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A Synthesis of (−)-Mintlactone

Roderick W. Bates* and S. Sridhar

Division of Chemistry and Biological Chemistry, School of Physical and Mathematical Sciences, 21 Nanyang Link, Nanyang Technological University, Singapore 637371

roderick@ntu.edu.sg

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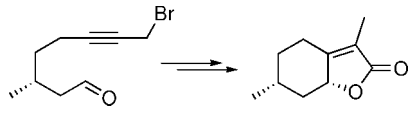


Mintlactone is synthesized in a concise and efficient way by using a highly diastereoselective intramolecular propargylic Barbier reaction, followed by an allenol cyclocarbonylation. Tin(II) chloride is found to be the most effective reagent for the Barbier reaction.

The butenolide moiety is widespread among natural products.[1] One way to synthesize butenolides is by the cyclocarbonylation of allenic alcohols.[2] Allenic alcohols may, in turn, be obtained by the Barbier reaction between propargylic halides and aldehydes.[3] This reaction, however, may give either allenic alcohols or propargylic alcohols according to the substitution pattern and the reagents employed. If such a propargylic Barbier reaction were carried out in an intramolecular fashion, it could be constrained to give only the allenic alcohol. To our knowledge, there are only two reports of such an intramolecular transformation, neither addressing stereochemical issues.[4] The intramolecular propargylic Barbier reaction would lead to a bicyclic butenolide after cyclocarbonylation (Scheme 1).

The simplest such bicyclic butenolide natural products are mintlactone **1** and isomintlactone **2** (Figure 1).[5,6] They make appropriate targets for exploring this route, but also raise the issue of diastereoselectivity during cyclization. In this paper we wish to report the application of this chemistry to the synthesis of (−)-mintlactone **1** (Scheme 2).

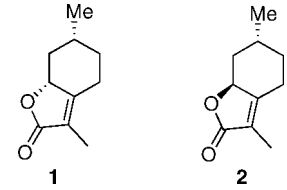
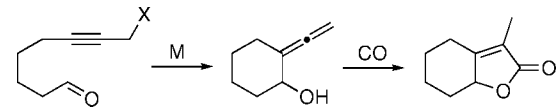
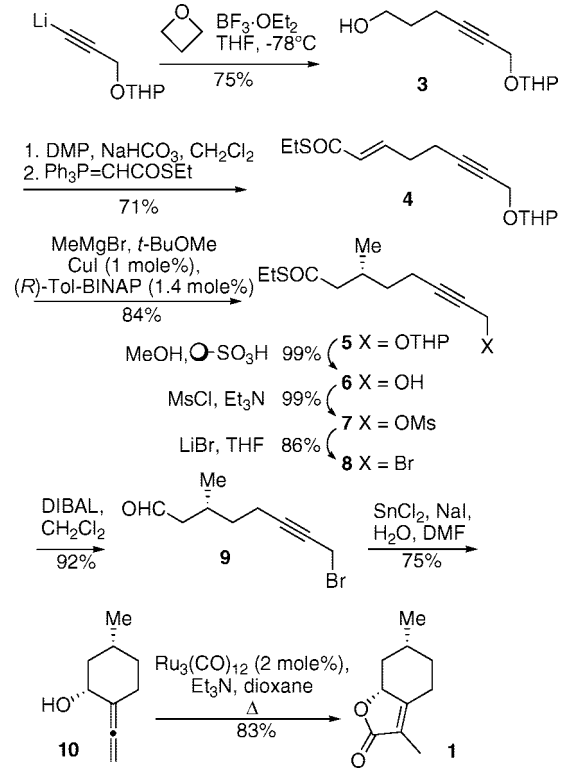


FIGURE 1. The mintlactones.

