

An efficient stereoselective total synthesis of 11 β -methoxycurvularin

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Abstract

A very short and efficient stereoselective total synthesis of a macrocyclic ketone, 11 β -methoxycurvularin was achieved by employing the Sharpless asymmetric epoxidation, formation of propargyl alcohols from an epoxy-chloride, and intramolecular Friedel-Crafts acylation as the key steps.

Keywords: Sharpless epoxidation, epoxy chloride, propargyl alcohol, intramolecular Friedel-Crafts acylation

Introduction

11 β -Methoxycurvularin (5) was first isolated from the mycelium of hybrid strain ME-005 which is a polyketide metabolite of various *Curvularia*, *Penicillium*, *Alternaria*, and *Cochiobolous* species. It was found to exhibit cytotoxicity¹ and antimicrobial activities^{2,3} against four types of human cancer cell lines such as [NCI-H460, MCF-7, SF-268, 41A Pa Ca-2].⁴ It also shows some effect in the spindle formation of embryos of sea urchin cells to give barrel like spindles and terminate the first step of cell division, which is a promising tool for anticancer drug discovery. Furthermore, it also shows binding affinity with tubulins.⁵

Structurally, 11 β -methoxycurvularin shows different configuration at C-11 in the 12-membered lactone ring. The first total synthesis of these natural products has been reported by Liang *et al.*⁶ which led to a revision of the spectroscopic data of the originally proposed structures (4 and 5).

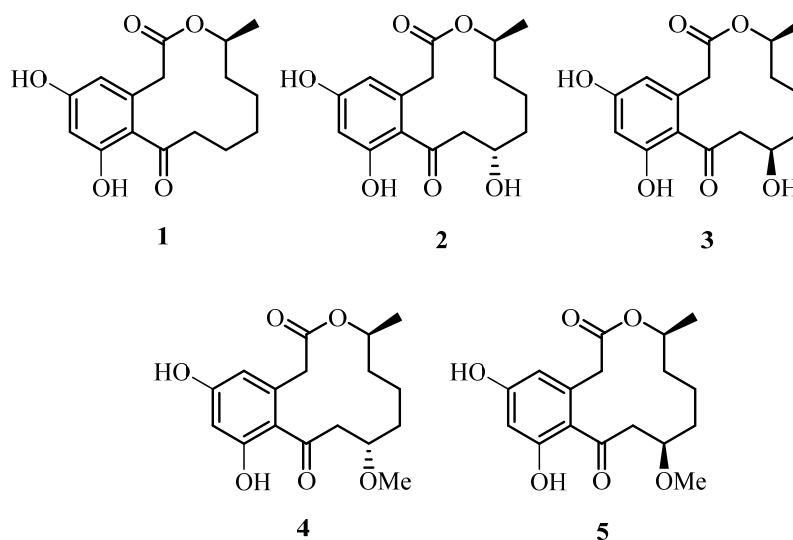
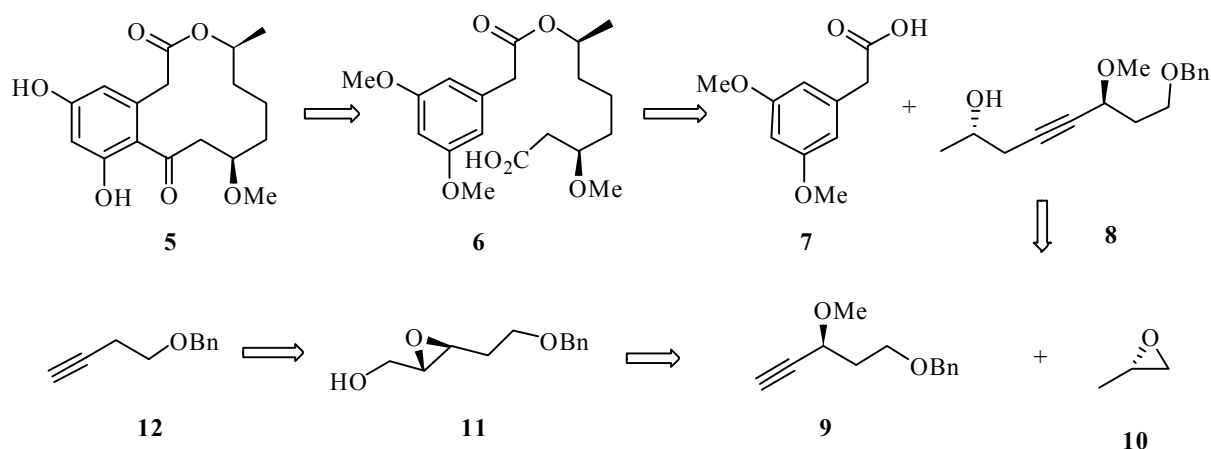


Figure 1. Curvularin (1), 11 α -hydroxycurvularin (2), 11 β -hydroxycurvularin, (3), 11 α -methoxycurvularin (4), 11 β -methoxycurvularin (5).

