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Stereo-controlled Alkylation of Cyclodecadienone Derivatives and the Total Synthesis of (-)- and (+)-4,5-cis-3β-Hydroxygermacranolides

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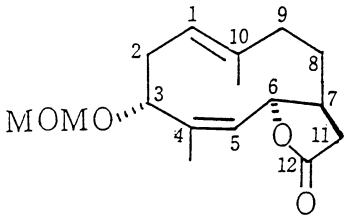
Direct trapping of the intermediate, produced by anionic oxy-Cope rearrangement of (1R,4S,6S)-4-alkoxy-1-ethenyl-3-methyl-6-(1-methylethenyl)-2-cyclohexen-1-ol, with ethyl bromoacetate gave ethyl [3S,7S,1(10)E,4Z]-3-alkoxy-6-oxo-13-nor-1(10),4-germacradien-12-oate stereoselectively, which was converted into a natural (-)-4,5-*cis*-3β-hydroxygermacranolide.

A number of synthetic studies on germacranolides have been developed.[1] We have previously reported the synthesis of optically active [3R,6S,7S,1(10)E,4Z]-3-methoxymethoxy-13-nor-1(10),4-germacradieno-12,6-lactone (1; a *trans*-lactone) from (-)-carvone (2) *via* a *cis*-hydroxy acid (3) using anionic oxy-Cope rearrangement as a key step reaction; this synthesis was exigent of an inversion of the asymmeric center at C-6 of 3 to give the *trans*-lactone (1).[1a] [3S,6S,7S,1(10)E,4Z]-3-Hydroxy-1(10),4,11(13)-germacratrieno-12,6-lactone [4a; (-)-4,5-*cis*-3β-hydroxygemacranolide] had been isolated from *Tanacetum tanacetioides*.[2] Its acetate (4b) and keto derivative (4c; hispanolide) had also been isolated from *Leucanthenopsis pulverulanta*.[3] This paper deals with the stereo-controlled alkylation of cyclodecadienone derivatives to give, after reduction with $NaBH_4$, *trans*-lactones (5a, 5b, and 5b') and the synthesis of naturally occurring heliangolide (4a) and its enantiomer (4a').

In the previous papers,[1a] a methoxymethoxy (MOMO) trienol (6a) derived from the trienediol (6b) was treated with KH and 18-crown-6 in THF to proceed the anionic oxy-Cope rearrangement; a cyclodecadienone (7) was obtained in 67% yield on quenching the intermediate with aqueous ammonium chloride. The ketone (7) was then treated with LDA to generate the 6(7)Z-enolate (8a), which was quenched with ethyl bromoacetate to afford keto ester (9a) having 7α-H stereostructure; hydrolysis of 9a followed by reduction with $LiBH_4$ gave the *cis*-hydroxy acid (3).[1a]

The ten-membered ring intermediate initially formed by the anionic oxy-Cope rearrangement of 6a was considered to have a structure like 10a, a conformational isomer of 8a. When the intermediate generated from 6c by anionic oxy-Cope rearrangement on treatment with $KN(TMS)_2$[1b] in DME at 80 °C was directly quenched with ethyl bromoacetate at -78 °C, a keto ester (11a) which was clearly different from 9b[4] on NMR spectral examination was obtained in 45% yield. This fact could be explained that 10b or an enolate, possessing the same conformational structure



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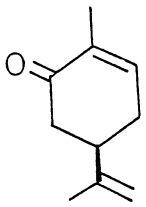
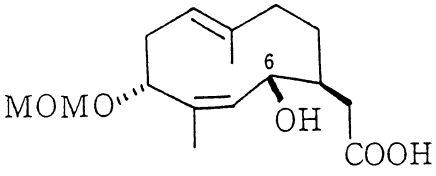


2

2' : Enantiomer of 2



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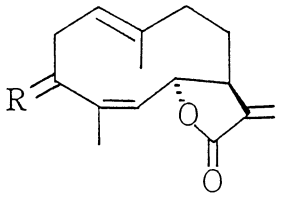
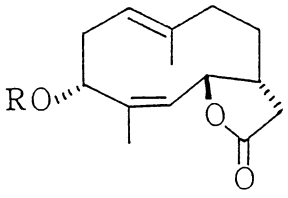
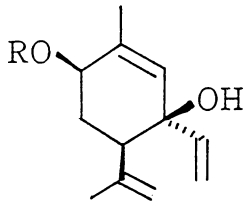


