First total synthesis of (±)-hyperolactone A

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The first total synthesis of (±)-hyperolactone A, isolated from *Hypericum chinense* L., is accomplished from 3-furoic acid and 2-methylbutanal.

Hyperolactone A[1] is a unique spiro compound isolated from *Hypericum chinense* L., which has a 2-alkyl-9-methyl-9-vinyl-1,7-dioxaspiro[4,4]non-2-ene-4,6-dione skeleton, and is thus an interesting compound as a target for synthesis. The structure[1a] was deduced by spectroscopic experiments, chemical transformations and X-ray crystallography. We describe herein the first total synthesis of (±)-hyperolactone A **8a** by condensation of two fragments, aldehyde **2** and lactone **4**.

The aldol reaction of the lithium enolate of lactone **4**, derived from 3-furoic acid, with the aldehyde **2**, derived from 2-methylbutanal (Scheme 1), afforded **5**† in 81% yield (Scheme 2). The crude alcohol **5** was oxidized to furnish **6** (a mixture of four diastereoisomers‡) by the Swern method in 92% yield. Attempted oxidation of **6** with MoO_5·pyridine·HMPA (MoOPH)[3] was unsuccessful, giving the undesired **7b** only in 18% yield, while with Davis reagent[4] a separable isomeric mixture of **7a** and **7b**§ was obtained in 57% yield in a ratio of 2 : 3. A NOE was observed between the 9-methyl group and the OH for the minor isomer **7a**, but not for the major isomer.

On treatment of **7a** with 3 M HCl in boiling THF to remove the ketal protecting group (which strongly resisted hydrolysis), a mixture of the final product **8a** and its isomer **8b** was obtained in 85% yield in a ratio of 1 : 1, which was separated to give (±)-hyperolactone **8a**¶ as an oil.

The advantages of this strategy are that it is short and efficient, and provides a one-step construction of the spirolactone by acid catalysis *via* deprotection, cyclization and elimination.

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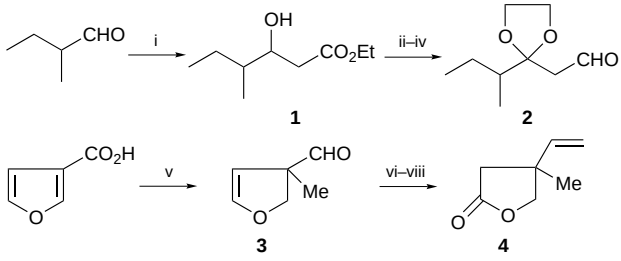
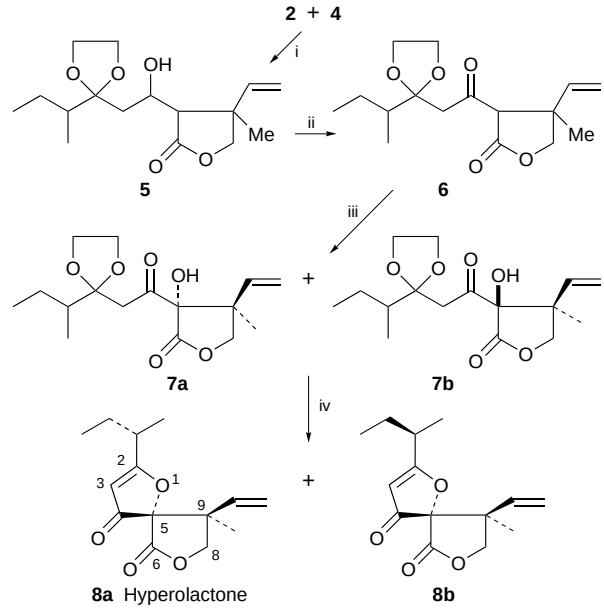


Scheme 1 *Reagents and conditions*: i, Zn, $BrCH_2CO_2Et$, C_6H_6, reflux, 1.5 h, 75%; ii, CrO_3, pyridine, CH_2Cl_2, room temp., 30 min, 83%; iii, $(CH_2OH)_2$, TsOH, PhMe, reflux, 7 h, 39%; iv, DIBAL-H, PhMe, −78 °C, 10 min, 98%; v, ref. 2; vi, Ph_3MeP^+ Br^-, BuLi, Et_2O, reflux, 12 h; vii, BuOH, TsOH, CH_2Cl_2; viii, CrO_3, H_2SO_4, acetone, 45% over three steps



Scheme 2 *Reagents and conditions*: i, LDA, THF, −78 °C, 1 h, then −40 °C, 1.5 h, 81%; ii, DMSO, $(COCl)_2$, CH_2Cl_2, Et_3N, −78 °C, 10 min, 92%; iii, Davis reagent, 57%; iv, 6 M HCl, THF, reflux, 10 h, 85%

Footnotes and References

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† Although a multitude of isomers are formed, in the light of the subsequent steps this does not matter.

‡ The relative proportion (2 : 2 : 2 : 1) was estimated from the carbonyl absorptions: δ_C 197.1, 198.8, 201.4 and 202.2.

§ The diastereoselectivity was not improved, even in the case of a less bulky electrophile such as the Davis reagent.

¶ *Selected data* [δ_H (400) MHz, $CDCl_3$)] for **8a**: 0.96 (3 H, t, *J* 7.3), 1.25 (3 H, d, *J* 7.3) 1.41 (3 H, s), 1.54–1.66 (1 H, m), 1.66–1.80 (1 H, m), 2.69 (1 H, tq, *J* 6.7), 4.04 (1 H, d, *J* 8.5), 4.89 (1 H, d, *J* 8.5), 5.24 (1 H, d, *J* 17.1), 5.28 (1 H, d, *J* 11.0), 5.37 (1 H, s), 5.93 (1 H, dd, *J* 11.0, 17.1). For **8b**: 0.98 (3 H, t, *J* 7.3), 1.27 (3 H, d, *J* 7.3), 1.41 (3 H, s), 1.50–1.60 (1 H, m), 1.62–1.80 (1 H, m), 2.66 (1 H, tq, *J* 6.7), 4.04 (1 H, d, *J* 8.5), 4.89 (1 H, d, *J* 8.5), 5.24 (1 H, d, *J* 17.1), 5.28 (1 H, d, *J* 11.0), 5.37 (1 H, s), 5.94 (1 H, dd, *J* 11.0, 17.1). The ^{1}H NMR spectrum of (±)-**8a** thus obtained was identical with that of the natural product recorded by Tada *et al.* [ref. 1(*a*)].

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