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 $16 \,\mu$ M. 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 ¹H and ¹³C 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–



^{*a*} (a) Dimethyl acetylenedicarboxylate, 180-200 °C (89%); (b) LiAlH₄, THF (99%); (c) concentrated HCl, Et₂O, 0 °C; (d) Jones' reagent, acetone; (e) aqueous NaOH, THF (72% in three steps).

Alder reaction of pyrone 2 with dimethyl acetylenedicarboxylate gave decarboxylated product 3.

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

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Scheme 2^a



^{*a*} (a) K, liquid NH₃, *t*-BuOH, then LiBr, 5-iodo-2-methyl-2pentene, THF-HMPA (62%); (b) 3 N HCl, THF (46%); (c) LDA, Ac₂O, THF; (d) BF₃(gas), CH₂Cl₂-H₂O, rt (90% in two steps); (e) DIBAL, CH₂Cl₂, -78 °C [91%(9) + 8%(10) from 8; 91% from 10]; (f) MnO₂, CH₂Cl₂ (84%); (g). Dess-Martin periodinane, CH₂Cl₂ (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 BF₃ in wet CH₂Cl₂, 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 MnO₂, 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 ¹³C NMR spectra of synthetic **1** showed different chemical shifts

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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 periodinane⁵ 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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⁽⁴⁾ In CDCl₃, the hemiacetal of the synthetic **1** equilibrated to an α/β = 1:3 mixture: ¹H NMR (500 MHz, in CDCl₃) 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, H₂-9), 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); ¹³C NMR (125 MHz, in CDCl₃) major isomer, δ 200.080, 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.

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