the 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (3.37 g, 14.8 mmol) over 5 min. The resulting mixture was then stirred for 1 h after that it was quenched using a saturated aqueous sodium bicarbonate solution (1 L) and extracted with diethyl ether (3×350 mL). The combined organic phases were washed with brine, dried over magnesium sulfate, filtered and concentrated. The crude compound **17** was used as is for the next step. A small fraction was purified by flash chromatography (15% ethyl acetate in hexanes to give a yellowish oil). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.68 (4H, m) and 7.39 (6H, m) (2×Ph (TBDPS)), 4.32 (2H, s, $CH_2OTBDMS$), 4.26 (2H, s, $CH_2OTBDPS$), 3.63 (2H, t, J=5.8 Hz, $HOCH_2$), 2.99 (1H, m, OH), 2.41 (2H, t, J=5.8 Hz, $CH_2C(CH_3)$=), 1.51 (3H, s, $C(CH_3)$=), 1.04 (9H, s, $SiC(CH_3)_3$ (TBDPS)), 0.90 (9H, s, $SiC(CH_3)_3$ (TBDMS)), 0.10 (6H, s, $Si(CH_3)_2$). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 135.6, 134.3, 134.2, 133.7, 129.6, 127.6, 61.6, 59.3, 58.9, 37.5, 26.8, 25.9, 19.2, 18.4, 17.8, −5.4. IR (film) ν 3440, 3050, 2954, 2857, 1662, 1590, 1472, 1428, 1361, 1256, 1036, 850. MS (EI): 441 ($M^+-C_4H_9$). HRMS ($M^+-C_4H_9$) calcd for $C_{25}H_{37}Si_2O_3$: 441.2281; found: 441.2288±0.0013.

5.1.7. (*E*)-5-Iodo-1-methoxy(*tert*-butyl)diphenylsilyl-2-(*tert*-butyl)dimethylsilyloxy-3-methylpent-2-ene (18). To a solution of the crude alcohol **17** (5.69 g, 11.4 mmol) in dichloromethane (60 mL) at 0°C was added successively triethylamine (6.32 mL, 45.6 mmol) and mesyl chloride (1.41 mL, 18.3 mmol). The mixture was stirred at the same temperature for 1.5 h after that it was quenched with a saturated aqueous sodium bicarbonate solution (40 mL) and extracted with diethyl ether (3×150 mL). The combined organic phases were washed with brine, dried over

magnesium sulfate, filtered and concentrated. The crude compound was used as is for the next step but a small fraction was purified by flash chromatography (15% ethyl acetate in hexanes to give a clear oil). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.67 (4H, m) and 7.39 (6H, m) (2×Ph (TBDPS)), 4.28 (2H, s, $CH_2OTBDMS$), 4.25 (2H, s, $CH_2OTBDPS$), 4.23 (2H, t, J=7.3 Hz, $CH_3SO_2CH_2$), 2.96 (3H, s, CH_3SO_2), 2.57 (2H, t, J=7.3 Hz, $CH_2C(CH_3)$=), 1.55 (3H, s, $C(CH_3)$=), 1.03 (9H, s, $SiC(CH_3)_3$ (TBDPS)), 0.89 (9H, s, $SiC(CH_3)_3$ (TBDMS)), 0.07 (6H, s, $Si(CH_3)_2$). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 135.6, 133.7, 130.0, 129.6, 127.7, 127.6, 68.4, 60.8, 59.4, 37.4, 34.3, 26.8, 26.0, 19.3, 18.7, 18.4, −5.3. IR (film) ν 3050, 2955, 2857, 1472, 1428, 1359, 1256, 1177, 1112, 1055, 950, 837. MS (EI): 519 ($M^+-C_4H_9$). HRMS ($M^+-C_4H_9$) calcd for $C_{26}H_{39}Si_2SO_2$: 519.2057; found: 519.2061±0.0016.

To a solution of the previous mesylate compound (6.58 g, 11.4 mmol) in acetone (100 mL) at room temperature was added sodium iodide (17.1 g, 114 mmol). The resulting mixture was then heated to reflux and stirred for 2.5 h. The solution was then cooled to room temperature, the solvent was evaporated and the residue was dissolved in dichloromethane (150 mL), filtered on celite and washed with dichloromethane (3×100 mL). The solvent was then evaporated and the residue was purified by flash chromatography (5% ethyl acetate in hexanes) to give the corresponding iodide **18** (5.09 g, 72% (4 steps), yellowish oil). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.68 (4H, m) and 7.39 (6H, m) (2×Ph (TBDPS)), 4.27 (2H, s, $CH_2OTBDMS$), 4.23 (2H, s, $CH_2OTBDPS$), 3.14 (2H, t, J=8.0 Hz, ICH_2), 2.68 (2H, t, J=8.0 Hz, $CH_2C(CH_3)$=), 1.49 (3H, s, $C(CH_3)$=), 1.03 (9H, s, $SiC(CH_3)_3$ (TBDPS)), 0.90 (9H, s, $SiC(CH_3)_3$ (TBDMS)), 0.08 (6H, s, $Si(CH_3)_2$). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 135.6, 134.5, 133.8, 129.6, 127.7, 127.6, 61.0, 59.4, 39.3, 26.8, 26.1, 19.3, 18.4, 17.9, 3.5, −5.2. IR (film) ν 3049, 2955, 2856, 1472, 1428, 1255, 1112, 1054, 836. MS (EI): 551 ($M^+-C_4H_9$). HRMS ($M^+-C_4H_9$) calcd for $C_{25}H_{36}ISi_2O_2$: 551.1298; found: 551.1289±0.0016.

