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SYNTHESIS OF 3-OXYGENATED 13-NORHELIANGOLIDES

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Optically active [3*R*,6*S*,7*S*,1(10)*E*,4*Z*]- and [3*R*,6*R*,7*S*,1(10)*E*,4*Z*]-3-methoxymethoxy-13-nor-1(10),4-germacradieno-12,6-lactones, key synthetic intermediates for 3-oxygenated heliangolides, were synthesized from (-)-carvone.

A number of germacradienolides with an α-methylene-γ-lactone ring have been reported in these years, some of them showing strong anti-tumor activity.1) Among these sesquiterpenes, [1(10)*E*,4*E*]-1(10),4-germacradienolides constitute a group of "germacrolides"2) and their synthesis have been reported by many groups.3) [1(10)*E*,4*Z*]-1(10),4-Germacradienolides possessing a skeletal structure (**1**) are also known1) as "heliangolides".2) For example, hiyodorilactone A, isolated from *Eupatorium sachalinense* Makino by one of us and co-workers, belongs to this group and showed a significant inhibitory activity *in vivo* against the Ehrlich ascites carcinoma.4) Although [1*E*,5*Z*]-1,5-cyclodecadiene derivatives without a lactone moiety were synthesized by the route involving oxy-Cope rearrangement,5) pyrolysis,6) or cyclization,7) no synthesis of heliangolides has yet been described to our knowledge. Most of natural heliangolides have an oxygen function at C-3 position. We chose optically active C-3 oxygenated 13-nor-heliangolides as synthetic targets, because the introduction of an α-methylene to the γ-lactone ring in the final synthetic stage has been well-investigated.8) In this paper, we wish to report the synthesis of [3*R*,6*S*,7*S*,1(10)*E*,4*Z*]- and [3*R*,6*R*,7*S*,1(10)*E*,4*Z*]-3-methoxymethoxy-13-nor-1(10),4-germacradieno-12,6-lactones (**2** and **3**) from (-)-carvone.

(-)-*cis*-Carveol (**4**),9) obtained from (-)-carvone by LiAlH$_4$ reduction, was acetylated and then oxidized with *t*-butyl chromate to afford a ketone **5** [45 % yield; oil; $[\alpha]_D^{14}$ -52° (EtOH); IR (neat) 1740, 1675 cm^{-1}; UV (EtOH) 228 nm (ε 9800); M$^+$ at *m/e* 208.1090 ($C_{12}H_{16}O_3$)]. Reaction of **5** with 1.4 equivalent moles of vinyl magnesium bromide gave trienes, **6** and **7**, in 28 and 6 % yields, respectively.10) [**6**: oil; $[\alpha]_D^{14}$ -30° (EtOH); IR (neat) 3500, 1735 cm^{-1}; NMR11) (CDCl$_3$) δ 5.87 (1H, dd, J=10 and J=17 Hz, -C$\underline{H}$=CH$_2$); **7**12): mp 142.5-144.5°C; $[\alpha]_D^{16}$ -24° (EtOH); IR (KBr) 3320, 3250 cm^{-1}; NMR (CDCl$_3$) δ 5.86 (1H, dd, J=10 and J=17 Hz, -C$\underline{H}$=CH$_2$)]. Since an oxy-Cope rearrangement for both **6** and **7** was unsuccessful, the protective group for the secondary hydroxyl group of **6** was replaced by a methoxymethyl (MOM) group to give **8** [76 % yield; oil; $[\alpha]_D^{16}$ -61° (EtOH); IR (neat) 3480 cm^{-1}; NMR (CDCl$_3$) δ 3.40 (3H, s, -OCH$_2$OC$\underline{H}_3$), 4.65 and 4.76 (each 1H, A and B parts of an ABq, J=6 Hz, -OC$\underline{H}_2$OCH$_3$)].

