Pergamon

Tetrahedron Letters 42 (2001) 917–919

TETRAHEDRON LETTERS

Synthesis and revision of the relative configuration of fudecalone

Hidenori Watanabe,* Takahiro Yamaguchi, Takeshi Furuuchi and Takeshi Kitahara

Department of Applied Biological Chemistry, Graduate School of Agricultural and Life Sciences, The University of Tokyo, 1-1-1 Yayoi, Bunkyo-ku, Tokyo 113-8657, Japan

Received 4 October 2000; revised 13 November 2000; accepted 17 November 2000

Abstract—We synthesized the proposed structure of fudecalone, whose NMR spectral data were not identical with those of the natural compound. As our synthetic fudecalone was a conformational isomer of the reported structure, we first investigated conformational isomerization. However, all our attempts resulted in failure, and we then changed the strategy to the synthesis of diastereomers. Finally, we found the *trans*-octalone derivative showed the identical NMR spectrum with that of natural fudecalone, and the relative configuration was determined to be 1*S**, 3a*S**, 6a*S**, 10a*S**.

Fudecalone (**1**) was isolated by Ōmura et al. in 1995 from a culture broth of *Penicillium* sp. FO-2030 as an anticoccidial sesquiterpene.[1] It completely inhibited schizont formation of monensin-resistant *Eimeria tenella* at concentrations of more than 16 μM. The structure was elucidated mainly by NMR experiments and the conformation was reported to be **1a** as illustrated in Fig. 1.

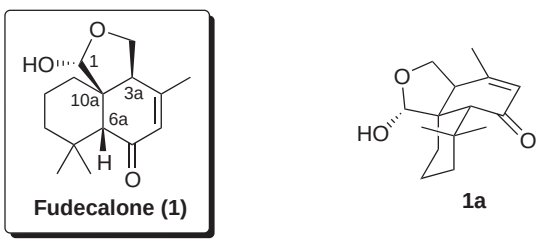


Figure 1.

As reported previously, we started our synthesis from the iodide (**2**) and the known phthalide (**3**), and obtained **5** via a keto-lactone (**4**) in six steps.[2] However, the ^{1}H and ^{13}C NMR spectral data of **5** were not identical with those of reported data and an analysis of its NOESY spectrum revealed the conformation of **5** to be **1b**, which was a conformational isomer of **1a** (Scheme 1).

According to MM3 calculation, **1b** was 2.1 kcal/mol more stable than **1a** (Fig. 2). So, we thought it would be

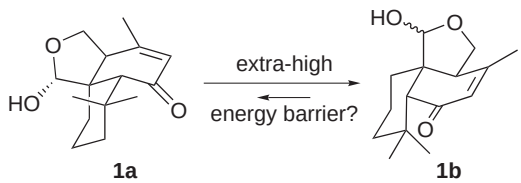
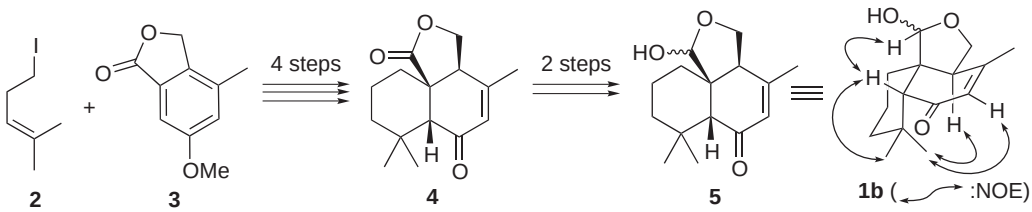


Figure 2.



Scheme 1.

* Corresponding author. Fax: 81-3-5841-8019; e-mail: ashuten@mail.ecc.u-tokyo.ac.jp

