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A Novel Rearrangement of 14-Mesyloxy-ent-Kaurenoids

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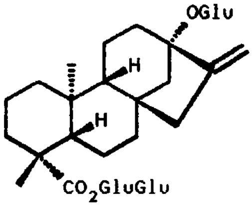
ABSTRACT: A rearrangement of 14β-mesyloxy-kaurenoids was studied and a new diterpenoid skeleton with a ring system of 6,7,5,5 was obtained.

Numerous of papers devoted to the study of rearrangement of tetracyclic diterpenoids and diterpenoid alkaloids have been published[1]. In some cases, rearrangement of such diterpenoids was carried out in solvolytic condition and usually gave a mixture of products[2-6]. The rearrangement of ent-kaurene diterpenoids usually occurred in centres at C12[4] and C16[2]. In the present paper we report a rearrangement of ent-kaurenoids with a centre at C14. To our knowledge, 14β-mesyloxy-kaurenoids have not been used previously for solvolysis.



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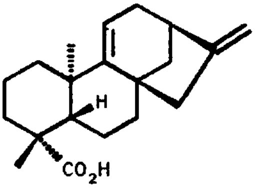

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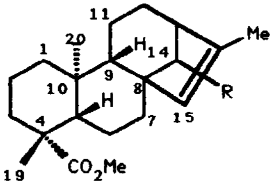
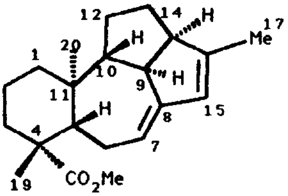


3 R=OMs

4 R=H



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In connection with our synthetic work on ent-kaurenoids[7], we are interested in the conversion of stevioside(**1**) occurred abundantly in Stevia rebaudiana Bertoni[8] into grandiflorenic acid(**2**), which was isolated from Mexical medicinal plant Zoapatle(Montanoa tomento) and possessed potent contragestational activity[9]. When the 14β-mesyloxy compound(**3**)[10] obtained from stevioside(**1**) was submitted to reduction with sodium iodide and zinc dust in dimethoxyethane[11],we did not obtain the demesyloxy compound **4**, but we obtained a rearranged product **5** in high yield[12].

Compound **5** is an oily substance, $[\alpha]_D$ -75.4° (c, 0.8, benzene), molecular formular $C_{21}H_{30}O_2$. Its UV spectrum(250nm, 16x10^4) shows a conjugated double bond. The ^{1}H-NMR spectrum of **5** has two vinyl protons and one methyl group attached to the double bond(Table 1). ^{13}C-NMR data(DEPT) of **5** have 21 carbon resonances and allow to be assigned five quaternary carbons, two of which are vinyl carbons and one carbonyl carbon,six methine carbons,two of which are vinyl carbons, six methylene carbons and four methyl carbons (Table 1).The presence of conjugated double bond indicates that **5** is a rearranged product.

The partial structure from C1 to C3, from C5 to C7 and ring C moiety was obtained by interpretation of ^{1}H-^{1}H-COSY and HMQC data. The HMBC spectrum showed connectivities between C20H3 and C1, C5, C11, and long-range couplings between C19H3 and C3, C4, C5(Table 1). These observations indicated that A-ring of **5** is the same as that of **3**.In addition,C6H showed the HMBC connectivity to two olefinic carbons C7 and C8, C7H showed the HMBC connectivity to olefinic carbon C15.C15 possesses a directly attached proton at 6.024 ppm, which in turn couples to olefinic carbon C16 and olefinic methyl carbon C17.This reveals a conjugated double bond from C7 to C16, which was further confirmed by the HMBC connectivities among C17H3,C15 and C16. Attachment of C9 to quaternal olefinic carbon C8 was deduced by the HMBC connectivity between C9H and C8 and was confirmed by long-range coupling of C7H and C15H to C9.Ring D was settled by the HMBC coupling between C14H and C16. Finally, seven membered B-ring was established on the basis of the HMBC connectivity between C20H3 and C10.

The stereochemistry of **5** was deduced by using 2D-NOE data(Fig.1).Substantial NOE between C20H3 and C9H and between C9H and C14H suggest that they are all in α-orientation.

