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Total synthesis of 1α ,25-dihydroxy-2 β -(3-hydroxypropoxy)vitamin D₃ (ED-71)

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ABSTRACT

Article history: Received Received in revised form Accepted Available online A convergent method for the synthesis of ED-71 has been developed. Starting from the reported epoxide 5 which could be easily prepared for D-mannitol, ED-71 was synthesized in 11 linear steps with 17% overall yield.

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1. Introduction

Osteoporosis^[1] is a condition in which bone becomes porous and fragile, leading to loss of bone mineral density that can result in bone fracture, a common disease of elder patients, associated with pain and a decrease in physical and social function. 1 α ,25-Dihydroxy-2 β -(3-hydroxypropoxy)vitamin D₃ (ED-71),^[2] an analog of vitamin D₃, can significantly increase bone mineral density, prevent bone fracture, and has been used as a once-a-day oral drug for the treatment of osteoporosis in Japan.^[3]

Extensive efforts have been made by Kubodera and co-workers for the development of practical synthesis method for production ED-71 (**Figure 1**). Initially, they reported the first synthesis route of ED-71 from lithocholic acid in 27 linear steps and with a 0.03% overall yield.^[4] And then, starting from cholesterol, they also developed a biomimetic method for the preparation of ED-71 in 16 linear steps and with a 0.5% overall yield.^[5]

Next, they reported two convergent approaches for the synthesis of ED-71 by Horner-Wadsworth-Emmons reaction and the Trost coupling, respectively.^[6] As shown in figure 1, starting from the known C₂-symmetrical epoxide **3**, Kubodera and co-workers prepared the A-ring phosphine oxide **1** in 11 linear steps with 2.5% overall yield. ED-71 could be obtained by the coupling of the A-ring phosphine oxide (**1**) and C/D-ring ketone (**2**) by Horner-Wadsworth-Emmons reaction.^[7]

In 1993, using the epoxide **4** as the key building block, Takahashi and workers developed a new route to synthesize the A-ring phosphine oxide of $1\alpha,2\beta,25$ -trihydroxyvitamin D₃.^[8] Starting from the same epoxide **4**, Liu and co-workers reported a new strategy to synthesize the A-ring phosphine oxide of ED-71.^[9] The designed A-ring phosphine oxide was obtained in 18 linear steps with 16% overall yield and the final product ED-71 was synthesized with 6% overall yield which was undoubtedly a big improvement for the construction of this molecule.



Figure 1. Structures and retrosynthetic analysis of ED-71.

Currently, the biomimetic linear route was used in industry for large scale synthesis of ED-71.^[5b, 10] But a lot of work have been done about the convergent synthesis because it not only has a higher yield, comparing with linear approach, but also provides a versatile planform for the discovering of new active vitamin D_3 analogs.^[6d, 11] In order to discover new active analogs of ED-71, we are interested in the construction of ED-71 by convergent approaches. Herein, we wish to report a new route to synthesize A-ring phosphine oxide and the total synthesis of ED-71.

Starting from the reported epoxide 5 (Figure 2), which is readily available from D-mannitol in five steps,^[12] the intermediate 6 was easily prepared with 93% yield by Michael addition. Using tert-butyl acrylate as the Michael acceptor is the key point for the reaction to get high yield. Intermediate 6 was converted to 7 with 87% yield. During our experiment, we found the order of adding the materials and the concentration of the reaction were very important for this conversion to get high yield. Boron trifluoride diethyl etherate should be added to the lithium solution of acetylide before epoxide 6, otherwise, only a small amount of product could be determined. Reduction of 7 with lithium tetrahydro aluminum led to alcohol 8 with 88% yield. The two hydroxyls of 8 were protected as TBS ether with *tert*-butyldimethylsilyl chloride to get **9**. The *p*-methoxybenzyl group (PMB) of 9 was cleaved with 2,3-dicyano-5,6-dichlorobenzoquinone (DDQ) oxidation to get propargyl alcohol 10 with 72% yield (2 steps). 10 was reduced with sodium bis(2-methoxyethoxy)aluminumhydride (Red-Al) at 0 °C, and then quenched with iodine at -55 °C to get the vinyl iodide 11 with 76% yield. Transformation of 11 to the exocyclic diene 12 was achieved by palladium catalyzed Heck cyclization. Chlorination the propargyl alcohol of **12** with triphosgen (BTC) to get 13 with 99% yield. The chloride of 13 was substituted with lithium diphenylphosphide, and then oxidized with hydrogen peroxide in one port to get 14 with 96% yield.



