Available online www.jocpr.com

Journal of Chemical and Pharmaceutical Research, 2015, 7(1):661-665

Research Article

ISSN : 0975-7384
CODEN(USA) : JCPRC5

A facile enantioselective synthesis of (*R*)-massoialactone

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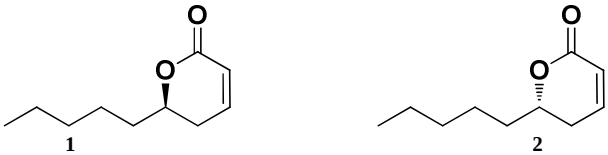
ABSTRACT

A novel and highly efficient synthesis of (R)-Massoialactone employing Sharpless asymmetric epoxidation of allyl alcohol has been accomplished. The synthesis also demonstrates the effective use of regioselective reductive opening of epoxy alcohols.

Key words: (*R*)-Massoialactone, pheromone, Sharpless epoxidation, selective hydride reduction.

INTRODUCTION

Natural products containing 6-subsitituted δ-lactone moiety exhibit interesting biological activities [1]. (*R*)-Massoialactone [2] (1, figure **1**), a member of this family, was isolated for the first time in 1937 by Abe [3] from the bark of *Cryptocarya massoia* which grows wild in New Guinea. It is a skin irritant and produces systolic standstill in frog heart muscle. Later, this lactone was also isolated from cane molasses [4] and jasmine blossoms [5] as a flavor substance. It is an alarm pheromone of two species of formicine ants of the genus *Componotus* collected in Western Australia [6]. The absolute configuration of **1** was determined to be (*R*) -form by the synthesis of unnatural (*S*)-form. (*R*)-Massoialactone (**1**) is characterized by a pleasant and sweet light coconut odor [7] and is used as aromatizer in perfumery and in the manufacture of alcoholic drinks and tinctures [8]. Synthetic compound [9] of **1** is widely used in food and perfume industry in order to save its natural resources.



1 **2**

Figure1: Structures of (*R*)-Massoialactone (1) and (*S*)-Massoialactones (2)

Owing to its promising biological activity and industrial applications, (*R*)-Massoialactone (**1**) has attracted the attention of synthetic organic chemists. Several syntheses [10, 11] of (*R*)-Massoialactone (**1**) have been reported in the literature. However, many of them suffer from one or more disadvantages, which include low yielding key reactions, use of harsh reaction conditions and the use of costly catalysts. With an aim to synthesize (*R*)-Massoialactone with high overall yield and employing relatively less number of steps, we have chosen the present synthetic route starting from commercially available and cheap n-hexanal.

EXPERIMENTAL SECTION

General information: Solvents were purified and dried by standard procedures before use. Optical rotations were measured using sodium D line on a JASCO-181 digital polarimeter. IR spectra were recorded on Thermo Scientific-Nicolet 380 FT-IR Instrument. ^{1}H NMR and ^{13}C NMR spectra were recorded on Brucker AC-200 spectrometer.

(E)- Oct-2-en-1-ol, 4

To a suspension of Lithium Aluminum hydride (12.8 mmol, 0.486 g) in dry THF at 0 ^{o}C under N_2 atmosphere was added a drop wise solution of $AlCl_3$ (0.577 g, 4.3 mmol) in THF. The reaction mixture was stirred at the same temperature for 30 min. To this stirred suspension, was added the drop wise solution of unsaturated ester **3** (1.4 g, 8.54 mmol) in THF over a period of 10 min and the contents were stirred at 0 ^{o}C for 1h. The reaction mixture was quenched with water and filtered through Celite and the residue was washed with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and finally evaporated under reduced pressure. The residue was chromatographed over silica gel (100-200 mesh, EtOAc/hexane 2:8) yielding pure alcohol **4** (78%) as colorless oil; IR (neat, cm^{-1}): 3352, 3042, 2911, 1642, 1125, 1094; ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.85-0.92 (t, J=6.32 Hz, 3H), 1.24-1.42 (m, 6H), 1.99-2.17 (m, 3H), 4.07-4.10 (d, J=4.8 Hz, 2H), 5.55-5.78 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 13.97, 22.46, 28.75, 31.32, 31.12, 63.7, 128.69, 133.51; ESI-MS: *m/z* = 141 (M+Na)

