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TWO CONVERGENT APPROACHES TO THE SYNTHESIS OF 1α,25-DIHYDROXY-2β-(3-HYDROXYPROPOXY)VITAMIN D_3 (ED-71) BY THE LYTHGOE AND THE TROST COUPLING REACTIONS*

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Abstract – Two convergent syntheses of 1α,25-dihydroxy-2β-(3-hydroxypropoxy)vitamin D_3 (ED-71) by the Lythgoe coupling reaction between the A-ring phosphine oxide and the C/D-ring ketone and the Trost coupling reaction between the A-ring ene-yne and the C/D-ring bromomethylene are described.

INTRODUCTION

1α,25-Dihydroxyvitamin D_3 ($1,25(OH)_2D_3$, **1**), an active vitamin D_3, is well recognized as a potent regulator of cell proliferation and differentiation processes in addition to possessing regulatory effects on calcium and phosphorus metabolism.[1] Various analogs of $1,25(OH)_2D_3$ (**1**) have been investigated in attempts to separate differentiation-induction and antiproliferation activities from calcemic activity with the aim of obtaining useful analogs for the medical treatment of psoriasis, secondary hyperparathyroidism, cancer, etc.[2] There is also intense interest in obtaining analogs more potent than $1,25(OH)_2D_3$ (**1**) in regulating calcium and phosphorus metabolism with the objective of treating bone diseases such as osteoporosis. 1α,25-Dihydroxy-2β-(3-hydroxylpropoxy)vitamin D_3 (ED-71, **2**), an analog of $1,25(OH)_2D_3$ (**1**) which possesses a hydroxypropoxy substituent at the 2β-position, is such an analog that shows potent

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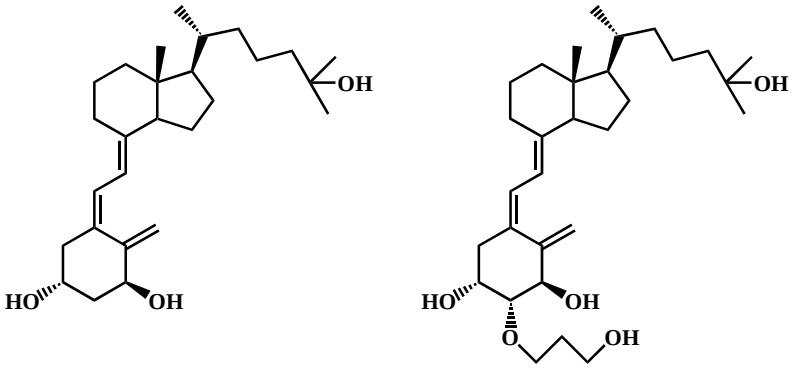
**Dedicated to Professor Steven M. Weinreb on the occasion of his 65th birthday.*

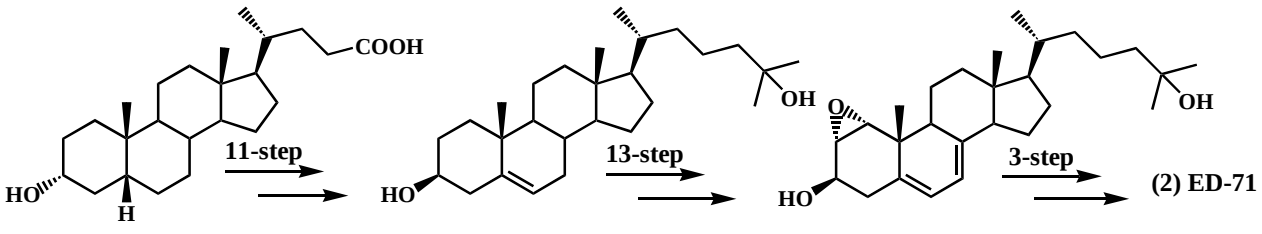
effects on bone therapy (Figure 1).[3-7] Phase III clinical studies of ED-71 (**2**) as a promising candidate for the treatment of osteoporosis and bone fracture prevention are now being successfully conducted in Japan.[8,9]



(1) 1,25(OH)$_2$D$_3$ **(2) ED-71**

Figure 1. Structure of the active vitamin D_3 and ED-71

Considering the potential clinical applications of ED-71 (**2**) as a useful drug in the near future, we have been investigating a practical synthesis of **2** for industrial scale production. ED-71 (**2**) was initially synthesized in a linear manner in which the 1,2α-epoxide (**5**), prepared from lithocholic acid (**3**) *via* 25-hydroxycholesterol (**4**),[10] served as a key intermediate for the introduction of the characteristic hydroxypropoxy substituent at the 2β-position (Scheme 1).[3] The 27-step linear sequence, however, was suboptimal due to its lengthiness and low overall yield. Herein, we report two new convergent approaches for the preparation of ED-71 (**2**) based on the Lythgoe and the Trost coupling reactions.