SCHEME 1. Butenolide Synthesis



SCHEME 2. Mintlactone Synthesis



For the synthesis of the natural product, we planned to introduce the methyl group using Feringa's asymmetric conjugate addition methodology.[7] The required thioester substrate was prepared by reacting the lithium derivative of the THP ether of propargyl alcohol with oxetane in the presence of $BF_3 \cdot OEt_2$ according to the procedure of Ganem.[8] Oxidation of primary alcohol **3** and Wittig reaction of the aldehyde without isolation of the intermediate aldehyde yielded the required unsaturated thioester **4** in 71% yield. Addition of methyl magnesium bromide in the presence of the copper(I)−(*R*)-Tol-BINAP complex (from copper(I) iodide 1 mol % and (*R*)-Tol-BINAP 1.4 mol %), as described by Feringa,[7] gave the desired

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TABLE 1. Barbier Reaction Conditions

entry	conditions	time/h	*T*/°C	yield/%
1	Zn, NH_4Cl, THF	12	0 to rt	36[a]
2	In, H_2O, DMF	24	rt	47[b]
3	$SnCl_2$, NaI, DMF	48	0	13
4	$SnCl_2$, NaI, H_2O, DMF	56	−10	75[b]
5	$Sn(BF_4)_2$, NaI, H_2O, DMF	48	−10	10
6	$Sn(O_2C_8H_{15})_2$, NaI, H_2O, DMF	48	−10	24
7	SnI_2, NaI, H_2O, DMF	12	−10	0

[a] 3:1 ratio of diastereoisomers; [b] ≤5% of the minor diastereoisomer.

β-methylated ester **5** in 84% yield. Removal of the THP group allowed determination of the ee as 94% by chiral HPLC of the corresponding 3,5-dinitrobenzoate **6a**. To continue the synthesis, the propargylic alcohol **6** was converted to bromide **8**, via the mesylate in an overall yield of 84% (three steps). The thioester was then reduced to aldehyde **9** by DIBAL reduction in 92% yield.[9] Bromoaldehyde **9** was subjected to propargylic Barbier cyclization by using a variety of reagents (Table 1). Cyclization with zinc/ammonium chloride[10] gave quite modest diastereoselectivity (entry 1). On the other hand, cyclization with indium[11] in water (entry 2) or tin(II) chloride in DMF in the presence of sodium iodide[12] proceeded with high diastereoselectivity to give the *cis*-cyclohexyl product **10**. As tin(II) chloride gave the cleanest conversion to the desired allenol and the highest yield, our efforts were focused on optimizing this reaction. Due to an initial concern about the possible deleterious effect of residual moisture in commercial "anhydrous" DMF, we examined the use of carefully dried DMF (distilled from CaH_2 under reduced pressure). To our surprise, the yield was reduced to a meagre 13% (entry 3). On the other hand, employing a DMF−water mixture at −10 °C resulted in an increase in yield to 75% (entry 4).[13] Only a trace (≤5%) of the other diastereoisomer was discernible by high-field ^{1}H NMR.[14] The choice of tin(II) reagent was also found to be critical: the use of tin(II) tetrafluoroborate (aq), tin(II) iodide, or tin(II) 2-ethylhexanoate resulted in low yields (0−24%, entries 5−7). Thus both water and chloride appear to be essential for this tin(II)-mediated reaction. The stereochemistry of the allenol product was assigned based upon the observation of coupling constants of 11 and 4.3 Hz for the proton α to the hydroxyl group, after decoupling of the allenic protons. These coupling constants are consistent with the alcohol group and, presumably, the methyl group being equatorial. This assignment was subsequently confirmed by X-ray crystallography. The stereochemistry is consistent with a chair transition state[15] with an equatorial methyl group during cyclization (Figure 2).

The synthesis was completed by treatment of the allenic alcohol **10** with triruthenium dodecacarbonyl and triethylamine under a pressure of 100 psi of CO.[2] A yield of 83% of mintlactone **1** was obtained by using only 2 mol % of $Ru_3(CO)_{12}$. This completed a concise and highly stereoselective synthesis of (−)-mintlactone **1**. The spectroscopic data (^{1}H and ^{13}C NMR) were in good agreement with that reported. An optical rotation of −59.2 (*c* 2.4, $CHCl_3$) was measured for the synthetic material (lit.[5,16] −51.8 (*c* 10, EtOH), −57 (*c* 2.4, $CHCl_3$)).