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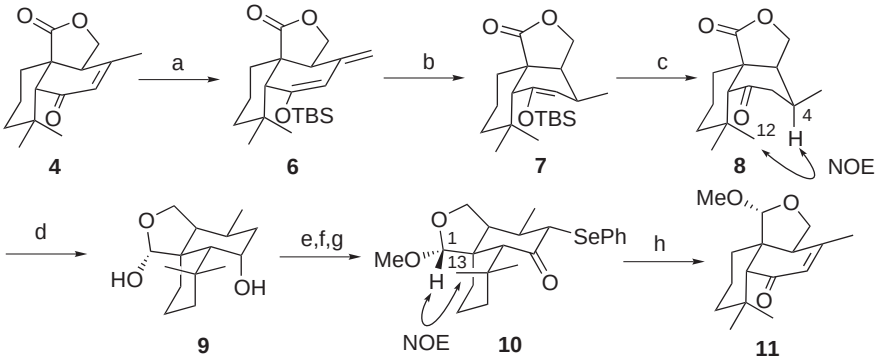
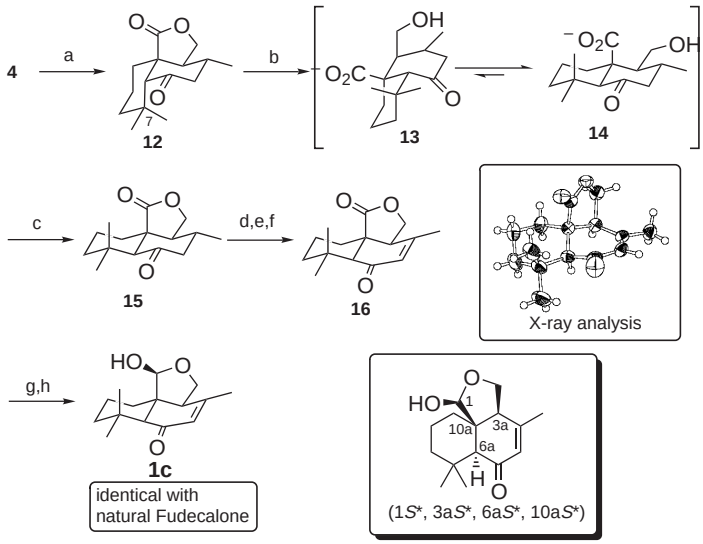


Scheme 2. (a) TBSOTf, 2,6-lut. CH_2Cl_2, 0°C (92%); (b) H_2, Pd–C, EtOAc, rt (82%, diastereo ratio was 4:1); (c) TBAF, THF, rt (83%); (d) DIBAL, CH_2Cl_2, −78°C; (e) *p*-TsOH, MeOH, rt (49% in two steps); (f) Dess–Martin periodinane, CH_2Cl_2, rt (83%); (g) LDA, THF; PhSeCl, HMPA, −78°C (82%); (h) *m*CPBA, CH_2Cl_2, 0°C (53%).



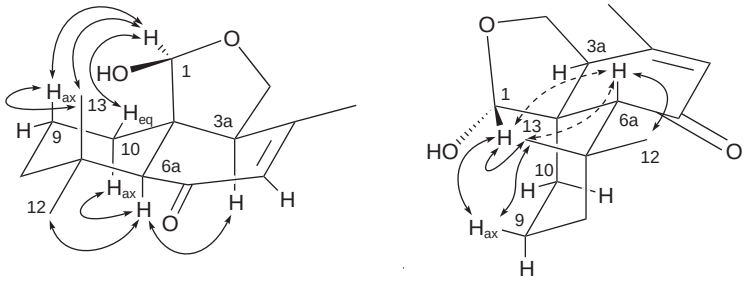
Scheme 3. (a) H_2, Pd–C, EtOH, rt (88%); (b) aq. LiOH, THF, reflux; (c) PPTS, benzene, reflux (69% in two steps, 92% based on recovered **12**); (d) LDA, THF; TMSCl, Et_3N, −78°C (91%); (e) NBS, THF, rt (93%); (f) DBU, THF, reflux (93%); (g) DIBAL, tol. −78°C; (h) MnO_2, CH_2Cl_2, rt (32% in two steps).

interesting to know if fudecalone could exist as an unstable conformation because of the extra-high energy barrier between **1a** and **1b**, and we started an investigation of the conformational isomerization from **1b** to **1a**.

We adopted intermediate (**4**) which was dienylsilylated with TBSOTf followed by hydrogenation to give silylether (**7**) (Scheme 2). This hydrogenation to *exo*-olefin of **6** occurred predominantly from the α face (α:β = 4:1). Treatment of **7** with TBAF afforded a ketone (**8**) in 50% yield over three steps. We expected that the conformation of **8** would change from **1b** type to **1a** type so that the β-methyl group would be stabilized in a more stable equatorial orientation. However, very strong NOE between H-4 and H_3-12 revealed that the B-ring was in the boat-form, and thus **6** still kept the **1b**-type conformation. When **8** was reduced to **9** with 4 equiv. of DIBAL, the conformation changed to **1a** type for the first time. As **9** was unstable, we converted it into a methylacetal with *p*-TsOH in MeOH (49% yield from **8**), which was oxidized with Dess–Martin periodinane[3] followed by selenylation to give **10**. The NOE between H-1 and H_3-13 revealed that **10** retained the same conformation. But when the selenide was eliminated by oxidizing with *m*CPBA, the conformation of the product reverted to the previous **1b** type, and **11** was obtained in 53% yield. The conformation of **11** was confirmed by NOE experiments and X-ray analysis.

