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Radical cyclization; towards the syntheses of tetranor metabolites of 15-F_{2t}-isoprostane

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Abstract—Radical cyclization of acyclic 1-substituted-2,4-dihydroxylated 5-hexenyl radicals produced functionalized cyclopentane derivatives. These cyclopentanic precursors after different protection/deprotection reactions followed by Wittig and Horner–Wadsworth–Emmons coupling reactions led to the main urinary tetranor metabolites of 15-F_{2t}-isoprostane (8-*epi*-$PGF_{2\alpha}$).

1. Introduction

Isoprostanes are a complex family of compounds produced from polyunsaturated fatty acids via a free radical-catalyzed mechanism. In vitro generation of autoxidation products derived from polyunsaturated fatty acids has been described more than 30 years ago,[1,2] but the first demonstration that these compounds were produced in humans was shown in 1990 by Morrow et al.[3] They reported the discovery of prostaglandin F_2-like compounds, termed F_2-isoprostanes (F_2-isoP), generated by free radical-induced peroxidation of arachidonic acid. Since that time, F_2-isoprostanes have been extensively used as clinical markers of lipid peroxidation in human diseases,[4] but knowledge of their metabolic fate may be useful, to better define their overall formation.[5] In fact, the identification of major metabolites of F_2-isoP might help find new analytical targets to monitor in addition to the parent compounds. Moreover, given that selected F_2-isoP isomers have potent biological effects,[6–8] it is important to establish whether and how these isomers are specifically degraded, in order to relate their levels in vivo to a putative biological effect. To date, the only F_2-isoP metabolites identified were 2,3-dinor-15F_{2t}-isoP, 2,3-dinor-5,6-dihydro-15F_{2t}-isoP[9–11] and putative tetranor isomers of 15F_{2t}-isoP.[9,12]

As a consequence, and in connection with our program directed toward the synthesis of isoprostanes, we report the total synthesis of 2,3,4,5-tetranor-15-oxo-5,6,13,14-tetrahydro-15F_{2t}-isoP methyl ester **1** and 20-carboxy-2,3,4,5-tetranor-15-oxo-5,6,13,14-tetrahydro-15F_{2t}-isoP dimethyl ester **2**,[11d] according to our general procedure shown in Figure 1.

2. Results and discussion

The synthesis of 2,3,4,5-tetranor-15-oxo-5,6,13,14-tetrahydro-15F_{2t}-isoP methyl ester **1** is shown in Schemes 1

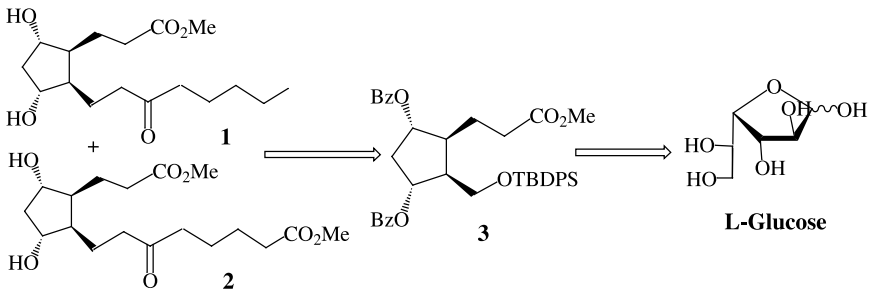

Figure 1. Retrosynthetic scheme.

Keywords: radical cyclization; tetranor metabolites; 15-$F_{2\alpha}$-isoprostane; cyclopentane precursors.

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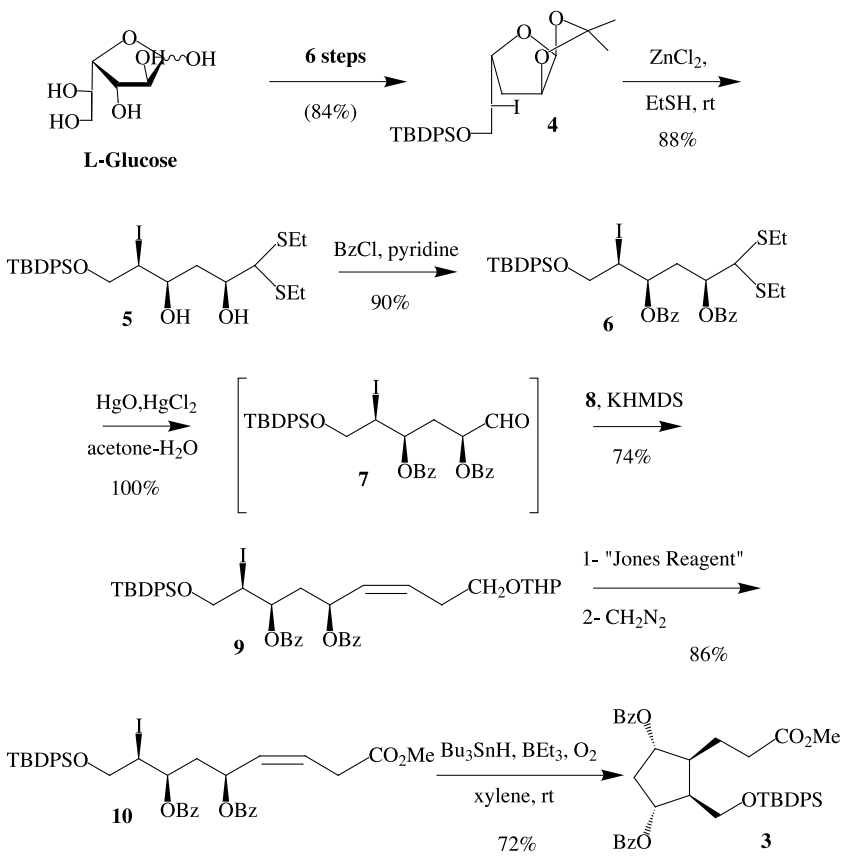
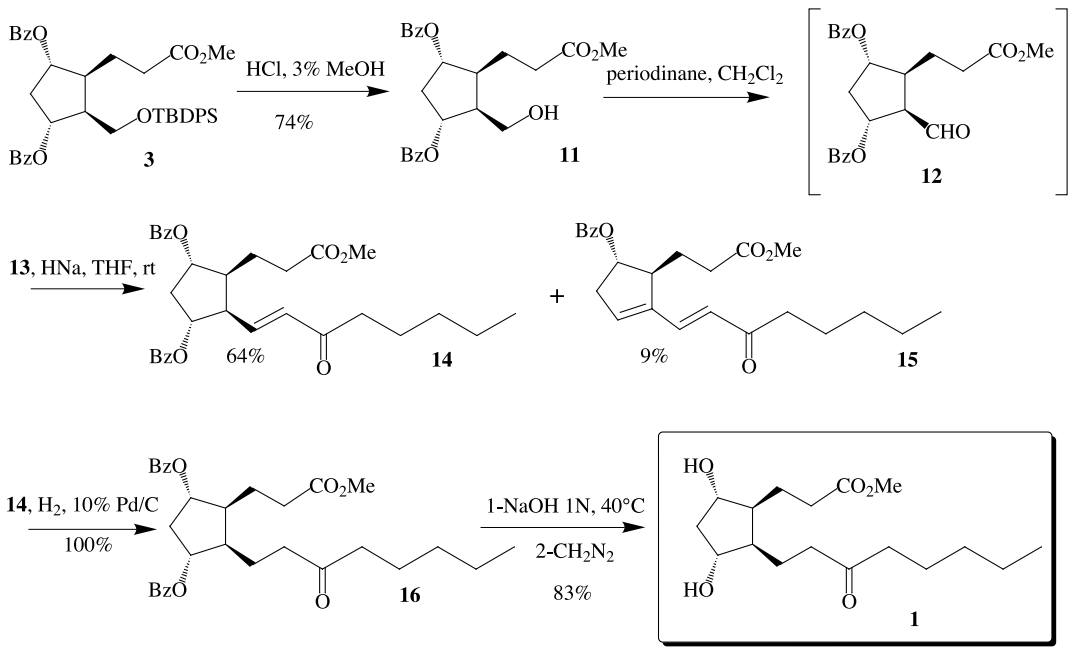
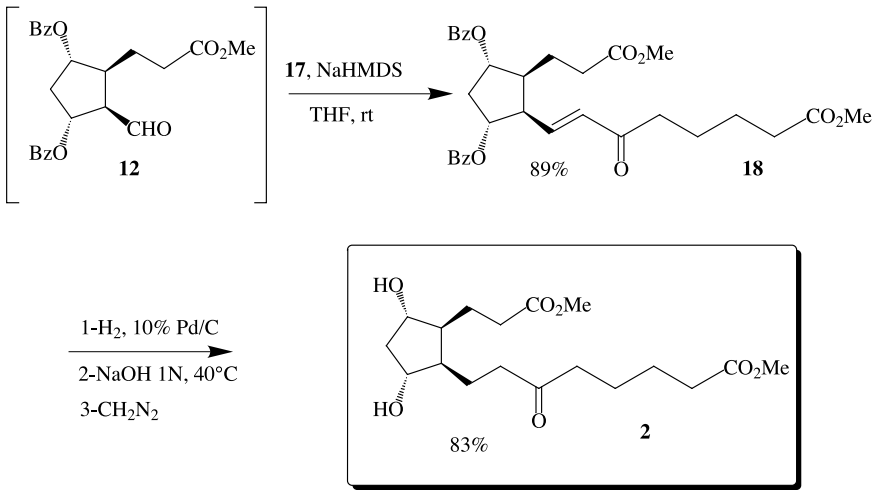


Scheme 1.

and 2. The first six steps leading to iodo derivative **4** were achieved in 84% overall yield by using the iodo pathway, according to our procedure.[13] Treatment of compound **4** with $ZnCl_2$ in ethanethiol at −15°C afforded the diol-thioacetal **5** in 88% yield, which was converted into dibenzoyl ester **6** in the presence of benzoyl chloride in pyridine at room temperature in 90% yield. Removal of the thioacetal group under neutral conditions ($HgO/HgCl_2$) in acetone/water gave the unstable aldehyde **7** which was immediately used in the next steps without further purification. The aldehyde **7** reacted with the ylide derived from 3-(tetrahydropyranyloxypropyl)triphenyl phosphonium



Scheme 2.



Scheme 3.

bromide **8**[14] and KHMDS to afford the pure *cis*-β,γ-ethylenic derivative **9** in 74% yield. No trace of *trans* compound could be detected by ^{13}C and ^{1}H NMR analysis.