(3) lithocholic acid **(4) 25-hydroxycholesterol** **(5) 1,2α-epoxide**

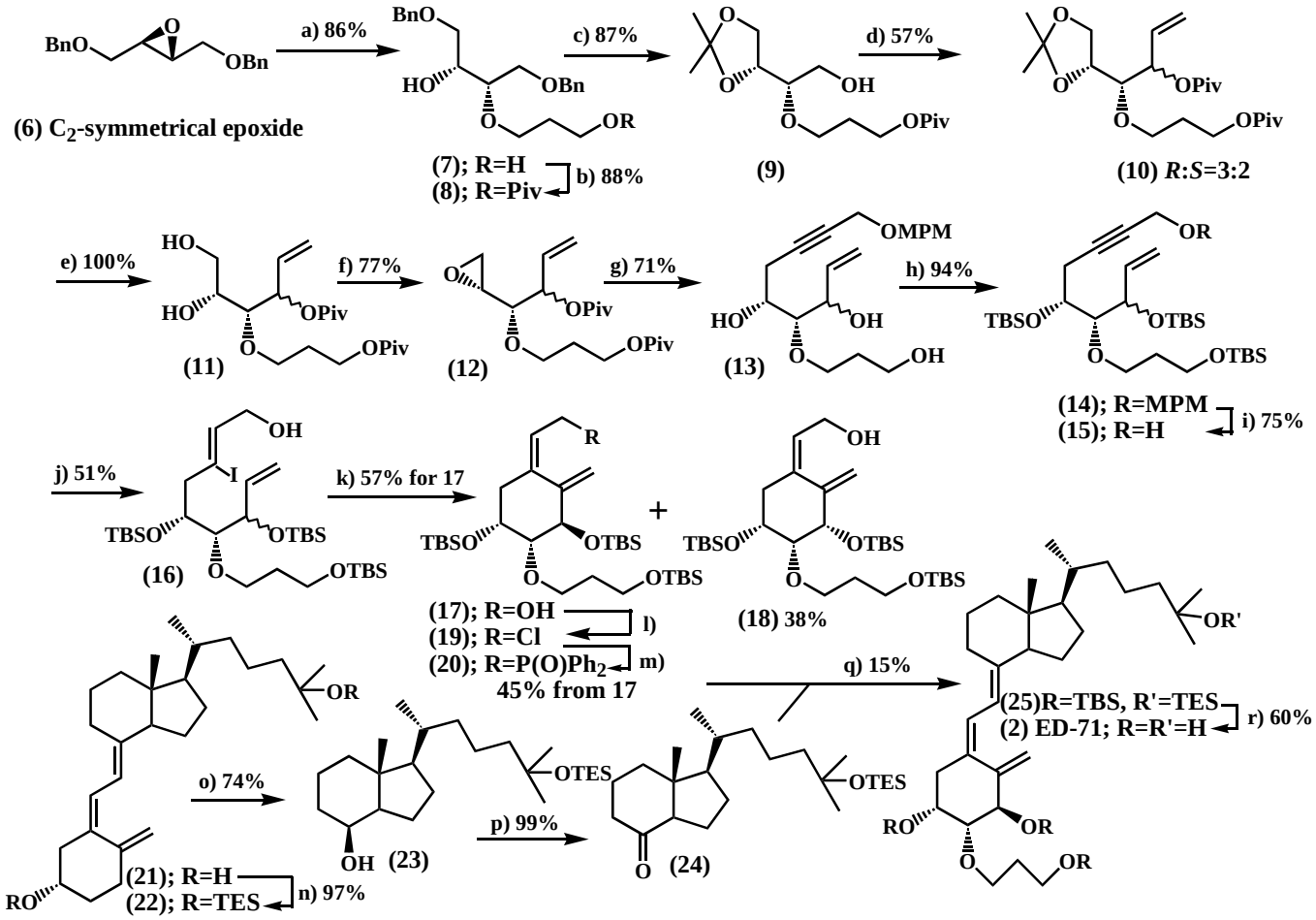
Scheme 1. Linear synthesis of ED-71 from lithocholic acid

RESULTS AND DISCUSSION

The first convergent route to ED-71 (**2**) involves the Lythgoe reaction, in which the A-ring phosphine

oxide (**20**) and the C/D-ring ketone (**24**) are coupled to produce the triene system of vitamin D_3.[11] The required A-ring phosphine oxide (**20**) was synthesized based on the methodology we have previously established.[12,13] Thus, cleavage of the known C_2-symmetrical epoxide (**6**)[14] with 1,3-propanediol in the presence of potassium *tert*-butoxide (*t*-BuOK) gave the diol (**7**) in 86% yield. After protection of the primary hydroxyl group giving the pivalate ester (**8**) in 88% yield, cleavage of the benzyl ether moiety in **8** and subsequent protection of the resulting 1,2-diol as the acetonide gave the alcohol (**9**) in 87% overall yield. Swern oxidation of **9** and Grignard reaction of the aldehyde afforded the dipivalate (**10**) as an epimeric mixture (*R/S* = 3/2) after protection of the hydroxyl group as the pivalate. Only poor diastereoselectivity was observed in the Grignard reaction, although we expected the desired *R*-isomer would be obtained in high diastereoselectivity *via* a five-membered chelated intermediate. Without separation of the epimeric mixture, the acetonide moiety in **10** was cleaved quantitatively to give the diol (**11**). Exposure of **11** to Mitsunobu conditions[15] afforded the epimeric epoxide (**12**) in 77% yield. The reaction of **12** with the lithium acetylide prepared from propargyl *p*-methoxybenzyl ether followed by hydrolysis with sodium hydroxide afforded the alkyne (**13**) in 71% yield. This alkyne was ultimately transformed to the vinyl iodide (**16**) in 36% overall yield *via* a three-step sequence involving (i) silylation of **13** with *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf), (ii) deprotection of *p*-methoxyphenyl methyl (MPM) moiety in **14** with dichlorodicyanobenzoquinone (DDQ), and (iii) reduction of **15** with sodium bis(2-methoxyethoxy)aluminum hydride (Red-Al) followed by iodination. The Heck reaction of **16** catalyzed by tetrakis(triphenylphosphine)palladium ($(Ph_3P)_4Pd$)[13] gave the cyclized alcohols (**17**) and (**18**) after separation by column chromatography, in 57% and 38% yields, respectively. The alcohol (**17**) is fully substituted with the requisite stereochemistry of the A-ring fragment of ED-71 (**2**), whereas the alcohol (**18**) corresponds to the diastereomer at position C-1. The reaction of the hydroxyl functionality in **17** with *N*-chlorosuccinimide (NCS) and dimethyl sulfide (Me_2S) gave the chloride (**19**), which was then converted to the phosphine oxide (**20**) by treatment with lithium diphenylphosphide and subsequent hydrogen peroxide (H_2O_2) (45% yield for two steps).

