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Expeditious Construction of (+)-Mintlactone via Intramolecular Hetero-Pauson−Khand Reaction

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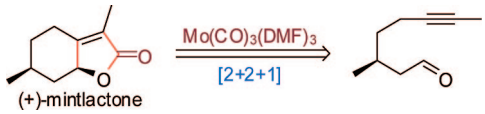


(+)-Mintlactone, a bicyclic monoterpene natural product, has been efficiently assembled from (−)-citronellol in three steps. The synthesis features nitrous acid-induced formal isopropylidene "demethanation" and the molybdenum-mediated intramolecular hetero-Pauson−Khand reaction.

(+)-Mintlactone (**1**) and (−)-isomintlactone (**2**) were isolated as endo α,β-unsaturated monoterpene-γ-lactones from the oil of the woods of *Bursera graveolens* by Iwabuchi (Figure 1).[1] Their enantiomers, *ent*-(−)-**1** and *ent*-(+)-**2**, were isolated for the first time in 1968 from *Mentha cardiaca*.[2] The latter two *p*-menthanolides are also present both in *Mentha arvensis*[3] and as minor constituents of the commercial essential oil (peppermint oil) of *Mentha piperita* L.[4] Surprisingly, the synthesis of these bicyclic monoterpene natural products has attracted immense attention in the field of synthetic organic chemistry.[5−8] For instance, Bates[7o] recently reported a novel ten-step synthesis of (−)-mintlactone from the THP ether of propargyl alcohol via a highly diastereoselective tin(II) chloride-mediated intramolecular propargylic Barbier reaction followed by an allenol cyclocarbonylation. In addition, starting from citronellal, Shishido and co-workers[7g] realized a total synthesis of (−)-mintlactone in ten steps by employing the fused butenolide

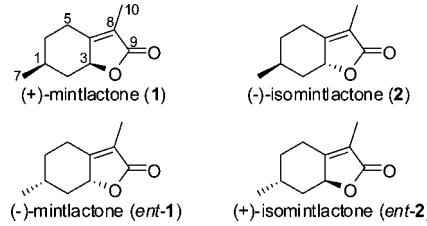
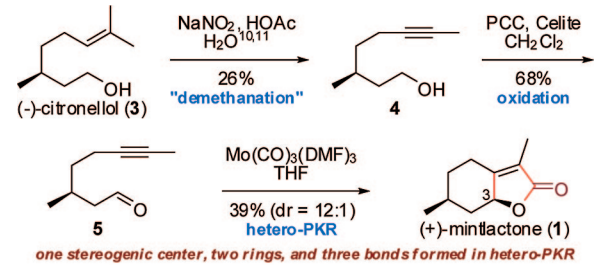


FIGURE 1. (+)- and (−)-mintlactone and (+)- and (−)-isomintlactone.

SCHEME 1. Synthesis of (+)-Mintlactone (1)



construction strategy based on an intramolecular [3 + 2] cycloaddition of nitrile oxide.

Its unique structural features prompted us to develop an original and concise strategy to construct mintlactone. The molybdenum-mediated intramolecular hetero-Pauson−Khand reaction (hetero-PKR) of 1,6- and 1,7-yne aldehydes has been identified as an ultraefficient method for the synthesis of fused γ-butenolides.[9] We envisioned that the intramolecular hetero-PKR should perfectly serve our initiative in the synthesis of mintlactone.

As outlined in Scheme 1, our synthesis commenced from formal "demethanation" of (−)-citronellol (**3**) with nitrous acid by following Abidi's protocol.[10] Thus alkynol **4** was produced directly in a single step from **3** in a yield (26%) identical with

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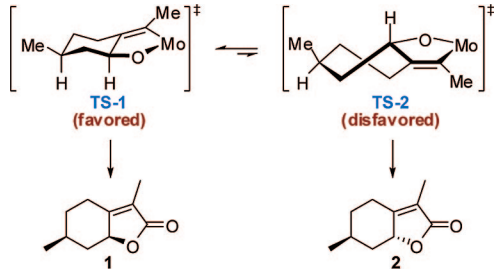
SCHEME 2. Conformational Analysis for the Hetero-PKR



that obtained from the racemic citronellol by Kraft and Berthold,[11] who failed to reproduce the reported 95% yield of Abidi for the same transformation.[10a] After treatment with PCC in dichloromethane at room temperature for 2 h, alcohol **4** was smoothly converted to ynal **5** in 68% yield. Even though **5** was reportedly preparable in one step (via formal "demethanation") from citronellal in moderate yield (70%),[10a] it remained irreproducible in our hand.

