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Synthesis of (−)-Mintlactone via Intramolecular Wittig–Horner Reaction

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ABSTRACT

An efficient synthesis of (−)-mintlactone has been described starting from (+)-pulegone and employing the intramolecular Wittig–Horner reaction as the key step.

Key Words: Mintlactone; Intramolecular Wittig–Horner reaction; Phosphonate; Stereoselectivity.

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INTRODUCTION

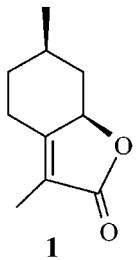
(−)-Mintlactone **1** and (+)-isomintlactone **2** (Fig. 1) are monoterpenic compounds found as minor components in the essential oil of several *Mentha* species.

These two diastereomeric *p*-menthanolides were isolated for the first time in 1968 from *Mentha cardiaca*[1] and later from *M. Pulegium L.*[2] and from a variety of *M. arvensis* known as Shubi.[3] The essential oil of *Mentha piperita L.*(peppermint oil), one of the most important commercial flavoring material is produced in many countries. Its chemical composition has been investigated showing more than 300 minor volatile components.[4] Among the minor constituents **1** and **2** are reported to be present in the oil of *M. piperita L.*[5]

The relative and absolute configurations of these two lactones were assigned by Takahashi et al.[6] Their synthesis has attracted attention of many organic chemists as is evident by number of literature reports[7] including a recent review article dealing with this subject (for the syntheses of mintlactone, see: review article,[8]). Most of the synthetic approaches are either nonstereoselective or suffer from low overall yields and/or large number of steps involved. As a part of our research interest in developing methodologies using phosphorus ylides and their subsequent application to biologically useful compounds,[9] we report here an efficient and enantioselective route to the synthesis of title compound starting from (+)-pulegone employing intramolecular Wittig-Horner reaction as the key step.

RESULTS AND DISCUSSION

The synthesis of (−)-mintlactone started from (+)-pulegone **3** as depicted in Sch. 1. (+)-Pulegone **3** was reduced to *cis*-pulegol **4**[10] using sodium



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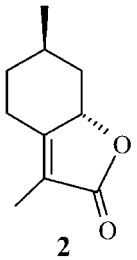

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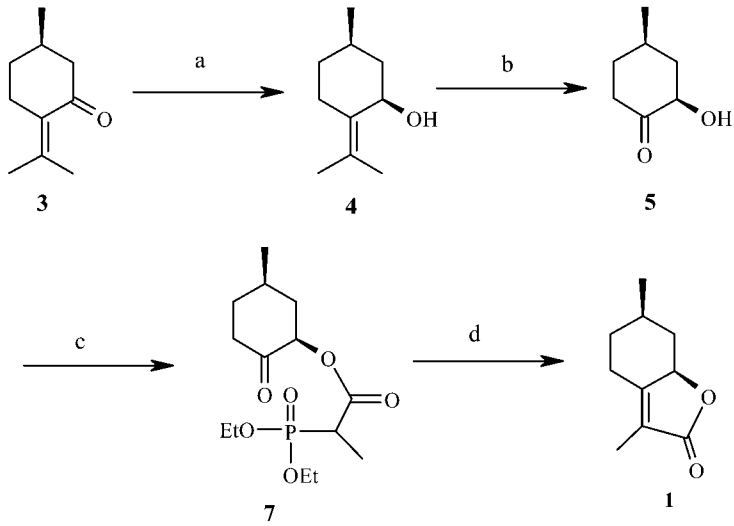
Figure 1. Structure of (−)-mintlactone **1** and (+)-isomintlactone **2**.



Scheme 1. Reagents and conditions: (a) $CeCl_3 \cdot 7H_2O$, MeOH, $NaBH_4$, 0°C, 30 min, 98%; (b) O_3, CH_2Cl_2, −78°C, 45 min, 95%; (c) $(EtO)_2P(O)CH(Me)COOH$ **6**, DCC, CH_2Cl_2, 0°C-rt, 24 hr, 85%; (d) NaH, THF, reflux, 6 hr, 90%.

borohydride and cerium chloride in 98% yield and 90% ee,[a] $[\alpha]_D^{25}$ −103 (*c* 1, MeOH). Compound **4** was subjected to ozonolysis to afford 2-hydroxy-4-methylcyclohexanone **5** in excellent yield. The other component **6**, required for the synthesis of phosphonate **7** was prepared in two steps in the following way. The Arbuzov reaction between triethylphosphite and ethyl 2-bromopropionate furnished triethyl 2-phosphonopropionate[11] which on subsequent hydrolysis with 85% aqueous potassium hydroxide gave the desired acid **6** in 90% yield. The coupling of alcohol **5** with acid **6** was readily performed under neutral condition using DCC as dehydrating agent to afford 2-(diethoxyphosphoryl)propionic acid 5-methyl-2-oxocyclohexyl ester **7** in 85% yield, $[\alpha]_D^{25}$ +39.0 (*c* 2, $CHCl_3$) which on treatment with sodium hydride in THF furnished (−)-mintlactone **1** in 90% yield $[\alpha]_D^{25}$ −57.0 (*c* 2, $CHCl_3$) [Lit.[7d] $[\alpha]_D^{25}$ −57.0 (*c* 2.4, $CHCl_3$)].

[a]The enantiomeric excess was determined by HPLC. HPLC model: Merck-Hitachi Lachrom PDA system D-7000 series; Column: Lichrospher RP-18 (4 mm ID × 125 mm); Mobile phase: methanol: water: (90 : 10); Flow: 1 mL/min.