Figure 2. Preparation of A-ring phosphine oxide.

At the beginning of our study, we had planned to protect all the hydroxyls with methoxymethyl (MOM) to get intermediate **18** (Figure 3). Thus, we first protected the hydroxyl of 7 with chloromethyl methyl ether (MOMCl), and then deprotected the PMB group of **15** with DDQ to lead compound **16**. But unfortunately, we found **16** could not be reduced with Red-Al. All the experiments to prepare **17** from **16** were failed. We thought the oxygen atom of the ester group could coordinate with Red-Al and form an inactive complex. Therefore, we had tried to reduce the ester group of **15** with lithium tetrahydro aluminum to get compound **19**, and then protected the new formed hydroxyl with MOMCl to get **20**. The PMB group of **20** could be easily cleaved with DDQ to obtain compound **21** with 94% yield. But we found **21** still could not be reduced with Red-Al, that indicate



Figure 3. Route for the preparation of MOM protected A-ring.

Next, we had planned to prepare all TBS protected A-ring phosphine oxide (Figure 4). Compound 23 was first prepared by the same process for the preparation of 5, and then reacted with tert-butyl acrylate. Just as Liu and his co-worker reported, the migration of TBS has also been observed and a mixture of 24 and 25 were obtained which was very difficult to be separated with column chromatograph. Thus, A-ring phosphine oxide 14 was used for the total synthesis of ED-71.



Figure 4. Migration of TBS under the Michael reaction conditions.



Figure 5. Preparation of ketone 29 and the completion of ED-71.

The C/D ring of ED-71 was prepared with the known procedure from Vitamin D_3 (**Figure 5**). The double bonds of Vitamin D_3 were cleaved with ozone in anhydrous methanol, and then reduced with sodium borohydride to get compound **26** with 66% yield.^[11a] The hydroxyl of **26** was oxidized with Dess-Martin reagent to get ketone **27** with 99% yield. Oxidational functionalization of **27** with

situ by the oxidation of trifluoroacetate with oxone to get compound **28**.^[11e] The new formed hydroxyl in **28** was protected with triethylsilyl trifluoromethanesulfonate (TESOTf) in dichloromethane to get compound **29** with 80% yield. Horner-Wadsworth-Emmons reaction was used to coupling **29** with **14** to get protected ED-71 which was deprotected with camphorsulfonic acid (CSA) in methanol to obtain ED-71 with 80% yield. Its spectral data were in full agreement with that reported by Kudodera and Liu, respectively.

3. Conclusion

In conclusion, a convergent method for the synthesis of ED-71 has been developed. Starting from the reported epoxide **5**, ED-71 could be synthesized in 11 linear steps with 17% overall yield.

4. Experimental Section

General. All experiments were performed under a dry N_2 atmosphere, unless noted otherwise. All the reagents were used as it purchased unless noted otherwise. ¹H, ¹³C NMR spectra, 2D HMBC and 2D HSQC were recorded on Bruker-400 NMR spectrometers. ¹H spectra were recorded relative to CDCl₃ (7.26 ppm) or TMS (0.00 ppm) as internal standard, and ¹³C NMR spectra were recorded relative to CDCl₃ (77.0 ppm). High resolution mass spectra were performed on BioTOF Q instrument by electrospray ionization (ESI). Column chromatography was performed on silica gel (300-400 mesh). THF was distilled from sodium, and DCM was distilled from CaH₂ before use.

