A Short Route to (−)-Mintlactone by Thallium(III)-Mediated Cyclization of (−)-Isopulegol

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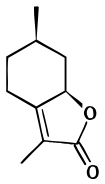
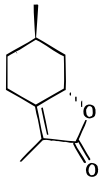
(−)-Mintlactone **1** and (+)-isomintlactone **2** are endo α,β-unsaturated monoterpene-γ-lactones, isolated for the first time in 1968 from *Mentha cardiaca*.[1] These two diastereomeric *p*-menthanolides are also found in *Mentha arvensis*,[2] and as minor constituents of the commercially important essential oil (peppermint oil) of *Mentha piperita* L.[3]



1

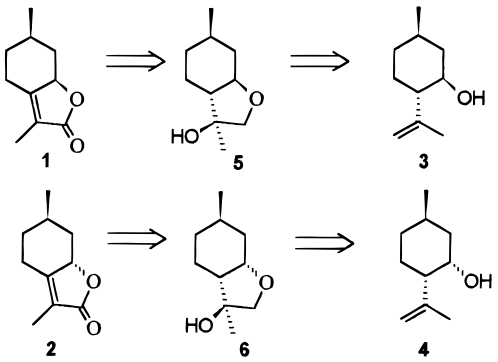


2

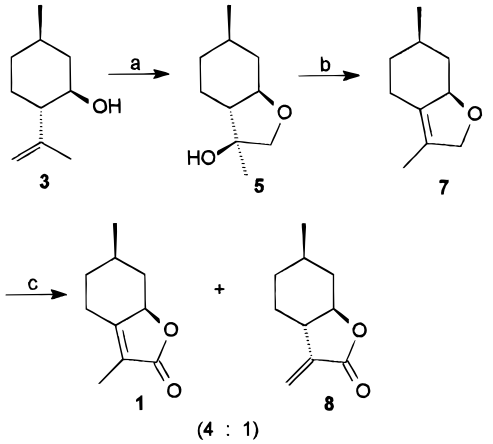
Their synthesis has attracted the attention of many organic chemists, as attested by the number of papers dealing with this subject.[4−14] The syntheses generally vary from multistep enantioselective to short but not even very diastereoselective, with the exception of the approach described by Chavan et al.[10] starting from (−)-isopulegol **3**.

In this note, we report a shorter route to the title compound **1**, employing as the key step the thallium triacetate (TTA)-mediated cyclization of (−)-isopulegol **3**, previously described by us.[15] This reaction leads in very good yield to the β-hydroxy cyclic ether **5**, in a highly regio- and stereoselective manner. Similarly,[15] (+)-neoisopulegol **4** furnishes the β-hydroxy cyclic ether **6**, so we proposed that regioselective dehydrations of **5** and **6**, followed by allylic oxidations, would give the desired lactones **1** and **2**, as shown in the following retrosynthetic analysis (Scheme 1).

Scheme 1



Scheme 2[a]



[a] Key: (a) TTA, AcOH/H_2O (1:1), 40 min, rt, 86%; (b) $SOCl_2$, Et_2O, 24 h, rt, 70%; (c) CrO_3·2py, CH_2Cl_2; chromatographic separation: 60% of **1**, 15% of **8**.

Thus, following this general strategy, the synthesis of **1** was accomplished in three steps, as shown in Scheme 2.

The dehydration of the tertiary hydroxyl group of **5** was tried in several different conditions, and the best results were obtained by using $SOCl_2$ in Et_2O. Under these conditions the endo unsaturated ether **7** is the only useful product obtained, whereas $SOCl_2$ in pyridine gave mainly the corresponding chloride.

