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Structure and Absolute Configuration of Isoclavukerin A, A Component from an Okinawan Soft Coral

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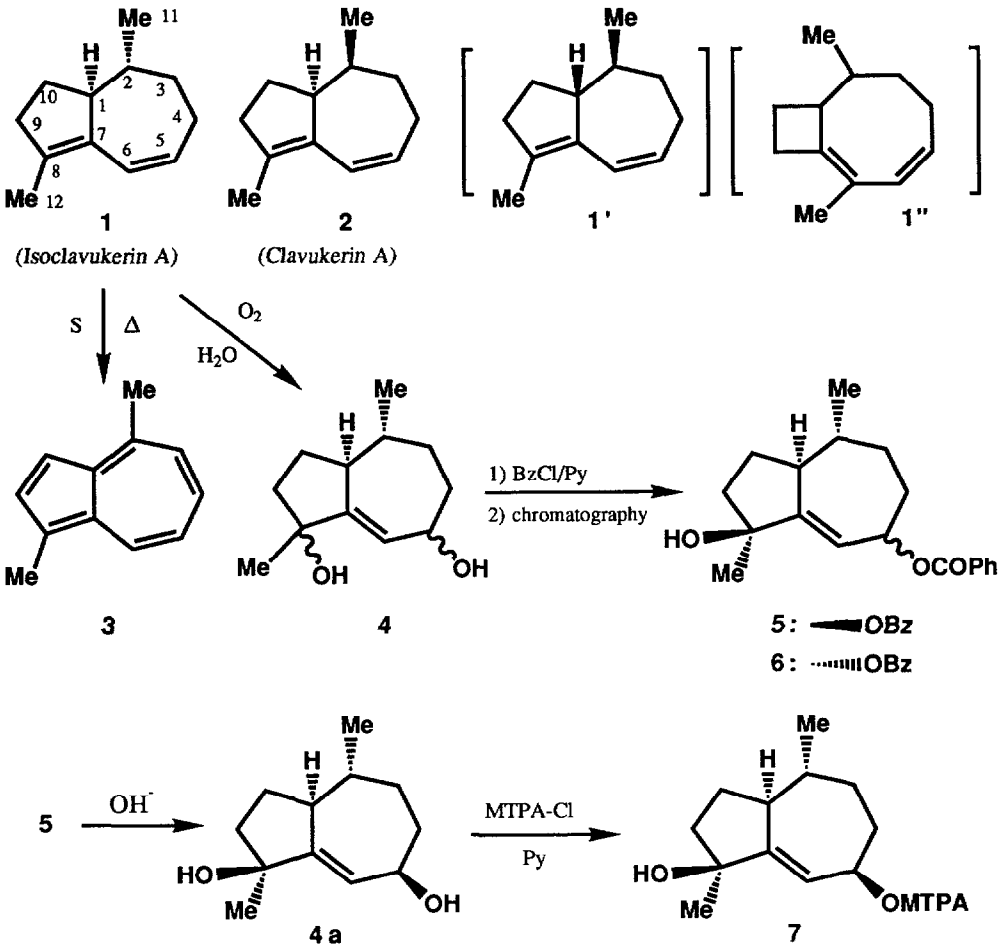
Abstract: *Structure of isoclavukerin A (1), a marine terpenoid isolated from the soft coral* Clavularia *species, has been determined spectroscopically, and its absolute configuration has been elucidated by the CD and the modified Mosher's methods that are applied to the derivatives of 1.*

Requirement of the convenient methods to elucidate the absolute configurations of organic compounds has been increasing not only in the academic field but in the practical area such as pharmaceutical industry. We have been developing the new methodology, the modified Mosher's method,[1] which can predict the absolute configurations of secondary alcohols and primary amines.[2] In the course of our works on the biologically active substances from marine sources, we were able to isolate a new compound designated isoclavukerin A (**1**) from the Okinawan soft coral of *Clavularia* species,[3] and this paper deals with its structure and absolute configuration. Comparison of the results obtained from the benzoate chirality and the modified Mosher's methods is also included.

Isoclavukerin A (**1**),[4] HRGCMS *m/z* 162.1420 (calcd for $C_{12}H_{18}$, 162.1408), $[\alpha]_D^{25}$ -100° (c 1.00, $CHCl_3$), was obtained as an extremely volatile [80-90°C (bath)/100 Torr] and colorless liquid. The ^{13}C NMR (125 MHz; $CDCl_3$) spectrum suggested the presence of two double bonds, and the UV spectrum [λ_{max} 246 nm (ε 10,400)] shows that they are involved in a conjugated diene system. The spectrum also suggested the presence of two CH_3, four CH_2, two sp^3-CH, and two sp^2-quaternary carbons. The ^1H NMR spectrum (500 MHz; C_6D_6) exhibited two olefinic protons at δ 5.73 and 6.40. They are coupled each other with J = 11 Hz, indicating their *cis*-relationship. One (δ 0.96, d, J = 7 Hz) of the two methyls is secondary, and the other (δ 1.68, bs) is linked to the olefinic bond.