5.1.8. Chiral hydrazone (20). To a solution of hydrazone **19** (2.86 g, 11.8 mmol, dried 2×benzene) in tetrahydrofuran (33 mL) at −78°C was added slowly *t*-butyllithium (8.77 mL, 12.98 mmol, 1.48 M in pentane). The solution was stirred for 2 h at the same temperature. It was then cooled down to −100°C. A pre-cooled (−78°C) solution of iodide **18** (8.8 g, 14.46 mmol) in tetrahydrofuran (10 mL) was then added via cannula and the resulting solution was stirred at −100°C for 1 h before being warmed-up to −78°C and stirred for 15 h. The reaction was quenched at −78°C using successively a buffer solution (pH=7, 30 mL) and brine (30 mL) and extracted with diethyl ether (3×150 mL). The combined organic phases were washed with brine, dried over magnesium sulfate, filtered and concentrated. The residue was purified by flash chromatography (10% ethyl acetate in hexanes with 2% triethylamine to neutralize the silica) to give alkylated hydrazone **20** (5.31 g, 62% (corrected yield for iodide 18:98%)), yellowish oil). $[\alpha]_D^{23}$=−52.9° (c=1.16, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.69 (4H, m) and 7.39 (6H, m) (2×Ph (TBDPS)), 4.5–4.2 (6H, m, 2×CH_2OR(silyls) and 2H), 3.95 (1H, d, J=12.5 Hz, COCHHC=N), 3.4–3.3 (2H, m), 3.31 (3H, s, CH_3OCH_2), 3.2–3.1 (2H, m), 2.6–1.5 (9H, m), 1.57 (3H, s, $C(CH_3)$=), 1.43 (3H, s) and 1.39 (3H, s) ($C(CH_3)_2$), 1.03 (9H, s, $SiC(CH_3)_3$ (TBDPS)), 0.89 (9H, s, $SiC(CH_3)_3$ (TBDMS)), 0.07 (6H, s, $Si(CH_3)_2$). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 160.6, 135.6, 134.9, 133.9, 133.1, 129.5, 127.6, 99.8, 76.0, 70.6, 66.7, 63.7, 60.5, 59.3, 59.1, 53.4, 29.7, 27.2, 27.1, 26.8, 26.5, 26.1, 24.4, 22.9, 19.3, 18.0, −5.2. IR (film) ν 3050, 2931, 2857, 1472, 1380, 1252, 1113, 1053, 836, 776. MS (EI): 722 $(M)^+$. HRMS $(M)^+$ calcd for $C_{41}H_{66}N_2Si_2O_5$: 722.4510; found: 722.4495±0.0022.

5.1.9. Ketone 21. To a solution of chiral hydrazone **20** (4.07 g, 5.63 mmol) in diethyl ether (100 mL) was added a saturated solution of oxalic acid (10 mL) at room temperature. The resulting solution was stirred for 2.5 h after which a saturated solution of sodium bicarbonate (30 mL) was slowly added. The mixture was extracted with diethyl ether (3×150 mL) and the combined organic phases were washed with brine, dried over magnesium sulfate, filtered and concentrated. The residue was purified by flash chromatography (10% ethyl acetate in hexanes) to give ketone **21** (3.08 g, 90%, clear oil). $[\alpha]_D^{23}$=+68.2° (c=1.06, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.69 (4H, m) and 7.39 (6H, m) (2×Ph (TBDPS)), 4.31 (2H, s, $CH_2OTBDMS$), 4.27 (1H, d, J=16.9 Hz, OCHHC=O), 4.26 (2H, s, CH_2-OTBDPS), 4.2 (1H, m, OCH(R)C=O), 3.99 (1H, d, J=16.9 Hz, OCHHC=O), 2.3–2.2 (2H, m, $CH_2C(CH_3)$=), 2.0–1.9 (1H, m) and 1.7–1.6 (1H, m) ($CHHCH_2C(CH_3)$=), 1.50 (3H, s, $C(CH_3)$=), 1.45 (6H, s, $C(CH_3)_2$), 1.03 (9H, s, $SiC(CH_3)_3$ (TBDPS)), 0.90 (9H, s, $SiC(CH_3)_3$ (TBDMS)), 0.07 (6H, s, $Si(CH_3)_2$). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 209.6, 135.6, 134.8, 134.0, 132.9, 129.5, 127.6, 100.7, 74.3, 66.6, 60.8, 59.2, 35.5, 29.7, 27.5, 26.8, 26.7, 26.1, 24.1, 23.6, 19.3, 18.5, 18.0, −5.3. IR (film) ν 3050, 2930, 2856, 1748, 1472, 1428, 1374, 1253, 1224, 1112, 1055, 837, 758. MS (EI): 553 (M^+ C_4H_9). HRMS ($M^+-C_4H_9$) calcd for $C_{31}H_{45}Si_2O_5$: 553.2805; found: 553.2802±0.0016.