Oxidation[16] of **7** with Collins' reagent led to a 4:1 mixture of the desired lactone **1** and the isomeric exo α-methylene-γ-lactone **8**,[17] which were separated by column chromatography on silica gel (60% isolated yield

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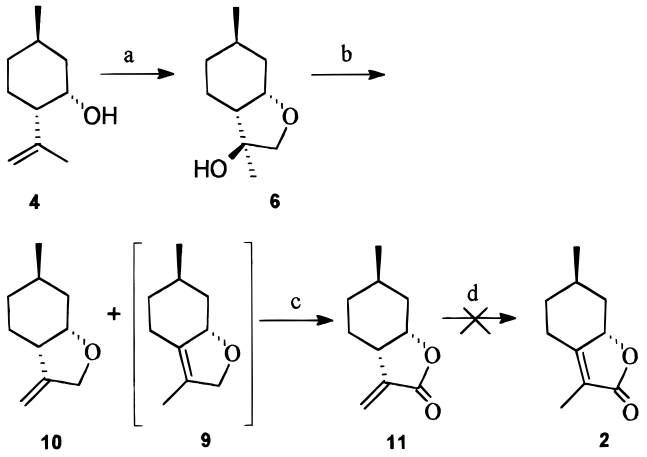
Scheme 3[a]



[a] Key: (a) TTA, AcOH/H_2O (1:1), 40 min, rt, 92%; (b) $SOCl_2$, Et_2O, 24 h, rt; (c) CrO_3·2py, CH_2Cl_2, chromatographic purification: 60% overall yield of **11** from **6**; (d) $(Ph_3P)_3RhCl$, EtOH or DMF, rt, 48 h; or sealed tube, 100 °C, 3 h.

of **1** and 15% of **8**). The structures of **1** and **8** were determined principally by ^1H and ^{13}C NMR spectral comparisons with literature data.[3,18]

On the other hand, when we tried to synthesize (+)-isomintlactone **2** from the *cis*-fused *β*-hydroxy ether **6**, the product of the dehydration step was the unstable exo unsaturated ether **10**,[17] which was oxidized directly to the known α-methylene-*γ*-lactone **11**[17] (60% yield starting from **6**), as shown in Scheme 3. Only traces of the endo unsaturated ether **9** were observed in the reaction mixture. Our attempts to isomerize both exo lactones **8** and **11** into the endo lactones **1** and **2** were unsuccessful using $(Ph_3P)_3RhCl$, although Crisp and Meyer[11] have achieved the similar reaction on the diastereomeric all *cis*-exo-lactone with $HRh(Ph_3P)_3CO$.

In conclusion, a very short synthesis of (−)-mintlactone **1** has been achieved starting from commercially available (−)-isopulegol; this route proved superior in all aspects to the alternative procedure, recently reported by us,[19] starting from carboxylic acids. Moreover, the approach here described is a further example of the usefulness of the thallium (III) salts in organic synthesis.[20]

Experimental Section

Caution! Thallium and its compounds are toxic and must be handled with care.

General. Column chromatography was performed on silica gel 60 (70−230 mesh ASTM, Merck). Thin-layer chromatography (TLC) was carried out with silica gel 60 F_{254} (Merck). Technical isopulegol (Aldrich) was chromatographed on silica gel 60 [(hexane:ethyl acetate (8.5:1.5)] to afford both isopulegol and neoisopulegol in greater than 98% purity. Thallium triacetate sesquihydrate (TTA) was purchased from Aldrich. All solvents were dried by standard methods.

