Tetrahedron Vol 46, No 5, pp 1523-1530, 1990
Printed in Great Britain

0040-4020/90 $3 00+ 00

SPIROJATAMOL, A NEW SKELETAL SESQUITERPENOID OF NARDOSTACHYS JATAMANSI ROOTS[1]

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(*Received in Japan* 26 *October* 1989)

Abstract— A new sesquiterpenoid **1** was isolated from the roots of Nardostachys jatamansi and its structure was established by means of spectroscopic data and chemical evidences. Compound **1** has a novel spiranic sesquiterpenoid skeleton.

Nardostachys jatamansi De Candolle, a member of the family Valerianaceae, is indigenous to the mountainous regions of India and rich in sesquiterpenoids and phenolics[3-14]. The roots and rhizomes of N. jatamansi have been used in traditional medicine as bitter tonic, stimulant, antispasmodic, antiseptic and diuretic. They are also employed in the treatment of epilepsy, hysteria, convulsions, mental disorders and diseases of blood and circulatory system[15]. During the course of phytochemical investigation of Valerianaceous plants[16-20], we took up N. jatamansi, and our efforts to isolate new constituents from its dichloromethane extract have resulted in the isolation of a novel sesquiterpenoid **1** for which we proposed the name spirojatamol in addition to known compounds valeranone and patchouli alcohol.

Spirojatamol (**1**), $[\alpha]_D$ +18.0°, was analyzed for the molecular formula $C_{15}H_{26}O$, in agreement with its molecular ion peak at m/z 222.1970 (m/z 222.1983 calcd. for $C_{15}H_{26}O$) and numbers of carbons and hydrogens counted from its ^{13}C and ^1H NMR spectra. The fifteen signals of the ^{13}C NMR spectrum were assigned as follows: CH_3- x 3, $-CH_2-$ x 6, >CH- x 2, >C< x 1, →C-O x 1 and >C=CH_2 x 1. The IR spectral band at 3450 cm^{-1} and ^{13}C NMR signal at w 82.4 (s) indicated that spirojatamol bears a tertiary hydroxyl group. The structural information of spirojatamol was secured from an analysis of its ^1H NMR spectrum (Table 1) which showed two secondary methyl and one tertiary methyl signals at δ 0.82 and 0.84 (3H, d each, J=7.0 Hz) and 1.38 (3H, s), respectively. The former two methyl groups were found to constitute an isopropyl system since they were collapsed to singlets by irradiation of a methine hydrogen signal at δ 1.32 (1H, octet, J=7.0 Hz). In addition, ^1H NMR signals due to two hydrogens of a vinylidene group and two allylic hydrogens next to this group were observed at δ 4.79 and 4.94 (1H, d each, J=1.5 Hz), and 2.32 (1H, dt, J=13.0 and 4.0 Hz) and 2.71 (1H, dt, J=4.0 and 13.0 Hz), respectively. The ^1H NMR spectrum of spirojatamol also displayed signals for one methine hydrogen at δ 2.21 (1H, m) and ten hydrogens of five methylenes at δ 0.96 (1H, t, J=13.0 Hz), 1.04 (1H, dq, J=4.0 and 13.0 Hz), 1.54 (1H, m), 1.59 (1H, m), 1.84 (1H, m), 1.87 (1H, m), 1.98 (1H, ddd, J=14.0, 10.0 and 7.0 Hz), 2.14 (1H, m), 2.16 (1H, ddd,

Table 1. ^{1}H NMR spectral data of **1-2** and **7-9** (500 MHz, $CDCl_3$, J(Hz))