5.1.10. Nitriles 22a and 22b. To a solution of ketone **21** (1.78 g, 2.91 mmol) in tetrahydrofuran (30 mL) at room temperature was successively added diethylcyanophosphonate (1.33 mL, 8.74 mmol) and lithium cyanide (288 mg, 8.74 mmol). The mixture was stirred for 1 h. Water (10 mL) was added and the reaction mixture was then extracted with ethyl acetate (3×80 mL) and the combined organic phases were washed with brine, dried over magnesium sulfate, filtered and concentrated. The cyanophosphonates was used as is for the next step.

Preparation of SmI_2: to a solution of diiodoethane (3.28 g, 11.7 mmol) (freshly washed: the product was dissolved in diethyl ether (30 mL) before being washed with a 1 M aqueous sodium thiosulfate solution (2×20 mL). The organic phase was then dried over magnesium sulfate, filtered and concentrated to give the desired white solid that was used directly) in tetrahydrofuran (30 mL) at room temperature was added samarium(0). The reaction was protected from light and a water bath was used to keep the temperature to 23°C since the reaction is quite exothermic. The mixture was then stirred for 2 h (away from light) before the addition of cyanophosphonates (in tetrahydrofuran (10 mL) using methanol (472 μL, 11.7 mmol)) as a proton source. The final solution was stirred in these

conditions for 2 h after that it was quenched by the addition of saturated aqueous ammonium chloride (20 mL) and 1N HCl (5 mL) before being extracted with diethyl ether (4×100 mL). The combined organic phases were washed with brine, dried over magnesium sulfate, filtered and concentrated. The residue was purified by flash chromatography (15% ethyl acetate in hexanes with 2% triethylamine to neutralize the silica) to give isomers **22a** and **22b** separately, with a 1:1.5 ratio, respectively (1.73 g, 96% (combined yield), yellowish oils).

Isomer **22a**. $[\alpha]_D^{23}=+8.35°$ ($c=1.03$, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.70 (4H, m) and 7.40 (6H, m) (2×Ph (TBDPS)), 4.4–4.3 (4H, m, 2×CH_2OR(silyls)), 4.1–3.9 (2H, m, $OCH_2C(CN)$), 3.9–3.8 (1H, m, OCH(R)C(CN)), 2.7–2.6 (1H, m, CH(CN)), 2.26 (2H, m, $CH_2C(CH_3)$═), 2.0–1.9 (1H, m) and 1.6–1.5 (1H, m) ($CHHCH_2C(CH_3)$═), 1.53 (3H, s, $C(CH_3)$═), 1.44 (3H, s) and 1.41 (3H, s) ($C(CH_3)_2$), 1.05 (9H, s, $SiC(CH_3)_3$ (TBDPS)), 0.91 (9H, s, $SiC(CH_3)_3$ (TBDMS)), 0.08 (6H, s, $Si(CH_3)_2$). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 135.6, 134.3, 133.9, 133.2, 129.6, 127.6, 117.3, 99.2, 69.3, 60.7, 60.6, 59.3, 32.8, 32.1, 29.2, 29.1, 26.8, 26.1, 19.3, 18.7, 17.9, −5.2. IR (film) ν 3060, 2942, 2860, 1467, 1426, 1385, 1256, 1197, 1115, 1051, 910, 845. MS (EI): 564 ($M^+-C_4H_9$). HRMS ($M^+-C_4H_9$) calcd for $C_{32}H_{46}Si_2NO_4$: 564.2965; found: 564.2955±0.0017.

Isomer **22b**. $[\alpha]_D^{23}=-1.07°$ ($c=1.22$, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.69 (4H, m) and 7.40 (6H, m) (2×Ph (TBDPS)), 4.30 (2H, m, $OCH_2CH(CN)$), 4.26 (2H, s, $CH_2OTBDMS$), 4.04 (2H, s, $CH_2OTBDPS$), 3.8 (1H, m, OCH(R)C(CN)), 2.61 (1H, m, CH(CN)), 2.3–2.2 (2H, m, $CH_2C(CH_3)$═), 1.9–1.8 (1H, m) and 1.7–1.6 (1H, m) ($CHHCH_2C(CH_3)$═), 1.51 (3H, s, $C(CH_3)$═), 1.47 (3H, s) and 1.41 (3H, s) ($C(CH_3)_2$), 1.04 (9H, s, $SiC(CH_3)_3$ (TBDPS)), 0.90 (9H, s, $SiC(CH_3)_3$ (TBDMS)), 0.07 (6H, s, $Si(CH_3)_2$). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 135.6, 134.4, 133.9, 133.2, 129.6, 127.6, 118.1, 99.5, 67.8, 61.1, 60.8, 59.3, 32.6, 32.5, 29.3, 26.8, 26.8, 26.1, 19.3, 18.7, 18.5, 17.9, −5.2. IR (film) ν 3050, 2955, 2857, 1621, 1472, 1428, 1384, 1253, 1200, 1049, 837, 758. MS (EI): 564 ($M^+-C_4H_9$). HRMS ($M^+-C_4H_9$) calcd for $C_{32}H_{46}Si_2NO_4$: 564.2965; found: 564.2955±0.0017.

