CHEMISTRY LETTERS, pp. 2073-2076, 1990.

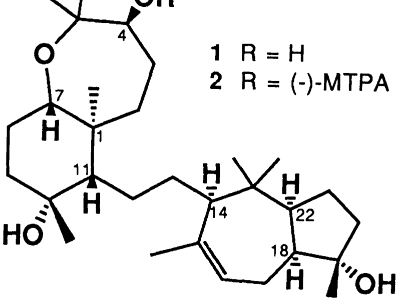
Absolute Configuration of Sipholenol-A. Presence of Two Conformers of MTPA Ester Moiety in a Crystalline State

Yoshinobu INOUYE, Ikuko OHTANI, Takenori KUSUMI, Yoel KASHMAN,[†]
and Hiroshi KAKISAWA*
Department of Chemistry, University of Tsukuba,
Tennodai, Tsukuba, Ibaraki 305
[†]Department of Chemistry, Tel-Aviv University, Ramat Aviv 69978, Israel

Absolute configuration of sipholenol-A was established as (4S) by a single crystal X-ray analysis of its (S)-(-)-MTPA ester. Two conformers of the MTPA ester moiety were recognized as an occupancy of 0.5:0.5 in crystalline state; the positions of the groups can be rationalized by van der Waals interactions to nearest molecules.

The recent development of NMR-techniques has resulted in establishing the absolute configuration of many natural products by comparison of differences in chemical shifts of protons in an alcohol part between two diastereomeric esters such as α-methoxy-α-(trifluoromethyl)benzeneacetic acid (MTPA)[1)] or α-methoxybenzeneacetic acid.[2)] Both methods are based on the assumption that the ester group fixes its geometry, and it is necessary to examine cautiously a steric environment around a hydroxyl group to be esterified when the methods are applied. The modified Mosher's method has shown satisfactorily to apply for compounds having a secondary equatorial alcohol.[3)]

Sipholenol-A(**1**), isolated from the sponge Siphonochalina siphonella, has a unique skeleton derived from squalene and its relative stereo-chemistry was elucidated by a X-ray crystal analysis.[4)] The hydroxyl group at C(4) in **1** is axial and, thus, application of the modified Mosher's method to this compound is of interest to examine the validity of the method. However, differences in chemical shifts between (R)-(+)- and (S)-(-)-MTPA



1 R = H
2 R = (-)-MTPA

esters were not systematic and the method could not be applied. When the hydroxyl group was converted to equatorial through a sequential reactions, the differences became systematic and the absolute configuration of C(4) was estimated as R, i.e., the original one in **1** is thus S.[5)] We present here a single crystal X-ray analysis of the (S)-(-)-MTPA ester **2** of **1** to establish unambiguously the absolute configuration of sipholenol-A(**1**) and to have informations concerning the conformation of the MTPA ester group in an axial position.

Compound **2**[6)] was obtained as colorless rods from ethyl acetate. The diffraction intensities were measured for a single crystal of about 0.5 x 0.5 x 0.5 mm^3 on an Enraf-Nonius CAD4 automated kappa-axis diffractometer with graphite-monochromated Mo $K\alpha$ radiation (50 kV and 26 mA) up to $2\theta=60°$. The intensities were corrected for Lorentz, polarization, and decay effects but not for absorption. Of 5406 unique reflections, 3918 with $|Fo| > 3\sigma(Fo)$ were used for structure determination. Several direct attempts with various starting phase-sets estimated from a convergence map failed to solve the structure. The RANTAN approach in MULTAN11/82[7)] finally succeeded in location of 23 atoms on the E-map. Successive weighted Fourier syntheses revealed the position of the remained non-hydrogen atoms. The structure was refined by the full-matrix least-squares method (SHELX76).[8)] All numerical calculations were carried out on a Facom M-780/20 computer at the Science Information Processing Center, University of Tsukuba.

After isotropic refinement on 49 atoms (R=0.255), a disorder was found around the MTPA ester moiety. Two conformations were estimated with an occupancy of 0.5 and 0.5. Final full-matrix least-squares refinement with anisotropic temperature factors for non-hydrogen atoms was achieved under the following constrains to converge R to 0.089 (R_w=0.085)[9)]: the benzene ring fixed as an ideal hexagon (C-C 1.395 Å) and the bond lengths in disordered part fixed to the mean values for two conformers. Stereoviews[10)] of both the conformers are shown in Fig. 1. Absolute configuration of sipholenol-A(**1**) was, thus, established unambiguously as shown and the