	1	1*	2	7	8	9*
H-1	1.43 ddd (14,9,4)	1.54 m	1.14 m	**	1.24 m	1.25 m
H-1	1.81 m	2.14 m	1.70 m	**	1.99 m	1.25 m
H-2	1.53 m	1.59 m	1.60 m	**	1.54 m	1.53 m
H-2	1.81 m	1.87 m	1.60 m	**	1.73 m	1.60 m
H-3	1.89 ddd (13,10,7)	1.98 ddd (14,10,7)	2.42 m	5.38 br s	2.20 m	2.27 ddd (13.5,10,6)
H-3	2.02 ddd (13,10,7)	2.16 ddd (14,10,7)	2.42 m		2.36 ddd (14,10,6)	2.42 ddd (13.5,9,4.5)
H-5_{ax}			2.25 dq (13,6)			
H-6_{ax}	0.87 t (14)	0.96 t (13)	1.10 q (13)	1.32 dd (13,10)	0.85 t (11)	1.15 dd (15,10)
H-6_{eq}	2.14 ddd (14,4,2)	2.52 ddd (13,4,2)	2.06 m	**	2.16 m	2.39 dt (15,4.5)
H-7_{ax}	1.74 m	2.21 m	1.58-1.48 m	2.09 m	1.90 m	2.10 m
H-8_{ax}	0.96 dq (4,13)	1.04 dq (4,13)	1.37 dq (5,13)	1.33 dq (6,13)	0.98 dq (3.5,13)	1.29 m
H-8_{eq}	1.72 m	1.84 m	2.01 m	1.65 m	1.86 m	1.86 m
H-9_{ax}	2.31 dt (4,13)	2.71 dt (4,13)	2.31 m	2.31 dt (7,13)	2.28 dt (5,13)	2.58 ddd (16,12,9)
H-9_{eq}	2.24 dt (13,4)	2.32 dt (13,4)	2.36 m	2.21 dt (13,6)	2.22 dt (13,3.5)	2.53 dt (16,4.5)
H-11	1.32 octet (7)	1.32 octet (7)	1.58-1.48 m	1.49 octet (7)	1.30 octet (7)	1.36 octet (6.5)
H_3-12	0.86 d (7)	0.84 d (7)	0.89 d (7)	0.87 d (7)	0.84 d (7)	0.89 d (6.5)
H_3-13	0.82 d (7)	0.82 d (7)	0.87 d (7)	0.85 d (7)	0.82 d (7)	0.86 d (6.5)
H_3-14	1.18 s	1.38 s	2.11 s	1.72 s	1.29 s	1.42 s
H-15	4.65 s	4.79 d (1.5)		4.59 d (1.5)	4.65 br s	
H-15	4.80 s	4.94 d (1.5)		4.67 d (1.5)	4.84 br s	
-OAc					1.97 s	2.05 s

*C_5D_5N; ** Obscure

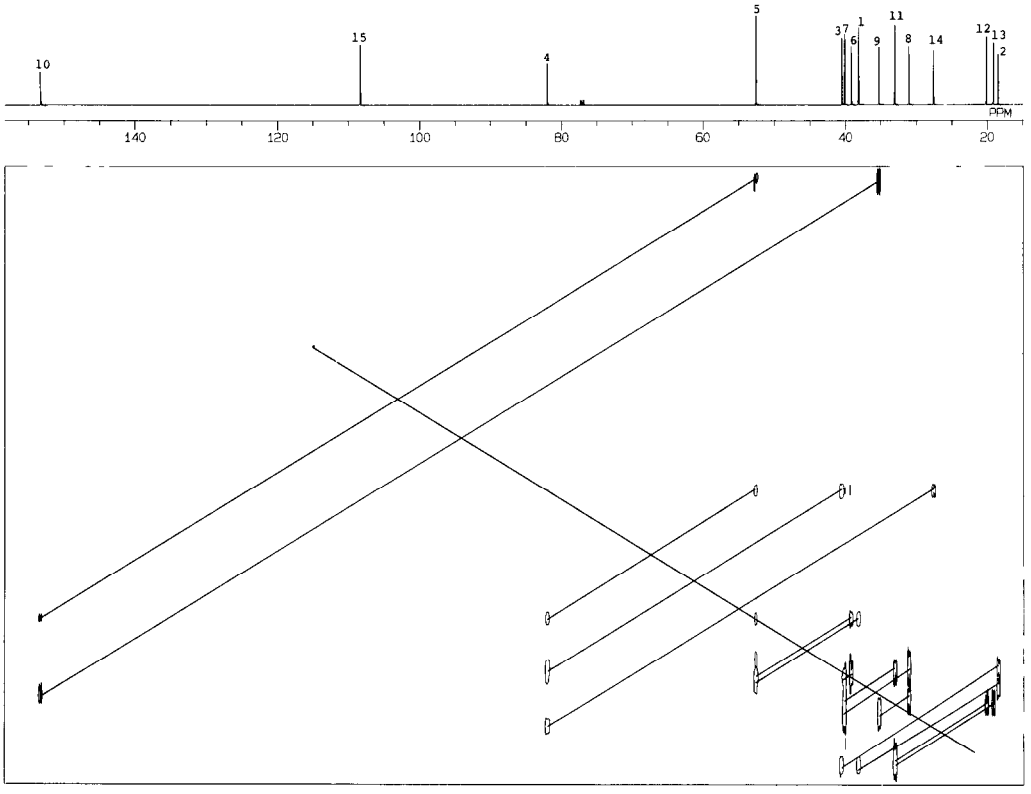
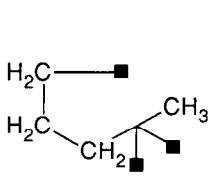
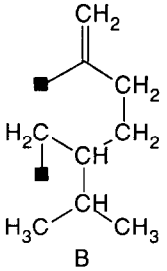


