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Asymmetric Synthesis of (*S*) – Massoialactone

Godwin C. G. Pais, Rodney A. Fernandes and Pradeep Kumar*

Division of Organic Chemistry : Technology
National Chemical Laboratory, Pune – 411008, India.

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Abstract : *An asymmetric synthesis of (S)-(+)-Massoialactone is described using the Sharpless asymmetric dihydroxylation and the regiospecific nucleophilic opening of a cyclic sulfate as key steps.*

Pheromones, allomones and kairomones are chemical substances that trigger inter- and intraspecific communication in a variety of bioorganism *e.g.* flies, moths, cockroaches, beetles, weevils, rootworms, ants and bees, *etc.*[1] Much of their application involves control of behaviour of these species and their developmental process. However these volatile secretions isolated from natural sources are obtained in only minute quantities. (-)-Massoialactone[2-3] is the major constituent of the bark oil of Cryptocarya massoia, isolated for the first time by Abe[4] in 1937. It is a powerful skin irritant and produces systolic standstill in frog heart muscle.[2] (-)-Massoialactone is the allomone of the two species of formicine ants[5] belonging to the Camponotus genus collected in Western Australia. This lactone has also been isolated from cane molasses[6] and jasmine blossoms[7] as flavor substance. Various methods[3,8-9] for the synthesis of massoialactone have been documented. The asymmetric synthesis reported in the literature either utilises the chiral pool as the starting material[10-13] or the chromatographic resolution of the diastereomeric derivatives of the lactone precursor.[14] Mori has reported the synthesis of (*S*)-massoialactone employing (*R*)-(+)-glyceraldehyde acetonide as the chiral pool material.[10] However, the optical purity of the product obtained in this case was not high presumably owing to one or more conversions having proceeded with partial racemisation. Therefore there is a genuine need for an efficient strategy for the synthesis of massoialactone. We would like to report now an expeditious asymmetric synthesis of (*S*)–massoialactone (**6**), where the Sharpless asymmetric dihydroxylation of 1-heptene and the regiospecific nucleophilic opening of a cyclic sulfate with methyl propiolate were employed as key steps.

The detailed information regarding the reagents, solvent and reaction conditions followed by usual work up is provided in Scheme-1 and experimental section. Thus, the dihydroxylation of 1-heptene (**1**) using the Sharpless asymmetric dihydroxylation procedure[15] gave the diol **2** in 85% ee having $[\alpha]_D^{20}$ - 6.23 (c 2.9, MeOH). The diol **2** was converted into its cyclic sulfite **3** using thionyl chloride and triethylamine.[16] It was

* E-mail : tripathi@dalton.ncl.res.in

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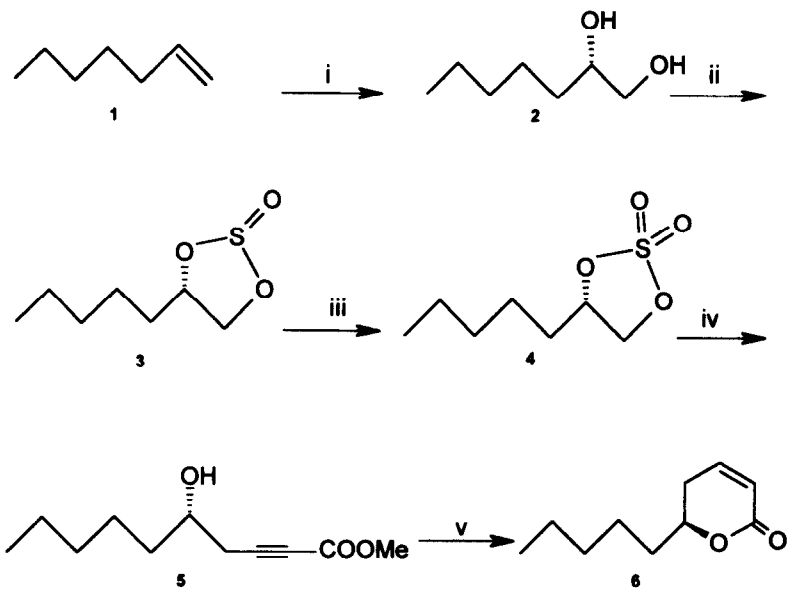
further oxidised to obtain the cyclic sulfate **4** in quantitative yield. The essential features of our synthetic strategy shown in the scheme was based on the presumption that the nucleophilic opening of the cyclic sulfate **4** would occur in a regiospecific manner at the terminal carbon. Indeed the cyclic sulfate on treatment with the anion of methyl propiolate furnished the desired alcohol **5**, which on hydrogenation followed by subsequent lactonisation afforded the target molecule **6**, having $[\alpha]_D^{20}$ +110.5 (c 2.4 , $CHCl_3$), $[\alpha]_D^{22.6}$ lit[14] +109.6 (c 2.0, $CHCl_3$).

