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Synthesis of 17-membered ring macrocycle: studies toward the enantioselective synthesis of fusidic acid [1]

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Summary — The synthesis of a 17-membered carbocycle by macrocyclization with a chloroketone is reported. Attempts to produce a tetracyclic intermediate for the synthesis of fusidic acid from the transannular aldol and Diels–Alder reactions on this key macrocyclic triene are described.

macrocycle / transannular reaction / aldol / Diels–Alder / cycloaddition 2 + 4 / fusidic acid / diterpene

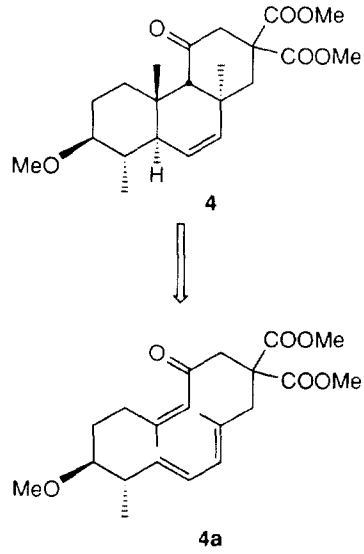
Résumé — La synthèse d'un macrocarbocycle à 17 membres: Étude vers la synthèse énantiosélective de l'acide fusidique. La synthèse d'un macrocycle à 17 membres par macrocyclisation d'une chlorocétone est rapportée. Différents essais en vue d'obtenir un intermédiaire tétracyclique pour la synthèse de l'acide fusidique en passant par des réactions d'aldolisation et de Diels–Alder transannulaires sur le triène macrocyclique sont décrits.

macrocycle / réaction transannulaire / aldol / Diels–Alder / cycloaddition 2 + 4 / acide fusidique / diterpène

Introduction

Fusidic acid **1** was isolated from the fermentation broth *Fusidium Coccineum* and the structure was determinated by Godtfredsen in 1962 [2]. Since its discovery, fusidic acid underwent many biological tests [3] and it is now a well-known antibiotic [4]. Moreover, with regard to its total synthesis by Dauben [5] and related chemical modifications [6], a wealth of knowledge has been collected on the chemistry of fusidic acid.

The structural analysis of fusidic acid **1** shows a *trans–syn–trans* (TST) ABC ring junction. This unusual stereochemistry includes a boat conformation for the B ring. In diterpenes, this conformation is very rare and is found only in the fusidane family, eg, cephalosporin P_1 **2** and helvolic acid **3** (fig 1). Our laboratory has been developing, in recent years, a strategy for the synthesis of polycyclic compounds via the transannular Diels–Alder reactjon (TADA) [7]. In principle, the transannular cycloaddition of a *trans–trans–cis* (TTC) cyclotetradecatriene should lead directly to an ABC[6.6.6] tricycle having the desired TST stereochemistry (eg, **4a** → **4**) (scheme 1). However, model studies with a TT diene bearing a methyl group indicated that this approach was not practical, since low yields for the cyclization of 14-membered macrocyclic trienes such as **4a** [8] were observed. We therefore decided to examine the ring construction strategy **7** → **6** → **5** (scheme 2) where a 17-membered ring would first be constructed to be followed by two consecutive



Scheme 1

transannular reactions, namely an aldol and a Diels–Alder. We wish to report our results on this approach.

Retrosynthetic approach

Fusidic acid **1** could be formally synthesized from the known tetracycle **5** through the use of Tanabe's proce-

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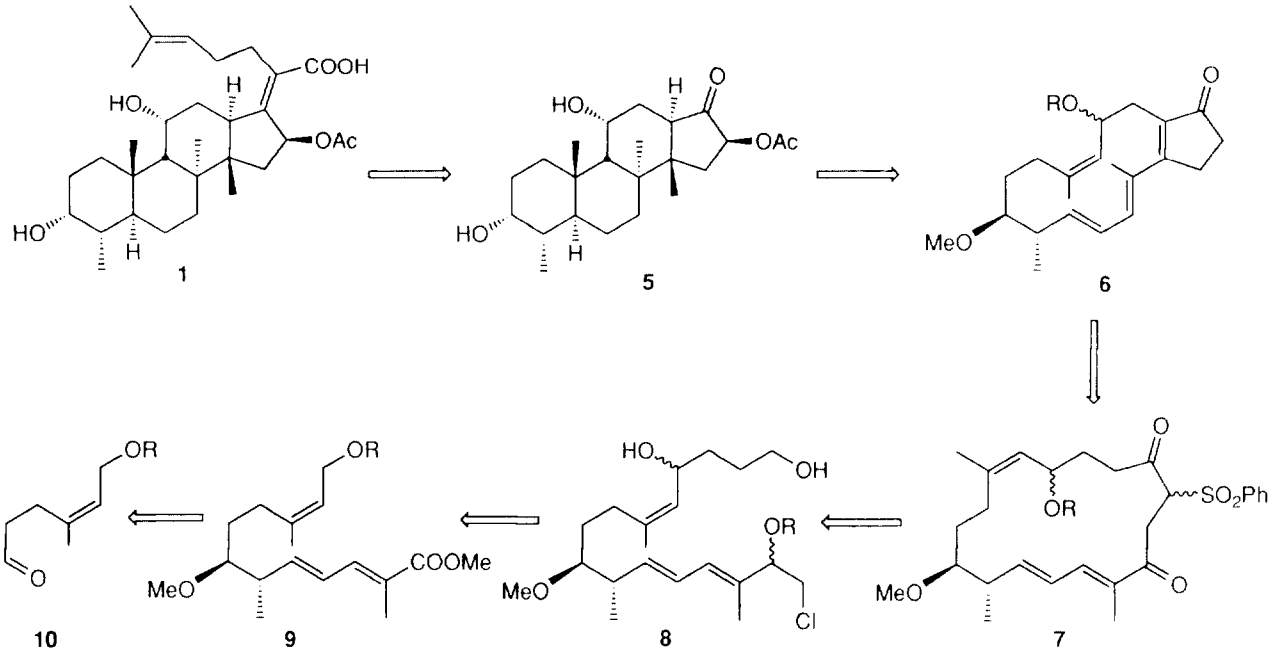


Scheme 2

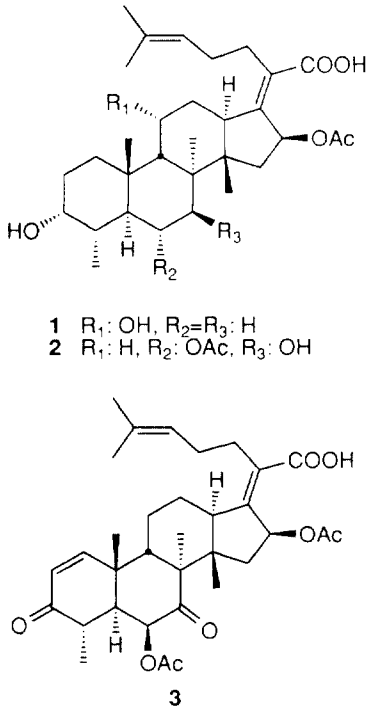


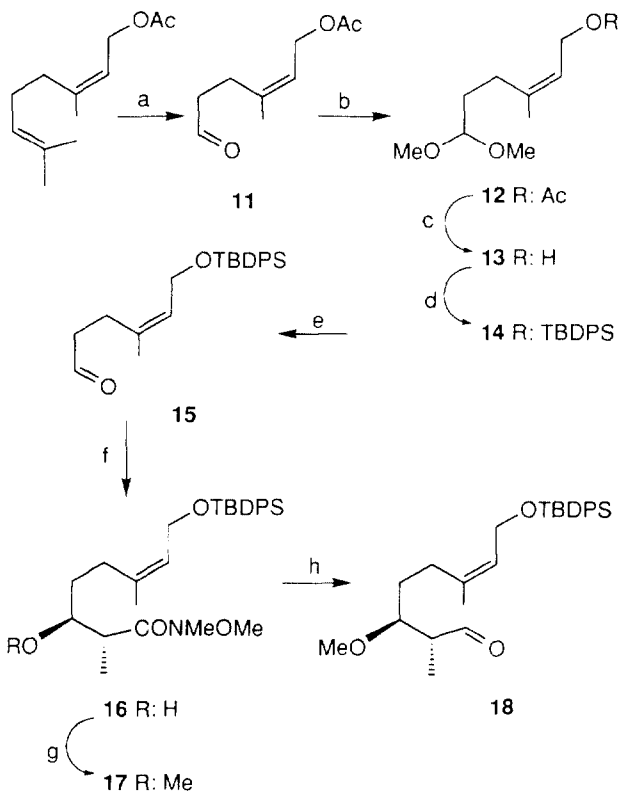
Fig 1.

dure [9]. Tetracycle **5** could derive from the TTC bicyclo[12.3.0]heptadecatetraene **6** which should undergo a highly diastereoselective transannular Diels–Alder reaction. Desulfonylation followed by transannular aldol reaction of the macrocycle **7** would create the D ring of macrocyclic precursor **6**. The required 17-membered ring macrocycle **7** could in turn be obtained via the linear chain **8**, itself produced from the ester **9**. Finally, starting from aldehyde **10** which can be readily obtained from neryl acetate, the ester **9** would be constructed using the Evans' enantioselective aldol methodology [10] followed by some relatively trivial synthetic reactions.

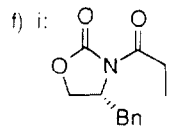
Results and discussion

The sequence started with selective ozonolysis [11] of the commercial available neryl acetate followed by protection [12] of the resulting aldehyde **11** to afford the dimethylacetal **12** in 94% yield (scheme 3). Transesterification of the acetate group with methanol gave the alcohol **13** (98%). Silyl ether protection of the resulting allylic alcohol followed by hydrolysis of the acetal function (98%) afforded the aldehyde **15** in 94% yield. The asymmetric aldol reaction developed by Evans [10] was used on the aldehyde **15** followed by a transamidation according to Weinreb's procedures [13] providing the corresponding amide **16** in 51% yield for the two steps.

The secondary alcohol **16** was protected [14] as a methyl ether giving **17** in 94% yield. A quantitative reduction of the amide **17** with DIBALH in tetrahydrofuran at −78 °C gave rise to the aldehyde **18** which was immediately used for the next reaction. A four-carbon homologation was carried out using the Wittig–Horner–Emmons phosphonate **19** [15] yielding in 80% an unseparable mixture of *E,E* and *Z,E* isomeric dienes **20** (ratio 16:1) (scheme 4). Reduction with DIBALH in dichloromethane at −78 °C gave a mixture of the corresponding geometrical isomers which were separated by flash chromatography without complication to furnish the pure *E,E* alcohol **21** in good yield. The chlorohydrin **23** was then readily obtained by oxidation of **21** with Dess–Martin periodinane [16] (80%) followed by an alkylation on **22** with $LiCH_2Cl$ (formed in situ) [17] in tetrahydrofuran at −78 °C (86%). The resulting secondary allylic alcohol **23** was protected by using

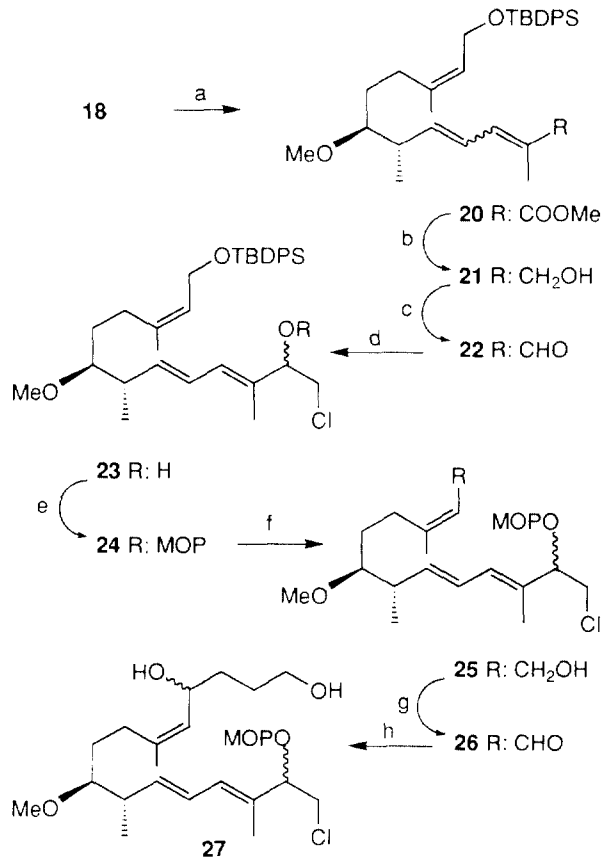


a) i: O_3, CH_2Cl_2, -78°C; ii: Zn, AcOH, 67%.
b) $LaCl_3 \cdot xH_2O$, $(MeO)_3CH$, MeOH, 94%.
c) K_2CO_3, MeOH, 98%.
d) TBDPS-Cl, imidazole, THF, 0°C, 98%.
e) Tos-OH, acetone/water (4:1), 69%.



f) i: Bu_2BOTf, Et_3N, CH_2Cl_2 0 to -78°C; ii: $AlMe_3$, NHMeOMe·HCl, CH_2Cl_2, -15 to 25°C, 51%.
g) MeI, NaH, THF/DMF, 0°C, 94%.
h) DIBALH, THF, -90°C, 100%.