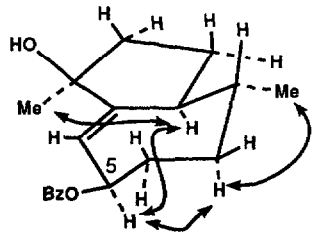
The planar structure of **1** was suggested by analysis of the 1D and 2D NMR spectra (H,H and H,C-COSY). Although the *INADEQUATE* spectrum confirmed most of the carbon framework, it was infeasible to eliminate the alternate possible structure **1'** due to the proximity of the chemical shifts of two quaternary sp^2 carbons (δ 137.0 and 137.7). The carbon framework was finally confirmed by dehydrogenation of **1** with sulfur (250 °C, 30 min)[5] to give 1,4-dimethylazulene (**3**),[6] λ_{max} 596 nm. In spite of the simple structure of **1**, attempts to elucidate the relative stereochemistry of 11-H_3 and 1-H by the NMR techniques including the NOESY spectrum were fruitless because the cyclopentene and cycloheptene rings can take various conforma-



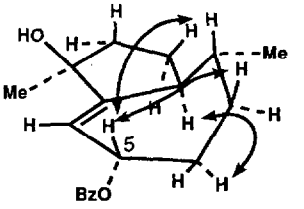
tions. Comparison of the physical properties of isoclavukerin A with those of clavukerin A (**2**),[7] the structure and absolute configuration of which have been firmly established by Kitagawa, led to the conclusion that **1** must be a diastereomer of **2**. Because the *anti*-relationship of 11-H_3 and 1-H of **2** has been clarified, they must have the *syn*-relationship in **1**.

Biosynthetically, it should be of interest to know if isoclavukerin A has structure **1** or **1'**. In the former case, isoclavukerin A is a C-2 epimer of **2**, and in the latter case it is a C-1 epimer of **2**.

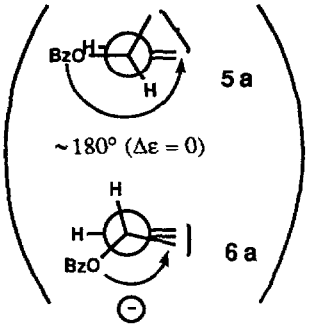
Isoclavukerin A (**1**) is rather labile; thus, allowing a 50 % aqueous acetone solution of **1** to stand in air for 10 h resulted in the formation of a mixture of oxidation products (**4**) in a good yield. This mixture was separable into two [polar (minor) and less polar (major)] fractions. Each fraction was still composed of two compounds, and the ^{1}H-chemical shifts of the methyls at C-8 of the components were identical in each fraction (polar: δ 1.25 ; less polar: δ 1.35). Therefore it was very likely that, in each fraction, the relative configuration of 8-OH's of the two components was identical, but that of 5-OH's was different. Because further separation of the fractions were impossible, the less polar fraction was benzoylated (BzCl/Py). Chromatographic separation of the products afforded two distinct compounds, **5**[8] and **6**[9]. The coupling pattern of H-5 (dq, J = 11, 3 Hz; homoallyl coupling with H-1 included) and the NOEs (depicted in **5a**) of the protons definitely suggested full stereochemistry as shown in **5a**. Disappointedly, however, the CD spectrum of **5**

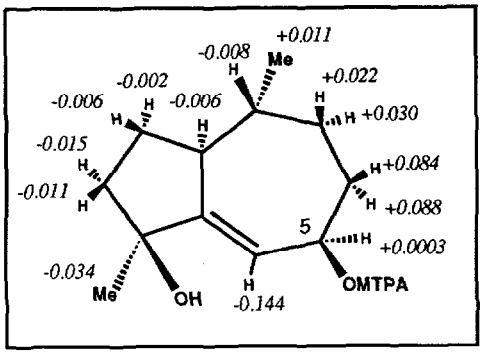


5a



6a





7a

showed no Cotton effect around 230 nm. Inspection of the molecular models indicated that the dihedral angle between the benzoyloxy group and C_6=C_7 is approximately 180°. In such a case, the benzoate chirality method is inapplicable.[10]

Contrary to **5**, several ^{1}H NMR signals are overlapped in its isomer **6**, which made the assignment of the stereochemistry rather difficult. The α-configuration of the benzoyloxy group was assigned on the basis of the NOEs (see **6a**) between the protons of the cycloheptene ring. The probable conformation is shown in **6a**, although other slightly different ones were still possible. By working on the models, however, we found that the spatial relationship between the benzoyloxy and the olefin groups were always counterclockwise so long as the absolute configuration was drawn as in **6**. Actually, the benzoate **6** exhibited negative Cotton effect [226 nm (Δε -6.5)], which led us to propose the *S*-configuration at C-5 of **6**.