Partial epimerization of **22a**. Metallic sodium (catalytic, washed 1×hexanes) was dissolved in methanol (10 mL) after which a solution of isomer **22a** (1.44 g, 2.31 mmol) in methanol (10 mL) was transferred *via cannula* at room temperature. The resulting solution was stirred for 3 days before being quenched with a saturated aqueous ammonium chloride solution (10 mL). The mixture was extracted with dichloromethane (4×75 mL) and the combined organic phases were dried over magnesium sulfate, filtered and concentrated. The residue was purified by flash chromatography (15% ethyl acetate in hexanes with 2% triethylamine to neutralize the silica) to give isomers **22a** and **22b** separately, with a 1.5:1 ratio, respectively (1.38 g, 96% (combined yield), yellowish oils).

5.1.11. Aldehyde 23. To a solution of nitrile **22b** (1.48 g, 2.38 mmol) in toluene (25 mL) at −78°C was added slowly a solution of DIBAL-H (2.38 mL, 3.57 mmol, 1.5 M in toluene). The reaction mixture was stirred for 1.5 h before the addition of ethyl acetate (10 mL). The reaction mixture was then poured into a saturated aqueous solution (40 mL) of sodium and potassium tartrate (Rochelle salts) and the resulting solution was stirred at room temperature for 30 min after which it was extracted with diethyl ether (4×150 mL). The combined organic phases were washed with brine, dried over magnesium sulfate, filtered and concentrated. The residue was purified by flash chromatography (20% ethyl acetate in hexanes, short column) to give aldehyde **23** as a clear oil (1.32 g, 89%). $[\alpha]_D^{23}=-7.93°$ ($c=1.88$, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 10.12 (1H, d, $J=4.1$ Hz, CHO), 7.69 (4H, m) and 7.38 (6H, m) (2×Ph (TBDPS)), 4.3–4.2 (4H, m, $CH_2OTBDMS$ and $OCH_2CH(CN)$), 4.1–4.0 (2H, m, $CH_2OTBDPS$), 4.04 (1H, m, $OCH(CH_2)$), 2.3–2.1 (2H, m, $CH_2C(CH_3)$═), 2.0 (1H, m, CH(CHO)), 1.8–1.6 (2H, m, $OCH(CH_2)$), 1.50 (3H, s, $C(CH_3)$═), 1.48 (3H, s) and 1.45 (3H, s) ($C(CH_3)_2$), 1.03 (9H, s, $SiC(CH_3)_3$ (TBDPS)), 0.90 (9H, s, $SiC(CH_3)_3$ (TBDMS)), 0.07 (6H, s, $Si(CH_3)_2$). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 204.8, 135.6, 134.5, 134.0, 133.0, 129.5, 127.6, 99.4, 69.6, 61.3, 60.8, 59.3, 49.9, 32.0, 29.9, 29.5, 26.8, 26.1, 19.3, 18.8, 18.0, −5.2. IR (film) ν 3050, 2955, 2857, 1723, 1472, 1428, 1382, 1256, 1198, 1112, 1054, 837, 703. MS (EI): 609 (M^+-CH_3). HRMS (M^+-CH_3) calcd for $C_{35}H_{53}Si_2O_5$: 609.3431; found: 609.3438±0.0018.

5.2. Alkylated aldehydes 24a and 24b

To a solution of aldehyde **23** (1.32 g, 2.11 mmol) in tetrahydrofuran (120 mL) at 0°C was added potassium hydride (847 mg, 21.1 mmol, washed 3×hexanes). The mixture was stirred for 5 min and it was cooled down to −16°C then a solution of methyl iodide (6.6 mL, 105.6 mmol) in tetrahydrofuran (10 mL) was transferred *via cannula*. The resulting solution was stirred at −16°C for 2 h and at 0°C for 30 min. The reaction mixture was quenched with a saturated aqueous solution of ammonium chloride (10 mL) and extracted with diethyl ether (3×100 mL). The combined organic phases were washed with brine, dried over magnesium sulfate, filtered and concentrated. The residue was used as is for the next step, the isomers were not separable by flash chromatography.

5.2.1. Allylic alcohol 25. To solid chromium dichloride(II) (2.6 g, 21.1 mmol, dried by heating under vacuum) was added successively 1,4-dioxan (30 mL) and tetrahydrofuran (20 mL) at room temperature. A solution of crude aldehydes **24a** and **24b** (1.34 g, 2.11 mmol) and iodoform (2.49 g, 6.34 mmol) in 1,4-dioxan (10 mL) was then added and the resulting mixture was stirred for 3 h. Water (15 mL) and brine (15 mL) were added and the solution was extracted with diethyl ether (3×150 mL) and diethyl acetate (1×100 mL). The combined organic phases were washed with brine, dried over magnesium sulfate, filtered and concentrated. The residue was used as is for the next step but a small fraction was purified by flash chromatography (5% ethyl acetate in hexanes to give a clear oil). $[\alpha]_D^{23}=-8.49°$ ($c=1.06$, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.69 (4H, m) and 7.39 (6H, m) (2×Ph (TBDPS)), 7.06 (1H, d, $J=14.9$ Hz, $C(CH_3)CH$═), 6.15 (1H, d, $J=14.9$ Hz, ═CHI), 4.3–4.2 (4H, m, 2×CH_2OR(silyls)), 3.63 (1H, d, $J=11.5$ Hz, $OCHHC(CH_3)$), 3.46 (2H, d, $J=11.5$ Hz,

