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A Direct Synthesis of Hyperolactone C

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Abstract

Hyperolactone C is prepared from furan **4**. The key transformation is a tandem Claisen rearrangement/lactonization.

The hyperolactones constitute a growing class of novel metabolites found in *Hypericum chinese* L.[1] The structures of hyperolactones A (**1**), B (**2**), and C (**3**) are depicted below. In the context of a study of the metabolites of *Hypericum* through bioassay-guided fractionations, we required an authentic sample of hyperolactone C, whose extended conjugation (via the phenyl substituent) and resemblance to known antiviral agents made it a metabolite of interest. Kinoshita and co-workers have reported interesting syntheses of hyperolactones A, B, and C from chiral precursors.[2,3] Although their syntheses defined absolute stereochemistry in this series, a more direct synthetic approach is needed to support biological studies. We report herein a direct synthesis of racemic **3** from ester **4**, which in turn is available from methyl acetoacetate.[4]

The *O*-alkylation of furanol **4** with **5**[5] proved to be very solvent dependent. With acetonitrile or DMF as solvents, the ratio of **6** to **7** was approximately 1:1. The structure of **6** was supported by the methylene doublet at 4.77 and the furan resonance at 6.60. With toluene as the solvent, only compound **7** was obtained. Fortunately, alkylation in HMPA afforded a 2.5:1 ratio in favor of furan **6**.

Heating furan **6** in an inert solvent was expected to provide hyperolactone C via a tandem Claisen rearrangement–lactonization protocol.[6] Such a protocol had not been reported, and it represented a novel strategy for constructing two adjacent quaternary centers. Although separable for analytical characterization, the mixture of **6** and **7** was heated in toluene at 130 °C to provide **3** in 25% yield. The ^{1}H NMR spectrum of **3** showed a methyl singlet at 1.53, resonances characteristic of a vinyl group attached to a quaternary carbon (doublets at 5.26 and 5.27 plus a doublet of doublets at 5.99), and a singlet at 5.98 for the enone hydrogen. The ^{13}C NMR showed 14 peaks, including a ketone resonance at 196.8 and a lactone resonance at 187.5. The ^{1}H NMR and ^{13}C NMR of our synthetic sample were identical to those reported for the natural product.[1,3]

The byproduct of the reaction, hydroxy ester **8**, was a mixture of diastereomers. It could not be converted into a lactone using heat, acid (PTSA), or base (*t*BuOK, NaH, or KH) catalysis. Although the yield of **3** is modest, the synthetic route is convenient and amenable to the production of quantities of hyperolactone C for testing for biological activity.

Experimental Section

General Experimental Procedures

Tetrahydrofuran was distilled from sodium benzophenone ketyl. Dichloromethane, toluene, and HMPA were distilled over calcium hydride. All experiments were performed under argon atmosphere. Organic extracts were dried over anhydrous sodium sulfate. Infrared spectra were obtained on a Perkin-Elmer model 1320 spectrophotometer. Nuclear magnetic resonance

experiments were performed with either a Varian 300 MHz or a Bruker 400 MHz instrument. High-resolution mass spectra were recorded on a Kratos model MS-50 spectrometer, and low-resolution mass spectra were performed with a Finnegan 4023 mass spectrometer. Standard grade silica gel (60 Å) was used for flash column chromatography.

Preparation of 6 and 7

To **4** (0.19 g, 0.87 mmol) in 4 mL of HMPA at room temperature was added 60% NaH in mineral oil (35 mg, 0.88 mmol). After 1 h, **5** (0.11 g, 0.9 mmol) in 4 mL of HMPA was added slowly at room temperature. The mixture was stirred at room temperature overnight. Then 0.4 mL of 0.5 M AcOH was added to quench the reaction, followed by 20 mL of H_2O. The solution was extracted twice with ethyl acetate, washed with brine, and dried over Na_2SO_4. Evaporation of solvent and purification by flash chromatography (hexane/ethyl acetate, 2:1) afforded O-alkylation product and C-alkylation product (0.19 g, 71%) in 2.5:1 ratio.

Compound 6

^{1}H NMR (300 MHz, $CDCl_3$) 1.79 (s, 3H), 3.90 (s, 3H), 4.09 (s, 2H), 4.77 (d, *J* = 6.3 Hz, 2H), 5.78–5.83 (m, 1H), 6.60 (s, 1H), 7.33–7.45 (m, 3H), 7.73–7.77 (m, 2H); MS *m*/*z* 186, 218, 302; HRMS *m*/*z* for $C_{17}H_{18}O_5$ calcd 302.1154, measd 302.1159.

Compound 7

^{1}H NMR (300 MHz, $CDCl_3$) 1.71 (s, 3H), 2.85–2.90 (m, 1H), 3.07–3.13 (m, 1H), 3.79 (s, 3H), 3.96 (s, 2H), 5.38–5.42 (m, 1H), 6.01 (s, 1H), 7.49–7.53 (m, 2H), 7.58–7.62 (m, 1H), 7.85–7.87 (m, 2H); HRMS *m*/*z* for $C_{17}H_{18}O_5$ calcd 302.1154, measd 302.1159.

Preparation of Hyperolactone C (3)

The O-alkylation and C-alkylation product mixture (0.13 g, 0.43 mmol) was dissolved in 5 mL of toluene and heated in a sealed tube at 130 °C for 15 h. Evaporation of the solvent and flash chromatography (hexane/ethyl acetate, 4:1) afforded hyperolactone C (21 mg, 25% based on O-alkylation product).

Compound 3

^{1}HNMR (300 MHz, $CDCl_3$) 1.53 (s, 3H), 4.11 (d, *J* = 8.4 Hz, 1H), 4.97 (d, *J* = 8.4 Hz, 1 H), 5.26 (d, *J* = 17.7 Hz, 1H), 5.27 (d, *J* = 10.8 Hz, 1H), 5.98 (s, 1H), 5.99 (dd, *J* = 17.7 Hz, 10.8 Hz, 2H), 7.49–7.55 (m, 2H), 7.58–7.64 (m, 1H), 7.84–7.87 (m, 2H); MS *m*/*z* 102, 160, 187, 211, 225, 270; HRMS *m*/*z* for $C_{16}H_{14}O_4$ calcd 270.0892, measd 270.0892; ^{13}C NMR (75 MHz) 19.8, 49.1, 74.4, 93.3, 100.5, 119.3, 127.6, 127.9, 129.3, 133.8, 134.5, 168.3, 187.5, 196.8.

Compound 8

^{1}HNMR (300 MHz, $CDCl_3$) 1.27 and 1.38 (s, 3H), 3.79 and 3.81 (s, 3H), 4.24–4.30 and 4.65–4.71 (m, 2H), 4.65 and 4.67 (s, 1H), 5.17–5.26 (m, 2H), 5.73–6.07 (m, 1H), 6.01 and 6.03 (s, 1H), 7.46–7.60 (m, 3H), 7.79–7.83 (m, 2H); MS *m*/*z* 303 (M + 1), 270, 243, 227, 213, 187, 160, 143, 105; CMR (75 MHz, $CDCl_3$) 16.2, 17.3, 44.4, 44.8, 55.1, 55.2, 70.8, 71.6, 86.5, 86.9, 102.6, 102.7, 117.2, 117.5, 127.3, 127.3, 129.2, 133.0, 136.3, 136.6, 155.8, 155.9, 185.2, 185.4, 202.3, 202.4.

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Figure 1.
Synthesis of hyperolactone C. Reagents: (i) NaH, (ii) toluene, 130 °C.