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Studies on the Total Synthesis of Hainanolide (VII) - Analysis of the Relative Stereochemistry of key Intermediate 2

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Abstract: The relative stereochemistry of an intermediate **2** in the total synthesis of hainanolide **1** was studied by various NMR spectroscopic techniques.

Keywords: Hainanolide, NOE, ^{1}H, ^{13}C-NMR, HMBC, HMQC, spectra.

The natural product, hainanolide[1] **1**, also under the name harringtonolide[2] demonstrated antitumor and antiviral activities in preliminary test. Its structure was determined by X-ray diffraction. The total synthesis of **1** was reported recently by Mander[3]. A different scheme of its synthesis has been studied in our laboratory[4]. Here the determination of the stereochemical structure of the key intermediate **2** in the synthesis was reported.

HMBC and HMQC spectra identified the skeleton and H, C correlation of compound **2** as shown in **Figure 2**. The results of ^{1}H and ^{13}C spectra were listed in **Table 1**. NOE revealed that A, B, C three rings being *cis* fused as that in hainanolide and with 5a-$COOCH_3$ and C_3-OH at the same side as H_{2a} and C_4-OCH_3 at back side being at the right positions for building lactone ring and oxobridge.

Based on the data of coupling constant (J Hz: H_{2a}/H_3=12 H_3/H_4=7.2, H_4/H_5=0) shown in **Table 1,** the dihedral angles of C_{2a}-H/C_3-H, C_3-H/C_4-H and C_4-H/C_5-H were evaluated about 180°, less than 180° and 90° respectively**.** The molecular model was thus constructed which seems to be comfortable as deformed boat for ring B, chair for A and envelop for C (**Figure 3**) to reduce possibly steric effect between substituents. It coincides nicely with what obtained from calculation using Alchemy III. Further confirmation of the stereochemical structure by X-ray analysis will be carried out later.

Figure 1

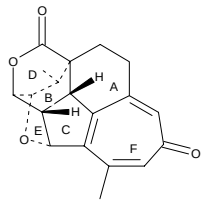

Figure 2

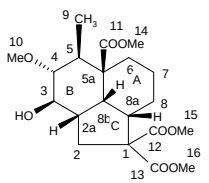

Figure 3

Table 1 ^{1}H(300MHz), and ^{13}C(75MHz) NMR data for **2**($CDCl_3$)

No	δ_C	δ_H	No	δ_C	δ_H
1	64.34		8b	37.42	3.13(dd,1H,$J_{8b,2a}$=7,$J_{8b,8a}$=12)
2	35.98	2.38(dd,1H$_\alpha$, $J_{2\alpha,2a}$=9, $J_{2\alpha,2\beta}$=14.5) 2.60(dd, 1H$_\beta$, $J_{2\beta,2a}$=8.5, $J_{2\beta,2\alpha}$=14.5)	9	19.40	0.91(d, 3H, $J_{9,5}$=7.5)
2a	37.42	2.10(dddd, 1H, $J_{2a,2\beta}$= 8.5, $J_{2a,2\alpha}$=9, $J_{2a,3}$=12, $J_{2a,8b}$=12)	10	57.38	3.42(s, 3H)
3	78.39	3.90(dd ,1H, $J_{3,4}$=7, $J_{3,2a}$=12)	11	170.23	
4	90.92	2.94(d, 1H, $J_{3,4}$=7)	12	171.97	
5	41.50	2.27(q , 1H, $J_{5,9}$=7.5)	13	176.81	
5a	49.66		14	52.42	3.70(s, 3H)
6	32.85	1.98(m, 1H$_\alpha$)1.57-1.65(m, 1H$_\beta$)	15	52.04	3.72 (s, 3H)
7	21.63	1.57-1.65(m, 1H$_\beta$) 1.04(m, 1H$_\alpha$)	16	52.76	3.75 (s, 3H)
8	25.24	1.44(m, 1H$_\beta$) 0.90(m, 1H$_\alpha$)	OH		1.57-1.65(m, 1H)
8a	43.48	2.94(dd, 1H, $J_{8a,8b}$=7, $J_{8a,8\beta}$=7, $J_{8a,8\alpha}$=12)			

Table 2 NOESY 1D of compound **2** (500MHz in $CDCl_3$)

Irradiation H	Correlation peaks
H_2	H_{2a}, H_3
H_{2a}	H_2, H_4+H_{8a}, C_5-Me, H_{8b}
H_3	$H_{2,}$, $H_{6\alpha}$
H_4+H_{8a}	H_{2a}, H_{8b}, $H_{8\beta}$, C_5-Me, C_4-OMe
H_5	$H_{6\beta}$, C_5-Me, C_4-OMe
H_{8b}	H_{2a}, H_4+H_{8a}, C_5-Me

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