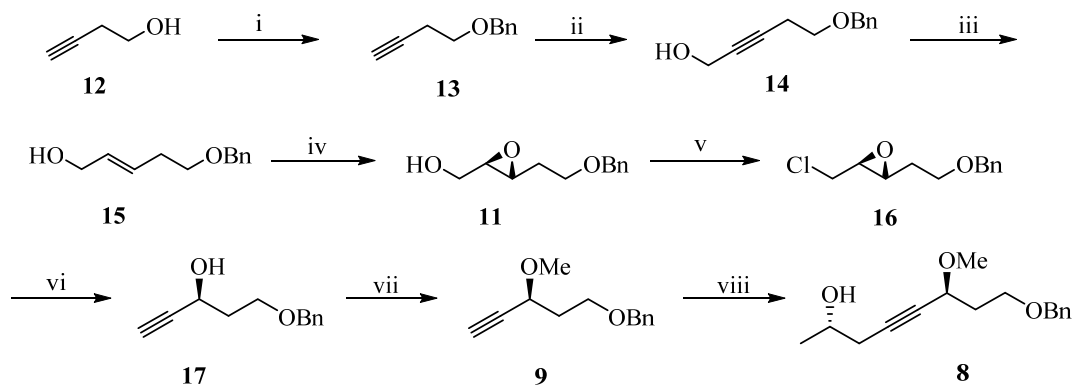
We herein report a new synthetic route for the stereoselective total synthesis of 11(β)-methoxycurvularin. Our approach utilizes mainly the Sharpless asymmetric epoxidation to introduce absolute stereocentre at C-11 for the construction of the key fragment **8**, which in turn comes from a commercially available homopropargyl alcohol **12**.



Scheme 1. Retrosynthetic strategy to 11 β -methoxycurvularin (**5**).

Accordingly, the aromatic portion was expected to arise from the readily available 3,5-dimethoxyphenylacetic acid **7**.^{7,8} Retrosynthesis of the 12-membered lactone ring **5** led to a known compound **6** along with the key fragment **8**, which in turn could be prepared from **9** and **10** in 65% yield. The fragment **9** was synthesized from homopropargyl alcohol **12** in seven steps.

Thus treatment of homopropargyl alcohol **12** with BnBr in the presence of NaH^{9,10} gave the benzyl ether **13** (Scheme 2) which upon reaction with paraformaldehyde in the presence of magnesium turnings and ethyl bromide gave the alcohol **14** in 72% yield. Reduction of **14** with LAH furnished an allyl alcohol **15**, which was then subjected to the Sharpless asymmetric epoxidation^{11,12} by using titanium isopropoxide, L(+)-DIPT, 4.5 M TBHP to afford the epoxide with 95% ee. This chiral epoxide was then converted into propargyl alcohol **17** which was subsequently protected as its methyl ether **9** by using NaH and MeI in 85% yield. Regioselective ring opening of (S)-methyloxirane **10** with **9** using *n*-BuLi, BF₃OEt₂ gave the secondary homopropargyl alcohol **8** in 65% overall yield.¹³