When the triene (**8**) was treated with 1.2 equivalent moles of KH and 18-crown-6 in THF,5) **8** underwent the oxy-Cope rearrangement to afford a cyclodecadienone (**9**)12) [67 % yield; mp 52-53 °C; $[\alpha]_D^{11}$ -111° (EtOH); IR (neat) 1680 cm^{-1}; UV (EtOH) 235 nm (ε 5300); NMR (270 MHz; $CDCl_3$) δ 3.42 (3H, s, $-OCH_2OC\underline{H}_3$), 4.65 and 4.67 (each 1H; A and B parts of an ABq, J=6 Hz, $-OC\underline{H}_2OCH_3$), and signals listed in Table 1]. The geometry of olefinic double bonds was confirmed by NOE experiments (270 MHz; $CDCl_3$). The result shown as Table 1 can only be interpreted based on the [1(10)*E*,4*Z*]-structure (**A**) for **9**. Treatment of **9** with LDA followed by ethyl bromoacetate gave a keto ester (**10**) as a sole product in 74 % yield. [**10**: oil; $[\alpha]_D^{12}$ -40° (EtOH); IR (neat) 1735, 1680 cm^{-1}; NMR ($CDCl_3$) δ 1.24 (3H, t, J=7 Hz, $-CO_2CH_2C\underline{H}_3$), 4.11 (2H, q, J=7 Hz, $-CO_2C\underline{H}_2CH_3$), 6.23 (1H, s, C(5)-H); M$^+$ at *m/e* 324.1948 ($C_{18}H_{28}O_5$)]. The stereochemistry at C-7 of **10** would be 7α*H* as a result of an attack of the reagent to the C-7 position from the less hindered side (outer side) (**B**) of the intermediate enolate anion molecule having a more stable 6(7)*Z*-double bond, which can conjugate with the 4(5)-double bond, while the corresponding 6(7)*E* enolate can not do. This stereochemical assignment was supported by the following chemical transformation.

The keto ester (**10**) was reduced with $NaBH_4$ to give a lactone (**3**) [12 % yield;13) oil; $[\alpha]_D^{24}$ -110° (EtOH); IR (neat) 1765 cm^{-1}; NMR ($CDCl_3$) δ 1.46 (3H, s), 1.75 (3H, s), 3.36 (3H, s, $-OCH_2OC\underline{H}_3$), 4.36 (1H, t, J=3 Hz, C(3β)-H), 4.51 and 4.65 (each 1H; A and B parts of an ABq, J=6.5 Hz, $-OC\underline{H}_2OCH_3$), *ca*. 5.37 (2H, m, C(1)-H and C(5)-H), 6.01 (1H, dd, J=7 and J=11 Hz, C(6α)-H); M$^+$ at *m/e* 280.1656 ($C_{16}H_{24}O_4$)]. The methoxymethoxyl group at C(3α) is in axial conformation judging from the coupling constant of C(3β)-H (t, J=3 Hz). The δ value (6.01) at fairly low field observed for C(6)-H shows that C(6)-H is situated close to the C(3α)-axial methoxymethoxyl oxygen. These facts together with large J values (7 and 11 Hz) observed for C(6)-H lead to a *cis*-lactone structure with C(6α)-H and C(7α)-H configurations for **3**. The *cis*-lactone structure (**3**) is also compatible with the formation mechanism that a hydride attack from the less hindered outer side of the ten-membered ring would be preferred.

Hydrolysis (K_2CO_3-aq. MeOH; 93 % yield) of **10** followed by reduction with $LiBH_4$ gave a hydroxy acid (**11**), which was easily lactonized to give **3** during isolation procedure. The treatment of crude **11** with *N*,*N*-dimethylformamide dineopentyl acetal in boiling toluene gave a *trans*-lactone (**2**) with inversion of the chiral center at the hydroxy-carrying carbon atom14) in 15 % yield from **10**.15) [**2**: oil; $[\alpha]_D^{19}$ +61° (EtOH); IR (neat) 1770 cm^{-1}; NMR ($CDCl_3$) δ 1.59 (3H, s), 1.75 (3H, br. signal), 3.37 (3H, s, $-OCH_2OC\underline{H}_3$), 4.20 (1H, dd, J=6 and J=9.5 Hz, C(3β)-H), 4.48 and 4.57 (each 1H; A and B parts of an ABq, J=7 Hz, $-OC\underline{H}_2OCH_3$), 4.55 (1H, br. signal, C(1)-H), 5.12 (2H, br. singlet, C(6β)-H and C(5)-H); M$^+$ at *m/e* 280.1672 ($C_{16}H_{24}O_4$)]. The NMR spectral data are compatible with the structure **2** when compared with those of a natural heliangolide, eupasimplicin A.16)

The synthesis of **2** and **3** constitutes the first example of the synthesis of [1(10)*E*,4*Z*]-1(10),4-cyclodecadienes with a γ-lactone fused to the C(6)-C(7) position.

