Tetrahedron Vol 49, No 29, pp. 6429-6436, 1993
Printed in Great Britain

0040-4020/93 $6.00+.00

A Short and Efficient Synthesis of (-) Mintlactone and (+) iso-Mintlactone#

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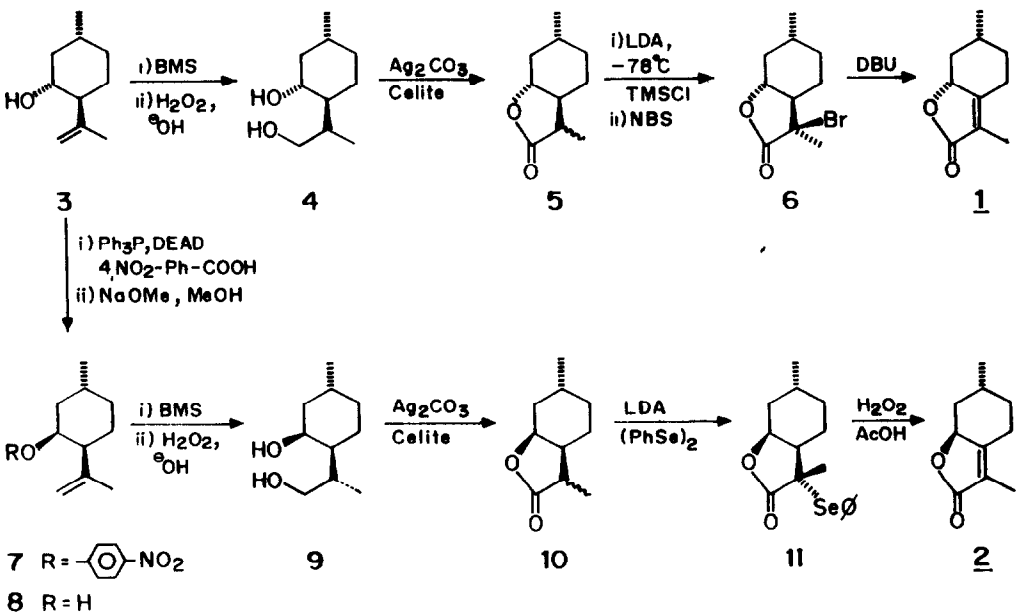
(*Received in UK* 18 *January* 1993)

Abstract: *A short, highly convenient stereoselective synthesis of (-) Mintlactone (1) and (+)iso-mintlactone (2) from (-) iso-pulegol (3) are described.*

(-) Mintlactone (**1**) & (+) *iso*-mintlactone (**2**), minor components of commercially important flavouring essential oils are found in peppermint oil & spearmint oil[1]. These monoterpenes compounds possess a butenolide moiety as the essential component. Our interest in butenolides has led us to devise a general methodology for butenolides construction,and synthesis of (±) mintlactone and (±)*iso*-mintlactone[2]. Since there was no report on the synthesis of optically pure **1** & **2**, we undertook their synthesis. During the course of development of butenolide methodology, Carda *et al*[3a] reported the first stereoselective synthesis of (-) Mintlactone (**1**) *via* intramolecular radical cyclisation as the key step comprising of more than twelve steps. The chiral starting material in turn was obtained by enzymatic hydrolysis in twelve steps. Recently Shishido *et al*[3b] have also reported the total synthesis of (-) **1** & (+) **2** involving an intramolecular [3+2] cycloaddition reaction to generate the butenolide as the key step.

Our strategy was to obtain dihydro mintlactone and *iso*-mintlactone, which in turn could be prepared from (-) *iso*-pulegol (**3**) as the common starting material and then introduce the double bonds to furnish (-) **1** & (+) **2** respectively. We describe a short and efficient synthesis of (-) **1** and (+) **2** starting from easily available starting materials. It was realised that (-) *iso*-pulegol (**3**) would be an ideal starting material for both (-) mintlactone (**1**) as well as (+) *iso*-mintlactone (**2**) as it incorporates a methyl as well as a hydroxy group in a *cis*-stereochemical disposition, well suited for conversion to (-) **1**; whereas,the required trans stereochemistry for (+)*iso*-mintlactone (**2**) could be easily obtained by a simple inversion at the C-OH centre.

