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Synthesis of 12-Hydroxy-10-methylenetricyclo[7.2.1.$0^{1,6}$]dodecan-11-one

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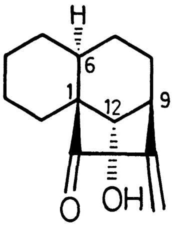
A new type of tricyclic compound, having bicyclo[3.2.1]octane skeleton with an α-methylenecyclopentanone moiety and *trans*-bicyclo-[4.4.0]decane structure, has been synthesized by skeletal transformation of *exo*-3-methylenetricyclo[6.4.0.$0^{1,4}$]dodecan-5-ol.

Much attention has been paid on tetracyclic diterpenoids which have bicyclo-[3.2.1]octane skeleton with an α-methylenecyclopentanone moiety and *cis*-bicyclo-[4.4.0]decane substructure because of their biological activities.[1] As an extension of our skeletal-rearrangement strategy to the synthesis of biologically active substances,[2] we disclose herein the synthesis of the title compound **1**, having a new type of tricyclic skeleton which consists of a bicyclo[3.2.1]octane with α-methylenecyclopentanone and *trans*-bicyclo[4.4.0]decane system, by solvolytic rearrangement of *exo*-3-methylenetricyclo[6.4.0.$0^{1,4}$]dodecan-5-ol (**2**).



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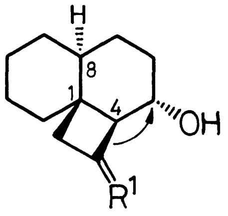
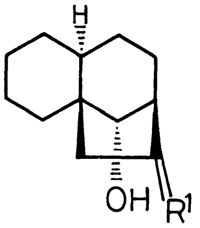
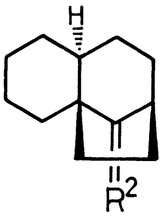


2 R^1=CH_2
3 R^1=H_2



4 R^1=CH_2
5 R^1=H_2

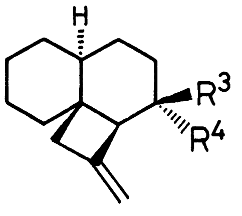


6 R^2=O
7 R^2=H_2

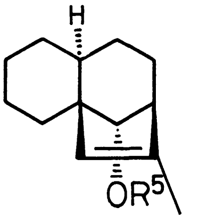
First of all, we investigated the rearrangement behavior of *exo*-tricyclo-[6.4.0.$0^{1,4}$]dodecan-5-ol (**3**)[3,4] as the model study. Reaction of **3** with 50% aqueous H_2SO_4 in tetrahydrofuran (THF) at 55 °C for 2 h gave the anticipated alcohol, tricyclo[7.2.1.$0^{1,6}$]dodecan-12-ol (**5**), in 80% yield. Since oxidation of **5** [CrO_3, Py, CH_2Cl_2, rt, 86%] followed by Wolff-Kishner reduction of the ketone **6** [N_2H_4, KOH, diethyleneglycol, 210 °C, 75%] gave tricyclo[7.2.1.$0^{1,6}$]dodecane (**7**),[5] the tricyclic skeleton of **5** was unambiguously confirmed. Comparison of the reduction behavior[6] of **6** with that[7] of bicyclo[3.2.1]octan-8-one and the rearrangement mechanism that the back side attack of the nucleophile to the developing p-orbital at C(4) indicate that the hydroxyl group locates on the opposite side of the ethano bridge.

With the success of the model study, we attempted the synthesis of the title compound 1. We chose 3-methylenetricyclo[6.4.0.0^{1,4}]dodecan-5-one (8)8) as the starting material. Stereoselective reduction of 8 with LiB(s-butyl)$_3$H [Et$_2$O, -78 °C, then 10% NaOH, 30% H_2O_2, 40 °C] afforded an endo-alcohol 9 and exo-alcohol 2 in 98% yield (endo : exo = 99 : 1). Inversion of the hydroxyl gruop of 9 by Mitsunobu reaction [(EtO$_2$CN)$_2$, PPh$_3$, PhCO$_2$H, THF, rt] followed by alkaline hydrolysis of the benzoate [KOH, MeOH, 65 °C] gave 2 in 86% overall yield. Treatment of 2 with 50% aqueous H_2SO_4 for 1 h gave two alcohols 4 and 10 in 4% and 44% yields.

