Tetrahedron Letters No. 19, pp 1691 - 1692.
©Pergamon Press Ltd. 1979. Printed in Great Britain.

0040-4039/79/0501-1691$02.00/0

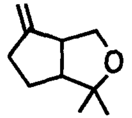
TOTAL SYNTHESIS OF dl-HOP ETHER, AN IRIDOID MONOTERPENE

Takeshi Imagawa,* Nobuyuki Murai, Tetsuo Akiyama,[1)] and Mituyosi Kawanisi
Department of Industrial Chemistry, Kyoto University, Kyoto 606, Japan

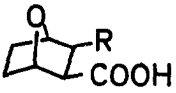
Summary: An iridoid monoterpene hop ether, 2,2-dimethyl-6-methylene-3-oxabicyclo[3.3.0]octane, was first synthesized in six steps starting from the protected lactol form of 3-formyl-2-methoxycarbonylcyclopentanol.

Hop ether (1) was isolated from Japanese hop.[2)] It occupies a unique position in the iridoid monoterpenes since it is the most straightforward one, in a biogenetical sense, from the geraniol precursor and it has no functional group on both of isopropyl methyl groups of the iridane skeleton.[3)] We wish here to report the first synthesis of dl-hop ether (1).

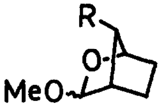
Recently we reported[4)] that anodic oxidation of the anion of 2 via oxygen-assisted Wagner-Meerwein rearrangement afforded the protected from (3) of 2-substituted 3-formylcyclopentanol. The synthetic sequence starts with this compound (3).



1



2



3

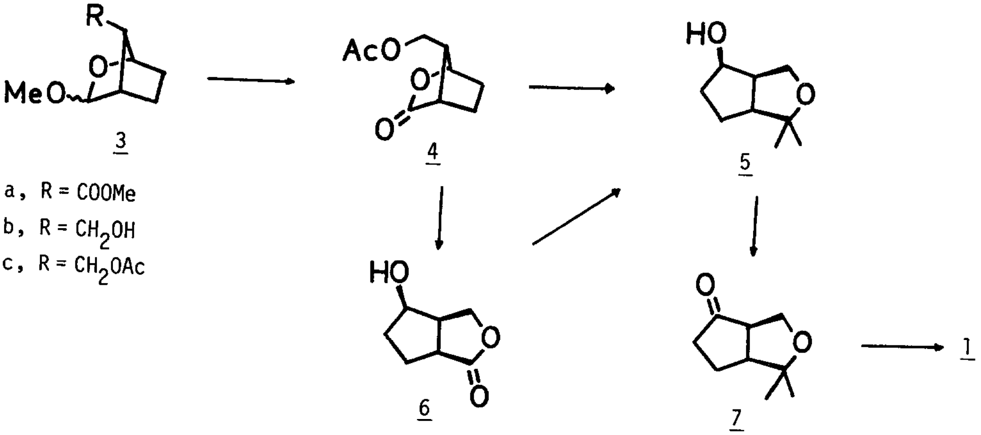
$LiAlH_4$ reduction (94%) of 3a (an endo/exo mixture of the acetal methoxy group), followed by acetylation (99%) gave acetal 3c as an endo/exo mixture of the same ratio as 3a; ^{13}C-NMR ($CDCl_3$): endo-OMe δ 20.4 (t), 30.5 (t), 43.0 (d), 51.3 (d), 61.7 (t), 79.0 (d), 105.4 (d), 56.4 (q), 22.1 (q), 166.5 (s), and exo-OMe δ 24.5 (t), 30.3 (t), 43.8 (d), 47.8 (d), 62.4 (t), 78.6 (d), 107.2 (d), 54.4 (q), 22.1 (q), 166.4 (s). Treatment of 3c with m-chloroperbenzoic acid in the presence of BF_3-OEt_2[5)] gave lactone 4 (97%); ^{13}C-NMR ($CDCl_3$): δ 26.2 (t), 31.4 (t), 42.1 (d), 43.1 (d), 66.9 (t), 76.3 (d), 204.9 (s), 21.0 (q), 181.8 (s).

Treatment of the lactone 4 with excess of methylmagnesium iodide, followed by acidic (HCl) workup afforded 3-oxabicyclo[3.3.0]octane derivative 5 (82%); ^{13}C-NMR ($CDCl_3$): δ 23.4 (q), 27.3

(q), 24.3 (t), 34.8 (t), 48.7 (d), 51.8 (d), 64.2 (t), 74.0 (d), 32.5 (s). 5 was also obtained by two-step method, i.e., hydrolytic recyclization of 4 into 6 (68%) and Grignard reaction of 6 (86%).

Collins oxidation of the alcohol 5 gave ketone 7 (96%), whose spectral characteristics are identical with those of 7 obtained by ozonolysis of the natural product 1;(3,6) ^{13}C-NMR: δ 22.7 (q), 26.8 (q), 23.2 (t), 39.4 (t), 50.5 (d), 52.8 (d), 67.4 (t), 83.4 (s), 219.5 (s).

The ketone 7 was converted into 1 (78%) by recently reported(7) carbonyl-methylenation metho (CH_2Br_2-Zn-$TiCl_4$), whose IR, ^{1}H-NMR, and mass characteristics are identical with those of the natural hop ether (1);(6) ^{13}C-NMR ($CDCl_3$): δ 23.4 (q), 27.4 (q), 25.6 (t), 34.9 (t), 49.5 (d), 54.2 (d), 67.9 (t), 72.2 (s), 105.8 (t), 143.2 (s). The reaction sequence verifies the cis-ring juncture of 1.(8,9)



a, R = COOMe
b, R = CH_2OH
c, R = CH_2OAc

References and Notes

1) Present address: Department of Fine Arts, Kyoto City University of Arts, Kyoto 605, Japan.
2) Y. Naya and M. Kotake, Tetrahedron Letters, 1645 (1968).
3) 2,2,6-Trimethyl-3-oxabicyclo[3.3.0]octan-6-ols and -oct-6-ene were already synthesized; Y. Yamada, H. Sanjoh, and K. Iguchi, J. Chem. Soc. Chem. Comm., 997 (1976).
4) T. Akiyama, T. Fujii, H. Ishiwari, T. Imagawa, and M. Kawanisi, Tetrahedron Letters, 2165 (1978).
5) P. A. Grieco, T. Oguri, and Y. Yokoyama, Tetrahedron Letters, 419 (1978).
6) We would like to thank Dr. Y. Naya, the Institute of Food Chemistry, for generous supply of copies of the spectra of the natural products, 1 and 7.
7) K. Takai, Y. Hotta, K. Oshima, and H. Nozaki, Tetrahedron Letters, 2417 (1978).
8) All new compounds gave satisfactory spectral data and elemental analyses.
9) Financial support of this work was provided by a Grant-in-Aid for Scientific Research from the Ministry of Education of Japan (No. 347074) and by the Kawakami Foundation to one of the authors (T.A.).

(Received in Japan 27 January 1979)