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Synthesis of the Proposed Structure of Fudecalone, an Anticoccidial Drimane Terpenoid

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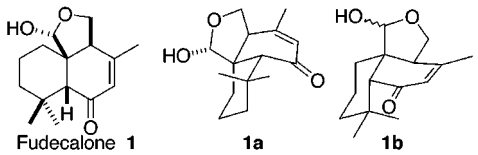
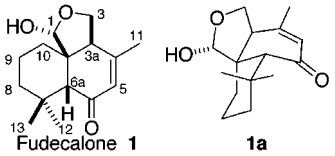
ABSTRACT



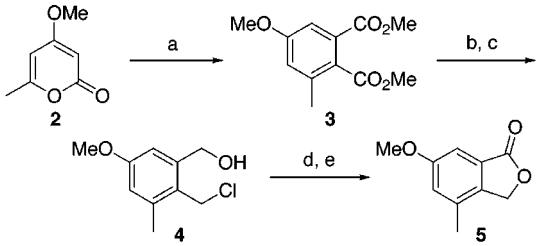
The proposed structure of fudecalone (1), an anticoccidial drimane sesquiterpene, was synthesized as a racemate in six steps starting from a known phthalide (5). Interestingly, our synthetic 1 showed conformation 1b, while the natural one was reported as 1a, and the NMR spectral data were not identical.

In 1995, Omura et al. isolated and identified a new drimane sesquiterpene, fudecalone (**1**), from a culture broth of *Penicillium* sp. FO-2030.[1] It exhibited an anticoccidial activity against monensin-resistant *Eimeria tenella* at 16 μM. The structure was elucidated mainly by various NMR experiments, and the conformation of **1** was reported to be **1a**. Herein, we report a synthesis of the proposed structure of **1**. Our synthetic **1** presented the conformation **1b** and showed nonidentical ^{1}H and ^{13}C NMR specrta.



We started our synthesis from the known phthalide **5**.[2] As the reported procedure for the synthesis of **5** was lengthy and complicated, we developed a simpler method for multigram preparation of **5** as shown in Scheme 1. Diels−Alder reaction of pyrone **2** with dimethyl acetylenedicarboxylate gave decarboxylated product **3**.

Scheme 1[a]



[a] (a) Dimethyl acetylenedicarboxylate, 180−200 °C (89%); (b) $LiAlH_4$, THF (99%); (c) concentrated HCl, Et_2O, 0 °C; (d) Jones' reagent, acetone; (e) aqueous NaOH, THF (72% in three steps).

Two ester groups of **3** were reduced, and HCl treatment of the resulting diol gave **4** regioselectively. Jones oxidation and successive base treatment caused lactone formation to afford **5** in 63% yield over five steps from **2**.

Birch reduction of **5** with potassium in liquid ammonia and homoprenylation of the resulting enolate gave **6** in 62% yield (Scheme 2). Acid hydrolysis of the enol ether and

(1) Tabata, N.; Tomoda, H.; Masuda, R.; Iwai, Y.; Omura, S. *J. Antibiot.* **1995**, *48*, 53−58.

(2) (a) Sargent, M. V. *J. Chem. Soc., Perkin Trans. 1* **1987**, 231−235. (b) Meldrum, A. N. *J. Chem. Soc.* **1911**, 1712−1721.

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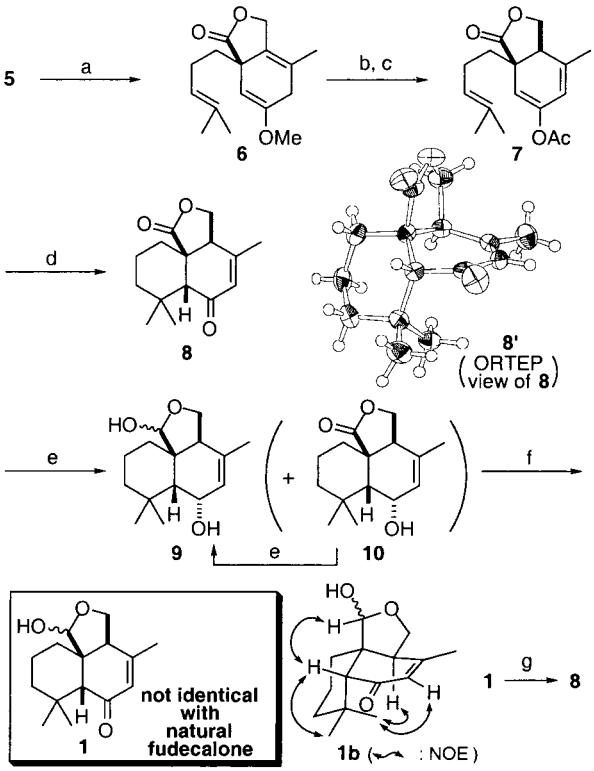
Scheme 2[a]

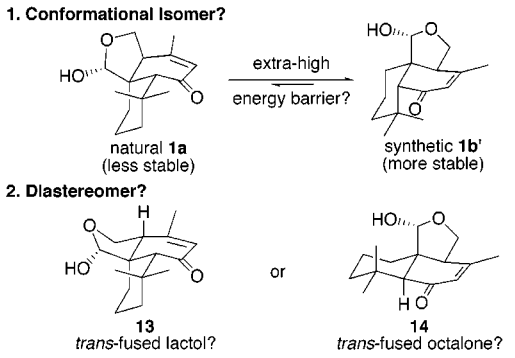


[a] (a) K, liquid NH_3, *t*-BuOH, then LiBr, 5-iodo-2-methyl-2-pentene, THF−HMPA (62%); (b) 3 N HCl, THF (46%); (c) LDA, Ac_2O, THF; (d) BF_3(gas), $CH_2Cl_2-H_2O$, rt (90% in two steps); (e) DIBAL, CH_2Cl_2, −78 °C [91%(**9**) + 8%(**10**) from **8**; 91% from **10**]; (f) MnO_2, CH_2Cl_2 (84%); (g). Dess−Martin periodinane, CH_2Cl_2 (72%).