OCHHC(CH_3) and OCH(CH_2)), 2.2–2.1 (2H, m, CH_2-C(CH_3)═), 1.48 (3H, s, C(CH_3)═), 1.44 (3H, s) and 1.42 (3H, s) (C(CH_3)$_2$), 1.3–1.2 (2H, m, OCH(CH_2)), 1.04 (9H, s, SiC(CH_3)$_3$ (TBDPS)), 0.90 (9H, s, SiC(CH_3)$_3$ (TBDMS)), 0.84 (3H, s, $OCH_2C(CH_3)$), 0.07 (6H, s, Si(CH_3)$_2$). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 147.9, 135.6, 135.2, 134.0, 132.7, 129.5, 127.6, 99.0, 76.1, 75.6, 70.0, 60.8, 59.4, 42.8, 30.2, 29.6, 28.5, 26.8, 26.1, 19.3, 18.8, 18.0, 17.5, −5.2. IR (film) ν 3070, 2955, 2857, 1472, 1383, 1256, 1202, 1112, 1057, 836. MS (EI): 747 (M^+-CH_3). HRMS (M^+-CH_3) calcd for $C_{37}H_{56}ISi_2O_4$: 747.2762; found: 747.2747±0.0022.

To the solution of the crude compound previously obtained (965 mg, 1.27 mmol) in ethanol 95% (12 mL) at room temperature was added a catalytic quantity of PPTS. The solution was stirred for 15 h before which a saturated aqueous solution of sodium bicarbonate (10 mL) was added. The mixture was then extracted with dichloromethane (3×50 mL) and the combined organic phases were dried over magnesium sulfate, filtered and concentrated. The residue was purified by flash chromatography (15% ethyl acetate in hexanes) to give alcohol **25** as a yellow oil (524 mg, 38% (3 steps)). $[\alpha]_D^{23}=-16.4°$ (c=1.63, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.70 (4H, m) and 7.42 (6H, m) (2×Ph (TBDPS)), 7.04 (1H, d, J=14.9 Hz, C(CH_3)CH═), 6.14 (1H, d, J=14.9 Hz, ═CHI), 4.35 (2H, s, CH_2OTBDPS), 4.3 (2H, m, CH_2OH), 3.63 (1H, d, J=11.5 Hz, OCHHC(CH_3)), 3.46 (1H, d, J=11.1 Hz, OCH(CH_2)), 3.45 (1H, d, J=11.5 Hz, OCHHC(CH_3)), 2.59 (1H, m, OH), 2.2–2.1 (2H, m, $CH_2C(CH_3)$═), 1.43 (6H, s, C(CH_3)$_2$), 1.41 (3H, s, C(CH_3)═), 1.4–1.3 (2H, m, OCH(CH_2)), 1.05 (9H, s, SiC(CH_3)$_3$), 0.83 (3H, s, OCH_2-C(CH_3)). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 147.9, 135.6, 135.1, 131.6, 129.9, 127.9, 127.8, 99.1, 76.1, 75.7, 69.9, 64.1, 61.3, 42.8, 30.2, 29.5, 28.6, 26.8, 19.1, 18.8, 17.8, 17.5. IR (film) ν 3472, 3070, 2932, 2858, 1472, 1428, 1384, 1263, 1202, 1112, 1058, 999, 824, 741, 703. MS (EI): 633 (M^+-CH_3). HRMS (M^+-CH_3) calcd for $C_{31}H_{42}ISiO_4$: 633.1897; found: 633.1893±0.0019.

5.2.2. Allylic chloride 26. To a solution of alcohol **25** (524 mg, 0.81 mmol) in tetrahydrofuran (15 mL) at room temperature was added triphenylphosphine (318 mg, 1.21 mmol). After complete dissolution the mixture was cooled down to −40°C and hexachloroacetone (184 μL, 1.21 mmol) was added. The solution was stirred at the same temperature for 30 min after which water (10 mL) and diethyl ether (10 mL) were added. The mixture was extracted with diethyl ether (3×70 mL) and the combined organic phases were washed with brine, dried over magnesium sulfate, filtered and concentrated. The residue was purified by flash chromatography (10% ethyl acetate in hexanes with 2% triethylamine to neutralize the silica) to give chloride **26** as a yellowish oil (522 mg, 97%). $[\alpha]_D^{23}=-22.6°$ (c=1.39, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.71 (4H, m) and 7.41 (6H, m) (2×Ph (TBDPS)), 7.07 (1H, d, J=14.9 Hz, C(CH_3)CH═), 6.18 (1H, d, J=14.9 Hz, ═CHI), 4.37 (2H, s, CH_2Cl), 4.32 (2H, s, CH_2OTBDPS), 3.66 (1H, d, J=11.5 Hz, OCHHC(CH_3)), 3.50 (1H, m, OCH(CH_2)), 3.48 (1H, d, J=11.5 Hz, OCHHC(CH_3)), 2.2–2.1 (2H, m, $CH_2C(CH_3)$═), 1.50 (3H, s, C(CH_3)═), 1.46 (3H, s) and 1.43 (3H, s) (C(CH_3)$_2$), 1.5–1.3 (2H, m, OCH(CH_2)), 1.07 (9H, s, SiC(CH_3)$_3$), 0.86 (3H, s, $OCH_2C(CH_3)$). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 147.8, 138.5, 135.6, 133.5, 130.1, 129.7, 127.7, 99.0, 76.1, 75.8, 69.9, 60.7, 42.8, 41.7, 30.5, 29.6, 28.3, 26.8, 19.3, 18.9, 18.1, 17.5. IR (film) ν 3065, 2931, 2857, 1472, 1428, 1383, 1261, 1202, 1112, 058, 824, 741, 702. MS (EI): 651 (M^+-CH_3). HRMS (M^+-CH_3) calcd for $C_{31}H_{41}ISiClO_3$: 651.1558; found: 651.1572±0.0019.

