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Structural revisions of the reported A-ring phosphine oxide synthon for ED-71 (Eldecalcitol) and a new synthesis

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ABSTRACT

In a reported procedure for the synthesis of the ED-71 A-ring phosphine oxide, we discovered that unusual TBS transfer occurred from the 1α-position to the sterically more constrained 2β-position, and the subsequent Michael addition of ethyl acrylate predominated at the 1α-position. The X-ray analysis of a key intermediate confirmed our observations. We made a structural revision of the reported A-ring phosphine oxide synthon and ED-71. In addition, we provided the first stereoselective synthetic approach to ED-71 A-ring phosphine oxide applying the stereochemistry of D-mannitol.

1. Introduction

1α,25-Dihydroxyvitamin D_3 [1,25$(OH)_2D_3$] is the hormonally active form of vitamin D_3. Apart from its classical roles on homeostasis and bone metabolism, an entirely new facet of vitamin D effects is increasingly being appreciated. As an important cell cycle regulator, 1,25$(OH)_2D_3$ influences cell proliferation, differentiation and apoptosis.[1–5] The regulatory effects of vitamin D on both the innate and adaptive immune responses may be a control point in immunity to infection and chronic inflammatory diseases.[6–10] These non-classical effects of vitamin D have now been recognized as important components of vitamin D physiology. 1,25$(OH)_2D_3$ and its derivatives have potential therapeutic applications for the treatment of hyperproliferative disorders (e.g., cancer and psoriasis), immune dysfunction, and endocrine disorders.[11–15] Therefore, extensive efforts have been made on the structural modifications of the A-ring, C/D-rings, and/or the side chain of 1,25$(OH)_2D_3$ to find more potent and selective vitamin D analogs.[16–20] The introduction of a 3-hydroxypropoxyl substituent at the 2β-position of 1,25$(OH)_2D_3$ leads to the discovery of ED-71 that possesses higher binding affinity to the vitamin D-binding protein and lower binding affinity to the vitamin D receptor (VDR) compared to the natural hormone.[21–23] ED-71 is now used in the name of Eldecalcitol in Japan for the treatment of patients with osteoporosis.[24,25]

ED-71 was prepared by the conventional linear steroidal approach from cholesterol or lithocholic acid,[21,26] or by the convergent Lythgoe[27] or Trost[28] coupling reactions of the CD-fragments with the A ring synthons to build the conjugated triene system of vitamin D_3.[29–33] The later approaches provide a versatile platform for the preparation of diverse vitamin D analogs varying in the A-ring, CD-ring, and/or side chains. As a continuous research for the discovery of more selective 1,25$(OH)_2D_3$ derivatives, we are interested in the construction of ED-71 related A-ring phosphine oxide intermediates, applying the stereochemistry of D-mannitol.

2. Results and discussion

The known epoxide **1**, which is readily available from D-mannitol,[34] was reacted with the lithium acetylide, generated from propargyl *p*-methoxybenzyl ether, in the presence of BF_3 to give an alcohol **2** in 61% yield (Scheme 1). Protection of the secondary hydroxyl group by TBS ether formation and removal of the PMB protective group with DDQ provided the propargylic alcohol **4** in good yield. Hydroalumination of the acetylenic alcohol **4** with sodium bis(2-methoxyethoxy)aluminumhydride (Red-Al) and quenching the resultant alkenyl-aluminum complex with iodine gave the vinyl iodide **5** in 93% yield. We found that the addition of

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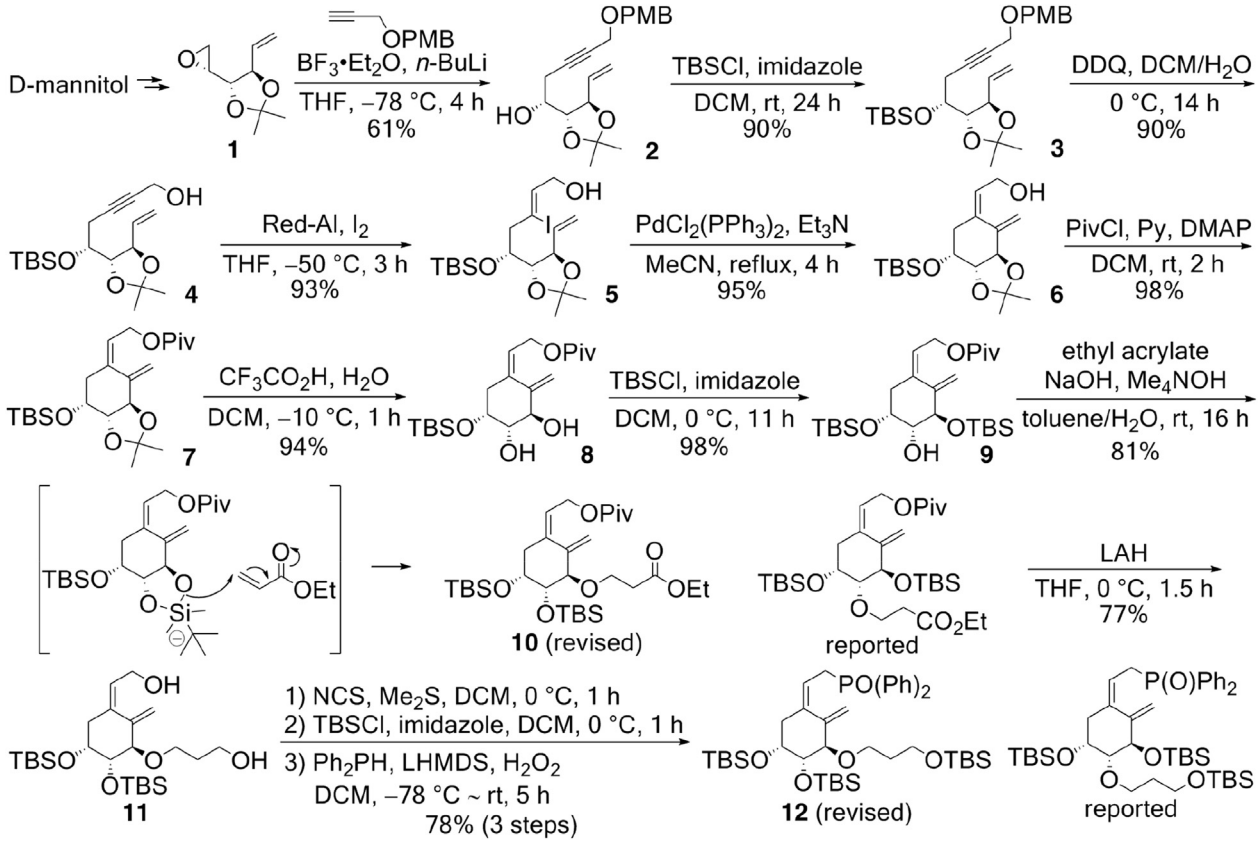


Scheme 1. A correction of the structure and former synthesis of the 'A-ring phosphine oxide' for ED-71.

alcohol **4** to Red-Al was crucial for the high yield conversion in this step. Transformation of the vinyl iodide **5** to the exocyclic (*Z*)-diene was achieved by Pd-catalyzed Heck cyclization. The structure of **6** was confirmed by comparison of its spectral data with that reported for the same compound derived from the epoxide opening of **1** with KCN followed by several transformations.[32] Reaction of **6** with pivaloyl chloride in dichloromethane in the presence of pyridine and DMAP gave the ester **7** in 98% yield. Treatment of **7** with aqueous trifluoroacetic acid in dichloromethane followed by the selective protection of the 1α-hydroxyl group as TBS ethers afforded the secondary alcohol **9**[33] in high yield.