Scheme-1



Reagents and conditions: i. $(DHQ)_2$-Pyr, $K_3[Fe(CN)_6]$, K_2CO_3, OsO_4(cat), *t*-BuOH-H_2O (1:1), RT, overnight (80%); ii. $SOCl_2$, Et_3N, CH_2Cl_2, 0°C, 20 min (99%); iii. $RuCl_3$, $NaIO_4$, CCl_4-MeCN-H_2O: 2:2:3, 0°C, 2 h, (100%); iv. n-BuLi, Methyl propiolate, THF, -78°C, 20 min, then RT, overnight (75%); v. Pd-$BaSO_4$, Quinoline, H_2 (1 atm), EtOAc, 1 h, RT, then NaOH, EtOH: H_2O (2:1), HCl, C_6H_6, 80^0 C, (60%).

In conclusion, an asymmetric synthesis of (*S*)-massoialactone has been realised using the Sharpless asymmetric dihydroxylation as the source of chirality for the first time. Thus the results described herein constitute a short and efficient synthesis of the unnatural isomer of massoialactone. The natural enantiomer can be synthesized *via* β-dihydroxylation of 1-heptene and following the reaction sequence as shown above.

EXPERIMENTAL SECTION

General information: Solvents were purified and dried by standard procedures before use; petroleum ether of boiling range 60-80^{0}C was used. Optical rotations were measured using sodium D line on JASCO-181 digital polarimeter. Infrared spectra were recorded on a Perkin-Elmer model 683 grating infrared spectrometer. Proton NMR spectra were recorded on Bruker AC-200 NMR spectrometer. The chemical shifts are reported in parts per million (δ) with tetramethylsilane as internal standard. Mass spectra were obtained with a Finnigan MAT-1020 B-70-ev mass spectrometer. Elemental analyses were carried out on a Carlo Erba CHNS-O analyzer. Enantiomeric excess was determined by ^{1}H NMR using the shift reagent, tris-[3-(heptafluoropropylhydroxymethylene)-(+)-camphorato] europium III derivative.[17]

(*S*)-(-)-Heptane-1,2-diol (2): A 250 mL round bottom flask, equipped with magnetic stirrer, was charged with *t*-BuOH (50 mL), water (50 mL), potassium ferricyanide (50.30 g, 0.153 mol), K_2CO_3 (21.11 g, 0.153 mol) and $(DHQ)_2$-Pyr (134 mg). The mixture was stirred at room temperature and 10 μL of OsO_4 (0.01 mol %) was added. The reaction flask was placed in an ice bath and 1-heptene (5 g, 50.9 mmol) was added. The mixture was stirred overnight at room temperature. Sodium sulfite (20 g) was added and after stirring for 1 h, EtOAc (100 mL) was added to the mixture and the phases were separated. The aqueous phase was extracted with EtOAc (3x 100 mL). The combined organic phases were dried (Na_2SO_4) and concentrated. The crude product was purified on a silica gel column using pet.ether: EtOAc (2:1) as eluent to give **2** as a colorless liquid (5.4 g, 80 %). $[\alpha]_D^{20}$ – 6.23 (c 2.9, MeOH); IRν_{max}/cm^{-1} (Neat): 3100-3600, 2840-2960, 1460, 1440, 1120, 1050, 520; ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 0.8-1.0 (t, *J* = 6.6 Hz, 3H), 1.1-1.55 (m, 8H), 3.3-3.4 (m, 3H), 4.0-4.45 (bs, 2H). Anal. calcd for $C_7H_{16}O_2$ (132.20): C, 63.59; H, 12.20. Found: C, 63.82; H, 12.08.