Fig. 1. ^{13}C shift correlation two-dimensional spectrum of spirojatamol



A



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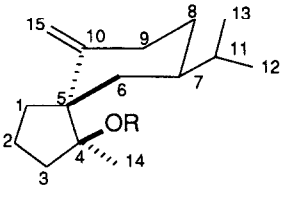
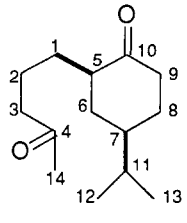


1 R=H
8 R=Ac



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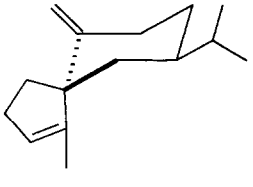

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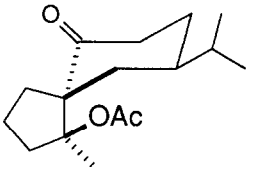

9

J=14.0, 10.0 and 7.0 Hz) and 2.52 (1H, ddd, J=13.0, 4.0 and 2.0 Hz). Sequence of these hydrogens obtained from decoupling experiments starting from the methylene hydrogen signal at δ 0.96 inferred two part structures A and B for spirojatamol.

In the long range ^{1}H-^{13}C shift correlation two-dimensional spectrum of spirojatamol, the quaternary carbon signal at δ 52.8 (s) exhibited long range couplings with the vinylidenic and allylic hydrogens as well as C-6 and tertiary methyl hydrogens, indicating that this quaternary carbon is located next to the vinylidene group. Moreover, the olefinic carbon signal at δ 153.5 (s) has a long range coupling with the C-6 hydrogen through three σ bond. These findings allowed us to connect two part structures A and B through the quaternary carbon resonating at δ 52.8 (s), and furnished the plain spiro-type structure **1** for spirojatamol.