Next, we investigated the synthesis of the C/D ring fragment (**24**). Although the alcohol (**23**) could be synthesized from the Inhoffen-Lythgoe diol by known route,[11,16] we adopted a different approach for the preparation of **23** in the present study. Thus, readily and commercially available 25-hydroxyvitamin D_3 (**21**) was protected with triethylsilyl trifluoromethanesulfonate (TESOTf) to the bis-TES ether (**22**) in 97% yield, which was converted to the alcohol (**23**) by ozonolysis and the subsequent treatment with sodium borohydride ($NaBH_4$) in 74% yield. The hydroxyl moiety in **23** was oxidized to the ketone (**24**) by tetrapropylammonium perruthenate (TPAP) and *N*-methylmolpholine *N*-oxide (NMO) in 99% yield.



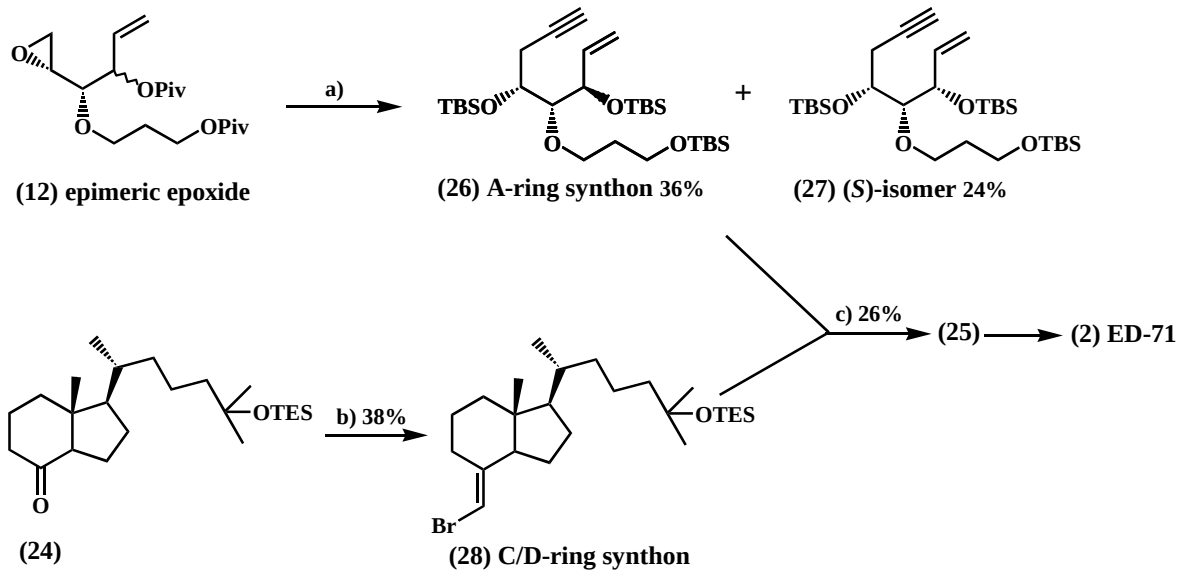
Scheme 2. First convergent synthesis of ED-71 by the Lythgoe coupling reaction. Reagents and conditions: a) $HO(CH_2)_3OH$/*t*-BuOK, 120°C. b) *t*-BuCOCl/pyridine/CH_2Cl_2, rt. c) 1) H_2/$Pd(OH)_2$/MeOH, rt. 2) $Me_2C(OMe)_2$/TsOH/acetone, rt. d) 1) DMSO/$(COCl)_2$/CH_2Cl_2, -60°C. 2) CH_2=CHMgBr/THF, -60°C. 3) *t*-BuCOCl/Et_3N/DMAP/CH_2Cl_2, rt. e) 1M HCl/MeOH, rt. f) Ph_3P/DEAD/benzene, reflux. g) 1) LiC ≡ CCH_2OMPM/BF_3-OEt_2/THF, -60°C~-10°C. 2) 10M NaOH/MeOH, reflux. h) TBSOTf/Et_3N/CH_2Cl_2, 0°C, i) DDQ/CH_2Cl_2, rt. j) Red-Al/Et_2O/toluene, 0°C~rt, then I_2/AcOEt, -78°C. k) $PdCl_2(PPh_3)_2$/Et_3N/MeCN, reflux. l) NCS/Me_2S/CH_2Cl_2, -20°C. m) 1) $LiPPh_2$/THF, -78°C. 2)H_2O_2, 0°C. n) TESOTf/Et_3N/CH_2Cl_2, 0°C. o) O_3/CH_2Cl_2/MeOH, -78°C then $NaBH_4$/MeOH, -78°C. p) NMO/TPAP/4Ams/CH_2Cl_2, rt. q) n-Buli/THF, -78°C. r) TBAF/THF.

The Lythgoe coupling reaction of the A-ring fragment (**20**) and the C/D-ring fragment (**24**) gave **25** in 15% yield. Finally, deprotection of the silyl protecting groups in **25** using tetrabutylammonium fluoride (TBAF) afforded ED-71 (**2**) in 60% yield (Scheme 2).[17]

Although a convergent synthesis of ED-71 (**2**) was achieved *via* the Lythgoe coupling reaction, the coupling yield was quite low (15%). Moreover, the route to the A-ring fragment (**20**) from the C_2-symmetrical epoxide (**6**) consisted of an 18-step sequence and thus, large scale production of ED-71 (**2**) did not seem feasible by this route.[18] We, therefore, further investigated the synthesis of a new A-ring synthon and coupling reaction. Since the epimeric epoxide (**12**) was obtained from the C_2-symmetrical epoxide (**6**) by a 9-step sequence in moderate overall yield (29%), we examined an alternative route to a

new A-ring synthon employing **12**. The acetylene unit was successfully introduced to **12** by the regioselective epoxide-opening with lithium trimethylsilylacetylide to provide the ene-yne (**26**)[12] as the A-ring synthon in 36% yield after protecting group exchange from pivalate to *tert*-butyldimethylsilyl (TBS) ether. The accompanied (*S*)-epimer (**27**) was separated in 24% yield by simple column chromatography. Next, we performed the synthesis of the new C/D-ring synthon (**28**) from the ketone (**24**) according to the procedure by Trost *et al.*[19,20] Wittig reaction of **24** with (bromomethylene)triphenylphosphonium bromide ($Ph_3P^+CH_2Br/Br^-$) and sodium hexamethyldisilazide (NaHMDS) gave rise to the bromomethylene (**28**) as the C/D-ring synthon in 38% yield (Scheme 3).