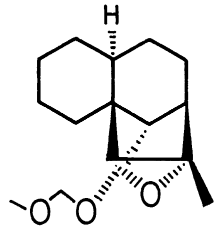
Introduction of an α-methylenecyclopentanone moiety was carried out as reported previously.2) After protection of the hydroxyl group of 10 as the methoxymethyl ether [CH$_3$OCH$_2$Cl, i-Pr$_2$NEt, CH$_2$Cl$_2$, rt], epoxidation of the ether 11 with m-chloroperbenzoic acid [Na$_2$HPO$_4$, CH$_2$Cl$_2$, 0 °C] furnished the single isomer 12 in 99% overall yield which was subjected to base-induced isomerization [LiNEt$_2$, Et$_2$O, 0 °C, then 35 °C] to give an allylic alcohol 13 in 98% yield. Finally, oxidation of 13 with pyridinium dichromate [CH$_2$Cl$_2$, rt] and subsequent deprotection of the α-methylene ketone 14 [17% HCl, THF, 50 °C] gave 1 in 66% overall yield.



8 R^3=R^4=O
9 R^3=OH,R^4=H



10 R^5=H
11 R^5=CH$_2$OCH$_3$



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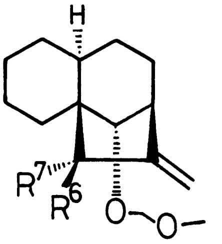

13 R^6=H,R^7=OH
14 R^6=R^7=O

References

1) For a recent review, see: E. Fujita and M. Node, Progress in the Chemistry of Natural Product, 46, 77 (1984).
2) K. Kakiuchi, M. Ue, M. Takeda, T. Tadaki, Y. Kato, T. Nagashima, Y. Tobe, H. Koike, N. Ida, and Y. Odaira, Chem. Pharm. Bull., 35, 617 (1987).
3) All new compounds gave satisfactory spectral and analytical data. Selected ^{13}C NMR (CDCl$_3$, δ) data are as follows:
6: 222.9 (s), 50.3 (s), 48.5 (d), 45.2 (d), 35.2 (d), 29.8 (t), 29.3 (t), 25.9 (t), 25.7 (t), 25.3 (t), 22.7 (t), 21.9 (t).
10: 140.1 (s), 126.1 (d), 79.7 (d), 49.4 (s), 47.3 (d), 32.3 (d), 32.1 (t), 31.5 (t), 26.4 (t), 26.1 (t), 24.0 (t), 17.3 (t), 16.2 (q).
1: 207.8 (s), 148.1 (s), 115.6 (t), 74.2 (d), 53.8 (s), 43.2 (d), 37.0 (d), 29.8 (t), 29.2 (t), 26.4 (t), 25.8 (t), 25.4 (t), 22.2 (t).
4) Prepared from tricyclo[6.4.0.0^{1,4}]dodecan-5-one as described for 2. Stereochemistry of the hydroxyl group was determined as reported previously, K. Kakiuchi, S. Kumanoya, M. Ue, Y. Tobe, and Y. Odaira, Chem. Lett., 1985, 989.
5) N. S. Vorob'eva, Z. K. Zemskova, T. Pehk, and A. A. Petrov, Neftekhimiya, 17, 22 (1977).
6) Reduction of 6 with LiAlH$_4$ gave 5 exclusively.
7) Reduction of the bicyclic ketone with metal hydrides gave an alcohol mainly, having the hydroxyl group on the opposite side of the ethano bridge, A. C. Cope, J. M. Grisar, and P. E. Peterson, J. Am. Chem. Soc., 82, 4299 (1960).
8) G. Marini-Bettolo, S. P. Sahoo, G. A. Poulton, T. Y. R. Tsai, and K. Wiesner, Tetrahedron, 36, 719 (1980).

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