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TRANSANNULAR CYCLIZATION OF [1(10)*E*,4*Z*]-3β,8β-DIHYDROXY-13-METHOXY-1(10),4-GERMACRADIENO-12,6α-LACTONE. FORMATION OF CADINANE-TYPE LACTONES

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On treatment with boron trifluoride etherate, [1(10)*E*,4*Z*]-3β,8β-dihydroxy-13-methoxy-1(10),4-germacradieno-12,6α-lactone (**1**) gave five cadinane-type 12,8β-lactones by transannular cyclization and concomitant lactonization with the C-8 hydroxyl group. Some of the cadinane-type lactones were also formed by thermal reaction of **1**.

Transannular cyclization of 1(10),4-germacradienolides has been studied by a number of groups.$^{1-4)}$ However, the investigated lactones were limited to (*E*,*E*)-1(10),4-diene derivatives which gave eudesmanolides,$^{1,2)}$ elemanolides,$^{3)}$ and guaianolides.$^{4)}$ Formation of cadinane-type lactone (**2**) has been reported only as an unusual minor product on alkaline hydrolysis of epitulipinolide (**3**).$^{2)}$ Although cadinane-type compounds have been derived from (*E*,*Z*)-1(10),4-germacradienes without a lactone moiety,$^{5)}$ no cyclization of (*E*,*Z*)-1(10),4-germacradienolides has yet been described to our knowledge. The present communication deals with a transannular cyclization of [1(10)*E*,4*Z*]-3β,8β-dihydroxy-13-methoxy-1(10),4-germacradieno-12,6α-lactone (**1**)$^{6)}$ yielding 12,8β-lactones (**4**-**8**) of a cadinane-type by simultaneous lactonization to the C-8 hydroxyl group.

Treatment of **1** with boron trifluoride etherate in tetrahydrofuran at room temperature for 20 h gave a product mixture from which five cadinane-type lactones (**4**-**8**) were isolated in 5%, 32%, 6%, 12%, and 9% yields, respectively. No formation of eudesmanolide and guaianolide was observed.

The cadinanolides (**4**, **5**, and **6**) were also formed in 17%, 13%, and 9% yields, respectively, when **1** was heated at 215 °C for 3 min under argon atmosphere. None of the lactones (**7**, **8**) nor elemanolide could be isolated from the reaction mixture.

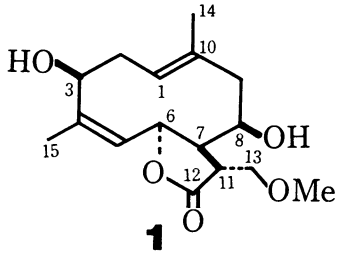
Spectral data of these products can only be interpreted based on cadinanolide structures (**4**-**8**) (*cf.* Table 1 and characterization). Stereochemistries were shown as follows. The observed $J_{7,8}$-values (4-7 Hz) show that a γ-lactone ring is *cis*-fused with 7α-H and 8α-H configurations for all products (**4**-**8**), the configuration at C_7 being the same as that of **1**. The C_6-H must be in an axial conformation (β-configuration) judging from the large $J_{6,7}$-values (10-12.5 Hz) for **5**-**8**. The A/B ring-juncture is *trans* ($J_{1,6}$ = 11 Hz) for **6**, while *cis* ($J_{1,6}$ = 5 Hz) for **7** and **8**. The stereochemistry at C_{11} was suggested to be 11α-H for **4**-**8** from their formation mechanism (*vide infra*) in accordance with the observed $J_{7,11}$-values

(6-9 Hz), a dihedral angle H-C_7-C_{11}-H being variable between 0°-*ca.*30°. Since the B-ring is fused with both aromatic and γ-lactone rings, the observed $J_{8,9}$-values ($J_{8,9\alpha}$= 3 and $J_{8,9\beta}$= 4.5 Hz) led to a unique conformation with the methyl group at C_{10} in an α (equatorial; $J_{9\alpha,10}$= 11 Hz) configuration for **4**. This received support from the presence of NOE (15%) between C_{10}-CH_3 (C_{14}-H's) and C_2-H.

In general a germacradienolide of type **1** may adopt two stable conformers, **A** and **B**. Compound **6** would be derived from **A** by transannular cyclization to form a C_1-C_6 linkage and successive lactonization with the hydroxyl group at C_8, while compounds **7** and **8** from **B**. Compounds **4** and **5** could be derived from both **A** and **B**.

The present studies constitute the first example for the formation of cadinane-type lactones by transannular cyclization of [1(10)*E*,4*Z*]-1(10),4-germacradienolide.