isomerization of the double bond afforded conjugated enone in 46% yield along with a nonconjugated enone (24%), which was then converted into enol acetate **7**. The next step was the key cyclization to form the tricyclic compound. When **7** was treated with BF_3 in wet CH_2Cl_2, an axial attack of a cationic side chain to the enol acetate took place and the desired **8** was obtained as a sole product in 90% yield (in two steps).[3] The stereochemistry including its conformation was confirmed as **8′** by NOE experiment and X-ray analysis.

For converting **8** into fudecalone, an unsaturated ketone and a lactone carbonyl were reduced with 4 equiv of DIBAL to give **9** in a maximum yield of 91%. This step was not reproducible, and sometimes **10** was obtained as a major product along with minor **9** (66% + 33%). Hydroxy lactone **10** could be converted into **9** in 91% yield by the further reduction with DIBAL. Allylic alcohol **9** was selectively reoxidized with MnO_2, and **1** was obtained as an inseparable crystalline diastereomeric mixture with a broad melting point (162−173 °C, after recrystallization) in 84% yield. The overall yield of **1** was 20% from **5** (in six steps) and 12% from **2** (in 11 steps).

Contrary to our expectation, however, the ^1H and ^{13}C NMR spectra of synthetic **1** showed different chemical shifts although the patterns of the peaks were quite similar to those of natural fudecalone.[1,4] The correctness of the structure of our synthetic **1** was confirmed by oxidizing it with Dess−Martin periodinane[5] to the undoubted precursor **8** in 72% yield. More interestingly, an NOE experiment revealed the conformation of synthetic **1** to be **1b**, which was different from that of natural **1**. Omura et al. reported the conformation of natural fudecalone to be **1a** from the results of the NOE experiment.[1] According to MM3 calculation, **1b′** is 2.1 kcal/mol more stable than **1a** and all our attempts of conformational isomerization of **1b** or its derivatives to **1a** resulted in failure.



Two explanations are possible for this disagreement: (1) Natural fudecalone is certainly the unstable conformer **1a**, but the five-membered hemiacetal ring restricts the flexibility of the molecule and makes the energy barrier between **1a** and **1b′** extraordinarily high. Therefore, it cannot isomerize to the more stable conformation **1b′**. (2) The proposed stereochemistries are incorrect and the real structure of fudecalone is that shown in **13** or **14**.

Building on these points of view, conformationally selective synthesis of **1a** and stereoselective synthesis of **13** and **14** are in progress and will be reported in due course.

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(3) Fairlie, J. C.; Hodgson, G. L.; Money, T. *J. Chem. Soc., Perkin Trans. 1* **1973**, 2109−2112.

(4) In $CDCl_3$, the hemiacetal of the synthetic **1** equilibrated to an α/β = 1:3 mixture: ^1H NMR (500 MHz, in $CDCl_3$) major isomer, δ 5.90 (br m, 1H, H-5), 4.94 (s, 1H, H-1), 4.33 (t, J = 9.0 Hz, 1H, H-3), 4.09 (dd, J = 9.0, 3.0 Hz, 1H, H-3), 2.72 (br d, J = 9.0 Hz, 1H, H-3a), 2.22 (s, 1H, H-6a), 1.91 (t, J = 1.0 Hz, 3H, H-11), 1.71 (m, 1H, H-10), 1.50−1.70 (m, 2H, H_2-9), 1.46 (m, 1H, H-8), 1.30 (m, 1H, H-8), 1.24 (m, 1H, H-10), 1.05 (s, 3H, H-13), 0.76 (s, 3H, H-12); minor isomer, δ 5.90 (br m, J = 1.0 Hz, 1H, H-5), 4.98 (s, 1H, H-1), 4.33 (dd, J = 9.0, 7.0 Hz, 1H, H-3), 3.97 (br d, J = 9.0 Hz, 1H, H-3), 2.81 (br d, J = 7.0 Hz, 1H, H-3a), 2.14 (s, 1H, H-6a), 1.95 (t, J = 1.0 Hz, 3H, H-11), 1.01 (s, 3H, H-13), 0.79 (s, 3H, H-12); ^{13}C NMR (125 MHz, in $CDCl_3$) major isomer, δ 200.80, 156.53, 128.47, 107.38, 70.00, 54.46, 48.44, 44.10, 41.54, 34.73, 33.40, 31.32, 24.60, 22.29, 18.16; minor isomer, δ 201.00, 158.84, 128.47, 102.71, 68.51, 55.46, 46.68, 46.20, 41.26, 33.79, 31.48, 25.88, 24.09, 22.01, 18.37.

(5) (a) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155−4156. (b) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277−7287. (c) Ireland, R. E.; Liu, L. *J. Org. Chem.* **1993**, *58*, 2899. (d) Meyer, S. D.; Schreiber, S. L. *J. Org. Chem.* **1994**, *59*, 7549−7552.