Scheme 3



a) $(MeO)_2OP$ COOMe (19), BuLi, THF, -10°C, 94%.
b) DIBALH, CH_2Cl_2, -78°C, 80%.
c) Dess-Martin, CH_2Cl_2, 25°C, 80%.
d) ICH_2Cl, BuLi, THF, -78°C, 86%.
e) 2-Methoxypropene, PPTS, CH_2Cl_2, 0°C, 83%.
f) TBAF, THF, 89%.
g) TPAP, NMO, CH_2Cl_2, 94%.
h) $ClMg(CH_2)_3OMgCl$, THF, -78°C, 84%.

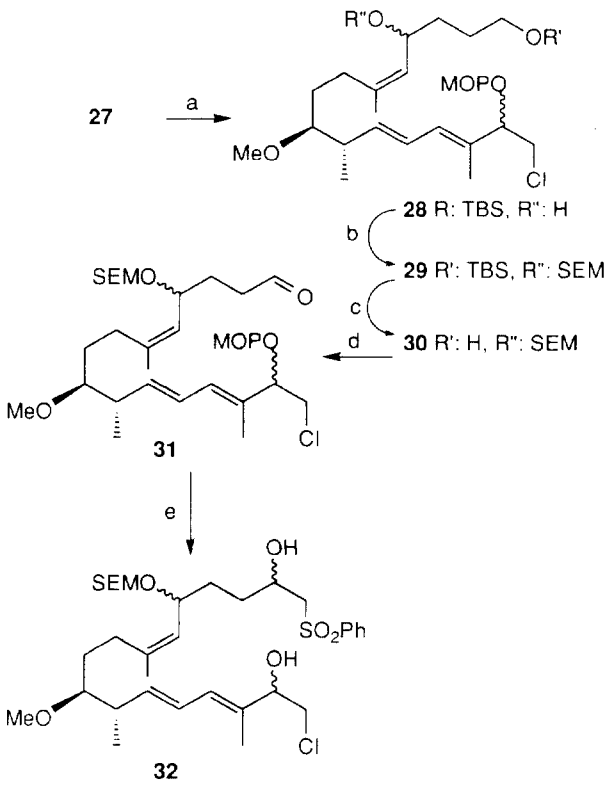
Scheme 4

2-methoxypropene and pyridinium *p*-toluenesulfonic acid in dichloromethane to give an acid sensitive acetal **24** in 83% yield. The alcohol **25** was obtained in 89% yield by the cleavage of the silylether **24** using TBAF in tetrahydrofuran.

The alcohol **25** was oxidized with tetrapropylammonium perruthenate [18] (TPAP) to lead the unsaturated aldehyde **26** (94%) which was reacted with the Grignard reagent $ClMg(CH_2)_3OMgCl$ [19] in tetrahydrofuran at −78 °C providing the diol **27** in 84% yield. A three-step sequence of protection and deprotection was carried out on diol **27** leading to the primary alcohol **30** in good yield (scheme 5). Oxidation of **30** with TPAP furnished the aldehyde **31** in 88% yield. Alkylation of **31** with lithium methylphenylsulfone in toluene followed by hydrolysis of the MOP acetal group yielded the diol **32** in 87% yield for the two steps. The chloroketone **33** was easily obtained by oxidation of the diol **32** with Dess–Martin periodinane (85%) (scheme 6).

We observed that the temperature plays an important part in the yield of macrocyclization. Indeed, the chloroketone function was found unstable at temperature above 50 °C. We found that the optimal temperature was 45 °C in acetonitrile (10^{-2} M) in presence of cesium carbonate. This condition led to the production of macrocycle **34** in 72% yield [20].

At this point, a simple desulfonylation should provide the desired 17-membered ring without complication. All attempts for the desulfonylation with the following reagent, SmI_2, Al(Hg) and Na(Hg) failed. In view of the negative results, we decided to remove the sulfone in two steps procedure. A base-catalyzed elimination on **34** with 1,7-diazabicyclo[4.5.0]undecene (DBU) in tetrahydrofuran led to the *trans*-enedione **35** in 90% yield. Unfortunately, the reduction of the enedione **35** with Mg, Zn or $[CuH(PPh_3)]_6$ failed or gave the dione **36** in low yield (<10%). After considerable experimentation, we found that the enedione **35** was easily reduced [21] with $Pd(PPh_3)_4$ and acetic acid in tetrahydrofuran yielding diene **36** in 91% yield.



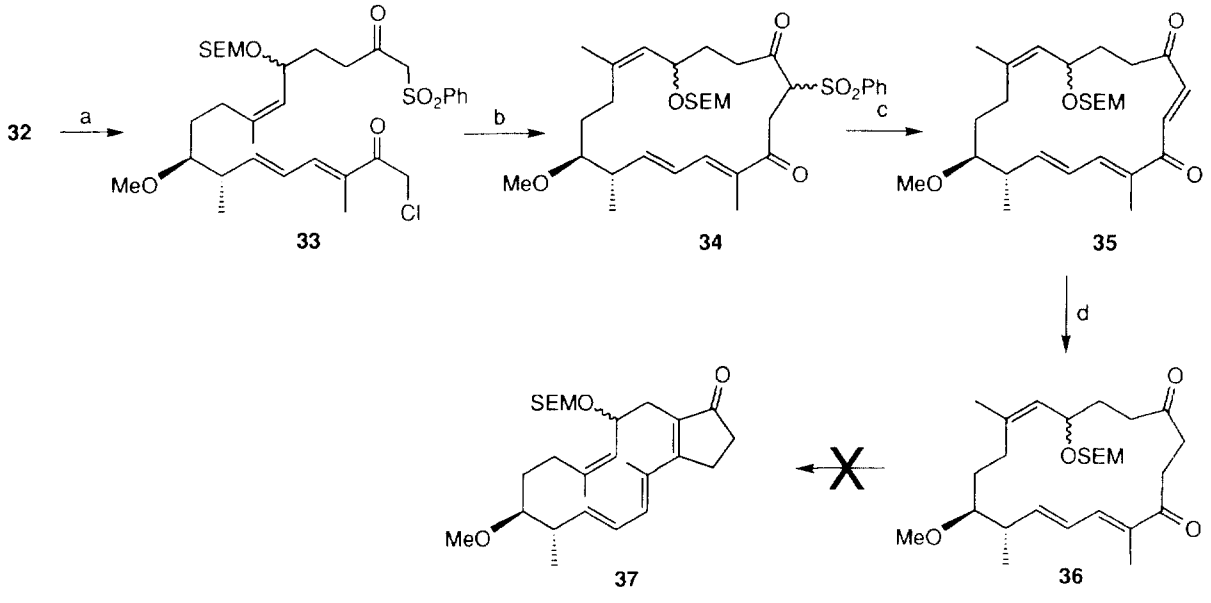
a) TBS-Cl, imidazole,THF, 0°C, 95%.
b) SEM-Cl, DIPEA, TBAI, CH_2Cl_2, 40°C, 100%.
c) TBAF, THF, 86%.
d) TPAP, NMO, CH_2Cl_2, 88%.
e) i: $MeSO_2Ph$, BuLi, THF, -78°C; ii: H_3O^+, 87%.

Scheme 5

The second stage of this project was to try the transannular aldol reaction to form the D ring of fusidic acid. Various conditions using different bases and solvents are summarized in table I and unfortunately, none of them were able to provide the transannular aldol adduct **37**. In some cases, we recovered only the starting material (entries 1, 2, 5 and 10) or in other cases, we observed only degradation. These results indicate that the transannular process is much more difficult than we anticipated. The difficulty resides probably in the acidity of the α-proton of the dienone leading to conjugated enol system and an unfavorable conformation for the transannular aldol step. Nevertheless, this approach has led to the asymmetric total synthesis of the interesting 17-membered ring macrocycles **35** and **36** using the chloroketone as electrophilic connector. The synthesis of intermediate **5** using an alternative transannular strategy is currently under active investigation.

Table I. Results for the transannular aldol reaction.

Entry	*Reagent*	*Solvent*	*Temp (°C)*	*Product*
1	NaOH (6 N)	THF	80	**36**
2	MeONa	MeOH	25	**36**
3	MeONa	MeOH	50	deg
4	*t*-BuOK	THF	25	deg
5	K_2CO_3	MeOH	50	**36**
6	$BF_3{\cdot}OEt_2/(AcO)_2O$	AcOH	0	deg
7	K_2CO_3	EtOH	72	deg
8	PPTS	C_6H_6	80	deg
9	—	C_6H_6	270	deg
10	—	C_6H_6	200	**36**
11	$SnCl_4$	C_6H_6	0	deg



a) Dess-Martin, CH_2Cl_2, 85%.
b) Cs_2CO_3, MeCN, 45°C, 72%.
c) DBU, THF, 25°C, 90%.
d) $Pd(PPh_3)_4$, $(Bu)_3SnH$, PhH, AcOH, 91%.

Scheme 6

Experimental section

All reactions were performed under nitrogen atmosphere with oven (150 °C) or flame-dried glassware. All solvents were distilled prior to use; diethyl ether and tetrahydrofuran were dried by distilling from sodium benzophenone ketyl. Toluene, acetonitrile, dichloromethane and dimethylformamide were distilled from calcium hydride. Cesium carbonate and lithium chloride were flame-dried under reduced pressure before use. Analytical and preparative thin layer chromatographies were carried out on glass plates precoated (0.25 mm) with 60 F-250 silicagel (Merck). Materials were detected by visualization under an ultraviolet lamp and/or by spraying with a solution of phosphomolybdic acid (10% in ethanol) followed by heating on a hot plate. Column chromatography was performed with 60 silica gel (230–400 mesh, Merck). Infrared spectra (IR) were taken on a Perkin-Elmer 1600 FT-IR spectrometer. The optical rotation ($[\alpha]_D$) measurements were obtained with a Perkin-Elmer 141 polarimeter. Proton and carbon nuclear magnetic resonance (NMR) spectra were recorded on a Bruker AC-300 instrument. The following abbreviations were used: s, singlet; d, doublet; t, triplet; q, quartet; and m, multiplet. Chemical shifts are reported in δ values relative to chloroform (7.26 ppm) for ^{1}H NMR and (77.0 ppm) for ^{13}C NMR as internal standard. Where necessary COSY, NOESY and J-resolved were performed. Mass spectral (MS) assays were obtained on a VG Micromass ZAB-2F instrument.

(Z)-6-Acetoxy-4-methylhex-4-enal **11**

To a solution of neryl acetate (107 g, 545 mmol) in dry dichloromethane (2.7 L) was bubbled ozone at −78 °C. The reaction was monitored by TLC until the starting material had almost entirely disappeared. The reaction was quenched with acetic acid (550 mL) and zinc dust (300 g, 4.6 mol) and the slurry mixture was stirred for 2 h at room temperature. The solid was removed by filtration on celite pad and the filtrate was washed (3×) with saturated aqueous sodium bicarbonate solution. The organic phase was purified by flash chromatography (20% ethyl acetate in hexanes) to afford a colorless oil **11** (62.1 g, 67%).