With the A-ring synthon (**26**) and the C/D-ring synthon (**28**) in hand, we then investigated these Trost coupling.[19,20] Thus, upon treatment of **26** and **28** with triethylamine (Et_3N), triphenylphosphine (PPh_3) and tris(dibenzylideneacetone)dipalladium-chloroform [$(dba)_3Pd_2$-$CHCl_3$] in boiling toluene, **25** was obtained in 26% yield together with recovered **26** (45%) and **28** (56%). Deprotection of the silyl moiety in **25** with TBAF afforded ED-71 (**2**) as described above (Scheme 3). Thus, an alternative convergent route to ED-71 (**2**) based on the Trost coupling reaction has been established and the overall efficiency is improved compared to the aforementioned Lythgoe approach.



Scheme 3. Alternative convergent synthesis of ED-71 by the Trost coupling reaction. Reagents and conditions: a) 1) $LiC{\equiv}CTMS/BF_3$-OEt_2, -78°C. 2) 10N NaOH/MeOH, rt. 3) TBSOTf/Et_3N, 0°C b) $Ph_3P^+CH_2BrBr^-$/NaHMDS/THF, -60°C~rt. c) $(dba)_3Pd_2$-$CHCl_3$/PPh_3/Et_3N/toluene, reflux.

CONCLUSION

We completed two convergent syntheses of ED-71 (**2**) based on the Lythgoe and the Trost coupling

strategies. Although the overall yield of the two convergent syntheses was better than the previous linear approach, significant improvements are still demanded for the practical production of ED-71 (**2**) and further investigations along this line of research are ongoing.

EXPERIMENTAL

All melting points were taken on Yanagimoto micro melting point apparatus and are uncorrected. Optical rotations were measured with JASCO DIP-140 polarimeter. Infrared (IR) spectra were obtained using JASCO FT/IR-5300, JEOR JIR-6000, and Hitachi 270-30 spectrophotometers. ^{1}H and ^{13}C NMR spectra were recorded on VARIAN Gemini-300, JEOR FX-200, and JNM-270EX spectrometers using $CDCl_3$ as a solvent. Chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane or calibrated from $CHCl_3$. Mass spectra (MS) were measured with JEOL JMS-HX-100, Shimadzu GCMS QP-1000, and Hitachi M1200H instruments. High resolution mass spectra (HRMS) were recorded on JEOL JMS-AX-500 and VG Auto Spec Q instruments. Ultra violet (UV) spectra were obtained with Shimadzu UV-240 spectrometer using EtOH as a solvent. All reactions were carried out under an atmosphere of argon unless otherwise noted. All extracts were dried over $MgSO_4$ and evaporated under reduced pressure with a rotary evaporator. Chromatographic purification was carried out with Merck silica gel 60 (column) or Merck silica gel 60 PFR_{254} (thin layer).

(3*RS*,4*R*,5*R*)-4-(3-Hydroxypropoxy)-9-(*p*-methoxyphenylmethoxy)non-1-en-7-yne-3,5-ol (13): To a stirred solution of *p*-methoxybenzyl 2-propynyl ether (2.42 g, 13.76 mmol) in THF (20 mL) at -60 °C, was added *n*-BuLi (1.56 M solution in *n*-hexane, 8.82 mL, 13.76 mmol). The resulting mixture was stirred at the same temperature for 15 min. After addition of BF_3-OEt_2 (1.69 mL, 13.76 mmol), **12**[12] (490 mg, 1.38 mmol) in THF (30 mL) was added to the resulting mixture at -60 °C. The resulting mixture was stirred at -60 °C ~ -10 °C for 18 h, quenched with saturated $NaHCO_3$, extracted with CH_2Cl_2, washed with saturated NaCl, evaporated and chromatographed on silica gel. Elution with *n*-hexane-AcOEt (10:1) gave crude product (786.6 mg), which was used without further purification. To a stirred crude product (786.6 mg) in MeOH (10 mL), was added 10 M NaOH (10 mL) at rt. The mixture was stirred at rt for 18 h, extracted with CH_2Cl_2, washed with saturated NaCl, evaporated and chromatographed on silica gel. Elution with *n*-hexane-AcOEt (1:1) gave **13** (358.7 mg, 71%) as a colorless oil. IR (neat): ν 3394, 1612, 1513, 1250, 1072 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 7.28 (2H, d, *J*=8.8 Hz), 6.88 (2H, d, *J*=8.8 Hz), 6.10-5.85 (1H, m), 5.40 (1H, br d, *J*=16.7 Hz), 5.25 (1H, br d, *J*=10.4 Hz), 4.52 (2H, s), 4.40 (1H, m), 4.12 (2H, s), 4.01-3.57 (9H, m), 3.49-3.29 (1H, m), 3.16-2.18 (5H, br), 1.82 (2H, quint, *J*=6.0 Hz). HRMS (EI) calcd for $C_{20}H_{27}O_6$

[(M-1)$^+$] 363.1807, found 363.1806.