Characterization of the products (**4**-**8**) are as follows; **4**: colorless crystals, mp 87.5-88 °C, $[\alpha]_D^{22}$ -108° (EtOH); IR (KBr) 1760 cm^{-1} (γ-lactone); UV (EtOH) nm (ε) 277 (670), 268 (620), and 263 (440) (aromatic ring); NOE [irradiated proton(s) - observed proton: observed NOE] C_{14}-H's - C_2-H: 15%; MS *m/z* 260.1389 (M^+, $C_{16}H_{20}O_3$); **5**: colorless needles, mp 129-130.5 °C, $[\alpha]_D^{21}$ -19° (EtOH); IR (KBr) 3450 (OH), 1765 (γ-lactone), 1670 (C=C), 1660 (C=C), and 820 cm^{-1} (C=CH); NOE C_{14}-H's - $C_{2\alpha}$-H: 8%, $C_{2\beta}$-H - $C_{2\alpha}$-H: 15%, $C_{2\beta}$-H - C_6-H: 7%, and C_7-H - C_8-H: 8%; MS (CI-MS) *m/z* 279 (M^++ 1); MS *m/z* 260.1444 (M^+-H_2O, $C_{16}H_{20}O_3$); **6**: colorless oil, $[\alpha]_D^{21}$ +33° (EtOH); IR (neat) 3450 (OH), 1760 (γ-lactone), 1675 (C=C), 1660



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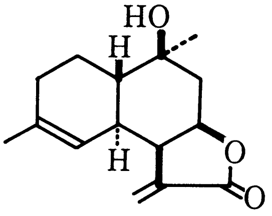

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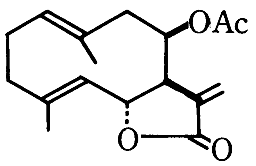

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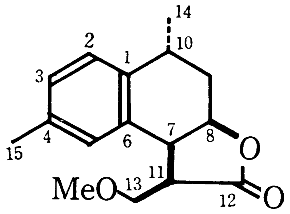

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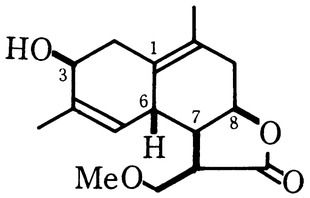

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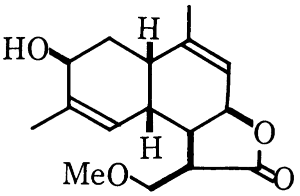

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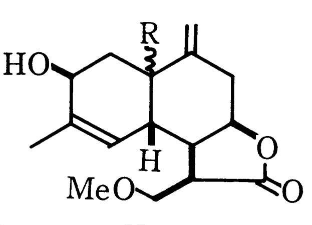
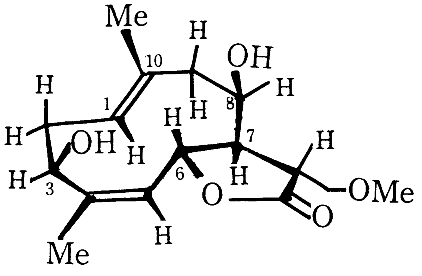
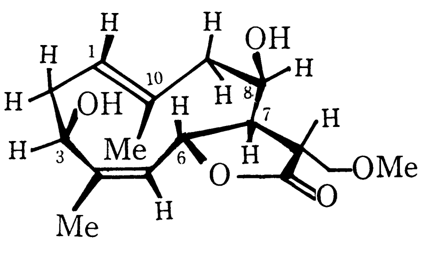


6 R = αH
8 R = βH



A



B

Table 1. ^{1}H NMR Spectral data for **4** - **8** (δ-values)$^{a)}$

	C_1-H	C_2-H_a	C_2-H_b	C_3-H	C_5-H	C_6-H	C_7-H	C_8-H
4	-	7.20 (1H,d)	-	7.07 (1H,d)	7.08 (1H,s)	-	4.00 (1H,dd)	5.05 (1H,ddd)
5	-	3.09(α) (1H,dd)	1.92(β) (1H,br dd)	4.09 (1H,m)	5.37 (1H,m)	2.58 (1H,m)	2.25 (1H,ddd)	4.54 (1H,dt)
6	1.96 (1H,br t)	2.4(α) (¶)	1.49(β) (1H,dt)	4.25 (1H,br t)	5.50 (1H,d)	1.87 (1H,br t)	2.4 (¶)	4.54 (1H,dt)
7	2.33 (1H,ddd)	1.96(β) (1H,dd)	1.52(α) (1H,dt)	4.00 (1H,br d)	5.60 (1H,d)	2.20 (1H,dt)	2.53 (1H,ddd)	4.68 (1H,dd)
8	1.77 (1H,m)	1.97(α) (1H,dt)	1.66(β) (1H,dt)	4.03 (1H,br dd)	5.55 (1H,dd)	2.14 (1H,br dt)	2.43 (1H,ddd)	4.50 (1H,dt)