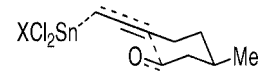

FIGURE 2. Chair transition state.

The completion of the synthesis demonstrates a concise route to butenolides and shows that the intramolecular propargylic Barbier reaction is a valuable transformation and can proceed with remarkably high diastereoselectivity. The role of water in these reactions requires further study.

Experimental Section

(1*R*,5*R*)-5-Methyl-2-vinylidenecyclohexanol (10). To a solution of compound **9** (780 mg, 3.5 mmol) in DMF (16 mL) and water (2 mL) under nitrogen at −10 °C was added $SnCl_2$ (1 g, 5.4 mmol) followed by NaI (808 mg, 5.4 mmol). After stirring at −10 °C for 56 h, 20 mL of water and 50 mL of Et_2O were added. The mixture was stirred at room temperature for 30 min, then filtered through celite, washing with Et_2O. The organic layer was separated and washed with water and brine and dried ($MgSO_4$). The solvent was removed under reduced pressure, and the residue was purified by column chromatography on silica gel (30 g, 10% EtOAc/hexane) to give allenic alcohol **10** (372 mg, 75%) as a colorless solid. Mp 54−56 °C. $[\alpha]^{24}_D$ +15.1 (*c* 1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.99−4.85 (2H, m), 4.05−3.91 (1H, m), 2.39 (1H, ddd, J = 13.7, 3.9, 2.6 Hz), 2.16−1.92 (3H, m), 1.79−1.63 (1H, m), 1.61−1.45 (1H, m), 1.08−0.97 (2H, m), 0.94 (3H, J = 6.6 Hz). ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 199.7, 107.1, 79.7, 67.9, 44.5, 34.7, 31.3, 29.5, 22.2. IR (KBr, cm^{-1}) ν_{max} 3382 (br), 2951, 2924, 1956, 1458, 1166. HRMS *m*/*z* calcd for $C_9H_{15}O$ 139.1123 (M^+ + H), found 139.1117.

(−)-Mintlactone (1). Triruthenium dodecacarbonyl (4.6 mg, 0.0072 mmol) was added to a mixture of compound **10** (50 mg, 0.36 mmol) and Et_3N (0.2 mL, 1.45 mmol) in dioxane (2 mL) at room temperature in a Fisher-Porter tube. The tube was flushed with carbon monoxide and pressurized to 100 psi, then stirred at 100 °C for 14 h. The reaction mixture was cooled to 0 °C for 10 min, then the carbon monoxide was released, the solvent was removed under reduced pressure, and the residue was purified by column chromatography on silica gel (10 g, 15% EtOAc/hexane) to give (−)-mintlactone **1** (50 mg, 83%) as a pale yellow oil. $[\alpha]^{24}_D$ −59.2 (*c* 2.4, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.60 (1H, dd, J = 11.0, 6.0 Hz), 2.77 (1H, ddd, J = 14.2, 4.3, 1.8 Hz), 2.43−2.35 (1H, m), 2.17 (1H, td, J = 13.7, 5.4 Hz), 1.95−1.85 (1H, m), 1.78 (3H, t, J = 1.4 Hz), 1.76−1.62 (1H, m), 1.09−0.86 (2H, m), 0.98 (3H, d, J = 6.6 Hz). ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 174.9, 162.4, 119.6, 80.0, 42.0, 34.6, 29.8, 25.5, 21.2, 8.2. IR (neat, cm^{-1}) ν_{max} 2953, 2927, 1747, 1730, 1687.

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Supporting Information Available: Experimental details for compounds **3**−**9**, spectroscopic data for compounds **1** and **3**−**10**, and the ORTEP structure and crystallographic information for compound **10**. This material is available free of charge via the Internet at http://pubs.acs.org.

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