In order to confirm the environment around the vinylidene group of spirojatamol, it was ozonized to afford the diketone **2**, $C_{14}H_{24}O_2$ (MS: m/z 224 (M^+)). The IR spectrum of **2** showed band for saturated keto carbonyl at 1705 cm^{-1} which was further substantiated by two ^{13}C NMR signals at δ 209.2 and 213.5 (s each). The ^{1}H NMR spectrum (Table 1) of **2** showed the presence of isopropyl methyls (δ 0.87 and 0.89 (3H, d each, J=6.5 Hz)) and a methyl ketone (δ 2.11 (3H, s)). In addition, five hydrogens a to carbonyl functions appeared at δ 2.25 (1H, dq, J=13.0 and 6.0 Hz), 2.31 and 2.36 (1H, m each) and 2.42 (2H, m). The ^{13}C NMR spectrum of **2** showed the absence of spiranic, oxymethine and vinylidenic carbon signals. These spectral data and an inspection of its mass fragmentation ion peaks at m/z 167 (M^+-C_3H_5O), 153 (M^+-C_4H_7O) and 140 (M^+-C_5H_8O), suggested that **2** is seco-spirojatamol which was derived from spirojatamol by the retro-aldol type reaction during ozonolysis. Further, a synthesis was carried out for the verification of structure **2**. In this process, methylation of 4-isopropylphenol (**3**) with dimethyl sulfate afforded the methylated derivative **4** which was converted to 4-isopropylcyclohexanone (**5**) by Birch reduction followed by acid hydrolysis and hydrogenation. A direct alkylation of **5** with 5-iodo-2-pentanone ethylene ketal (**6**) in presence of sodium hydride and potassium hydride in refluxing THF[21] followed by acid hydrolysis afforded a compound indistinguishable from **2** in all respects.

All the above findings as well as ^{13}C shift correlation two-dimensional spectrum (2D-INADEQUATE) (Fig. 1) of spirojatamol, which unambiguously clarified the carbon connectivity mainly around the spiranic carbon at C-5, confirmed the structure **1** (without stereochemistry).

An analysis of the coupling patterns of the ^{1}H NMR signals of spirojatamol revealed that the cyclohexane ring adopted a chair-like conformation where the C-7 isopropyl group takes an equatorial orientation. In the nOe difference measurement, saturation of the C-4 tertiary methyl signal at δ 1.38 caused a significant nOe at the C-7 and C-9 axial hydrogen signals at δ 2.21 and 2.71, indicating that the C-4 tertiary methyl group is spatially close to these two axial hydrogens. Moreover, the C-6 equatorial and C-7 axial hydrogens were resonating at much more low field than those of

common methylene and methine hydrogens, due to proximity of the C-4 hydroxyl group. All these informations and the Dreiding model study showed the configuration at C-4 and C-5 as described in figure **1**.

In the remaining problem to solve the absolute stereochemistry of spirojatamol, it was acetylated with acetic anhydride and p-tolunesulfonic acid in THF to afford two products **7** and **8** in 1:4 ratio. The compound **7**, $C_{15}H_{24}$ (MS: m/z 204 (M^+)), showed isopropyl methyls (δ 0.85 and 0.87 (3H, d each, J=7.0 Hz)), a vinylic methyl (δ 1.72 (3H, s)), an olefinic hydrogen (δ 5.38 (1H, br s)), vinylidenic hydrogens (δ 4.59 and 4.67 (1H, d each, J=1.5 Hz)) in its ^{1}H NMR spectrum (Table 1). The decoupling experiments carried out in the ^{1}H NMR spectrum of **7** disclosed that the hydrogen sequence of the six-membered ring is identical to that of the parent compound, therefore, **7** was advanced as a dehydrated derivative of spirojatamol. The compound **8**, $C_{17}H_{28}O_2$ (MS: m/z 264 (M^+)), showed in its IR spectrum band at 1725 cm^{-1} for ester carbonyl which was further substantiated by the ^{13}C NMR signal at δ 168.7 (s) and 21.3 (q). The ^{1}H NMR spectrum (Table 1) of **8** displayed an acetyl methyl signal at δ 1.97 (3H, s) as well as isopropyl methyls at δ 0.82 and 0.84 (3H, d each, J=7.0 Hz) and a tertiary methyl at δ 1.29 (3H, s). Moreover, the vinylidenic and allylic hydrogens were discernible at δ 4.65 and 4.84 (1H, br s each) and δ 2.22 (1H, dt, J=13.0 and 3.5 Hz) and 2.28 (1H, dt, J=5.0 and 13.0 Hz), respectively. The double resonance experiments starting with the irradiation of the isopropyl methyl at 0.82 led to the complete assignments of the ^{1}H NMR signals and gave the structure **8** for the acetylated derivative. Further, lithium aluminum hydride reduction of **8** resulted in the deacetylated compound identical to spirojatamol, confirming the identity of structure **8**.

