

Studies Towards the Total Synthesis of Methyl Isosartortuoate: The Synthesis of a Cyclic Precursor of the Diene Unit[†]

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The preparation of the key intermediate **4** of the methyl isosartortuoate is described. The macrocyclization was completed through an intramolecular [2,3]-Wittig ring contraction. The four necessary stereogenic carbons were established by Sharpless asymmetric AE and AD reaction.

Keywords methyl isosartortuoate, [2,3]-Wittig ring contraction

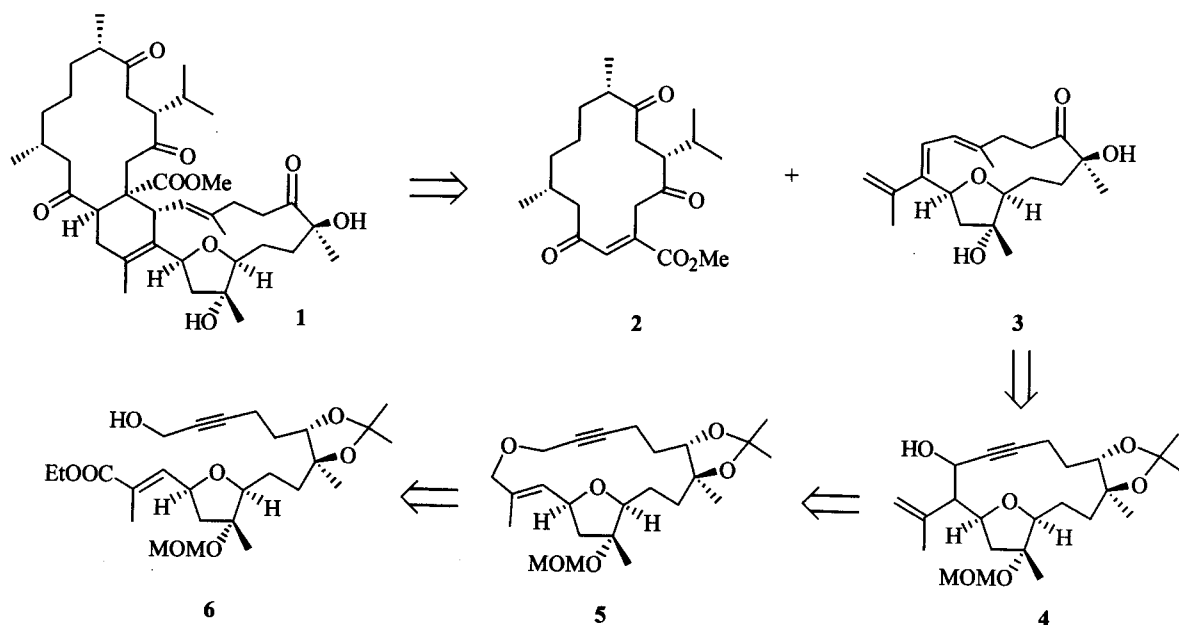
Methyl isosartortuoate **1** was a marine natural product with unique and complex architectures, which was first disclosed in 1986.¹ The presence of eleven stereogenic centers and the four rings heighten the challenge of synthesis for the target compound. Su and co-workers² have presented a provocative hypothesis to explain the biogenetic path of methyl isosartortuoate, involving an intermolecular Diels-Alder cycloaddition between the dienophile **2** and diene **3** (Scheme 1). This interesting possibility as well as

the unusual structure features of methyl isosartortuoate promoted us to initiate a research project aimed at its total synthesis. Herein we report the full results of the enantioselective synthesis of 14-membered carbocyclic nucleus **4**, in which all of the chiral centers in the diene unit **3** have been established.

Our retrosynthesis is shown in Scheme 1. Although carbocyclization has been successfully employed in several total syntheses,³ we chose to employ a [2,3]-Wittig ring contraction of the 17-membered cyclic propargyl allylic ether, leading to the 14-membered carbocyclic nucleus **4**.

The synthetic work first focused on the construction of the chiral tetrahydrofuran ring by using of twice Sharpless AE reactions and epoxide-opening process (Scheme 2). The commercially available geraniol was first converted into the secondary allylic alcohol **8** as a known procedure,⁴

Scheme 1



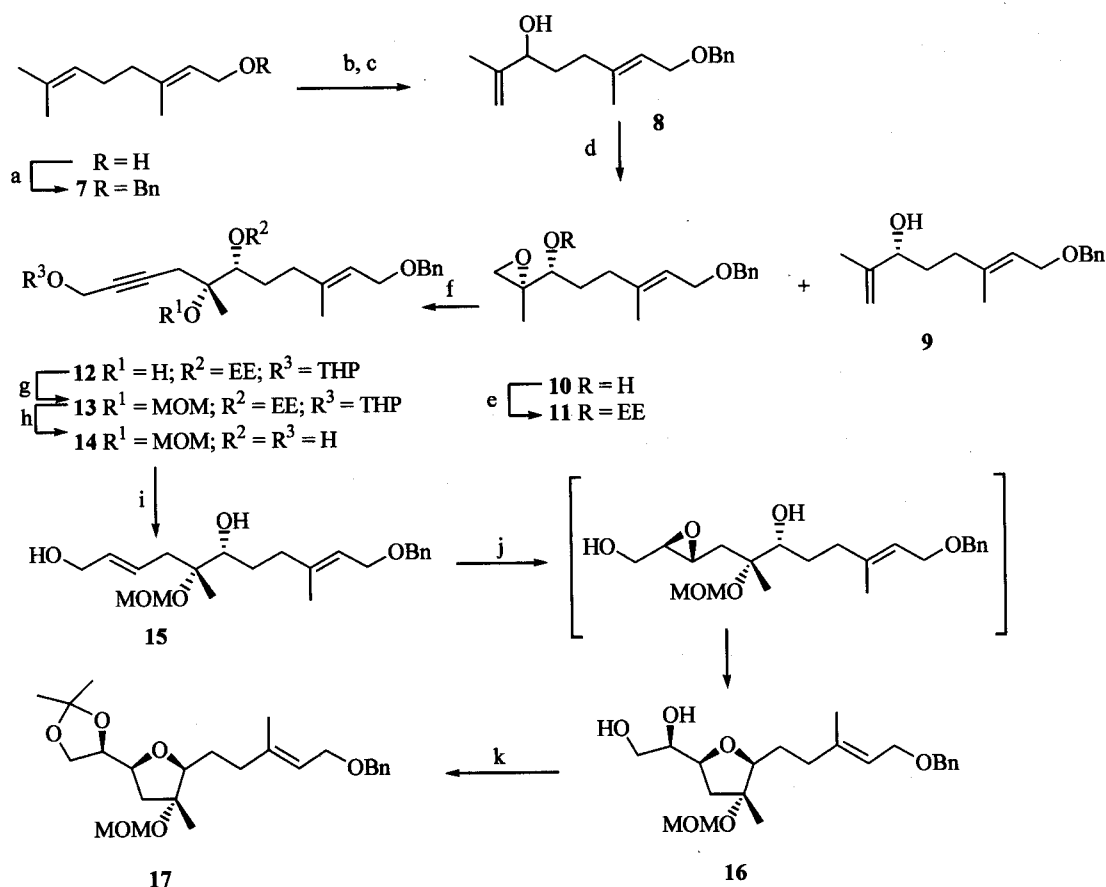
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[†]Dedicated to Professor ZHOU Wei-Shan on the occasion of his 80th birthday.