((2R, 3R)-3-pentyloxiran-2-yl) methanol, 5

(+)-Diethyl tartarate (0.2 g, 1 mmol), $Ti(O\text{-}iPr)_4$ (0.23 g, 0.8 mmol) were added sequentially to a suspension of 4 A^o molecular sieves (3 g) in CH_2Cl_2 (20 mL) at -20 ^{o}C and the suspension was stirred for 30 min. A solution of compound **4** (0.35 g, 2.6 mmol) in dry CH_2Cl_2 (15 mL) was then added drop wise at the same temperature followed by the addition of tBuOOH (0.45 g, 2 mmol) and the reaction mixture was stirred for 12 h at -10 °C. When the starting material was not observed on the TLC, the reaction was quenched with 20% NaOH solution saturated with NaCl (1 mL) and the reaction mixture was stirred vigorously for another 30 min at RT. The resulting reaction mixture was filtered through celite, the solvent was evaporated and the crude product was purified by column chromatography over silica gel (60-120 mesh, EtOAc/hexane 3:7) to afford pure epoxy alcohol **5** in 87% yield;$[\alpha]_D^{25}$: + 21.9 (*c* 1, $CHCl_3$); IR (neat, cm^{-1}): 3402, 2912, 1268, 1112, 894, 764 ; ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.87-0.93 (t, J=6.69 Hz, 3H), 1.27-1.63 (m, 8H), 2.92-2.99 (m, 3H), 3.58-3.66 (m, 1H), 3.89-3.96 (dd, J=2.4 Hz, 10.23 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 13.92, 22.50, 25.56, 27.88, 31.47, 56.06, 58.53, 61.72; ESI-MS: *m/z* = 145 (M+1)

(R)-Octane-1, 3-diol, 6

To a stirred solution of epoxy alcohol (0.11 g, 0.75 mmol) in THF (5 mL) at -15 °C was added drop wise solution of sodium bis (methoxyethoxy) aluminum hydride (Red-al) (3.5 M solution in toluene, 1.2 mmol). The reaction mixture was stirred for 6 h at the same temperature. When no starting material was observed on TLC, the temperature was raised to 0 ^{o}C, reaction mixture was quenched with citric acid solution and the resultant reaction mixture was stirred for another 10 min. Then contents were decanted leaving behind a residue, which was further dissolved in water and extracted with EtOAc thrice. The combined organic layers were evaporated under reduced pressure, and the residue was chromatographed over silica gel (60-120 mesh, EtOAc/hexane 3:7) yielding pure diol **6** (96 %) as viscous liquid; $[\alpha]_D^{25}$: - 9.2 (*c* 0.6, $CHCl_3$); IR (neat, cm^{-1}): 3462, 2944, 1361, 1124; ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.86-0.92 (t, J=6.06 Hz, 3H), 1.30-1.47 (m, 8H), 1.63-1.74 (m, 2H), 2.73 (brs, 2H), 3.76-3.92 (m, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 13.99, 22.59, 25.17, 31.79, 37.76, 38.21, 61.80, 72.32; ESI-MS: *m/z* = 147 (M+1).