tert-Butyl

3-(((1S,2R)-2-(methoxymethoxy)-1-((R)-oxiran-2-yl)but-3-en-1-y 1)oxy)propanoate (6). To a stirred solution of compound 5 (930 mg, 5.3 mmol) in tert-butyl acrylate (12 mL), NaH(104 mg, 60% in oil) was added slowly and stirred at $15 \square$ for 4 h, and then quenched with H₂O, extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered, and concentrated under vacuo. The residue was purified by silica gel column chromatography (hexane/EtOAc = 5:1) to give compound 6 (1.5 g, 93%) as a yellowish oil. ¹H NMR (400 MHz, CDCl₃) δ 5.84 (ddd, J = 17.9, 10.3, 7.7 Hz, 1H), 5.34 (d, J = 17.4 Hz, 2H), 4.71 (d, J = 6.7 Hz, 1H), 4.60 (d, J = 6.7Hz, 1H), 4.21 (dd, J = 7.4, 3.9 Hz, 1H), 3.88 – 3.81 (m, 1H), 3.77 -3.71 (m, 1H), 3.38 (s, 3H), 3.26 (t, J = 4.6 Hz, 1H), 3.14-3.11(m, 1H), 2.80 (d, J = 3.2 Hz, 2H), 2.52 – 2.42 (m, 2H), 1.43 (s, 9H). ¹³C NMR (101 MHz, CDCl₃) δ 170.6, 134.2, 119.0, 93.9, 81.2, 80.5, 77.2, 67.4, 55.5, 50.7, 45.5, 36.4, 28.0. HRMS (ESI) m/z calcd for $C_{15}H_{26}O_6 [M+Na]^+$ 325.1627, found 325.1618.

tert-Butvl 3-(((3R,4R,5R)-5-hydroxy-9-((4-methoxybenzyl) oxy)-3-(methoxymethoxy)non-1-en-7-yn-4-yl)oxy)propanoate (7). To a solution of 1-methoxy-4-((prop-2-yn-1-yloxy)methyl) benzene (1.9 g, 10.8 mmol) in THF (30 mL) was added n-BuLi (3.0 mL, 2.5 M solution in hexane) at -78 \square under nitrogen, and the mixture was stirred for 2 h. BF₃·OEt₂ (3.0 mL, 23.8 mmol) was added and stirred for another 30 min, and then a solution of compound 6 (1.1 g, 3.6 mmol) in THF (10 mL) was added at the same temperature. The mixture was stirred for another 4 h, and then quenched with saturated NaHCO₃ solution, extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered, and concentrated under vacuo. The residue was purified by silica gel column chromatography (hexane/EtOAc = 3:1) to give compound 7 (1.52) g, 87%) as a yellowish oil. ¹H NMR (400 MHz, CDCl₃) δ 7.27 (d, J = 8.4 Hz, 2H), 6.86 (d, J = 8.6 Hz, 2H), 5.85 (ddd, J = 17.5, 10.4, 7.3 Hz, 1H), 5.33 (t, J = 14.0 Hz, 2H), 4.67 (d, J = 6.6 Hz, 1H), 4.60 (d, J = 6.6 Hz, 1H), 4.51 (s, 2H), 4.30 (dd, J = 7.1, 4.7

Hz, 1H), 4.14 (t, J = 2.0 Hz, 2H), 3.94 – 3.83 (m, 3H), 3.79 (s, 3H), 3.45 (dd, J = 6.3, 4.6 Hz, 1H), 3.38 (s, 4H), 2.60 – 2.43 (m, 4H), 1.44 (s, 9H). ¹³C NMR (101 MHz, CDCl₃) δ 171.1, 159.3, 134.3, 129.6, 129.5, 118.8, 113.6, 94.3, 83.5, 80.7, 78.0, 77.5, 70.8, 69.4, 68.2, 57.3, 55.8, 55.2, 36.3, 28.0, 23.2. HRMS (ESI) m/z calcd for C₂₆H₃₈O₈ [M+Na]⁺ 501.2464, found 501.2462.

(3R,4R,5R)-4-(3-hydroxypropoxy)-9-((4-methoxybenzyl)oxy) -3-(methox-ymethoxy)non-1-en-7-yn-5-ol (8). To a stirred solution of compound 7 (1.5 g, 3.1 mmol) in THF (20 mL), LiAlH₄ (238 mg, 6.3 mmol) was added slowly and stirred at room temperature for 2 h, and then quenched by the addition of H₂O (250 µL), aqueous NaOH (250 µL,15%) and H₂O (750 µL). The whole mixture was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered, and concentrated under vacuo. The residue was purified by silica gel column chromatography (hexane/EtOAc = 1:2) to give compound 8 (1.12 g, 88%) as a yellowish oil. ¹H NMR (400 MHz, CDCl₃) δ 7.26 (d, J = 8.5 Hz, 2H), 6.87 (d, J = 8.6 Hz, 2H), 5.87 (ddd, J = 17.4, 10.4, 7.2 Hz, 1H), 5.38 (d, J = 17.4 Hz, 1H), 5.34 (d, J = 10.8 Hz, 1H), 4.68 (d, J = 6.5 Hz, 1H), 4.61 (d, J = 6.5 Hz, 1H), 4.51 (s, 2H), 4.36 (dd, J = 7.0, 3.7 Hz, 1H), 4.14 (t, J = 1.8 Hz, 2H), 3.92 (dd, J = 11.5, 5.5 Hz, 1H), 3.85 - 3.67 (m, 7H), 3.43 (dd, J = 7.1, 3.8 Hz, 1H), 3.39 (s, 3H), 3.18 (bs, 1H), 2.62 (dd, J = 4.9, 1.9 Hz, 2H), 2.46 (bs, 1H), 1.86 - 1.74 (m, 2H). ¹³C NMR (101 MHz, CDCl₃) δ 159.3, 134.5, 129.6, 129.4, 118.9, 113.8, 94.6, 83.2, 83.0, 78.5, 77.2, 71.2, 71.0, 69.1, 60.8, 57.3, 55.9, 55.3, 32.4, 23.4. HRMS (ESI) m/z calcd for $C_{22}H_{32}O_7$ [M+Na]⁺ 431.2046, found 431.2040.