5.2.3. Macrocyclic precursor 28. To a solution of allylic chloride **26** (522 mg, 0.78 mmol) and stannane **27** in acetone (10 mL) at room temperature were added successively cesium carbonate (1.78 g, 5.48 mmol), cesium iodide (1.42 g, 5.48 mmol) and 18-C-6 crown ether (414 mg, 1.57 mmol) and the resulting mixture was stirred for 3 days. It was then quenched using a saturated aqueous solution of ammonium chloride (4 mL) after which it was concentrated and extracted with diethyl ether (3×50 mL). The combined organic phases were washed with brine, dried over magnesium sulfate, filtered and concentrated. The residue was purified by flash chromatography (gradient of 1, 3 and 5% ethyl acetate in hexanes) to give compound **28** as an epimeric mixture at position 15 (804 mg, 92%, yellowish oil). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.66 (4H, m) and 7.41 (6H, m) (2×Ph (TBDPS)), 7.06 (1H, d, J=14.9 Hz, C(CH_3)CH═), 6.15 (1H, d, J=14.9 Hz, ═CHI), 5.91 (2H, m, CH═CH–$SnBu_3$), 4.3–4.2 (2H, m, CH_2OTBDPS), 3.8–3.7 (1H, m, $CHCO_2$tBu), 3.64 (1H, d, J=11.5 Hz, OCHHC(CH_3)), 3.50 (1H, m, OCH(CH_2)), 3.46 (1H, d, J=11.5 Hz, OCHHC(CH_3)), 2.9–1.9 (8H, m, 4CH_2), 1.6–1.4 (26H, m, 4CH_2, C(CH_3)═, C(CH_3)$_2$), OC(CH_3)$_3$)), 1.29 (6H, sext., J=7.3 Hz, CH_2 of $SnBu_3$), 1.04 (9H, s, SiC(CH_3)$_3$), 0.9–0.8 (18H, m, $OCH_2C(CH_3)$), CH_2 and CH_3 of $SnBu_3$). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 205.2, 204.9, 169.1, 148.1, 148.1, 135.6, 133.6, 133.3, 129.7, 128.8, 128.7, 128.4, 127.7, 99.0, 81.4, 76.2, 75.5, 70.0, 62.6, 58.5, 42.9, 41.6, 41.3, 31.4, 30.7, 29.6, 29.1, 27.9, 27.9, 27.3, 26.9, 18.8, 17.5, 13.7, 9.4. IR (film) ν 3071, 2956, 2856, 1736, 1714, 1598, 1458, 1368, 1261, 1202, 1152, 1113, 1070, 702. MS (EI): 1061 ($M^+-C_4H_9$). HRMS ($M^+-C_4H_9$) calcd for $C_{51}H_{78}ISiO_6Sn$: 1061.3634; found: 1061.3646±0.0030.

5.2.4. Macrocycle-ester 29. To a solution of compound **28** (804 mg, 0.72 mmol) in a mixture of tetrahydrofuran/DMF (1:1, 500 mL total) at room temperature was added DIPEA (1.25 mL, 7.2 mmol). The resulting solution was stirred with nitrogen bubbling for 15 min before the bis(trifurylphospine)palladium dichloride(II) (47 mg, 0.072 mmol) addition, after which some nitrogen was again bubbled through solution for 5 min. The mixture was finally warmed-up to 50°C for 3 h, after that the reaction was concentrated and the residue was purified by flash chromatography (10% ethyl acetate in hexanes) to give compound **29** as an epimeric mixture at position 15 (285 mg, 56%, yellowish oil). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.66 (4H, m) and 7.40 (6H, m) (2×Ph (TBDPS)), 6.3–5.9 and 5.7–5.6 (4H, m, CH═CHCH═CH), 4.3–4.0 (2H, m, CH_2OTBDPS), 3.9–3.4 (4H, m), 2.7–2.2 (7H, m), 1.8–1.6 (1H, m), 1.5–1.4 (18H, m, OC(CH_3)$_3$, C(CH_3)═, C(CH_3)$_2$), 1.3–1.2 (2H, m), 1.06 (9H/2, s) and 1.03 (9H/2, s) (SiC(CH_3)$_3$), 0.90 (3H, s,

$OCH_2C(CH_3)$). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 208.5, 207.9, 170.1, 169.2, 135.5, 134.3, 133.4, 132.7, 131.5, 131.0, 129.6, 128.9, 128.6, 127.6, 99.2, 98.9, 81.0, 76.5, 74.8, 70.3, 69.9, 61.7, 60.7, 60.2, 40.3, 39.9, 31.1, 30.7, 29.4, 28.8, 27.9, 27.5, 26.9, 21.0, 20.5, 19.3, 18.4, 18.2. IR (film) ν 3072, 2932, 2858, 1732, 1709, 1472, 1428, 1368, 1248, 1226, 1198, 1160, 1113, 1069, 998, 824, 758, 703. MS (EI): 643 ($M^+-C_4H_9$). HRMS ($M^+-C_4H_9$) calcd for $C_{39}H_{51}SiO_6$: 643.3455; found: 643.3472±0.0019.