The acetylated compound **8** was ozonized to afford the ketone **9**, $C_{16}H_{26}O_3$ (MS: m/z 266 (M^+)), the IR spectrum of which showed in addition to acetate carbonyl (1732 cm^{-1}) a saturated keto carbonyl band at 1698 cm^{-1}. The coupling patterns of the ^{1}H NMR signals (Table 1) of **9** revealed that the cyclohexanone ring adopts a chair-like conformation . Its CD spectrum showed a positive Cotton effect at 300 nm ([θ] +5380), establishing the stereostructure **1** for spirojatamol.

To the best of our knowledge, no natural or synthetic compound with this skeleton has been in records.

Experimental

Optical rotations were measured on a JASCO DIP-360 polarimeter and CD spectra on a JASCO A-3 instrument. IR sprctra were recorded on a SHIMADZU IR-408 spectrometer, ^{1}H and ^{13}C NMR spectra on a JEOL JNM FX-100 and FX-500 spectrometers (TMS as internal standard). High and low resolution EIMS were determined with JEOL-JMS-DX 303 and HITACHI M-52 spectrometers.

Isolation of Spirojatamol (1): Dried roots and rhizomes of N. jatamansi (2.0 kg) were extracted with CH_2Cl_2 (4l x 3) at room temperature to give the extract (130 g). The CH_2Cl_2 extract (130 g) was chromatographed over silica gel (400 g) and column was eluted with n-hexane, C_6H_6, $CHCl_3$, EtOAc and MeOH. The repeated silica gel column chromatography of the C_6H_6 eluates (4 g) followed by HPLC (column: Tosoh TSK gel Silica-150: 30 cm x 2.15 cm I.D; solvent: n-hexane-EtOAc (19:1); flow rate: 5ml/min) afforded spirojatamol (**1**) (0.8 g) in addition to valeranone (0.4 g) and patchouli alcohol (0.2 g).

Spirojatamol (**1**), viscous oil; $[\alpha]_D$ +18.0° (c 4.20, $CHCl_3$); HREIMS m/z: 222.1970 (M^+, $C_{15}H_{26}O$); EIMS m/z: 222 (M^+), 204, 179, 164, 161, 121, 109, 105, 95, 93, 91, 81, 79, 71, 67, 55; IR (neat) ν_{max} cm^{-1}: 3450, 1630, 1450, 1370, 890; ^{13}C NMR (125 MHz, $CDCl_3$) δ: 153.5 (s, C-10), 108 4 (t, C-15), 82.4 (s, C-4), 52.8 (s, C-5), 40.7 (t, C-3), 40.3 (d, C-7), 39.3 (t, C-6), 38.2 (t, C-1), 35.5 (t, C-9), 33.2 (d, C-11), 31.2 (t, C-8), 27.7 (q, C-14), 20.3 (q, C-12), 19.4 (q, C-13), 18.6 (t, C-2).

Ozonolysis of Spirojatamol (1) to 2: To a solution of spirojatamol (**1**) (20 mg) in CH_2Cl_2 (3 ml) at -70°C, an ozone saturated CH_2Cl_2 solution (3 ml) was added and the reaction mixture was stirred for 5 min. After addition of $(CH_3)_2S$ (0.5 ml), it was continued to stir at room temperature for 30 min. The excess solvent was removed by reduced pressure to afford a residue (20 mg) which was chromatographed over silica gel (20 g). Elution of the column with n-hexane-EtOAc (9:1) yielded **2** (9 mg) as an oil; $[\alpha]_D$ +30.1° (c 0.62, $CHCl_3$); EIMS m/z: 224 (M^+), 167, 153, 140; IR ($CHCl_3$) ν_{max} cm^{-1}: 1705; ^{13}C NMR (125 MHz, $CDCl_3$) δ: 213.5 (s, C-10), 209.2 (s, C-4), 49.7 (d, C-5), 44.0 (t, C-3), 43.2 (d, C-7), 41.7 (t, C-9), 37.2 (t, C-1), 32.1 (d, C-11), 30.7 (t, C-6), 30.0 (q, C-14), 28.9 (t, C-8), 21.6 (t, C-2), 20.0 (q, C-12), 19.9 (q, C-13).