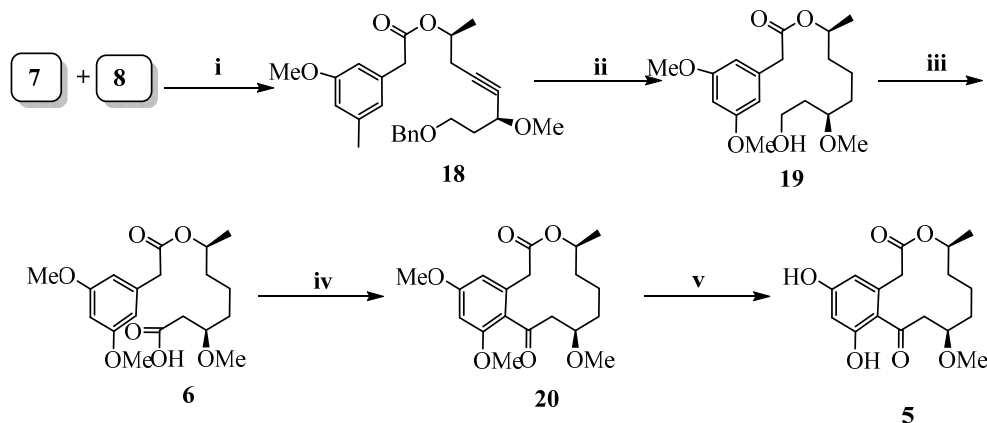


Reagents and conditions: i) BnBr, NaH, dry THF, 0°-rt, 93%; ii) EtMgBr, Mg turnings, (HCHO)_n, dry THF 72%; iii) LAH, dry THF, reflux, 90%; iv) 4 Å MS, L (+)-DIPT, Ti(OiPr)₄, 4.5 M TBHP, DCM, 27 °C, 70%; v) TPP, NaHCO₃, CCl₄, reflux, 80%; vi) Li, liq NH₃, Fe(NO₃)₃, -33 °C, 70%; vii) NaH, MeI, dry THF, 85%; viii) methyloxirane, *n*-BuLi, -78 °C, dry THF, 65%.

Scheme 2. Synthesis of the ynol **8**.

As shown in the Scheme 3, the esterification⁷ of **8** with 3,5-dimethoxyphenylacetic acid **7** using DCC and DMAP at room temperature afforded compound **18** in 80% yield. Subsequent deprotection of the benzyl group and reduction of the triple bond were achieved by hydrogenation using 10% Pd/C¹⁴ in ethyl acetate to afford the alcohol **19** in 70% yield. Oxidation of **19** using Jones reagent^{15,16} (CrO₃, H₂O, H₂SO₄; acetone, 0°-rt) gave the desired carboxylic acid **6** in 80% yield.

Intramolecular Friedel-Crafts acylation of **6** was achieved using a mixture of trifluoroacetic acid and trifluoroacetic anhydride¹⁷⁻²⁰ to give a macrolide **20** in 50% yield. Finally, the deprotection of **20** with freshly prepared AlI₃ in benzene gave the target molecule, 11β-methoxycurvularin **5** in 65% yield as colorless oil.



Reagents and conditions: (i) DCC, DMAP, DCM, 80%; (ii) 10% Pd/C, EtOAc, 70%; (iii) CrO₃, acetone, H₂SO₄, 80%; (iv) TFA, TFAA, 50%; (v) AlI₃, TBAI, benzene, 15 °C, 65%.

Scheme 3

Conclusions

In summary, we have successfully demonstrated an efficient total synthesis of 11β-methoxycurcularin in a highly stereoselective manner. The synthesis utilizes the Sharpless asymmetric epoxidation, and an intramolecular Friedel-Crafts acylation to construct 12-membered macrocyclic lactone ring system.

Experimental Section

General. The reactions were conducted under N₂ atmosphere using anhydrous solvents such as DCM, THF. All reactions were monitored by thin layer chromatography (TLC) using silica-coated plates and visualizing under UV light. Yields refer to chromatographically pure products by ¹H and ¹³C NMR. Air sensitive reagents were transferred by a syringe or with a double-ended needle. Evaporation of the solvent was performed at reduced pressure using a Buchi rotary evaporator. ¹H NMR spectra were recorded on Varian FT-200MHz (Gemini) and Bruker UXNMR FT-300MHz (Avance) in CDCl₃. Chemical shift values were reported in ppm relative to tetramethylsilane (δ 0.0) as an internal standard. Mass spectra were recorded under electron impact at 70eV on LC-MS (Agilent Technologies). Column chromatography was performed on silica gel (60-120 mesh) supplied by Acme Chemical Co., India. Thin-layer chromatography was performed on Merck 60 F-254 silica gel plates. Optical rotations were measured with JASCO DIP-370 polarimeter.

[(But-3-ynyloxy)methyl]benzene (13). To a suspension of NaH (1.13 g, 27.85 mmol) in THF (50 mL), was added alcohol **12** (1.5 g, 21.42 mmol) at 0 °C. After stirring for 20 min, BnBr (3.66 g, 21.42 mmol) was added slowly and the resulting mixture was stirred for another 4 h. After completion, the reaction was quenched with ice-cold H₂O (20 mL) and extracted with EtOAc (2×50 mL). The combined organic layers were dried over anhydrous Na₂SO₄. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography (EtOAc/hexanes 1:9) to afford compound **13** as a yellow oily liquid (3.1 g, 93%).

IR (neat) ν_{max} : 3031, 2916, 2865, 2120, 1454, 1363, 1204, 1028, 820, 739, 698 cm⁻¹. ¹H NMR (CDCl₃, 500 MHz): δ 7.21-7.31 (m, 5H), 4.52 (s, 2H), 3.56 (t, *J* 6.8 Hz, 2H), 2.46 (td, *J* 2.9, 6.8 Hz, 2H), 1.88 (t, *J* 2.9 Hz, 1H). EI-MS: *m/z*: 159 (M-H).