From these results, it was clarified that the energy barrier between **1a** and **1b** was not so high and that this compound could not exist as **1a** but only as **1b**. We concluded therefore that the proposed relative stereochemistry was incorrect and decided to synthesize a *trans*-fused octalone, **1c**.

We started a synthesis of **1c** from the same intermediate (**4**), which was hydrogenated with Pd–C to afford **12** as an almost single isomer (Scheme 3). This direct hydrogenation made the methyl group of **12** α-oriented, because the α-face of the B-ring is sterically protected



Synthetic Fudecalone **1c** Reported Fudecalone **1a**

Figure 3.

by the 7-methyl group. In the presence of the lactone ring, *cis*-fused decalone **12** could not be isomerized to *trans*-fused decalone **15** by using an organic base, DBU, LDA or LHMDS. However, when treated with aq. LiOH, the lactone was saponified first. Then the conformation of hydroxycarboxylic acid changed to **13** and the equilibrium favored **14**, and then **15** was obtained after the relactonization with PPTS under reflux in benzene for 4 h in 69% yield over two steps. Thus, the lactone-opening was essential for this isomerization. On the other hand, **15** completely isomerized to the more stable **12** by heating with PPTS for a longer period. The enolate derived from **15** by LDA treatment was trapped with TMSCl followed by bromination, dehydrobromination afforded an enone (**16**) in 79% yield over three steps, and the stereochemistry of **16** was confirmed by X-ray analysis. The unsaturated ketone and the lactone carbonyls of **16** were reduced with 4.4 equiv. of DIBAL, and the resultant allylic alcohol was reoxdized with MnO_2 to furnish **1c** in 32% yield over two steps. ^{1}H and ^{13}C NMR spectral data of **1c** showed complete accordance with that of natural fudecalone except the NOE data.[4]

The NOESY spectrum of our **1c** showed slight differences from the reported data, as illustrated in Fig. 3. NOEs of **1c** between H-6a and each of H-3a, H-10_{ax} and H_3-12 indicated that C-6a had the *S** configuration, and NOEs between H-1 and each of H-9_{ax}, H-10_{eq} and H_3-13 indicated that C-1 also had the *S** configuration. On the other hand, NOEs between H-6a and each of H-1 and H_3-13 of **1** indicated by dashed arrows, which were the decisive factor to determine fudecalone to be **1a**,[1] were not observed.

In conclusion, our investigation of the conformational isomerization from **1b** to **1a** via selenide (**10**) proved fruitless. However, by utilizing the intermediate of the previous synthesis of **1b**, we completed the synthesis of *trans*-fused octalone **1c** as a racemate and found that it showed the identical NMR spectral data with those of the natural fudecalone. By further NOESY experiments we were able to determine the relative configuration of fudecalone to be 1*S**, 3a*S**, 6a*S** and 10a*S**.

Enantioselective synthesis and the determination of the absolute configuration of natural fudecalone are in progress and will be reported in a full account.

Acknowledgements

We thank Prof. S. Ōmura and Dr. N. Tabata of the Kitasato Institute for the valuable gift of the spectral data of natural fudecalone, and Mr. M. Bando of Otsuka Pharmaceutical Co., Ltd., for X-ray analysis of **11** and **16**. We also thank Dr. K. Furihata of the University of Tokyo for measuring various NMR spectra.

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4. ^{1}H NMR (500 MHz, in $CDCl_3$) δ 1.16 (3H, s), 1.24 (3H, s), 1.25 (1H, dt, J=4.0, 13.5 Hz), 1.26 (1H, dt, J=4.0, 13.5 Hz), 1.44 (1H, m), 1.53 (1H, quint. t, J=3.5, 14.0 Hz), 1.63 (1H, tq, J=3.5, 14.0 Hz), 1.82 (3H, s), 1.86 (1H, m), 2.38 (1H, s), 2.46 (1H, d, J=3.5 Hz), 2.61 (1H, dd, J=4.0, 9.0 Hz), 3.96 (1H, dd, J=4.0, 9.0 Hz), 4.24 (1H, t, J=9.0 Hz), 5.47 (1H, d, J=3.5 Hz), 5.82 (1H, s); ^{13}C NMR (125 MHz, in $CDCl_3$) δ 19.62, 21.41, 21.78, 32.20, 32.60, 37.59, 43.07, 51.09, 51.97, 56.53, 68.41, 100.87, 128.58, 153.11, 197.74; mp 186–196°C.