Table 1. The ^{1}H-NMR and ^{13}C-NMR chemical shifts(ppm) of **5** and protons to which a long-range connectivity was observed in the HMBC experiment

Carbon	^{13}C^{a}	m^{b}	1H^{c}	m	J in Hz	HMBC(^{1}H)
1	41.89	t	1.310(β)	m		1.230(CH3-20)
			1.790(α)	brd	12.9	
2	19.84	t	1.740(β)	m		
			2.380(α)	tq	13.9,3.6	
3	39.07	t	1.250(β)			1.520(CH3-19)
			2.670(α)	brd	13.8	
4	44.92	s				3.001(H-6),1.520(CH3-19)
5	58.46	d	1.550	brd	9.0	3.001(H-6),1.520(CH3-19), 1.230(CH3-20)
6	26.61	t	3.001	m		6.007(H-7)
7	117.03	d	6.007	m		3.001(H-6)
8	156.25	s				3.001(H-6),3.387(H-9)
9	47.25	d	3.387	brt	8.4	6.024(H-15),6.007(H-7)
10	60.14	d	1.500	m		3.387(H-9),1.230(CH3-20)
11	40.37	s				1.230(CH3-20)
12	29.32	t	1.880(α)	m		
			1.460(β)	m		
13	30.67	t	1.380(β)	m		3.205(14-H)
			2.220(α)	ddd	5.7,8.4,11.8	
14	52.56	d	3.205	brq	8.4	
15	124.67	d	6.024	s		2.030(H-17),6.007(H-7)
16	157.86	s				2.030(H-17),3.205(H-14), 6.024(H-15)
17	15.67	q	2.030	s		6.024
18	29.32	q	1.520	s		
19	177.97	s				1.520(CH3-19)
20	12.04	q	1.230	s		
OCH3	51.04	q	3.693	s		

a. C_6D_6; Assignments aided by ^{1}H-^{1}H COSY, HMQC, and HMBC experiment

b. Deduced by DEPT experiment.

c. C_6D_6; TMS=0; Bruker AMX 600 Spectrometer

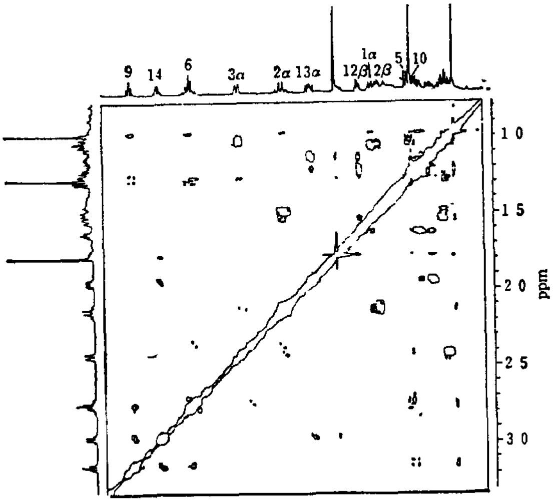
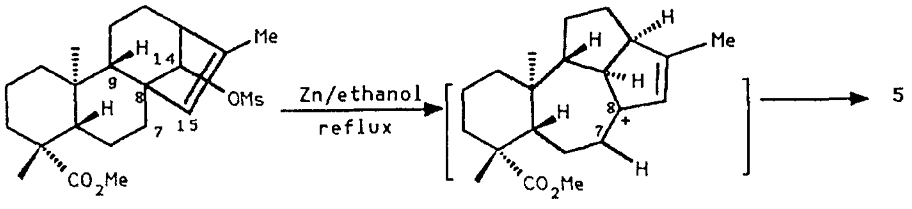


Fig. 1 Selected portion of 600 MHz 2D NOESY spectrum of 5 in C_6D_6



3

Scheme 1

It is obvious that the solvolysis of the mesylate 3 proceeds predominantly with rearrangement and elimination to give 5,its formation involves the leaving of mesyloxy group at C14, followed by the antiperiplanar C8-C9 bond migration and C7-C8 double bond formation(Scheme 1). Because the rearrangement occurs through the intramolecular nucleophilic substitution, the configuration of 9-H could be assigned as α-configuration which is thus consistent with the NOESY experimental result.

The structural and conformational evaluation of 3 reveals that this compound fully meets the requirement for undergoing rearrangement. Thus, even when 3 was heated only in ethanol, it rearranged to afford 5 in good yield(Table 2, entry 5), although this reaction is more effective in the basic solvent(Tab. 2, entry 4 and 6).

In order to obtain more information of this rearrangement, 17-carbaldehyde compound 6 and 17-hydroxymethyl compound 7 were prepared and treated with the same rearrangement conditions as that of 3. 6 was prepared by SeO_2 -t-BuOOH oxidation of 3; 7 was prepared by reduction of 6 with DIBAL-H or

Table 2 Solvolysis of **3**

Entry	Substrate	Solvent and Reagent[a]	Time(h)	Product	Yield
1	3	DME,NaI,Zn,H_2O[b]	8	5	70
2	3	DME,NaI,Zn	8	5	70
3	3	EtOH,NaI,Zn	3	5	81
4	3	EtOH,Zn	3	5	92
5	3	EtOH	3	5	65
6	3	EtOH,AcONa	3	5	70