(5R,6S)-6-((R)-1-((tert-butyldimethylsilyl)oxy)-5-((4-methoxy benzyl)oxy)pent-3-yn-1-yl)-12,12,13,13-tetramethyl-5-vinyl-2,4, 7,11-tetraoxa-12-silatetradecane (9). A mixture of 8 (200 mg, 0.5 mmol), imidazole (536 mg, 7.9 mmol) and TBSCl (588 mg, 3.9 mmol) in DCM (5 mL) was stirred at 40 \square for 16 h. The reaction was quenched with saturated NaHCO3 solution, and the whole mixture was extracted with DCM. The organic layer was washed with brine, dried over anhydrous Na2SO4, filtered, and concentrated under vacuo. The residue was purified by silica gel column chromatography (hexane/EtOAc = 10:1) to give compound 9 (364 mg) as a yellowish oil which contained a small amount of TBSC1. The oil was used without further purification in the next reaction. ¹H NMR (400 MHz, CDCl₃) δ 7.27 (d, J = 8.3 Hz, 2H), 6.87 (d, J = 8.5 Hz, 2H), 5.86 (ddd, J = 17.9, 10.3, 7.9 Hz, 1H), 5.32 (d, J = 17.9 Hz, 1H), 5.29 (d, J = 10.4 Hz, 1H), 4.69 (d, J = 6.6 Hz, 1H), 4.61 (d, J = 6.6 Hz, 1H), 4.51 (s, 2H), 4.16 – 4.12 (m, 3H), 3.99 (dd, J = 9.4, 5.2 Hz, 1H), 3.85 – 3.80 (m, 4H), 3.75 - 3.65 (m, 3H), 3.37 (s, 4H), 2.56 (d, J = 4.5 Hz, 2H), 1.82 - 1.76 (m, 2H), 0.93 (s, 9H), 0.90 (s, 9H), 0.15 (s, 3H), 0.11 (s, 3H) 0.06 (s, 6H). ¹³C NMR (101 MHz, CDCl₃) δ 159.3, 135.9, 129.7, 129.6, 118.4, 113.8, 94.5, 85.4, 84.8, 78.0, 77.6, 71.7, 70.9, 70.1, 60.2, 57.4, 55.6, 55.2, 33.6, 29.7, 25.9, 25.8, 23.4, 18.3, 18.1, -4.4, -4.6, -5.3. HRMS (ESI) m/z calcd for C₃₄H₆₀O₇Si₂ [M+Na]⁺ 659.3775, found 659.3775.

(5R, 6S, 7R)-5-((tert-butyldimethylsilyl)oxy)-6-(3-((tert-butyl dimethylsilyl)oxy)propoxy)-7-(methoxymethoxy)non-8-en-2-yn-1-ol (**10**). A mixture of compound **9** (0.5 mmol), H₂O (0.4 mL) and DDQ (162 mg, 0.7 mmol) in DCM (4 mL) was stirred at room temperature for 2 h. The reaction was diluted with DCM and filtered through celite. The organic layer was washed with brine, dried over anhydrous Na₂SO₄, filtered, and evaporated under vacuo. The residue was purified by silica gel column chromatography (hexane/EtOAc = 1:1) to give compound **10** (187 mg, 72% for two steps) as a yellowish oil. ¹H NMR (400 MHz, CDCl₃) δ 5.87 – 5.76 (m, 1H), 5.33 (d, *J* = 17.2 Hz, 1H),