In order to confirm the absolute configuration, the modified Mosher's method was applied to **4a**,[11] which was prepared by saponification (KOH/MeOH) of **5**. The (*R*) and (*S*)-MTPA esters (**7**) were prepared by treating **4a** with (+) and (-)-MTPA chlorides in pyridine. In each reaction, 1 mg of **4a** was used. Assignment of the protons of **7** was achieved by use of the COSY and relayed COSY spectra, and Δδ values (δ_S - δ_R) were calculated for all the protons. As is shown in **7a**, the Δδ values (ppm) are systematically arranged; that is, positive Δδ's are located on the right-hand side and negative Δδ's are on the left-hand side of the MTPA plane. The absolute value of the Δδ is inversely proportionate to the distance between the protons and the MTPA group. Thus, *R*-configuration of C-5 of **7**, and therefore structure of **1** (not **1'**) of isoclavukerin A, has been confirmed.[12]

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2. T. Kusumi, T. Fukushima, I. Ohtani, H. Kakisawa, *Tetrahedron Lett.*, **1991**, *32*, 2939.
3. The voucher specimen is preserved at this laboratory.
4. ^{1}H-NMR ($CDCl_3$): δ 0.96 (3H, d, J=7, H-11), 1.3-1.4 (3H, m, H-2, 3, 10), 1.72 (1H, m, H-3), 1.74 (3H, s, H-12), 2.04 (1H, m, H-10), 2.11 (1H, m, H-4), 2.23 (2H, m, H-9), 2.30 (1H, m, H-1), 2.36 (1H, m, H-4), 5.65 (1H, dt, J=11, 5, H-5), 6.23 (1H, d, J=11, H-6). ^{13}C-NMR ($CDCl_3$): δ 14.7 (q, C-12), 22.0 (q, C-11), 29.3 (t, C-4), 30.4 (t, C-10), 36.8 (t, C-9 or 3), 36.8 (t, C-3 or 9), 40.0 (d, C-2), 55.7 (d, C-1), 124.3 (d, C-6), 129.3 (d, C-5), 136.7 (s, C-7), 138.6 (s, C-8). ^{1}H-NMR (C_6D_6): δ 0.96 (3H, d, J=7, H-11), 1.3-1.4 (3H, m, H-2, 3, 10), 1.68 (3H, s, H-12), 1.72 (1H, m, H-3), 2.00 (1H, m, H-10), 2.10 (1H, m, H-4), 2.20 (2H, m, H-9), 2.33 (1H, m, H-4), 2.39 (1H, m, H-1), 5.73 (1H, dt, J=11, 5, H-5), 6.40 (1H, d, J=11, H-6). ^{13}C-NMR (C_6D_6): δ 14.4 (q, C-12), 21.9 (q, C-11), 29.2 (t, C-4), 30.4 (t, C-10), 36.8 (t, C-9 or 3), 36.8 (t, C-3 or 9), 40.0 (d, C-2), 55.8 (d, C-1), 124.9 (d, C-6), 129.0 (d, C-5), 137.0 (s, C-7), 137.7 (s, C-8).
5. R. Weiss, *Organic Syntheses, Coll. Vol.3*, p 729, John Wiley & Sons, New York, 1955.
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8. ^{1}H-NMR ($CDCl_3$): δ 0.97 (3H, d, J=7 Hz), 1.38 (3H, s), 1.40 (1H, m), 1.46 (1H, dt, J=7, 13 Hz), 1.53 (1H, ddt, J=3, 14, 13 Hz), 1.68 (1H, ddt, J=7, 10, 13 Hz), 1.77 (1H, ddt, J=3, 11, 13 Hz), 1.83 (1H, brdd, J=7, 13 Hz), 1.90 (brdt, J=13, 7 Hz), 1.95 (1H, ddt, J=7, 14, 3 Hz), 2.01 (1H, tdd, J=3, 7, 13 Hz), 2.29 (1H, dtt, J=7, 3, 10 Hz), 5.58 (1H, dq, J=11, 3 Hz), 5.88 (1H, brq, J=3), 7.45 (2H), 7.56 (1H), 8.06 (2H).
9. ^{1}H-NMR ($CDCl_3$): δ 1.00 (3H, d, J=7 Hz), 1.37 (3H, s), 1.49 (1H, dt, J=7, 13 Hz), 1.62 (2H, m), 1.71 (1H, m), 1.83 (2H, m), 1.86-1.88 (2H, m), 2.15 (1H, brdq, J=2, 11 Hz), 2.50 (1H, brq, J=10 Hz), 5.58 (1H, ddt, J=5, 8, 2 Hz), 5.99 (1H, dd, J=3, 5 Hz), 7.45 (2H), 7.56 (1H), 8.06 (2H).
10. N. Harada, K. Nakanishi, *Circular Dichroic Spectroscopy-Exciton Coupling in Organic Stereochemistry*, University Science Books; Mill Valley, CA, 1983.
11. ^{1}H-NMR ($CDCl_3$, 90 MHz): δ 0.92 (3H, d, J=7 Hz), 1.35 (3H, s), 4.30 (1H, m), 5.82 (1H, m).
12. After this manuscript was submitted, a total synthesis of the enantiomer of **1** (**1'**) as well as clavukerin A (**2**) was published. The reported NMR properties of **1'** are identical with those of isoclavukerin A, but the sign of specific rotation, $[\alpha]_D^{21}$ +110.4° (c 0.66, $CHCl_3$), is different from that of **1**. See; M. Asaoka, T. Kosaka, H. Itahana, H. Takei, *Chemistry Lett.*, **1991**, 1295.

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