5-(Benzyloxy)pent-2-yn-1-ol (14). To a suspension of Mg metal (2.5 g, 15.62 mmol) in dry THF (50 mL) was added ethyl bromide (1.7 mL, 23.43 mmol) at 0 °C. The mixture was stirred for 30 min at room temperature and then compound **13** in dry THF was added at 0 °C. After stirring for 2 h at room temperature, paraformaldehyde was added slowly at 0 °C. The resulting mixture was stirred for another 5-6 h. After completion, the reaction was quenched with saturated NH₄Cl (20 mL) and extracted with EtOAc (2 × 50 mL) and dried over Na₂SO₄. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography (EtOAc/hexanes, 2:8) as eluent to afford compound **14** as a colourless oily liquid (1.65 g (72%).

IR (neat) ν_{max} : 3064, 3031, 2289, 2237, 1958, 1718, 1417, 1363, 1273, 1137, 1014, 744, 699 cm⁻¹. ¹H NMR (CDCl₃, 300 MHz): δ 7.20 -7.35 (m, 5H), 4.52 (s, 2H), 4.16 (s, 2H), 3.54 (t, *J* 6.8 Hz, 2H), 2.49 (t, *J* 6.8 Hz, 2H), 1.89-1.95 (bs, 1H). ¹³C NMR (CDCl₃, 75 MHz): δ 137.3, 127.8, 127.2, 127.1, 81.7, 79.4, 72.2, 67.7, 50.0, 19.5. EI-MS: *m/z* 189 [M-H].

(E)-5-(Benzyloxy)pent-2-en-1-ol (15). To a suspension of LiAlH₄ (540 mg, 14.21 mmol) in THF (30 mL) was added a solution of **14** (1.8 g, 9.47 mmol) in THF (10 mL) in a dropwise manner. After stirring the mixture for 2 h at reflux, water was added. The resulting mixture was filtered through a short pad of Celite and washed with EtOAc (3 × 50 mL). The filtrate was dried over anhydrous Na₂SO₄. The solvent was removed and the residue was purified on silica gel column using (EtOAc/hexanes 2:8) as the eluent to afford **15** as a colourless oil (1.65 g (90 %).

IR (neat) ν_{max} : 2862, 2359, 1686, 1453, 1363, 1309, 1205, 1098, 971, 910, 739, 698 cm⁻¹. ¹H NMR: (CDCl₃, 300 MHz): δ 7.21 -7.33 (m, 5H), 5.68 (td, *J* 4.53, 18.8 Hz, 2H), 4.48 (s, 2H), 4.04 (d, *J* 2.83 Hz, 2H), 3.52 (t, *J* 2.83 Hz, 2H), 2.34 (td, *J* 2.8, 4.5 Hz, 2H). ¹³C NMR: (CDCl₃, 75 MHz): δ 137.8, 130.9, 128.0, 127.3, 127.2, 72.4, 69.2, 62.6, 32.2. EI-MS: *m/z*: 191 [M-H].

[(2S,3S)-3-[2-(Benzyloxy)ethyl]oxiran-2-yl]methanol (11). To a suspension of 4Å molecular sieves (1.5 g) in 30 mL CH₂Cl₂ were added L-(+)-diisopropyl tartrate (0.18 mL, 0.782 mmol), Ti(OiPr)₄ (0.22 mL, 0.782 mmol), and ^tBuOOH (4.5 M in toluene (2.6 mL, 11.71 mmol) sequentially at -27 °C. The mixture was stirred for 30 min and compound **15** (2.06 g, 10 mmol) was then added. The reaction mixture was stored overnight (12 h) in the freezer at -25 °C without stirring. The reaction was then warmed to 25 °C and quenched by the addition of 10% NaOH/saturated aqueous NaCl (4.0 mL). Upon further warming to -10 °C the mixture was diluted with Et₂O (100 mL) and then treated with MgSO₄ (4.0 g) and Celite (1.0 g) and was

stirred for an additional 15 min. The resulting mixture was then allowed to settle for 1 h before filtration through Celite using Et₂O and then concentrated under reduced pressure. The residue was purified on silica gel column chromatography using (EtOAc/hexanes, 3:7) as eluent to afford compound **11** as colourless oil (1.63 g, 70 %).