(1*R*,3*R*,4*R*,8*R*)-3,9-Oxa-*p*-menthanol-8 (5) and (1*R*,3*S*, 4*R*,8*R*)-3,9-Oxa-*p*-menthanol-8 (6).[15] To a solution of isopulegol **3** or neo-isopulegol **4** (154 mg, 1 mmol) in aqueous AcOH (3 mL, 50% v/v) was added TTA (490 mg, 1.2 mmol). The mixture was stirred at room temperature for 40 min and then poured into a dilute $NaHCO_3$ solution until neutral. The resulting brown mixture was filtered through Celite, and the filtrate was extracted with ethyl acetate. The combined organic layers were washed with water and then with brine and dried over anhydrous $MgSO_4$. The solvent was evaporated, and the residue was purified by chromatography on silica gel [hexane:ethyl acetate (9:1)] to yield **5** (146 mg, 86%) or **6** (156 mg, 92%), both as colorless oils. **5**: ^1H NMR ($CDCl_3$) δ: 0.98 (3H, d, J = 6.5 Hz), 0.95−2.12 (5H, m), 1.21 (3H, s), 2.74 (1H, br), 3.25 (1H, dt, J = 4.0, 10.9 Hz), 3.66 (1H, d, J = 9.2 Hz), 3.85 (1H, d, J = 9.2 Hz); ^{13}C NMR ($CDCl_3$) δ: 21.8, 22.7, 22.8, 30.9, 34.3, 40.2, 56.4, 77.7, 81.2, 82.2. **6**: ^1H NMR ($CDCl_3$) δ: 0.86 (3H, d, J = 6.5 Hz), 0.73−2.40 (6H, m), 1.39 (3H, s), 3.59 (1H, d, J = 8.7), 3.75 (1H, d, J = 8.7), 4.03 (1H, br s); ^{13}C NMR ($CDCl_3$) δ: 22.1, 22.8, 26.4, 27.9, 32,7, 37.3, 47.7, 77.6, 77.9, 79.5.

(1*R*,3*R*)-3,9-Oxa-4(8)-*p*-menthene (7). To a solution of *β*-hydroxy ether **5** (986 mg, 5.8 mmol) in anhydrous ethyl ether (30 mL) at 0° was slowly added $SOCl_2$ (1.30 g, 12 mmol). After stirring at room temperature for 24 h, saturated $NaHCO_3$ solution was added and the mixture was extracted with ether. The combined organic layers were washed with water, brine, dried over anhydrous $MgSO_4$, and concentrated to afford a yellow oil, which was cromatographed on silica gel (eluent CH_2Cl_2) to yield **7** (617 mg, 70%), as a colorless oil. ^1H NMR ($CDCl_3$) δ: 0.94 (3H, d, J = 6.5 Hz), 1.61 (3H, s), 0.85−2.51 (4H, m), 4,5 (2H, m); ^{13}C NMR ($CDCl_3$) δ: 9.4, 21.9, 23.6, 29.9, 34.7, 43.5, 78.5, 86.1, 123.4, 132.8.

(1*R*,3*R*)-3,9-Oxa-9-Oxo-4(8)-*p*-menthene (Mintlactone) (1) and (3*R*,4*R*)-3,9-Oxa-9-oxo-8(10)-*p*-menthene (8). To dry pyridine (12 mL) and CH_2Cl_2 (20 mL), under nitrogen, was added chromium trioxide (6.0 g, 60 mmol). The mixture was stirred vigorously for 15 min at 5 °C and 15 min at room temperature, and then a solution of **7** (456 mg, 3 mmol) in CH_2Cl_2 (5 mL) was added dropwise. The mixture was stirred for 12 h at room temperature and then filtered through Celite. The filtrate was washed with 10% aqueous $CuSO_4$ solution (3 × 50 mL), distilled water, and brine, dried over anhydrous $MgSO_4$ and concentrated. The residue was purified by silica gel flash chromatography [hexane:ethyl acetate (8.5:1.5)] to yield **1** (299 mg, 60%) as a colorless liquid and **8** (75 mg, 15%) as an oil. The ^1H NMR, ^{13}C NMR, and IR spectral data for **1**[3] and **8**[18] are identical with those reported in the literature.

(3*S*,4*S*)-3,9-Oxa-9-oxo-8(10)-*p*-menthene (11). As described for **7**, the *β*-hydroxy ether **6** (510 mg, 3 mmol) afforded the unstable product **10**, which was immediately oxidized to **11**, following the same procedure described for **1** and **8**. Yield: 298 mg (60% overall yield from **6**). The ^1H NMR, ^{13}C NMR, and IR spectral data of **11** are identical with those reported in the literature.[17]

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