Since the 1,6-yne aldehyde **5** was not very stable in air at room temperature, it should be used in the next step immediately. Exposure[9] of the ynal to the freshly prepared organomolybdenum catalyst, $Mo(CO)_3(DMF)_3$,[12] in tetrahydrofuran at room temperature for 1 h led to (+)-mintlactone (**1**, 39%) along with its inseparable diastereomer, presumably (−)-isomintlactone (**2**, 3%), in an optimized combined yield of 42% {$[\alpha]^{18}_D$ +54.4 (*c* 0.95, $CHCl_3$); lit.[7n] (−)-mintlactone $[\alpha]^{25}_D$ −57 (*c* 2, $CHCl_3$); lit.[7o] (−)-mintlactone $[\alpha]^{24}_D$ −59.2 (*c* 2.4, $CHCl_3$)}. One stereogenic center, two rings, and three covalent bonds (1 C−O and 2 C−C) were formed in this remarkable intramolecular hetero-PKR, which proceeded in high diastereoselectivity (C-3, dr = 12:1) according to the line integrals of the ^{1}H NMR spectrum. The diastereoselectivity observed in the hetero-PKR can be explained by a conformational analysis (Scheme 2). Because a chair conformation (TS-1) for a simplified transition state structure theoretically has lower energy than a twist boat one (TS-2), (+)-mintlactone (**1**) should emerge as a major product.

In summary, we have accomplished a three-step assembly of (+)-mintlactone (despite the relatively low yields for the first and third steps), which may somehow be used as an example to illustrate the significance of the concepts of "step economy"[13] and "strategic efficiency".[14] Key features of the current synthesis include HNO_2-induced formal isopropylidene "demethanation" and the $Mo(CO)_3(DMF)_3$-mediated intramolecular hetero-Pauson-Khand reaction.

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Experimental Section

Compound 4. $NaNO_2$ (25.0 g, 362 mmol) was added portionwise to a vigorously stirred solution of (−)-citronellol (2.10 g, 13.4 mmol) in HOAc−H_2O (5:2, 63 mL) at 0 °C and a large amount of gas (NO_x) and lather was produced. After the reaction mixture was stirred at 0 °C for 1 h, the cooling bath was removed and stirring continued at rt for 24 h. The reaction mixture was heated at 54 °C for 24 h and then at rt for 24 h before being poured into H_2O (140 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were washed successively with H_2O (50 mL) and brine (50 mL), dried (Na_2SO_4), and concentrated under reduced pressure. Chromatography (petroleum ether (30−60 °C)/Et_2O, 4:1) provided compound **4** (498 mg, 26%) as a light yellow oil: $[\alpha]^{20}_D$ −4.21 (*c* 2.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.89 (d, J = 6.0 Hz, 3H), 1.23−1.42 (m, 2H), 1.48−1.68 (m, 4H), 1.76 (s, 3H), 2.11−2.25 (m, 2H), 3.60−3.76 (m, 2H).

Compound 5. To a solution of compound **5** (193 mg, 1.38 mmol) in CH_2Cl_2 (40 mL) were added PCC (297 mg, 1.38 mmol) and Celite (1.40 g). The reaction mixture was stirred under argon for 2 h, filtered, and concentrated to give a residue, which was quickly chromatographed (petroleum ether (30−60 °C)/Et_2O, 20:1) to afford compound **5** (129 mg, 68%) as a colorless oil: $[\alpha]^{21}_D$ −18.4 (*c* 1.9, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.97 (d, J = 6.0 Hz, 3H), 1.37−1.54 (m, 2H), 1.77 (t, J = 2.4 Hz, 3H), 2.13−2.28 (m, 4H), 2.38−2.45 (m, 1H), 9.76 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 3.4, 16.3, 19.4, 27.2, 35.8, 50.5, 75.9, 78.4, 202.8; MS (EI) 138 (M^+, 2), 123 (44), 109 (41), 79 (100), 67 (87), 41 (97). HRMS (EI) calcd for $C_9H_{14}O$ 138.1045, found 138.1046.

Compound 1. A Schlenk flask was charged under argon with freshly prepared $Mo(CO)_3(DMF)_3$ (180 mg, 0.45 mmol), capped with a rubber septum, and evacuated and backfilled with argon twice. A solution of freshly prepared yne-aldehyde **6** (62 mg, 0.45 mmol) in THF (10 mL) was added via syringe. The reaction mixture was stirred at rt for 1 h and the crude reaction mixture was filtered through a plug of Celite with the aid of CH_2Cl_2.The solvents were evaporated to give a residue, which was purified by chromatography (petroleum ether (30−60 °C)/EtOAc, 20:1) to afford an inseparable mixture (31 mg, 42%, dr = 12:1) of (+)-mintlactone (**1**, 39%) and (−)-isomintlactone (**2**, 3%) as a colorless oil: $[\alpha]^{18}_D$ +54.4 (*c* 0.95, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.99 (d, J = 6.8 Hz, 3H), 0.86−1.04 (m, 2H), 1.62−1.76 (m, 1H), 1.78 (t, J = 1.6 Hz, 3H), 1.85−1.95 (m, 1H), 2.17 (td, J = 14.0, 5.6 Hz, 1H), 2.35−2.43 (m, 1H), 2.77 (ddd, J = 14.0, 4.4, 2.0 Hz, 1H), 4.60 (dd, J = 11.2, 6.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 8.1, 21.2, 25.4, 29.7, 34.5, 41.9, 79.9, 119.5, 162.3, 174.8; MS (EI) 166 (M^+, 9), 137 (6), 65 (100); HRMS (EI) calcd for $C_{10}H_{14}O_2$ 166.0994, found 166.0996.

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Supporting Information Available: The Experimental procedures and copies of ^{1}H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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