IR (film, ν cm^{-1}): 2 970, 2 729, 1 737, 1 235, 1 024.

^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 9.77 (1H, s, C*H*O), 5.39 (1H, t, J = 7 Hz, C(CH$_3$)=C*H*), 4.58 (2H, d, J = 7 Hz, C*H*$_2$OAc), 2.60–2.40 (4H, m, C*H*$_2$C*H*$_2$C(CH$_3$)=CH), 2.05 (3H, s, C*H*$_3$CO$_2$). 1.75 (s, 3H, C(C*H*$_3$)=CH).

^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 201.1, 170.9, 140.3, 120.5, 60.6, 42.1, 24.3, 23.0.

(Z)-1-Acetoxy-6,6-dimethoxy-3-methylhex-2-ene **12**

To a solution of aldehyde **11** (19 g, 111 mmol) in methanol (400 mL) were added hydrated lanthanum chloride (50 g, 76 mmol) and trimethyl orthoformate (82 g, 777 mmol). After stirring for 4 h, the reaction was quenched with saturated aqueous sodium bicarbonate solution (200 mL) and the mixture was concentrated. The aqueous residue was extracted with diethyl ether (3×). The combined organic phases were dried over magnesium sulfate, filtered and concentrated. The residue was purified by flash chromatography (20% ethyl acetate in hexanes) to provide a colorless oil **12** (22.5 g, 94%).

IR (film, ν cm^{-1}): 2 938, 2 831, 1 738, 1 235, 1 127.

^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 5.39 (1H, t, J = 7 Hz, C(CH$_3$)=C*H*), 4.59 (2H, d, J = 7 Hz, C*H*$_2$OAc), 4.33 (1H, t, J = 6 Hz, (CH$_3$O)$_2$C*H*), 3.28 (6H, s, (C*H*$_3$O)$_2$CH), 2.14 (2H, m, C*H*$_2$C(CH$_3$)), 2.05 (3H, s, C*H*$_3$CO), 1.77 (s, 3H, C(C*H*$_3$)=CH), 1.70 (2H, m, C*H*$_2$CH$_2$C(CH$_3$)).

^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 170.8, 141.6, 119.5, 103.6, 60.8, 52.5, 30.5, 26.9, 23.2, 20.9.

MS (m/e): 185 (M$^+$–OCH$_3$).

HMRS: calc for $C_{10}H_{17}O_3$: 185.1178; found: 185.1170.

(Z)-6,6-Dimethoxy-3-methylhex-2-en-1-ol **13**

To a solution of acetate **12** (17.5 g, 81 mmol) in methanol was added potassium carbonate (552 mg, 4.05 mmol). After stirring for 15 h, the reaction was quenched with a saturated aqueous ammonium chloride solution (300 mL) and the resulting mixture was concentrated. The aqueous residue was extracted several times with dichloromethane. The combined organic phases were dried over magnesium sulfate, filtered and concentrated. The residue was purified by flash chromatography (50% ethyl acetate in hexanes) to afford a colorless oil **13** (13.7 g, 98%).

IR (film, ν cm^{-1}): 3 421, 2 938, 1 669, 1 446, 1 054.

^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 5.49 (1H, t, J = 7 Hz, C(CH$_3$)=C*H*), 4.33 (1H, t, J = 6 Hz, (CH$_3$O)$_2$C*H*), 4.05 (2H, d, J = 7 Hz, CHC*H*$_2$OH), 3.28 (6H, s, (C*H*$_3$O)$_2$CH), 2.13 (3H, t, J = 7 Hz, C*H*$_2$C(CH$_3$) and O*H*), 1.73 (2H, m, C*H*$_2$CH$_2$C(CH$_3$)), 1.72 (s, 3H, C(C*H*$_3$)=CH).

^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 138.8, 125.1, 102.9, 58.4, 52.1, 29.6, 26.4, 23.0.

MS (m/e): 173 (M$^+$ - H).

HMRS: calc for $C_9H_{17}O_3$: 173.1178; found: 173.1175.

(Z)-1-(t-Butyldiphenylsiloxy)-6,6-dimethoxy-3-methylhex-2-ene **14**

A solution of alcohol **13** (15.0 g, 86 mmol), *t*-butyldiphenylchlorosilane (35.4 g, 33.5 mL,129 mmol) and imidazole (17.6 g, 258 mmol) in THF (500 mL) was stirred for 1 h. The reaction was quenched with saturated aqueous ammonium chloride solution (300 mL) and extacted with diethyl ether (3×300 mL). The organic phase was dried over magnesium sulfate and concentrated. The oil was purified by flash chromatography (20% ethyl acetate in hexanes) yielding a colorless oil **14** (34.7 g, 98%).

IR (film, ν cm^{-1}): 3 049, 2 955, 1 467, 1 382, 1 111.

^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 7.72–7.40 (10H, m, (C$_6$H$_5$)$_2$), 5.45 (1H, t, J = 7 Hz, C(CH$_3$)=C*H*), 4.12 (2H, d, J = 7 Hz, C*H*$_2$OTBDPS), 3.25 (6H, s, (C*H*$_3$O)$_2$CH), 1.95 (2H, m, C*H*$_2$C(CH$_3$)), 1.72 (3H, s, C(C*H*$_3$)=CH), 1.60 (2H, m, C*H*$_2$CH$_2$C(CH$_3$)), 1.10 (9H, s, (C*H*$_3$)$_3$C).

^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 136.7, 135.6, 134.0, 129.6, 127.6, 125.4, 103.9, 60.7, 52.5, 30.6, 27.1, 26.9, 23.3, 19.2.

MS (m/e): 355 (M$^+$ – C$_4$H$_9$).

HMRS: calc for $C_{21}H_{27}O_3Si$: 155.1729; found: 355.1734.

(Z)-6-(t-Butyldiphenylsiloxy)-4-methylhex-4-enal **15**

To a solution of silyl ether **14** (35.5 g, 86 mmol) in wet acetone (500 mL) was added *p*-toluenesulfonic acid (812 mg, 1.8 mmol). The reaction was monitored by TLC until the starting material was consumed. The reaction was quenched with a saturated aqueous sodium bicarbonate solution and the mixture was extracted several times with diethyl ether. The combined organic phases were dried over magnesium sulfate and concentrated. The residue was purified by flash chromatography (20% acetone in hexanes) to afford a colorless oil **15** (21.6 g, 69%).

IR (film, ν cm^{-1}): 3 048, 2 930, 2 856, 1 725, 1 427, 1 111.

^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 9.65 (1H, s, C*H*O), 7.70–7.39 (10H, m, $(C_6H_5)_2$), 5.45 (1H, t, J = 7 Hz, $C(CH_3)$=C*H*), 4.20 (2H, d, J = 7 Hz, CH_2OTBDPS), 2.40 (2H, t, J = 8 Hz, OHCCH_2), 2.20 (2H, t, J = 8 Hz, CH_2CH_2), 1.70 (3H, s, $C(CH_3)_3$=CH), 1.10 (9H, s, $(CH_3)_3$C).

^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 201.8, 135.6, 134.6, 134.8, 133.8, 129.6, 127.6, 126.1, 60.5, 42.2, 26.9, 26.6, 24.4, 23.1, 19.1.

MS (m/e): 309 (M^+ – C_4H_9).

HMRS: calc for $C_{19}H_{21}O_2Si$: 309.1311; found: 309.1305.

(Z)-(2R,3S)-8-(t-Butyldiphenylsiloxy)-3-hydroxy-N-methoxy-N,2,6-trimethyloct-6-enamide **16**

To a solution of (*R*)-3-(propionyl)-4-benzyl-2-oxazolidinone (12.15 g, 52 mmol) in dichloromethane (75 mL) was added, at 0 °C, di-*n*-butylboron triflate (15.4 mL, 60.8 mmol) slowly over a period of 10 min. Triethylamine (6.87 g, 9.47 mL, 67.6 mmol) was added slowly to the reaction then the solution was cooled to −78 °C and a solution of aldehyde **15** (21 g, 57.2 mmol) in dichloromethane (25 mL) was added slowly. After stirring for 3 h at −78 °C, the reaction was quenched with a mixture of buffer pH 7 and methanol (1:3, 165 mL). The resulting mixture was warmed to 0 °C and a mixture of hydrogen peroxide 35% and methanol (2:1, 120 mL). After stirring for 1 h, the resulting mixture was extracted several times with dichloromethane. The combined organic phases were washed with saturated aqueous sodium bicarbonate solution and brine. The organic phase was dried over magnesium sulfate, filtered and concentrated. The residue was purified by flash chromatography (20% ethyl acetate and hexanes) to afford a viscous oil (19.6 g).

To a suspension of *N,O*-dimethylhydroxylamine hydrochloride (6.37 g, 65.3 mmol) in dry dichloromethane (120 mL) was added slowly, at 0 °C, trimethylaluminum (2.0 M in toluene, 32.7 mL, 65.3 mmol). The ice bath was removed and the reaction was stirred 30 min at room temperature then the reaction was cooled to −15 °C and a solution of the crude imide (19.6 g) in dichloromethane (30 mL) was added via canula plus rince (10 mL). The reaction mixture was slowly warmed to room temperature and stirred 12 h. The resulting mixture was transferred via canula into a mixture of hexanes and tartaric acid 1 M (1:1, 320 mL). After stirring for 1 h, the resulting mixture was extracted with dichloromethane (3×). The combined organic phases were washed with brine, dried over magnesium sulfate, filtered and concentrated. The residue was purified by flash chromatography (50% ethyl acetate in hexanes) to give a colorless oil **16** (12.9 g, 51% over two steps).

$[\alpha]_D^{20}$ = −3.83 (c = 2.03, dichloromethane).

IR (film, ν cm^{-1}): 3 455, 3 069, 2 934, 2 859, 1 641, 1 108.

^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 7.70 (4H, m, $OSi(C_6H_5)_2$), 7.40 (6H, m, $OSi(C_6H_5)_2$), 5.40 (1H, t, J = 7 Hz, $C(CH_3)$=C*H*), 4.25 and 4.15 (2H, dd, J = 12 Hz and 7 Hz, CH_2OTBDPS), 3.73 (1H, m, C*H*OH), 3.64 (3H, s, NOCH_3), 3.17 (3H, s, NCH_3), 2.80 (1H, m, C*H*CH_3), 2.17 (1H, dt, J = 13 Hz and J = 8 Hz, $CH_2C(CH_3)$), 1.97 (1H, m, $CH_2C(CH_3)$), 1.71 (3H, d, J = 1 Hz, $C(CH_3)$=CH), 1.55 and 1.40 (2H, m, $CH_2CH_2C(CH_3)$), 1.13 (3H, d, J = 7 Hz, CHCH_3), 1.03 (9H, s, $OSiC(CH_3)_3$).

^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 138.2, 136.5, 133.9, 129.5, 127.5, 124.8, 70.6, 61.5, 60.3, 39.2, 32.1, 28.2, 26.7, 23.4, 19.2, 11.3.

MS (m/e): 426 (M^+ – C_4H_9).

HMRS: calc for $C_{25}H_{32}O_4SiN$: 426.2100; found: 426.2097.

(Z)-(2R,3S)-8-(t-Butyldiphenylsiloxy)-N,3-dimethoxy-N,2,6-trimethyloct-6-enamide **17**

To a solution of amide **16** (12.7 g, 26.2 mmol) in dry tetrahydrofuran (120 mL) and dimethylformamide (55 mL) were added, at 0 °C, iodomethane (37.6 g, 265 mmol) and sodium hydride (60% in oil, 2.65 g, 66.3 mmol) under nitrogen flux. After stirring for 3 h at 0 °C, the reaction was quenched with buffer pH 7 (150 mL). The resulting mixture was extracted several times with diethyl ether and the combined organic phases were dried over magnesium sulfate, filtered and concentrated. The oily residue was purified by flash chromatography (50% ethyl acetate in hexanes) to provide a colorless oil **17** (12.3 g, 94%).

$[\alpha]_D^{20}$ = +3.0 (c = 1.24, dichloromethane).