Scheme 2



Reagents and conditions: (a) NaH, BnCl, DMF. (b) MCPBA, CH_2Cl_2 , -20°C . (c) $\text{Al}(\text{OPr}^i)_3$, toluene, reflux. (d) 4ÅMS, *L*-(+)-DIPT, $\text{Ti}(\text{OPr}^i)_4$, TBHP, -20°C . (e) PPTS, ethyl vinyl ether. (f) *n*-BuLi, -78°C , $\text{THPOCH}_2\text{C}\equiv\text{CH}$, $\text{BF}_3\cdot\text{Et}_2\text{O}$. (g) MOM-Cl, $^i\text{Pr}_2\text{NEt}$, DMAP, CH_2Cl_2 . (h) PTS, CH_3OH . (i) LiAlH_4 , THF, reflux. (j) 4ÅMS, *D*-(-)DIPT, $\text{Ti}(\text{OPr}^i)_4$, TBHP, -20°C . (k) PPTS, dimethoxypropane, CH_2Cl_2 .

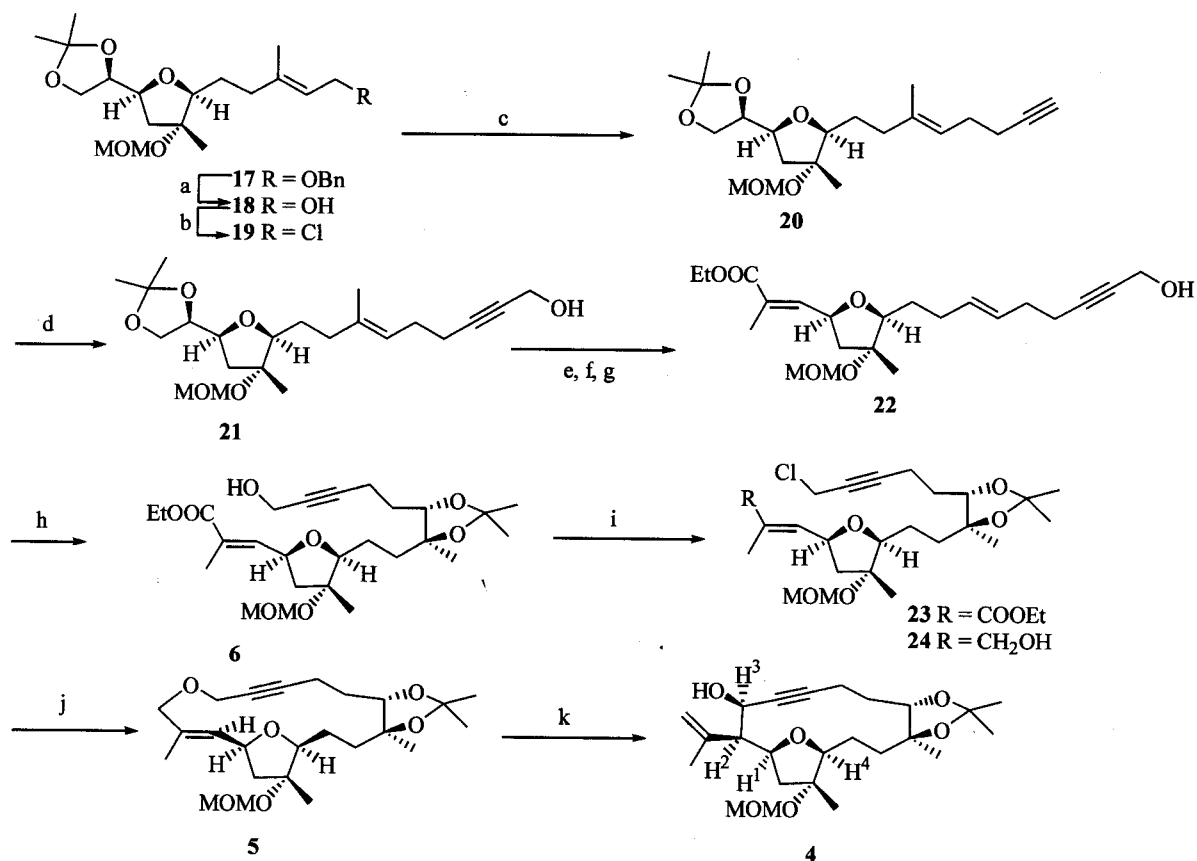
then Sharpless kinetic resolution⁵ of **8** provided an optically active terminal epoxy alcohol **10** in 40% yield and 94% *ee*. After protection of the hydroxyl group of **10** with ethyl vinyl ether, subsequent opening of the terminal epoxide with the lithium salt of propargyl-*O*-THP⁶ in the presence of $\text{BF}_3\cdot\text{Et}_2\text{O}$ at -78°C gave **12** in 61% yield. Protection of the resulting tertiary hydroxyl group with MOM ether, deprotection of the primary alcohol with accompanying a hydrolysis of the EE group and an E-selective reduction of the alkyne with LAH afforded the desired allylic alcohol **15**. Sharpless asymmetric epoxidation⁵ of **15** provided the epoxide, which rapidly underwent an intramolecular epoxy-opening⁷ in situ to furnish the necessary 2,5-disubstituted THF compound **16** in 84% yield.

