Tetrahedron Letters, Vol. 33, No. 15, pp. 2019-2022, 1992
Printed in Great Britain

0040-4039/92 $3.00 + .00
Pergamon Press Ltd

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

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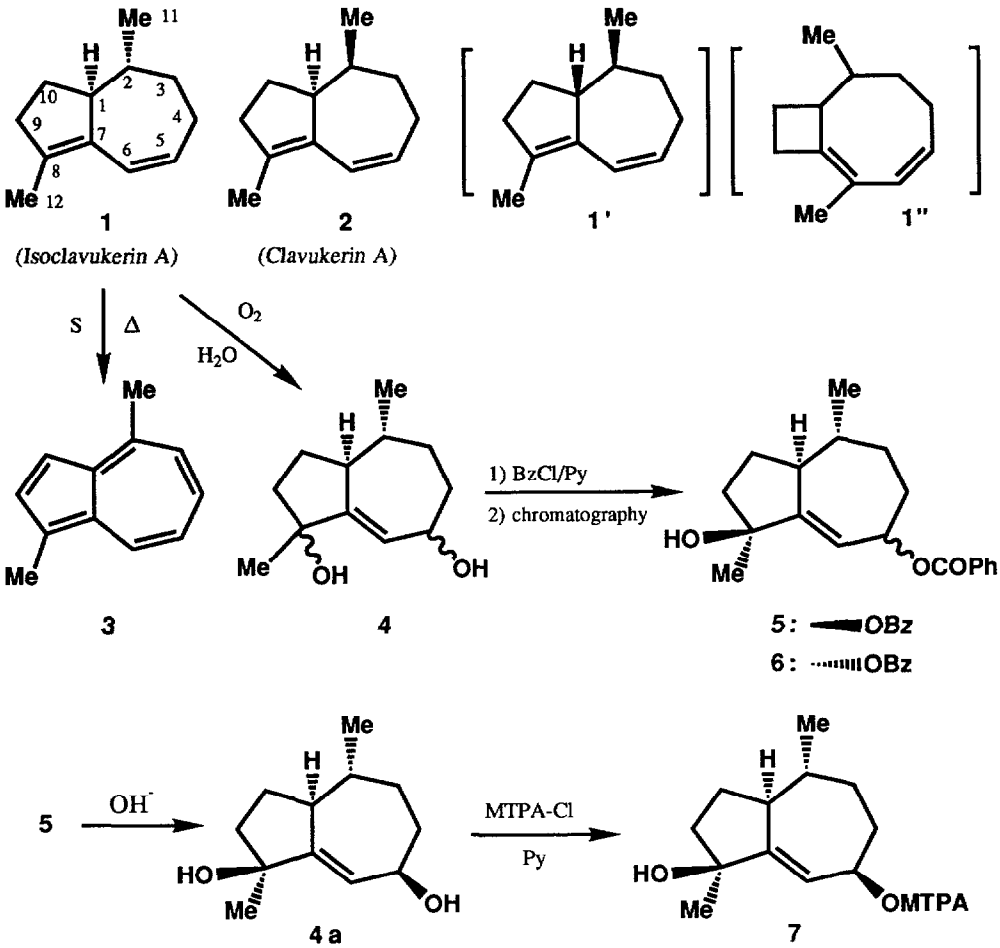
Key Words: marine terpenes, NMR, CD, Mosher's method, absolute configuration.

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**