$[\alpha]_D^{27} + 2.8$ (c, 0.5, CHCl₃). IR (neat) $\nu_{\max}$: 2927, 2872, 1453, 1277, 1098, 1074, 1027, 750, 716, 699 cm⁻¹. ¹H NMR (CDCl₃, 300 MHz): δ 7.21–7.32 (m, 5H), 4.49 (s, 2H), 3.20 (dd, *J* 2.2, 10.5 Hz, 1H), 3.50–3.59 (m, 3H), 3.04 (td, *J* 2.2, 6.7 Hz, 1H), 2.87–2.91 (m, 1H), 2.34–2.41 (bs, 1H), 1.71–1.95 (m, 2H). ¹³C NMR: (CDCl₃, 75 MHz): δ 137.6, 127.8, 127.5, 127.3, 123.9, 125.9, 72.4, 66.3, 61.3, 58.2, 53.2, 31.5, 31.0. ESI-MS: *m/z*: 231 [M+Na]. HRMS calcd for C₁₂H₁₆O₃Na 231.0997, found 231.0996.

(2S,3R)-2-[2-(Benzyloxy)ethyl]-3-(chloromethyl)oxirane (16). To a stirred solution of **11** (800 mg, 3.84 mmol) in anhydrous CCl₄ (15ml) was added triphenylphosphine (102 g, 4.61 mmol) under nitrogen atmosphere and then sodium bicarbonate (969 mg, 11.5 mmol) was added. The mixture was heated under reflux until triphenylphosphine oxide separated from the reaction mixture. After 6 h, the mixture was filtered and the solvent was removed from the filtrate under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc / hexanes 1:9) to afford compound **16** as a colourless liquid. (691 mg, 80%).

$[\alpha]_D^{27} + 7.7$ (c, 0.5, CHCl₃). IR (neat) $\nu_{\max}$: 3031, 2921, 2852, 1454, 1360, 1264, 1028, 878, 736, 698 cm⁻¹. ¹H NMR: (CDCl₃, 300 MHz): δ 7.22–7.34 (m, 5H), 4.50 (s, 2H), 3.56 (tdd, *J* 5.2, 6.0, 11.3 Hz, 3H), 3.44 (dd, *J* 5.2, 11.33 Hz, 1H), 2.99 (td, *J* 2.2, 5.2, 6.0 Hz, 2H), 1.73–1.96 (m, 2H). ¹³C NMR (CDCl₃, 75 MHz): 137.89, 128.02, 127.24, 127.73, 72.64, 67.50, 66.29, 66.20, 56.78, 56.20, 44.49, 31.61. ESI-MS: *m/z*: 251 [M+Na]. HRMS calcd for C₁₂H₁₅O₂Na 249.0658, found 249.0660.

(S) 5-(Benzyloxy)pent-1-yn-3-ol (17). To freshly distilled ammonia (25 mL) in a 100 mL two neck round bottom flask fitted with a cold finger condenser, was added catalytic amount of ferric nitrite, followed by the piecewise addition of lithium metal (166 mg, 18.5 mmol) at -33 °C. The resulting grey color suspension was stirred for 30 min. To this was added the chloride **16** (600 mg, 2.64 mmol) in dry THF (3 mL) over a period of 5 min. After stirring the reaction mixture for 30 min, solid NH₄Cl (2 g) was added and ammonia was allowed to evaporate. The residue was partitioned between water and ether and the aqueous layer was extracted with ether (2 × 50 mL). The combined organic layers were dried over anhydrous Na₂SO₄ and the solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography (EtOAc/hexanes, 2.5:7.5) to afford compound **17** as a colourless liquid (346 mg, 70%).

$[\alpha]_D^{27} + 4.5$ (c, 0.5, CHCl₃). IR (neat) $\nu_{\max}$: 3410, 3292, 2926, 2866, 2113, 1724, 1601, 1450, 1364, 1206, 1084, 1023, 740, 696 cm⁻¹. ¹H NMR: (CDCl₃, 300 MHz): δ 7.21–7.35 (m, 5H), 4.46–4.66 (m, 3H), 3.83 (td, *J* 4.5, 9.8 Hz, 1H), 3.65 (td, *J* 4.5, 9.8 Hz, 1H), 2.89–2.94 (bs, 1H), 2.37 (d, *J* 2.2 Hz, 1H), 2.02–2.15 (m, 1H), 1.86–1.97 (m, 1H). ¹³C NMR: (CDCl₃, 75 MHz): δ 137.65, 128.30, 127.63, 127.59, 126.82, 84.23, 73.17, 72.83, 67.23, 64.92, 60.74, 36.51, 29.55. EI-MS: *m/z*: 189 [M-H].