For the purpose of measuring the enantiomeric excess, the diol **2** was converted into its diacetate by the following procedure.

(*S*)-(-)-Heptane-1,2-diol acetate: To an ice-cold solution of the diol **2** (0.1 g, 0.76 mmol) in CH_2Cl_2 (5 mL) were added successively acetic anhydride (0.15 mL, 1.52 mmol) and DMAP (0.19 g, 1.52 mmol). The reaction mixture was stirred at that temperature for 30 min. Saturated aq. $NaHCO_3$ (10 mL) was then added to it and the organic layer was separated, washed with saturated $CuSO_4$ solution (3 x 5 mL), water (3 x 5 mL), dried (Na_2SO_4) and concentrated under reduced pressure to obtain the crude diacetate. Purification on a silica gel column using pet. ether: EtOAc (9.5:0.5) gave pure diacetate as a colorless liquid (0.12 g, 95%). $[\alpha]_D^{20}$ –1.59 (c 2.4, $CHCl_3$); IRν_{max}/cm^{-1} (Neat): 2900, 1730, 1430, 1370, 1220, 1020, 950, 600; ^{1}H-NMR (200 MHz,

$CDCl_3$) δ: 0.85-0.95 (t, J = 6.6 Hz, 3H), 1.2-1.45 (m, 6H), 1.5-1.65 (m, 2H), 2.05 (s, 6H), 4.0-4.1 (dd, J = 12, 6 Hz, 1H), 4.2-4.3 (dd, J = 12, 4 Hz, 1H), 5.05-5.15 (m, 1H). Anal. calcd for $C_{11}H_{20}O_4$ (216.27): C, 61.09; H, 9.32. Found: C, 61.35; H, 9.01.

The enantiomeric excess of **2** was 85% as determined by complexing its diacetate with the shift reagent tris-[3-(heptafluoropropylhydroxymethylene)-(+)-camphorato] europium III derivative. For comparison the ^{1}H-NMR shift experiments were also carried out with racemic diol.

(*S*)- 5-Pentyl-1,3,2-dioxathiolane-2-oxide (3): To a solution of the diol **2** (1.0 g, 7.57 mmol) in CH_2Cl_2 (25 mL) was added Et_3N (2.5 mL, 17.4 mmol). The mixture was cooled in an ice bath and thionyl chloride (0.7 mL, 9.6 mmol) was added dropwise. The reaction mixture was stirred for 20 min and then quenched by adding water (15 mL). The phases were separated and aqueous phase was extracted with CH_2Cl_2 (3x 30 mL). The combined organic phases were dried (Na_2SO_4), concentrated and purified by silica gel column chromatography using pet.ether: EtOAc (9:1) as eluent to give **3** as a yellow liquid (1.335 g, 99 %). $[\alpha]_D^{20}$ -12.35 (c 5.14, $CHCl_3$); IRν_{max}/cm^{-1} (Neat): 2920, 1460, 1200, 950, 840, 680, 500, 390; ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 0.85-0.9 (t, J = 6.6 Hz, 3H), 1.15-1.6 (m, 4H), 1.6- 1.95 (m, 2H), 3.85-3.95 (m, 1H), 4.25-4.4 (m, 1H), 4.9-5.05 (m, 1H). Anal. calcd for $C_7H_{14}O_3S$ (178.24): C, 47.17; H, 7.91; S, 17.99. Found: C, 47.19; H, 7.86; S, 17.97.

