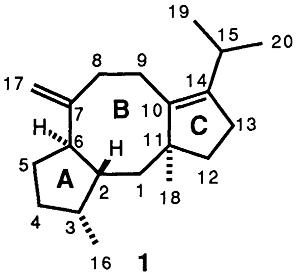
CHEMISTRY LETTERS, pp. 91-94, 1989.

Structure Elucidation of "Hydroxycycloaraneosene" by Unambiguous Total Synthesis. An Eight-Membered Ring Formation via a Lewis Acid-Catalyzed Ene-Reaction

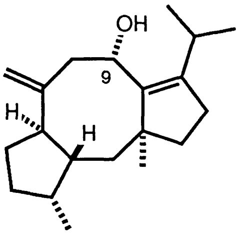
Nobuo KATO,* Xue WU,† Shinya TANAKA,†† and Hitoshi TAKESHITA*
Institute of Advanced Material Study, 86, Kyushu University,
Kasuga-koen, Kasuga, Fukuoka 816
††Graduate School of Engineering Sciences, 39, Kyushu University,
Kasuga-koen, Kasuga, Fukuoka 816

An improved eight-membered ring closure by means of a Lewis acid-catalyzed ene-reaction of an iridoid dimer produced a tricyclic derivative which was further converted to cycloaraneosene and its congener, "hydroxycycloaraneosene". Total synthesis of the latter established its structure to be 8β-hydroxy derivative, not as the originally-proposed 9α-.

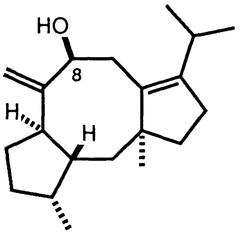
In the last decade, total syntheses of the 5-8-5-membered tricyclic di- and sesterterpenoids have been attracted much attention.$^{1)}$ During our synthetic study$^{2)}$ of cycloaraneosene (**1**), a 5-8-5-membered tricyclic diterpene isolated by Borschberg from <u>Sordaria</u> <u>araneosa</u>,$^{3)}$ we have prepared 9α$^{4)}$-hydroxycycloaraneosene (**2**), whose structure corresponded to the proposed for a congener, "hydroxycycloaraneosene" (**A**). The ^{1}H NMR spectra of **2** and **A** were, however, not the same, and the structure of **A** should be revised. The reported spectral data suggested that **A** might be 8β-hydroxycycloaraneosene (**3**).$^{2)}$ To obtain a concrete proof for this we aimed to synthesize **3** in an unambiguous way; since a hydroxyl epimer of **A** has been prepared,$^{3)}$ synthetic attention was paid only on the regio-selective introduction of the hydroxyl at C-8 position of **1**. Herein, we describe structure elucidation of **A** as **3** by a synthesis via an improved eight-membered ring closure.



1



2



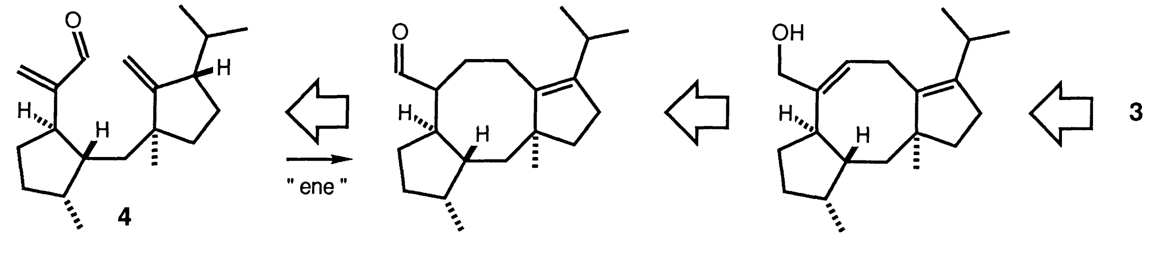
3

In general, a medium ring formation by an ene-reaction may not be practical. However, the cyclization from an appropriate precursor, e.g., an iridoid dimer,

