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Studies on the Total Synthesis of Hainanolide (VIII) -Introducing C_4-Methoxy Group, and Forming the Ring E (Lactone)

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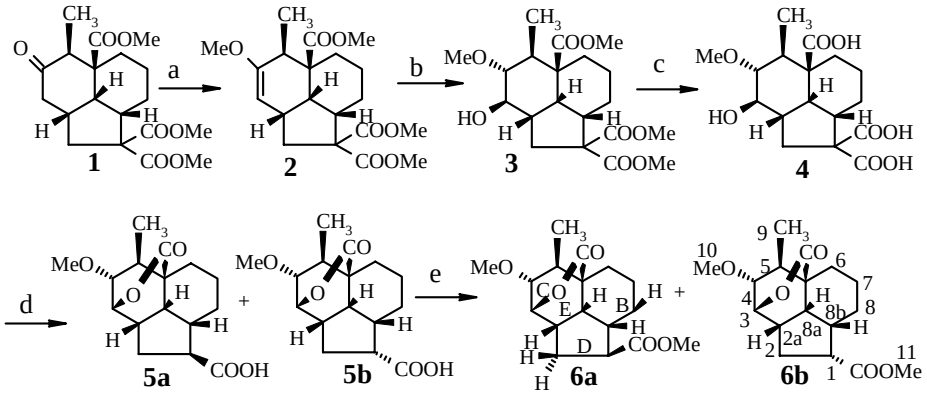
Abstract: The titled compound **6a** and **6b** were synthesized from tricyclic ketone **1** through five steps.

Keywords: Hainanolide, reductive-oxidation, lactonization, decarboxylation, borane.

A series of reports concerning the attempted synthesis of hainanolide, a potential anticancer and antiviral compound, has been reported. This paper is a continuation of the previous work[1-5]. The synthesis of tricyclic ketone **1** was reported by Yang[5]. The route of transformation of ketone **1** to **6a** and **6b** of present report was showed in **Scheme 1**.

Scheme 1



a. LICA/THF, TsOMe, -78°C; b. B_2H_6; H_2O_2/THF, 0°C; c. $Ba(OH)_2$, H_2O/MeOH, 70°C; d. TsOH/xylene, boiling; e. CH_2N_2, r. t.

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Ketone **1** was kinetically enolized[6] and the enolate was trapped with methyl *p*-toluenesulfonate in THF at –78°C to afford a colorless crystal with m.p. 135.6-136.4 °C in 80% yield. Comparing its IR spectrum with that of ketone **1** the enolate showed the absence of C=O band at 1734cm^{-1} and instead appearance of a new band at 1672 cm^{-1} for C=C. The ^{1}H NMR spectrum showed the =CH- signal at δ 4.38 ppm, a quartet for C_5-H at δ 2.30 ppm and a singlet for C_4-OCH_3 at δ 3.50 ppm. The IR and NMR spectra coincide nicely with the structure of compound **2**. Reductive-oxidation[7] of compound **2** was carried out with borane followed by H_2O_2 to give compound **3** as crystalline solid (m.p. 137.5-138.6 °C) in 68% yield. No double bond signals were observed in its ^{1}HNMR spectrum. Signals at δ 3.90 ppm (dd, 1H, J=7Hz, 12Hz) and δ 2.95 ppm (d, 1H, J=7Hz) were assigned to O-C_3-H and C_4-H respectively. The stereochemistry of compound **3** was discussed in previous report[8]. Intended selective hydrolysis of the three carboxyl ester groups by heating with barium hydroxide in MeOH/H_2O was failed[3]. The hydrolyzed product **4** showed absence of signals of ester-methyl groups in its ^{1}HNMR spectrum. Apparently all the three ester groups were hydrolyzed and gave compound **4** with m.p. 206.8-207.6°C in 87% yield. Treatment of compound **4** with a catalytic amount of *p*-toluenesulfonic acid in boiling xylene to decarboxylate one of the two carboxyl groups at C_1 and meanwhile the C_3-OH and C_{5a}-COOH proceeded ring close to form two isomers **5a** and **5b** with m.p.129.1-130.8°C and m.p. 146.2-147.9°C, respectively. The ratio of **5a**:**5b** was 3:4. They were methylated by treating with diazomethane separately to give corresponding esters **6a** (mp 102.1-102.9°C) and **6b** (mp 121.4-122.1°C). Two absorption bands of -COO- showed at 1734 cm^{-1} and 1759 cm^{-1} in IR spectra of both **6a** and **6b**. The latter band (1759 cm^{-1}) was assigned to δ-lactone carbonyl. This was supported by the reported lactone absorption in the IR spectrum of hainanolidol[9] at wavelength of 1760 cm^{-1}. The band at 1734 cm^{-1} is related to the ester methyl group at C_1 and only one ester methyl group was found in the ^{1}HNMR spectrum of **6a** and **6b** (**Table 2**). This demonstrated that both lactonization and decarboxylation have taken place under the reaction condition as expected. The two compounds **6a** and **6b** are different from each other only in the position of the C_1-$COOCH_3$. The stereochemistry of H-1 was determined by the NOE spectra. Irradiation of H-1 caused enhancement of signals of both H-2a and H-5 in compound **6a** and both H-2β and H-8a in compound **6b**. All the above results indicated that H-1 in **6a** is at α position while that in **6b** is at β position (**Table 1**).

Based on the above spectra analysis the structures of 6a and 6b were proposed as shown in Scheme 1.

Table 1 NOESY 1D of compound **6a** and **6b** (500MHz in $CDCl_3$)

Irradiation H	Correlation peeks in compound **6a**	Correlation peeks in compound **6b**
H_1	$H_{2\alpha}$, H_5	H_{8a}, $H_{2\beta}$
H_{2a}	H_{8b}, H_3, $H_{2\beta}$	H_{8b}, H_3, $H_{2\beta}$
H_{8a}	H_{8b}, $H_{8\beta}$	H_{8b}, $H_{8\beta}$, H_1
H_5	H_1, $H_{7\alpha}$, H_9	$H_{7\alpha}$, H_9

Table 2 ^{1}H NMR data for **6a** and **6b** (500MHz in $CDCl_3$) (δ ppm, J Hz)

No	δ_H for **6a**	No	δ_H for **6b**
1	3.035(m,1H)	1	3.131-3.076(m, 1H)
2α,8a	2.506-2.447(m, 2H)	2α, 2a	2.692-2.747(m, 2H)
2β,6α	2.009-1.921(m, 2H)	2β	1.835(m, 1H)
2a	2.954(m, 1H)	3	4.747(dd,1H, J=2.5, 4)
3	4.690(dd,1H, J=3, 5.5)	4	3.103(dd,1H, J=2.5, 7)
4	3.183(dd, 1H, J=3, 6)	5	2.373(quintet,1H, J=7)
5, 8b	2.258-2.197(m, 2H)	6, 7,8	1.917(m, 1H);
6β,7,8	1.787(m,1H);		1.703-1.611(m, 2H);
	1.682(m,1H)		1.499-1.399(m, 3H)
	1.553(m,1H);	8a	2.652 (m,1H)
	1.416-1.381(m, 2H)	8b	2.301(t, 1H, J=10)
9	1.008(d,3H, J=7)	9	1.046(d, 3H, J=7)
10	3.453(s, 3H)	10	3.444(s, 3H)
11	3.692(s, 3H)	11	3.671(s, 3H)

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