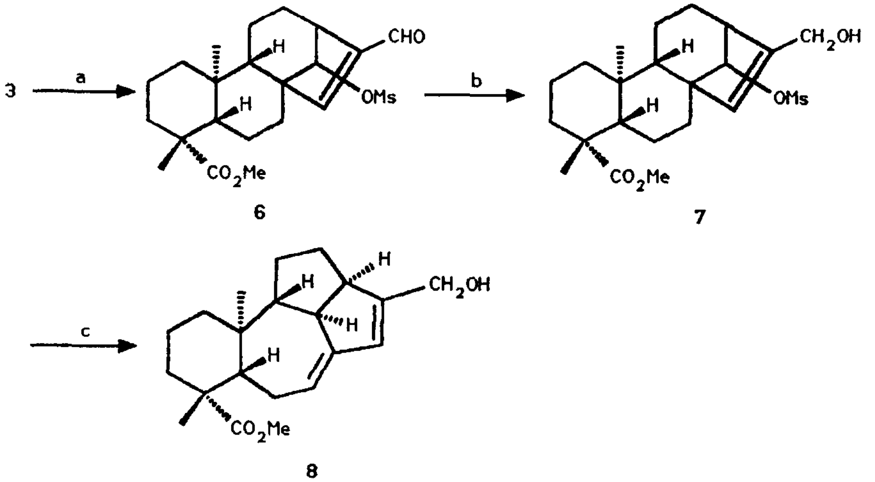
a. the reactions take place under refluxing

b. trace of H_2O

Table 3 ^{1}HNMR data[a] of compound **5** and **8**

5	5.57(1H,s,15-H), 5.46(1H,t,J=8.3Hz,7-H),3.05(2H,m,9-H,14-H), 2.45[2H,m,2x(6-H)]
8	5.81(1H,s,15-H), 5.56(1H,t, J=6.6Hz,7-H), 4.17[2H, s, 2x(17-H)], 3.10(2H,m,9-H,14-H),2.48[2H,m,2x(6-H)]

a. acetone-d_6, Varian XL-200



Reagents: a. SeO2-t-BuOOH,AcOH-CH2Cl2(1:1). b. NaBH4,CH3OH. c. Zn,ethanol,reflux.

Scheme 2

$NaBH_4$[13](Scheme 2). The best comparative result in the rearrangement of **7** was obtained when using EtOH-Zn or EtOH-AcONa as basic system(Scheme 2), the structure of **8** was elucidated by comparison of ^{1}HNMR with **5**(Table 3).

In the case of 17-carbaldehyde **6**, no rearrangement occurred, and only starting material was recovered. Owing to the electron-withdrawing effect of the α,β -unsaturated aldehyde group on the molecule, the rearrangement of **6** could not happen.So the formation of carbonium ion at C8 is inhibited and the expected rearrangement does not occur in this compound.

Experimental

Melting points were determined on a Buchi 535 instrument and uncorrected. IR spectra were recorded on Shimadzu 440 spectrometer. ^{1}H-NMR spectra were obtained on a Varian XL-200(200MHz) spectrometer, using $CDCl_3$ as solvent and TMS as an internal standard. All the 2D spectral were recorded on Bruker AMX-600 spectrometre with a sample containing 10 mg of **5** in 0.5 mL of C_6D_6. The double-quantum filtered COSY spectrum was obtained from a 2x512x1024 data matrix, which resulted after zero filling in both dimensions in a 1024x1024 data matrix for the absorptive part of 2D spectrum. HMQC spectrum was recorded by using a invb pulse sequence, HMBC data were aquisited using inv4lplrnd pulse sequence. NOESY spectrum was measured using noesytp pulse sequence from a 2x512x1024 data matrix.Mass spectra were run on a JMS-01U spectrometer. High-resolution mass spectra were recorded with a Finnigan MAT 8430 spectrometer. The optical rotation was measured on Autpol III polarimeter. Elemental analyses were performed by the Analytical Department of this Institute. Flash column chromatography was performed on silica gel H (10-40μ).

1. Rearrangement of **3**

a. To a solution of 200mg of **3** in 20ml of dried DME was added 300mg of NaI, 300mg of zinc dust and 0.3 ml of water,the reaction mixture was heated to reflux for 8 hours,cooled to room temperature and filtered. The filtrate was successively washed with $Na_2S_2O_3$ solution and brine, dried over anhydrous sodium sulfate, and evaporated in vacuo. The crude product was chromatographed(petroleum ether/EtOAc 30:1) to give 105mg of **5** as an oil in 70% yield. $[\alpha]_D$ -75.4° (c, 0.2, benzene), UV 250nm(1.6×10^4,EtOH). IR(film) ν 1720cm^{-1}. m/z 314[M^+], 254$[M-60]^+$, 239$[M-CO_2Me]^+$. HRMS: $C_{21}H_{30}O_2$ Calcd 314.2246. Found 314.2276.

b. To a solution of 100mg of **3** in 20ml EtOH was added 100mg of zinc dust, then the reaction mixture was heated to reflux for 3 h, the solvent was removed in vacuo, and the residue was extracted with EtOAc. The organic layer was successively washed with $NaHCO_3$ solution, and brine, dried over anhydrous sodium sulfate and evaporated in vacuo to give crude product **5**, which was chromatographed to afford 70mg of **5**(92%). $[\alpha]_D$ -75.4°(c,0.2, benzene).