Conversion of (-) *iso*-pulegol (**3**) to (-) mintlactone (**1**) was achieved by the following set of reactions. Hydroboration[4] (Scheme-1) of **3** furnished the desired diol **4** in excellent yields (98%). The 1,4-diol **4** thus obtained was smoothly transformed to the butyrolactone **5** using Ag_2CO_3/ celite[5] in high yields (85%) as a mixture of diastereomers. Having constructed dihydromintlactone **5**, the next task was of to introduce, the double bond. This was acccomplished as follows. Treatment of the lactone **5** with LDA at -78°C and subsequent treatment of the resultant enolate, with chlorotrimethyl silane and NBS[6] in one pot furnished the bromolactone **6** in 95% yield.The final dehydrohalogenation of **6** was smoothly achieved by refluxing it in benzene (1 h) in the presence of DBU[7] to furnish (-) mintlactone (**1**) in 89% yield. Spectral and physical data of mintlactone (**1**) thus obtained were found to be identical in all respects with the data reported in literature[1,3a] for natural **1**. Additionally, the optical purity of (-) **1** was also confirmed by GC analysis on chirasil val. column: temp 120°C, split ratio (1:100), retention time 9.12 mn.



Scheme - 1

Iso-mintlactone (**2**) was also conveniently obtained from **3** by the following set of reactions. The stereochemistry at the C-OH centre was inverted by employing a modified version of Mitsunobu conditions[8]. Thus *neo-iso*-pulegol (**8**) was obtained from **3** through its 4-nitrobenzoate (**7**) followed by hydrolysis in 83% overall yields. Having obtained **8** with desired stereochemistry as required in *iso*-mintlactone (**2**), it was subjected to hydroboration[4] to furnish diol **9** in excellent yields. Selective oxidation of the primary alcohol in preference to the secondary alcohol with Ag_2CO_3/celite[5] in refluxing benzene failed to furnish the desired lactone **10**. However, this problem was successfully circumvented by performing the reaction at elevated temperature employing toluene as the solvent and, under these condition the lactone **10** was obtained in 69% yield. To introduce the double bond in **10** a different strategy than that employed for mintlactone had to be adopted. Thus, treatment of **10** with LDA followed by quenching the anion with diphenyl diselnide furnished the seleno lactone **11** as a colourless solid in 82% yield. Oxidation of **11**, with H_2O_2[9] furnished (+) *iso*-mintlactone (**2**) as a colourless solid (mp=79°C, lit.[1] mp=77-79°C) after recrystallisation. ^{1}H-NMR values of **2** were in perfect agreement with those reported[1a] for **2** obtained from natural source. Optical purity of **2** thus obtained was also confirmed by GC analysis on Chirasil val. column: temp 120°C; retention time 12.67 min.

Thus, a very short, convenient and highly stereoselective syntheses (-) mintlactone (**1**) and (+) *iso*-mintlactone (**2**) have been achieved starting from a common precursor *viz.* (-) *iso*-pulegol **3**.

Acknowledgements: P.K. Zubaidha thanks CSIR, India for the award of fellowship. We thank Prof. Miguel Carda for supplying us the spectra (^{1}H & ^{13}C NMR) of **1**.

EXPERIMENTAL

All mps & bps are uncorrected. Melting points were determined in open capillaries & Kofler block instrument Infra red spectra (IR) (ν_{max} in cm^{-1}) were recorded as smears or nujol mulls (solids) or in solution on a Perkin Elmer 683 and with sodium chloride optics. ^{1}H NMR spectra were recorded on Varian 80, WH-90 or Varian 200 spectrometer in $CDCl_3$ containing TMS as an internal standard. All chemical shifts are reported in parts per million (δ) downfield from TMS. Mass spectra were recorded on Finnigan-MAT 1020 automated GC/MS spectrometer using an ionisation potential of 70 ev. All

solvents and reagents were purified & dried by standard techniques. Progress of the reaction was monitored by thin layer chromatography (tlc).

(-)-(1R, 3R, 4S, 8R)-p-Menthane-3,9-diol (4): The diol **4** was obtained by the hydroboration oxidation of (-)-*iso*pulegol **3** as described Schulte-Elte et al[4]. This material was sufficiently pure by NMR and optical rotation ($[\alpha]_D$ = -17, c=5.8 $CHCl_3$, lit.[4] $[\alpha]_D$ = -18) for use in the next reaction.