(*S*)-(-)-Methyl 5-hydroxy-2-decynoate (5): The cyclic sulfite **3** (0.420 g, 2.35 mmol) was dissolved in CCl_4- MeCN – H_2O (2:2:3, 21 mL) and $RuCl_3.H_2O$ (25 mg, 0.12 mmol) was added followed by $NaIO_4$ (0.9 g, 4.2 mmol). The mixture was stirred at 0°C for 2 h and then extracted with EtOAc (5x 50 mL) . The combined organic phases were washed with water (15 mL) and brine (15 mL). After drying (Na_2SO_4), the organic solution was filtered through a short column of silica gel and concentrated to give **4** as a yellow liquid in quantitative yield which was used as such for the next step without further purification.

To a stirred solution of methyl propiolate (0.25 mL, 2.83 mmol) in dry THF (10 mL) cooled at –78°C was added dropwise n-BuLi (1.4 mL, 2.0 M, 2.83 mmol) under nitrogen. The reaction mixture was stirred at -78°C for 20 min and to this a solution of cyclic sulfate **4** (0.457 g, 2.36 mmol) in THF (5 mL) was added dropwise. The solution was allowed to come to room temperature. After stirring overnight at room temperature conc. H_2SO_4 (0.16 mL, 2.8 mmol) was added and the stirring continued for an additional 8 h at room temperature followed by an extractive work-up (EtOAc-$NaHCO_3$). The combined organic phases were dried (Na_2SO_4) and concentrated. The crude product was purified on a silica gel column using pet.ether: EtOAc (9:1) as eluent to give **5**[14] as a colorless liquid (0.35 g, 75%). $[\alpha]_D^{20}$ - 2.38 (c 0.42, $CHCl_3$); IRν_{max}/cm^{-1} (Neat): 3600-3100, 2900, 2840,1730, 1440, 1260, 1030, 740, 620; ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 0.85-0.95 (t, J = 6.6 Hz, 3H), 1.2-1.4 (m, 6H), 1.7 (m, 2H), 2.0-2.2 (brs, 1H), 2.6-2.7 (d, J =5.8 Hz, 2H), 3.4-3.55 (m, 1H),

3.7 (s, 3H); MS: m/z 197 (M^+ 0.5%), 175 (2.17) , 159 (13.47), 143 (15.65), 127 (11.30), 111 (83.91), 103 (80), 85 (100), 71 (62.60). Anal. calcd for $C_{11}H_{18}O_3$ (198.25): C, 66.64; H, 9.15. Found: C, 66.50; H, 9.23.

(*S*)-(+)-Decen-5-olide (6): To a solution of **5** (0.35 g, 1.76 mmol) in EtOAc (10 mL) was added 5% Pd on $BaSO_4$ (60 mg) and quinoline (60 mg). The reaction mixture was shaken under H_2 (1 atm) for 1 h at room temperature. The catalyst was filtered off and the solvent concentrated to afford the crude hydroxy olefinic ester which was stirred for 1 h at reflux in EtOH: H_2O (2:1, 12 mL) containing NaOH (0.4 g, 10 mmol). The solution was cooled to 0^0C and acidified with 1N hydrochloric acid (25 mL) and extracted with ether (2 x 10 mL). The combined organic layers were dried (Na_2SO_4) and concentrated to afford the crude hydroxy olefinic acid which was lactonised in benzene (30 mL) at reflux for 1.5 h (azeotropic removal of water). The solution was concentrated and the residue was distilled under reduced pressure to give **6** as a colorless liquid (0.179 g, 60%), bp 130^0C/5 torr, lit[10] 119-120^0C/3 torr; $[\alpha]_D^{20}$ +110.5 (c 2.4 , $CHCl_3$), $[\alpha]_D^{22.6}$ lit[14] +109.6 (c 2.0, $CHCl_3$). Spectroscopic properties (IR, ^{1}H-NMR, Mass) were in full agreement with the literature data.[10,14]

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