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Synthesis and Absolute Configuration of (+)-Hyperolactone B

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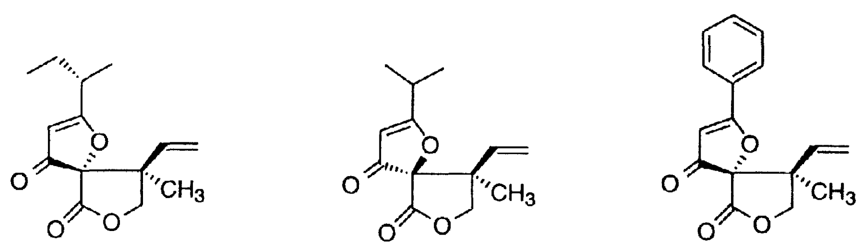
Abstract: The synthesis of (+)-hyperolactone B **2** , isolated from *Hypericum chinense* L., was accomplished from (*S*)-malic acid. This synthesis unambiguously established the absolute stereochemistry of hyperolactone B.

Hyperolactones A, B and C (**1**, **2** and **3**) are unique spiro compounds isolated from *Hypericum chinense* L.,[1] which have a 2-alkyl (or phenyl)-9-methyl-9-vinyl-1,7-dioxaspiro[4.4]non-2-ene-4,6-dione skeleton. Recently, we have reported the first total synthesis of (±)-hyperolactone A **1** from 3-furoic acid.[2] We now describe herein the synthesis of (+)-hyperolactone B **2** from (*S*)-malic acid in a stereoselective fashion, which enables us to establish its absolute stereochemistry unambiguously.



1 (-)-Hyperolactone A

2 (+)-Hyperolactone B

3 (-)-Hyperolactone C

Diethyl (2*S*, 3*R*)-(+)-3-methyl-2-hydroxysuccinate **4**[3] was successively exposed to alkylation,[4] selective alkaline hydrolysis, and reduction conditions to give α-hydroxy-γ-lactone derivative **6**. As presented in the reaction scheme, **6** was converted to the known compound **9**[5], isolated from *Marshallia tenuifolia*, *via* key compound **8a**. It became apparent that the stereochemistry of the constructed quaternary carbon center of **8b** was *S*-configuration.

The aldol reaction of the lithium enolate of **8a** with aldehyde **10**[2] afforded **11** in 75% yield. Successive treatment with Jones reagent provided **12** in 95% yield (**a** : **b** =1:1) as a separable mixture. Acid-catalyzed hydrolysis (3 M HCl, THF, reflux) of **12a**[6] gave **2**[7] in 91% yield, which was identified as (+)-hyperolactone B.

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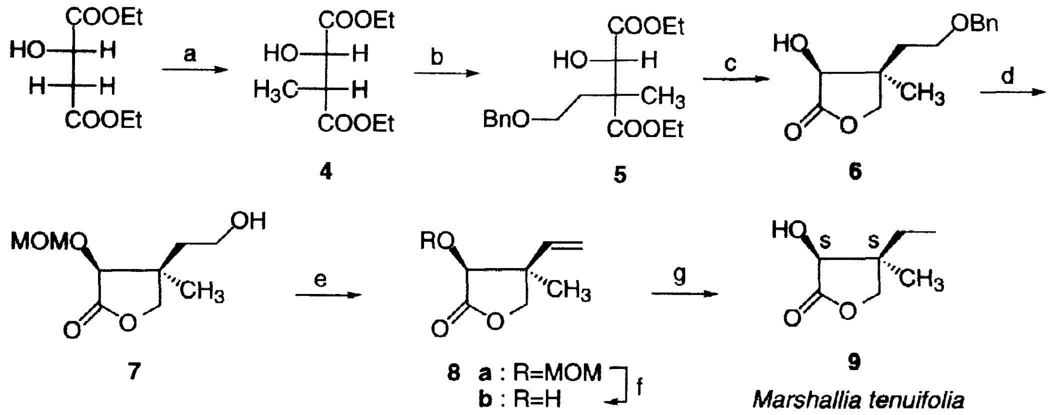
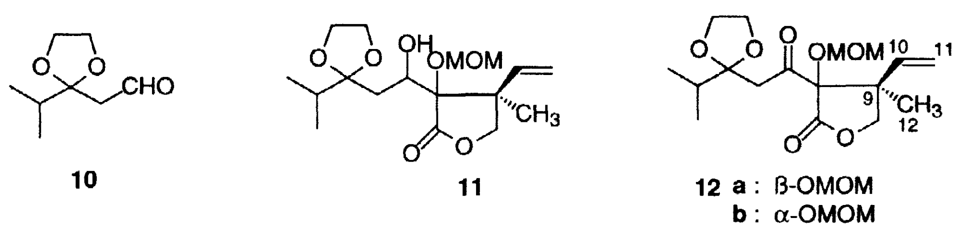