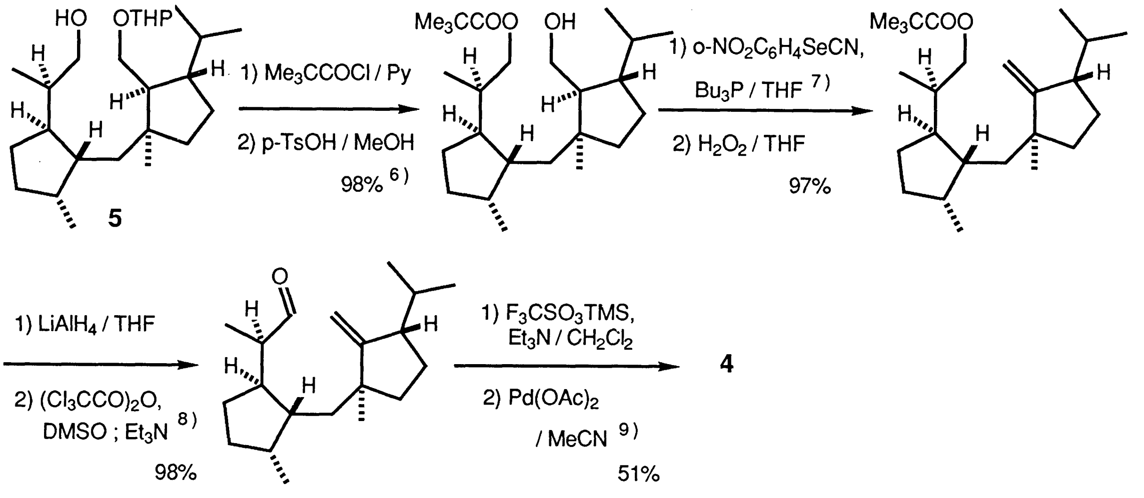
---

† On leave from Yambian University, Yanji, Jilin, Peoples' Republic of China.

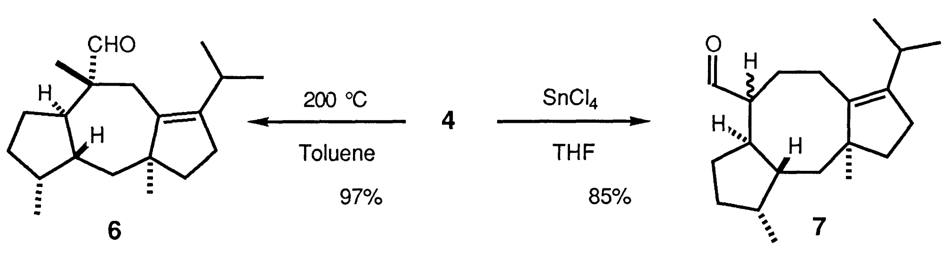
may become feasible, since two five-membered rings fused to the system must greatly reduce a freedom in conformational change (entropy factor) of the ground state compared with that of a simple open-chain material. Therefore, the following retrosynthetic scheme should be worthwhile to be examined.



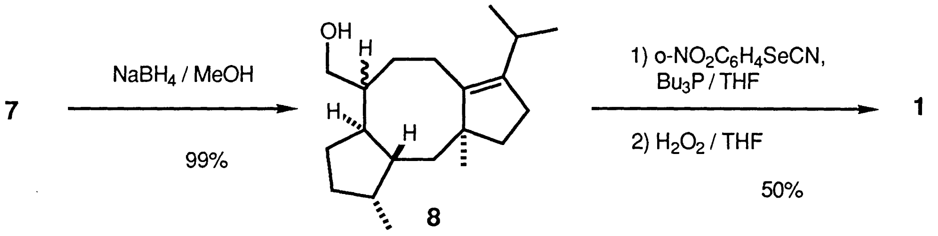
The key compound, a dienal (**4**),5) was prepared from **5**.2)