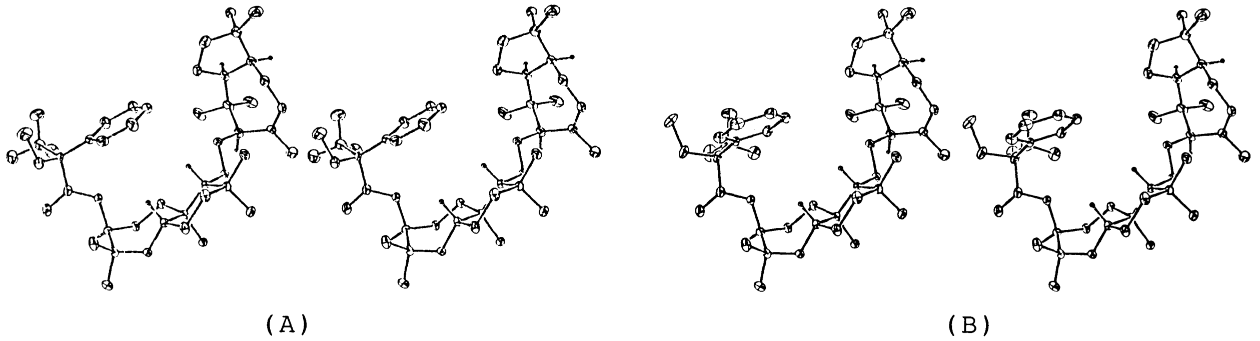
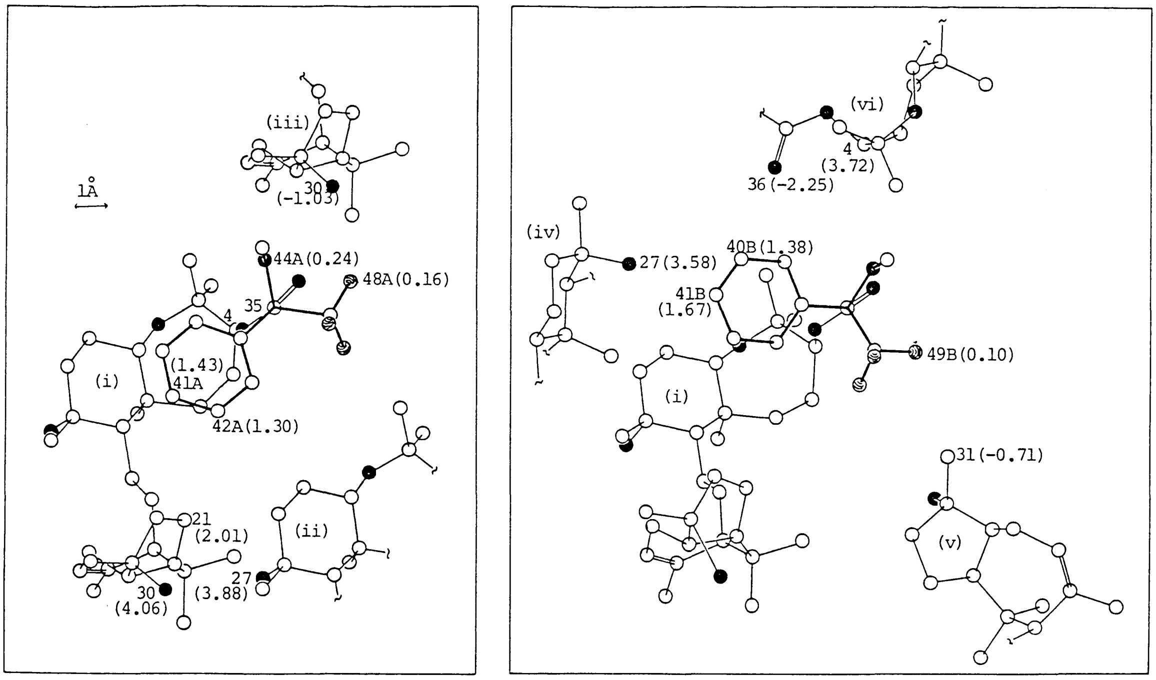

(A) (B)

Fig. 1. Stereoviews of two conformers of **2**.

prediction of S-configuration at C(4) from the modified Mosher's method was consistent with the present result.