Oxidation of the protected primary alcohol from **9** gave the corresponding acid, which in the presence of an excess of diazomethane was transformed in 86% yield to the methyl ester **10**. The highly functionalized hex-5-enyl radical derived from iodoester **10** underwent intramolecular cyclization[15] to yield 72% of the protected *syn–anti–syn* cyclopentane **3** accompanied by a mixture of non isolated cyclopentanic derivatives. The *tert*-butyldiphenylsilyl ether in **3** was converted to the alcohol **11** in 74% yield with a solution of 3% hydrogen chloride in methanol/ethyl ether (1:1, v/v).[16] Dess–Martin oxidation[17] of **11** with periodinane in CH_2Cl_2 gave the unstable aldehyde **12** which was immediately used in the next step without purification to avoid any epimerization of the aldehyde. It is important to note that this Dess–Martin oxidation gave a higher yield in avoiding any epimerization than our first attempts using Swern conditions. The condensation of **12** with diethyl oxoheptylphosphonate **13**, in the presence of NaH, in anhydrous THF, afforded the *trans*-α,β-enone **14** in 64% overall yield from the alcohol **11**. During the Horner–Wadsworth–Emmons reaction, it was not possible to avoid the formation of the compound **15** derived from the elimination of the benzoyl group at C11 (Scheme 2).

Reduction of the *trans* double bond on the ω chain was achieved using H_2 on 10% Pd/C, giving the corresponding oxo derivative **16** in 100% yield. Finally, cleavage of the ester functions of **16** with 1N NaOH, followed by treatment with diazomethane gave the 2,3,4,5-tetranor-15-oxo-5,6,13,14-tetrahydro-15F_{2t}-isoP methyl ester **1** in 83% yield (Scheme 2).

Our synthesis of 20-carboxy-2,3,4,5-tetranor-15-oxo-5,6,13,14-tetrahydro-15F_{2t}-isoP dimethyl esters **2** from **12** is shown in Scheme 3. The condensation of **12** with diethyl [6-(methoxycarbonyl)-2-oxohexyl]phosphonate **17**,[18] in the presence of NaHMDS, in anhydrous THF at −78°C, afforded the *trans*-α,β-enone **18** in 89% overall yield from the alcohol **11**.

Reduction of the *trans* double bond on the ω chain, was achieved using H_2 on 10% Pd/C, giving the corresponding oxo derivative **19**. Finally, cleavage of the ester functions with 1N NaOH, followed by treatment with diazomethane gave the 20-carboxy-2,3,4,5-tetranor-15-oxo-5,6,13,14-tetrahydro-15F_{2t}-isoP dimethyl esters **2** in 83% yield.

The advantage of our strategy depicted in Schemes 1–3 was demonstrated by several difficulties encountered in alternative routes during the course of this work and listed below:

(i) Our first goal was the introduction of the α chain of the isoprostane by using a one-carbon homologation, starting from our well-known cyclopentane precursor **20**, leading to the introduction of the α chain as shown in the following Figure 2.

The first attempt was the Arndt–Eistert reaction, starting from the cyclopentane **20**,[11b,13] using thionyl chloride followed by addition of excess of CH_2N_2 then treatment

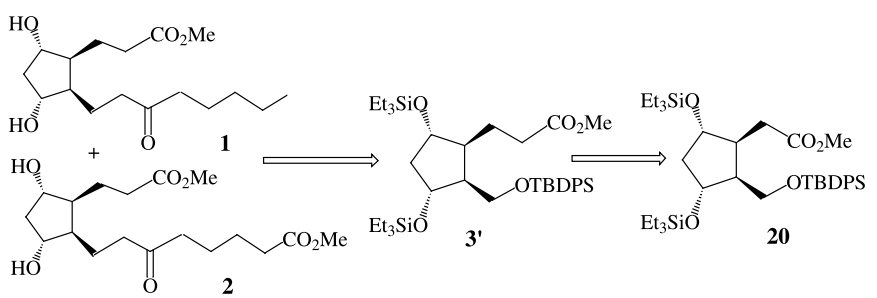
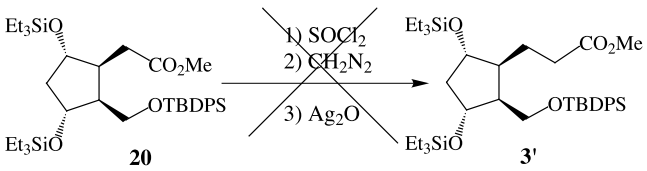
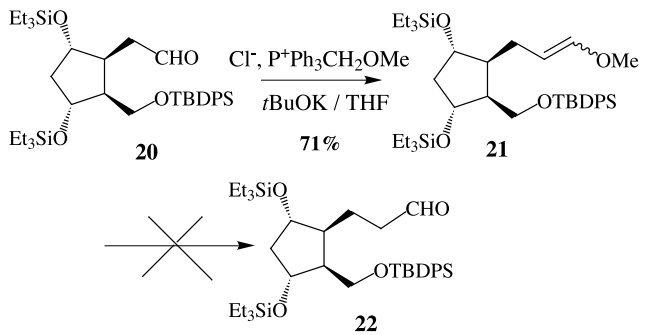


Figure 2. Original retrosynthetic scheme.



Scheme 4.

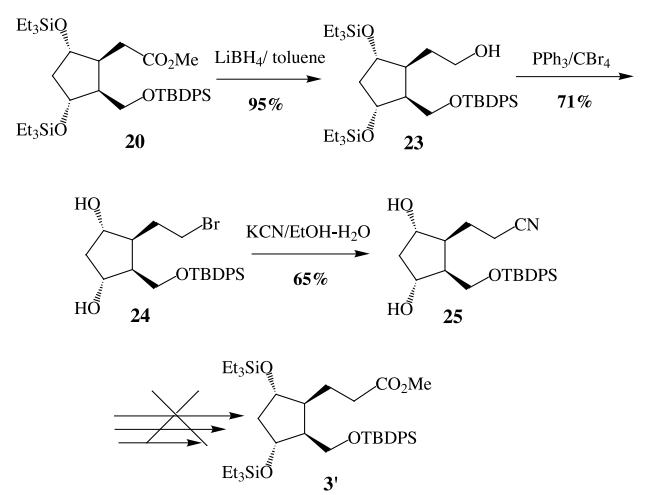


Scheme 5.

of the crude product by Ag_2O. Under these conditions we never obtained the desired ester **3′** and got only full degradation of starting material (Scheme 4).

We have also tried a Wittig reaction using the methoxymethyltriphenylphosphonium chloride on aldehyde **20**.[11b,13] If we got the corresponding enolether **21** in 71% yield, all our attempts to hydrolyse the enolether on **21** in the presence of hydrogen fluoride in CH_3CN or mild conditions as oxalic acid in THF/H_2O did not give the expected carbaldehyde group on **22** (Scheme 5).

Finally, our last attempt was the full reduction of the methyl ester **20** to the corresponding alcohol **23** in 95% yield using a solution of $LiBH_4$ (2 M in THF). Introduction of bromine was achieved using PPh_3/CBr_4 in CH_3CN leading to the bromo diol **24** in 71% yield, then in the presence of KCN in EtOH/H_2O (2:1) the desired cyano derivative **25** was obtained in 65% yield (Scheme 6). Unfortunately, once more, we never obtained the desired methyl ester **3′** derived from manipulation of cyano function **25**. In all experiments we got back the starting material **25**.



Scheme 6.

(ii) After all these above attempts, we found out that a better alternative to this one-carbon homologation was the introduction of the α chain before the cyclization reaction, able to obtain directly the *syn–anti–syn* cyclopentane compound **3′** or analogs, depending of the function at C1 position.

Our first approach based on our earlier work, using a three-carbon homologating agent: the (3,3-diisopropoxypropyl)-triphenylphosphonium bromide[19] is presented in Scheme 7.

As it is shown in the above scheme, if we obtained the corresponding ylide in the presence of NaHMDS, we never obtained the desired diol **27** and got back the starting hemiacetal **26**. The second difficulty were unexpected reactions during the deprotection of the diisopropyl acetal on compound **32** (Scheme 8).

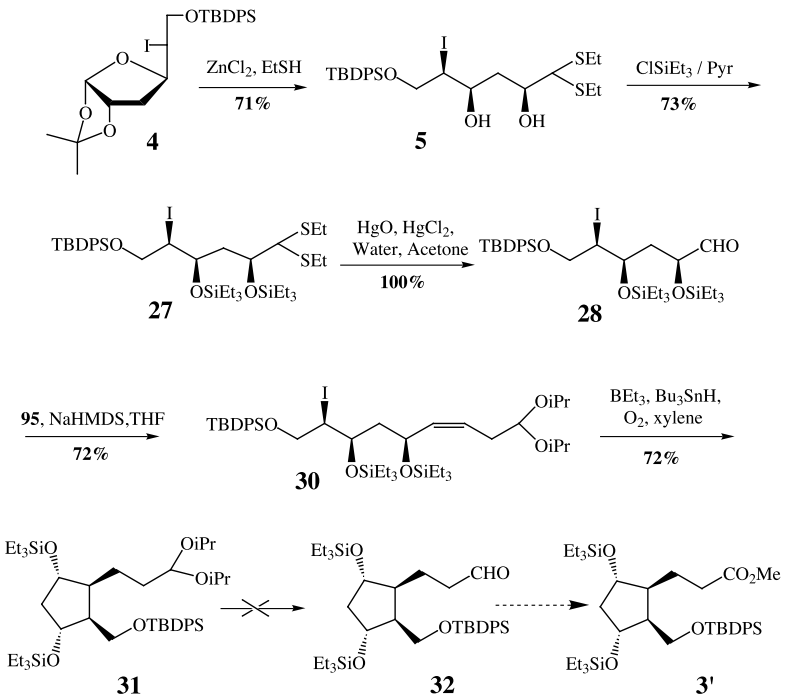
Treatment of iodo derivative **4** with $ZnCl_2$ in ethanthiol at −15°C afforded diol-thioacetal **5** in 71% yield, which was protected as disilyl ether **28** in 73% yield by use of triethylsilyl chloride in pyridine at room temperature. The introduction of the α chain of the isoprostane was achieved by using as the three-carbon homologating agent (3,3-diisopropoxypropyl)triphenyl phosphonium bromide **30**.[19] The aldehyde **29** reacted with the ylide derived from this phosphonium salt and NaHMDS to afford the pure *cis*-β-γ-ethylenic diisopropyl acetal **31** in 72% yield.

The cyclization of **31** was achieved using Bu_3SnH (1.2 equiv.) and BEt_3 (1 equiv.) in dry xylene at room temperature, under a stream of air, to yield 72% of the protected *syn–anti–syn* cyclopentane compound **32** and a mixture of unseparated cyclopentane byproducts in 24% yield. Finally, all our attempts to hydrolyse the diisopropyl acetal on **32**, with aqueous $FeCl_3$ in acetone, or other acidic conditions did not give the desired aldehyde **22**, but only different undesired byproducts (Scheme 8).

2.1. Structure determination of compound 3

We have shown that the NOE ^1H NMR experiment is a simple and efficient method for the determination of the relative functional configuration of the tetrasubstituted cyclopentane.[13,20] Thus, the relative configuration in

Scheme 7.