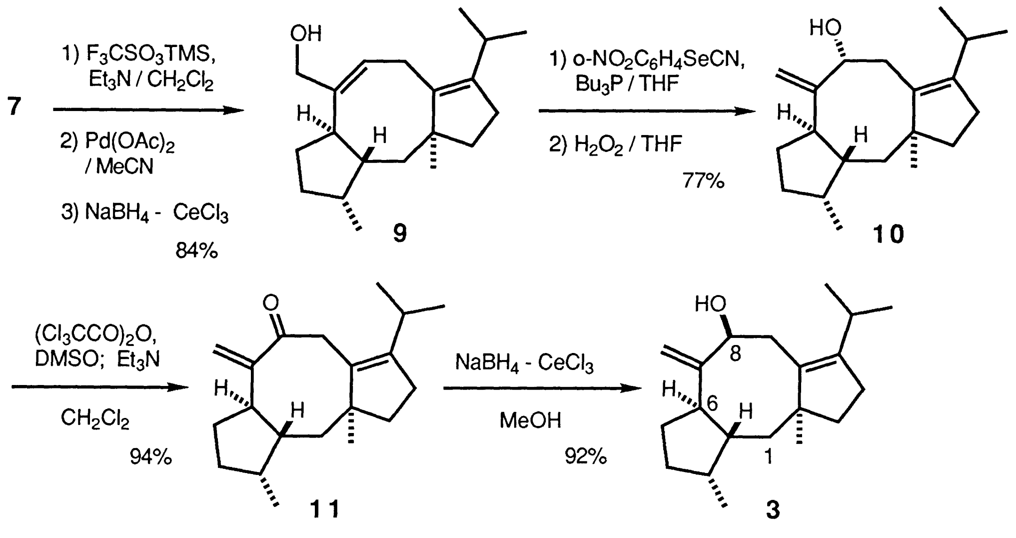
Interestingly, the results of the ene-reaction of **4** were completely different under two conditions, a thermal and a Lewis acid-catalyzed conditions. While heating of **4** at 200 °C in a sealed tube furnished a 5-7-5-membered derivative (**6**)10) as judged from appearance of five methyl signals in its ^{1}H NMR spectrum, an $SnCl_4$-treatment of **4** in THF formed the desired 5-8-5-membered aldehyde (**7**).



An unexpected formation of **6** from **4**, a conjugated aldehyde, can be explained in terms of the preference of the smaller ring formation under the sterically crowded circumstances in the transition state; the π-system of the enal moiety might not be co-planar. On the other hand, $SnCl_4$ was sufficient enough to polarize the aldehyde to make the electronic control predominant. The ring structure and stereochemical arrangement of **7** were proven by its transformation to **1** via the $NaBH_4$-reduction to an tricyclic alcohol (**8**) and its dehydration. The product, **1**, was identical with our former sample.$^{2)}$ Thus, an ene-reaction opened an improved route for **1**.



In order to introduce an oxygen function at C-8, **7** was first converted into an allyl alcohol (**9**) by consecutive treatments with trimethylsilyl trifluoromethanesulfonate-Et_3N, $Pd(OAc)_2$, and $NaBH_4$-$CeCl_3$.$^{11)}$ A stereoselective conversion of **9** to 8-hydroxy derivative (**10**) was facilitated by the same treatment employed in the dehydration of **8**, i.e., an o-nitrophenylselenocyanide-treatment$^{7)}$ followed by H_2O_2-oxidation.$^{12)}$ The alcohol **10**, colorless needles, mp 128.5-130 °C, $[\alpha]_D$ -16° ($CHCl_3$) (lit.$^{3)}$ 129-130 °C, $[\alpha]_D$ -10°), was identical with the epimer of the natural **A** from the ^{13}C NMR [δ=14.8(+0.1),$^{13)}$ 20.5, 21.2, 26.5(+0.1), 27.0, 28.0(+0.1), 29.6 (+0.2), 34.1(-0.1), 34.6, 34.7(+0.1), 41.4, 42.1, 42.5(+0.2), 50.0(-0.1), 50.2, 77.0(+0.2), 112.5(+0.3), 135.1, 143.1(+0.3), and 159.0].