A pivotal step in Takahashi's synthesis of ED-71 A-ring phosphine oxide is the Michael addition of alcohol **9** with ethyl acrylate in aqueous toluene under basic conditions.[33] However, in TLC monitoring the reaction process, we suspected that silyl migration might occur, and the TBS group transferred from the less hindered 1α-position to the sterically more constrained 2β-position. Comparison of the data of the ED-71 A-ring phosphine oxide provided by Takahashi[33] with that reported by Kubodera[30] indicated that some chemical shifts in ^{1}H and ^{13}C NMR spectra were different, and their specific rotations in chloroform solution were opposite (+56.4 vs −16.3). In a parallel experiment without adding the ethyl acrylate, a partially TBS migration was also observed. Silyl migrations are well-known in carbohydrate and related chemistry.[35,36] Therefore, under basic conditions, the 2β-hydroxyl group might act as a nucleophile to attack on the silicon to form the five-membered intermediate, and the subsequent Michael addition occurs preferentially from the less sterically hindered trajectory giving the migrated silyl ether **10** as the major product (Scheme 1). In fact, this silyl migration can happen easily, whether it is a TBS or a more basic stable triisopropylsilyl (TIPS) group, and even under less basic (aq K_2CO_3) conditions.

Reduction of diester **10** with LAH led to a diol **11**, which can be easily crystalized in *n*-heptane. X-ray analysis of **11** confirmed the TBS migration. In a chair-like conformation, both the 1α-(3-hydroxypropoxy) and the 2β-*t*-butyldimethylsilyloxy substituents occupy the less favored axial positions. The ω-hydroxyl group in 1α-position forms an intermolecular hydrogen bond with the allylic oxygen, and the allylic oxygen also forms a hydrogen bond with the 1α-(ω)-hydroxyl group in another molecule (Fig. 1). These hydrogen

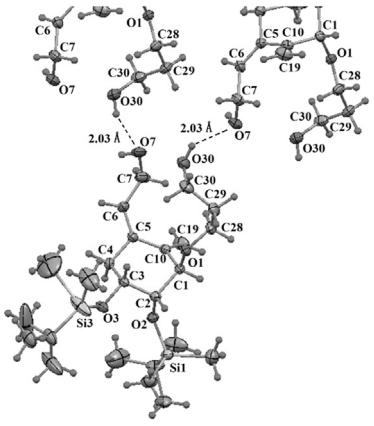


Fig. 1. ORTEP drawing of the crystal structure of diol **11**.

binding may compensate the high energies required for its 'axial-rich' conformation.

Treatment of diol **11** with *N*-chlorosuccinimide (NCS) in the presence of dimethyl sulfide selectively converted the allylic

hydroxyl group into the allylic chloride. After the protection of the ω-primary hydroxyl group through TBS ether formation, the allylic chloride was transformed into the A-ring phosphine oxide **12** in 78% yield (3 steps from **11**) by treatment with lithium diphenylphosphide and subsequent hydrogen peroxide oxidation. The spectral data of **12** are identical with that wrongly assigned 'ED-71 A-ring phosphine oxide'.[33] In the 2D HMBC (heteronuclear multiple bond correlation) spectra of **12**, the C1–H at 3.61 ppm shows long-range correlations with C2 (74.7), C3 (70.4), and the neighbouring methylene (65.5) in the 1α-(3-*tert*-butyl dimethylsiloxy)propoxy substituent, while the C6–H (δ_H 5.32) correlates with C4 (40.3), C7 (31.3), C10 (141.4), and the C19–H (δ_H 5.09) with C1 (84.7), C5 (141.1).

Since the Takahashi's approach[33] did not lead to the ED-71 A-ring phosphine oxide, we applied a new hydroxyl protective strategy by using the methoxymethyl (MOM) group that is more stable to basic hydrolysis. Attempts have been made to protect the 2β-hydroxyl by acyl groups, however, in the following TBS deprotection step (TBAF/THF), the acyl group (acetyl; benzoyl; pivaloyl) migration to both the 1α- and 3β-positions was observed. As shown in Scheme 2, THP protective group became the choice. After the THP protection of the 2β-hydroxyl group, the TBS groups were removed by the treatment with TBAF. The resulting diol was reacted with MOMCl in dichloromethane to generate ether **15**. Treatment of **15** with acetic acid in aqueous/THF solutions could selectively remove the THP protective group. The Michael addition of 2β-alcohol **16** with ethyl acrylate in aqueous toluene under basic conditions went smoothly to yield the ester **17**. The diester **17** was converted to the ED-71 A-ring phosphine oxide **19** via the ester reduction, conversion of the allylic alcohol to chloride, protection the ω-primary hydroxyl by MOM group, reaction with lithium diphenylphosphide and subsequent oxidation. Long-range correlations between the following protons and carbons were found in compound **19** by HMBC: C1–H (δ_H 4.18) and C2 (81.8), C3 (73.2), C5 (139.6), C10 (141.6), C19 (116.0); C2–H (δ_H 3.44) and C10 (141.6), the neighbouring methylene (67.4) in the 2β-(3-methoxymethoxy) propxy substituent; C3–H (δ_H 3.96) and C4 (38.3), C5 (139.6); C6–H (δ_H 5.40) and C7 (31.1), C10 (141.6); C19–H (δ_H 5.33, 5.11) and C5 (139.6), C10 (141.6).

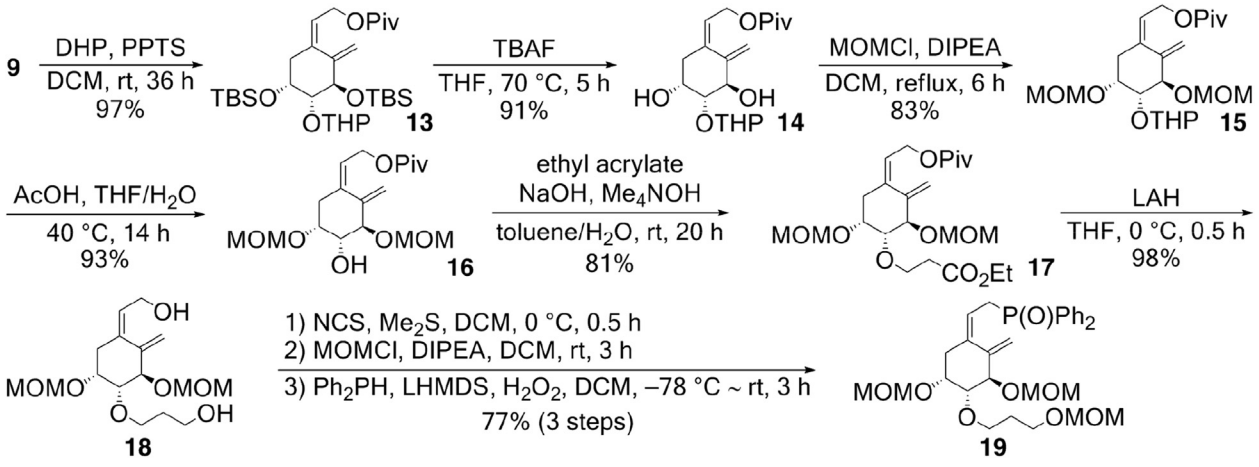
step, and the diastereomeric separation of the 1α-isomer from its 1β-epimer (3/2).[30] Our approach provided the first stereoselective construction of the ED-71 A-ring phosphine oxide applying the stereochemistry of D-mannitol. In addition, the 2β-alcohol **16** may facilate the synthesis of a variety of 2-substituted 1,25$(OH)_2D_3$ analogs.