Scheme 8.

compound **3** was determined by homonuclear ^{1}H steady-state difference NOE spectroscopy (DNOES) experiments, as shown in Figure 3. For compound **3** the relative *cis* configuration of the protons 3-H, 5-H, 7-H, and 9-H was determined by irradiation of 5-H, which induced NOEs of 1.5% on 3-H and 0.5% on 9-H, and by irradiation of 7-H, which induced NOEs of 0.4% on 3-H and 1.6% on 9-H. These observations allow one to check the relative *syn* configuration of the side chains situated on C4 and C8, and the relative *anti* configuration between the side chains and the benzoyl groups situated on C5 and C7.

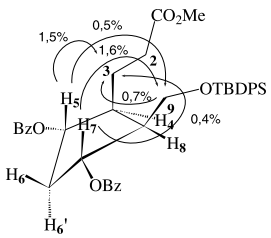


Figure 3. Relative configuration observed by steady-state NOE difference spectroscopy of compound **3**.

3. Conclusion

In this study, we describe the first stereoselective synthesis of 2,3,4,5-tetranor-15-oxo-5,6,13,14-tetrahydro-15F$_{2t}$-isoP methyl ester **1** in 17 steps and 20-carboxy-2,3,4,5-tetranor-15-oxo-5,6,13,14-tetrahydro-15F$_{2t}$-isoP dimethyl ester **2** in 18 steps from commercially available L-glucose. This route allows the enantiospecific synthesis of two main urinary metabolites of 15F$_{2t}$-isoP which provides the basis for the development of methods of assay for its quantification in different fluids. Such studies are currently in progress.

4. Experimental

4.1. General

Reagents were obtained from commercial suppliers and were used as received, unless otherwise noted. All reactions were conducted under nitrogen in distilled and dry solvents. Methylene chloride (CH_2Cl_2) was distilled from CaH_2. THF and Et_2O were distilled from sodium-benzophenone. Pyridine was distilled from KOH. Xylene and MeOH were distilled from Na. Acetone was dried with anhydrous $CaSO_4$. Reactions were monitored by thin-layer chromatography (TLC) and judged complete when starting material was no longer visible in the reaction mixture. Analytical TLC was performed using precoated silicagel plates (Merck silicagel, 0.25 mm, 60 F_{254}) with *p*-anisaldehyde in ethanol as indicator, and UV (254 nm) absorption. The extracts were dried over anhydrous sodium sulfate and the solvent removed under reduced pressure. The residue was purified by flash silica gel chromatography with the eluting solvent indicated. The structures of compounds were assigned on the basis of their ^{1}H NMR and ^{13}C NMR spectra at 360 and 91 MHz, respectively, and by a combination of NMR techniques which included ^{1}H–^{1}H COSY, HMBC and HMQC. For unstable products, the NMR spectra were obtained on Brucker 100 MHz.

4.1.1. (2*S*,4*R*,5*R*)-6-*O*-(*tert*-Butyldiphénylsilyl)-1,1-diethylthio-5-iodo-hexan-2,4-diol (5). To the iodo derivative **4** (1 g, 1.81 mmol), in 5 mL of ethanethiol was added anhydrous zinc chloride (0.98 g, 4.24 mmol) at −20°C. After 0.5 h, the excess of ethanethiol was removed at −20°C in vacuo. The foamy residue was deposed on a flash chromatography column and was eluted (5–20% ethyl acetate in cyclohexane). 0.79 g (71%) of **5** was obtained; TLC R_f: 0.62 (cyclohexane/ethyl acetate, 7:3). IR (neat): ν

3465, 1732, 1425 cm^{-1}. ^1H NMR (360 MHz, $CDCl_3$): δ 1.07 (9H, s, $C(CH_3)_3$), 1.19–1.34 (6H, m, CH_3CH_2S), 1.85–1.95 (1H, m, 3-H), 2.00–2.07 (1H, m, 3′-H), 2.54–2.80 (4H, m, CH_3CH_2S), 3.38 (2H, s, OH), 3.56–3.61 (1H, m, 4-H), 3.80 (1H, d, J=6.5 Hz, 1-H), 3.83–3.96 (1H, m, 2-H), 3.93–4.12 (2H, m, 6-H), 4.16–4.20 (1H, m, 5-H), 7.35–7.46 (6H, m, Ar-H), 7.64–7.75 (4H, m, Ar-H). ^{13}C NMR (91 MHz, $CDCl_3$): δ 14.6 (CH_3CH_2S), 14.7 (CH_3CH_2S), 19.3 ($C(CH_3)_3$), 24.8 (CH_3CH_2S), 25.8 (CH_3CH_2S), 26.9 ($C(CH_3)_3$), 41.1 (C-3), 43.5 (C-5), 58.6 (C-1), 67.2 (C-6), 70.1 (C-4), 72.2 (C-2), 127.7 (C-Ar), 127.8 (C-Ar), 129.9 (C-Ar), 132.8 (C-Ar), 133.0 (C-Ar), 135.6 (C-Ar), 135.7 (C-Ar). Anal. calcd for $C_{26}H_{39}IO_3S_2Si$: C, 50.47; H, 6.35. Found: C, 50.51; H, 6.33.

4.1.2. (2*S*,4*R*,5*R*)-6-*O*-(*tert*-Butyldiphenylsilyl)-2,4-di-*O*-(benzoyl)-1,1-diethylthio-5-iodo-hexane (6). To the diol **5** (400 mg, 647 μmol) in 5.5 mL of dry pyridine was added benzoyl chloride (263 μL, 2.26 mmol). The reaction mixture was stirred at room temperature overnight. The pyridine was evaporated. The residue was purified by chromatography (0–2% diethyl ether in cyclohexane) to give 471 mg (88%) of **6**. TLC R_f: 0,57 (cyclohexane/ethyl acetate, 9:1). IR (neat): ν 1721, 1451 cm^{-1}. ^1H NMR (360 MHz, $CDCl_3$): δ 0.82 (9H, s, $C(CH_3)_3$), 1.19 (3H, t, J=7.5 Hz, CH_3CH_2S), 1.30 (3H, t, J=7.5 Hz, CH_3CH_2S), 2.48–2.56 (1H,m, 3-H), 2.58–2.70 (1H, m, 3′-H), 2.65 (2H, q, J=7.5 Hz, CH_3CH_2S), 2.77 (2H, q, J=7.5 Hz, CH_3CH_2S), 3.78–3.88 (2H, m, 6-H), 4.22 (1H, d, J= 4.2 Hz, 1-H), 4.41–4.46 (1H, m, 5-H), 5.21 (1H, td, J=2.5, 6.8 Hz, 4-H), 5.48 (1H, td, J=4.2, 8.2 Hz, 2-H), 7.04 (2H, d, J=7.5 Hz, Ar-H), 7.15–7.24 (1H, m, Ar-H), 7.25–7.44 (7H, m, Ar-H), 7.36–7.46 (2H, m, Ar-H), 7.43–7.58 (2H, m, Ar-H), 7.50–7.60 (2H, m, Ar-H), 7.95–8.07 (4H, m, Ar-H). ^{13}C NMR (91 MHz, $CDCl_3$): δ 14.4 (CH_3CH_2S), 14.6 (CH_3CH_2S), 18.9 ($C(CH_3)_3$), 26.1 (CH_3CH_2S), 26.2 (CH_3CH_2S), 26.4 ($C(CH_3)_3$), 36.5 (C-5), 36.6 (C-3), 53.9 (C-1), 65.7 (C-6), 68.7 (C-4), 72.9 (C-2), 127.5 (C-Ar), 127.8 (C-Ar), 128.4 (C-Ar), 129.6 (C-Ar), 129.7 (C-Ar), 129.8 (C-Ar), 130.0 (C-Ar), 132.5 (C-Ar), 132.7 (C-Ar), 133.1 (C-Ar), 135.4 (C-Ar), 135.5 (C-Ar), 165.2 (C(O)), 166.1 (C(O)). Anal. calcd for $C_{40}H_{47}IO_5S_2Si$: C, 58.10; H, 5.73 Found: C, 58.15; H, 5.74.

4.1.3. (2*S*,4*R*,5*R*)-6-*O*-(*tert*-Butyldiphenylsilyl)-2,4-di-*O*-(benzoyl)-5-iodo-hexanal (7). To the thioacetal **6** (100 mg, 2 mmol) in 4.6/0.46 mL of acetone/water, was added mercuric oxide (243 mg, 1.12 mmol) and mercuric chloride (105 mg, 387 μmol). The heterogeneous mixture was refluxed overnight. 4 mL of saturated sodium bicarbonate solution was added. The mixture was filtered through Celite, extracted with 3×10 mL of methylene chloride. The organic layers were washed with 3×5 mL of potassium iodide solution and with 5 mL of brine. The extracts were dried over Na_2SO_4 and evaporated. 87 mg (100%) of aldehyde **7** was obtained. TLC R_f: 0.82 (cyclohexane/ethyl acetate, 7:3). IR (neat): ν 1722 cm^{-1}. ^1H NMR (360 MHz, $CDCl_3$): δ 0.94 (9H, s, $C(CH_3)_3$), 2.44–2.51 (1H, m, 3-H), 2.57–2.66 (1H, m, 3′-H), 3.43–3.50 (2H, m, 6-H), 4.32 (1H, ddd, J=2.5, 5.8, 8.6 Hz, 5-H), 5.36–5.44 (2H, m, 2-H), 5.37–5.47 (2H, m, 4-H), 7.12 (2H, q, J=7.5 Hz, Ar-H), 7.22–7.27 (1H, m, Ar-H), 7.28–7.45 (7H, m, Ar-H), 7.46–7.50 (2H, m, Ar-H), 7.51–7.61 (4H, m, Ar-H), 7.93–8.02 (2H, m, Ar-H), 8.04–8.09 (2H, m, Ar-H), 9.60 (1H, s, CHO). ^{13}C NMR (91 MHz, $CDCl_3$): δ 15.3 ($C(CH_3)_3$), 26.6 ($C(CH_3)_3$), 34.8 (C-3), 36.0 (C-5), 65.7 (C-6), 68.0 (C-4), 75.6 (C-2), 127.6 (C-Ar), 127.8 (C-Ar), 128.5 (C-Ar), 129.8 (C-Ar), 129.9 (C-Ar), 130.0 (C-Ar), 132.4 (C-Ar), 132.7 (C-Ar), 133.4 (C-Ar), 133.6 (C-Ar), 135.5 (C-Ar), 165.1 (C(O)), 165.9 (C(O)), 197.2 (C-1).