(S)-[(3-Methoxyoct-4-yn-1-yloxy)methyl]benzene (9). To a suspension of NaH (1.26 mg, 3.2 mmol) in THF (10 mL), was added alcohol **17** (300 mg, 1.578 mmol) at 0 °C. After stirring for 20 min, MeI (448 mg, 3.15 mmol) was added slowly and the resulting mixture was stirred for a further 2 h. After completion, the reaction was quenched with ice-cold H₂O (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were dried over anhydrous Na₂SO₄, the solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (EtOAc/hexanes, 1:9) to afford compound **9** as a yellow oily liquid (275 mg, 85%).

$[\alpha]_D^{27} + 4.2$ (c, 0.5, CHCl₃). IR (neat) $\nu_{\max}$: 3292, 3030, 2931, 2863, 2106, 1728, 1454, 1362, 1108, 1028, 739, 696 cm⁻¹. ¹H NMR: (CDCl₃, 300 MHz): δ 7.20–7.33 (m, 5H), 4.48 (s, 2H), 4.12 (td, *J* 2.2, 6.0 Hz, 1H), 3.58 (td, *J* 2.2, 6.0 Hz, 2H), 3.38 (s, 3H), 2.35 (d, *J* 2.26 Hz, 1H), 1.88–2.08 (m, 2H); ¹³C NMR: (CDCl₃, 75 MHz): δ 138.2, 128.1, 127.7, 127.4, 82.2, 73.8, 72.8, 67.9, 65.9, 56.3, 35.7; ESI-MS: *m/z*: 227[M+Na]. HRMS calcd for C₁₃H₁₆O₂Na 227.1047, found 227.1048.

(2S,6S)-8-(Benzyloxy)-6-methoxyoct-4-yn-2-ol (8). *n*-BuLi (1.6 M in hexanes, 1.22 mL, 1.83 mmol) was added dropwise to a solution of **9** (250 mg, 1.22 mmol) in anhydrous THF (20 mL) at –78 °C under N₂ atmosphere. The mixture was allowed to stir for 30 min and then treated with BF₃·OEt₂ (270 mg, 1.83 mmol). After 10 min, a solution of (S)-propylene oxide (**10**, 142 mg, 2.45 mmol) in anhydrous THF (5 mL) was added and the mixture was allowed to stir for 3 h at –78 °C. The resulting mixture was quenched with a mixture of NaHCO₃ (10 mL) and NH₄Cl (10 mL) solutions at –78 °C. The mixture was then allowed to warm to room temperature and extracted with EtOAc (3 × 20 mL), washed with H₂O (10 mL) and dried over Na₂SO₄. Removal of the solvent followed by purification on silica gel column chromatography (EtOAc/hexanes, 3:7) afforded compound **8** as colourless oil (220 mg, 65%).

$[\alpha]_D^{27} + 21.3$ (c, 0.5, CHCl₃). IR (neat) $\nu_{\max}$: 3422, 3030, 2967, 2930, 2867, 2196, 1726, 1453, 1367, 1206, 1107, 940, 742, 699 cm⁻¹. ¹H NMR: (CDCl₃, 500 MHz): δ 7.21–7.33 (m, 5H), 4.47 (s, 2H), 4.10 (t, *J* 6.76 Hz, 1H), 3.85–3.91 (m, 1H), 3.57 (t, *J* 5.79 Hz, 2H), 3.35 (s, 3H), 2.28–2.41 (m, 2H), 1.86–2.03 (m, 2H), 1.23 (d, *J* 6.7 Hz, 3H). ¹³C NMR (CDCl₃, 75 MHz): δ 138.2, 128.2, 127.5, 127.5, 82.7, 81.0, 74.4, 74.0, 72.9, 68.5, 66.2, 66.2, 56.3, 36.0, 29.1, 22.2. ESI-MS: *m/z*: 263[M+H]. HRMS calcd for C₁₆H₂₄O₃ 263.1647, found 263.1657.

(2S,6S)-8-(Benzyloxy)-6-methoxyoct-4-yn-2-yl(3,5-dimethoxyphenyl)acetate (18). To a stirred solution of **8** (150 mg, 0.56 mmol) in CH₂Cl₂ (10 mL) at 0 °C was added DCC (232 mg, 1.12 mmol), followed by a catalytic amount of DMAP. After 5 min, 3,5-dimethoxybenzoic acid (121 mg, 0.62 mmol) was added and the resulting mixture was stirred for 1 h at room temperature. Upon completion, the mixture was quenched with water (10 mL) and then extracted with CH₂Cl₂ (20 mL). The organic layer was washed successively with 10% aq. HCl solution followed by sat. NaHCO₃ solution and brine. The organic layer was dried over Na₂SO₄, and concentrated *in vacuo* and the residue was purified by column chromatography (AcOEt / hexanes, 2:8) to afford compound **18** (200 mg, 80%) as a colourless oil (200 mg, 80%).

