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ABSOLUTE CONFIGURATION AND CONFORMATIONAL MOBILITY OF DILOPHOL AND 3-ACETOXYACETYLDILOPHOL

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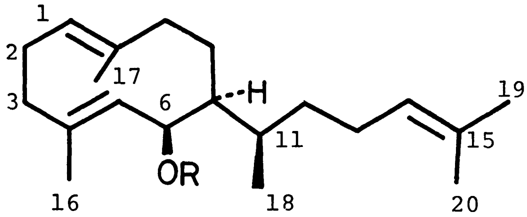
Dilophol and 3-acetoxyacetyldilophol were isolated from Dictyota dichotoma and their absolute configurations and conformational behavior were clarified by X-ray analysis, NMR spectroscopy and molecular mechanics calculations.

Dilophol (**1**) is a potential precursor for many of the alga bicyclic diterpenes and was found in a Mediterranean alga Dilophus ligulatus.[1)] The structure of **1** was assigned as formula **1** based on NMR studies[1)] but absolute configuration remained unclear. We isolated **1** and its new analog, 3-acetoxyacetyldilophol (**3**), from a brown alga "Amijigusa" (Dictyota dichotoma) which was collected at Oshoro bay, Hokkaido. Determination of the absolute configurations and studies on the conformational aspects of the above two diterpenes, **1** and **3**, will be described below.

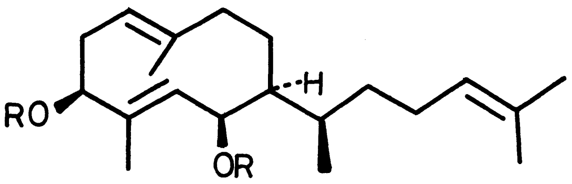
X-ray diffraction analysis was carried out on a crystalline p-bromobenzoate **2** ($C_{27}H_{37}O_2Br$, mp 84-85 °C). The crystal data were as follows: orthorhombic, space group $p2_12_12_1$, $a=12.228(2)$, $b=30.992(8)$, $c=6.786(1)$ Å, $Z=4$, $D_c=1.223$ g cm^{-1}. Intensity of 2376 unique reflections with 2θ values up to 130° were collected on a Rigaku four-circle diffractometer with graphite-monochromated Cu Kα radiation, using the ω-2θ scanning technique.[2)] The structure was solved by the Monte Carlo direct method,[3)] and was refined by the block-diagonal least-squares method with anisotropic thermal parameters. From the R ratio of 1.038,[4)] the absolute configuration was established as shown in Fig. 1. Further least-squares refinements were performed including 34 hydrogen atoms; the final R value was 0.045.

The ^{1}H-NMR spectrum of **1** on a 60 MHz spectrometer showed peaks at δ 0.99 (3H, d, J=7 Hz, W_H of the single peak=2 Hz), 1.47 (3H, brs), 1.58 (6H, brs), 1.67 (3H,



1: R= H

2: R= $\underset{\underset{\textstyle O}{\|}}{\text{C}}\text{-C}_6\text{H}_4\text{-Br}$



3: R= Ac

4: R= H

brs), 4.57 (1H, brd, J=8 Hz), and 4.70-5.59 (3H, complex pattern) in $CDCl_3$, while the spectrum on a 400 MHz instrument exhibited broad peaks at δ 1.02 (3H, W_H=16 Hz), 1.33 (6H, W_H=16 Hz), 1.61 (3H, brs), 1.70 (3H, brs), 4.57 (1H, W_H=32 Mz), 4.88 (1H, W_H=44 Hz), 4.99 (1H, W_H=36 Hz), and 5.28 (1H, t, J=7 Hz) in the same solvent. The ^{13}C-NMR spectrum (25 MHz) of 1 in $CDCl_3$ showed at room temperature merely broad signals due to carbon atoms of the ten-membered ring and sharp signals at δ 16.5, 17.4, 24.5, 25.7, 34.4, 124.3, and 131.6 due to those of the side chain. However, each of the broad signals observed at room temperature separated into a pair of sharp peaks with an intensity ratio of about 1:1 in toluene-d_8 solution at -28 °C. Moreover at higher temperature (+100 °C, toluene-d_8), these pairs of separated signals coalesced into a set of single sharp signals. These spectral phenomena suggested that some or two conformers of the ten-membered ring of 1 are rapidly inverting each other at +100 °C and they are separated into two conformers or two groups of conformers in NMR time scale at below -28 °C. Then, empirical force field calculations were carried out in order to obtain conformational information. The ten-membered carbocycle is so small that two endocyclic double bonds must be placed perpendicularly to an averaged plane of the ten-membered ring. Therefore, the combination of two factors determining the conformation of 1, direction of two double bond planes and a dihedral angel C(6)-C(7)-C(8)-C(9), claimed eight strain minimum conformations. They were ααCT, ααCC, αβTC, αβTT, ββCT, ββCC, βαTC, and βαTT-1a which were depicted in Fig. 2 with assistance of a molecular model. For the calculations a germacrene-type compound 5 was adopted as an adequate model of 1 since a long side chain of 1 effected apparantly little on conformational stability of the ten-membered ring. Results of the calculations[5)] performed with each of the eight principal conformers showed that the two conformers ααCT and αβTT were equilibrated at room temperature in a ratio 60:40 (Table 1). We concluded that the two sets of signals exhibited in cmr were due to