With the chiral THF-ring compound in hand, the chain extension in both directions was explored. After the vicinal diol was temporarily protected with dimethoxypropane and the benzyl group was removed with lithium naphthalenide,⁸ the resulting allylic alcohol was treated with 2 equiv. of triphosgene⁹ to afford the chloride **19** in 80% yield. This chloride **19** was homologated to the acetylene **20** in 70% yield via coupling with TIPS-protected

propargylmagnesium bromide¹⁰ in the presence of CuI followed by fluoride cleavage of the silyl protecting group. Treatment of the acetylene **20** with *n*-BuLi at -78°C , followed by addition of paraformaldehyde yielded the alcohol **21** in 88% yield. After the right side chain was installed, the acetonide was removed smoothly with $\text{HOAc}:\text{H}_2\text{O}^5$ (4:1, *V*:*V*). Oxidative cleavage of the resulting diol using silica gel-supported metaperiodate¹¹ produced an aldehyde without purification, which underwent olefination with carbethoxylidetriphenylphosphorane to give the unsaturated ester **22** as shown in Scheme 3.

Sharpless asymmetric dihydroxylation¹² of **22** to establish the desired stereochemistry (according to the empirical rule) and protection of the resultant diol by dimethoxypropane gave the acetonide **6** in 78% yield for two steps (ratio 9:1). After the propargylic alcohol of **6** was converted to the chloride **23** with $\text{MsCl}/\text{LiCl}/2,6$ -lutidine, another terminal ester was reduced with DIBALH to provide the compound **24**. Treatment of **24** with NaH and Bu_4NI in refluxing toluene (slow addition) gave the macrocyclic allylic propargylic ether **5** in 33% yield, while the cyclization of **24** with EtMgBr as base in THF-HMPA gave the same yield.¹⁰

Scheme 3



Reagents and conditions: (a) lithium naphthalenide, $-20\text{ }^{\circ}\text{C}$. (b) Triphosgene, Et₃N, $-78\text{ }^{\circ}\text{C}$. (c) CuI, 3-(triisopropylsilyl)-2-propynylmagnesium bromide, THF, $-78\text{--}20\text{ }^{\circ}\text{C}$; TBAF. (d) *n*-BuLi, (CH₂O)_{*n*}. (e) HOAc:H₂O (4:1). (f) NaIO₄. (g) Ph₃C=C(CH₃)CO₂Et, toluene. (h) K₂CO₃, K₃Fe(CN)₆, NaHCO₃, K₂OsO₂(OH)₄, (DHQ)₂PHAL, CH₃SO₂NH₂, H₂O/*t*-BuOH (1:1), $0\text{ }^{\circ}\text{C}$; PPTS, dimethoxypropane. (i) MsCl, LiCl, 2,6-lutidine; DIBAL-H. (j) NaH, 18-C-6, (*n*-Bu)₄NI, toluene. (k) *n*-BuLi, pentane:THF (1:1).

Finally, intramolecular [2,3]-Wittig ring constriction was executed. Treatment of **5** with *n*-BuLi at $-78\text{ }^{\circ}\text{C}$ gave **4** with near quantitative yield.¹³ The result showed that the rearrangement was not affected by the presence of THF ring and exhibited an excellent stereoselectivity. The intense NOE correlation was observed between H¹ (δ 4.43–4.37) and H² (δ 2.73), H² (δ 2.73) and H³ (δ 4.49), H¹ (δ 4.43–4.37) and H⁴ (δ 3.72), indicating that the configuration of the forming stereogenic carbon was erythro (*cis*).

Further synthetic studies directed towards the cembra-noid diene **3** are now undergoing in our laboratory.

Experimental

General methods

All reactions were carried out under argon in oven-dried glassware using standard gastight syringes, cannulas and septa. Solvents and reagents were purified and dried by standard methods prior to use. Optical rotations were measured at room temperature. IR spectra were recorded on an FT-IR instrument. ¹H NMR spectra were recorded at

300 MHz and are reported in ppm (δ) downfield relative to TMS as internal standard. Flash column chromatography was performed on silica gel (10–40 μm) using a mixture of petroleum ether (60–90 $^{\circ}\text{C}$) and acetate as the eluant.

Synthesis of **8**

To an ice-cooled and stirred solution of NaH (16 g, 0.4 mol, 60% content) in DMF (300 mL) was added geraniol (30.8 g, 0.2 mol, 34.65 mL) dropwise for 30 min and stirred for another 1.5 h at that temperature, and then 34.4 mL (0.3 mol) of BnCl was added dropwise during 40 min. the reaction mixture was slowly warmed to room temperature and stirred overnight. The reaction was quenched with saturated NH₄Cl and extracted with petroleum. The combined organic layer was washed with water and brine, dried and filtered. The solvent was removed under reduced pressure, and the residue was directly used for the next step without further purification. ¹H NMR (CCl₄, 60 MHz) δ : 7.3 (m, 5H), 5.5–5.0 (m, 2H), 4.5 (s, 2H), 4.0 (d, $J = 6.5\text{ Hz}$, 2H), 2.1 (m, 4H), 1.7 (s, 6H).

To the solution of geraniol benzyl ether (crude prod-

uct) and NaOAc (21 g, 0.26 mol) in CH_2Cl_2 (350 mL) cooled to $-20\text{ }^\circ\text{C}$ was added 3-chloro-peroxybenzoic acid (63 g, 84.7 mol, 72.5% content) portionwise maintaining the inner temperature at $-20\text{ }^\circ\text{C}$. After completion addition the resulting mixture was stirred at that temperature for 1.5 h. The reaction was quenched with saturated $\text{Na}_2\text{S}_2\text{O}_3$ and 30% NaOH, and then extracted with ether. The combined organic layer was washed with water and brine, dried. Filtration and concentration provided crude product 68 g without further purification. $^1\text{H NMR}$ (CCl_4 , 60 MHz) δ : 7.3 (m, 5H), 5.4 (t, $J = 6.5\text{ Hz}$, 1H), 4.5 (s, 2H), 4.0 (d, $J = 6.5\text{ Hz}$, 2H), 2.7–2.1 (m, 4H), 1.7 (s, 3H), 1.3 (s, 3H); IR (film) ν : 2926, 1670, 1454, 1378, 1070, 737, 698 cm^{-1} ; EIMS m/z (%): 261 ($\text{M}^+ + 1$, 1.72), 260 (M^+ , 1.72), 259 ($\text{M}^+ - 1$, 3.20).