Conversion of 3 to 4: To an alkaline solution of **3** (10 g/200 ml of 15% KOH), $(CH_3)_2SO_4$ (100 ml) was added and stirred for 4 hrs at room temperature. The reaction mixture was extracted with $CHCl_3$ and the combined $CHCl_3$ solution was purified through a silica gel column (100 g) using n-hexane-EtOAc (19:1) as a eluting solvent to yield oily **4** (9.5 g); EIMS m/z: 150 (M^+); ^1H NMR (100 MHz, $CDCl_3$) δ: 7.10 (2H, dd, J=8.5 and 2.5 Hz), 6.80 (2H, dd, J=8.5 and 2.5 Hz), 3.75 (3H, s), 2.85 (1H, septet, J=7.0 Hz), 1.20 (6H, d, J=7.0 Hz).

Birch reduction, Hydrolysis and Hydrogenation of 4 to 5: To a solution of **4** in EtOH (9 g/100 ml), liq. NH_3 (500 ml) was added followed by Na (7 g). After addition of Na, NH_4Cl (10 g) was added and the reaction mixture was stirred for 1 hr. The reaction mixture was allowed to stand at room temperature to evaporate NH_3, and the residue was dissolved in water (300 ml) and extracted with EtOAc. The combined EtOAc layer was hydrolyzed with 0.6N oxalic acid (100 ml) for 12 hrs at room temperature. After neutralization of excess acid with 15% $KHCO_3$, it was extracted with $CHCl_3$. The $CHCl_3$ layer was washed with water, dried over K_2CO_3 and chromatographed over silica gel (100 g). Elution with n-hexane-EtOAc (19:1) afforded oily unsaturated ketone (8 g); EIMS m/z: 138 (M^+), 96, 81, 67; ^1H NMR (100 MHz, $CDCl_3$) δ: 5.35 (1H, dt, J=1.5 and 4.0

Hz), 2.74 (2H, br s), 2.36 (2H, t, J=7.0 Hz), 2.30 (2H, t, J=7.0 Hz), 2.21 (1H, septet, J=7.0 Hz), 0.93 (6H, d, J=7.0 Hz); ^{13}C NMR (25 MHz, $CDCl_3$) δ: 211.1 (s), 145.5 (s), 115.4 (d), 42.4 (t), 40.9 (t), 34.6 (d), 26.2 (t), 21.0 (q x 2). The MeOH solution of unsaturated ketone (7 g/100 ml) was hydrogenated over 5% Pd/C (500 mg) for 12 hrs at room temperature. Purification of the reaction mixture on silica gel (70 g) using n-hexane-EtOAc (17:3) as a solvent furnished oily **4** (6.5 g), EIMS m/z: 140 (M^+), 125, 97, 84, 69, 55; ^{1}H NMR (100 MHz, $CDCl_3$) δ: 2.33 (2H, dt, J=14.5 and 3.0 Hz), 2.27 (2H, dt, J=6.0 and 14.5 Hz), 1.95 (2H, ddd, J=14.5, 6.0 and 3.0 Hz), 1.54 (1H, octet, J=6.0 Hz), 1.47 (1H, m), 1.40 (2H, dq, J=4.0 and 14.5 Hz), 0.86 (6H, d, J=6.0 Hz); ^{13}C NMR (25 MHz, $CDCl_3$) δ: 212.6 (s), 42.5 (d), 41.1 (t x 2), 31.8 (d), 29.6 (t x 2), 20.0 (q x 2).