5.30 (d, J = 10.3 Hz, 1H), 4.67 (d, J = 6.6 Hz, 1H), 4.62 (d, J = 6.7 Hz, 1H), 4.22 (s, 3H), 4.00 – 3.96 (m, 1H), 3.86 – 3.65 (m, 4H), 3.45 – 3.30 (m, 4H), 2.55 – 2.51 (m, 2H), 1.93 (bs, 1H), 1.79 – 1.73 (m, 2H), 0.92 (s, 9H), 0.90 (s, 9H), 0.12 (s, 3H), 0.10 (s, 3H), 0.02 (s, 6H). ¹³C NMR (101 MHz, CDCl₃) δ 135.8, 118.8, 94.4, 85.6, 84.2, 80.1, 77.6, 71.7, 70.2, 60.3, 55.6, 51.3, 33.6, 25.9, 25.8, 23.2, 18.3, 18.0, -4.4, -4.6, -5.3. HRMS (ESI) m/z calcd for C₂₆H₅₂O₆Si₂ [M+Na]⁺ 539.3200, found 539.3194.

(5R,6S,7R)-5-((tert-butyldimethylsilyl)oxy)-6-(3-((tert-butyl dimeth-ylsilyl)oxy)propoxy)-3-iodo-7-(methoxymethoxy)nona-2, 8-dien-1-ol (11). To a solution of compound 10 (130 mg, 0.25 mmol) in THF (3.5 mL) under nitrogen, Red-Al (0.5 mL, 3.6 M solution in toluene) was added dropwise at $0 \square$. The mixture was stirred at 0 \square for 17 h and then cooled to -55 \square , quenched by ethyl acetate (0.2 mL). Then a solution of iodine (190 g, 0.75 mmol) in THF (1.5 mL) was added dropwise, and the suspension was stirred for another 2 h. The reaction was quenched by the addition of the saturated Na₂S₂O₃ and NaHCO₃ solution, and the mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous Na₂SO₄, filtered, and concentrated under vacuo. The residue was purified by silica gel column chromatography (hexane/EtOAc = 8:1) to give compound 11 (123 mg, 76%) as a greenish oil. ¹H NMR (400 MHz, CDCl₃) δ 5.90 (t, J = 5.7 Hz, 1H), 5.75 (ddd, J = 17.9, 10.3, 7.9 Hz, 1H), 5.40 (d, J = 17.0 Hz, 1H), 5.36 (d, J = 13.9 Hz, 1H), 4.69 (d, J = 6.6 Hz, 1H), 4.63 (d, J = 6.8 Hz, 1H), 4.21 – 4.10 (m, 2H), 4.04 - 3.94 (m, 2H), 3.83 - 3.89 (m, 1H), 3.77 -3.65 (m, 3H), 3.39 - 3.42 (m, 4H), 2.81 - 2.69 (m, 2H), 1.86 -1.73 (m, 2H), 1.65 (bs, 1H), 0.91 (s, 9H), 0.89 (s, 9H), 0.09 (s, 3H), 0.07 (s, 6H), 0.05 (s, 3H). ^{13}C NMR (101 MHz, CDCl₃) δ 136.9, 134.6, 119.7, 106.8, 94.0, 86.4, 77.7, 71.3, 70.1, 67.4, 60.4, 55.5, 48.3, 33.7, 29.7, 25.9, 25.8, 18.3, 17.9, -4.1, -4.2, -5.2, -5.3. HRMS (ESI) m/z calcd for $C_{26}H_{53}IO_6Si_2$ [M+Na]⁺ 667.2323, found 667.2331.