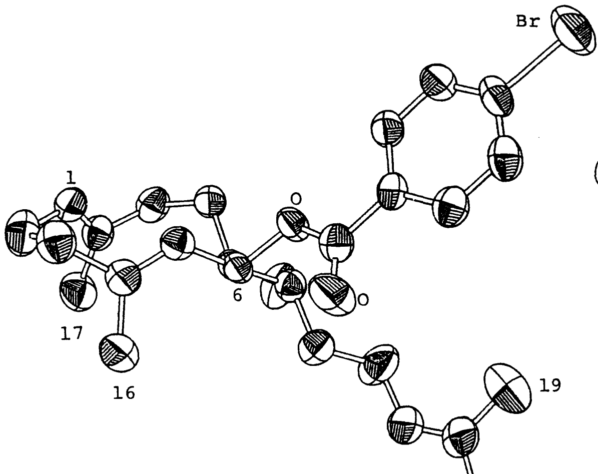


Fig. 1.

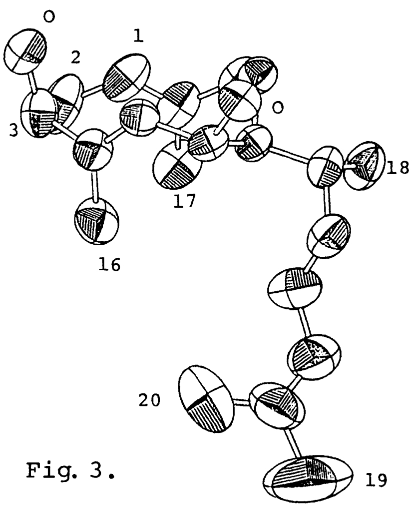


Fig. 3.

Fig. 2.