IR (film, ν cm^{-1}): 3 048, 2 934, 2 859, 1 662, 1 107, 1 070.

^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 7.69 (4H, m, $OSi(C_6H_5)_2$), 7.39 (6H, m, $OSi(C_6H_5)_2$), 5.38 (1H, dt, J = 7 Hz and 1 Hz, $C(CH_3)$=C*H*), 4.22 (2H, dd, J = 7 Hz and 0.5 Hz, CH_2OTBDPS), 3.56 (3H, s, NOCH_3), 3.26 (3H, s, CHOCH_3), 3.25 (1H, m, C*H*OCH$_3$), 3.08 (3H, s, NCH_3), 2.95 (1H, m, C*H*CH$_3$), 1.95 (2H, t, J = 9 Hz, $CH_2C(CH_3)$), 1.68 (3H, d, J = 1 Hz, $C(CH_3)$=CH), 1.61–1.35 (2H, m, $CH_2CH_2C(CH_3)$), 1.15 (3H, d, J = 7 Hz, CHCH_3), 1.03 (9H, s, $OSiC(CH_3)_3$).

^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 137.1, 135.5, 129.5, 127.6, 125.0, 82.4, 61.3, 60.7, 58.1, 39.3, 30.4, 27.4, 26.8, 23.2, 19.1, 14.3.

MS (m/e): 440 (M^+ – C_4H_9).

HMRS: calc for $C_{25}H_{34}O_4SiN$: 440.2257; found: 440.2255.

(Z)-(2R,3S)-8-(t-Butyldiphenylsiloxy)-N,3-dimethoxy-N,2,6-trimethyloct-6-enal **18**

To a solution of methoxyamide **17** (12.3 g, 24.6 mmol) in dry tetrahydrofuran (200 mL) was added, at −90 °C, DIBALH (1.5 M in toluene, 49.1 mL, 73.7 mmol). After stirring for 1 h at −90 °C, the mixture was transferred via canula into a solution of 1 M tartaric acid and hexanes (1:1, 400 mL) and extracted with diethyl ether (3×). The organic phases were washed with brine, dried over magnesium sulfate, filtered and concentrated. The residue was purified by flash chromatography (30% ethyl acetate in hexanes) to afford a colorless oil **18** (10.71 g, 99%).

$[\alpha]_D^{20}$ = −25.0 (c = 1.0, dichloromethane).

IR (film, ν cm^{-1}): 3 068, 2 933, 2 858, 2 712, 1 725, 1 108.

^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 9.69 (1H, d, J = 1 Hz, C*H*O), 7.69 (4H, m, $OSi(C_6H_5)_2$), 7.40 (6H, m, $OSi(C_6H_5)_2$), 5.42 (1H, dt, J = 7.5 Hz and 1 Hz, $C(CH_3)$=C*H*), 4.18 (2H, d, J = 7.5 Hz, CH_2OTBDPS), 3.42 (1H, m, C*H*OCH$_3$), 3.21 (3H, s, CHOCH_3), 2.42 (1H, dq, J = 7 Hz and 3 Hz, C*H*CH$_3$), 1.90 (2H, t, J = 8 Hz, $CH_2C(CH_3)$), 1.70 (3H, d, J = 1 Hz, $C(CH_3)$=CH), 1.60–1.45 (2H, m, $CH_2CH_2C(CH_3)$), 1.02 (9H, s, $OSiC(CH_3)_3$), 1.00 (3H, d, J = 7 Hz, CHCH_3).

^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 204.3, 136.7, 135.6, 133.9, 129.6, 127.6, 125.4, 80.3, 60.6, 57.5, 49.1, 29.7, 28.2, 26.8, 23.2, 19.2, 7.9.

MS (m/e): 381 (M^+ – C_4H_9).

HMRS: calc for $C_{23}H_{29}O_3Si$: 381.1886; found: 381.1890.

Methyl (2E,4E,10Z)-(6S,7S)-12-(tert-Butyldiphenylsiloxy)-7-methoxy-2,6,10-trimethyldodeca-2,4,10-trienoate **20**

To a solution of phosphonate **19** (11.8 g, 53.2 mmol) in dry diethyl ether (200 mL) was added, at −10 °C, *n*-butyl-

lithium (1.48 M in hexanes, 32.7 mL, 48.4 mmol). After stirring for 20 min, a solution of aldehyde **18** (10.6 g, 24.2 mmol) in diethyl ether (40 mL) was added via canula into the peach mixture. After stirring for 30 min at −20 °C, the reaction was quenched with saturated aqueous ammonium chloride solution (200 mL) and extracted several times with diethyl ether. The combined organic phases were dried over magnesium sulfate, filtered and concentrated. The yellowish residue was purified by flash chromatography (5% methanol in hexanes) to afford a colorless oil **20** (12.2 g, 94%).

$[\alpha]_D^{20} = -11.5$ (c = 1.0, dichloromethane).

IR (film, ν cm^{-1}): 2 932, 2 858, 1 709, 1 638, 1 107.

^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 7.69 (4H, m, $OSi(C_6H_5)_2$), 7.38 (6H, m, $OSi(C_6H_5)_2$), 7.15 (1H, d, J = 11 Hz, CH=C(CH_3)), 6.29 (1H, ddd, J = 15 Hz, 11 Hz and 1 Hz, CH=CHCH=C(CH_3)), 6.01 (1H, dd, J = 15 Hz and 7 Hz, CH=CHCH=C(CH_3)), 5.40 (1H, dt, J = 6 Hz and 1 Hz, C(CH_3)=CH), 4.20 (2H, d, J = 6 Hz, CH_2OTBDPS), 3.74 (3H, s, CO_2CH_3), 3.23 (3H, s, CHOCH_3), 2.90 (1H, m, CHOCH_3), 2.51 (1H, m, $CH$$CH_3$), 1.95 (2H, m, CH_2C(CH_3)), 1.91 (3H, d, J = 1 Hz, CH=C(CH_3)), 1.67 (3H, d, J = 1 Hz, C(CH_3)=CH), 1.39 (2H, m, CH_2CH_2C(CH_3)), 1.04 (9H, s, OSiC(CH_3)$_3$), 1.00 (3H, d, J = 7 Hz, CHCH_3).

^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 169.0, 144.7, 138.7, 137.3, 135.6, 134.0, 129.5, 127.6, 125.5, 125.3, 125.1, 84.3, 60.7, 57.4, 51.7, 39.8, 29.2, 28.0, 26.8, 23.3, 19.2, 15.4, 12.6.

MS (m/e): 477 ($M^+ - C_4H_9$).

HMRS: calc for $C_{29}H_{37}O_4Si$: 477.2461; found: 477.2473.

(2E,4E,10Z)-(6S,7S)-12-(tert-Butyldiphenylsiloxy)-7-methoxy-2,6,10-trimethyldodeca-2,4,10-trien-1-ol ***21***

To a solution of triene ester **20** (12.1 g, 22.7 mmol) in dry dichloromethane (200 mL) was added, at −78 °C, DIBALH (1.5 M in toluene, 45.4 mL, 68.1 mmol). After stirring for 1 h at −78 °C, the reaction was quenched with crushed sodium sulfate decahydrate (10 g). The resulting mixture was stirred at room temperature for 2 h. The slurry was filtered and the solid residue was washed several times with ethyl acetate. The filtrate was concentrated and the residue was purified by flash chromatography (30% ethyl acetate in hexanes) to give a colorless oil **21** (9.18 g, 80%).

$[\alpha]_D^{20} = -10$ (c = 1.0, dichloromethane).

IR (film, ν cm^{-1}): 3 409, 3 012, 2 931, 2 857, 1 667, 1 461, 1 235, 1 068.

^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 7.69 (4H, m, $OSi(C_6H_5)_2$), 7.40 (6H, m, $OSi(C_6H_5)_2$), 6.21 (1H, dd, J = 15 Hz and 11 Hz, CH=CHCH=C(CH_3)), 5.98 (1H, d, J = 11 Hz, CH=C(CH_3)), 5.61 (1H, dd, J = 15 Hz and 8 Hz, CH=CHCH=C(CH_3)), 5.37 (1H, dt, J = 6 Hz and 1 Hz, C(CH_3)=CH), 4.19 (2H, d, J = 6 Hz, CH_2OTBDPS), 4.03 (2H, s, CH_2OH), 3.22 (3H, s, CHOCH_3), 2.86 (1H, q, J = 7 Hz, CHOCH_3), 2.42 (1H, q, J = 7 Hz, $CH$$CH_3$), 1.93 (2H, m, CH_2C(CH_3)), 1.75 (3H, d, J = 1 Hz, CH=C(CH_3)), 1.67 (3H, d, J = 1 Hz, C(CH_3)=CH), 1.45–1.35 (2H, m, CH_2CH_2C(CH_3)), 1.03 (9H, s, OSiC(CH_3)$_3$), 0.97 (3H, d, J = 7 Hz, CHCH_3).

^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 137.4, 136.5, 135.5, 134.0, 129.4, 127.5, 125.5, 125.2, 124.9, 84.5, 68.5, 60.7, 57.2, 39.5, 29.1, 27.9, 26.8, 23.2, 19.1, 15.9, 15.2, 14.0.

MS (m/e): 449 ($M^+ - C_4H_9$).

HMRS: calc for $C_{28}H_{37}O_3Si$: 449.6840; found: 449.6835.

(2E,4E,10Z)-(6S,7S)-12-(tert-Butyldiphenylsiloxy)-7-methoxy-2,6,10-trimethyldodeca-2,4,10-trienal ***22***

To a solution of aldehyde **21** (7.18 g, 14.2 mmol) in dichloromethane (140 mL) was added Dess-Martin periodinane (7.8 g, 18.4 mmol) at room temperature. After stirring for 20 min, the reaction was quenched with a saturated aqueous sodium bicarbonate solution (100 mL). Sodium thiosulfate was added and the mixture was stirred for 30 min. The resulting mixture was extracted several times with dichloromethane. The combined organic phases were dried over magnesium sulfate, filtered and concentrated. The residue was purified by a flash chromatography (30% ethyl acetate in hexanes) to afford **22** as a colorless oil (6.13 g, 86%).

$[\alpha]_D^{20} = -23.1$ (c = 1.0, dichloromethane).

IR (film, ν cm^{-1}): 3 057, 2 932, 2 858, 2 702, 1 680, 1 633, 1 108.

^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 9.39 (1H, s, CHO), 7.69 (4H, m, $OSi(C_6H_5)_2$), 7.39 (6H, m, $OSi(C_6H_5)_2$), 6.77 (1H, d, J = 11 Hz, CH=C(CH_3)), 6.43 (1H, ddd, J = 15 Hz, 11 Hz and 1 Hz, CH=CHCH=C(CH_3)), 6.16 (1H, dd, J = 15 Hz and 8 Hz, CH=CHCH=C(CH_3)), 5.40 (1H, dt, J = 6 Hz and 1 Hz, C(CH_3)=CH), 4.19 (2H, d, J = 6 Hz, CH_2OTBDPS), 3.25 (3H, s, CHOCH_3), 2.94 (1H, m, CHOCH_3), 2.57 (1H, q, J = 7 Hz, $CH$$CH_3$), 1.93 (2H, m, CH_2C(CH_3)), 1.81 (3H, d, J = 1 Hz, CH=C(CH_3)), 1.68 (3H, d, J = 1 Hz, C(CH_3)=CH), 1.41 (2H, m, CH_2CH_2C(CH_3)), 1.03 (9H, s, OSiC(CH_3)$_3$), 1.02 (3H, d, J = 7 Hz, CHCH_3).

^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 195.0, 149.0, 147.1, 137.2, 135.6, 134.0, 129.5, 127.6, 125.4, 125.2, 84.1, 60.7, 57.4, 39.7, 29.1, 28.0, 26.8, 23.2, 19.1, 15.2, 9.4.

MS (m/e): 504 (M^+).

HMRS: calc for $C_{32}H_{44}O_3Si$: 504.3080; found: 504.3051.