Reaction Conditions : (a) ref. 3 (b) 2 equiv. of LDA, $BnOCH_2CH_2I$, THF, - 78°C, 58% (c) 1) KOH, MeOH-H_2O, 97% 2) Super hydride®, 75% (d) 1) MOMCl, $(i\text{-}Pr)_2EtN$, CH_2Cl_2, 2) Pd-C, H_2, MeOH, 87% (2 steps), (e) 1)o-$O_2NC_6H_4SeCN$, Bu_3P, THF, 2) 30% H_2O_2, THF, 67% (2 steps) (f) TMSBr, CH_2Cl_2, 87% (g) Pd-C, H_2, 91%.



The NMR spectra[8] of synthetic **2** was in agreement with that of the natural product.[1b] Thus, we have completed the total synthesis of **2**. This synthesis discloses that the stereochemistry should be depicted as (5*R*, 9*S*)-(+)-9-ethenyl-9-methyl-2-isopropyl-1,7-dioxaspiro[4.4]non-2-ene-4,6-dione for hyperolactone **B**. The absolute configuration of hyperolactones A and C will soon be decided by the similar synthetic method.

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3. Seebach, D.; Aebi, J.; Wasmuth, D. *Org. Synth. Coll. Vol. VII.* **1990**, 153-159.
4. Diastereoselectivity: >90% *erythro*-selective branching of malic esters by alkylation. Seebach, D.; Wasmuth, D. *Helv. Chim. Acta* **1980**, *63*, 197-200.
5. $[\alpha]_D^{25}$ + 5.7° (c 0.26, $CHCl_3$) : $[\alpha]_{546}^{20}$ + 4.7° For natural **9**. Herz, W; Bruno, M. *Phytochemistry* **1987**, *26*, 1175-1180. $[\alpha]_D$+ 3.5° For the synthetic **9**. Tadano, K.; Kanazawa, S.; Ogawa, S. *J. Org. Chem.* **1988**, *53*, 3868-3870.
6. The structure of **12** were deduced from the lower chemical shifts of H_{10} (δ 6.19, dd, 1H) in **12a** and H_{12} (δ 1.31, s, 3H) in **12b** compared with those of H_{10} (δ 5.79, dd, 1H) in **12b** and H_{12} (δ 1.13, s, 3H) in **12a** by the anisotropic effect of the OMOM and the carbonyl groups.
7. mp 55°, $[\alpha]_D^{28}$ + 371° (c 0.0135, EtOH) : lit.[1b] mp 53°, $[\alpha]_D$ + 411°.
8. ^{1}H-NMR (300 MHz, $CDCl_3$) : δ 1.16 (s), 1.22 (d, J=6.9 Hz), 1.23 (d, J=6.9 Hz), 2.78 (sep, J=6.9 Hz), 4.25 (d, J=8.8 Hz), 4.64 (d, J=8.8 Hz), 5.21 (d, J=17.6 Hz), 5.24 (d, J=10.9 Hz), 5.36 (s), 5.87 (dd, J= 10.9 Hz, J=17.6 Hz); ^{13}C-NMR : δ 15.3, 19.3, 19.6, 30.4, 48.4, 73.2, 91.8, 101.2, 116.0, 136.7, 168.0, 197.4, 201.2.