(3R, 6R, 7aR, 8S) 3,6-dimethyl hexahydro-2(3H) benzofuranone (5): The solution of diol **4** (0.520 g, 3.0 mmol) in dry benzene (10 ml) was taken in two necked (50 ml) flask fitted with a Dean and Stark apparatus. To this solution reaction Ag_2CO_3/celite (2.499 g, 9.06 mmol) was added and the reaction mixture was refluxed 24 hours. The reaction mixture was cooled and filtered. Benzene was removed under reduced pressure to furnish a residue which was purified by column chromatography (SiO_2) using 5% ethyl acetate in pet ether as eluent to furnish saturated lactone **5** (0.420 g, 83%) as a mixture of stereoisomers (88:12) as a viscous oil. Spectral property of the major isomer IR (Neat): 1770, 1460, 1000 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 200 MHz): δ 1.25 (3H, d, J = 6.4 Hz); 1.15 (3H, d, J = 7.5 Hz); 1.25 (m, 5H); 1.5 -1.7 (m, 1H); 1.6-2.05 (m, 1H); 2.2 (m, 1H); 2.55 (q, 1H); 4.05 (ddd, 1H, J = 3.78, 11.1 Hz). ^{13}C-NMR ($CDCl_3$): 180 (s), 81.3 (d), 47.1 (d), 38.7 (d), 38.18 (t), 31.24 (t), 31.36 (t), 23.78 (t), 22 (q), 9.56 (q). Mass: m/z M^+ (168, 7%), 113 (100), 85 (88), 81 (82), 95 (77), 67 (71), 109 (63), 124 (58), 156 (51), 56 (31), 139 (6). Optical rotation (mixture) $[\alpha]_D$ = +63.3, (c= 11.7, $CHCl_3$). Analysis: Calculated for $C_{10}H_{16}O_2$: C, 71.42; H, 9.52. Found C, 71.4; H, 9.48.

(3R, 6R, 7aR, 8S) 3,6 dimethyl 3-bromo hexahydro-2(3H) benzofuranone (6): Saturated lactone **5** (0.4 g, 2.3 mmol) in dry THF (5 ml) was added to the solution of lithium diisopropylamide [prepared from diisopropylamine (0.280 g, 2.7 mmol) and butyllithium (0.2 g, 3.1 mmol) in dry THF 7 (ml) at 0°C under argon atmosphere] at -78°C. After 30 minutes chlorotrimethylsilane (0.333 g, 3.0 mmol) was added. To the resultant solution , NBS (0.550 g, 3.0 mmol) was added after a further 15 minutes. The reaction mixture was stirred at -78°C and warmed to room temperature and stirred overnight. Water was added and the residue thus obtained by usual work up was further purified by column chromatography (SiO_2) using 5% ethyl acetate in pet ether as eluent to furnish bromolactone **6**

(0.560 g, 95%) as a colourless solid. mp = 107-110°C IR ($CHCl_3$): 1780, 1460, 1400, 1230, 1100, 1010 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 1.05 (3H, d, J = 7 Hz); 1.1-1.5 (m, 6H); 1.7 (m, 1H); 1.95 (s, 3H); 2.3 (m, 1H); 4.1 (ddd, 1H, J = 4.1, 9.4, 13.4 Hz). ^{13}C-NMR ($CDCl_3$): 174.5 (s), 80.7 (s), 59.56 (d), 56.26 (d), 37.85 (t), 33.63 (t), 31.24 (d), 25.33 (t), 24.91 (q), 22.15 (q). Mass : m/z. M^+ (247, 0%), 81 (100), 67 (4), 123 (51), 55 (81), 95 (14), 41 (10). Optical rotation $[\alpha]_D$ = +16.8 (c = 1.5, $CHCl_3$). Analysis: calculated for $C_{10}H_{15}BrO_2$: C, 48.78; H, 6.09. Found C, 48.60; H, 6.43.

(6R, 7aR) 3,6 dimethyl-5,6,7,7a tetrahydro-2 (4H) benzofuranone (1): To a solution of bromolactone **6** (0.240 g, 0.9 mmol) in benzene (10 ml), DBU (0.148 g, 0.9 mmol) was added. The reaction mixture was refluxed for 45 min, filtered and solvent was removed under reduced pressure to furnish a residue. Purification of the residue by column chromatography (SiO_2) using 5% ethyl acetate in pet ether as eluent afforded (-) mintlactone (1) (0.122 g, 76%) as a viscous oil. IR (Neat): 1760, 1700. ^{1}H-NMR ($CDCl_3$, 200 MHz): δ 1.00 (d, 3H, J = 6.5 Hz); 1.1-1.5 (m, 2H); 1.75 (m, 1H); 1.8 (t, 3H, J = 1.4 Hz); 2.00 (m, 1H); 2.25 (m, 1H); 2.45 (m, 1H); 2.8 (ddd, 1H, J = 1.9, 4.6, 14.0 Hz); 4.66 (dd, 1H, J = 6.0, 11.0 Hz). ^{13}C-NMR ($CDCl_3$): δ 174.86 (s), 162.62 (s), 119.85 (s), 80.24 (d), 42.27 (t), 34.82 (t), 29.19 (d), 25.75 (t), 21.45 (q), 8,38 (q). Mass: m/z M^+ (166, 100%), 137 (60), 109 (53), 67 (50), 81 (47.5), 95 (42), 123, 53 (17.5), 77 (10), 51 (8), 91 (7), 63 (3). Optical rotation $[\alpha]_D$ = -57 (c = 2.4 $CHCl_3$), $[\alpha]_D$ = -56.6 (c = 2.2, EtOH), lit.[1,3a] $[\alpha]_D$ = 51.8 (c = 10, EtOH). Analysis: Calculated for $C_{10}H_{14}O_2$: C, 72.28; H, 8.43. Found C, 72.02; H, 8.08.