A solution of above crude product and aluminum isopropoxide (68 g, 0.33 mol) in dry toluene (100 mL) was refluxed and stirred for 8 h. After cooling to room temperature, ether was added to the resulting mixture and then water was added dropwise. The precipitated white solid was filtered off and the solvent was removed under reduced pressure. The residue was chromatographed with petroleum-ethyl acetate (7:1, $V:V$) to give the product **8** (40 g, 77% three steps). $^1\text{H NMR}$ (CCl_4 , 60 MHz) δ : 7.3 (m, 5H), 5.4 (t, $J = 6.5\text{ Hz}$, 1H), 5.0–4.8 (m, 2H), 4.5 (s, 2H), 4.0 (d, $J = 6.5\text{ Hz}$, 2H), 2.4–1.9 (m, 4H), 1.80 (s, 3H), 1.7 (s, 3H); IR (film) ν : 3429, 2942, 1652, 1454, 1070 cm^{-1} ; EIMS m/z (%): 261 ($\text{M}^+ + 1$, 0.53), 260 (M^+ , 1.30), 243 ($\text{M}^+ - \text{OH}$, 1.20).

Synthesis of **10**

An oven-dried 500 mL three neck round flask equipped with a magnetic stirbar, pressure equalizing addition funnel, thermometer, argon inlet, and bubbler was charged with 1.8 g of 4Å powered, activated molecular sieves and **8** (9.0 g, 34.5 mmol) in 60 mL of dry CH_2Cl_2 . The flask was cooled to $-20\text{ }^\circ\text{C}$. *L*-(+)-Diethyl tartrate (1.1 mL, 5.2 mmol) and $\text{Ti}(\text{O}-i\text{-Pr})_4$ (1 mL, 3.4 mmol via syringe) was added sequentially with stirring. After the reaction mixture was stirred at $-20\text{ }^\circ\text{C}$ for 30 min, TBHP (3 mL, 5.75 N, 17.25 mmol) was added through the addition funnel at the moderate. The mixture was stirred at $-20\text{ }^\circ\text{C}$ for 4 h. The freshly prepared solution of ferrous sulfate heptahydrate and tartaric acid was added to the reaction mixture. After the resulting mixture was stirred for 30 min, the organic layer was separated and the aqueous layer was extracted with ether. The combined organic layers was treated with 30% NaOH (W/V) in saturated brine. Following transfer to a separated funnel and dilution with water, the phases were separated and the aqueous layer was extracted with ether. The combined organic layers were dried over sodium sulfate, filtered, and concentrated. The residue was chromatographed ($P:E =$

5:1, $V:V$) to give the product **10** (4.45 g, 47%). $[\alpha]_D^{20} + 2.78$ ($c\ 1.0$, CHCl_3); $^1\text{H NMR}$ (CDCl_3 , 300 MHz) δ : 7.3 (m, 5H), 5.44 (t, $J = 6.8\text{ Hz}$, 1H), 4.5 (s, 2H), 4.03 (d, $J = 6.7\text{ Hz}$, 2H), 3.61 (dd, $J = 2.5, 9\text{ Hz}$, 1H), 2.88 (d, $J = 4.7\text{ Hz}$, 1H), 2.60 (d, $J = 4.7\text{ Hz}$, 1H), 2.27–2.13 (m, 2H), 1.8–1.47 (m, 2H), 1.66 (s, 3H), 1.33 (s, 3H); HPLC: *ee* 94%; IR (film) ν : 3448, 2924, 1739, 1669, 1454, 1371, 1089, 1067, 699 cm^{-1} ; EIMS m/z (%): 277 ($\text{M}^+ + 1$, 9.82), 259 ($\text{M}^+ - \text{OH}$, 0.93). Anal. calcd for $\text{C}_{17}\text{H}_{24}\text{O}_3$: C 73.87, H 8.76; found C 73.71, H 8.63.

Synthesis of **11**

To the solution of **10** (1.813 g, 6.93 mmol) in 15 mL of dry CH_2Cl_2 was added vinyl ethyl ether (1.26 mL, 13.14 mmol) and 54 mg of PPTS. The reaction mixture was stirred for overnight and quenched with saturated Na_2CO_3 . The mixture was extracted with ether. The combined organic layers was dried over sodium sulfate, filtered, and concentrated. The residue was chromatographed ($P:E = 5:1$, $V:V$) to give the product **11** (2.314 g, 98.2%). $^1\text{H NMR}$ (CDCl_3 , 300 MHz) δ : 7.3 (m, 5H), 5.43 (m, 1H), 4.82–4.67 ($2 \times q$, $J = 5.4\text{ Hz}$, 1H), 4.5 (s, 2H), 4.03 (d, $J = 6.7\text{ Hz}$, 2H), 4.01–3.45 (m, 2H), 3.3–3.0 ($2 \times q$, $J = 5.1\text{ Hz}$, 1H), 2.77 (m, 1H), 2.62 (m, 1H), 2.3–1.67 (m, 4H), 1.66 (s, 3H), 1.36 (s, 3H), 1.29 (s, 3H), 1.2 (t, $J = 8.0\text{ Hz}$, 3H); IR (film) ν : 2980, 1753, 1671, 1454, 1376, 1274, 1128, 1060, 738 cm^{-1} ; FABMS m/z (%): 347 ($\text{M}^+ - 1$, 6.00). Anal. calcd for $\text{C}_{21}\text{H}_{32}\text{O}_4$: C 72.38, H 9.55; found C 72.44, H 9.40.