4.1.4. (5*S*,7*R*,8*R*)-9-*O*-(*tert*-Butyldiphenylsilyl)-5,7-di-*O*-(benzoyl)-1-*O*-(tetrahydropyranyl)-8-iodo-3(*Z*)-nonene (9). A 0.5 M toluene solution of KHMDS (604 μL, 314 μmol) was added to a suspension of 3-(tetrahydropyranyl oxypropyl)triphenyl phosphonium bromide (153 mg, 314 μmol) **8** in 1.6 mL of THF at −80°C. The resulting orange solution of ylide was stirred 10 min. This solution was added to aldehyde **7** solution in 1.6 mL of THF. After slow warming to room temperature over 1 h, the reaction mixture was hydrolyzed with 3 mL of water. The aqueous layer was extracted with diethyl ether (3×3 mL), and the combined extracts were washed with brine (5 mL). All organic layers were dried with Na_2SO_4 and concentrated. The residue was purified by chromatography (10% diethyl ether in cyclohexane) to give 76 mg (74%) of **9**. TLC R_f: 0.25 (cyclohexane/ethyl acetate, 9:1). IR (neat): ν 1720 cm^{-1}. ^1H NMR (360 MHz, $CDCl_3$): δ 0.83 (9H, s, $C(CH_3)_3$), 1.39–1.52 (1H, m, THP-H), 1.41–1.59 (2H, m, THP-H), 1.49–1.60 (1H, m, THP-H), 1.60–1.73 (1H, m, THP-H), 1.72–1.85 (1H, m, THP-H), 2.10–2.28 (1H, m, 6-H), 2.44–2.62 (1H, m, 6′-H), 2.47–2.66 (2H, m, 2-H), 3.39–3.52 (1H, m, 1-H), 3.40–3.52 (1H, m, THP-H), 3.71–3.81 (1H, m, 1′-H), 3.76–3.87 (1H, m, THP-H), 3.81–3.90 (2H, m, 9-H), 4.48 (1H, ddd, J=2.2, 6.5, 8.5 Hz, 8-H), 4.55–4.61 (1H, m, THP-H), 5.20–5.54 (2H, t, J=6.5, 11.1 Hz, 4-H, 7-H), 5.64 (1H, td, J=7.3, 11.1 Hz, 3-H), 5.91 (1H, ddd, J=4.6, 9.0, 13.3 Hz, 5-H), 7.00–7.10 (2H, m, Ar-H), 7.16–7.24 (1H, m, Ar-H), 7.26–7.47 (7H, m, Ar-H), 7.38–7.47 (2H, m, Ar-H), 7.45–7.61 (2H, m, Ar-H), 7.50–7.60 (2H, m, Ar-H), 7.97–8.08 (4H, m, Ar-H). ^{13}C NMR (91 MHz, $CDCl_3$): δ 18.9 ($C(CH_3)_3$), 19.4 (C-THP), 25.5 (C-THP), 26.5 ($C(CH_3)_3$), 28.6 (C-2), 30.6 (C-THP), 36.6 (C-8), 39.7 (C-6), 62.1 (C-THP), 65.7 (C-9), 66.5 (C-1), 67.8 (C-5), 68.7 (C-7), 98.6 (C-THP), 127.6 (C-3), 127.7 (C-Ar), 128.3 (C-Ar), 128.4 (C-Ar), 128.5 (C-Ar), 129.6 (C-Ar), 129.8 (C-Ar), 130.1 (C-Ar), 131.4 (C-4), 132.5 (C-Ar), 132.9 (C-Ar), 133.1 (C-Ar), 135.4 (C-Ar), 135.5 (C-Ar), 165.1 (C(O)). Anal. calcd for $C_{44}H_{51}IO_7Si$: C, 62.40; H, 6.07. Found: C, 62.44; H, 6.02.

4.1.5. Methyl (5*S*,7*R*,8*R*)-9-*O*-(*tert*-butyldiphenylsilyl)-5,7-di-*O*-(benzoyl)-8-iodo-non-3(*Z*)-enoate (10). To a stirred solution of **9** (500 mg, 0.59 mmol) in 12 mL of freshly distilled acetone at −10°C was added Jones reagent (1.15 mL, 2.95 mmol, 2.17 M). After slow warming to room temperature over 2 h, the reaction was terminated using propan-2-ol. The solution was filtered on Celite. 10 mL of water was added and the aqueous phase was extracted with 3×10 mL of ethyl acetate. The organic layers were washed with 10 mL of brine, dried with Na_2SO_4 and concentrated in vacuo. An etheral solution of diazomethane was added. After concentration, flash chromatography over silica gel (cyclohexane/diethyl ether, 95:5), 401 mg of **10** was obtained (86%). TLC R_f: 0.52 (cyclohexane/ethyl acetate, 8:2). IR (neat): ν 1718 cm^{-1}. ^1H NMR (360 MHz, $CDCl_3$):

δ 0.84 (9H, s, C(CH_3)$_3$), 2.17 (1H,ddd, J=4.8, 6.6, 14.4 Hz, 6-H), 2.5 (1H, ddd, J=6.6, 8.9, 14.4 Hz, 6-H), 3.39 (2H, dt, J=1.8, 7.1 Hz, 2-H), 3.66 (3H, s, OCH_3), 3.80–3.89 (2H, m, 9-H), 4.41 (1H, ddd, J=2.1, 6.1, 8.6 Hz, 8-H), 5.20 (1H, td, J=2.1, 6.6 Hz, 7-H), 5.60 (1H, ddt, J=1.8, 8.9, 10.8 Hz, 4-H), 5.78 (1H, td, J=4.8, 8.9 Hz, 5-H), 5.86 (1H, dt, J=7.1, 10.7 Hz, 3-H), 7.05 (2H, t, J=7.3 Hz, Ar-H), 7.21 (1H, tt, J=1.5, 7.3 Hz, Ar-H), 7.27–7.35 (2H, m, Ar-H), 7.31–7.38 (2H, m, Ar-H), 7.28–7.39 (1H, m, Ar-H), 7.38–7.45 (2H, m, Ar-H), 7.40–7.45 (2H, m, Ar-H), 7.49 (1H, tt, J=1.5, 7.3 Hz, Ar-H), 7.52–7.57 (2H, m, Ar-H), 7.53–7.59 (1H, m, Ar-H), 7.98–8.03 (2H, m, Ar-H), 7.99–8.04 (2H, m, Ar-H). ^{13}C NMR (91 MHz, $CDCl_3$): δ 18.9 (*C*(CH$_3$)$_3$), 26.4 (C(*C*H$_3$)$_3$), 33.1 (C-2), 36.6 (C-8), 39.6 (C-6), 51.9 (OCH_3), 65.6 (C-9), 67.6 (C-5), 68.4 (C-7), 126.4 (C-3), 127.5 (C-Ar), 127.7 (C-Ar), 128.3 (C-Ar), 128.4 (C-Ar), 129.6 (C-Ar), 129.7 (C-Ar), 129.8 (C-Ar), 129.9 (C-4), 132.4 (C-Ar), 132.7 (C-Ar), 132.9 (C-Ar), 133.2 (C-Ar), 135.4 (C-Ar), 135.5 (C-Ar), 165.1 (C(O)), 165.6 (C(O)), 171.3 (C-1). Anal. calcd for $C_{40}H_{43}IO_7Si$: C, 60.76; H, 5.48. Found: C, 60.80; H, 5.50.

4.1.6. (1*R*,2*S*,3*S*,4*S*)-2-*tert*-Butyldiphenylsilyloxy methyl-1,4-di-*O*-(benzoyl)-3-(methoxycarbonylethyl) cyclopentane (3). To a solution of **10** (250 mg, 316 μmol) in 5 mL of *p*-xylene was added tributyltin hydride (102 μL, 380 μmol) under a stream of dry argon. At room temperature, a 1N triethyl borane solution (63 μL, 63 μmol) was added under a stream of dry air. The mixture was stirred 40 min. The solvent was removed and the mixture was subjected to flash chromatography (0–10% diethyl ether in cyclohexane) to give 151 mg (72%) of **3**. TLC R_f: 0.5 (cyclohexane/ethyl acetate, 8:2). IR (neat): ν 1715 cm^{-1}. ^{1}H NMR (360 MHz, $CDCl_3$): δ 1.09 (9H, s, C(CH$_3$)$_3$), 1.70–1.85 (2H, m, 3-H), 1.90 (1H, dq, J=2.8, 15.7 Hz, 6-H), 2.37 (2H, t, J=8.6 Hz, 2-H), 2.49–2.59 (1H, m, 8-H), 2.54–2.64 (1H, m, 4-H), 2.95 (1H, dt, J=7.4, 15.7 Hz, 6′-H), 3.60 (3H, s, OCH_3), 3.70 (1H, dd, J=5.1, 11.1 Hz, 9-H), 3.86 (1H, dd, J=5.1, 11.1 Hz, 9′-H), 5.31 (1H, m, 5-H), 5.40 (1H, dt, J=2.8, 7.4 Hz, 1H, 7-H), 7.31–7.38 (4H, m, Ar-H), 7.35–7.45 (2H, m, Ar-H), 7.36–7.45 (4H, m, Ar-H), 7.49–7.57 (2H, m, Ar-H), 7.63–7.71 (4H, m, Ar-H), 7.95–8.06 (4H, m, Ar-H). ^{13}C NMR (91 MHz, $CDCl_3$): δ 19.1 (*C*(CH$_3$)$_3$), 23.2 (C-3), 26.9 (C(*C*H$_3$)$_3$), 32.7 (C-2), 38.8 (C-6), 45.0 (C-4), 48.8 (C-8), 51.5 (OCH_3), 61.7 (C-9), 77.4 (C-7), 79.2 (C-5), 127.8 (C-Ar), 128.3 (C-Ar), 129.6 (C-Ar), 129.8 (C-Ar), 130.3 (C-Ar), 132.9 (C-Ar), 132.9 (C-Ar), 135.6 (C-Ar), 135.6 (C-Ar), 135.7 (C-Ar), 166.0 (C(O)), 166.1 (C(O)), 173.4 (C-1). Anal. calcd for $C_{40}H_{44}O_7Si$: C, 72.26; H, 6.67. Found: C, 72.24; H, 6.68. $[\alpha]_D^{20}$=+11.5 (c=10^{-3}, MeOH).