(+)-(1R, 3S, 4S, 8S)-p-menthane-3,9 diol (9): *Iso*pulegol (4.647 g, 3 mmol), triphenyl phosphine (9.48 g, 3.6 mmol) and p-nitrobenzoic acid (6.030 g, 3.6 mmol) were dissolved in dry benzene (40 ml) in a two necked flask (100 ml) under nitrogen atmosphere. Diethyl azodicarboxylate (6.3, 3.6 mmol) was added dropwise at 0°C. The clear yellow reaction mixture was stirred at R.T. for 3 hours. The reaction mixture was filtered and benzene was removed under reduced pressure to furnish a residue. The residue was purified by column chromatography (SiO_2) using pet ether as a eluent to furnish benzoate **7** (7.655 g, 84%) as a yellow solid, which was recrystallised from methanol. mp = 92°C, IR ($CHCl_3$): 1750, 1460, 1400, 1340, 1140, 1160, 1240 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 90 MHz): δ 0.8 (d, 3H, J = 8 Hz); 1.15 (m, 6H); 4.66 (s, 1H); 5.4 (s, 1H); 8.1 (m, 4H). Mass: M^+ (303,

20%): 150 (100), 136 (91), 104 (55), 121 (54), 93 (44), 76 (22), 69 (10), 55 (9). Optical rotation $[\alpha]_D$ = +53 (c = 4.9, $CHCl_3$).

Benzoate **7** (4.822 g, 1.5 mmol) was added to a solution of MeONa/MeOH [prepared from sodium (0.726 g, 3.1 mmol) and MeOH (30 ml)] at room temperature, and the reaction mixture was stirred at room temperature for 30 minutes. Water was added, extracted with ether and the ether layer was washed with water (2 x 30 ml). The ether was removed under reduced pressure to furnish *Neo-iso*pulegol **8** (2.360 g, 97%) as a oil. Spectral data and physical data of *Neo-iso*pulegol (**8**) were found to be identical in all respects with data reported in literature[4].

The diol **9** was obtained by the oxidative hydroboration, of (+)-*Neo*-isopulegol **8** as described Schulte-Elte et al[4]. This material was sufficiently pure by NMR and optical rotation for use in the next reaction.

(3S, 6R, 7aS, 8S)-3,6 dimethyl hexahydro -2(3H) benzofuranone (10): The solution of diol **9** (1.752 g 10.1 mmol) in dry toluene (20 ml) was taken in two necked (50 ml) flask fitted with a Dean and Stark apparatus. To this solution Ag_2CO_3/Celite (9.6 g, 34 mmol) was added and the reaction mixture was refluxed for 24 hrs. The reaction mixture was cooled and filtered, and toluene was removed under reduced pressure to furnish a residue. The residue was purified by column chromatography (SiO_2) using 5% ethyl acetate in pet ether as eluent to furnish saturated lactone **10** as a mixture of stereoisomers (92:8) (1.186 g, 70%) mp = 41-45°C spectral data : IR ($CHCl_3$): 1770, 1460, 1210, 1180 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 200 MHz): δ 0.95 (d, 3H, J = 6.4 Hz); 1.3 (d, 3H, J = 7.2 Hz); 1.05-1.25 (m, 2H); 1.55-1.75 (m, 3H); 1.75-2.05 (m, 2H); 2.1-2.3 (m, 1H); 2.4 (q, 1H); 4.7 (dd, J = 3.4, 7 Hz). ^{13}C-NMR ($CDCl_3$): 180.66 (s), 77.66 (d), 44.32 (d), 41.5 (d), 36.18 (t), 31.85 (t), 27.54 (t), 26.23 (d), 21.70 (q), 14.32 (q). Mass: m/z. M^+ (168, 2%), 95 (100), 67 (71), 81 (60.5), 55 (40.5), 109 (26.5), 124 (22). Optical rotation (mixture) $[\alpha]_D$ = - 36 (c = 2.6, $CHCl_3$). Analysis calculated for $C_{10}H_{16}O_2$, C. 71.42; H, 9.52. Found C, 71.83; H, 9.66.