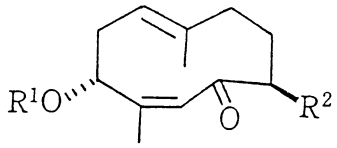
4a : R = β-OH, α-H
4a': Enantiomer of 4a
4b : R = β-OAc, α-H
4c : R = O



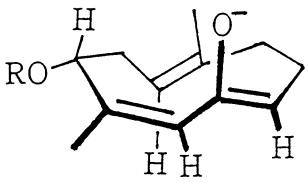
5a : R = CH_2Ph
5b : R = TBDMS
5b': Enantiomer of 5b



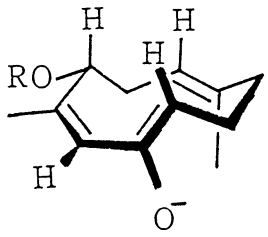
6a : R = MOM
6b : R = H
6b': Enantiomer of 6b
6c : R = CH_2Ph
6d : R = TBDMS
6d': Enantiomer of 6d



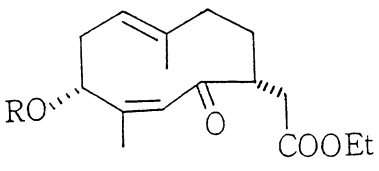
7 : R^1 = MOM, R^2 = H
9a : R^1 = MOM, R^2 = CH_2COOEt
9b : R^1 = CH_2Ph, R^2 = CH_2COOEt



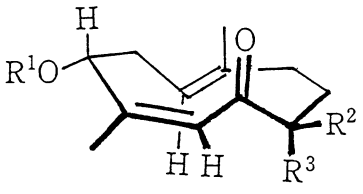
8a : R = MOM
8b : R = CH_2Ph



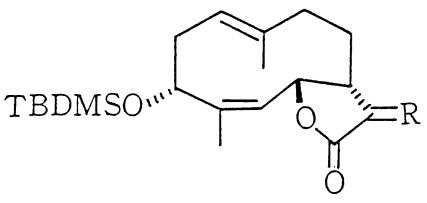
10a : R = MOM
10b : R = CH_2Ph
10c : R = TBDMS
10c' : Enantiomer of 10c



11a ; R = CH_2Ph
11b : R = TBDMS
11b': Enantiomer of 11b



A



12 : R = CH_2OH, H
12': Enantiomer of 12
13 : R = CH_2
13': Enantiomer of 13

around the enolate part as 10b, was trapped with ethyl bromoacetate.

Treatment of 11a with $NaBH_4$ gave the *trans*-γ-lactone (5a) stereospecifically. The structure of this lactone including the stereochemistry was confirmed by 400 MHz ^1H NMR as [3R,6R,7R,1(10)E,4Z]-3-benzyloxy-13-nor-1(10),4-germacradieno-12,6-lactone (5a) with 7β-H. The stereoselectivity on the hydride reduction reaction of 6-keto derivatives (9a and 11a) could be explained as follows. That is, regardless of the orientation of substituents at C-7 position, conformation of these reactants (9a and 11a) would be fixed as A, in which the 3α-substituted group was oriented to equatorial; hydride attack to the carbon at C-6 of A took place preferentially from the less hindered outer side of the ten-membered ring to give 6α-H compounds (3 and 5a).

As the removal of the benzyl protecting group (H_2/Pd-C; or TMSI/CCl_4) of 5a was ineffective,[5] the protective group of the hydroxyl group of 6b was changed from benzyl into t-butyldimethylsilyl (TBDMS) group. The t-butyldimethylsilyloxy trienol (6d), obtained from 6b by treatment with TBDMSCl and imidazole in DMF, was treated with 5 equivalent moles of $KN(TMS)_2$ in DME followed by ethyl bromoacetate to afford the corresponding cyclodecadiene derivative (11b) in 32% yield *via* the intermediate (10c). Reduction of 11b with $NaBH_4$ gave a lactone (5b) in 50% yield.

Exo-methylene group in the γ-lactone moiety was introduced by the known method;[6] 5b was treated with LDA followed by HCHO (gas) to afford the hydroxymethyl derivative (12) in 47% yield, which was dehydrated with MsCl and 4-dimethylaminopyridine in pyridine to give the α-methylene-γ-lactone (13) in 45% yield.