4.1.7. (1*R*,2*S*,3*S*,4*S*)-1,4-Di-*O*-(benzoyl)-2-hydroxy-methyl-3-(methoxycarbonylethyl) cyclopentane (11). Acetyl chloride (1 mL) was added dropwise to methanol (17 mL), and the hydrogen chloride solution obtained was cooled to 20°C. A solution of **3** (500 mg, 0.8 mmol) in freshly distilled diethyl ether (17 mL) was added and the mixture was stirred at room temperature for 20 h. Then neutralized with saturated $NaHCO_3$. The aqueous layer was extracted with ethyl acetate (3×10 mL), and the combined extracts were washed with brine (10 mL). All organic solution were dried with Na_2SO_4 and concentrated, giving a crude material. Flash chromatography over silica gel (cyclohexane/ethyl acetate, 7:3) gave 216 mg of **11** (68%). TLC R_f: 0.51 (cyclohexane/ethyl acetate, 1:1). IR (neat): ν 3525, 1715 cm^{-1}. ^{1}H NMR (360 MHz, $CDCl_3$): δ 1.57–1.72 (1H, m, 3-H), 1.87–1.96 (1H, m, 3′-H), 2.01 (1H, ddd, J=3.7, 7.5, 15.4 Hz, 6-H), 2.32 (1H, s, OH), 2.49 (2H, t, J=7.5 Hz, 2-H), 2.48–2.60 (1H, m, 4-H), 2.58–2.69 (1H, m, 8-H), 2.92 (1H, dt, J=7.5, 15.4 Hz, 6′-H), 3.63 (3H, s, OCH_3), 3.72–3.80 (1H, m, 9-H), 3.85–3.92 (1H, m, 9′-H), 5.21 (1H, ddd, J=4.2, 5.3, 7.5 Hz, 5-H), 5.34 (1H, td, J=3.7, 7.5 Hz, 7-H), 7.38–7.45 (4H, m, Ar-H), 7.52–7.58 (2H, m, Ar-H), 7.99–8.05 (4H, m, Ar-H). ^{13}C NMR (91 MHz, $CDCl_3$): δ 22.6 (C-3), 32.5 (C-2), 38.0 (C-6), 45.2 (C-4), 49.2 (C-8), 51.7 (OCH_3), 60.7 (C-9), 76.9 (C-7), 78.6 (C-5), 128.4 (C-Ar), 129.6 (C-Ar), 130.1 (C-Ar), 130.2 (C-Ar), 133.0 (C-Ar), 133.1 (C-Ar), 166.1 (C(O)), 166.7 (C(O)), 173.8 (C-1). Anal. calcd for $C_{24}H_{26}O_7$: C, 67.59; H, 6.15. Found: C, 67.60; H, 6.22.

4.1.8. (1*R*,2*S*,3*S*,4*S*)-1,4-Di-*O*-(benzoyl)-2-formyl-3-(methoxycarbonylethyl) cyclopentane (12). To a solution of **11** (108 mg, 0.253 mmol) in 18 mL of CH_2Cl_2 and 14 μL of water at room temperature was added Dess–Martin periodinane (322 mg, 0.76 mmol). The reaction mixture was stirred for 30 min. The mixture was washed with a solution of 1/1 $NaHCO_3$ (10%)/$Na_2S_2O_3$ (10%) (3×5 mL). The aqueous layers were extracted with diethyl ether (3×6 mL). The organic layer was washed with 6 mL of brine, dried over Na_2SO_4 and concentrated. The crude material **12** was used immediately for the next step. TLC R_f: 0.7 (cyclohexane/ethyl acetate, 1:1). ^{1}H NMR (100 MHz, $CDCl_3$): δ 1.53–2.23 (3H, m, 3-H, 6-H), 2.37–3.06 (5H, m, 2-H, 4-H, 8-H, 6′-H), 3.56 (3H, s, OCH_3), 5.00–5.76 (2H, m, 5-H, 7-H), 7.23–7.63 (6H, m, Ar-H), 7.83–8.01 (4H, m, Ar-H), 9.93 (1H, s, 9-H).

4.1.9. (1*R*,2*S*,3*S*,4*S*)-1,4-Di-*O*-(benzoyl)-3-(methoxy-carbonyl ethyl)-2-((*E*) 3-oxo-oct-1-enyl) cyclo pentane (14) and (1*R*,2*S*)-1-*O*-(benzoyl)-2-(2-methoxycarbonyl-ethyl)-3-(methoxycarbonyl-3-oxo-oct-1*E*-enyl) cyclo-pent-3*E*-ene (15). To a solution of **12** (0.253 mol) in 2 mL of THF was added dropwise a solution of ylide prepared at room temperature from diethyl 2-oxoheptyl-phosphonate (145 μL, 0.696 mmol) and NaH (10 mg, 0.633 mmol, 60% in oil) in 2 mL of THF. The reaction was stirred for 10 min, neutralized with saturated NH_4Cl (2 mL) and extracted with diethyl ether (3×5 mL). The organic layers were washed with brine (5 mL), dried with Na_2SO_4 and evaporated in vacuo. The crude material was purified by flash chromatography on silica gel (cyclo-hexane/ethyl acetate, 8:2) to give 84 mg of **14** (64% in two steps) and 9.1 mg of **15** (9% in two steps).

Compound **14**. TLC R_f: 0.79 (cyclohexane/ethyl acetate, 1:1). IR (neat): ν 1717 cm^{-1}. ^{1}H NMR (360 MHz, $CDCl_3$): δ 0.87 (3H, t, J=7.0 Hz, 16-H), 1.21–1.33 (2H, m, 14-H), 1.25–1.35 (2H, m, 15-H), 1.55–1.64 (2H, m, 13-H), 1.66–1.85 (2H, m, 3-H), 2.03 (1H, ddd, J=3.2, 6.5, 15.4 Hz, 6-H), 2.40–2.46 (2H, m, 2-H), 2.53 (2H, t, J=7.5 Hz, 12-H), 2.59–2.68 (1H, m, 4-H), 2.98 (1H, td, J=7.5, 15.4 Hz, 6′-H), 3.23–3.29 (1H, m, 8-H), 3.61 (3H, s, OCH_3), 5.21–5.27 (1H, m, 5-H), 5.28–5.33 (1H, m, 7-H), 6.29 (1H, dd, J=0.8, 15.7 Hz, 10-H), 6.70 (1H, dd, J=9.1, 15.8 Hz, 9-H),

7.39–7.45 (4H, m, Ar-H), 7.45–7.58 (2H, m, Ar-H), 7.98–8.04 (4H, m, Ar-H). ^{13}C NMR (91 MHz, $CDCl_3$): δ 13.9 (C-16), 22.4 (C-15), 23.7 (C-13), 23.8 (C-3), 31.4 (C-14), 32.2 (C-2), 38.0 (C-6), 41.0 (C-12), 47.0 (C-4), 50.3 (C-8), 51.6 (OCH_3), 77.3 (C-7), 78.0 (C-5), 128.4 (C-Ar), 129.6 (C-Ar), 129.9 (C-Ar), 130.0 (C-Ar), 132.8 (C-10), 133.2 (C-Ar), 140.9 (C-9), 165.9 (C(O)), 166.1 (C(O)), 173.2 (C-1), 199.8 (C-11). Anal. calcd for $C_{31}H_{36}O_7$: C, 71.52; H, 6.97. Found: C, 71.55; H, 6.93.

Compound **15**. TLC R_f: 0.85 (cyclohexane/ethyl acetate, 1:1). ^{1}H NMR (360 MHz, $CDCl_3$): δ 0.87 (3H, t, J=7.0 Hz, 16-H), 1.21–1.33 (2H, m, 14-H), 1.25–1.35 (2H, m, 15-H), 1.43–1.66 (3H, m, 3-H, 13-H), 2.01–2.12 (1H, m, 3′-H), 2.40–2.73 (5H, m, 2-H, 6-H, 12-H), 2.86–3.00 (2H, m, 4-H, 6′-H), 3.67 (3H, s, OCH_3), 5.28–5.37 (1H, m, 5-H), 6.18–6.20 (1H, m, 7-H), 6.27 (1H, d, J=16.1 Hz, 10-H), 7.28 (1H, d, J=16.1 Hz, 9-H), 7.35–7.47 (2H, m, Ar-H), 7.49–7.53 (1H, m, Ar-H), 7.92–8.11 (2H, m, Ar-H). ^{13}C NMR (91 MHz, $CDCl_3$): δ 13.9 (C-16), 22.5 (C-15), 23.9 (C-13), 25.4 (C-3), 31.4 (C-2), 31.4 (C-14), 39.0 (C-6), 41.1 (C-12), 50.4 (C-4), 51.6 (OCH_3), 78.8 (C-5), 127.2 (C-10), 128.3 (C-Ar), 129.6 (C-Ar), 130.2 (C-Ar), 133.0 (C-Ar), 136.4 (C-9), 137.3 (C-7), 143.0 (C-8), 166.2 (C(O)), 173.6 (C-1), 200.9 (C-11). Anal. calcd for $C_{24}H_{30}O_5$: C, 72.34; H, 7.59. Found: C, 72.40; H,7.63.

4.1.10. (1*R*,2*S*,3*S*,4*S*)-1,4-Di-*O*-(benzoyl)-3-(methoxycarbonylethyl)-2-(3-oxo-octanyl) cyclopentane (16). A mixture of **14** (70 mg, 134 μmol) and 10% Pd/C (6 mg) in absolute ethanol (2.7 mL) was hydrogenated at atmospheric pressure for 4 h. The mixture was filtered through celite and washed with ethyl acetate. The organic layer was concentrated to provide 70 mg of **16** (100%). TLC R_f: 0.79 (cyclohexane/ethyl acetate, 1:1). IR (neat): ν 1735, 1715 cm^{-1}. ^{1}H NMR (360 MHz, $CDCl_3$): δ 0.85 (3H, t, J=6.9 Hz, 16-H), 1.16–1.28 (2H, m, 14-H), 1.21–1.33 (2H, m, 15-H), 1.40–1.51 (1H, m, 9-H), 1.49–1.60 (2H, m, 13-H), 1.60–1.72 (1H, m, 3-H), 1.78–1.90 (1H, m, 9′-H), 1.82–1.94 (1H, m, 3′-H), 1.83–1.98 (1H, m, 6-H), 2.30–2.41 (1H, m, 8-H), 2.34–2.45 (2H, m, 12-H), 2.41–2.51 (1H, m, 4-H), 2.42–2.58 (2H, m, 2-H), 2.53–2.69 (2H, m, 10-H), 2.91 (1H, td, J=7.6, 15.6 Hz, 6′-H), 3.62 (3H, s, OCH_3), 5.10–5.16 (1H, m, 7-H), 5.11–5.18 (1H, m, 5-H), 7.38–7.46 (4H, m, Ar-H), 7.50–7.58 (2H, m, Ar-H), 7.98–8.06 (4H, m, Ar-H). ^{13}C NMR (91 MHz, $CDCl_3$): δ 13.9 (C-16), 20.6 (C-9), 22.4 (C-15), 22.6 (C-3), 23.5 (C-13), 29.7 (C-14), 31.9 (C-2), 37.7 (C-6), 40.4 (C-10), 43.0 (C-12), 45.8 (C-4. C-8), 51.6 (OCH_3), 78.2 (C-7), 78.4 (C-5), 128.4 (C-Ar), 129.6 (C-Ar), 130.2 (C-Ar), 133.0 (C-Ar), 166.2 (C(O)), 173.6 (C-1), 210.5 (C-11). Anal. calcd for $C_{31}H_{38}O_7$: C, 71.24, H, 7.34. Found: C, 71.30, H, 7.30.