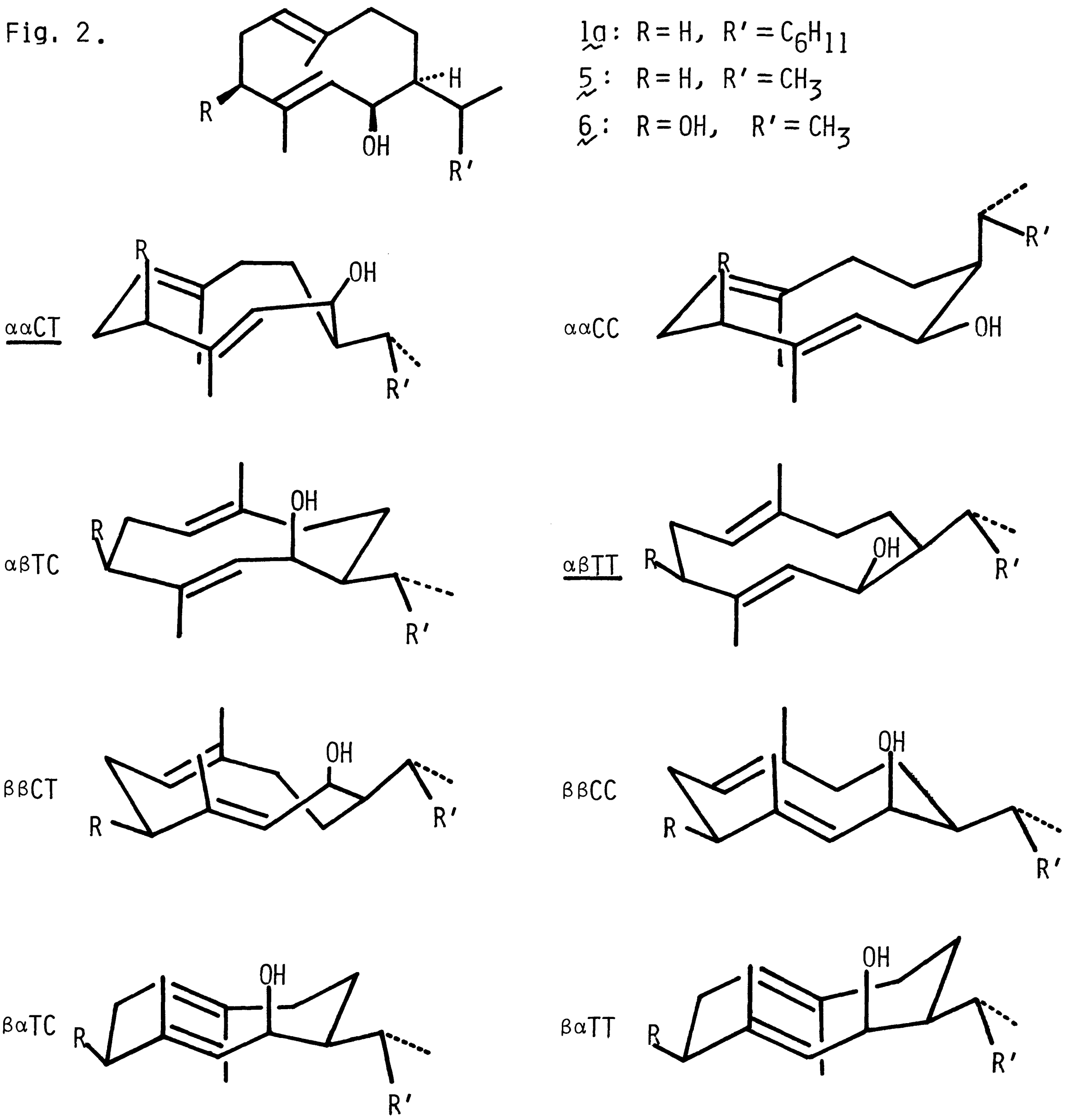


Table 1. Relative strain energy (kJ/mol) of eight strain minimum conformers. (Populations are also shown in parenthesis)

	ααCT	ααCC	αβTC	αβTT
5	0.00 (59.8%)	8.91 (1.6%)	22.84 (0.0%)	1.09 (38.6%)
6	0.00 (62.0%)	10.46 (0.9%)	24.64 (0.0%)	1.34 (36.0%)
	ββCT	ββCC	βαTC	βαTT
5	41.17 (0.0%)	21.76 (0.0%)	21.92 (0.0%)	49.12 (0.0%)
6	35.65 (0.0%)	13.64 (0.0%)	13.93 (0.0%)	40.58 (0.0%)

the above two conformers and the results of the calculations had been realized by NMR spectra. The most popular conformer ααCT appeared in the crystal form shown by X-ray analysis.

A new germacrene-type diterpene, 3-acetoxyacetyldilophol (**3**), (mp 73-74 °C, $[\alpha]_D^{25}$ +7.9° (c 2.2, $CHCl_3$)), was crystallized from hexane. The crystalline material had molecular formula $C_{24}H_{38}O_4$ (m/z M^+ found 390.2790, calcd 390.2772), which together with IR bands at 1745 and 1240 cm^{-1}, suggested that the compound was a diacetate of a diterpene diol. This was supported by the facts that treatment of acetate **3** with lithium aluminum hydride in ether gave the corresponding diol **4**, ($C_{20}H_{34}O_2$, mp 105-106 °C) and the mass spectrum of **3** showed peaks at 330 (M^+-AcOH) and 270 (M^+-2AcOH). The 400 MHz ^1H-NMR spectrum of **3** exhibited broad signals at δ 0.97 (3H, W_H=22 Hz, 18Me), 1.52 (3H, brs), 1.57 (3H, brs), 1.64 (3H, bs), 1.68 (3H, brs), 2.03 (3H, brs), 2.09 (3H, brs), 5.05 (1H, t, J=7 Hz, H on a trisubstituted double bond in the side chain), 5.08-5.32 (3H, complex pattern, two ten-membered olefinic protons and one acetoxymethine proton), 5.69 (1H, brd, J=7 Hz, an acetoxymethine proton). In order to establish the structure of **4**, X-ray crystallographic study was undertaken. The crystal data for **4** were as follows: orthorhombic, space group $P2_12_12_1$, a=20.933(9), b=22.577(6), c=16.687(4) Å, Z=16, D_c=1.032 g cm^{-3}. Intensities data of 5896 unique reflections for 2θ<130° were obtained in the same manner as used for the preceding measurements. The structure was elucidated by the Monte Carlo direct method$^{4)}$; the 819th random phase set for the 70 strongest reflections led to the correct solution. Block-diagonal least-squares refinements including 108 hydrogen atoms reduced the R value to 0.085. One of the skeletons of the four independent molecules is illustrated in Fig. 3 which shows absolute configuration. Concerning ten-membered ring, **3** takes almost same conformation as **1** in crystalline state. The ^{13}C-NMR spectrum ($CDCl_3$, room temperature) of 3-acetoxyacetyldilophol showed many broad and small peaks, together with sharp and strong signals (δ 17.1, 17.6, 25.2, 25.7, 30.3, and 34.1) due to the side chain. At temperature lower than -28 °C (toluene-d_8) two sets of sharp signals with an intensity ratio of about 3:2 were observed at δ 76.6 and 75.3. Very similar spectral feature to the preceding case prompted us to do again force field calculations. The calculations concerning a model compound **6** with an abrebiated side chain gave also very similar results to the case of **1** (Table 1). The diacetate **3** was considered to be equilibrated between two conformers, ααCT and αβTT in a ratio 60:40 at room temperature.

References

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