The CD-ring ketone **22** was prepared by the reaction of the sulfonate **20**, which is readily derived from VD_2,[37] with 4-bromo-2-methylbutan-2-yl methoxymethyl ether,[38] followed by the Oxone/TEMPO oxidation.[39] Convergent Lythgoe coupling reaction of phosphine oxide **19** with the Grundmann's ketone **22**, and the subsequent removal the MOM protecting groups completed the synthesis of ED-71 (Scheme 3). Its spectral data are completely identical to that reported by Kubodera.[31] In the HMBC spectra of **23**, C1–H at 4.30 ppm showed correlation with C2 (85.4), C10 (144.2), C19 (111.8); the C2–H at 3.24 with C3 (66.5), C10 (144.2), and the neighbouring methylene (68.2) in the 2β-(3-hydroxy)propxy substituent; the C3–H (δ_H 4.25) with C1 (71.5), C5 (132.1); the C6–H (δ_H 6.33) with C7 (117.2), C8 (142.9), C10 (144.2); the C7–H (δ_H 6.02) with C5 (132.1); and the C19–H (δ_H 5.49, 5.07) with C5 (132.1), C10 (144.2).

In a similar way, coupling the A-ring fragment **12** with the CD-ring ketone **22** followed by the deprotection of TBS and MOM groups furnished the ED-71 isomer **24**. Its spectral data are in agreement with the wrongly assigned 'ED-71' by Takahashi's group.[33] Long-range correlations between the following protons and carbons were observed in compound **24** by HMBC: C1–H (δ_H 3.83) and C2 (74.7), C3 (70.1), C5 (135.4), C10 (144.1), the neighbouring methylene (67.2) in the 1α-(3-hydroxy)propoxy substituent; C2–H (δ_H 3.79) and C3 (70.1), C10 (144.1); C6–H (δ_H 6.33) and C7 (118.7), C8 (143.1), C10 (144.1); C7–H (δ_H 6.05) and C5 (135.4); C19–H (5.33, 5.10) and C1 (84.9), C5 (135.4), C10 (144.1).

3. Conclusion

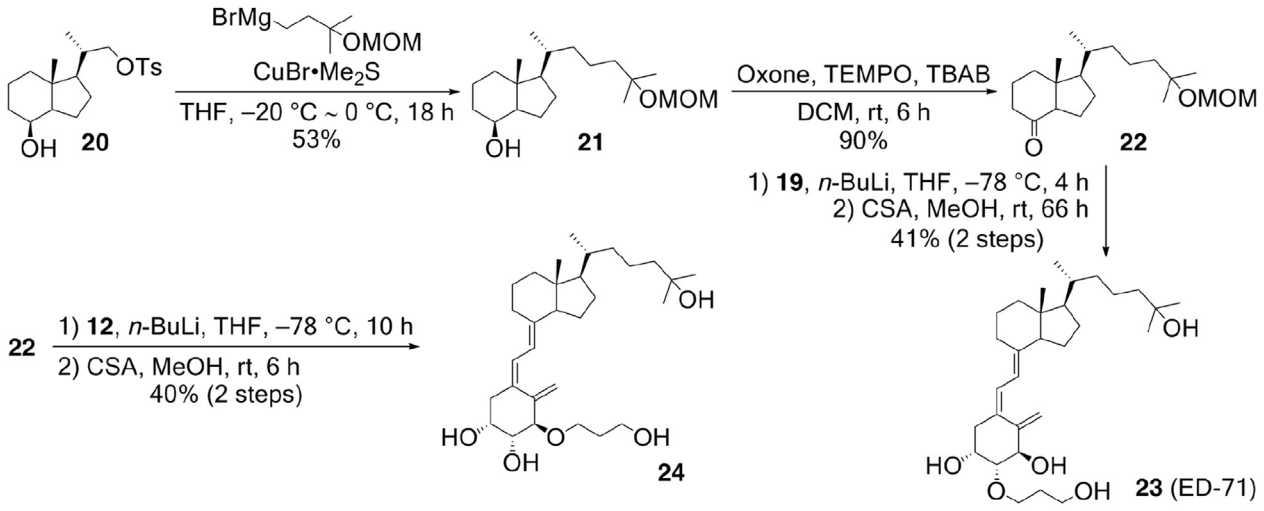
In conclusion, unusual TBS migration from the 1α-to the 2β-position was identified in a reported procedure for the synthesis of ED-71 A-ring phosphine oxide. Therefore, a revision of its structure was made. We also developed a new synthetic route to the ED-71



Scheme 2. A new synthetic route to the ED-71 A-ring synthon.

Kubodera's group reported a correct synthesis of the ED-71 A-ring phosphine oxide from a known C2-symmetrical epoxide via several steps, including the regiospecific ring openging of epoxide to introduce the 2β-(3-hydroxypropoxy) substituent at the first

A-ring fragment by the careful selection of the proper hydroxyl protective groups. Finally, ED-71 and its analog were prepared very efficiently by the convergent Lythgoe approach. The application of our discovery in the preparation of various ED-71 analogs with



Scheme 3. Synthesis of ED-71 and its 1α-isomer.

modifications both in the A-ring and the vitamin D side chain are in progress.

4. Experimental section

4.1. General information

^{1}H, ^{13}C NMR spectra and 2D HMBC were recorded on Bruker-400 or Bruker-600 NMR spectrometers. ^{1}H spectra were recorded relative to $CDCl_3$ (7.26 ppm) or TMS (0.00 ppm) as internal standard, and ^{13}C NMR spectra were recorded relative to $CDCl_3$ (77.0 ppm). High resolution mass spectra (HRMS) were performed on Agilent 6520 QTOF instrument by electrospray ionization (ESI). Optical rotations were recorded on a JASCO DIP-370 digital polarimeter. Ultra violet (UV) spectra were performed on TU-1901 spectrophotometer (Purkinje General Co., Ltd). Melting points were determined on X-6 micro-melting point apparatus (Beijing Tech. Co., Ltd) without correction. Column chromatography was performed on silica gel (200–300 mesh). All experiments were performed under a dry N_2 atmosphere, unless otherwise noted. THF and toluene were distilled from sodium, and DCM was distilled from CaH_2 before use.