(3*RS*,4*R*,5*R*)-3,5-Bis(*tert*-butyldimethylsilyloxy)-4-(3-*tert*-butyldimethylsilyloxypropoxy)-9-(*p*-methoxyphenylmethoxy)non-1-en-7-yne (14): A mixture of **13** (242.9 mg, 0.67 mmol), TBSOTf (766 μL, 3.34 mmol) and Et_3N (930 μL, 6.67 mmol) in CH_2Cl_2 (25 mL) was stirred at 0 °C for 2 h, extracted with CH_2Cl_2, washed with saturated NaCl, evaporated and chromatographed on silica gel. Elution with *n*-hexane-AcOEt (10:1) gave **14** (446.5 mg, 94%) as a colorless oil. IR (neat): ν 1513, 1471, 1252, 1093 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 7.27 (2H, d, *J*=8.7 Hz), 6.88 (2H, d, *J*=8.7 Hz), 5.96-5.80 (1H, m), 5.30-5.08 (2H, m), 4.51 (0.8H, s), 4.49 (1.2H, s), 4.32-4.04 (3H, m), 4.01-3.58 (5H, m), 3.79 (3H, s), 3.35 (0.4 H, t, *J*=4.4 Hz), 3.25 (0.6 H, dd, *J*=2.3, 6.5 Hz), 2.60-2.38 (2H, m), 1.86-1.68 (2H, m), 0.94-0.84 (27H, s x 6). HRMS (EI) calcd for $C_{34}H_{61}O_6Si_3$ ([M-*t*-Bu]$^+$) 649.3776, found 649.3763.

(5*R*,6*S*,7*RS*)-5,7-Bis(*tert*-butyldimethylsilyloxy)-6-(3-*tert*-butyldimethylsilyloxypropoxy)non-8-en-2-yn-1-ol (15): A mixture of **14** (170 mg, 0.24 mmol) and DDQ (110 mg, 0.48 mmol) in CH_2Cl_2 (3.4 mL) and H_2O (0.17 mL) was stirred at rt for 6 h, quenched with saturated $NaHCO_3$, extracted with CH_2Cl_2, washed with saturated NaCl, evaporated and chromatographed on silica gel. Elution with *n*-hexane-AcOEt (10:1) gave **15** (110.1 mg, 75%) as a colorless oil. IR (neat): ν 3438, 1472, 1258, 1095, 1024, 1009 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 5.94-5.76 (1H, m), 5.28-5.05 (2H, m), 4.28-4.08 (3H, m), 3.94 (0.6 H, br t, *J*=7.0 Hz), 3.83 (0.4 H, br q, *J*=5.5 Hz), 3.78-3.56 (4H, m), 3.31 (0.4 H, t, *J*=4.8 Hz), 3.24 (0.6 H, dd, *J*=1.8, 6.8 Hz), 2.54-2.36 (2H, m), 1.82-1.62 (2H, m), 1.00-0.70 (27H, m), 0.15-0.05 (18H, m).

(*Z*,5*R*,6*R*,7*RS*)-5,7-Bis(*tert*-butyldimethylsilyloxy)-6-(3-*tert*-butyldimethylsilyloxypropoxy)iodonona-2,8-dien-1-ol (16): To a stirred mixture of **15** (89.1 mg, 0.15 mmol) in Et_2O (3 mL), was added RedAl (3.4 M solution in toluene, 220 μL, 0.75 mmol) at 0 °C. The resulting mixture was stirred at rt for 5h. To the mixture, was added I_2 (77 mg, 0.3 mmol) at -78 °C. The resulting mixture was stirred at rt for 3 h, quenched with saturated $Na_2S_2O_3$ and saturated $NaHCO_3$, extracted with Et_2O, washed with saturated NaCl, evaporate and chromatographed on silica gel. Elution with *n*-hexane-AcOEt (10:1) gave **16** (54.9 mg, 51%) as a colorless oil. IR (neat): ν 3352, 1472, 1462, 1257, 1093, 1022, 1004 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 5.92-5.70 (2H, m), 5.33-5.10 (2H, m), 4.30-3.88 (4H, m), 3.62-3.15 (4H, m), 2.82-2.47 (2H, m), 1.85-1.60 (2H, m), 1.00-0.68 (27H, m), 0.19-0.14 (18H, m).

(*Z*)-2-[(3*R*,4*R*,5*R*)-3,5-Bis(*tert*-butyldimethylsilyloxy)-4-(3-*tert*-butyldimethylsilyloxypropoxy)-2-

methylenecyclohexylidene]ethanol (17) and (*Z*)-2-[(3*S*,4*R*,5*R*)-3,5-Bis(*tert*-butyldimethylsilyloxy)-4-(3-*tert*-butyldimethylsilyloxypropoxy)-2-methylenecyclohexylidene]ethanol (18): A mixture of **16** (33.5 mg, 0.047 mmol), Et_3N (6.54 μL, 0.047 mmol) and $PdCl_2(PPh_3)_2$ (2.7 mg, 0.0023 mmol) in MeCN (2.5 mL) was refluxed for 4 h and evaporated. The residue was purified by preparative TLC developed with benzene-AcOEt (10:1) to give **17** (16.0 mg, 57%) and **18** (10.5 mg, 38%) each as a colorless oil. **17**: $[\alpha]_D$ +4.2 ° (*c* 0.24, $CHCl_3$), $[\alpha]_D$ -23.4 ° (*c* 0.15, EtOH). IR (neat): ν 3426, 1469, 1386, 1362, 1257, 1127 cm^{-1}. ^1H NMR ($CDCl_3$): δ 5.51 (1H, t, *J*=6.9 Hz), 5.23 (1H, br s), 4.83 (1H, dd, *J*=1.1, 2.3 Hz), 4.23 (1H, d, *J*=6.9 Hz), 4.21-4.12 (3H, m), 3.70-3.63 (3H, m), 3.59 (1H, dd, *J*=6.6, 9.4 Hz), 3.17 (1H, dd, *J*=2.0, 6.6 Hz), 2.40 (1H, dd, *J*=7.3, 13.0 Hz), 2.19 (1H, dd, *J*=3.2, 13.0 Hz), 1.76 (2H, m), 0.88 (9H, s), 0.87 (9H, s), 0.86 (9H, s), 0.07 (3H, s), 0.05 (3H, s), 0.04 (3H, s), 0.02 (6H, s). **18**: $[\alpha]_D$ +12.0 ° (*c* 0.15, $CHCl_3$). IR (neat): ν 3446, 1463, 1260, 1034 cm^{-1}. ^1H NMR ($CDCl_3$): δ 5.52 (1H, tt, *J*=2.1, 5.5 Hz), 5.33 (1H, t, *J*=2.3 Hz), 4.82 (1H, t, *J*=2.3 Hz), 4.28 (1H, dd, *J*=8.0, 12.8 Hz), 4.12 (1H, br d, *J*=11.2 Hz), 3.95 (1H, dd, *J*=2.3, 4.8 Hz), 3.78-3.63 (5H, m), 3.51 (1H, s), 2.64 (1H, t, *J*=12.1 Hz), 2.12 (1H, dd, *J*=4.6, 12.1 Hz), 1.75 (2H, m), 0.92-0.85 (27H, m), 0.92 (9H, s), 0.89 (9H, s), 0.85 (9H, s), 0.05-0.00 (18H, m), 0.05 (6H, s), 0.04 (6H, s), 0.00 (6H, s).