Synthesis of **12**

To the solution of $\text{THPOCH}_2\text{C}\equiv\text{CH}$ (14 g, 0.1 mol) and **11** (7 g, 0.02 mol) in dried THF (130 mL) cooled to $-78\text{ }^\circ\text{C}$ was added 55.5 mL (1.8 mol/L, 0.1 mol) of *n*-BuLi for 15 min and stirred for 1.5 h, and then added $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (12.6 mL). The reaction mixture was stirred for 4 h at -78 – $-40\text{ }^\circ\text{C}$. The reaction was quenched with saturated NH_4Cl at $0\text{ }^\circ\text{C}$ and extracted with ether. The combined layer was washed with water and brine, dried over anhydrous Na_2SO_4 . The solvent was removed under vacuum and the residue was chromatographed with petroleum-ethyl acetate (10:1–7:1) to give **12** (6 g, 61%). $^1\text{H NMR}$ (CDCl_3 , 300 MHz) δ : 7.29 (m, 5H), 5.43 (t, $J = 7.5\text{ Hz}$, 1H), 5.08 (m, 1H), 4.8 (m, 1H), 4.5 (s, 2H), 4.27–4.22 (m, 2H), 4.03 (d, $J = 6.7\text{ Hz}$, 2H), 3.83–3.44 (m, 5H), 2.36–2.04 (m, 4H), 2.3–1.67 (m, 11H), 1.35 (m, 3H), 1.3 (m, 3H), 1.2 (m, 3H); IR (film) ν : 3426, 2939, 1722, 1669, 1454, 1378, 1118, 1055, 1024 cm^{-1} ; FABMS m/z (%): 511 ($\text{M}^+ + \text{Na}$, 4.00).

Synthesis of 13

To the solution of **12** (4 g, 8.2 mmol) and 8.49 mL (49 mmol) of the *i*-Pr₂NEt and DMAP (100 mg, 0.82 mmol) was added 2.46 mL (32 mmol) of MOMCl at 0 °C. The reaction mixture was brought to room temperature and stirred for a further two days, and then extracted with ether. The combined organic layer was washed with 1 N HCl and saturated NaHCO₃ and brine, dried over anhydrous Na₂SO₄. Filtration, concentration and flash chromatography provide the product **13** (6.8 g, 96%). ¹H NMR (CDCl₃, 300 MHz) δ: 7.3 (m, 5H), 5.44 (m, 1H), 4.76 (m, 4H), 4.5 (s, 2H), 4.28–4.15 (m, 2H), 4.05 (d, *J* = 6.7 Hz, 2H), 4.0–3.4 (m, 5H), 3.5 (s, 3H), 2.37–2.19 (m, 8H), 2.2 (s, 2H), 1.76–1.51 (m, 4H), 1.35 (s, 3H), 1.32 (s, 3H), 1.2 (m, 3H); IR (film) ν: 2940, 1670, 1454, 1378, 1132, 1026 cm⁻¹; EIMS *m/z* (%): 533 (M⁺ + 1). Anal. calcd for C₃₁H₄₈O₇: C 69.89, H 9.08; found C 69.96, H 9.28.

Synthesis of 14

The solution of **13** (6.6 g, 12.4 mmol) in 150 mL CH₃OH was added 150 mg of PTS and stirred for 15 min. The reaction mixture was quenched with saturated Na₂CO₃ (25 mL) and extracted with ethyl acetate. The combined organic layer was washed with water and brine, dried over anhydrous Na₂SO₄. After the removal of solvent the residue was chromatographed with petroleum-ethyl acetate (2:1, *V:V*) to give 4.3 g (92%) of the title compound **14**. ¹H NMR (CDCl₃, 300 MHz) δ: 7.3 (m, 5H), 5.46 (t, *J* = 6.5 Hz, 1H), 4.75 (AB, *J* = 7.5 Hz, 2H), 4.5 (s, 2H), 4.15 (s, 2H), 4.03 (d, *J* = 7.8 Hz, 2H), 3.62 (dd, *J* = 1.4, 10.4 Hz, 1H), 3.39 (s, 3H), 2.6 (AB, *J* = 18 Hz, 2H), 2.81 (br., 1H), 2.3–2.1 (m, 2H), 1.76–1.42 (m, 2H), 1.6 (s, 3H), 1.3 (s, 3H); IR (film) ν: 3421, 2931, 2225, 1668, 0454, 1380, 1139, 1029, 699 cm⁻¹.

Synthesis of 15

To the solution of **14** (2.2 g, 5.8 mmol) in 10 mL THF was added LiAlH₄ portionwise at 0 °C. After the complete addition, the reaction mixture was warmed to reflux until all the starting material was consumed (4 h, TLC analysis). After the dilution of ether, the reaction mixture was stirred vigorously and quenched with water, which was added dropwise for 5 h, and then precipitated white solid was filtered off. The solvent was removed under vacuum, and the residue was chromatographed on silica gel (*P:E* = 1:1, *V:V*) to give 1.92 g (87%) of **15**. ¹H NMR (CDCl₃, 300 MHz) δ: 7.3 (m, 5H), 5.70 (m, 2H), 5.44 (t, *J* = 7.1 Hz, 1H), 4.75 (AB, *J* = 7.5 Hz, 2H), 4.5 (s, 2H), 4.09–4.0 (m, 2H), 3.38 (s, 3H), 2.54–2.03 (m, 4H), 1.66 (s, 3H), 1.54–1.41 (m, 2H), 1.15 (s, 3H); IR (film) ν: 3420, 2930, 1724, 1669,