4.1.11. 2,3,4,5-Tetranor-15-oxo-5,6,13,14-tetrahydro-15F$_{2t}$-isoP methyl ester (1). To the solution of **16** (38 mg, 72 μmol) in 580 μL of methanol and 380 μL of THF was added 1N solution of NaOH (670 μL). The mixture was stirred 2 h at 40°C. 1N solution of $NaHSO_4$ (710 μL) was then added for neutralization. The reaction was diluted in water (1 mL) and extracted with ethyl acetate (3×5 mL). The organic layers were dried with Na_2SO_4 and evaporated. The residue was esterified with an etheral solution of diazomethane. After evaporation of solvents, the crude product was purified by flash chromatography on silica gel (cyclohexane/ethyl acetate, 1:1) to give 18.8 mg of **1** (83%). TLC R_f: 0.34 (ethyl acetate/acetic acid, 19:1). IR (neat): ν 3415, 1736, 1712 cm^{-1}. ^{1}H NMR (360 MHz, $CDCl_3$): δ 0.87 (3H, t, J=0.9 Hz, 16-H), 1.16–1.30 (2H, m, 14-H), 1.22–1.32 (2H, m, 15-H), 1.32–1.45 (1H, m, 9-H), 1.36–1.49 (1H, m, 3-H), 1.52–1.61 (1H, m, 6-H), 1.50–1.60 (2H, m, 13-H), 1.59–1.72 (1H, m, 9′-H), 1.66–1.79 (1H, m, 3′-H). 1.95–2.03 (1H, m, 4-H), 1.98–2.07 (1H, m, 8-H), 2.33–2.44 (3H, m, 6′-H, 12-H), 2.35–2.43 (2H, m, 2-H), 2.49 (2H, dd, J=7.3, 7.8 Hz, 10-H), 3.65 (3H, s, OCH_3), 3.87–3.93 (1H, m, 5-H), 3.91–3.97 (1H, m, 7-H). ^{13}C NMR (91 MHz, $CDCl_3$): δ 13.9 (C-16), 21.7 (C-9), 22.4 (C-15), 23.1 (C-3), 23.5 (C-13), 31.4 (C-14), 32.7 (C-2), 41.1 (C-10), 42.9 (C-12), 42.9 (C-6), 48.9 (C-8), 49.0 (C-4), 51.6 (OCH_3), 76.0 (C-7), 76.3 (C-5), 174.0 (C-1), 211.3 (C-11). Anal. calcd for $C_{17}H_{30}O_5$: C, 64.97; H, 9.61. Found: C, 64.97; H, 9.61. $[\alpha]_D^{20}$=+1.34 (c=10^{-3}, MeOH).

4.1.12. (1*R*,2*S*,3*S*,4*S*)-1,4-Di-*O*-(benzoyl)-3-(methoxy carbonylethyl)-2-(methoxycarbonyl-3-oxo-oct-1*E*-enyl) cyclopentane (18). To a solution of **12** (0.513 mol) in 4 mL of THF was added dropwise a solution of ylide prepared at room temperature from dimethyl [6 (methoxycarbonyl)-2-oxohexyl] phosphonate (415 μL, 1.41 mmol) and NaH (51 mg, 1.27 mmol, 60% in oil) in 4 mL of THF. The reaction was stirred for 10 min, neutralized with saturated NH_4Cl (2 mL) and extracted with diethyl ether (3×2 mL). The organic layers were washed with brine (2 mL), dried with Na_2SO_4 and evaporated in vacuo. The crude material was purified by flash chromatography on silica gel (cyclohexane/ethyl acetate, 8:2) to give 258 mg of **18** (89% in two steps. TLC R_f: 0.68 (cyclohexane/ethyl acetate, 1:1). IR (neat): ν 1733, 1710 cm^{-1}. ^{1}H NMR (360 MHz, $CDCl_3$): δ 1.58–1.69 (4H, m, 13-H, 14-H), 1.75–1.83 (2H, m, 3-H), 2.03 (1H, td, J=3.5, 15.9 Hz, 6-H), 2.32 (2H, t, J=7.1 Hz, 15-H), 2.35–2.52 (2H, m, 2-H), 2.56 (2H, t, J=7.1 Hz, 12-H), 2.57–2.68 (1H, m, 4-H), 2.98 (1H, td, J=7.5, 15.9 Hz, 6′-H), 3.22–3.30 (1H, m, 8-H), 3.61 (3H, s, OCH_3), 3.64 (3H, s, OCH_3), 5.24 (1H, ddd, J=3.5, 5.3, 8.8 Hz, 5-H), 5.30 (1H, td, J=3.5, 7.5 Hz, 7-H), 6.29 (1H, dd, J=1.0, 15.8 Hz, 10-H), 6.72 (1H, dd, J=9.1, 15.8 Hz, 9-H), 7.38–7.45 (4H, m, Ar-H), 7.52–7.58 (2H, m, Ar-H), 7.98–8.05 (4H, m, Ar-H). ^{13}C NMR (91 MHz, $CDCl_3$): δ 23.3 (C-13), 23.8 (C-3), 24.5 (C-14), 32.2 (C-2), 33.8 (C-15), 38.0 (C-6), 40.5 (C-12), 47.1 (C-4), 50.3 (C-8), 51.5 (OCH_3), 51.6 (OCH_3), 77.3 (C-7), 78.0 (C-5), 128.4 (C-Ar), 129.6 (C-Ar), 129.9 (C-Ar), 130.0 (C-Ar), 132.6 (C-10), 133.2 (C-Ar), 141.3 (C-9), 165.9 (C(O)), 166.1 (C(O)), 173.2 (C-1), 173.8 (C-16), 199.0 (C-11). Anal. calcd for $C_{32}H_{36}O_9$: C, 68.07; H, 6.43. Found: C, 68.10; H, 6.45.

4.1.13. (1*R*,2*S*,3*S*,4*S*)-1,4-Di-*O*-(benzoyl)-3-(methoxycarbonylethyl)-2-(methoxycarbonyl-3-oxo-octanyl) cyclopentane (19). A mixture of **18** (20 mg, 35 μmol) and 10% Pd/C (1.6 mg) in absolute ethanol (0.7 mL) was hydrogenated at atmospheric pressure for 4 h. The mixture was filtered through celite and washed with ethyl acetate. The organic layer was concentrated to provide 20 mg of **19** (100%). TLC R_f: 0.68 (cyclohexane/ethyl acetate, 1:1). IR (neat): ν 1733, 1710 cm^{-1}. ^{1}H NMR (360 MHz, $CDCl_3$): δ 1.39–1.51 (1H, m, 9-H), 1.52–1.62 (4H, m, 13-H, 14-H), 1.62–1.73 (1H, m, 3-H), 1.77–1.89 (1H, m, 9′-H),

1.80–1.92 (1H, m, 3′-H), 1.83–1.98 (1H, m, 6-H), 2.22–2.34 (2H, m, 15-H), 2.29–2.40 (1H, m, 8-H), 2.37–2.48 (2H, m, 12-H), 2.40–2.50 (1H, m, 4-H), 2.41–2.56 (2H, m, 2-H), 2.52–2.70 (2H, m, 10-H), 2.90 (1H, td, J=7.6, 15.6 Hz, 6′-H), 3.62 (3H, s, OCH_3), 3.63 (3H, s, OCH_3), 5.09–5.14 (1H, m, 7-H), 5.10–5.17 (1H, m, 5-H), 7.38–7.45 (4H, m, Ar-H), 7.51–7,58 (2H, m, Ar-H), 7.98–8.05 (4H, m, Ar-H). ^{13}C NMR (91 MHz, $CDCl_3$): δ 20.5 (C-9), 22.6 (C-3), 23.2 (C-13), 24.4 (C-14), 32.2 (C-2), 33.8 (C-15), 37.6 (C-6), 40.4 (C-10), 42.5 (C-12), 45.7 (C-8), 45.8 (C-4), 51.5 (OCH_3), 51.6 (OCH_3), 78.1 (C-7), 78.3 (C-5), 128.4 (C-Ar), 129.6 (C-Ar), 130.2 (C-Ar), 133.0 (C-Ar), 166.2 (C(O)), 173.6 (C-16), 173.8 (C-1), 209.7 (C-11). Anal. calcd for $C_{32}H_{38}O_9$: C, 67.83; H, 6.76. Found: C, 67.90; H, 6.74.

4.1.14. 20-Carboxy-2,3,4,5-tetranor-15-oxo-5,6,13,14-tetrahydro-15F$_{2t}$-isoP dimethyl ester (2). To the solution of **19** (38 mg, 67 μmol) in 580 μL of methanol and 380 μL of THF was added 1N solution of NaOH (890 μL). The mixture was stirred 2 h at 40°C. 1N solution of $NaHSO_4$ (945 μL) was then added for neutralization. The reaction was diluted in water (1 mL) and extracted with ethyl acetate (3×5 mL). The organic layers were dried with Na_2SO_4 and evaporated. The residue was esterified with an etheral solution of diazomethan. After evaporation of solvents, the crude product was purified by flash chromatography on silica gel (cyclohexane/ethyl acetate, 2:3) to give 20 mg of **2** (83%). TLC R_f: 0.46 (ethyl acetate/acetic acid, 19:1). IR (neat): ν 3409, 1732, 1713 cm^{-1}. ^{1}H NMR (360 MHz, $CDCl_3$): δ 1.31–1.44 (1H, m, 9-H), 1.35–1.48 (1H, m, 3-H), 1.51–1.60 (1H, m, 6-H), 1.53–1.60 (2H, m, 13-H), 1.54–1.64 (2H, m, 14-H), 1.59–1.71 (1H, m, 9′-H), 1.65–1.77 (1H, m, 3′-H), 1.94–2.02 (1H, m, 4-H), 1.97–2.05 (1H, m, 8-H), 2.29 (2H, t, J=7.1 Hz, 15-H), 2.32–2.43 (3H, m, 2-H, 6′-H), 2.35–2.44 (2H, m, 12-H), 2.49 (2H, t, J=7.3 Hz, 10-H), 3.64 (3H, s, OCH_3), 3.65 (3H, s, OCH_3), 3.85–3.91 (1H, m, 5-H), 3.90–3.95 (1H, m, 7-H). ^{13}C NMR (91 MHz, $CDCl_3$): δ 21.6 (C-9), 23.1 (C-13), 23.2 (C-3), 24.4 (C-14), 32.7 (C-2), 33.8 (C-15), 41.1 (C-10), 42.4 (C-12), 42.9 (C-6), 48.8 (C-8), 48.9 (C-4), 51.5 (OCH_3), 51.6 (OCH_3), 76.0 (C-7), 76.2 (C-5), 173.9 (C-16), 174.0 (C-1), 210.5 (C-11). Anal. calcd for $C_{32}H_{36}O_9$: C, 60.32; H, 8.44. Found: C, 60.35; H, 8.42. $[\alpha]_D^{20}$=+1.13 (c=10^{-3}, MeOH).