(R)-2,2,3,3,9,9,10,10-octamethyl-5-pentyl-4,8-dioxa-3,9-disilaundecane, 7

To a stirred solution of diol **6** (1 g, 4.8 mmol) in dry CH_2Cl_2 (80 ml), Imidazole (0.68 g, 10 mmol) were added and the reaction mixture was cooled to 0 ^{o}C, a solution of t-Butyldimethylsilyl chloride (1.4 g, 9.6 mmol) in dry CH_2Cl_2 (20 mL) was added drop wise at 0^{o}C and the reaction mixture was stirred at room temperature for 12 h. Upon completion of the reaction (as monitored by TLC) reaction mixture was diluted with CH_2Cl_2 (40 ml) and washed with water, organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was chromatographed over silica gel (60-120 mesh, EtOAc/hexane 1:9) yielding pure compound **7** (96%) as colorless oil; $[\alpha]_D^{25}$: + 8.9 (*c* 0.5, $CHCl_3$): IR (neat, cm^{-1}): 2924, 1121, 1089, 825; ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.04 (s, 12H), 0.88-0.89 (d, J=1.26 Hz, 21H), 1.27 (brs, 8H), 1.59-1.69 (q, J=6.57 Hz, 2H), 3.63-3.82 (m, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ -5.30, -4.41, 14.04, 18.12, 18.28, 22.66, 24.84, 25.94, 32.03, 37.34, 40.11, 60.08, 69.39; ESI-MS: *m/z* = 397 (M+Na).

(R)-3-((tert-butyldimethylsilyl) oxy) octan-1-ol, 8

Camphor sulphonic acid (0.074 g, 0.33 mmol) was added to a stirred solution of compound **7** (0.368 g, 1mmol) in 1:1 mixture of MeOH and CH_2Cl_2 at room temperature. The reaction mixture was stirred for 1.5 h and upon completion; the reaction was quenched with saturated $NaHCO_3$ solution. The product was extracted into CH_2Cl_2,the organic layer was evaporated under reduced pressure and the residue was column chromatographed over silica gel (60-120 mesh, EtOAc/hexane 1:9) to yield pure alcohol **8** (85 %); $[\alpha]_D^{25}$: + 12.1 (*c* 1, $CHCl_3$); IR (neat, cm^{-1}): 3354, 2924, 1121, 1089, 825; ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.02 (s, 6H), 0.82 (s, 12H), 1.17-1.35 (brs, 8H), 1.51-1.59 (q, J=6.17 Hz, 2H), 3.28 (brs, 1H), 3.72-3.82 (m, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ -4.41, 14.04, 18.12, 22.66, 24.84, 25.94, 32.03, 37.34, 40.11, 60.08, 69.39; ESI-MS: *m/z* = 283 (M+Na).

(R,Z)-ethyl 5-((tert-butyldimethylsilyl)oxy)dec-2-enoate, 9

To a solution of compound **8** (1.4 g, 5.34 mmol) in DMSO (5 mL) in a round-bottomed flask was added IBX (1.68 g, 6 mmol) in one portion and the reaction mixture was stirred for 1 h at ambient temperature. The reaction mixture was quenched with diethylether (5 mL), H_2O (0.5 mL) and filtered through a pad of celite. The residue was repeatedly washed with diethyl ether. The filtrate was then washed with water, brine, dried over anhydrous Na_2SO_4 and concentrated to give the crude aldehyde, which was pure enough and used in the next step without further purification.

60 % dispersion of NaH (0.448 g, 13.30 mmol) in mineral oil was added to a stirred solution of ethyl P,P bis (2,2,2-trifluoroethyl) phosphonoacetate (3.496 g, 10.52 mmol) in dry THF (50 mL) at 0 ^{o}C, resulting ylide solution was stirred for 45 min at the same temperature, then the reaction mixture was cooled to -78 ^{o}C. The crude aldehyde obtained above dissolved in dry THF (10 mL) was added drop wise and stirring was continued for further 3 h. After completion of the reaction, the reaction was quenched with saturated NH_4Cl solution (2 mL) at 0 ^{o}C, concentrated under reduced pressure. Residue obtained was dissolved in EtOAc washed with water and brine. Organic layer was dried over Na_2SO_4, evaporated under *vacuum* and the crude product was purified by silica gel column chromatography (100-200 mesh, EtOAc/hexane 2:8) to obtain **9** (74%) as colorless oily compound; $[\alpha]_D^{25}$: + 7.12 (*c* 1, $CHCl_3$);; IR (neat, cm^{-1}): 1728, 1682, 1080, 820; ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.04 (s, 6H), 0.82 (brs,12H), 1.25-1.32 (m, 11H), 2.88-2.99 (m, 2H) 3.73-3.85 (m, 1H), 4.13-4.24 (q, 2H) 5.88 (d, J=11.2 Hz, 1H), 6.38 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ -4.55, 14.31, 18.01, 22.46, 25.17, 31.79, 37.76, 38.21, 59.66, 71.35, 121.04, 146.41, 166.13; ESI-MS: *m/z* = 341 (M+Na).