$[\alpha]_D^{27}$ -16.6 (c, 0.5, CHCl_3). IR (neat) ν_{max} : 3448, 2936, 2130, 1722, 1600, 1462, 1290, 1203, 1154, 1107, 1065, 960, 837, 744, 695 cm^{-1} . ^1H NMR: (CDCl_3 , 500 MHz): δ 7.17-7.30 (m, 5H), 6.37 (d, J 6.7 Hz, 2H), 6.29 (s, 1H), 4.90-5.04 (m, 1H), 4.42 (s, 2H) 3.94-4.08 (m, 2H), 3.71 (s, 9H), 3.43-3.56 (m, 5H), 2.35-2.47 (m, 2H), 1.27 (d, J 5.79 Hz, 3H), 1.15 (d, J 6.76 Hz, 2H).

^{13}C NMR: (CDCl_3 , 75 MHz): δ 170.5, 160.6, 138.3, 135.9, 128.2, 127.5, 107.1, 99.0, 81.5, 80.7, 72.8, 70.3, 69.7, 68.3, 66.2, 56.2, 25.6, 19.0. ESI-MS: m/z : 458 $[\text{M}+\text{NH}_4]$. HRMS calcd for $\text{C}_{26}\text{H}_{36}\text{NO}_6$ 458.2542 $[\text{M}+\text{NH}_4]$, found 458.2558.

(2S,6R)-8-Hydroxy-6-methoxyoctan-2-yl (3,5-dimethoxyphenyl)acetate (19). To a stirred solution of **18** (200 mg, 0.45 mmol) in EtOAc (10 mL), 10% Pd/C (25 mg) was added and the mixture was stirred under H_2 atmosphere at room temperature for 12 h. After complete conversion, the mixture was filtered through Celite and the filtrate was concentrated under reduced pressure and then by purified by silica gel column chromatography (EtOAc/hexanes, 6:4) to afford compound **19** as an oily liquid (152 mg, 70%).

$[\alpha]_D^{27}$ -0.9 (c, 0.5, CHCl_3). IR (neat) ν_{max} : 3327, 2923, 2849, 1702, 1612, 1463, 1417, 1334, 1294, 1238, 1205, 1152, 1062, 915, 818, 735, 654 cm^{-1} . ^1H NMR: (CDCl_3 , 500 MHz): δ 6.38 (d, J 6.7 Hz, 2H), 6.28 (m, 1H), 4.83-4.94 (m, 1H), 3.76 (s, 9H), 3.65-3.74 (m, 2H), 3.52 (s, 1H), 3.47 (s, 1H), 3.30 (s, 2H), 1.24-1.64 (m, 8H), 1.21 (d, J 6.2 Hz, 3H). ESI-MS: m/z : 458 $[\text{M}+\text{NH}_4]$. HRMS calcd for $\text{C}_{21}\text{H}_{25}\text{NO}_6\text{Na}$ 410.1575, found 410.1579.

(3R,7S)-7-[2-(3,5-Dimethoxyphenyl)acetoxy]-3-methoxyoctanoic acid (6): Compound **19** (15 mg, 0.38 mmol) was taken in 5 mL of distilled acetone at 0 °C. Then a freshly prepared Jones reagent was added slowly at the same temperature until the orange brown color persists. The mixture was allowed to attain room temperature and the stirring was continued for further 30 min. The mixture was then quenched with water and extracted with EtOAc. Purification by silica gel column chromatography gave the acid **6** (100 mg, 80%).

$[\alpha]_D^{27}+9.1$ (c, 0.8, CHCl_3). IR (neat) ν_{max} : 3447, 2928, 1721, 1596, 1458, 1301, 1267, 1198, 1165, 1035, 765, 637 cm^{-1} . ^1H NMR (CDCl_3 , 500 MHz): δ 6.75 (s, 2H), 6.30 (s, 1H), 4.81-4.94 (m, 1H), 3.78 (s, 6H), 3.49 (m, 1H), 3.45 (s, 2H), 3.30 (s, 3H), 2.47 (dd, J 15.7, 6.3 Hz, 1H), 2.35 (dd, J 15.7, 5.3 Hz, 1H), 1.21-1.61 (m, 6H), 1.98 (d, J 6.2 Hz, 3H); ^{13}C NMR: (CDCl_3 , 75 MHz): δ 175.4, 171.2, 170.2, 159.9, 137.2, 107.2, 99.7, 78.3, 70.2, 55.9, 55.1, 41.7, 38.7, 35.3, 32.2. ESI-MS: m/z : 286 $[\text{M}+\text{NH}_4]$. HRMS calcd for $\text{C}_{19}\text{H}_{21}\text{O}_7\text{Na}$ 391.1732, found 391.1714.