4.2. Detailed procedure

*4.2.1. [3R-(3α,4β,5β)]-3,4-Isopropylidenedioxy-9-(p-methoxyphenylmethoxy)non-1-en-7-yn-5-ol (**2**).* To a solution of *p*-methoxybenzyl 2-propynyl ether (16.8 g, 95.3 mmol) in THF (60 mL) was added *n*-BuLi (2.5 M solution in *n*-hexane, 38.0 mL, 95.0 mmol) at −78 °C under nitrogen, and the mixture was stirred for another 20 min. $BF_3{\cdot}OEt_2$ (12.0 mL, 97.2 mmol) and a solution of compound **1** (3.10 g, 18.2 mmol) in THF (10 mL) were added successively at the same temperature, and the mixture was stirred for another 4 h. The reaction was quenched by the addition of the saturated $NaHCO_3$ aqueous solution, and the whole was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane/EtOAc, 10:1) to give alcohol **2** (3.84 g, 61%) as a light yellow oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.26 (d, *J*=8.8 Hz, 2H), 6.87 (d, *J*=8.8 Hz, 2H), 5.88 (ddd, *J*=6.8, 10.4, 17.2 Hz, 1H), 5.42 (d, *J*=17.2 Hz, 1H), 5.25 (d, *J*=10.4 Hz, 1H), 4.51 (s, 2H), 4.44 (t, *J*=7.6 Hz, 1H), 4.14 (d, *J*=2.0 Hz, 1H), 4.13 (d, *J*=2.0 Hz, 1H), 3.90–3.96 (m, 1H), 3.83–3.85 (m, 1H), 3.80 (s, 3H), 2.54–2.57 (m, 2H), 2.24 (d, *J*=4.4 Hz, 1H) 1.43 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 159.3, 136.2, 129.7, 129.4, 118.4, 113.8, 109.3, 82.1, 81.7, 78.92, 78.89, 71.1, 70.1, 57.2, 55.2, 26.9, 23.9; HRMS (ESI) *m/z* calcd for $C_{20}H_{26}O_5$ $[M+Na]^+$ 369.1672, found 369.1667.

*4.2.2. [3R-(3α,4β,5β)]-5-(tert-Butyldimethylsilyloxy)-3,4-isopropylidenedioxy-9-(p-methoxyphenylmethoxy)non-1-en-7-yne (**3**).* A mixture of alcohol **2** (490 mg, 1.41 mmol), imidazole (340 mg, 4.99 mmol) and TBSCl (610 mg, 4.05 mmol) in DCM (3 mL) was stirred at rt for 24 h. The reaction was quenched by the addition of the saturated $NaHCO_3$ aqueous solution, and the whole was extracted with DCM. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane/EtOAc, 50:1) to give compound **3** (589 mg, 90%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26–7.29 (m, 2H), 6.86–6.89 (m, 2H), 5.88 (ddd, *J*=6.8, 10.4, 17.2 Hz, 1H), 5.39 (dt, *J*=1.2, 17.2 Hz, 1H), 5.22 (d, *J*=1.2, 10.4 Hz, 1H), 4.51 (s, 2H), 4.45–4.48 (t, *J*=7.2 Hz, 1H), 4.12–4.13 (t, *J*=2.4 Hz, 2H), 3.97–4.02 (m, 2H), 3.81 (s, 3H), 2.41–2.54 (m, 2H), 1.42 (s, 3H), 1.41 (s, 3H), 0.91 (s, 9H), 0.12 (s, 3H), 0.11 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.4, 136.9, 129.71, 129.67, 118.0, 113.8, 108.9, 83.0, 82.0, 78.3, 78.2, 71.0, 70.8, 57.3, 55.3, 27.1, 27.0, 25.9, 24.8, 18.1, −4.4, −4.5; HRMS (ESI) *m/z* calcd for $C_{26}H_{40}O_5Si$ $[M+Na]^+$ 483.2537, found 483.2536.

*4.2.3. [7R-(5β,6β,7α)]-5-(tert-Butyldimethylsilyloxy)-6,7-isopropylidenedioxynon-8-en-2-yn-1-ol (**4**).* A solution of compound **3** (182 mg, 0.395 mmol), H_2O (0.2 mL) and DDQ (134 mg, 0.59 mmol) in DCM (2 mL) was stirred at 0 °C for 14 h. The reaction was diluted with DCM and filtered through Celite. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and evaporated in vacuo. The residue was purified by silica gel column chromatography (hexane/EtOAc, 10:1) to give compound **4** (121 mg, 90%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.87 (ddd, *J*=6.8, 10.4, 17.2 Hz, 1H), 5.38 (dt, *J*=1.2, 17.2 Hz, 1H), 5.23 (dt, *J*=1.2, 10.4 Hz, 1H), 4.43 (t, *J*=6.8 Hz, 1H), 4.25 (t, *J*=2.0 Hz, 1H), 4.23 (t, *J*=2.0 Hz, 1H), 3.91–4.00 (m, 2H), 2.43–2.47 (m, 2H), 1.42 (s, 3H), 1.41 (s, 3H), 0.91 (s, 9H), 0.12 (s, 3H), 0.10 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.8, 118.1, 109.0, 82.6, 82.0, 80.5, 78.2, 70.7, 51.4, 27.1, 27.0, 25.8, 24.7, 18.1, −4.4, −4.5; HRMS (ESI) *m/z* calcd for $C_{18}H_{32}O_4Si$ $[M+Na]^+$ 363.1962, found 363.1965.

*4.2.4. [7R-(Z,5β,6β,7α)]-5-(tert-Butyldimethylsilyloxy)-6,7-isopropylidenedioxy-3-iodonon-2,8-dien-1-ol (**5**).* To a solution of

Red-Al (3.6 M solution in toluene, 6.80 mL, 24.5 mmol) in THF (6.5 mL) was added compound **4** (2.48 g, 7.28 mmol) in THF (13.5 mL) dropwise at 0 °C. The mixture was stirred at 0 °C for 3 h, quenched by ethyl acetate (2.48 mL, 25.2 mmol) and cooled to −50 °C. Then a solution of iodine (4.87 g, 19.2 mmol) in THF (6.8 mL) was added dropwise, and the suspension was stirred for another 3 h. The reaction was quenched by the addition of the saturated $Na_2S_2O_3$ and $NaHCO_3$ aqueous solution, and the whole was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane/EtOAc, 15:1) to give compound **5** (3.16 g, 93%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.89 (t, J=5.6 Hz, 1H), 5.81 (ddd, J=7.6, 10.4, 17.6 Hz, 1H), 5.41 (dt, J=1.2, 17.2 Hz, 1H), 5.28 (d, J=10.0 Hz, 1H), 4.37 (t, J=8.0 Hz, 1H), 4.16–4.20 (m, 3H), 3.77 (dd, J=2.0, 8.4 Hz, 1H), 2.63–2.72 (m, 2H), 1.43 (s, 3H), 1.40 (s, 3H), 0.89 (s, 9H), 0.11 (br s, 3H), 0.08 (br s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.2, 136.6, 119.2, 109.0, 105.5, 82.8, 77.8, 69.6, 67.3, 49.4, 27.0, 26.9, 26.0, 18.1, −4.0, −4.1; HRMS (ESI) *m/z* calcd for $C_{18}H_{33}O_4SiI$ $[M+Na]^+$ 491.1085, found 491.1081.