(2Z,8E,10E)-(6S,7S,12S)-1-(t-Butyldiphenylsiloxy)-13-chloro-6-methoxy-3,7,11-trimethyltrideca-2,8,10-trien-12-ol and (2Z,8E,10E)-(6S,7S,12R)-1-(t-butyldiphenylsiloxy)-13-chloro-6-methoxy-3,7,11-trimethyltrideca-2,8,10-trien-12-ol ***23***

To a solution of aldehyde **22** (6.09 g, 12.06 mmol) in dry tetrahydrofuran (200 mL) were added, at −78 °C, chloroiodomethane (3.8 g, 1.58 mL, 21.7 mL) and butyllithium (1.40 M in hexanes, 15.1 mL, 21.1 mmol). After stirring for 30 min, the reaction was quenched with saturated aqueous ammonium chloride solution (150 mL) and the resulting mixture was extracted with diethyl ether (3×). The combined organic phases were dried over magnesium sulfate, filtered and concentrated. The residue was purified by flash chromatography (30% ethyl acetate in hexanes) to afford a colorless oil as a mixture of two diastereoisomers **23** (5.75 g, 86%).

$[\alpha]_D^{20} = -6.7$ (c = 1.26, dichloromethane).

IR (film, ν cm^{-1}): 3 410, 3 057, 2 932, 2 858, 1 591, 1 108.

^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 7.70 (4H, m, $OSi(C_6H_5)_2$), 7.39 (6H, m, $OSi(C_6H_5)_2$), 6.10 (2H, m, CH=$CHCH$=C(CH_3)), 5.64 (1H, dd, J = 15 Hz and 8 Hz, CH=CHCH=C(CH_3)), 5.42 (1H, dt, J = 6 Hz and 1 Hz, C(CH_3)=CH), 4.21 (3H, m, CHOH and CH_2OTBDPS), 3.58 (2H, m, CH_2Cl), 3.22 (3H, s, CHOCH_3), 2.87 (1H, m, CHOCH_3), 2.43 (1H, m, $CH$$CH_3$), 1.92 (2H, m, CH_2C(CH_3)), 1.73 (3H, s, CH=C(CH_3)), 1.67 (3H, d, J = 1 Hz, C(CH_3)=CH), 1.39 (2H, m, CH_2CH_2C(CH_3)), 1.03 (9H, s, OSiC(CH_3)$_3$), 0.96 (3H, d, J = 7 Hz, CHCH_3).

^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 138.0, 137.4, 135.6, 134.0, 133.2, 129.5, 127.6, 125.2, 125.0, 84.5, 76.6, 60.7, 57.3. 48.6, 39.5, 29.1, 28.0, 26.9, 23.3, 19.2, 15.9.

MS (m/e): 553 ($M^+ - H$).

HMRS: calc for $C_{33}H_{46}O_3SiCl$: 553.2905; found: 553.2099.

(2Z,8E,10E)-(6S,7S,12S)-1-(t-Butyldiphenylsiloxy)-13-chloro-6-methoxy-12-(2-methoxypropan-2-yloxy)-3,7,11-trimethyltrideca-2,8,10-triene and (2Z,8E,10E)-(6S,7S,12R)-1-(t-butyldiphenylsiloxy)-13-chloro-6-methoxy-12-(2-methoxypropan-2-yloxy)-3,7,11-trimethyltrideca-2,8,10-triene **24**

To a solution of alcohol **23** (5.70 g, 10.3 mmol) in dichloromethane (100 mL) were added, at 0 °C, 2-methoxypropene (2.97 g, 3.94 mL, 41.2 mmol) and pyridinium *p*-toluenesulfonate acid (258 mg, 1.03 mmol). After stirring for 30 min at 0 °C, the reaction was poured into a saturated aqueous sodium bicarbonate solution and the mixture was extracted several times with diethyl ether. The combined organic phases were dried over magnesium sulfate, filtered and concentrated. The resulting oil was purified by flash chromatography (30% ethyl acetate in hexanes) to give a colorless oil as a mixture of two diastereoisomers **24** (5.35 g, 83%).

$[\alpha]_D^{20} = -8.8$ ($c = 3.05$, dichloromethane).

IR (film, ν cm^{-1}): 2 933, 2 858, 1 665, 1 590, 1 108.

^{1}H NMR (300 MHz, C_6D_6, δ ppm): 7.83 (4H, m, $OSi(C_6H_5)_2$), 7.23 (6H, m, $OSi(C_6H_5)_2$), 6.25 (1H, dd, J = 15 Hz and 11 Hz, CH=C*H*CH=C(CH_3)), 6.07 (1H, d, J = 11 Hz, C*H*=C(CH_3)), 5.60 (2H, m, C*H*=CHCH=C(CH_3) and C(CH_3)=C*H*), 4.38 (2H, d, J = 6 Hz, CH_2OTBDPS), 4.31 (1H, t, J = 6 Hz, C*H*OMOP), 3.38 and 3.30 (2H, m, CH_2Cl), 3.08 (3H, s, $CHOCH_3$), 3.05 (3H, s, $C(CH_3)_2OCH_3$), 2.73 (1H, m, C*H*OCH_3), 2.38 (1H, m, C*H*CH_3), 1.98 (2H, m, $CH_2C(CH_3)$), 1.61 (3H, s, CH=C(C*H*$_3$)), 1.58 (3H, m, C(C*H*$_3$)=CH), 1.45–1.30 (2H, m, $CH_2CH_2C(CH_3)$), 1.24 and 1.20 (6H, s, $OC(CH_3)_2OCH_3$), 1.17 (9H, s, $OSiC(CH_3)_3$), 0.96 (3H, d, J = 7 Hz, $CHCH_3$).

^{13}C NMR (75 MHz, C_6D_6, δ ppm): 137.5, 137.3, 135.7, 134.1, 129.5, 128.5, 125.4, 125.1, 100.9, 84.1, 76.3, 60.8, 56.7, 48.9, 46.0, 39.6, 29.1, 27.7, 26.8, 25.3, 24.9, 23.0, 19.1, 15.8, 11.9.

MS (m/e): 626 (M^+).

HMRS: calc for $C_{37}H_{55}O_4SiCl$: 626.3558; found: 626.3553.

(2Z,8E,10E)-(6S,7S,12S)-13-Chloro-6-methoxy-12-(2-methoxypropan-2-yloxy)-3,7,11-trimethyltrideca-2,8,10-trien-1-ol and (2Z,8E,10E)-(6S,7S,12R)-13-chloro-6-methoxy-12-(2-methoxypropan-2-yloxy)-3,7,11-trimethyltrideca-2,8,10-trien-1-ol **25**

To a solution of silyl ether **24** (5.27 g, 8.4 mmol) in tetrahydrofuran (100 mL) was added tetra-*n*-butylammonium fluoride (1.0 M in THF, 16.8 mL, 16.8 mmol). After stirring for 1 h, the mixture was concentrated and the residue was purified by flash chromatography (30% ethyl acetate in hexanes) to afford a colorless oil as a mixture of two diastereoisomers **25** (2.90 g, 89%).

$[\alpha]_D^{20} = -13.0$ ($c = 0.95$, dichloromethane).

IR (film, ν cm^{-1}): 3 402, 2 933, 1 456, 1 377, 1 074.

^{1}H NMR (300 MHz, C_6D_6, δ ppm): 6.33 (1H, m, CH=C*H*CH=C(CH_3)), 6.14 (1H, d, J = 11 Hz, C*H*=C(CH_3)), 5.65 (1H, m, C*H*=CHCH=C(CH_3)), 5.46 (1H, t, J = 7 Hz, C(CH_3)=C*H*), 4.37 (1H, t, J = 6.5 Hz, C*H*OMOP), 4.11 (2H, m, CH_2OH), 3.45 (1H, dd, J_{AB} = 11 Hz and 6.5 Hz, CH_2Cl), 3.35 (1H, dd, J_{AB} = 11 Hz and 6.5 Hz, CH_2Cl), 3.16 (3H, s, $CHOCH_3$), 3.13 (3H, s, $C(CH_3)_2OCH_3$), 2.88 (1H, m, C*H*OCH_3), 2.46 (1H, q, J = 7 Hz, C*H*CH_3), 2.30–2.00 (2H, m, $CH_2C(CH_3)$), 1.69 (3H, s, CH=C(C*H*$_3$)), 1.64 (3H, s, C(C*H*$_3$)=CH), 1.55 (2H, m, $CH_2CH_2C(CH_3)$), 1.29 and 1.26 (6H, s, $C(CH_3)_2OCH_3$), 1.06 (3H, d, J = 7 Hz, $CHCH_3$).

^{13}C NMR (75 MHz, C_6D_6, δ ppm): 138.6, 137.5, 135.3, 134.6, 129.7, 128.7, 125.9, 101.2, 84.1, 76.6, 58.9, 56.4, 49.3, 46.3, 40.0, 31.4, 29.1, 27.4, 26.8, 25.6, 25.2, 23.3, 19.2, 16.5, 12.2.

(2Z,8E,10E)-(6S,7S,12S)-13-Chloro-6-methoxy-12-(2-methoxypropan-2-yloxy)-3,7,11-trimethyltrideca-2,8,10-trienal and (2Z,8E,10E)-(6S,7S,12R)-13-chloro-6-methoxy-12-(2-methoxypropan-2-yloxy)-3,7,11-trimethyltrideca-2,8,10-trienal **26**

To a solution of alcohol **25** (2.84 g, 7.3 mmol) in dichloromethane (80 mL) were added molecular sieve 4 Å (3.65 g), 1-methylmorpholine-1-oxide (1.28 g, 11 mmol) and tetrapropylammonium perrhutenate (128 mg, 365 μmol). After stirring for 30 min, the reaction was concentrated and the residue was purified by flash chromatography (30% ethyl acetate in hexanes) to give a colorless oil as a mixture of two diastereoisomers **26** (2.66 g, 94%).

$[\alpha]_D^{20} = -8.1$ ($c = 1.2$, dichloromethane).

IR (film, ν cm^{-1}): 2 935, 1 674, 1 456, 1 073.

^{1}H NMR (300 MHz, C_6D_6, δ ppm): 10.01 (1H, dd, J = 8 Hz, 1 Hz, C*H*O), 6.27 (1H, dd, J = 15 Hz and 11 Hz, CH=C*H*CH=C(CH_3)), 6.10 (1H, d, J = 11 Hz, C*H*=C(CH_3)), 5.78 (1H, d, J = 8 Hz, C(CH_3)=C*H*), 5.57 (1H, m, C*H*=CHCH=C(CH_3)), 4.35 (1H, t, J = 6.5 Hz, C*H*OMOP), 3.43 (2H, m, CH_2Cl), 3.09 (3H, s, $CHOCH_3$), 3.03 (3H, s, $C(CH_3)_2OCH_3$), 2.67 (1H, q, J = 6 Hz, C*H*OCH_3), 2.35 and 2.17 (3H, 2m, C*H*CH_3 and $CH_2C(CH_3)$), 1.66 (3H, s, CH=C(C*H*$_3$)), 1.38 (3H, d, J = 1.5 Hz, C(C*H*$_3$)=CH), 1.35 (2H, m, $CH_2CH_2C(CH_3)$), 1.25 and 1.23 (6H, 2s, $C(CH_3)_2OCH_3$), 0.95 (3H, d, J = 7 Hz, $CHCH_3$).

^{13}C NMR (75 MHz, C_6D_6, δ ppm): 189.5, 162.3, 136.8, 135.3, 129.4, 128.4, 126.2, 101.6, 84.1, 76.6, 57.2, 49.3, 46.5, 46.4, 39.8, 29.6, 29.5, 28.1, 28.0, 27.2, 26.1, 25.0, 24.2, 16.6, 12.3.

MS (m/e): 387 ($M^+ - H$).

(5Z,11E,13E)-(4S and 4R,9S,10S,14S and 14R)-16-Chloro-4-hydroxy-9-methoxy-15-(2-methoxypropan-2-yloxy)-6,10,14-trimethylhexadeca-5,11,13-trien-1-ol **27**

To a solution of Grignard's reagent (0.6 M in THF, 22 mL, 13.2 mmol) in dry tetrahydrofuran (60 mL) was added slowly via canula, at −78 °C, a solution of the aldehyde **26** (2.56 g, 6.6 mmol) in tetrahydrofuran. After stirring for 30 min at −78 °C, the reaction was quenched with water (60 mL) and extracted several times with diethyl ether. The combined organic phases were washed with brine, dried on magnesium sulfate, filtered and concentrated. The residue was purified by flash chromatography (100% ethyl acetate) to provide a viscous colorless oil as a mixture of four diastereoisomers **27** (2.47 g, 84%).