4.1.15. (1*S*,2*R*,3*R*,4*R*)-3-(3′-Methoxyprop-2′(*E*,*Z*)-enyl)-2-(*tert*-butyldiphenylsilyloxymethyl)-1,4-di-*O*-(triethylsilyl) cyclopentane(21). A solution of *t*BuOK (44 mg, 0.4 mmol) in 1.2 mL of THF at 0°C was added to a suspension of (methoxymethyl)triphenylphosphonium chloride (135 mg, 0.394 mmol) in 0.3 mL of THF at 0°C. The solution became red. The ylide was stirred 10 min and added to a solution of aldehyde[11b,13] (84 mg, 0.13 mmol) in 0.25 mL of THF at 0°C. After 30 min, 0.9 mL of brine was added. The mixture was extracted with diethyl ether (3×5 mL). The organic layers were dried and evaporated under reduce pressure. The residue was purified by chromatography on silica gel (0–2% of ethyl acetate in cyclohexane) to give 62 mg of **21** (71%) in ratio *E*/*Z*: 7:3. TLC R_f: 0.72 (cyclohexane/ethyl acetate, 90:10).

E Isomer. ^{1}H NMR (100 MHz, $CDCl_3$): δ 0.30–0.70 (12H, m, SiCH_2CH$_3$), 0.70–1.00 (18H, m), 1.00 (9H, s, C(CH_3)$_3$), 1.90–2.60 (6H, m, 2-H, 3-H, 5-H, 7-H), 3.25–3.70 (5H, m, 6-H, OCH3), 3.80–4.40 (2H, m, 1-H, 4-H), 4.45–4.80 (1H, m, 8-H), 6.06 (1H, d, J=12.5 Hz, 9-H), 7.25–7.50 (6H, m, Ar-H), 7.55–7.70 (4H, m, Ar-H). ^{13}C NMR (25 MHz, $CDCl_3$): δ 4.7 (SiCH_2CH$_3$), 4.9 (SiCH_2CH$_3$), 6.6 (SiCH$_2$-CH_3), 19.1 (C(CH$_3$)$_3$), 26.9 (C(CH$_3$)$_3$), 48,6 (C-3 or C-7), 45.2 (C-3 or C-7), 50.4 (C-2), 59.2 (OCH_3), 62.4 (C-6), 73.2 (C-1), 76.2 (C-4), 102.0 (C-8), 127.6 (C-Ar), 129.7 (C-Ar), 133.2 (C-Ar), 135.7 (C-Ar), 147.1 (C-9).

Z Isomer. ^{1}H NMR (100 MHz, $CDCl_3$): δ 0.30–0.70 (12H, m, SiCH_2CH$_3$), 0.70–1.00 (18H, m, 1.00 (9H, s, C(CH_3)$_3$), 1.90–2.60 (6H, m, 2-H, 3-H, 5-H, 7-H), 3.25–3.70 (5H, m, 6-H, OCH3), 3.80–4.40 (2H, m, 1-H, 4-H), 4.45–4.80 (1H, m, 8-H), 5.80 (1H, d, J=5.7 Hz, 9-H), 7.25–7.50 (6H, m, Ar-H), 7.55–7.70 (4H, m, Ar-H). ^{13}C NMR (25 MHz, $CDCl_3$): δ 4.7 (SiCH_2CH$_3$), 4.9 (SiCH_2CH$_3$), 6.6 (SiCH$_2$ CH_3), 19.1 (C(CH$_3$)$_3$), 26.9 (C(CH$_3$)$_3$), 48,6 (C-3 or C-7), 45.2 (C-3 or C-7), 50.4 (C-2), 59.2 (OCH_3), 62.4 (C-6), 72.3 (C-1), 76.5 (C-4), 105.9 (C-8), 127.6 (C-Ar), 129.7 (C-Ar), 133.2 (C-Ar), 135.7 (C-Ar), 146.2 (C-9). Anal. calcd for $C_{38}H_{64}O_4Si_3$: C, 88.20; H, 9.64. Found: C, 88.24; H, 9.59.

4.1.16. (1*S*,2*R*,3*R*,4*R*)-3-(Hydroxyethyl)-2-(*tert*-butyldiphenylsilyloxymethyl)-1,4-di-*O*-(triethylsilyl) cyclopentane(23). To the (1*S*,2*R*,3*R*,4*R*)-3-(carbomethoxymethyl)-2-(*tert*-butyldiphenylsilyloxymethyl)-1,4-di-*O*-(triethylsilyl)-cyclopentane (544 mg, 0.81 mmol) in 1.2 mL of toluene, was added 2 M THF solution of $LiBH_4$ (446 μL, 0.89 mmol) at room temperature. The mixture was refluxed 3 h, and 3 mL of water were added. The solution was neutralized with 2 M HCl solution and stirred 30 min. The aqueous layer was saturated with K_2CO_3 and extract with diethyl ether (3×5 mL). The organic layer was dried with Na_2SO_4 and concentrated. The residue was purified by chromatography (5–20% ethyl acetate in heptane) to give 494 mg of **23** (95%). TLC R_f: 0.65 (heptane/ethyl acetate, 70:30). IR (neat) 3370 cm^{-1}. ^{1}H NMR (360 MHz, $CDCl_3$): δ 0.45–0.63 (12H, m, SiCH_2CH$_3$), 0.85–0.97 (18H, m, SiCH$_2$$CH_3$), 1.05 (9H, s, C(C$H_3$)$_3$), 1.50–1.73 (3H, m, 5-H, 7-H), 2.00 (1H, m, 2-H), 2.24–2.39 (2H, m, 5′-H, 3-H), 2.75 (1H, bs, OH), 3.56–3.70 (4H, m, 6-H, 8-H), 4.00 (1H, q, J=8.6 Hz, 4-H), 4.10–4.12 (1H, m, 1-H), 7.24–7.42 (6H, m, Ar-H), 7.61–7.64 (4H, m, Ar-H). ^{13}C NMR (91 MHz, $CDCl_3$): δ 4.7 (SiCH_2CH$_3$), 5.0 (SiCH_2CH$_3$), 6.8 (SiCH$_2$-CH_3), 19.1 (C(CH$_3$)$_3$), 26.9 (C(CH$_3$)$_3$), 31.8 (C-7), 44.9 (C-5), 45.7 (C-3), 52.1 (C-2), 62.4, 62.6 (C-6 and C-8), 73.3 (C-1), 77.5 (C-4), 127.7 (C-Ar), 129.7 (C-Ar), 133.2 (C-Ar), 135.7 (C-Ar). Anal. calcd for $C_{36}H_{62}O_4Si_3$: C, 67.23; H, 9.72. Found: C, 67.21; H, 9.75.

4.1.17. (1*S*,2*R*,3*R*,4*R*)-3-(Bromoethyl)-2-(*tert*-butyldiphenylsilyloxymethyl) cyclopentan 1,4 diol (24). To a solution of **23** (96 mg, 0.15 mmol) and triphenylphosphin (62 mg, 0.239 mmol) in 0.9 mL of acetonitrile was added carbon tetrabromide (79 mg, 0.239 mmol) at room temperature and under N_2 atmosphere. The mixture was stirred 50 min. The solution was concentrated in vacuo and was purified by chromatography (20–70% ethyl acetate in cyclohexane) to give 50.5 mg of **24** (71%). TLC R_f: 0.76 (ethyl acetate). ^{1}H NMR (360 MHz, $CDCl_3$): δ 1.04 (9H, s, C(CH_3)$_3$), 1.60 (1H, td, J=4, 14.1 Hz, 5-H), 1.79–1.89 (2H, m, 7-H), 2.24–2.30 (2H, m, 2-H, 3-H), 2.40 (1H, m, 5′-H),

3.32–3.42 (2H, m, 8-H), 3.53 (1H, d, J=6.6 Hz, 6-H), 3.67 (1H, dd, J=4.6, 10.5 Hz, 6-H), 3.92–3.99 (1H, m, 4-H), 4.18–4.20 (1H, m, 1-H), 7.24–7.44 (6H, m, Ar-H), 7.62–7.65 (4H, m, Ar-H). ^{13}C NMR (91 MHz, $CDCl_3$): δ 19.1 ($C(CH_3)_3$), 26.9 ($C(CH_3)_3$), 32.1 (C-7 and C-8), 43.1 (C-5), 47.2 (C-3), 51.2 (C-2), 62.8 (C-6), 74.8 (C-1), 76.8 (C-4), 127.8 (C-Ar), 129.9 (C-Ar), 133.0 (C-Ar), 135.5 (C-Ar). Anal. calcd for $C_{36}H_{61}BrO_3Si_3$: C, 61.24; H, 8.71. Found: C, 61.25; H, 8.68.

4.1.18. (1*S*,2*R*,3*R*,4*R*)-3-(Cyanoethyl)-2-(*tert*-butyldiphenylsilyloxymethyl) cyclopentan 1,4 diol (25). At room temperature, potassium cyanide (7 mg, 94.2 μmol) was added to **24** (100 mg, 31.4 μmol) in a solution of 51 μL of ethanol/water: 2:1. After 5 min, the mixture was refluxed 1 day and evaporated under reduced pressure. The residue was stirred vigorously with 50 μL of 2N KOH solution and 50 μL of diethyl ether. The aqueous layer was extracted with ethyl acetate (3×1 mL). The organic layers were dried with Na_2SO_4 and evaporated. The residue was purified by chromatography on silica gel (50–100% of ethyl acetate in cyclohexane) to give 9 mg of **25** (65%). TLC R_f: 0.70 (ethyl acetate). IR (neat): 3420, 2930, 2250, 1440 cm^{-1}. ^{1}H NMR (100 MHz, $CDCl_3$): δ 1.0 (9H, s, $C(CH_3)_3$), 1.5–1.8 (3H, m, 5-H, 7-H), 2.1–2.6 (5H, m, 2-H, 3-H, 5′-H, 8-H), 3.4–3.7 (2H, m, 6-H), 3.8–4.0 (1H, m, 4H), 4.1–4.3 (1H, m, 1-H), 7.2–7.5 (6H, m, Ar-H), 7.6–7.7 (4H, m, Ar-H). ^{13}C NMR (25 MHz, $CDCl_3$): δ 16.1 (C-8), 19.1 ($C(CH_3)_3$), 24.7 (C-7), 26.9 ($C(CH_3)_3$), 43.3 (C-5), 47.2 (C-3), 51.2 (C-2), 62.5 (C-6), 74.5 (C-1), 77.0 (C-4), 119.9 (CN), 127.8 (C-Ar), 129.9 (C-Ar), 132.8 (C-Ar), 135.5 (C-Ar). Anal. calcd for $C_{37}H_{61}NO_3Si_3$: C, 68.14; H, 9.43. Found: C, 68.17; H, 9.41.