(4S,8R)-8,11,13-Trimethoxy-4-methyl-4,5,6,7,8,9-hexahydro-1H-benzo[d][1]oxacyclododecine-2,10-dione (20). The compound **6** (100 mg, 0.27 mmol) was dissolved in CF_3COOH (7.5 mL) and $(\text{CF}_3\text{CO})_2\text{O}$ (1.2 mL). The solution was stirred overnight at room temperature and poured into an excess of NaHCO_3 solution. The mixture was extracted with Et_2O (3.5 mL) and the extract was dried over anhydrous Na_2SO_4 and concentrated *in vacuo* and the residue was purified by column chromatography (EtOAc/hexanes, 1: 5) to afford compound **20** as a colorless oil (52 mg, 50%).

$[\alpha]_D^{27}$ -16 (c, 0.8, CHCl_3). IR (neat) ν_{max} : 3387, 2936, 1728, 1659, 1601, 1457, 1310, 1271, 1157, 1084, 973, 681 cm^{-1} . ^1H NMR: (CDCl_3 , 500 MHz): δ 6.51 (s, 1H), 6.42 (s, 1H), 6.21 (d, J 15.4 Hz, 1H), 4.85 (t, J 6.3 Hz, 1H), 3.81 (s, 2H), 3.80 (s, 6H), 3.31 (d, J 18.6 Hz, 3H), 2.31 (t, J 6.7

Hz, 1H), 2.16 (t, *J* 6.7 Hz, 1H), 1.90 – 1.73 (m, 2H), 1.51 – 1.36 (m, 4H), 1.13 (d, *J* 6.3 Hz, 3H). ¹³C NMR (CDCl₃, 75 MHz): δ 198.3, 170.2, 160.7, 157.3, 156.2, 133.0, 122.3, 106.3, 97.5, 72.7, 55.3, 55.1, 55.0, 39.3, 34.0, 39.9, 24.1, 20.1. ESI-MS: *m/z*: 373 [M+Na]. HRMS calcd for C₁₉H₂₆O₆Na 373.1629, found 373.1627.

(4S,8R)-11,13-Dihydroxy-8-methoxy-4-methyl-4,5,6,7,8,9-hexahydro-1H-benzo[d][1]oxa-cyclododecine-2,10-dione (5). To a stirred solution of iodine (1.1 g, 4.33 mmol) in dry benzene (10 mL) was added Al powder (167 mg, 4.70 mmol). The mixture was refluxed for 0.5 h and cooled to 10 °C. To this mixture Bu₄NI (253 mg) and a solution of compound **20** (50 mg, 0.14 mmol) in dry benzene (4 mL) were added. The mixture was stirred for 15 min at 10 °C and quenched with 2 M HCl at 0 °C. The mixture was then extracted with ethyl acetate (3 × 20 mL), the organic phase was washed with NaHCO₃ solution followed by brine solution and dried over Na₂SO₄ and concentrated *in vacuo*. The residue was purified by column chromatography (EtOAc/hexanes, 2 : 1) gave the compound **5** as a colorless oil (30 mg, 65%).

[α]_D²⁷ -3.0 (c, 1.0, EtOH). IR (neat) ν_{max}: 3390, 2921, 2850, 1709, 1618, 1532, 1319, 1258, 1157, 1028, 976, 841, 750, 643 cm⁻¹; ¹H NMR: (CDCl₃, 300 MHz): δ 6.50 (s, 1H), 6.19 (s, 1H), 4.90 (t, *J* 6.2 Hz, 1H), 3.87 (d, *J* 15.7 Hz, 1H), 3.71 (d, *J* 14.09 Hz, 1H), 3.57 (d, *J* 16.3 Hz, 1H), 3.30 (d, *J* 5.1 Hz, 1H), 3.25 (s, 3H), 3.12 (dd, *J* 14.11, 8.1 Hz, 1H), 1.51 – 1.83 (m, 6H), 1.21 (d, *J* 5.1 Hz, 3H). ¹³C NMR, (CDCl₃, 75 MHz): δ 170.7, 160.2, 157.3, 133.0, 117.2, 112.4, 101.7, 73.9, 72.1, 54.1, 49.2, 41.0, 31.2, 30.4, 19.2, 17.2. ESI-MS: *m/z*: 345 [M+Na]. HRMS calcd for C₁₇H₂₂O₆Na 345.1307, found 345.1311.

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