$[\alpha]_D^{20} = -7.1$ ($c = 1.0$, dichloromethane).

IR (film, ν cm^{-1}): 3 049, 2 931, 1 089.

^{1}H NMR (300 MHz, C_6D_6, δ ppm): 6.31 (1H, m, CH=C*H*CH=C(CH_3)), 6.13 (1H, d, J = 11 Hz,

CH=C(CH_3)), 5.62 (1H, m, CH=CHCH=C(CH_3)), 5.27 (1H, t, J = 10 Hz, C(CH_3)=CH), 4.45 (1H, m, CHOH), 4.34 (1H, t, J = 6.5 Hz, CHOMOP), 3.53 (2H, m, CH_2OH), 3.35 (1H, 2dd, J_{AB} = 11 Hz and 6.5 Hz, CH_2Cl), 3.35 (1H, 2dd, J_{AB} = 11 Hz and 6.5 Hz, CH_2Cl), 3.14, 3.10 and 3.09 (6H, 3s, CHOCH_3, C(CH_3)$_2$OCH_3), 2.86 (1H, m, CHOCH_3), 2.43 (1H, m, CHCH_3), 2.29–2.05 (2H, m, CH_2C(CH_3)), 1.66–1.54 (12H, m, C(CH_3)=CH, CH=C(CH_3), $CH_2CH_2CH_2$OH and CH_2CH_2C(CH_3)=CH), 1.25 and 1.22 (6H, 2s, OC(CH_3)$_2$OCH_3), 1.05 and 1.01 (3H, 2d, J = 7 Hz, CHCH_3).

^{13}C NMR (75 MHz, C_6D_6, δ ppm): 137.5, 130.5, 129.5, 128.7, 126.0, 84.7, 83.5, 76.6, 68.1, 67.9, 62.7, 49.3, 46.3, 35.4, 29.7, 28.7, 28.0, 27.7, 25.6, 25.2, 23.2, 16.6, 12.2.

MS (m/e): 397 (M^+ – CH_5O_2).

HMRS: calc for $C_{23}H_{37}O_3Cl$: 397.2509; found: 397.2496.

(5Z,11E,13E)-(4S and 4R,9S,10S,14S and 14R)-1-(tert-Butyldiphenylsiloxy)-16-chloro-4-hydroxy-9-methoxy-15-(2-methoxypropan-2-yloxy)-6,10,14-trimethylhexadeca-5,11,13-triene **28**

To a solution of the diol **27** (2.39 g, 5.36 mmol) in tetrahydrofuran (70 mL) were added, at 0 °C, *t*-butylchlorodimethylsilane (1.21 g, 8.04 mmol) and imidazole (729.8 mg, 10.7 mmol). After stirring for overnight, the reaction was poured into a saturated aqueous ammonium chloride solution (100 mL) and the resulting mixture was extracted several times with diethyl ether. The combined organic phases were dried over magnesium sulfate, filtered and concentrated. The residue was purified by flash chromatography (50% ethyl acetate in hexanes) to give a colorless oil as a mixture of four diastereoisomers **28** (2.85 g, 95%).

$[\alpha]_D^{20}$ = −10.7 (c = 1.62, dichloromethane).

IR (film, ν cm^{-1}): 3 423, 2 932, 1 461, 1 096.

^{1}H NMR (300 MHz, C_6D_6, δ ppm): 6.30 (1H, m, CH=CHCH=C(CH_3)), 6.11 (1H, d, J = 11 Hz, CH=C(CH_3)), 5.61 (1H, m, CH=CHCH=C(CH_3)), 5.27 (1H, m, C(CH_3)=CH), 4.44 (1H, m, CHOH), 4.32 (1H, t, J = 6.5 Hz, CHOMOP), 3.57 (2H, m, CH_2OTBDMS), 3.40 (1H, dd, J_{AB} = 11 Hz and 6.5 Hz, CH_2Cl), 3.32 (1H, dd, J_{AB} = 11 Hz and 6.5 Hz, CH_2Cl), 3.16, 3.13 and 3.09 (6H, 3s, CHOCH_3 and C(CH_3)$_2$OCH_3), 2.89 (1H, m, CHOCH_3), 2.44 (1H, m, CHCH_3), 2.30–1.95 (2H, m, CH_2C(CH_3)), 1.75–1.44 (12H, m, C(CH_3)=CH, CH=C(CH_3), $CH_2CH_2CH_2$OTBDMS and CH_2CH_2C(CH_3)), 1.24 and 1.21 (6H, 2s, C(CH_3)$_2$OCH$_3$), 1.04 and 1.01 (3H, 2d, J = 7 Hz, CHCH_3), 0.95 (9H, s, OSiC(CH_3)$_3$), 0.04 (6H, s, OSi(CH_3)$_2$).

^{13}C NMR (75 MHz, C_6D_6, δ ppm): 137.9, 137.6, 137.5, 134.6, 130.7, 130.2, 128.7, 126.0, 101.3, 84.8, 83.6, 76.6, 68.0, 67.8, 63.5, 57.0, 55.8, 49.3, 46.3, 40.1, 39.9, 35.1, 35.0, 29.6, 28.9, 28.0, 27.8, 26.1, 25.9, 25.7, 25.2, 23.4, 23.2, 18.5, 16.5, 16.4, 12.2, −5.17.

MS (m/e): 511 (M^+ – CH_5O_2).

HMRS: calc for $C_{29}H_{51}O_3Cl$: 511.3374; found: 511.3358.

(5Z,11E,13E)-(4S and 4R,9S,10S,14S and 14R)-1-(tert-Butyldiphenylsiloxy)-16-chloro-9-methoxy-15-(2-methoxypropan-2-yloxy)-6,10,14-trimethyl-4-[(4-trimethylsilyl-2-oxabutanyl)oxy]hexadeca-5,11,13-triene **29**

To a solution of alcohol **28** (2.81 g, 5.01 mmol) in dry dichloromethane (70 mL) were added diisopropylamine (2.58 g, 3.48 mL, 20 mmol), tetrabutylammonium iodide (1.85 g, 5.01 mmol) and [2-(trimethylsilyl)ethoxy]methyl chloride (1.67 g, 1.77 mL, 10.0 mmol). After stirring for 4 h, the reaction was carried out to reflux (40 °C) for 2 h. Saturated aqueous sodium bicarbonate solution (70 mL) was added and the mixture was extracted with dichloromethane (3 × 100 mL). The combined organic phases were dried over magnesium sulfate, filtered and concentrated. The residue was purified by flash chromatography (30% ethyl acetate in hexanes) to afford a colorless oil as a mixture of four diastereoisomers **29** (3.45 g, 100%).

$[\alpha]_D^{20}$ = −4.5 (c = 1.0, dichloromethane).

IR (film, ν cm^{-1}): 2 954, 2 859, 1 461, 1 378, 1 250, 1 099.

^{1}H NMR (300 MHz, C_6D_6, δ ppm): 6.35 (1H, m, CH=CHCH=C(CH_3)), 6.11 (1H, d, J = 11 Hz, CH=C(CH_3)), 5.74 (1H, dd, J = 15 Hz and 8 Hz, CH=CHCH=C(CH_3)), 5.17 (1H, d, J = 10 Hz, C(CH_3)=CH), 4.87 and 4.86 (1H, 2d, J_{AB} = 8 Hz, OCH_2O), 4.65 (1H, d, J_{AB} = 8 Hz, OCH_2O), 4.61 (1H, m, CHOSEM), 4.36 (1H, t, J = 6.5 Hz, CHOMOP), 3.95–3.30 (6H, m, OCH_2CH$_2$TMS, CH_2Cl and CH_2OTBDMS), 3.28 and 3.24 (3H, 2s, CHOCH_3), 3.11 and 3.09 (3H, 2s, C(CH_3)$_2$OCH_3), 2.92 (1H, m, CHOCH$_3$), 2.50 (1H, m, CHCH$_3$), 2.45–2.04 (2H, m, CH_2C(CH_3)), 1.90–1.55 (6H, m, CH_2CH_2C(CH_3) and $CH_2CH_2CH_2$OTBDMS), 1.65 (6H, s, C(CH_3)=CH and CH=C(CH_3)), 1.26 and 1.21 (6H, 2s, C(CH_3)$_2$OCH$_3$), 1.12 and 1.08 (3H, d, J = 7 Hz, CHCH_3), 0.94 (2H, m, CH_2TMS), 0.94 (9H, s, OSiC(CH_3)$_3$), 0.09 (6H, s, OSi(CH_3)$_2$), 0.01 (9H, m, SiC(CH_3)$_3$).

^{13}C NMR (75 MHz, C_6D_6, δ ppm): 140.2, 140.1, 137.8, 134.5, 128.8, 126.9, 125.8, 101.3, 91.6, 85.0, 84.7, 76.6, 71.3, 71.2, 65.0, 63.4, 57.4, 57.1, 49.3, 46.3, 40.3, 40.0, 33.0, 32.9, 30.0, 29.8, 29.6, 28.3, 26.2, 25.6, 25.2, 23.5, 18.5, 18.4, 16.3, 16.2, 12.2, −1.3, −5.2.

MS (m/e, ammoniac): 708 (M^+ + NH_4).

(5Z,11E,13E)-(4S and 4R,9S,10S,14S and 14R)-16-Chloro-9-methoxy-15-(2-methoxypropan-2-yloxy)-6,10,14-trimethyl-4-[(4-trimethylsilyl-2-oxabutanyl)oxy]hexadeca-5,11,13-trien-1-ol **30**

To a solution of silyl ether **29** (3.42 g, 4.95 mmol) in tetrahydrofuran (50 mL) was added tetrabutylammonium fluoride (1.0 M in THF, 7.43 mL, 7.43 mmol). After stirring for 3 h, the reaction was quenched with a saturated aqueous sodium bicarbonate solution (50 mL) then the resulting mixture was extracted with diethyl ether several times. The organic phases were dried over magnesium sulfate, filtered and concentrated. The residue was purified by flash chromatography (30% ethyl acetate in hexanes) to give a colorless oil as a mixture of four diastereoisomers **30** (2.44 g, 86%).

$[\alpha]_D^{20}$ = −5.7 (c = 2.97, dichloromethane).

IR (film, ν cm^{-1}): 3 452, 2 948, 1 096, 1 025.

^{1}H NMR (300 MHz, C_6D_6, δ ppm): 6.31 (1H, m, CH=CHCH=C(CH_3)), 6.11 (1H, m, CH=C(CH_3)), 5.69 (1H, m, CH=CHCH=C(CH_3)), 5.15 (1H, d, J = 10 Hz, C(CH_3)=CH), 4.81 (1H, d, J_{AB} = 8 Hz, OCH_2O), 4.60 (1H, d, J_{AB} = 8 Hz, OCH_2O), 4.59 (1H, m, CHOSEM), 4.32 (1H, t, J = 6.5 Hz, CHOMOP), 3.91–3.28 (6H, m, CH_2Cl, CH_2OH and OCH_2CH$_2$TMS), 3.25 and 3.20 (3H, 2s, CHOCH_3), 3.09 and 3.07 (3H, 2s, C(CH_3)$_2$OCH_3), 2.90 (1H, m, CHOCH$_3$), 2.52–2.31 (2H, m, CHCH$_3$ and CH_2C(CH_3)), 2.07 (1H, m, CH_2C(CH_3)), 1.85–1.42 (6H, m, $CH_2CH_2CH_2$OH and CH_2CH_2C(CH_3)), 1.66 (6H, m, C(CH_3)=CH and CH=C(CH_3)), 1.25 and 1.22 (6H, s, C(CH_3)$_2$OCH$_3$), 1.07 (3H, d, J = 7 Hz, CHCH_3), 0.95 (2H, m, CH_2TMS), 0.02 (9H, s, Si(CH_3)$_3$).