Alkylation of 5 with 6: **6** was prepared from commercially available 5-chloro-2-pentanone ethylene ketal by iodination (NaI/$NaHCO_3$/acetone/reflux). A mixture of **4** (220 mg), **5** (400 mg) and NaH/KH (130 mg/6.0 mg) was refluxed in THF (5 ml) for 24 hrs. Reaction was quenched by addition of water and extracted with EtOAc. The organic layer was dried over K_2CO_3, concentrated and chromatographed over silica gel (10 g). Elution with n-hexane-EtOAc (9:1) gave a residue (20 mg) which was hydrolyzed with 1N HCl (0.3 ml) at 50°C for 50 min in dioxane. After neutralization of excess acid with $NaHCO_3$, it was extracted with $CHCl_3$ to afford **2** (t.l.c., IR, MS and ^{1}H NMR).

Acetylation of Spirojatamol (1) to 7 and 8: A mixture of spirojatamol (**1**) (100 mg) in THF (5 ml), 5% p-TsOH in THF (0.5 ml) and Ac_2O (1 ml) was refluxed at 60°C for 3 hrs. The reaction was checked by addition of water and neutralized with $NaHCO_3$ and extracted with $CHCl_3$. The combined $CHCl_3$ layer, after usual work-up, was chromatographed over silica gel (10 g). Elution with n-hexane-EtOAc (98:2) yielded oily **7** (22 mg) and **8** (78 mg), **7**: EIMS m/z: 204 (M^+), 161, 105, 94, 79; ^{13}C NMR (25 MHz, $CDCl_3$) δ: 151.9 (s, C-10), 146.5 (s, C-4), 125.9 (d, C-3), 106.6 (t, C-15), 54.7 (s, C-5), 40.3 (t, C-1 and C-6), 40.0 (d, C-7), 31.8 (t, C-8), 31.6 (d, C-11), 29.3 (t, C-2 and C-9), 20.4 (q, C-12), 20.1 (q, C-13), 15.8 (q, C-14); **8**. EIMS m/z: 264 (M^+), 204, 163, 161, 145, 121, IR (neat) ν_{max} cm^{-1}: 1725, 1635, 890; ^{13}C NMR (25 MHz, $CDCl_3$) δ: 168.7 (s, OAc), 150.9 (s, C-10), 107.8 (t, C-15), 89.9 (s, C-4), 52.5 (s, C-5), 39.4 (d, C-7), 39.1 (t, C-6), 35.2 (t, C-9), 34.7 (t, C-3), 33.8 (t, C-1), 32.2 (d, C-11), 30.9 (t, C-8), 21.9 (q, C-14), 21.3 (q, OAc), 19.1 (q, C-12), 18.7 (q, C-13), 17.2 (t, C-2).

Lithium Aluminum Hydride Reduction of 8 to 1: A solution of **8** (20 mg) in dry THF (3 ml) was stirred with LAH (10 mg) for 2 hrs at room temperature. Excess LAH was destroyed by addition of water, and the solution was neutralized with 1N H_2SO_4 and extracted with EtOAc to afford **1** (t.l.c. and ^{1}H NMR).

Ozonolysis of 8 to 9: Ozonolysis of **8** (10 mg) was carried out in the same manner as mentioned above to yield **9** (8 mg) as an oil; EIMS m/z: 266 (M^+), 224, 206, 166, 153; IR ($CHCl_3$) ν_{max} cm^{-1}: 1732, 1698; ^{13}C NMR (25 MHz, $CDCl_3$) δ: 212.5 (s, C-10), 168.3 (s, OAc), 89.2 (s, C-4), 60.2 (s, C-5), 40.6 (t, C-9), 39.6 (t, C-6), 38.9 (d, C-7), 35.5

(t, C-3), 32.4 (t, C-1), 31.6 (d, C-11), 29.0 (t, C-8), 21.3 (q, C-14 and OAc), 19.1 (q, C-12), 18.8 (q, C-13), 17.6 (t, C-2); CD (dioxane): $[\theta]_{300}$ +5380.

Acknowledgements: We are thankful to Dr. S. Hatakeyama of this Institute and Dr. S. C. Sinha of Research Institute of Non-Aqueous Solutions of this University for their valuable suggestions.

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