(*Z*,1*R*,2*R*,3*R*)-1,3-Bis(*tert*-butyldimethylsilyloxy)-2-(3-*tert*-butyldimethylsilyloxypropoxy)-5-(2-chloroethylidene)-4-methylenecyclohexane (19): To a stirred mixture of NCS (377.5 mg, 2.84 mmol) in CH_2Cl_2 (9.4 mL), was added Me_2S (210 μL, 2.86 mmol) at 0 °C and the resulting mixture was stirred at 0 °C for 40 min and cooled to -20 °C. To a stirred solution of **17** (57.8 mg, 0.099 mmol) in CH_2Cl_2 (0.8 mL), was added the above cooled mixture at -20°C. The resulting mixture was stirred at rt for 1 h, diluted with *n*-hexane, washed with H_2O and saturated NaCl, evaporated and chromatographed on silica gel. Elution with *n*-hexane-AcOEt (10:1) gave **19** (50.3 mg) as a yellow oil, which was used for the next reaction without further purification. FT-IR (neat): ν 1467, 1254, 1105 cm^{-1}. ^1H NMR ($CDCl_3$): δ 5.52 (1H, t, *J*=7.8 Hz), 5.32 (1H, s), 5.05 (1H, t, *J*=12 Hz), 4.27 (1H, d, *J*=7.2 Hz), 4.20-4.15 (1H, m), 4.14 (2H, dd, *J*=8.1, 2.4 Hz), 3.70-3.57(4H, m), 3.17 (1H, d, *J*=6.6 Hz), 2.40 (1H, dd, *J*=7.5, 13.2 Hz), 2.23 (1H, d, *J*=10.8 Hz), 1.79 (2H, quint, *J*=6.6 Hz), 0.94 (9H, s), 0.91 (9H, s), 0.88 (9H, s), 0.26-0.09 (18H, m). ^{13}C NMR ($CDCl_3$): δ 145.0, 141.5, 123.0, 113.5, 84.5, 74.1, 69.0, 68.3, 60.5, 41.8, 41.3, 33.6, 26.1, 25.9, 18.4, 18.3, 18.2, -4.5, -4.7, -5.2.

(*Z*)-2-[(3*R*,4*R*,5*R*)-3,5-Bis(*tert*-butyldimethylsilyloxy)-4-(3-*tert*-butyldimethylsilyloxypropoxy)-2-

methylenecyclohexylidene]ethyldiphenylphosphine Oxide (20): To a stirred solution of diphenylphosphine (500 μL, 2.69 mmol) in THF (9.7 mL), was added *n*-BuLi (1.53 M solution in *n*-hexane, 1.57 mL, 2.40 mmol) at 0 °C. The resulting mixture was stirred at 0 °C for 10 min and cooled to -78 °C. To a stirred solution of **19** (50.3 mg) in THF (0.8 mL), was added the above cooled mixture at -78 °C. The resulting mixture was stirred at -78 °C for 45 min, quenched with H_2O, diluted with $CHCl_3$ (4 mL) and 5% H_2O_2 (2.6 mL). The mixture was stirred at rt for 30 min, diluted with $CHCl_3$, washed with saturated $Na_2S_2O_3$ and H_2O and evaporated. The residue was purified by preparative TLC developed with *n*-hexane-AcOEt (1:1) to give **20** (33.8 mg, 45% yield from **17**) as a colorless oil. $[\alpha]_D^{29}$ -16.3 ° (*c* 1.50, $CHCl_3$). IR (neat): ν 1467, 1253, 1105 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.73-7.69 (4H, m), 7.54-7.48 (2H, m), 5.32 (1H, td, *J*=3.0, 6.0 Hz), 5.23 (1H, s), 4.80 (1H, t, *J*=1.5 Hz), 4.24 (1H, d, *J*=7.5 Hz), 4.12 (1H, dt, *J*=8.0, 14.9 Hz), 3.68-3.57 (4H, m), 3.34 (1H, dt, *J*=8.0, 14.0 Hz), 3.19 (1H, d, *J*=6.0 Hz), 3.17 (1H, dt, *J*=8.0, 14.0 Hz), 2.33 (1H, dd, *J*=6.0, 13.5 Hz), 2.17 (1H, d, *J*=13.5 Hz), 1.78 (2H, dquint, *J*=2.0, 6.5 Hz), 0.91 (9H, s), 0.88 (9H, s), 0.81 (9H, s), 0.09 (3H, s), 0.04 (3H, s), 0.03 (6H, s), 0.02 (3H, s), 0.01 (3H, s). ^{13}C NMR ($CDCl_3$): δ 145.3, 140.6 (d, J_{cp}=12.5 Hz), 133.1 (d, J_{cp}=98 Hz), 132.7 (d, J_{cp}=98 Hz), 131.9, 131.8, 131.8, 131.2 (d, J_{cp}=9.0 Hz), 131.1 (d, J_{cp}=9.0 Hz), 128.7, 128.7 (d, J_{cp}=11.4 Hz), 128.6 (d, J_{cp}=12.5 Hz), 115.2 (d, J_{cp}=8.0 Hz), 113.1, 84.9, 73.9, 69.2, 68.5, 60.5, 42.0, 33.6, 32.0, 31.1, 29.8, 26.0, 25.9, 18.4, 18.2, -4.5, -4.8, -5.2.