1454, 1377, 1141, 1089, 1031, 739 cm⁻¹.**Synthesis of 16**

To the suspension of molecular sieves 4Å powder (1.13 g) in freshly distilled CH₂Cl₂ (105 mL) was added Ti(OPr^{*i*})₄ (5.0 mL, 16.9 mmol) and *D*-(-)-DIPT (4.0 mL, 18.8 mmol) at -20 °C. A solution of **15** (4.687 g, 11.9 mmol) in CH₂Cl₂ (20 mL) was added. After 20 min, *tert*-butyl hydroperoxide in CH₂Cl₂ (6.66 N, 6 mL, 44 mmol) was added dropwise at -20 °C over 30 min, and the mixture was stirred overnight. Aqueous tartaric acid was added, and the mixture stirred at room temperature for 1 h. The mixture was diluted with EtOAc, and the organic phase was separated. The aqueous phase was extracted with EtOAc. The combined organic layers were treated with 1 N NaOH solution. After stirring for 1 h, two phases was separated, the aqueous phase was extracted with EtOAc. The combined organic layers was washed with brine, dried over sodium sulfate, filtered, and concentrated. The residue was chromatographed on silica gel (*P:E* = 1:1, *V:V*) to give **16** (4.105 g, 84%). ¹H NMR (CDCl₃, 300 MHz) δ: 7.3 (m, 5H), 5.43 (t, *J* = 3.2 Hz, 1H), 4.75 (AB, *J* = 7.6 Hz, 2H), 4.5 (s, 2H), 4.06–4.0 (m, 2H), 3.8–3.6 (m, 3H), 3.37 (s, 3H), 2.22–1.72 (m, 4H), 1.65 (s, 3H), 1.39–1.34 (m, 2H), 1.25 (s, 3H); IR (film) ν: 3423, 2937, 1670, 1454, 1378, 1145, 1036, 739 cm⁻¹. Anal. calcd for C₂₂H₃₄O₆: C 69.98, H 8.68; found C 69.65, H 8.87.

Synthesis of 17

To the solution of **16** (1 g, 2.54 mmol) in 10 mL CH₂Cl₂ was added 3 mL of dimethoxypropane and 50 mg of PPTS at room temperature. After the total consumption of the starting material, the reaction mixture was quenched with saturated Na₂CO₃ and extracted with ether, dried over anhydrous Na₂SO₄. After the solvent was removed under reduced pressure, the residue was chromatographed with petroleum-ethyl acetate (3:1) to give 1.1 g (100%) of the compound **17**. [α]_D²⁰ - 15.9 (*c* 1.3, CHCl₃); ¹H NMR (CDCl₃, 300 MHz) δ: 7.31 (m, 5H), 5.41 (t, *J* = 6.7 Hz, 1H), 4.74 (AB, *J* = 7.7 Hz, 2H), 4.50 (s, 2H), 4.03 (m, 3H), 3.77 (m, 2H), 3.37 (s, 3H), 2.22 (m, 2H), 2.06 (m, 2H), 1.73 (m, 2H), 1.70 (s, 3H), 1.43 (s, 3H), 1.37 (s, 3H), 1.28 (s, 3H); IR (film) ν: 2985, 1746, 1670, 1454, 1380, 1212, 1145, 1037, 850, 699 cm⁻¹; EIMS *m/z* (%): 419 (M⁺ - CH₃, 0.60).

Synthesis of 18

To the solution of 1.142 g (2.63 mmol) of **17** in THF was added 14 mL (0.57 N) of lithium-naphthalene in THF at -30 °C. The reaction mixture was stirred at that temperature until the total starting material was consumed.

Pouring into NH_4Cl quenched the reaction. The organic layer was separated, and the water layer was extracted with ether. The combined organic layer was washed with water and brine, dried over Na_2SO_4 , and filtered. After removal of the solvent, the residue was chromatographed with petroleum-ethyl acetate (4:1—1:1, $V:V$) to give 0.858 g (98%) of the compound **18**. $[\alpha]_D^{20} - 17.7$ (c 1.7, CHCl_3); $^1\text{H NMR}$ (CDCl_3 , 300 MHz) δ : 5.42 (br., 1H), 4.72 (AB, $J = 7.0$ Hz, 2H), 4.14—3.69 (m, 7H), 3.37 (s, 3H), 2.1—1.9 (m, 4H), 1.63 (s, 3H), 1.47 (m, 2H), 1.40 (s, 3H), 1.34 (s, 3H), 1.24 (s, 3H); IR (film) ν : 3446, 2986, 1668, 1454, 1372, 1145, 1037, 849 cm^{-1} ; EIMS m/z (%): 329 ($\text{M}^+ - \text{CH}_3$, 0.51).

Synthesis of 19

To the solution of the alcohol **18** (50 mg, 0.145 mmol) and 0.13 mL Et_3N in 3 mL CH_2Cl_2 was added Triphosgene (41 mg, 0.17 mmol). The reaction mixture was warmed to room temperature slowly for 30 min. The reaction mixture was quenched with NH_4Cl . The organic layer was separated; the water layer was extracted with ether. The combined organic layer was washed with 1 N HCl , saturated NaHCO_3 and brine, dried over Na_2SO_4 , and filtered. The solvent was removed under reduced pressure, and the residue was chromatographed ($P:E = 5:1$, $V:V$) to give 44 mg (83%) of the chloride **19**. $^1\text{H NMR}$ (CDCl_3 , 300 MHz) δ : 5.47 (t, $J = 8.0$ Hz, 1H), 4.76 (AB, $J = 7.0$ Hz, 2H), 4.11—3.68 (m, 7H), 3.37 (s, 3H), 2.33—2.00 (m, 4H), 1.72 (s, 3H), 1.6 (m, 2H), 1.41 (s, 3H), 1.35 (s, 3H), 1.27 (s, 3H).

Synthesis of 20

To a slurry of 1.32 g (7 mmol) of CuI in 20 mL of THF at -78°C was added 3-(triisopropylsilyl)-2-propynylmagnesium bromide dropwise. The resulting slurry was stirred at -78°C for 30 min, and the mixture was transferred to a -20°C bath. After 15 min, 1.26 g (3.5 mmol) of chloride **19** in 12 mL of THF were added. The mixture was stirred for 3 h at -20°C , then 10 mL of saturated aqueous NH_4Cl was added, the mixture was allowed to reach room temperature, and ether was added. The organic layer was washed with 30% NH_4OH until the washings were clear, the blue aqueous layers were extracted with ether, and the combined extracts were washed with water and dried over Na_2SO_4 . Removal of the solvent left oil, which was dissolved in 10 mL of THF and treated with 8 mL of tetra-*n*-butylammonium fluoride (1 mol/L). The dark solution was stirred overnight and then poured into 50 mL of water. The solution was extracted three times with ether, and the combined extracts were washed with water and dried with anhydrous Na_2SO_4 . Removal of the solvent left oil, which was purified by column chromatography on silica gel ($P:E = 9:1$, $V:V$), providing 1.01 g (80%) of