Geometry around the MTPA ester moiety is briefly discussed. Although only one conformer had been recognized in hitherto analyzed crystals,11) the presence of two conformers had been confirmed by analyses of the IR spectra.12) Merckx et al. calculated the energy profile in rotating the MTPA moiety and found two energy maxima for the conformations, in which a phenyl or a methoxyl group nearly eclipses with the alcoholic oxygen.12) Newman projections of the MTPA ester groups in both conformers of **2** are shown in Fig. 2 with several nearest molecules. The carbonyl group nearly eclipses to the C(4)-H bond (16.8°). Interatomic distances are all within van der Waals contacts and the shortest ones are: O(30)(i)-O(27)(ii)(2.938 Å); O(44A)(i)-O(30)(iii)(3.268Å) and F(48A)(i)-O(30)(iii)(3.155 Å) in conformer A; C(41B)(i)-O(27)(iv)(3.338 Å) and F(49B)(i)-C(31)(v)(3.439 Å) in conformer B. When the MTPA moiety in the conformer A rotates anti-clockwise (e.g., a distance in -25.0° rotation are shown in parentheses), the interaction between F(48A)(i) and O(30)(iii)(2.313 Å) becomes severe along with intramolecular C(41A)-C(21) (2.974 Å). On the other hand, when the MTPA moiety in the conformer B rotates clockwise (+16.2°), the



(A) (B)

Fig. 2. Newman projections of the conformer A viewed down C(37A)-C(35) (A) and the conformer B viewed down C(37B)-C(35) (B). Values (Å) in parentheses show the height of the atom from the plane. Equivalent positions are: (i) x, y, z; (ii) x, y, z+1; (iii) -1+x, y, -1+z; (iv) 1-x, -0.5+y, 1-z; (v) -x, -0.5+y, 1-z; (vi) 1-x, -0.5+y, 2-z.

interaction between C(40B)(i) and O(36)(vi)(2.887 Å) becomes larger.

The present result is first case of finding the presence of the two conformers of MTPA group in a crystalline state and shows that the existence of the energy maximum at the eclipse state of the phenyl group and the alcoholic oxygen, and the van der Waals interactions with nearest molecules fix the geometries of both conformers as shown.

References

1) J. A. Dale and H. S. Mosher, J. Am. Chem. Soc., 95, 512(1973).

2) B. M. Trost, J. L. Belletire, S. Godleski, P. G. McDougal, and J. M. Balkovec, J. Org. Chem., 51, 2370(1986).

3) T. Kusumi, I. Ohtani, Y. Inouye, and H. Kakisawa, Tetrahedron Lett., 29, 4731(1988); I. Ohtani, T. Kusumi, M. O. Ishitsuka, and H. Kakisawa, ibid., 30, 3147(1989).

4) U. Shmueli, S. Carmely, A. Groweiss, and Y. Kashman, Tetrahedron Lett., 22, 709(1981).

5) I. Ohtani, T. Kusumi, Y. Kashman, and H. Kakisawa, submitted to J. Org. Chem.

6) **2**: mp 183-184°C, $C_{40}H_{59}O_6F_3$, FW 692.87, monoclinic, $P2_1$, a=13.863(3), b=14.105(1), c=10.574(2) Å, β=110.83(1)°, V=1932.5(6) $Å^3$, Z=2, d_x=1.19, d_m=1.17(2) g cm^{-3}.

7) P. Main, S. J. Fiske, S. E. Hull, L. Lessinger, G. Germain, J.-P. Declercq, and M. M. Woolfson, "MULTAN11/82. A System of Computer Programs for the Automatic Solution of Crystal Structures from X-Ray Diffraction Data", Dept. of Physics, Univ. of York, England (1982).

8) G. M. Sheldrick, "SHELX76. Program for Crystal Structure Determination", Univ. of Cambridge, England (1976).

9) Atomic parameters, bond lengths, and bond angles are available from authors on request.

10) C. K. Johnson, "ORTEPII. Report ORNL-5138." Oak Ridge National Laboratory, Tennessee, U.S.A. (1976).

11) H. M. Doesburg, G. H. Petit, and E. M. Merckx, Acta Cryst., B38, 1181(1982); S. K. Balani, D. R. Boyd, E. S. Cassidy, G. I. Devine, J. F. Malone, K. M. McCombe, N. D. Sharma, and W. B. Jennings, J. Chem. Soc., Perkin Trans. 1, 1983, 2751; S. S. Oh, W. M. Butler, and M. Koreeda, J. Org. Chem., 54, 4499(1989).

12) E. M. Merckx, L. Vanhoeck, J. A. Lepoivre, F. C. Alderweireldt, B. J. van der Veken, J. P. Tollenaere, and L. A. Raymaekers, Spectrosc. Int. J., 2, 30(1983).

(Received August 22, 1990)