(3S, 6R, 7aS, 8S)-3,6 dimethyl-3-phenyl seleno-2 (3H) benzofuranone (11): Saturated lactone **10** (0.3 g, 1.78 mmol) in dry THF (5 ml) was added to the solution of LDA [prepared from diisopropyl amine (0.2 g, 1.98 mmol), butyllithium (0.150 g, 2.3 mmol) in dry THF (7 ml) at 0°C under argon

atmosphere] at -78°C. After 30 minutes diphenyl diselenide (0.555 g, 1.78 mmol) was added, the reaction mixture stirred at -78°C for 60 minutes, warmed to RT and stirred overnight. The reaction mixture was quenched with water and extracted with ether.Drying and evaporation of solvent furnished a residue which was purified by column chromatography (SiO_2) using 5% ethyl acetate in pet ether as eluent to furnish selenolactone **11** (0.476 g, 83%) as a colourless solid, mp = 140°C. Spectral data: IR ($CHCl_3$): 1770, 1540, 1251, 1209, 1097 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 200 MHz): δ 0.95 (d, 3H, J = 6.5 Hz); 1.1-1.3 (m, 3H); 1.55 (s, 3H); 1.75 (m, 3H); 2.25 (m, 2H); 5.1 (dd, 1H, J = 3.5, 6.9 Hz); 7.7-7.3 (m, 5H). ^{13}C-NMR ($CDCl_3$): 177.18 (s), 138.19 (s), 129.87 (d), 129.26 (d), 125.8 (d), 76.951 (s), 51.83 (d), 45.46 (d), 36.312 (t), 32.305 (t), 26.58 (d), 25.29 (t), 22.04 (q), 19.06 (q). Mass: m/z. M^+ (323, 64%), 167 (100), 149 (88), 93 (57), 121 (50), 81 (50), 55 (51), 158 (41), 77 (41), 111 (16), 139 (16). Optical rotation $[\alpha]_D$ = +40.5 (c=2.2, $CHCl_3$), Analysis: Calculated for $C_{16}H_{20}O_2Se$; C, 59.44; H, 5.84. Found C, 59.27; H, 6.19.

(6R, 7aS) 3,6-dimethyl-5,6,7,7a tetrahydro-2(4H) benzofuranone (2):To a solution of α-phenyl selenolactone **11** (0.2 g, 0.6 mmol) in THF (10 ml) containing 0.1 ml of CH_3COOH cooled to 0°C, was added 30% H_2O_2(0.14 ml). The reaction mixture was stirred for 30 minutes at 0°C, then poured into cold saturated sodium bicarbonate solution and extracted with ether. The ether was removed under reduced pressure to furnish a residue which was purified by column chromatography over silica gel,eluting with 5% ethyl acetate in pet ether as eluent to afford (+)-*iso* mintlactone (**2**) (0.074 g, 73%) as a colourless solid, mp=78-79°C. Spectral data: IR ($CHCl_3$): 1760, 1690, 1460, 1410, 1260 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 200 MHz): δ 1.15 (d, 3H, J = 7.3 Hz); 1.37 (ddd, 1H, J = 11.9, 4.5 Hz); 1.59 (ddd, 1H, J = 13.3, 4.6 Hz); 1.8 (t, 3H, J = 1.5 Hz), 1.8 (m, 1H), 2.2-2.5 (m, 3H), 2.7 (ddd, 1H, J = 14.4, 4.9, 2.1 Hz); 4.8 (dd, 1H, J = 11.2, 6 Hz). ^{13}C-NMR ($CDCl_3$): δ 175.11 (s), 163.20 (s), 119.56 (s), 77.64 (d), 39.77 (t), 31.85 (t), 27.55 (q), 21.97 (t), 17.45 (d), 8.35 (q). Mass: m/z M^+ (166, 95%), 81 (100), 67 (89), 95 (85), 109 (82), 137 (73), 123 (37), 55 (35), 91 (18), 73 (8), 60 (7), 151 (3). Optical rotation $[\alpha]_D$ = +79 (c = 0.7, EtOH) lit.[1] $[\alpha]_D$ = +76.9 (c=5, EtOH). Optical purity of (+)-*iso*-mintlactone (**2**) was also confirmed by GC analysis on chirasil val. column: temperature 120°C, split ratio (1:100). Retention time 12.67 min. Analysis calculated for $C_{10}H_{14}O_2$, C, 72.2,; H, 8.43. Found C, 72.17; H, 8.39.

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