(Z)-2-((3R,4S,5R)-5-((tert-butyldimethylsilyl)oxy)-4-(3-((tertbutyldimethylsilyl)oxy)propoxy)-3-(methoxymethoxy)-2-methyl enecyclohexy-lidene)ethan-1-ol (12). A solution of compound 11 (300 mg, 0.46 mmol), PdCl₂(PPh₃)₂ (35 mg, 0.05 mmol) and DIEA (0.5 mL, 3.0 mmol) in MeCN (10 mL) was refluxed for 3 h. The mixture was evaporated and diluted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous Na₂SO₄, filtered, and concentrated under vacuo. The residue was purified by silica gel column chromatography (hexane/EtOAc = 5:1) to give compound 12 (220 mg, 91%) as a yellow oil. 1 H NMR (400 MHz, CDCl₃) δ 5.57 (t, J = 6.8 Hz, 1H), 5.30 (d, J =0.8 Hz, 1H), 4.96 (d, J = 1.7 Hz, 1H), 4.64 (q, J = 6.6 Hz, 2H), 4.29 - 4.10 (m, 4H), 3.79 - 3.61 (m, 4H), 3.43 - 3.33 (m, 4H), 2.55 - 2.45 (m, 1H), 2.21 (dd, J = 13.0, 3.7 Hz, 1H), 1.83 - 1.71 (m, 2H), 1.65 (bs, 1H), 0.88 (s, 18H), 0.10 (s, 3H), 0.09 (s, 3H), 0.06 (s, 6H). ¹³C NMR (101 MHz, CDCl₃) δ 141.5, 137.8, 127.4, 116.6, 94.6, 82.4, 78.0, 69.4, 68.1, 60.2, 59.4, 55.5, 40.5, 33.5, 29.6, 25.9, 25.9, 18.3, 18.1, 14.05, -4.7, -5.3. HRMS (ESI) m/z calcd for C₂₆H₅₂O₆Si₂ [M+Na]⁺ 539.3200, found 539.3198.

tert-Butyl(3-(((1S,2R,6R,Z)-6-((*tert-butyldimethylsilyl*)*oxy*)-4-(2-*chloroethylidene*)-2-(*methoxymethoxy*)-3-*methylene*

cyclohexyl)oxy)propoxy)dimethylsilane (13). A solution of compound 12 (50 mg, 0.1 mmol) and triphosgene (60 mg, 0.2 mmol) in hexane (1mL), and a solution of pyridine (46 uL, 0.6 mmol) in hexane (1 mL) were mixed at 0 \Box , and then warmed to room temperature, stirred for 2 h. The reaction was quenched with saturated NaHCO₃ solution, and then extracted with hexane. The organic layer was washed with brine, dried over anhydrous Na₂SO₄, filtered, and concentrated under vacuo. The residue was purified by

silica gel column chromatography (hexane/EtOAc = 15:1) to give compound **13** (51 mg, 99%) as a yellowish oil. ¹H NMR (400 MHz, CDCl₃) δ 5.55 (t, J = 8.0 Hz, 1H), 5.35 (s, 1H), 5.16 (s, 1H), 4.64 (q, J = 6.6 Hz, 2H), 4.26 – 4.05 (m, 4H), 3.82 – 3.57 (m, 4H), 3.36 (s, 4H), 2.48 (dd, J = 12.8, 8.5 Hz, 1H), 2.21 (dd, J = 13.1, 3.5 Hz, 1H), 1.83 – 1.68 (m, 2H), 0.90 (s, 9H), 0.89 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H), 0.04 (s, 6H). ¹³C NMR (101 MHz, CDCl₃) δ 141.5, 140.8, 123.4, 95.0, 82.7, 77.9, 69.2, 68.1, 60.2, 55.6, 41.4, 40.6, 33.5, 25.9, 25.8, 18.3, 18.1, -4.6, -4.8, -5.3. HRMS (ESI) m/z calcd for C₂₆H₅₁ClO₅Si₂ [M+Na]⁺ 557.2861, found 557.2860.