^{13}C NMR (75 MHz, C_6D_6, δ ppm): 139.9, 137.6, 137.4, 134.3, 128.7, 126.7, 125.7, 101.1, 91.5, 91.3, 85.0, 84.4, 76.5, 71.1, 71.0, 70.8, 64.9, 62.4, 62.3, 57.2, 56.6, 54.1, 49.1, 46.1, 40.2, 39.9, 39.8, 32.8, 31.7, 29.9, 29.7, 29.6, 29.3. 29.1, 28.1, 25.4, 25.0, 23.4, 23.1, 20.8, 18.2, 16.3, 16.2, 16.1, 14.2, 12.0, −1.4.

MS (m/e): 559 (M^+ − OH).

HMRS: calc for $C_{30}H_{56}O_5ClSi$: 559.3585; found: 559.3579.

(5Z,11E,13E)-(4S and 4R,9S,10S,14S and 14R)-16-Chloro-9-methoxy-15-(2-methoxypropan-2-yloxy)-6,10,14-trimethyl-4-[(4-trimethylsilyl-2-oxabutanyl)oxy]hexadeca-5,11,13-trienal **31**

To a solution of alcohol **30** (300 mg, 520 μmol) in dichloromethane (5 mL) were added molecular sieves 4 Å (259 mg), 1-methylmorpholine-1-oxide (91.2 mg, 780 μmol) and tetrapropylammonium perrhutenate (9.12 mg, 26 μmol). After stirring for 30 min, the black mixture was concentrated and the residue was purified by flash chromatography (30% ethyl acetate in hexanes) to give a colorless oil as a mixture of four diastereoisomers **31** (263 mg, 88%).

$[\alpha]_D^{20}$ = −3.0 (c = 1.0, dichloromethane).

IR (film, ν cm^{-1}): 2 952, 2 892, 2 720, 1 726, 1 665, 1 465, 1 379, 1 098, 1 024.

^{1}H NMR (300 MHz, C_6D_6, δ ppm): 9.45 (1H, m, C*H*O), 6.35 (1H, m, CH=C*H*CH=C(CH$_3$)), 6.12 (1H, d, J = 11 Hz, C*H*=C(CH$_3$)), 5.70 (1H, dd, J = 15 Hz and 8 Hz, C*H*=CHCH=C(CH$_3$)), 5.01 (1H, d, J = 10 Hz, C(CH$_3$)=C*H*), 4.75 (1H, d, J_{AB} = 8 Hz, OC*H*$_2$O), 4.55 (1H, d, J_{AB} = 8 Hz, OC*H*$_2$O), 4.50 (1H, m, C*H*OSEM), 4.32 (1H, t, J = 6.5 Hz, C*H*OMOP), 3.70–3.30 (4H, m, OC*H*$_2$CH$_2$TMS and C*H*$_2$Cl), 3.27 and 3.22 (3H, 2s, CHOC*H*$_3$), 3.10 (3H, s, C(CH$_3$)$_2$OC*H*$_3$), 2.92 (1H, m, C*H*OCH$_3$), 2.50 (1H, m, C*H*CH$_3$), 2.39–2.05 (4H, m, C*H*$_2$CHO and C*H*$_2$C(CH$_3$)), 1.95–1.45 (4H, m, C*H*$_2$CH$_2$C(CH$_3$) and C*H*$_2$CH$_2$CHO), 1.66 (6H, m, C(C*H*$_3$)=CH and CH=C(C*H*$_3$)), 1.25 and 1.21 (6H, 2s, (C*H*$_3$)$_2$OCH$_3$), 1.10 (3H, d, J = 7 Hz, CHC*H*$_3$), 0.95 (2H, t, J = 7 Hz, C*H*$_2$TMS), 0.02 (9H, s, Si(C*H*$_3$)$_3$).

^{13}C NMR (75 MHz, C_6D_6, δ ppm): 202.1, 202.0, 141.1, 137.1, 134.0, 128.4, 128.3, 125.5, 125.1, 101.7, 91.5, 91.4, 84.9, 84.6, 76.3, 76.2, 70.5, 70.4, 65.0, 57.6, 49.4, 46.1, 46.0, 40.2, 39.7, 39.6, 29.5, 28.4, 28.2, 28.0, 25.4, 25.0, 23.4, 18.1, 16.0, 15.9, 12.3, 12.2, −1.42.

MS (m/e, ammoniac): 592 (M^+ + NH_4).

HMRS: calc for $C_{30}H_{59}O_6ClNSi$: 592.3800; found: 592.3781.

(6Z,12E,14E)-(2S and 2R,5R and 5S,10S,11S,16S and 16R)-17-Chloro-10-methoxy-7,11,15-trimethyl-5-[(4-trimethylsilyl-2-oxabutanyl)oxy]-1-(phenylsulfonyl)heptadeca-6,12,14-triene-2,16-diol **32**

To a solution of benzyl methyl sulfone (105 mg, 676 μmol) in dry tetrahydrofuran (3 mL) was added, at 0 °C, butyllithium (1.6 M in hexanes, 422 μL, 676 μmol) and the solution was stirred for 30 min at 0 °C. The reaction mixture was transferred via canula into a solution of the aldehyde **31** (195 mg, 338 μmol) in tetrahydrofuran (3 mL) at −78 °C. After stirring for 1 h at −78 °C, the reaction was quenched with a saturated aqueous ammonium chloride solution (10 mL) and the mixture was extracted several times with diethyl ether. The combined organic phases were concentrated and the residue was dissolved in acetone (6 mL) and a solution of HCl 1 N (1 mL) was added. After stirring for 20 min, the mixture was concentrated and aqueous residue was extracted with diethyl ether (3×). The organic phases were dried over magnesium sulfate, filtered and concentrated. The residue was purified by flash chromatography (60% acetone in hexanes) to afford a colorless oil as a mixture of eight diastereoisomers **32** (194 mg, 87%).

$[\alpha]_D^{20}$ = −1.3 (c = 1.10, dichloromethane).

IR (film, ν cm^{-1}): 3 481, 2 929, 1 447, 1 304, 1 148, 1 085.

^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 7.87–7.45 (5H, m, C$_6$*H*$_5$), 6.20 (1H, m, CH=C*H*CH=C(CH$_3$)), 6.05 (1H, m, C*H*=C(CH$_3$), 5.61 (1H, m, C*H*=CHCH=C(CH$_3$)), 4.88 (1H, m, C(CH$_3$)=C*H*), 4.50 (2H, m, OC*H*$_2$O), 4.30–4.05 (3H, m, C*H*(OH)CH$_2$Cl, C*H*OH and C*H*OSEM), 3.73–3.05 (9H, m, OC*H*$_2$CH$_2$TMS, C*H*$_2$Cl, C*H*$_2$SO$_2$Ph and CHOC*H*$_3$), 2.95 (1H, m, C*H*OCH$_3$), 2.45 (1H, m, C*H*CH$_3$), 2.30–1.65 (2H, m, C*H*$_2$C(CH$_3$)), 1.67 (3H, s, C(C*H*$_3$)=CH), 1.62 (3H, s, CH=C(C*H*$_3$)), 1.70–1.45 (6H, m, C*H*$_2$CH$_2$C(CH$_3$) and C*H*$_2$C*H*$_2$CHOH), 0.96 (3H, m, CHC*H*$_3$), 0.81 (2H, m, C*H*$_2$TMS), −0.09 (9H, s Si(C*H*$_3$)$_3$).

^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 140.3, 140.2, 139.4, 139.2, 137.6, 133.7, 133.5, 129.2, 128.9, 128.6, 127.7, 127.4, 127.2, 127.1, 127.0, 126.2, 125.2, 91.3, 90.9, 84.8, 84.6, 84.4, 84.0, 76.5, 76.2, 76.1, 71.1, 70.7, 65.9, 65.6, 65.5, 64.8, 62.2, 62.1, 57.4, 57.1, 57.0, 56.4, 48.0, 47.9, 47.8, 44.2, 39.8, 39.7, 39.6, 39.5, 35.2, 32.5, 32.4, 32.3, 31.3, 31.1, 31.0, 30.7, 29.6, 29.4, 29.3, 29.2, 29.0, 27.9, 27.4, 27.2, 27.1, 25.0, 23.3, 22.4, 17.8, 16.4, 16.2, 16.1, 13.9, 12.9, 12.7, 12.3, 12.2, −1.6.

MS (m/e, ammoniac): 658 (M^+ + NH_4 − H_2O).

HMRS: calc for $C_{33}H_{53}O_6ClNSSi$: 658.3364; found: 658.3377.

(6Z,12E,14E)-(5S,10S,11S)-17-Chloro-10-methoxy-7,11,15-trimethyl-5-[(4-trimethylsilyl-2-oxabutanyl)-oxy]-1-(phenylsulfonyl)heptadeca-6,12,14-triene-2,16-dione and (6Z,12E,14E)-(5R,10S,11S)-17-chloro-10-methoxy-7,11,15-trimethyl-5-[(4-trimethylsilyl-2-oxabutanyl)oxy]-1-(phenylsulfonyl)heptadeca-6,12,14-triene-2,16-dione **33**

To a solution of diol **32** (170 mg, 275 μmol) in dichloromethane (10 mL) was added Dess–Martin periodinane (257 mg, 605 μmol). After stirring for 1 h, the reaction was quenched with a saturated aqueous sodium bicarbonate (5 mL) and sodium thiosulfate (1 g) was added. After stirring for 20 min, the resulting mixture was extracted several times with dichloromethane. The combined organic phases were dried over magnesium sulfate, filtered and concentrated. The residue was purified by flash chromatography (30% ethyl acetate in hexanes) to provide a yellowish oil as a mixture of two diastereoisomers **33** (144 mg, 85%).

$[\alpha]_D^{20}$ = −6.2 (c = 1.04, dichloromethane).

IR (film, ν cm^{-1}): 2 946, 1 721, 1 629, 1 318, 1 153, 1 086.

^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 7.87–7.51 (5H, m, C$_6$*H*$_5$), 7.01 and 6.99 (1H, 2d, J = 11 Hz, CH=CHC*H*=C(CH$_3$)), 6.42 (1H, dd, J = 15 Hz and 11 Hz, CH=C*H*CH=C(CH$_3$)), 6.39 (1H, dd, J = 15 Hz and 7.5 Hz, C*H*=CHCH=C(CH$_3$)), 4.96 and 4.94 (1H, 2d, J = 8 Hz, C*H*=C(CH$_3$)), 4.58 and 4.56 (1H, 2d, J_{AB} = 7 Hz, OC*H*$_2$O), 4.47 (1H, d, J_{AB} = 7 Hz, OC*H*$_2$O), 4.43 and 4.42 (2H, 2s, C*H*$_2$SO$_2$Ph), 4.28 (1H, m, C*H*OSEM), 4.14 and 4.13 (2H, 2s, C*H*$_2$Cl), 3.62 and 3.47 (2H, 2m, OC*H*$_2$CH$_2$TMS), 3.36 and 3.34 (3H, 2s, CHOC*H*$_3$), 3.06 (1H, m, C*H*OCH$_3$), 2.70 (3H, m, C*H*$_2$CO and C*H*CH$_3$), 2.24–1.90 (2H, m, C*H*$_2$C(CH$_3$)), 1.89 (3H, s, C(C*H*$_3$)=CH), 1.80–1.30 (4H, m, C*H*$_2$CH$_2$C(CH$_3$) and C*H*$_2$CH$_2$CO), 1.69 (3H, s, C(C*H*$_3$)=CH), 1.06 (3H, d, J = 7 Hz, CHC*H*$_3$), 0.90 and 0.88 (2H, 2t, J = 8 Hz, C*H*$_2$TMS), −0.01 (9H, s, Si(C*H*$_3$)$_3$).

^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 197.7, 192.4, 147.1, 146.9, 140.6, 134.1, 132.1, 129.2, 128.1, 125.8, 125.2, 125.1, 91.5, 91.4, 84.6, 84.2, 70.2, 66.6, 65.0, 52.5, 57.3, 45.0, 40.5, 39.8, 39.7, 29.5, 28.3, 23.4, 18.0, 15.4, 15.3, 11.7, −1.4.