*4.2.5. [3R-(1Z,3α,4β,5β)]-2-(5-tert-Butyldimethylsilyloxy-3,4-isopropylidenedioxy-2-methylenecyclohexylidene)ethanol (**6**).* A solution of compound **5** (3.88 g, 8.28 mmol), $PdCl_2(PPh_3)_2$ (378 mg, 0.54 mmol) and Et_3N (6.5 mL, 46.6 mmol) in MeCN (130 mL) was refluxed for 4 h. The mixture was evaporated and diluted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane/EtOAc, 10:1) to give compound **6** (2.67 g, 95%) as a light yellow oil. The ^{1}H NMR spectral data are identical with that reported by Takahashi' group.[32]

*4.2.6. [3R-(1Z,3α,4β,5β)]-2-(5-tert-Butyldimethylsilyloxy-3,4-isopropylidenedioxy-2-methylenecyclohexylidene)ethyl trimethylacetate (**7**).* This compound was obtained in a yield of 98% according to a similar reported procedure[33] by the use of alcohol **6** (102 mg, 0.30 mmol), pyridine (320 μL, 3.96 mmol), PivCl (160 μL, 1.30 mmol) and DMAP (4.0 mg, 0.0327 mmol) in DCM (1 mL). The ^{1}H NMR spectral data are identical with that reported by Takahashi' group.[33]

*4.2.7. [3R-(1Z,3α,4β,5β)]-2-(5-tert-Butyldimethylsilyloxy-3,4-dihydroxy-2-methylenecyclohexylidene)ethyl trimethylacetate (**8**).* A suspension of H_2O (400 μL), CF_3CO_2H (800 μL) and compound **7** (1.17 g, 2.76 mmol) in DCM (20.8 mL) was stirred at −10 °C for 1 h. The reaction was quenched by the addition of the saturated $NaHCO_3$ aqueous solution, and the whole was extracted with DCM. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane/EtOAc, 3:1) to give compound **8** (1.0 g, 94%) as a colorless oil. The ^{1}H NMR spectral data are identical with that reported by Takahashi' group.[33]

*4.2.8. [3R-(1Z,3α,4β,5β)]-2-[3,5-Bis(tert-butyldimethylsilyloxy)-4-hydroxy-2-methylenecyclohexylidene]ethyl trimethylacetate (**9**).* This compound was obtained in a yield of 98% according to a similar procedure[33] by the use of alcohol **8** (427 mg, 1.11 mmol), imidazole (333 mg, 4.89 mmol) and TBSCl (528 mg, 3.50 mmol) in DCM (3 mL). The ^{1}H NMR spectral data are identical with that reported by Takahashi' group.[33]

*4.2.9. [3R-(1Z,3α,4β,5β)]-2-[4,5-Bis(tert-butyldimethylsilyloxy)-3-[2-(ethoxycarbonyl)ethoxy]-2-methylenecyclohexylidene]ethyl trimethylacetate (**10**).* Compound **9** (626 mg, 1.25 mmol) was dissolved in toluene (38 mL). Ethyl acrylate (3.40 mL, 31.3 mmol), 25% Me_4NOH aqueous solution (0.9 mL) and 50% NaOH aqueous solution (14 mL) were added and vigorously stirred at rt for 16.5 h. The mixture was partitioned between water and ethyl acetate. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and evaporated in vacuo. The residue was purified by silica gel column chromatography (hexane/DCM, 1:1) to give compound **10** (608 mg, 81%) as a colorless oil. The ^{1}H NMR spectral data are in agreement with that reported for the wrongly stated '2β-' derivative.[33]

*4.2.10. [3R-(1Z,3α,4β,5β)]-2-[4,5-Bis(tert-butyldimethylsilyloxy)-3-(3-hydroxypropoxy)-2-methylenecyclohexylidene]ethanol (**11**).* To a solution of diester **10** (14.2 mg, 0.0237 mmol) in THF (0.5 mL) was added LAH (6.50 mg, 0.171 mmol) at 0 °C under nitrogen, and the mixture was stirred for 1.5 h. The reaction was quenched by the addition of diluted HCl (0.2 mol/L, 10 mL) aqueous solution, and the whole was extracted by ethyl acetate. The organic layer was washed with saturated $NaHCO_3$ aqueous solution and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane/EtOAc, 1:1) to give diol **11** (8.60 mg, 77%) as white crystal. Mp 96–98 °C; the ^{1}H NMR spectral data are identical with that reported for the wrongly stated '2β-' derivative (**43**) in Ref. 33.

*4.2.11. [3R-(1Z,3α,4β,5β)]-[2-[4,5-Bis(tert-butyldimethylsilyloxy)-3-[3-(tert-butyldimethylsilyloxy)propoxy]-2-methylenecyclohexylidene]ethyl] diphenylphosphine oxide (**12**).* A solution of NCS (219 mg, 1.64 mmol) and dimethyl sulfide (270 μL, 3.69 mmol) in DCM (4.5 mL) was stirred at 0 °C for 25 min. Then compound **11** (125 mg, 0.264 mmol) in DCM (2.5 mL) was added dropwise, and the mixture was stirred at 0 °C for 1 h. The whole was quenched by the addition of the saturated $NaHCO_3$ aqueous solution, and the whole was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo to give the unstable crude allyl chloride, which was used for the next step without purification.

A solution of the above allyl chloride (0.264 mmol), imidazole (77.5 mg, 1.14 mmol) and TBSCl (117 mg, 0.776 mmol) in DCM (2 mL) was stirred at 0 °C for 1 h. The reaction was quenched by the addition of the saturated $NaHCO_3$ aqueous solution, and the whole was extracted with DCM. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified (less than 10 min) by flash silica gel column chromatography (hexane/EtOAc, 50:1) to give the unstable crude compound as a light yellow oil, which was put into the next step without purification.

To a solution of the above compound (0.264 mmol) and diphenylphosphine (300 μL, 1.72 mmol) in DCM (1 mL) was added LHMDS (1.80 mL, 1 mol/L in THF, 1.80 mmol) at −78 °C under nitrogen, and the mixture was allowed to warm to rt gradually for 5 h. Then water (1.5 mL) and H_2O_2 (6.5 mL, 30% in water) were added successively, and the mixture was stirred at rt for another 2 h. The reaction was quenched by the addition of the saturated Na_2SO_3 aqueous solution, and the whole was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane/EtOAc, 5:1) to give compound **12** (160 mg, 78% for three steps) as a colorless oil. The ^{1}H NMR spectral data are identical with that reported for the wrongly stated '2β-' derivative (**44**) in Ref. 33.

*4.2.12. [3R-(1Z,3α,4β,5β)]-2-[3,5-Bis(tert-butyldimethylsilyloxy)-4-(2-tetrahydropyranyloxy)-2-methylenecyclohexylidene]ethyl trimethylacetate (**13**).* A mixture of compound **9** (500 mg, 1.0 mmol), DHP (848 mg, 10.1 mmol) and PPTS (47.0 mg, 0.187 mmol) in DCM (3 mL) was stirred at rt for 36 h. The reaction was quenched by the addition of the saturated $NaHCO_3$ aqueous solution, and the whole

was extracted with DCM. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane/EtOAc, 50:1) to give compound **13** (566 mg, 97%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.49 (t, J=7.2 Hz, 1H), 5.25 (br s, 1H), 4.93 (d, J=1.2 Hz, 1H), 4.89 (t, J=3.2 Hz, 1H), 4.59 (d, J=7.2 Hz, 2H), 4.27 (d, J=5.2 Hz, 1H), 4.21–4.24 (m, 1H), 3.91–3.97 (m, 1H), 3.72 (d, J=3.6 Hz, 1H), 3.46–3.50 (m, 1H), 2.50 (t, J=10.8 Hz, 1H), 2.19 (dd, J=4.0, 12.8 Hz, 1H), 1.41–1.87 (m, 6H), 1.19 (s, 9H), 0.88 (s, 9H), 0.86 (s, 9H), 0.09 (s, 3H), 0.06 (s, 3H), 0.05 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.5, 144.2, 141.1, 121.7, 115.4, 98.6, 79.3, 75.2, 68.7, 62.3, 61.8, 40.4, 38.6, 30.5, 27.2, 25.8, 25.7, 25.6, 19.5, 18.1, −4.6, −4.8, −4.86, −4.88; HRMS (ESI) m/z calcd for $C_{31}H_{58}O_6Si_2$ $[M+Na]^+$ 605.3664, found 605.3668.