5.2.5. Macrocycle 30. To a solution of compound **29** (54 mg, 0.078 mmol) in toluene (10 mL) was added triethylamine (216 μL, 1.55 mmol). This solution was transferred into a pre-conditioned pyrex tube (washed 3×NH_4OH conc., 3×H_2O, 3×acetone and flame dried) and was degassed 3 times (tube freezing in liquid nitrogen under nitrogen, then degassing under vacuum while letting the tube warming-up to room temperature). The tube was then sealed under vacuum and allowed to warm-up to room temperature. The tube was finally heated to 190°C for 15 h after which it was broken and rinsed with dichloromethane (4×10 mL). The solvents were evaporated and the residue was purified by flash chromatography (10% ethyl acetate in hexanes) to give compound **30** as a clear oil (32 mg, 68%). $[\alpha]_D^{23}$=+39.2° (c=1.28, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.68 (4H, m) and 7.39 (6H, m) (2×Ph (TBDPS)), 6.2–5.9 and 5.7–5.6 (4H, m, CH=CHCH=CH), 4.17 (1H, d, J=12.1 Hz) and 4.09 (1H, d, J=12.1 Hz) ($CH_2OTBDPS$), 3.7–3.6 (1H, m, $OCH(CH_2)$), 3.58 (1H, d, J=11.4 Hz) and 3.46 (1H, d, J=11.4 Hz) ($OCH_2C(CH_3)$), 2.5–2.2 (8H, m, CH_2CH_2-$COCH_2CH_2$), 2.01 (1H, td, J=13.1, 4.6 Hz) and 1.80 (1H, td, J=13.1, 4.6 Hz) ($CH_2C(CH_3)$=), 1.45 (3H, s, $C(CH_3)$=), 1.42 (6H, s, $C(CH_3)_2$), 1.4–1.2 (2H, m, $OCH(CH_2)$), 1.02 (9H, s, $SiC(CH_3)_3$), 0.92 (3H, s, OCH_2-$C(CH_3)$). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 213.2, 135.6, 134.8, 134.5, 133.1, 130.6, 129.6, 129.6, 129.0, 127.7, 127.6, 99.0, 75.7, 70.1, 62.7, 45.7, 41.6, 39.8, 29.9, 29.4, 29.3, 28.4, 26.8, 26.6, 23.2, 19.8, 18.8, 18.5. IR (film) ν 3071, 2956, 2931, 2857, 1709, 1472, 1428, 1382, 1198, 1112, 1070, 998, 824, 757, 703. MS (EI): 585 (M^+-CH_3). HRMS (M^+-CH_3) calcd for $C_{37}H_{49}SiO_4$: 585.3400; found: 585.3408±0.0017.

5.2.6. Macrocycle-aldehyde 31. To a solution of protected alcohol **30** (95 mg, 0.16 mmol) in tetrahydrofuran (7 mL) at 0°C was added slowly the tetrabutylammonium fluoride (789 μL, 0.79 mmol, 1.0 M in THF). The solution was then allowed to warm-up to room temperature and it was stirred for 24 h before being concentrated and directly purified by flash chromatography (60% ethyl acetate in hexanes) to give the corresponding alcohol as a clear oil (44 mg, 77%). $[\alpha]_D^{23}$=+54.8° (c=1.62, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 6.2–6.0 and 5.6 (4H, m, CH=CHCH=CH), 4.10 (1H, d, J=11.7 Hz) and 4.01 (1H, d, J=11.7 Hz) (CH_2OH), 3.7 (1H, m, $OCH(CH_2)$), 3.59 (1H, d, J=11.4 Hz) and 3.47 (1H, d, J=11.4 Hz) (OCH_2-$C(CH_3)$), 2.6–2.1 (8H, m, $(CH_2)_2CO(CH_2)_2$), 2.09 (1H, td, J=13.3, 4.6 Hz) and 1.80 (1H, td, J=13.3, 4.6 Hz) (CH_2-$C(CH_3)$=), 1.71 (3H, s, $C(CH_3)$=), 1.42 (3H, s) and 1.41 (3H, s) ($C(CH_3)_2$), 1.4–1.2 (2H, m, $OCH(CH_2)$), 0.90 (3H, s, $OCH_2C(CH_3)$). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 213.1, 135.4, 134.6, 133.1, 131.1, 129.5, 128.9, 99.0, 75.5, 70.1, 62.1, 53.1, 45.6, 41.8, 39.7, 30.0, 29.2, 28.5, 24.5, 20.9, 19.6, 18.6. IR (film) ν 3448, 2933, 2860, 1707, 1458, 1380, 1249, 1198, 1159, 1122, 1070, 998, 864, 759. MS (EI): 347 (M^+-CH_3). HRMS (M^+-CH_3) calcd for $C_{21}H_{31}O_4$: 347.2222; found: 347.2229±0.0010.