MS (m/e): 672 ($M^+ + NH_4$).

HMRS: calc for $C_{33}H_{55}O_7ClNSSi$: 672.3157; found: 672.3176.

(8Z,14E,16E)-(3S and 3R,7S and 7R,12S,13S)-12-Methoxy-9,13,17-trimethyl-7-[(4-trimethylsilyl-2-oxabutanyl)oxy]-3-(phenylsulfonyl)cycloheptadeca-8,14,16-triene-1,4-dione **34**

To a suspension of cesium carbonate (391 mg, 1.2 mmol) in acetonitrile (155 mL) was added, at 45 °C, a solution of the chloroketone **33** (158 mg, 241 μmol) in acetonitrile (5 mL) over a period for 2 h. After stirring for 1 h, the reaction was quenched with a saturated aqueous ammonium chloride solution (100 mL) and the mixture was extracted several times with a solution of hexanes and diethyl ether (3×, 1:1). The combined organic phases were dried over magnesium sulfate, filtered and concentrated. The residue was purified by flash chromatography (30% ethyl acetate in hexanes) to afford a colorless oil as two fractions containing a mixture of two diastereoisomers each **34** (107 mg, 72%).

$[\alpha]_D^{20} = -1.4$ ($c = 1.07$, dichloromethane).

IR (film, ν cm^{-1}): 2 952, 1 719, 1 656, 1 628, 1 325, 1 152, 1 099.

^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 7.90–7.46 (5H, m, C_6H_5), 6.92 (1H, m, CH=CHC*H*=C(CH_3)), 6.40 (1H, m, CH=C*H*CH=C(CH_3)), 6.10 (1H, m, C*H*=CHCH=C(CH_3), 4.90 (1H, d, J = 7.5 Hz, C*H*=C(CH_3)), 4.70–4.25 (3H, m, OCH_2O and C*H*OSEM), 3.86 (1H, t, J = 11 Hz, C*H*SO_2Ph), 3.84–3.35 (5H, m, OCH_2CH_2TMS and CHOCH_3), 3.10–2.20 (5H, m, C*H*OCH_3, CH_2CO and CH_2CH), 2.05 (1H, m, C*H*CH_3), 1.97–1.30 (6H, m, CH_2CH_2C(CH_3) and CH_2CH_2CO), 1.70 (6H, m, C(CH_3)=CH and CH=C(CH_3)), 1.13 (3H, m, CHCH_3), 0.90 (2H, m, CH_2TMS), 0.02 (9H, m, Si(CH_3)$_3$).

^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 201.4, 197.8, 148.5, 148.2, 147.7, 144.3, 142.9, 142.0, 140.3, 138.5, 136.6, 134.6, 133.6, 133.4, 129.4, 129.0, 126.8, 126.7, 126.2, 125.8, 125.3, 124.7, 93.3, 93.0, 91.8, 91.6, 85.3, 84.6, 84.2, 73.8, 72.7, 72.6, 72.4, 72.1, 70.6, 70.2, 65.4, 65.1, 65.0, 60.4, 58.4, 57.2, 56.7, 44.9, 43.0, 42.8, 42.6, 40.6, 39.7, 34.9, 34.6, 34.2, 34.0, 33.8, 30.4, 29.9, 29.5, 29.4, 29.1, 28.6, 27.9, 26.2, 23.9, 23.8, 23.2, 21.0, 18.8, 18.1, 18.0, 17.6, 15.5, 14.2, 11.6, 11.5, 11.3, −1.2, −1.4, −4.2.

MS (m/e): 560 ($M^+ - CH_2O_2$).

(2E,8Z,14E,16E)-(7S,12S,13S)-12-Methoxy-9,13,17-trimethyl-7-[(4-trimethylsilyl-2-oxabutanyl)oxy]cycloheptadeca-2,8,14,16-tetraene-1,4-dione and (2E,8Z,14E,16E)-(7R,12S,13S)-12-methoxy-9,13,17-trimethyl-7-[(4-trimethylsilyl-2-oxabutanyl)oxy]cycloheptadeca-2,8,14,16-tetraene-1,4-dione **35**

To a solution of the macrocycle **34** (65.3 mg, 105 μmol) in tetrahydrofuran (5 mL) was added diazabicyclo[2.2.2]undecene (24.1 mg, 157 μmol). After stirring for 1 h at room temperature, the reaction was quenched with saturated aqueous ammonium solution (10 mL) and the resulting mixture was extracted with diethyl ether (3×). The combined organic phases were dried over magnesium sulfate, filtered and concentrated. The residue was purified by flash chromatography (30% ethyl acetate in hexanes) to give a yellowish oil as a mixture of two diastereoisomers **35** (45.2 mg, 90%).

$[\alpha]_D^{20} = -35.3$ ($c = 1.15$, dichloromethane).

IR (film, ν cm^{-1}): 2 950, 2 880, 1 698, 1 647, 1 626, 1 248, 1 096.

Diastereoisomer A: ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 7.02 (1H, d, J = 16 Hz, COC*H*=CH), 6.91 (1H, d, J = 11 Hz, C*H*=C(CH_3)), 6.63 (1H, d, J = 16 Hz, COCH=C*H*), 6.44 (1H, dd, J = 15 Hz and 11 Hz, CH=C*H*CH=C(CH_3), 6.03 (1H, dd, J = 15 Hz and 8 Hz, C*H*=CHCH=C(CH_3)), 5.03 (1H, d, J = 7.5 Hz, C*H*=C(CH_3)), 4.64 (1H, d, J_{AB} = 7 Hz, OCH_2O), 4.56 (1H, d, J_{AB} = 7 Hz, OCH_2O), 4.41 (1H, m, C*H*OSEM), 3.70 and 3.50 (2H, 2m, OCH_2CH_2TMS), 3.43 (3H, s, CHOCH_3), 2.95 (1H, m, C*H*OCH_3), 2.61 (2H, m, CH_2CO), 2.47 (1H, m, C*H*CH_3), 2.18 (2H, m, CH_2C(CH_3)), 1.94 (3H, d, J = 1 Hz, C(CH_3)=CH), 1.83–1.50 (4H, m, CH_2CH_2C(CH_3) and CH_2CH_2CO), 1.77 (3H, d, J = 1 Hz, C(CH_3)=CH), 1.16 (3H, d, J = 7 Hz, CHCH_3), 0.90 (2H, m, CH_2TMS), 0.03 (9H, s, Si(CH_3)$_3$).

Diastereoisomer B: ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 7.00 (1H, d, J = 16 Hz, COC*H*=CH), 6.95 (1H, dd, J = 11 Hz and 1 Hz, C*H*=C(CH_3)), 6.65 (1H, d, J = 16 Hz, COCH=C*H*), 6.41 (1H, ddd, J = 15 Hz, 11 Hz and 1 Hz, CH=C*H*CH=C(CH_3), 6.30 (1H, dd, J = 15 Hz and 5.5 Hz, C*H*=CHCH=C(CH_3)), 5.02 (1H, d, J = 7.5 Hz, C*H*=C(CH_3)), 4.63 (1H, d, J_{AB} = 7 Hz, OCH_2O), 4.56 (1H, d, J_{AB} = 7 Hz, OCH_2O), 4.41 (1H, m, C*H*OSEM), 3.70–3.50 (2H, m, OCH_2CH_2TMS), 3.39 (3H, s, CHOCH_3), 3.02 (1H, m, C*H*OCH_3), 2.75 (1H, m, C*H*CH_3), 2.62 (2H, m, CH_2CO), 2.45 (1H, dt, J = 12 Hz and 5 Hz, CH_2C(CH_3)), 1.95 (3H, s, C(CH_3)=CH), 1.83 (3H, m, CH_2C(CH_3) and CH_2CH_2CO), 1.78 (3H, d, J = 1 Hz, C(CH_3)=CH), 1.55 and 1.30 (2H, 2m, CH_2CH_2C(CH_3)), 1.14 (3H, d, J = 7 Hz, CHCH_3), 0.90 (2H, m, CH_2TMS), 0.02 (9H, s, Si(CH_3)$_3$).

^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 199.6, 199.4, 197.6, 197.3, 147.9, 147.7, 145.0, 144.5, 140.9, 140.8, 137.7, 137.6, 136.7, 135.8, 133.7, 133.1, 129.3, 125.3, 125.0, 124.6, 91.6, 91.5, 85.7, 85.0, 70.5, 70.1, 65.4, 65.2, 57.8, 56.6, 43.0, 39.9, 39.6, 38.5, 32.4, 31.9, 31.7, 30.9, 29.9, 28.7, 24.4, 23.6, 18.1, 18.0, 17.2, 15.1, 12.0, 11.9, −1.5.

MS (m/e): 476 (M^-).

HMRS calc for $C_{27}H_{44}O_5Si$: 476.2958; found: 476.2968.

(8Z,14E,16E)-(7S,12S,13S)-12-Methoxy-9,13,17-trimethyl-7-[(4-trimethylsilyl-2-oxabutanyl)oxy]cycloheptadeca-8,14,16-triene-1,4-dione and (8Z,14E,16E)-(7S,12S,13S)-12-methoxy-9,13,17-trimethyl-7-[(4-trimethylsilyl-2-oxabutanyl)oxy]cycloheptadeca-8,14,16-triene-1,4-dione **36**

To a solution of the enedione **35** (127 mg, 266 μmol) in a mixture of benzene (10 mL) and acetic acid (16.7 mg, 279 μmol), previously degassed, were added tri-*n*-butyltin (92.9 mg, 319 μmol) and tetrakis(triphenylphosphine)palladium (9.2 mg, 7.98 μmol) under argon. After stirring for 30 min, the reaction was quenched with water (10 mL) and the resulting mixture was extracted several times with diethyl ether. The combined organic phases were dried over magnesium sulfate, filtered and concentrated. The residue was purified by flash chromatography (30% ethyl acetate in hexanes) to afford a yellowish oil as a mixture of two diastereoisomers **36** (115 mg, 91%).

$[\alpha]_D^{20} = -34.0$ ($c = 1.15$, dichloromethane).

IR (film, ν cm^{-1}): 2 952, 2 927, 1 714, 1 657, 1 632, 1 248, 1 099, 1 030.

^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 7.00 and 6.91 (1H, 2d, J = 11 Hz, C*H*=C(CH_3)), 6.43 and 6.39 (1H, 2dd, J = 15 Hz and 11 Hz, CH=C*H*CH=C(CH_3)), 6.09 and 6.07 (1H, 2dd, J = 15 Hz and 7 Hz, C*H*=CHCH=C(CH_3)), 4.96 (1H, d, J = 7.5 Hz, C*H*=C(CH_3)), 4.10–3.90 (2H, m, OCH_2O), 4.13 and 3.82 (1H, 2m, C*H*OSEM), 3.73–3.45 (2H, m, OCH_2CH_2TMS), 3.41 and 3.36 (3H, 2s, CHOCH_3), 3.01 (1H, m, C*H*OCH_3), 2.95–2.32 (5H, m, CH_2COCH_2 and C*H*CH_3), 2.25–1.83 (8H, m, CH_2CH_2C(CH_3), COCH_2 and CH_2CH_2CO), 1.82 and 1.81 (3H, 2s, C(CH_3)=CH), 1.72 (3H, s, C(CH_3)=CH), 1.13 and 1.10 (3H, 2d, J = 7 Hz, CHCH_3), 0.85 (2H, m, CH_2TMS), 0.02 and −0.01 (9H, 2s, Si(CH_3)$_3$).

^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 209.3, 208.7, 203.0, 146.6, 146.2, 142.1, 140.9, 139.9, 139.1, 133.2, 129.3, 126.5, 126.3, 126.1, 126.0, 92.5, 91.7, 85.4, 84.2, 72.1, 71.1, 65.0, 57.7, 56.6, 42.7, 41.3, 40.0, 39.8, 39.3, 32.1, 31.9, 29.8, 29.5, 29.2, 28.6, 26.4, 26.1, 24.0, 23.6, 18.1, 17.9, 16.9, 14.1, 11.4, −1.5.

MS (m/e): 448 (M^+ − CH_2O).

HMRS: calc for $C_{26}H_{44}O_4Si$: 448.3009; found: 448.3014.

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