*4.2.13. [3R-(1Z,3α,4β,5β)]-2-[3,5-Dihydroxy-4-(2-tetrahydropyranyloxy)-2-methylenecyclohexylidene]ethyl trimethylacetate (**14**).* A mixture of compound **13** (566 mg, 0.971 mmol) and TBAF (2.73 g, 10.4 mmol) in THF (11 mL) was stirred at 70 °C for 5 h. The reaction was quenched by the addition of the saturated $NaHCO_3$ aqueous solution, and the whole was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane/EtOAc, 50:1) to give compound **14** (314 mg, 91%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.50–5.65 (m, 1H), 5.52 (br s, 1H×6/11), 5.38 (br s, 1H×5/11), 5.00 (br s, 1H×6/11), 4.95 (br s, 1H×5/11), 4.81 (dd, J=8.4, 12.4 Hz, 1H×5/11), 4.62–4.65 (m, 2H), 4.42 (dd, J=6.0, 12.0 Hz, 1H×6/11), 4.31 (d, J=7.6 Hz, 1H×6/11), 4.28 (d, J=6.8 Hz, 1H×5/11), 4.14 (br s, 1H), 4.02 (d, J=11.6 Hz, 1H×6/11), 3.95–3.98 (d, J=10.8 Hz, 1H×5/11), 3.71 (dd, J=2.8, 6.4 Hz, 1H×6/11), 3.49–3.58 (m, 1H), 3.29 (d, J=6.0 Hz, 1H×5/11), 2.45–2.53 (m, 1H), 2.39 (br s, 1H), 1.72–1.93 (m, 2H), 1.42–1.62 (m, 4H), 1.17 (s, 9H×6/11), 1.16 (s, 9H×5/11); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.8, 178.5, 143.2, 143.1, 140.4, 139.7, 123.2, 122.6, 114.6, 112.9, 101.6, 100.6, 85.3, 83.7, 73.1, 70.9, 68.7, 68.1, 64.93, 64.88, 61.6, 61.5, 40.0, 39.8, 38.70, 38.65, 31.5, 31.3, 27.2, 27.1, 25.0, 24.9, 21.0, 20.8; HRMS (ESI) m/z calcd for $C_{19}H_{30}O_6$ $[M+Na]^+$ 377.1935, found 377.1939.

*4.2.14. [3R-(1Z,3α,4β,5β)]-2-[4-(2-Tetrahydropyranyloxy)-3,5-bis(methoxymethoxy)-2-methylenecyclohexylidene]ethyl trimethylacetate (**15**).* A mixture of compound **14** (389 mg, 1.10 mmol), DIPEA (4.40 mL, 26.6 mmol) and MOMCl (1.68 mL, 22.1 mmol) in DCM (3 mL) was refluxed for 6 h. The reaction was quenched by the addition of diluted HCl aqueous solution (0.2 mol/L, 10 mL), and the whole was extracted with DCM. The organic layer was washed with saturated $NaHCO_3$ aqueous solution and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane/EtOAc, 50:1) to give compound **15** (401 mg, 83%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.51–5.59 (m, 1H), 5.37 (br s, 1H×2/5), 5.33 (br s, 1H×3/5), 5.10 (d, J=1.2 Hz, 1H×2/5), 5.03 (br s, 1H×3/5), 4.87–4.92 (m, 1H), 4.80–4.81 (m, 1H), 4.56–4.72 (m, 5H), 4.26–4.29 (m, 1H), 3.85–4.12 (m, 3H), 3.43–3.54 (m, 1H), 3.38 (br s, 3H×3/5), 3.37 (br s, 3H×3/5), 3.36 (br s, 3H×2/5), 3.34 (br s, 3H×2/5), 2.61–2.67 (m, 1H), 2.37 (br s, 1H×3/5), 2.34 (br s, 1H×2/5), 1.48–1.88 (m, 6H), 1.18 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.3, 141.9, 140.8, 140.3, 140.1, 122.7, 122.6, 118.3, 115.9, 98.6, 98.5, 95.6, 95.5, 95.4, 94.5, 93.6, 78.5, 77.4, 76.5, 74.2, 73.5, 62.2, 62.1, 61.5, 55.9, 55.6, 55.43, 55.42, 38.6, 38.2, 37.3, 30.9, 30.6, 27.2, 25.5, 25.4, 19.4, 19.2; HRMS (ESI) m/z calcd for $C_{23}H_{38}O_8$ $[M+Na]^+$ 465.2459, found 465.2461.

*4.2.15. [3R-(1Z,3α,4β,5β)]-2-[4-Hydroxy-3,5-bis(methoxymethoxy)-2-methylenecyclohexylidene]ethyl trimethylacetate (**16**).* A mixture of compound **15** (369 mg, 0.834 mmol) in water (3 mL), AcOH (12 mL) and THF (6 mL) was stirred at 40 °C for 14 h. The reaction was quenched by the addition of the NaOH aqueous solution (2.6 mol/L, 150 mL), and the whole was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane/EtOAc, 3:1) to give compound **16** (279 mg, 93%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.57 (t, J=7.2 Hz, 1H), 5.41 (br s, 1H), 5.09 (br s, 1H), 4.62–4.75 (m, 6H), 4.21 (d, J=6.0 Hz, 1H), 4.05–4.07 (m, 1H), 3.86 (d, J=3.2 Hz, 1H), 3.41 (s, 6H), 2.58 (dd, J=7.6, 13.6 Hz, 1H), 2.39 (d, J=13.2 Hz, 1H), 1.20 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 178.3, 140.9, 139.7, 123.0, 116.7, 96.1, 95.2, 79.5, 75.6, 73.2, 61.4, 55.7, 55.6, 38.6, 37.5, 27.2; HRMS (ESI) m/z calcd for $C_{18}H_{30}O_7$ $[M+Na]^+$ 381.1884, found 381.1884.

*4.2.16. [3R-(1Z,3α,4β,5β)]-2-[4-[2-(Ethoxycarbonyl)ethoxy]-3,5-bis(methoxymethoxy)-2-methylenecyclohexylidene]ethyl trimethylacetate (**17**).* A mixture of compound **16** (94.0 mg, 0.262 mmol), ethyl acrylate (300 μL, 2.76 mmol), Me_4NOH (25% in H_2O, 0.08 mL) and NaOH (50% in H_2O, 0.6 mL) in toluene (1.5 mL) was stirred vigorously at rt for 20 h. The suspension was partitioned between water and EtOAc. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane/EtOAc, 4:1) to give compound **17** (97.2 mg, 81%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.54 (t, J=7.2 Hz, 1H), 5.34 (br s, 1H), 5.06 (d, J=1.2 Hz, 1H), 4.55–4.72 (m, 6H), 4.25 (d, J=5.6 Hz, 1H), 4.10 (q, J=7.2 Hz, 2H), 4.03–4.06 (m, 1H), 3.85–3.93 (m, 2H), 3.61 (dd, J=2.4, 5.6 Hz, 1H), 3.38 (s, 3H), 3.36 (s, 3H), 2.56–2.64 (m, 3H), 2.32 (dd, J=4.0, 13.2 Hz, 1H), 1.22 (t, J=7.2 Hz, 3H), 1.18 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.4, 171.5, 140.9, 139.9, 122.8, 117.6, 95.7, 94.8, 81.0, 77.3, 73.8, 66.4, 61.5, 60.4, 55.7, 55.4, 38.6, 37.5, 35.5, 27.2, 14.2; HRMS (ESI) m/z calcd for $C_{23}H_{38}O_9$ $[M+Na]^+$ 481.2408, found 481.2408.