(5*Z*,7*E*)-(3*S*)-3,25-Bis(triethylsilyoxy)-9,10-secocholesta-5,7,10(19)-triene (22): To a stirred solution of **21** (28.5 mg, 0.071 mmol) and Et_3N (60 μL, 0.426 mmol) in CH_2Cl_2 (0.71 mL), was added TESOTf (48 μL, 0.213 mmol) at 0 °C. The resulting mixture was stirred at 0 °C for 1 h, quenched with H_2O, extracted with Et_2O, washed with saturated NaCl, evaporated and chromatographed on silica gel. Elution with *n*-hexane-AcOEt (50:1) gave **22** (43.2 mg, 97%) as a colorless viscous oil. $[\alpha]_D^{26}$ +15.4 ° (*c* 1.09, $CHCl_3$). FT-IR (neat): ν 2954, 2877, 1460, 1373, 1080 cm^{-1}. ^1H NMR ($CDCl_3$): δ 6.17 (1H, d, *J*=11.4 Hz), 6.01 (1H, d, *J*=11.1 Hz), 5.01 (1H, s), 4.78 (1H, d, *J*=1.2 Hz), 3.80 (1H, hept, *J*=3.9 Hz), 2.84 (1H, br d, *J*=11.4 Hz), 2.46 (1H, dd, *J*=4.2, 12.0 Hz), 2.37 (1H, td, *J*=4.8, 13.5 Hz), 1.21-2.30 (33H, m), 1.19 (6H, s), 0.90-1.14 (18H, m), 0.48-0.67 (12H, m). ^{13}C NMR ($CDCl_3$): δ 145.9, 142.2, 136.8, 122.0, 118.4, 112.8, 74.0, 71.0, 68.9, 57.2, 56.9, 46.1, 37.8, 37.0, 36.7, 35.2, 30.6, 30.5, 28.3, 24.1, 22.8, 21.3, 19.4, 19.3, 18.6, 12.7, 7.7, 7.4, 5.5. MS (EI) *m/z* 629 (M^+), 354, 279, 149, 69, 44 (100%). HRMS (EI) calcd for $C_{39}H_{72}O_2Si_2$ (M^+) 629.5114, found 629.5148.

(1*R*,4*S*,7a*R*)-1-[(*R*)-6-Methyl-6-(triethylsilyloxy)heptan-2yl]octahydro-7a-methyl-1*H*-inden-4-ol (23): To a stirred mixture of **22** (43.2 mg, 0.069 mmol) and $NaHCO_3$ (500 mg, 5.95 mmol) in CH_2Cl_2 (6.4 mL) and MeOH (1.6 mL), was introduced O_3 at -78 °C. After disappearance of **22** on TLC, excess O_3 was bubbled out by argon. The resulting mixture was diluted with MeOH (6.6 mL). To the stirred mixture, was added $NaBH_4$ (91.4 mg, 2.42 mmol) at -78 °C. The resulting mixture was allowed to worm to 0 °C, stirred at 0 °C for 1h, diluted with CH_2Cl_2, washed with saturated NaCl, evaporated and chromatographed on silica gel. Elution with *n*-hexane-AcOEt (4:1) gave **23** (20.2 mg, 74%) as a colorless oil. $[\alpha]_D^{25}$ +24.2 ° (*c* 1.01, $CHCl_3$). FT-IR (neat): ν 3427, 1739, 1461, 1373, 1090, 1043 cm^{-1}. ^1H NMR ($CDCl_3$): δ 4.17 (1H, brs), 2.00 (1H, td, *J*=3.0, 13.5 Hz), 1.92-1.72 (3H, m), 1.18 (6H, s), 1.65-1.00 (22H, m), 0.97-0.87 (9H, m), 0.56 (6H, q, *J*=7.8 Hz). ^{13}C NMR ($CDCl_3$): δ 73.6, 69.6, 56.8, 52.7, 45.6, 42.0, 40.5, 36.5, 35.4, 33.7, 30.1, 29.9, 27.3, 22.6, 20.9, 18.6, 17.6, 13.6, 7.2, 6.9. MS (EI) *m/z* 381 [$(M-CH_3)^+$], 338, 247, 173, 103 (100%). HRMS (EI) calcd for $C_{23}H_{45}O_2Si$ [$(M-CH_3)^+$] 381.3189, found 381.3182.

(1*R*,7a*R*)-1-[(*R*)-6-(*Tert*-butyldimethylsilyloxy)-6-methylheptan-2-yl]octahydro-7a-methyliden-4-one (24): To a stirred solution of **23** (20.2 mg, 0.051 mmol) in CH_2Cl_2 (2 mL), were added 4A molecular sieves (22 mg) and NMO (9.0 mg, 0.077 mmol). The resulting mixture was stirred at rt for 1 h. To the stirred mixture, was added TPAP (0.9 mg, 0.0025 mmol) at rt. The resulting mixture was stirred at rt for 2 h, diluted with CH_2Cl_2, filtered through Celite pad, concentrated and chromatographed on silica gel. Elution with *n*-hexane-AcOEt (4:1) gave **24** (19.9 mg, 99%) as a colorless oil. $[\alpha]_D^{26}$ +27.9 ° (*c* 1.01, $CHCl_3$). FT-IR (neat): ν 1716, 1462, 1375, 1043 cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.32 (1H, br s), 2.21-1.08 (24H, m), 1.19 (6H, s), 0.94 (9H, t, *J*=7.8 Hz), 0.56 (6H, q, *J*=7.8 Hz). ^{13}C NMR ($CDCl_3$): δ 159.6, 73.2, 62.1, 56.8, 50.0, 45.6, 41.1, 39.1, 36.4, 35.6, 30.1, 29.9, 27.6, 24.2, 20.8, 19.2, 18.8, 12.6, 7.2, 6.9. MS (EI) *m/z* 395 [$(M-C_2H_5)^+$], 365, 263, 217, 189, 173 (100%). HRMS (EI) calcd for $C_{22}H_{41}O_2Si$ [$(M-C_2H_5)^+$] 365.2867, found 365.2876.