2. Preparation of 17-carbaldehyde **6**

To a solution of 1.2 g of **3** in 20ml CH_2Cl_2 and 20ml AcOH, was added 100mg of selenium dioxide and 1.5ml of t-butyl hydroperoxide, and the reaction mixture stirred at room temperature for 2 days. After addition of 100 mL of EtOAc, this acidic solution was neutralized with 5% KOH under cooling. The organic layer was separated and washed with saturated $NaHCO_3$, brine and dried over anhydrous Na_2SO_4, evaparated in vacuo and chromatographed(petroleum ether/EtOAc 5:1) to afford 0.8 g of 17-carbaldehyde **6** in a yield of 72%. m.p. 130-130.5°C(decomposed). $[\alpha]_D$ -75° (c, 1.2, $CHCl_3$), IR (film): ν 1720, 1680cm^{-1}; ^{1}HNMR(200MHz, acetone-d_6):δ 9.78(1H,s,17-H), 6.74 (1H, s, 15-H), 5.31(1H, s, 14-H), 3.62(3H, s, OCH_3), 3.16(3H, s, OMs),1.20, 0.87(each 3H, s, 19, 20-CH_3) ppm. m/z 328$[M-CH_3SO_3H]^+$. $C_{22}H_{32}O_6S$: Calcd C, 62.26, H, 7.55. Found C, 62.31, H, 7.55.

3. Preparation of 17-alcohol **7**

To a solution of 1.1 g **6** in 20 ml of methanol was added portionwise 200mg of $NaBH_4$. The reaction mixture was stirred for 1h, and the excess $NaBH_4$ was destroyed by 5% HCl, and the solvent was removed in vacuo. The residue was dissolved in 100 ml of EtOAc and washed with saturated $NaHCO_3$ and brine, dried over anhydrous sodium sulfate, and evaporated in vacuo. The crude product was chromatographed (petroleum ether/EtOAc 3:1) to give 1.07 g of **7** in yield of 97%. m.p. 123-124°C(decomposed), $[\alpha]_D$ -72.3 (c,4.5, EtOH-$CHCl_3$); IR: ν 3500,1720 cm-1; ^{1}HNMR(200MHz, $CDCl_3$):δ 5.34(1H, s, 15-H), 5.27(1H, s, 14-H), 4.24[2H, br.s, 2x(17-H)], 3.65(3H, s, OCH_3), 3.06(3H, s, OMs), 1.18, 0.90(each 3H,s,19, 20-CH_3). m/z 330$[M-CH_3SO_3H]^+$, 312$[M-CH_3SO_3H-H_2O]^+$. $C_{22}H_{34}O_6S$: Calcd C 61.97, H, 7.98. Found C, 62.26, H, 7.94.

4. Solvolysis of Methyl 14β-Mesyloxy, 17-hydroxy-ent-Kaur-15-en-19-oate(7)

To a solution of 200mg of 7 in 20ml EtOH was added 200mg of zinc dust, then the reaction mixture was heated to reflux for 3 h,and the solvent was removed in vacuo. The residue was extracted with EtOAc, and the organic layer was washed with $NaHCO_3$ solution and brine, dried over anhydrous sodium sulfate and evaporated in vacuo to give crude product **8**, which was chromatographed(petroleum ether/EtOAc 5:1) to afford 134mg of oily **8** in a yield of 83%. UV 255nm(ϵ=1.55x10^4, EtOH), IR(film) 3500, 1720 cm^{-1}. ^{1}HNMR (200MHz, acetone-d_6): 5.81(1H, s, 15-H), 5.56(1H, t, J=6.6 Hz, 7-H), 4.17 [2H, s, 2x(17-H)], 3.63(3H, s, OCH_3), 3.10(2H, m, 9, 14-H), 2.48[2H, m, 2x (6-H)], 1.23, 0.86(each 3H, s, 19, 20-CH_3) ppm. m/z: 330[M^+], 313$[M-OH]^+$. HRMS: $C_{21}H_{30}O_3$: Calcd 330.2166; Found 330.2196.

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