*4.2.17. [3R-(1Z,3α,4β,5β)]-2-[4-(3-Hydroxypropoxy)-3,5-bis-(methoxymethoxy)-2-methylenecyclohexylidene]ethanol (**18**).* To a solution of compound **17** (674 mg, 1.47 mmol) in THF (15 mL) was added LAH (162 mg, 4.26 mmol) in portions, and the mixture was stirred at 0 °C for 30 min. The reaction was quenched by the addition of cold water, and the whole was extracted by ethyl acetate. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (EtOAc) to give compound **18** (480 mg, 98%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.63 (t, J=6.0 Hz, 1H), 5.32 (br s, 1H), 5.04 (br s, 1H), 4.71 (br s, 2H), 4.64 (d, J=6.4 Hz, 1H), 4.56 (d, J=6.0 Hz, 1H), 4.24–4.29 (m, 2H), 4.06–4.15 (m, 2H), 3.67–3.85 (m, 5H), 3.39 (s, 3H), 3.36 (s, 3H), 2.56 (t, J=11.2 Hz, 1H), 2.37 (d, J=12.8 Hz, 1H), 1.81 (br s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.8, 137.0, 128.2, 118.3, 95.5, 94.4, 80.4, 77.4, 73.8, 70.1, 61.7, 59.4, 55.7, 55.5, 37.3, 32.1; HRMS (ESI) m/z calcd for $C_{16}H_{28}O_7$ $[M+Na]^+$ 355.1727, found 355.1720.

*4.2.18. [3R-(1Z,3α,4β,5β)]-[2-[3,5-Bis(methoxymethoxy)-4-[3-(methoxymethoxy)propoxy]-2-methylenecyclohexylidene]ethyl] diphenylphosphine oxide (**19**).* A solution of NCS (202 mg, 1.51 mmol) and dimethyl sulfide (160 μL, 2.19 mmol) in DCM (8 mL) was stirred at 0 °C for 20 min. Then compound **18** (158 mg, 0.475 mmol) in DCM (3 mL) was added dropwise, and the mixture was stirred at 0 °C for 30 min. The reaction was quenched by the addition of cold water, and the whole was extracted by DCM. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo to give the unstable crude allyl chloride, which was used for the next reaction without purification.

A mixture of the above allyl chloride (0.475 mmol), DIPEA (470 μL, 2.84 mmol) and MOMCl (180 μL, 2.37 mmol) in DCM

(1.5 mL) was stirred at rt for 3 h. The reaction was quenched by the addition of diluted HCl (0.2 mol/L, 2.5 mL) aqueous solution, and the whole was extracted by DCM. The organic layer was washed with saturated $NaHCO_3$ aqueous solution and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified (less than 10 min) by flash silica gel column chromatography (hexane/EtOAc, 3:1) to give the unstable crude compound as a light yellow oil, which was put into the next step immediately.

To a solution of the above compound (0.475 mmol) and diphenylphosphine (210 μL, 1.21 mmol) in DCM (2 mL) was added LHMDS (1.20 mL, 1 mol/L in THF, 1.20 mmol) at −78 °C under nitrogen, and the mixture was allowed to warm to room temperature gradually for 3 h. Then water (0.5 mL) and H_2O_2 (10 mL, 30% in water) were added successively, and the mixture was stirred at rt for another 13 h. The reaction was quenched by the addition of saturated Na_2SO_3 aqueous solution, and the whole was extracted by DCM. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (EtOAc/MeOH, 20:1) to give compound **19** (206 mg, 77% for three steps) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67–7.73 (m, 4H), 7.44–7.52 (m, 6H), 5.40 (dd, J=7.2, 15.2 Hz, 1H), 5.33 (br s, 1H), 5.11 (br s, 1H), 4.56–4.80 (m, 6H), 4.18 (d, J=6.8 Hz, 1H), 3.96–3.99 (m, 1H), 3.56–3.70 (m, 4H), 3.13–3.46 (m, 3H), 3.36 (s, 3H), 3.32 (s, 3H), 3.28 (s, 3H), 2.49–2.54 (m, 1H), 2.21 (d, J=13.2 Hz, 1H), 1.81–1.85 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.6, 139.6, 139.5, 133.0 (d, $J_{C,P}$=40.0 Hz), 132.1 (d, $J_{C,P}$=40.0 Hz), 131.72, 131.70, 131.0, 130.94, 130.91, 130.85, 128.6, 128.5, 116.3, 116.2, 116.0, 96.4, 95.4, 95.3, 81.8, 77.3, 73.2, 67.4, 64.7, 55.7, 55.3, 55.1, 38.3, 31.1 (d, $J_{C,P}$=70.0 Hz), 30.4; HRMS (ESI) m/z calcd for $C_{30}H_{41}O_8P$ $[M+H]^+$ 561.2612, found 561.2619.

*4.2.19. (1R,2S,6R,7R)-7-[(R)-6-(Methoxymethoxy)-6-methylheptan-2-yl]-6-methylbicyclo[4.3.0]nonan-2-ol (**21**).* To stirred magnesium turnings (470 mg, 19.3 mmol), a solution of 4-bromo-2-methylbutan-2-yl methoxymethyl ether (1.60 g, 7.58 mmol) in THF (6 mL) was added dropwise at rt under nitrogen, and the mixture was stirred for 1 h. The resulting Grignard reagent was added to a suspension of compound **20** (110 mg, 0.30 mmol) and CuBr•Me_2S (62.0 mg, 0.302 mmol) in THF (3 mL) at −20 °C, and the mixture was stirred at 0 °C for 18 h. The reaction was quenched by the addition of diluted aqueous HCl (0.2 mol/L, 20 mL) solution, and the whole was extracted by ethyl acetate. The organic layer was washed with saturated $NaHCO_3$ aqueous solution and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane/EtOAc, 10:1) to give compound **21** (52.2 mg, 53%) as a colorless oil. The ^{1}H NMR spectral data are identical with that reported by Kittaka's group.[40]

*4.2.20. (1R,6R,7R)-7-[(R)-6-(Methoxymethoxy)-6-methylheptan-2-yl]-6-methylbicyclo[4.3.0]nonan-2-one (**22**).* A solution of compound **21** (224 mg, 0.686 mmol), TBAB (50.0 mg, 0.155 mmol), TEMPO (34.0 mg, 0.218 mmol) and Oxone (556 mg, 1.59 mmol) in DCM (20 mL) was stirred at rt for 6 h. The reaction was quenched by the addition of saturated $NaHCO_3$ aqueous solution, and the whole was extracted with DCM. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane/EtOAc, 10:1) to give compound **22** (200 mg, 90%) as a pale yellow oil. The ^{1}H NMR spectral data are identical with that reported by Kittaka's group.[40]