EXPERIMENTAL

Solvents were purified and dried by standard procedure before use; petroleum ether of boiling range 60–80°C was used. Optical rotations were measured using sodium D line on a JASCO P-1020 microprocessor base polarimeter. Infrared spectra were recorded on ATI MATTSON RS-1 FT-IR spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker AC-200 spectrometer. The chemical shifts were expressed in ppm (δ) down field from TMS with residual $CDCl_3$ (δ 7.27) as internal standard. Mass spectra were obtained with TSQ 70, Finningen MAT mass spectrometer.

2-Hydroxy-4-methylcyclohexanone (5). To a solution of *cis*-pulegol **4** (7.0 g, 45.5 mmol) in dichloromethane (75 mL) cooled to −78°C was bubbled ozone. The color of reaction mixture became blue–green over a period of 45 min. Then oxygen was passed for 15 min and dimethyl sulfide (2 mL) was added. The reaction mixture was stirred at 0°C for 15 min and then at room temperature for 15 min. The evaporation of solvent gave the product **5** (5.53 g, 95%) as a viscous liquid, which was subsequently used in the next reaction without any further purification. $[\alpha]_D^{25}$ −15.8 (*c* 0.54, $CHCl_3$). IR (Neat): cm^{-1} 3443, 2930, 1719, 1672, 1455. ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 1.00$ (d, $J = 7.4$ Hz, 3H), 1.11–2.60 (m, 7H), 3.85 (bs, 1H), 4.20 (m, 1H). ^{13}C NMR (200 MHz, $CDCl_3$): $\delta = 18.85$, 27.50, 35.00, 36.35, 40.35, 88.85, 208.25. EIMS (*m*/*z*): M^+ 128 (24), 112 (12), 84 (100), 71 (57). Anal. calc. for $C_7H_{12}O_2$: C, 65.59; H, 9.44; Found: C, 65.34; H, 9.17.

2-(Diethoxyphosphoryl)propionic acid 5-methyl-2-oxo-cyclohexyl ester (7). To a solution of 2-hydroxy-4-methylcyclohexanone **5** (2.50 g, 19.5 mmol) and 2-(diethoxyphosphoryl)propionic acid **6** (4.10 g, 19.5 mmol) in dry dichloromethane (25 mL) cooled to 0°C was added DCC (4.82 g, 23.4 mmol) under vigorous stirring. The reaction mixture was stirred at room temperature for 24 hr under nitrogen. Solid was separated by filtration, water was added to the filtrate, and extracted with dichloromethane (2 × 50 mL). The combined organic layers were washed with water, brine, and dried over Na_2SO_4. The evaporation of solvent gave the crude product which on purification by silica gel column chromatography using petroleum ether : ethyl acetate (4 : 6) as eluent afforded the phosphonate **7** (5.31 g, 85%) as a viscous liquid. $[\alpha]_D^{25}$ +39.0 (*c* 2, $CHCl_3$). IR (Neat): cm^{-1} 2930, 1727, 1455. ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 1.02$ (d, $J = 7$ Hz, 3H), 1.27–1.55 (m, 12H), 2.04–2.29 (m, 2H), 2.42 (m, 2H), 3.09–3.24 (m, 1H), 4.08–4.21 (m, 4H), 5.20–5.30 (m, 1H). ^{13}C NMR (200 MHz, $CDCl_3$): $\delta = 10.73$, 15.28, 19.88, 29.58, 33.99, 36.49, 37.04, 38.33, 39.00, 39.66, 61.81, 75.20, 167.57, 202.60. EIMS (*m*/*z*): M^+ 320 (2), 261 (5), 219 (5), 179 (27), 151 (44), 123 (100), 81 (95), 65 (54). Anal. calc. for $C_{14}H_{25}O_6P$: C, 52.49; H, 7.87; Found: C, 52.75; H, 7.53.

(−)-Mintlactone (1). To a solution of phosphonate **7** (750 mg, 2.34 mmol) in dry THF (35 mL) was added sodium hydride [(225 mg, 4.69 mmol) 50% in mineral oil washed with THF]. The reaction mixture was refluxed for 6 hr, cooled to room temperature and then water was added. The reaction mixture was then extracted with ethyl acetate (3 × 25 mL). The organic layer was separated, washed with brine, and dried over anhydrous Na_2SO_4. Evaporation of solvent gave the crude product which on silica gel column chromatography using petroleum ether : ethyl acetate (9 : 1) as eluent afforded (−)-mintlactone **1** (350 mg, 90%) as an oil. $[\alpha]_D^{25}$ −57 (*c* 2, $CHCl_3$) [lit.[7d] $[\alpha]_D^{25}$ −57 (*c* 2.4, $CHCl_3$). IR (Neat): cm^{-1} 2929, 2870, 1754, 1688, 1455. ^1H NMR (200 MHz, $CDCl_3$): $\delta = 1.00$ (d, $J = 6.6$ Hz, 3H), 1.10–1.50 (m, 2H), 1.75 (m, 1H), 1.80 (t, $J = 1.4$ Hz, 3H). 1.95–2.25 (m, 2H), 2.41 (m, 1H), 2.82 (m, 1H), 4.61 (m, 1H).

CONCLUSION

In conclusion, a very short synthesis of (−)-mintlactone has been achieved starting from commercially available (+)-pulegone and using intramolecular Wittig-Horner reaction as the key step. The synthetic strategy described here has significant potential for further extension to (+)-isomintlactone via Mitsunobu inversion of configuration. Currently studies are in progress in this direction.

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