((Z)-2-((3R,4S,5R)-5-((tert-butyldimethylsilyl)oxy)-4-(3-((tert -butyldimethylsilyl)oxy)propoxy)-3-(methoxymethoxy)-2-methyl enecyclohexy-lidene)ethyl)diphenylphosphine oxide (14). To a solution of diphenylphosphine (245 µL, 1.4 mmol) in THF (3 mL), n-BuLi (0.8 mL, 2.5 M solution in hexane) was added at -78 \square under nitrogen. And then stirred for 25 min before a solution of compound 13 (130 mg, 0.24 mmol) in THF (1 mL) was added. After stirring for another 3 h, the mixture was warmed to 0 \Box . Then water (1 mL) and H₂O₂ (1.5 mL, 30% in H₂O) were added successively. The mixture was stirred at 0 \square for another 1 h, and then quenched with saturated Na₂SO₃ solution. The whole mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous Na₂SO₄, filtered, and concentrated under vacuo. The residue was purified by silica gel column chromatography (hexane/EtOAc = 2:1) to give compound 14 (164 mg, 96%) as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 7.68 – 7.75 (m, 4H), 7.55 – 7.41 (m, 6H), 5.38 (q, J = 7.4 Hz, 1H), 5.28 (s, 1H), 5.01 (s, 1H), 4.67 – 4.61 (m, 2H), 4.20 (d, *J* = 6.5 Hz, 1H), 4.11 – 4.01 (m, 1H), 3.76 - 3.56 (m, 4H), 3.43 - 3.26 (m, 5H), 3.25 - 3.16 (m, 1H), 2.47 -2.36 (m, 1H), 2.17 (d, J = 13.0 Hz, 1H), 1.94 (bs, 1H), 1.82 -1.68 (m, 2H), 0.89 (s, 9H), 0.82 (s, 9H), 0.05 (s, 6H), 0.04 (s, 3H), 0.01 (s, 3H). ¹³C NMR (101 MHz, CDCl₃) & 140.1, 139.9, 132.0, 131.8, 131.7, 131.1, 131.0, 130. 9, 128.6, 128.5, 115.7, 94.9, 83.1, 77.72, 69.3, 68.2, 60.2, 55.6, 41.3, 33.5, 31.7, 31.0, 29.7, 25.9, 25.8, 18.3, 18.1, -4.7, -4.8, -5.3. HRMS (ESI) m/z calcd for $C_{38}H_{61}O_6Si_2P [M+Na]^+$ 723.3642, found 723.3649.

(1R,2R,3R,Z)-5-(2-((1R,7aR,E)-1-((R)-6-hydroxy-6-methyl heptan-2-yl)-7a-methyloctahydro-4H-inden-4-ylidene)ethyli dene)-2-(3-hydroxypropoxy)-4-methylenecyclohexane-1,3-diol (ED-71). To a cooled solution of compound 14 (90 mg, 0.128 mmol) in THF (1.5 mL) at -78 \square under nitrogen was added n-BuLi (130 uL, 2.5 M solution in hexane) dropwise, and then stirred for 40 min. A solution of compound 29 (36 mg, 0.09 mmol) in THF (0.5 mL) was added, and then stirred for another 4 h. The reaction was quenched with H₂O, and then extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous Na₂SO₄, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane/EtOAc = 70:1) to give the protected ED-71 (50 mg, 63%) as a colorless oil. To a stirred solution of the protected ED-71 (80 mg, 0.09 mmol) in methanol (4 mL), CSA (220 mg, 0.95 mmol) was added. The mixture was stirred at room temperature for 43 h. The reaction was quenched with saturated NaHCO₃ solution and extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous Na₂SO₄, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (DCM/MeOH = 20:1) to give compound ED-71 (36 mg, 80%) as a white foam. ¹H NMR (400 MHz, CDCl₃) δ 6.35 (d, J = 11.3 Hz, 1H), 6.04 (d, J = 11.3 Hz, 1H), 5.49 (t, J = 2.0 Hz, 1H), 5.07 (t, J = 2.0 Hz, 1H), 4.28 (dd, J = 22.4, 6.0 Hz, 2H), 3.97 – 3.67 (m, 5H), 3.25 (dd, J

= 9.0, 2.8) Hz, 1H), 2.86 − 2.73 (m, 1H), 2.53 (dd, J = 14.5, 3.9 Hz, 1H), 2.41 (d, J = 13.9 Hz, 1H), 2.00 − 1.77 (m, 5H), 1.67 (dd, J = 24.9, 10.3 Hz, 3H), 1.55 − 1.25 (m, 11H), 1.21 (s, 6H), 1.04 (dd, J = 19.2, 9.2 Hz, 1H), 0.93 (d, J = 6.4 Hz, 3H), 0.54 (s, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 144.31, 142.74, 132.29, 124.67, 117.21, 111.74, 85.29, 71.36, 71.07, 68.15, 66.45, 60.85, 56.49, 56.30, 45.81, 44.34, 40.42, 36.33, 36.05, 31.75, 29.64, 29.26, 29.12, 29.06, 27.60, 23.64, 22.29, 20.76, 18.77, 11.88. These spectral data are completely identical to that reported by Kubodera and Liu, respectively.

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A convergent method for the synthesis of ED-71 has been developed. Starting from the reported epoxide 5 which could be easily prepared for D-mannitol, ED-71 was synthesized in 11 linear steps with 17% overall yield.

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Declaration of interests



AThe authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

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