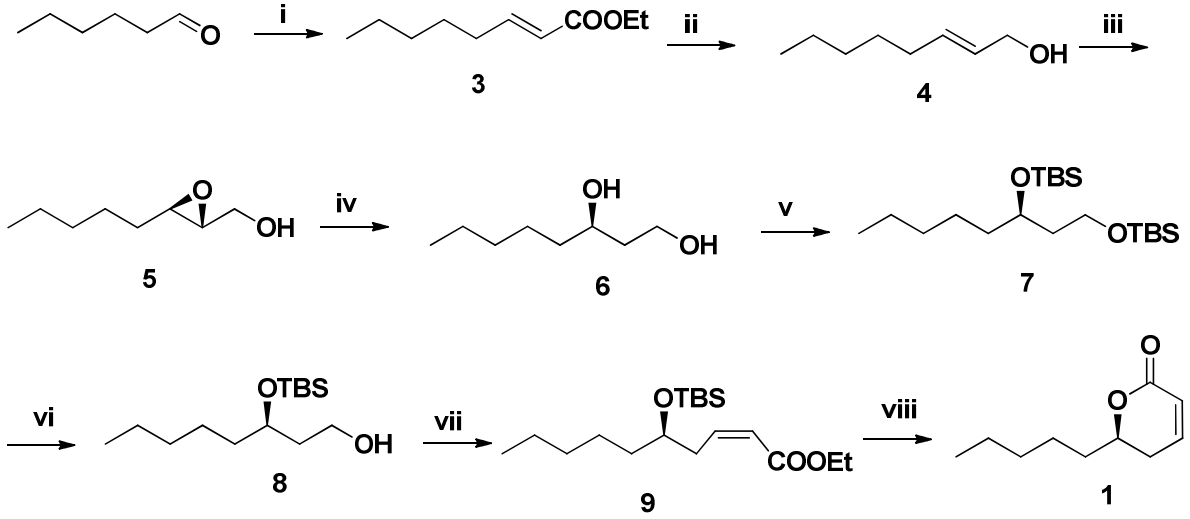
(R)-6-pentyl-5,6-dihydro-2H-pyran-2-one, (R)- Massoialactone, 1

To a stirred solution of compound **10** (0.594g, 3 mmol) in MeOH was added catalytic amount of PTSA and the contents were stirred for 3h at room temperature. When no starting material was observed on TLC, the reaction mixture was concentrated under reduced pressure, dissolved in EtOAc and washed with Na_2CO_3 solution (5 mL, 10%). Organic layer was separated and dried over anhydrous Na_2SO_4, concentrated under *vacuum* and the obtained residue was chromatographed over silica gel (100-200 mesh, CH_2Cl_2/hexane 1:9) yielding (*R*)-**1** (91%) as a colorless oil; $[\alpha]_D^{25}$: -108.8 (*c* 1, $CHCl_3$); IR (neat, cm^{-1}): 2930, 1716, 1610, 1048, 835; ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.86-0.91 (t, *J* = 6.4 Hz, 3H), 1.21- 1.30 (m, 5H), 1.62–1.86 (m, 3H), 2.28-2.38 (m, 2H), 4.4-4.45 (m, 1H), 6.1 (d, *J* = 9.8 Hz, 1H), 6.81-6.90 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 13.91, 22.43, 24.54, 29.42, 31.49, 34.81, 78.02, 121.45, 144.82, 164.43; ESI-MS: *m/z* = 191 (M+Na).