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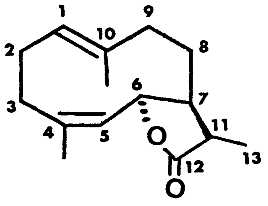
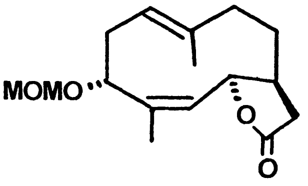


1



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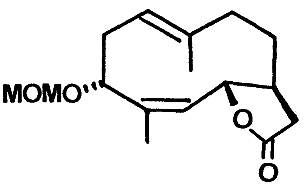

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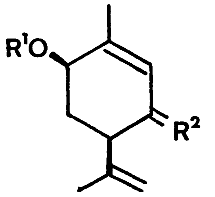
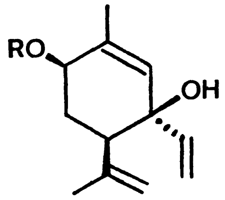
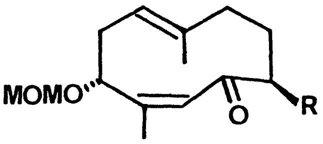


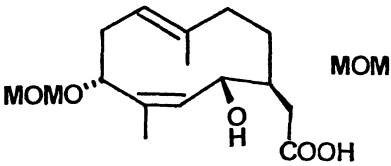
	R^1	R^2
4	H	H_2
5	Ac	O



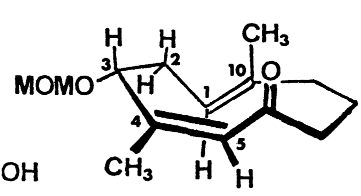
6 R = Ac
7 R = H
8 R = MOM



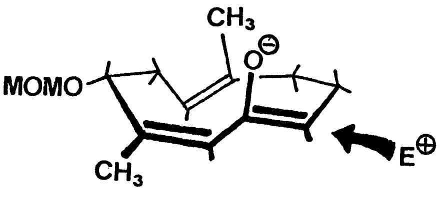
9 R = H
10 R = $CH_2COOC_2H_5$



11



A



B

Table 1[a] NOE data for **9**

irradiated proton(s)	observed proton	NOE[b]
C(10)-CH_3 (δ 1.56, 3H, s)	C(1)-H (δ 5.03, 1H, t, $J_{1,2\alpha}=J_{1,2\beta}=8$ Hz)	< 2 %
	C(2β)-H (δ 2.51, 1H, ddd, $J_{1,2\beta}=8$ Hz, $J_{2\alpha,2\beta}=13$ Hz, $J_{2\beta,3\beta}=5.5$ Hz)	7 %
	C(3β)-H (δ 4.88, 1H, dd, $J_{2\alpha,3\beta}=11$ Hz, $J_{2\beta,3\beta}=5.5$ Hz)	10 %
C(4)-CH_3 (δ 1.79, 3H, s)	C(1)-H	15 %
	C(5)-H (δ 6.07, 1H, s)	20 %
C(2β)-H	C(3β)-H	12 %

a) Assignment of signals was determined by decoupling experiments.
b) Accuracies are about ±2 %.

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10) No diastereomer of **6** nor **7** was obtained. The stereochemistry at the vinyl- and hydroxy-carrying carbon atom for **6** and **7** was deduced from their formation mechanism. Other products showing small Rf values on TLC were also formed. However, their structures remained undetermined.

11) Determined at 90 MHz unless otherwise cited.

12) The result of elementary analysis was fully compatible with the structure.

13) Other products suggested to be a keto alcohol and a diol were also formed.

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15) Other products showing small Rf values on TLC were also formed.

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