4.1.19. (2*S*,4*R*,5*R*)-6-*O*-(*tert*-Butyldiphenylsilyl)-2,4-di-*O*-(triethylsilyl)-1,1-diethylthio-5-iodo-hexane (28). To the diol **5** (259 mg, 420 μmol) in 3.5 mL of dry pyridine was added chlorotriethylsilane (560 μL, 3.35 mmol). The reaction mixture was stirred overnight at room temperature. The mixture was evaporated. The residue was purified by flash chromatography on silica gel (2% diethyl ether in cyclohexane) to give 258 mg of **28** (73%). TLC R_f: 0.76 (cyclohexane/ethyl acetate, 95:5). ^{1}H NMR (360 MHz, $CDCl_3$): δ 0.43–0.69 (12H, m, $SiCH_2CH_3$), 0.83–1.00 (18H, m, $SiCH_2CH_3$), 1.07 (9H, s, $C(CH_3)_3$), 1.16–1.41 (6H, m, SCH_2CH_3), 1.82–1.92 (1H, m, 3-H), 2.13–2.22 (H, m, 3′-H), 2.58–2.80 (4H, m, SCH_2CH_3), 3.42–3.50 (1H, m, 4-H), 3.79–3.98 (3H, m, 1-H, 6-H), 4.01–4.07 (1H, m, 2-H), 4.22–4.29 (2H, m, 5-H), 7.35–7.40 (6H, m, Ar-H), 7.61–7.69 (4H, m, Ar-H). ^{13}C NMR (91 MHz, $CDCl_3$): δ 5.2 ($SiCH_2CH_3$), 5.3 ($SiCH_2CH_3$), 6.9 ($SiCH_2CH_3$), 14.5 (SCH_2CH_3), 14.7 (SCH_2CH_3), 19.3 ($C(CH_3)_3$), 25.6 (SCH_2CH_3), 25.9 (SCH_2CH_3), 26.9 ($C(CH_3)_3$), 42.6 (C-3), 44.5 (C-5), 57.5 (C-1), 66.9 (C-6), 68.4 (C-4), 73.1 (C-2), 127.6 (C-Ar), 129.7 (C-Ar), 133.1 (C-Ar), 133.3 (C-Ar), 135.6 (C-Ar). Anal. calcd for $C_{38}H_{67}IO_3S_2Si_3$: C, 53.87, H, 7.97. Found: C, 53.91, H, 7.95.

4.1.20. (2*S*,4*R*,5*R*)-6-*O*-(*tert*-Butyldiphenylsilyl)-2,4-di-*O*-(triethylsilyl)-5-iodo-hexanal (29). To the thioacetal **28** (100 mg, 118 μmol) in 7.6/0.8 mL of acetone/water, was added mercuric oxide (243 mg, 1.12 mmol) and mercuric chloride (105 mg, 387 μmol). The heterogeneous mixture was refluxed overnight. 4 mL of saturated sodium bicarbonate solution was added. The mixture was filtered through Celite, extracted with 3×10 mL of methylene chloride. The organic layers were washed with 3×5 mL of potassium iodide solution and with 5 mL of brine. The extracts were dried over Na_2SO_4 and evaporated. 87 mg (100%) of aldehyde **30** was obtained. TLC R_f: 0.60 (cyclohexane/ethyl acetate, 95:5). ^{1}H NMR (100 MHz, $CDCl_3$): δ 0.40–0.77 (12H, m, $SiCH_2CH_3$), 0.83–0.97 (18H, m, $SiCH_2CH_3$), 1.10 (9H, s, $C(CH_3)_3$), 1.66–2.00 (1H, m, 3-H), 2.13–2.43 (1H, m, 3-H), 3.33–4.36 (5H, m, 2-H, 4-H, 5-H, 6-H), 7.28–7.49 (6H, m, Ar-H), 7.52–7.81 (4H, m, Ar-H), 9.60 (1H, s, CHO). ^{13}C NMR (25 MHz, $CDCl_3$): δ 4.8 ($SiCH_2CH_3$), 5.2 ($SiCH_2CH_3$), 6.7 ($SiCH_2CH_3$), 6.8 ($SiCH_2CH_3$), 19.2 ($C(CH_3)_3$), 26.8 ($C(CH_3)_3$), 39.1 (C-3), 42.0 (C-5), 65.4 (C-2), 68.4 (C-4), 74.6 (C-6), 127.7 (C-Ar), 129.8 (C-Ar), 133.0 (C-Ar), 135.6 (C-Ar), 203.3 (C-1).

4.1.21. (5*S*,7*R*,8*R*)-9-*O*-(*tert*-Butyldiphenylsilyl)-1-(diisopropylacetal)-5,7-di-*O*-(triethylsilyl)-8-iodo-3(*Z*)-nonene (31). A 1 M THF solution of NaHMDS (177 μL, 177 μmol) was added to a suspension of (3,3-diisopropoxypropyl)triphenylphosphonium bromide **30** (93 mg, 185 μmol) in 1 mL of THF at −80°C. The resulting orange solution of ylide was stirred 10 min. This solution was added to aldehyde **29** (46 mg, 62 μmol) solution in 0.75 mL of THF. After slow warming to room temperature over 1 h, the reaction mixture was hydrolyzed with 3 mL of water. The aqueous layer was extracted with diethyl ether (3×3 mL), and the combined extracts were washed with brine (5 mL). All organic layers were dried with Na_2SO_4 and concentrated. The residue was purified by chromatography (10% diethyl ether in cyclohexane) to give 49 mg of **31** (72%). TLC R_f: 0.54 (cyclohexane/ethyl acetate, 95:5). ^{1}H NMR (100 MHz, $CDCl_3$): δ 0.43–0.66 (12H, m, $SiCH_2CH_3$), 0.80–0.97 (18H, m, $SiCH_2CH_3$), 1.00 (9H, s, $C(CH_3)_3$), 1.11–1.26 (12H, m, $CH(CH_3)_2$), 1.62–1.88 (2H, m, 6-H), 2.31–2.46 (2H, m, 2-H), 3.34–3.51 (1H, m, 7-H), 3.71–4.00 (2H, m, 9-H), 3.80–3.83 (2H, m, $OCH(CH_3)_2$), 4.40–4.63 (2H, m, 5-H, 8-H), 4.49 (1H, t, J=5.5 Hz, 1-H), 5.34–5.46 (2H, m, 3-H, 4-H), 7.28–7.43 (6H, m, Ar-H), 7.60–7.71 (4H, m, Ar-H). ^{13}C NMR (91 MHz, $CDCl_3$): δ 5.0 ($SiCH_2CH_3$), 5.3 ($SiCH_2CH_3$), 6.9 ($SiCH_2CH_3$), 19.2 ($C(CH_3)_3$), 22.5 ($CH(CH_3)_2$), 22.7 ($CH(CH_3)_2$), 23.3 ($C(CH_3)_3$), 34.1 (C-2), 45.5 (C-6), 46.5 (C-8), 65.9 (C-9), 67.1 (C-5), 67.1 (C-7), 67.9 ($OCH(CH_3)_2$), 99.5 (C-1), 124.3 (C-3), 127.6 (C-Ar), 129.7 (C-Ar), 133.1 (C-Ar), 133.4 (C-Ar), 134.8 (C-4), 135.6 (C-Ar). Anal. calcd for $C_{43}H_{75}IO_5Si_3$: C, 58.48; H, 8.56. Found: C, 58.50; H, 8.55.

4.1.22. (1*R*,2*S*,3*S*,4*S*)-2-*tert*-Butyldiphenylsilyloxy methyl-1,4-di-*O*-(triethylsilyl)-3-(diisopropylacetal propyl) cyclopentane (32). To a solution of **31** (103 mg, 116 μmol) in 1.6 mL of *p*-xylene was added tributyltin hydride (39 μL, 140 μmol) under a stream of dry argon. At room temperature, a 1N triethyl borane solution (23 μL, 23 μmol) was added under a stream of dry air. The mixture was stirred 10 min. The solvent was removed and the mixture was subjected to flash chromatography (cyclohexane/diethyl ether, 95:5) to give 63 mg of **32** (72%). TLC R_f: 0.55 (cyclohexane/ethyl acetate, 95:5). ^{1}H NMR (360 MHz, $CDCl_3$): δ 0.45 (6H, q, J=8.0 Hz, $(CH_3CH_2)_3Si$), 0.54 (6H, q, J=8.0 Hz, $(CH_3CH_2)_3Si$), 0.85 (9H,

t, J=8.0 Hz, ($CH_3CH_2)_3Si$), 0.92 (9H, t, J=8.0 Hz, ($CH_3CH_2)_3Si$), 1.04 (9H, s, C($CH_3)_3$), 1.07 (3H, d, J=6.0 Hz, OCH($CH_3)_2$), 1.09 (3H, d, J=6.0 Hz, OCH($CH_3)_2$), 1.14 (3H, d, J=6.0 Hz, OCH($CH_3)_2$), 1.15 (3H, d, J=6.0 Hz, OCH($CH_3)_2$), 1.30–1.38 (2H, m, 3-H), 1.43–1.53 (1H, m, 6-H), 1.50–1.57 (2H, m, 2-H), 1.98–2.03 (1H, m, 8-H), 2.08–2.12 (1H, m, 4-H), 2.25–2.36 (1H, m, 6′-H), 3.53–3.60 (2H, m, 9-H), 3.77–3.86 (2H, m, OCH($CH_3)_2$), 3.90 (1H, dd, J=7.3, 15.2 Hz, 5-H), 4.08–4.12 (1H, m, 7-H), 4.45 (1H, t, J=5.3 Hz, 1-H), 7.30–7.43 (6H, m, Ar-H), 7.59–7.67 (4H, m, Ar-H). ^{13}C NMR (91 MHz, $CDCl_3$): δ4.7 (($CH_3CH_2)_3Si$), 4.9 (($CH_3CH_2)_3Si$), 6.8 (($CH_3CH_2)_3Si$), 6.9 (($CH_3CH_2)_3Si$), 19.1 (C($CH_3)_3$), 22.5 (OCH($CH_3)_2$), 22.7 (OCH($CH_3)_2$), 23.1 (C-3), 23.2 (C-2), 23.4 (OCH($CH_3)_2$), 26.9 (C($CH_3)_3$), 45.3 (C-6), 47.6 (C-4), 50.8 (C-8), 62.4 (C-9), 67.4 (OCH($CH_3)_2$), 67.5 (OCH($CH_3)_2$), 73.4 (C-7), 77.2 (C-5), 100.5 (C-1), 127.6 (C-Ar), 129.6 (C-Ar). 135.7 (C-Ar). Anal. calcd for $C_{43}H_{76}O_5Si_3$: C, 68.20; H, 10.12. Found: C, 68.15; H, 10.09. $[\alpha]_D^{20}$=+23.8 (c=10^{-3}, MeOH).

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