To a solution of the previous alcohol (44 mg, 0.12 mmol) in dichloromethane (7 mL) at room temperature was added Dess–Martin periodinane (154 mg, 0.36 mmol). The solution was stirred for 1 h after which diethyl ether (5 mL) and a saturated aqueous solution of sodium bicarbonate (5 mL) were added. Solid sodium thiosulfate pentahydrated (214 mg, 1.08 mmol) was also added and the resulting mixture was stirred until cloudiness has disappeared. The clear solution was then extracted using diethyl ether (3×15 mL). The combined organic phases were washed with brine, dried over magnesium sulfate, filtered and concentrated. The residue was purified by flash chromatography (40% ethyl acetate in hexanes) to give aldehyde **31** as a white solid (35 mg, 80%, mp=157–164°C). $[\alpha]_D^{23}$=+96.8° (c=1.06, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 10.06 (1H, s, CHO), 6.2–5.9 and 5.6–5.5 (4H, m, CH=CHCH=CH), 3.77 (1H, t, J=6.4 Hz, $OCH(CH_2)$), 3.66 (1H, d, J=11.4 Hz) and 3.46 (1H, d, J=11.4 Hz) ($OCH_2C(CH_3)$), 2.7–2.0 (9H, m, $(CH_2)_2$-$CO(CH_2)_2$ and $CHHC(CH_3)$=), 2.15 (3H, s, $C(CH_3)$=), 1.97 (1H, td, J=13.3, 4.0 Hz, $CHHC(CH_3)$=), 1.8–1.4 (2H, m, $OCH(CH_2)$), 1.44 (3H, s) and 1.43 (3H, s) ($C(CH_3)_2$), 0.89 (3H, s, $OCH_2C(CH_3)$). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 212.2, 191.3, 159.8, 135.7, 134.5, 133.1, 129.7, 128.9, 99.1, 75.3, 70.1, 45.7, 41.2, 39.4, 31.5, 30.0, 29.0, 27.7, 19.8, 19.2, 17.9. IR (film) ν 2991, 2936, 2860, 1708, 1662, 1446, 1378, 1306, 1249, 1198, 1122, 1082, 1000, 892, 755. MS (EI): 345 (M^+-CH_3). HRMS (M^+-CH_3) calcd for $C_{21}H_{29}O_4$: 345.2066; found: 345.2069±0.0010.

5.2.7. Tetracycle 32. To a solution of compound **31** (11 mg, 0.031 mmol) in toluene (3 mL) was added triethylamine (60 μL, 0.41 mmol). This solution was transferred into a pre-conditioned quartz tube (washed 3×NH_4OH conc., 3×H_2O, 3×acetone and flame dried) and was degassed 3 times (tube freezing in liquid nitrogen under nitrogen, then degassing under vacuum while letting the tube warming-up to room temperature). The tube was then sealed under vacuum and allowed to warm-up to room temperature. The tube was finally heated to 250°C for 48 h after which it was broken and rinsed with dichloromethane (4×10 mL). The solvents were evaporated and the residue was purified by flash chromatography (50% ethyl acetate in hexanes) to give compound **32** as a white solid (9 mg, 77%, mp=213–218°C). Recrystallization system: EtOAc/hexanes $[\alpha]_D^{23}$=−76.8° (c=1.16, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 5.79 (1H, dAB, J=9.3 Hz) and 5.69 (1H, dt, J=9.3, 3.6 Hz) (CH=CH), 4.33, (1H, m, CHOH), 3.73 (1H, m, $OCH(CH_2)$), 3.50 (1H, d, J=12.0 Hz) and 3.43 (1H, d, J=12.0 Hz) ($OCH_2C(CH_3)$), 2.8–2.6 (2H, m), 2.5–2.3 (3H, m), 2.19 (1H, td, J=13.3, 3.6 Hz), 2.1–1.2 (7H, m) (CH and CH_2), 1.45 (3H, s) and 1.43 (3H, s) ($C(CH_3)_2$), 1.01 (3H, s, $(CH_2)_2C(CH_3)$), 0.92 (3H, s, $OCH_2C(CH_3)$). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 214.9, 133.3, 129.4, 97.8, 78.8, 72.0, 69.4, 57.0, 50.0, 41.1, 38.9, 37.8, 35.5, 33.6, 30.5, 30.0, 27.6, 27.1, 23.6, 19.7, 19.0, 18.7. IR (film) ν 3388, 2991, 2936, 2871, 1704, 1459, 1378, 1252, 1201,

1092. MS (EI): 360 $(M)^+$. HRMS $(M)^+$ calcd for $C_{22}H_{32}O_4$: 360.2300; found: 360.2305±0.0011.

Acknowledgements

A research Chair in organic chemistry from BioChem Pharma Inc. is gratefully acknowledged as well as financial support from NSERC Canada and FCAR Quebec. The authors wish to thank Mr Andreas Decken for X-ray analyses, as well as Mr Gaston Boulay for MS analyses.

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