(5*Z*,7*E*)-(1*R*,2*R*,3*R*)-1,3-Bis(*tert*-butyldimethylsilyloxy)-2-(3-*tert*-butyldimethylsilyloxy-propoxy)-25-triethylsilyloxy-9,10-secocholesta-5,7,10(19)-triene (25) by Lythgoe coupling reaction: To a stirred solution of **20** (92.9 mg, 0.120 mmol) in THF (2 mL), was added *n*-BuLi (1.58 M solution in *n*-hexane, 80 μL, 0.126 mmol) at -78 °C. The resulting mixture was stirred at -78 °C for 20 min. To the stirred mixture, was added **24** (10.8 mg, 0.027 mmol) in THF (0.5 mL) at -78 °C. The resulting mixture was stirred at -78 °C for 4 h, quenched with saturated NH_4Cl, extracted with CH_2Cl_2, washed with H_2O and saturated NaCl, evaporated and chromatographed on silica gel. Elution with *n*-hexane-AcOEt

(15:1-1:1) gave **25** (3.9 mg, 15%) as a colorless oil and recovered **20** (76.7 mg) and **24** (7.1 mg). IR (neat): ν 1465, 1379, 1255, 1110 cm^{-1}. ^1H NMR ($CDCl_3$): δ 6.23 (1H, d, *J*=11.5 Hz), 6.01 (1H, d, *J*=11.5 Hz), 5.26 (1H, s), 4.98 (1H, d, *J*=3.0 Hz), 4.23 (1H, d, *J*=6.5 Hz), 4.20 (1H, m), 3.73-3.61 (4H, m), 3.23 (1H, d, *J*=4.5 Hz), 2.82 (1H, m), 2.46 (1H, dd, *J*=2.5, 5.6 Hz), 2.21 (1H, dd, *J*=3.5, 13.0 Hz), 2.05-0.80 (57H, m), 1.78 (2H, dquint, *J*=2.5, 5.6 Hz), 1.26 (3H, s), 1.19 (3H, s), 1.18 (3H, s), 0.59-0.51 (6H, m), 0.09-0.04 (18H, m). ^{13}C NMR ($CDCl_3$): δ 142.7, 141.2, 134.4, 124.8, 123.2, 117.9, 84.2, 74.7, 73.5, 69.5, 68.2, 60.5, 56.6, 56.3, 45.8, 45.5, 41.4, 40.6, 36.5, 36.2, 33.6, 31.9, 30.3, 30.0, 29.8, 29.7, 28.9, 27.7, 26.0, 25.9, 25.8, 23.5, 22.7, 22.1, 20.9, 18.8, 18.3, 18.2, 18.2, 14.1, 11.9, 7.1, 6.8, 6.8, 6.4, 1.0, -4.6, -4.7, -4.9, -5.3, -5.3.

(5*Z*,7*E*)-(1*R*,2*R*,3*R*)-2-(3-Hydroxypropoxy)-9,10-secocholesta-5,7,10(19)-triene-1,3,25-triol (ED-71) (2): A mixture of **25** (4.47 mg, 4.73 μmol) and TBAF (1 M solution in THF, 237 μL, 237 μmol) in toluene (0.5 mL) was stirred at 105 °C for 2 h. The mixture was extracted with AcOEt, washed with H_2O and saturated NaCl and evaporated. The residue was purified by preparative TLC developed twice with CH_2Cl_2-EtOH (20:3) to give **2** (1.39 mg, 60%) as a colorless foam, which was completely identical with the authentic material obtained by the linear synthetic methodology.[3]

(*E*,1*R*,7a*R*)-4-Bromomethylene-1-[(*R*)-6-methyl-6-(triethylsilyloxy)heptan-2-yl]octahydro-7a-methyl-1*H*-indene (28): To a stirred solution of $Ph_3P^+CH_2BrBr^-$ (205 mg, 0.47 mmol) in THF (1.1 mL), was added NaHMDS (1 M solution in THF, 455 μL, 0.455 mmol) at -60 °C. After being stirred at -60 °C for 1 h, **24** (23.1 mg, 0.059 mmol) in THF (0.3 mL) was added. The mixture was stirred at rt for 1 h, diluted with *n*-hexane, filtered through silica gel and evaporated. The residue was purified by preparative TLC developed with *n*-hexane to give **28** (10.0 mg, 38%) as a yellow oil. $[\alpha]_D^{23}$ +62.1 ° (*c* 0.33, $CHCl_3$). IR (neat): ν 1462, 1235 cm^{-1}. ^1H NMR ($CDCl_3$): δ 5.64 (1H, s), 3.18 (1H, s), 1.20-2.10 (24H, m), 1.18 (6H, s), 0.94 (9H, t, *J*=8.0 Hz), 0.49-0.62 (6H, m).

(5*Z*,7*E*)-(1*R*,2*R*,3*R*)-1,3-Bis(*tert*-butyldimethylsilyloxy)-2-(3-*tert*-butyldimethylsilyloxy-propoxy)-25-triethylsilyloxy-9,10-secocholesta-5,7,10(19)-triene (25) by Trost coupling reaction: A mixture of PPh_3 (1.7 mg, 0.0065 mmol), $(dba)_3Pd_2$-$CHCl_3$ (0.9 mg, 0.00087 mmol) and Et_3N (0.3 mL) in toluene (0.3 mL) was stirred at rt for 10 min. To the stirred mixture, were added **26**[12] (8.2 mg, 0.015 mmol) and **28** (10.0 mg, 0.021 mmol) in toluene (0.2 mL). The resulting mixture was refluxed for 4.5 h, diluted with *n*-hexane, filtered through silica gel and purified by preparative TLC developed with

n-hexane-benzene (2:1) to give **28** (5.6 mg, 56%), **26** (3.7 mg, 45%), and **25** (3.5 mg, 26%) (46% based on recovered **26**) as a colorless oil, which was completely identical with the material obtained by the Lythgoe coupling reaction.

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