The other 8-hydroxy derivative of **1** was synthesized by a slightly modified method of known procedures;$^{3)}$ Swern oxidation$^{8)}$ of **10** to **11**, colorless needles, mp 73-74.5 °C (lit.$^{3)}$ 75-76 °C), and its 1,2-reduction with $NaBH_4$-$CeCl_3$. As expected, the physical data of this colorless-oily alcohol (**3**) [$[\alpha]_D$ +15° (lit.$^{3)}$

$[\alpha]_D$ +7.5°). ^{13}C NMR δ=16.7, 21.17, 21.23, 27.3, 27.9(2C), 29.6, 31.8, 33.9, 36.7, 39.4, 42.5, 46.5, 48.7, 50.8, 73.2, 107.1, 134.2, 144.6, and 157.7], were in good accord with natural **A**. The stereochemistry of the hydroxyl group of **3** was confirmed by distinct observation of NOE on H-6 (δ=2.09, br td, J=10, 8 Hz) and H-1α (1.44, dd, J=15, 8 Hz) by an irradiation with the frequency of H-8 (4.46, dd, J=8, 6 Hz). Therefore, the structure of natural **A** is 8β-hydroxycycloaraneosene, **3**.

We thank a finantial assistance of the Ministry of Education, Science and Culture through a Grant-in-Aid for Scientific Research to N. K. (No. 63540428).

References

1) M. Rowley and Y. Kishi, Tetrahedron Lett., 29, 4909 (1988); H. Takeshita and N. Kato, Yuki Gosei Kagaku Kyokai Shi (J. Syn. Org. Chem. Jpn.), 44, 1081 (1986). See also references cited therein.
2) N. Kato, S. Tanaka, and H. Takeshita, Chem. Lett., 1986, 1989; Bull. Chem. Soc. Jpn., 61, 3231 (1988).
3) H. J. Borschberg, Ph. D. Dissertation, Eignossischen Technischen Hochschule, Zurich, Switzerland, 1975.
4) The positional numberings and the ring letters are used as shown in **1**.
5) All new compounds described here gave satisfactory elemental analyses together with the pertinent physical data.
6) Actually, **5** was contaminated with the stereoisomers about C-2 and C-3. Separation of the isomers was carried out at this stage. The yield was calculated as started from pure **5**. For a discussion on the stereoselectivity in the formation of **5**, see Ref. 2.
7) K. B. Sharpless and M. W. Young, J. Org. Chem., 40, 947 (1975); P. A. Grieco, S. Gilman, and M. Nishizawa, ibid., 41, 1485 (1976).
8) K. Omura, A. K. Sharma, and D. Swern, J. Org. Chem., 41, 957 (1976); E. J. Corey, R. L. Danheiser, S. Chandrasekaran, P. Siret, G. E. Keck, and J. -L. Gras, J. Am. Chem. Soc., 100, 8031 (1978).
9) Y. Ito, T. Hirao, and T. Saegusa, J. Org. Chem., 43, 1011 (1978).
10) Stereostructure of **6** was tentatively assigned as depicted from the mechanistic view point.
11) J. -L. Luche, J. Am. Chem. Soc., 100, 2226 (1978).
12) D. L. Clive, G. Chittattu, N. J. Curtis, and S. M. Menchen, J. Chem. Soc., Chem. Commun., 1978, 770.
13) The values in parentheses are deviated magnitudes from the reported values.

(Received October 6, 1988)