RESULTS AND DISCUSSION

As outlined in scheme 1, the α,β- unsaturated ester **3** was obtained from commercially available, cheap n-hexanal. The Horner-Wardsworth-Emmons olefination of aldehyde with triethylphosphonoacetate using NaH as base in benzene afforded α,β-unsaturated ester **3** in 95% yield. The compound **3** was then reduced to allyl alcohol **4** by employing alane reduction [12] conditions ($LiCl/LiAlH_4$) in THF. At first, alane (AlH_3) is produced in situ by the reaction between LiCl and $LiAlH_4$, which later selectively reduces the ester functionality in α,β-unsaturated ester to yield allyl alcohol in 82 % yield. The allyl alcohol compound **4** was then subjected to Sharpless asymmetric epoxidation [13] with Titanium isopropoxide and t-butyl hydroperoxide in presence of (+)- Diethyl tartarate in dichloromethane solvent at -15 ^{o}C afforded epoxy alcohol compound **5** in 85% yield. The next task was to open the epoxide in **5** regioselectively to get 1, 3- diol compound **6**, which was accomplished by treating the epoxy alcohol **5** with Red-al [14] in THF solvent at -20 ^{o}C for 8 hours. The 1, 3- diol is exclusively produced and the other isomer 1, 2-diol was almost not detected in the reaction mixture. The two hydroxy groups in **6** were completely protected as

silyl ethers using TBSCl and triethyl ethyl amine (Et_3N) in Presence of dimethyl aminopyridine (DMAP) catalyst to yield **7** in 96% yield. Further, the primary hydroxy group in compound **7** was selectively deprotected using camphor sulfonic acid (CSA) in methanol and dichloromethane mixture to yield compound **8** in 85% yield. The free hydroxy group in compound **8** was then oxidized to aldehyde using Iodoxy benzoic acid (IBX) in dimethyl sulfoxide (DMSO) solvent, thus obtained crude aldehyde was then immediately subjected to Still - Gennari modification of Horner – Emmons olefination [15] using ethyl(bistrifluoroethyl) phosphonoacetate in the presence of NaH in THF to afford Z-isomer exclusively. Finally, cylization of Z-ester **9** was accomplished using catalytic amount of p-toluenesulfonic acid (p- TsOH) in methanol to yield (*R*)- Massoialactone, **1** in 91% yield by the in situ deprotection of TBS group.



Scheme 1: ***Reagents and conditions:(i) triethyl phosphonoacetate, NaH, dry Benzene, 0 ºC- RT, 8 h, 95%; (ii) $LiAlH_4$, $AlCl_3$, THF, 0 °C, 1 h, 82%;(iii) (+)- DET, Ti(O-i-Pr)$_4$, TBHP, CH_2Cl_2, molecular sieves 4 A°, -15 °C, 85%; (iv) Red-al, THF, -20 °C, 6h, 96% (v) TBDMSCl, Et_3N, DMAP, CH_2Cl_2, RT, 8 h., 96%. (vi) CSA, MeOH:CH_2Cl_2 (1:1), RT, 85% (vii) (a) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, -78°C, 1h; (b) $EtO_2CCH_2P(O)(OCH_2CF_3)_2$, NaH, dry THF, -78°C, 2 h, 74%. (viii) p-TSOH, MeOH, 3 h, 91%***

CONCLUSION

The enantioselective synthesis of naturally occurring bioactive compound (*R*) - Massoialactone has been successfully achieved employing Sharpless asymmetric epoxidation of allyl alcohol and selective hydride reduction of epoxy alcohol reactions as the key steps. The synthetic route can conveniently be utilized for the preparation of various analogs of (*R*)-Massoialactone.

Acknowledgements
One of the authors, B.N.R. thanks CSIR, New Delhi for the award of research fellowship. The authors are also thankful to the Director, NCL for constant support and encouragement.

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