acetylene **20**. $[\alpha]_D^{20} - 17.7$ (c 1.7, CHCl_3); $^1\text{H NMR}$ (CDCl_3 , 300 MHz) δ : 5.20 (br., 1H), 4.72 (AB, $J = 7.0$ Hz, 2H), 4.09—3.71 (m, 5H), 3.36 (s, 3H), 2.4—1.94 (m, 3H), 2.2 (s, 3H), 1.77 (s, 3H), 1.56 (s, 3H), 1.94—1.42 (m, 7H), 1.40 (s, 2H), 1.32 (s, 3H), 1.25 (s, 3H); IR (film) ν : 2986, 2292, 1454, 1372, 1255, 1145, 1037, 920, 850, 633 cm^{-1} ; EIMS m/z (%): 351 ($\text{M}^+ - \text{CH}_3$, 3.42).

Synthesis of 21

To the solution of acetylene **20** (110 mg, 0.3 mmol) in 3 mL of THF at -78°C was added *n*-BuLi. The resulting dark solution was stirred at -78°C for 1 h, and then bubbled into formaldehyde until the total starting material consumed. The reaction mixture was warmed to reach room temperature. After 2.5 h later, the reaction mixture was quenched with 5 mL of saturated NH_4Cl , and extracted with ethyl acetate. The extracts were dried over Na_2SO_4 , and filtered and the solvent was removed. The resulting oil was purified by column chromatography on silica gel (petroleum:ethyl acetate = 4:1, $V:V$), affording 105 mg (88%) of alcohol **21**. $[\alpha]_D^{20} - 15$ (c 2.4, CHCl_3); $^1\text{H NMR}$ (CDCl_3 , 300 MHz) δ : 5.21 (br., 1H), 4.73 (AB, $J = 7.3$ Hz, 2H), 4.23 (s, 2H), 4.13—3.72 (m, 5H), 3.37 (s, 3H), 2.23 (s, 3H), 2.20—1.95 (m, 3H), 1.69 (s, 3H), 1.80—1.50 (m, 7H), 1.44 (s, 3H), 1.37 (s, 3H), 1.18 (s, 3H); IR (film) ν : 3460, 2985, 1452, 1372, 1256, 1144, 1036, 921, 849 cm^{-1} ; EIMS m/z (%): 381 ($\text{M}^+ - \text{CH}_3$, 0.65).

Synthesis of 22

To the solution of 9 mL of $\text{HOAc}:\text{H}_2\text{O}$ (4:1) was added **21** (1.336 mg, 3.37 mmol). The reaction mixture was stirred at 55°C . After 2 h later, the reaction was quenched with 30% ammonia and extracted with EtOAc . The organic layer was dried over sodium sulfated, filtered, and concentrated to give the diol. The crude product was dissolved in 100 mL of CH_2Cl_2 , and then added the NaIO_4 absorbed on silica gel. The reaction mixture was stirred over 30 min and filtered. The sorbent was washed with CH_2Cl_2 . The combined organic layers were dried over sodium sulfate, filtered, and concentrated. The residue was dissolved in 40 mL of dry toluene. The solution was added the 2-(triphenylphosphanylidene)-propionic acid ethyl ester (1.856 g). The reaction mixture was stirred over 6 h, and then removed toluene under reduced pressure. The residue was chromatographed ($P:E = 5:1$, $V:V$) to give **22** (0.937 g, 68.1%). $^1\text{H NMR}$ (CDCl_3 , 300 MHz) δ : 6.69 (d, $J = 7.8$ Hz, 1H), 5.12 (br., 1H), 4.85—4.67 (m, 3H), 4.20 (m, 4H), 3.85 (m, 1H), 3.40 (s, 3H), 2.40 (q, $J = 6.8$ Hz, 1H), 2.19 (s, 3H), 1.83 (s, 3H), 2.2—1.3 (m, 9H), 1.56 (s, 7H), 1.27 (m, 3H); IR (film) ν : 3449, 2935, 1721, 1449, 1251, 1141, 1034, 747 cm^{-1} . Anal. calcd for $\text{C}_{23}\text{H}_{36}\text{O}_6$: C 67.72, H 8.88; found C 67.38, H 8.74.

Synthesis of 6

A solution of $K_3Fe(CN)_6$ (521 mg, 1.58 mmol), $NaHCO_3$ (112 mg, 1.35 mmol), K_2CO_3 (182 mg, 1.32 mmol) and $CH_3SO_2NH_2$ (42 mg, 0.5 mmol) in 8 mL of *t*-BuOH/ H_2O (1:1) was added $K_2OsO_2(OH)_4$ (4 mg, 0.01 mmol) and $(DHQ)_2PHAL$ (17 mg, 0.02 mmol). The reaction mixture was stirred at 0 °C over 0.5 h, and then added 161 mg of **24** in 3 mL of *t*-BuOH. After 8 h later, the reaction was quenched with Na_2SO_3 . The reaction mixture was extracted with EtOAc, dried over Na_2SO_4 , filtered, and concentrated. The residue was dissolved in 10 mL CH_2Cl_2 . To the solution was added 5 mL of dimethoxypropane and PPTS (cat). The reaction mixture was stirred overnight, and then the reaction was quenched with saturated Na_2CO_3 , extracted with ether, dried and concentrated. The residue was chromatographed (P:E = 3:1, V:V) to give **6** (137 mg, 72%). $[\alpha]_D^{20} - 25.2$ (*c* 1.0, CH_3OH); 1H NMR ($CDCl_3$, 300 MHz) δ : 6.75 (d, *J* = 8.0 Hz, 1H), 4.77 (m, 2H), 4.24 (s, 2H), 4.19 (q, *J* = 7.1 Hz, 2H), 3.95 (m, 1H), 3.82 (m, 1H), 3.39 (s, 3H), 2.42 (m, 2H), 2.17 (m, 1H), 2.05 (m, 1H), 1.85 (s, 3H), 1.42 (s, 3H), 1.32 (s, 3H), 1.29 (m, 6H), 1.25 (s, 3H), 1.09 (s, 3H); IR (film) ν : 3450, 2926, 1713, 1459, 1251, 1141, 1038, 748 cm^{-1} ; EIMS *m/z* (%): 467 ($M^+ - CH_3$, 0.81).