	C_9-H_a	C_9-H_b	C_{10}-H	C_{11}-H	C_{13}-H_a	C_{13}-H_b	C_{14}-H	C_{15}-H	OMe
4	2.33(β) (1H,dt)	1.57(α) (1H,ddd)	2.92 (1H,m)	3.30 (1H,dt)	3.57 (1H,dd)	3.20 (1H,t)	1.31 (3H,d)	2.33 (3H,s)	3.15 (3H,s)
5	2.44 (1H,m)	2.40 (1H,m)	-	3.14 (1H,ddd)	3.83 (1H,dd)	3.59 (1H,t)	1.71 (3H,s)	1.77 (3H,br s)	3.41 (3H,s)
6	2.84 (1H,dd)	2.4 (¶)	-	3.14 (1H,ddd)	3.81 (1H,dd)	3.46 (1H,t)	4.92 (1H,s) 4.80 (1H,s)	1.78 (3H,s)	3.37 (3H,s)
7	5.70 (1H,d)	-	-	3.21 (1H,ddd)	3.87 (1H,dd)	3.67 (1H,dd)	1.85 (3H,s)	1.85 (3H,s)	3.41 (3H,s)
8	2.68 (1H,dd)	2.50 (1H,br dd)	-	3.13 (1H,ddd)	3.83 (1H,dd)	3.60 (1H,t)	4.99 (1H,s) 4.87 (1H,s)	1.84 (3H,s)	3.41 (3H,s)

Coupling constants in Hz

4 $J_{2,3}=8$, $J_{7,8}=7$, $J_{7,11}=9$, $J_{8,9a}=4.5$, $J_{8,9b}=3$, $J_{9a,9b}=13.5$, $J_{9a,10}=4.5$, $J_{9b,10}=11$, $J_{10,14}=7$, $J_{11,13a}=3$, $J_{11,13b}=9$, $J_{13a,13b}=9$

5 $J_{2a,2b}=13$, $J_{2a,3}=5.5$, $J_{2b,3}=\mathit{ca.}\,12$, $J_{5,6}=\mathit{ca.}\,0$, $J_{6,7}=10$, $J_{7,8}=4$, $J_{7,11}=6$, $J_{8,9a}$(or $J_{8,9b}$)=2, $J_{8,9b}$(or $J_{8,9a}$)=4, $J_{11,13a}=3.5$, $J_{11,13b}=10$, $J_{13a,13b}=10$

6 $J_{1,2b}=11$, $J_{1,6}=11$, $J_{2a,2b}=11$, $J_{2a,3}=\mathit{ca.}\,8$, $J_{2b,3}=\mathit{ca.}\,8$, $J_{5,6}=1$, $J_{6,7}=11$, $J_{7,8}=3$, $J_{7,11}=6.5$, $J_{8,9a}=3$, $J_{8,9b}=2.5$, $J_{9a,9b}=15$, $J_{11,13a}=3.5$, $J_{11,13b}=10.5$, $J_{13a,13b}=10.5$

7 $J_{1,2a}=2$, $J_{1,2b}=13$, $J_{1,6}=5$, $J_{2a,2b}=13$, $J_{2a,3}=\mathit{ca.}\,0$, $J_{2b,3}=4$, $J_{5,6}=5$, $J_{6,7}=12.5$, $J_{7,8}=5$, $J_{7,11}=7.5$, $J_{8,9}=3.5$, $J_{11,13a}=4$, $J_{11,13b}=9$, $J_{13a,13b}=10$

8 $J_{1,2a}=14$, $J_{1,2b}=2$, $J_{1,6}=5$, $J_{2a,2b}=14$, $J_{2a,3}=4$, $J_{2b,3}=2$, $J_{3,5}=1$, $J_{5,6}=5$, $J_{6,7}=11$, $J_{7,8}=4$, $J_{7,11}=6.5$, $J_{8,9a}$(or $J_{8,9b}$)=4, $J_{8,9b}$(or $J_{8,9a}$)=3, $J_{9a,9b}=16$, $J_{11,13a}=4$, $J_{11,13b}=10$, $J_{13a,13b}=10$

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a) Measured in chloroform-d at 270 MHz using TMS as internal standard. Assignment of signals was determined by decoupling experiments. s; singlet, d; doublet, dd; double doublets, ddd; doublet of double doublets, t; triplet, dt; double triplets, m; multiplet, br; broad, ¶; could not be determined because of overlapping with other signals.

(C=C), 895 ($C=CH_2$), and 820 cm^{-1} (C=CH); MS *m/z* 278.1437 (M^+, $C_{16}H_{22}O_4$); **7**: colorless needles, mp 171.5-172.5 °C, $[\alpha]_D^{20}$ -124° (EtOH); IR (Nujol) 3280 (OH), 1752 (γ-lactone), and 838 cm^{-1} (C=CH); MS *m/z* 278.1491 (M^+, $C_{16}H_{22}O_4$); **8**: colorless needles, mp 157-158 °C, $[\alpha]_D^{22}$ -15° (EtOH); IR (Nujol) 3455 (OH), 1738 (γ-lactone), 1655 (C=C), and 873 cm^{-1} ($C=CH_2$); MS *m/z* 278.1497 (M^+, $C_{16}H_{22}O_4$).

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6) T. Takahashi, H. Eto, T. Ichimura, and T. Murae, Chem. Lett., 1978, 1345; the stereochemistry at C-11 was determined as shown in **1** on the basis of observed $J_{7,11}$-value (<1 Hz).

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