*4.2.21. (1α,2β,3β,5Z,7E)-2-(3-Hydroxypropoxy)-9,10-secocholesta-5,7,10(19)-triene-1,3,25-triol (**23**; ED-71).* To a cooled solution of compound **19** (70.0 mg, 0.125 mmol) in THF (0.5 mL) at −78 °C under nitrogen was added n-BuLi (2.5 M in hexane, 50.0 μL, 0.125 mmol) dropwise, and the mixture was stirred for another 10 min. A solution of compound **22** (24.0 mg, 0.074 mmol) in THF (0.5 mL) was added, and the mixture was stirred for another 4 h. The reaction was quenched by the addition of cold water, and the whole was extracted by ethyl acetate. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane/EtOAc, 3:1) to give the protected ED-71 (30 mg, 61%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.32 (d, J=11.2 Hz, 1H), 5.99 (d, J=11.2 Hz, 1H), 5.37 (br s, 1H), 5.17 (br s, 1H), 4.70–4.74 (m, 5H), 4.58–4.60 (m, 3H), 4.26 (d, J=5.6 Hz, 1H), 4.06–4.08 (m, 1H), 3.66–3.73 (m, 2H), 3.59–3.62 (m, 3H), 3.39 (s, 3H), 3.38 (s, 3H), 3.36 (s, 3H), 3.35 (s, 3H), 2.80 (d, J=12.4 Hz, 1H), 2.62–2.68 (m, 1H), 2.34 (dd, J=3.2, 12.8 Hz, 1H), 1.90–2.00 (m, 2H), 1.85–1.89 (m, 3H), 1.60–1.70 (m, 3H), 0.98–1.53 (m, 12H), 1.21 (s, 6H), 0.91 (d, J=6.0 Hz, 3H), 0.51 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.7, 141.7, 133.0, 124.1, 117.8, 117.2, 96.5, 95.5, 94.4, 91.0, 80.7, 76.4, 74.1, 67.4, 64.8, 56.6, 56.3, 55.6, 55.4, 55.12, 55.07, 45.9, 42.3, 40.5, 38.1, 36.4, 36.1, 30.5, 29.0, 27.7, 26.4, 26.3, 23.5, 22.2, 20.5, 18.8, 11.9; HRMS (ESI) m/z calcd for $C_{38}H_{66}O_9$ $[M+Na]^+$ 689.4599, found 689.4600.

To a stirred solution of the protected ED-71 (200 mg, 0.30 mmol) in methanol (10 mL), CSA (718 mg, 3.09 mmol) was added. The mixture was stirred at rt for 66 h. The reaction was quenched by the addition of saturated $NaHCO_3$ aqueous solution, and the whole was extracted by ethyl acetate. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (DCM/MeOH, 30:1) to give compound ED-71 (100 mg, 68%) as a light yellow foam. Mp 126–128 °C; ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.2, 142.9, 132.1, 124.9, 117.2, 111.8, 85.4, 71.5, 71.1, 68.2, 66.5, 61.1, 56.5, 56.4, 45.9, 44.4, 40.5, 36.4, 36.1, 31.8, 29.3, 29.2, 29.1, 27.6, 23.7, 22.3, 20.8, 18.8, 11.9; UV (EtOH) λ=264 nm; HRMS (ESI) m/z calcd for $C_{30}H_{50}O_5$ $[M+Na]^+$ 513.3550, found 513.3549. The ^{1}H NMR spectral data are identical with that reported by Kubodera's group.[31]

*4.2.22. (1α,2β,3β,5Z,7E)-1-(3-Hydroxypropoxy)-9,10-secocholesta-5,7,10(19)-triene-2,3,25-triol (**24**).* To a cooled solution of compound **12** (73.4 mg, 0.0952 mmol) in THF (0.5 mL) at −78 °C under nitrogen was added n-BuLi (2.5 M in hexane, 40.0 μL, 0.10 mmol) dropwise, and the mixture was stirred for another 10 min. Then a solution of compound **22** (34.0 mg, 0.105 mmol) in THF (0.5 mL) was added by cannula, and the mixture was stirred for another 10 h. The reaction was quenched by the addition of cold water, and the whole was extracted by ethyl acetate. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane/EtOAc, 70:1) to give the silyl ether (46.5 mg, 56%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.25 (d, J=11.2 Hz, 1H), 5.99 (d, J=11.2 Hz, 1H), 5.17 (d, J=2.0 Hz, 1H), 5.11 (d, J=2.0 Hz, 1H), 4.70 (s, 2H), 4.02 (ddd, J=2.4, 4.4, 10.8 Hz, 1H), 3.86 (br s, 1H), 3.54–3.70 (m, 3H), 3.31–3.46 (m, 2H), 3.37 (s, 3H), 2.81 (d, J=12.4 Hz, 1H), 2.57 (t, J=11.2 Hz, 1H), 2.09 (dd, J=4.4, 12.4 Hz, 1H), 1.83–2.04 (m, 3H), 1.62–1.71 (m, 5H), 1.00–1.56 (m, 12H), 1.21 (s, 6H), 0.92 (d, J=6.4 Hz, 3H), 0.90 (s, 9H), 0.89 (s, 9H), 0.85 (s, 9H), 0.52 (s, 3H), 0.08 (s, 6H), 0.07 (s, 3H), 0.06 (s, 3H), 0.040 (s, 3H), 0.037 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.4, 141.6, 134.6, 123.2, 117.6, 91.0, 84.7, 76.4, 74.6, 70.3, 64.6, 60.4, 56.5, 56.2, 55.1, 45.8, 42.2, 40.6, 40.2, 36.4, 36.1, 33.0, 28.9, 27.7, 26.41, 26.35, 26.1, 26.0, 25.8, 23.4, 22.3, 20.5, 18.8, 18.4, 18.3, 18.2, 12.0, −4.3, −4.4, −4.5, −4.8, −5.31, −5.33; HRMS (ESI) m/z calcd for $C_{50}H_{96}O_6Si_3$ $[M+Na]^+$ 899.6407, found 899.6410.

To a solution of the above silyl ether (57.6 mg, 0.0656 mmol) in methanol (4 mL) was added CSA (280 mg, 1.21 mmol). After stirring at rt for 6 h, saturated $NaHCO_3$ aqueous solution was added, and the

mixture was extracted by ethyl acetate. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (DCM/MeOH, 15:1) to give compound **24** (23 mg, 71%) as a colorless oil. $[\alpha]_D^{25}$+63.3 (*c* 0.15, MeOH); UV (EtOH) λ=267 nm; HRMS (ESI) *m/z* calcd for $C_{30}H_{50}O_5$ $[M+Na]^+$ 513.3550, found 513.3550. The ^1H NMR spectral data are identical with that reported for the wrongly assigned 'ED-71' in Ref. 33.

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Supplementary data

Supplementary data (Synthesis of compound **1** from D-mannitol, spectroscopic data (^1H, ^{13}C NMR and HMBC), HRMS for the key compounds, and the crystal parameters of compound **11** are available free of charge via the internet at. Crystallographic data for compound **11** in this paper have been deposited with the Cambridge Crystallographic Data Center as CCDC−1401159.) associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2015.08.055.

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