Synthesis of 23

A solution of anhydrous LiCl (100 mg, 2.43 mmol) in 4 mL of DMF was cooled to 0 °C, and added 50 mg of allylic alcohol **6** in 0.3 mL of 2,6-lutidine. After 20 min, 0.2 mL of methanesulfonyl chloride was added. The resulting solution was stirred overnight. Water and ether was added. The layers were separated, and the organic layer was washed with water. The combined aqueous layers were extracted with ether, the extracts was washed with water and brine, dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure to yield 47 mg of chloride **23**. 1H NMR ($CDCl_3$, 300 MHz) δ : 6.6 (d, *J* = 8.0 Hz, 1H), 4.79 (m, 3H), 4.21 (q, *J* = 7.0 Hz, 2H), 4.14 (s, 2H), 3.85 (m, 2H), 3.40 (s, 3H), 2.5—2.3 (m, 3H), 1.86 (s, 3H), 1.42 (s, 3H), 1.32 (s, 3H), 1.6—1.2 (m, 7H), 1.25 (s, 3H), 0.88 (s, 3H); IR (film) ν : 2983, 2237, 1713, 1655, 1448, 1376, 1250, 1143, 1041, 692 cm^{-1} .

Synthesis of 24

To a solution of 2 mg of chloride **23** in 1 mL of CH_2Cl_2 was added 0.05 mL DIBAL-H (1.0 mol/L) in hexanes) at -78 °C. After consumption of the ester, the reaction was quenched with aqueous Na_2SO_4 and stirred vigorously for 2 h. The precipitated white solid was filtered off. After removal of the solvent, the residue was purified

on column chromatography silica gel to give 2 mg of chloro alcohol **24**. 1H NMR ($CDCl_3$, 300 MHz) δ : 5.46 (m, 1H), 4.80—3.53 (m, 3H), 4.14 (s, 2H), 4.02 (s, 2H), 3.90—3.71 (m, 2H), 3.40 (s, 3H), 2.45—1.97 (m, 3H), 1.69 (s, 3H), 1.41 (s, 3H), 1.33 (s, 3H), 1.25 (s, 6H), 1.82—1.07 (m, 7H); IR (film) ν : 3362, 2924, 1459, 1376, 1263, 1039, 919, 691 cm^{-1} .

Synthesis of 5

A mixture of 106 mg (2.65 mmol) of sodium hydride, 288 mg (1.07 mmol) of 18-crown-6, 7 mg of tetrabutylammonium iodide, and 60 mL toluene (freshly distilled from calcium hydride) was heated to reflux. To the mixture was added 53 mg (0.112 mmol) of chloro alcohol in 20 mL of toluene by syringe pump over 4 h. After the addition, the mixture was heated for 6 h until all the chloro alcohol **24** was consumed. The mixture was cooled to room temperature and filtered through a pad of silica gel. The solvent was removed, and the residue was chromatographed on Et_3N -deactivated silica gel (P:E = 5:1, V:V) to give 20 mg (40.9%) of macrocyclic ether **5**. 1H NMR ($CDCl_3$, 300 MHz) δ : 5.73 (d, *J* = 0.7 Hz, 1H), 4.96 (dd, *J* = 7, 16 Hz, 1H), 4.78 (AB, *J* = 7.5 Hz, 2H), 4.16—3.9 (m, 6H), 3.41 (s, 3H), 2.58—2.42 (m, 3H), 1.93—1.86 (m, 1H), 1.79—1.72 (m, 3H), 1.60 (s, 3H), 1.55 (m, 3H), 1.44 (s, 3H), 1.33 (s, 3H), 1.32 (s, 3H), 1.26—1.15 (m, 3H), 1.12 (s, 3H); IR (film) ν : 2930, 2232, 1725, 1376, 1085, 1067, 960 cm^{-1} ; EIMS *m/z* (%): 407 ($M - CH_3$, 1.96); HRMS calcd for $C_{24}H_{38}O_6$ 422.2669, found 422.2652.

Synthesis of 4

To a solution of 27 mg (0.062 mmol) of macrocyclic allylic propargylic ether **5** in 8 mL of THF-pentane (1:1, V:V) was added 0.6 mL (2 N, 1.2 mmol) of *n*-BuLi at -78 °C. The reaction was quenched with 10 mL of saturated ammonium chloride after 1 h and allowed to room temperature. The mixture was extracted with ether. The combined extracts was washed with water and brine, dried over anhydrous Na_2SO_4 , and filtered. The solvent was removed under reduced pressure, and the residue was chromatographed on Et_3N -deactivated silica gel (P:E = 3:1, V:V) to give 27 mg (100%) of macrocyclic ether **4**. $[\alpha]_D^{20} - 33$ (*c* 0.35, $CHCl_3$); 1H NMR ($CDCl_3$, 300 MHz) δ : 5.03 (s, 1H), 4.94 (s, 1H), 4.72 (AB, *J* = 7.4 Hz, 2H), 4.49 (d, *J* = 8.3 Hz, 1H), 4.42—4.38 (m, 1H), 4.32 (t, *J* = 6.1 Hz, 1H), 3.72 (dd, *J* = 11, 1.1 Hz, 1H), 3.36 (s, 3H), 2.73 (dd, *J* = 8, 2.7 Hz, 1H), 2.52—2.45 (m, 1H), 2.42—2.35 (m, 1H), 2.16 (dd, *J* = 13, 6 Hz, 1H), 1.97 (m, 1H), 1.86 (s, 3H), 1.78—1.63 (m, 4H), 1.44 (s, 3H), 1.34 (s, 3H), 1.15 (m, 2H), 1.11 (s, 3H), 0.88 (s, 3H); IR (film) ν : 2929, 1376, 1144, 1115, 1041

cm^{-1} ; EIMS m/z (%): 407 ($\text{M}^+ - \text{CH}_3$, 5.53); HRMS calcd for $\text{C}_{24}\text{H}_{38}\text{O}_6$ 422.2669, found 422.2682.

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