The t-butyldimethylsilyl group of 13 was smoothly deprotected by treatment with tetrabutylammonium fluoride to yield [3R,6R,7R,1(10)E,4Z]-3-hydroxy-1(10),4,11(13)-germacratrieno-12,6-lactone (4a'), the enantiomer of natural lactone (4a), in 85% yield. The spectral data (IR, ^1H NMR, and MS) of synthetic 4a' were identical with those of natural compound (4a).

A compound having the same sign on optical rotation as that of natural product (4a) could be obtained starting from (+)-carvone (2') by the same procedures [2'→→6b'→6d'→(10c')→11b'→5b'→12'→13'→4a] as described above; the overall yield of 4a from 6b' was 6%. The $[\alpha]_D$ value of our synthetic 4a (-53°) was different from those (-80°[2] and -18.1°[3]) reported for natural compound (4a). The synthetic compound (4a) was converted into a MTPA ester with (+)-MTPACl [(R)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride] to check the optical purity. The GC and GC-MS of the MTPA ester of 4a showed 88% e.e., which was almost identical with that of starting material, (+)-carvone (2'; 90% e.e.).

Characterization of synthetic 4a, 5a, 5b', 6d', 9b, and 11a is as follows;
4a: crystals, mp 153.5-154.5 °C (hexane-ether); IR (KBr) 3480, 1730, and 1660 cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz) δ 1.71 (3H, d, J=1.5 Hz), 1.74 (3H, d, J=1.5 Hz), 4.44 (1H, t, J=3 Hz), 5.10 (1H, br t, J=8 Hz), 5.16 (1H, dq, J=10.5 and 1.5 Hz), 5.63 (1H, d, J=3 Hz), 5.75 (1H, dd, J=10.5 and 3 Hz), and 6.27 (1H, d, J=3 Hz); $C_{15}H_{20}O_3$ (m/z 248.1442).
5a: crystals, mp 88-89.5 °C (ether); IR (KBr) 1775 and 1195 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.66 (3H, br s), 1.70 (3H, d, J=1.5 Hz), 4.03 (1H, t, J=6 Hz), 4.26 and

4.66 (2H, ABq, J=11.6 Hz), 5.15 (1H, br), 5.40 (1H, dd, J=10 and 1.5 Hz), 5.63 (1H, dd, J=10 and 3 Hz), and 7.33 (5H, m); $C_{21}H_{26}O_3$ (m/z 326.1916).
5b': oil, IR (neat) 1775 and 1675 cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz) δ 0.0 (6H, s), 0.85 (9H, s), 1.60 (3H, d, J=1.5 Hz), 1.62 (3H, s), 4.20 (1H, t, J=3 Hz), 5.00 (1H, br t, J=9 Hz), 5.10 (1H, dd, J=10.5 and 1.5 Hz), and 5.54 (1H, dd, J=10.5 and 3 Hz); $C_{20}H_{34}O_3Si$ (m/z 350.2243).
6d': oil, IR (neat) 3490 cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz) δ 0.0 (6H, s), 0.84 (9H, s), 1.63 (3H, d, J=1.5 Hz), 1.69 (3H, d, J=1.5 Hz), 4.05 (1H, br t, J=6 Hz), 4.69 (1H, br d, J=1.5 Hz), 4.85-5.25 (4H, m), and 5.77 (1H, dd, J=18 and 10.5 Hz); $C_{18}H_{32}O_2Si$ (m/z 308.2186).
9b: oil, IR (neat) 1730, 1675, and 1620 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 1.23 (3H, t, J=7 Hz), 1.43 (3H, s), 1.83 (3H, s), 4.09 (2H, ABq, J=7 Hz), 4.47 (2H, s), 4.73 (1H, dd, J=12 and 6 Hz), 5.01 (1H, t, J=7 Hz), and 6.30 (1H, br s); $C_{23}H_{30}O_4$ (m/z 370.2134).
11a: oil, IR (neat) 1730, 1680, and 1630 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 1.27 (3H, t, J=7 Hz), 1.48 (3H, s), 1.87 (3H, s), 4.15 (2H, ABq, J=7 Hz), 4.50 (2H, s), 4.7-5.2 (2H, m), and 6.13 (1H, br s); $C_{23}H_{30}O_4$ (m/z 370.2102).

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References

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2) F. Bohlmann, A. Suwita, A. A. Natu, H. Czerson, and A. Suwita, Chem. Ber., 110, 3572 (1977).
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4) The compound (9b) was obtained from 6c using the previous method.[1a]
5) When 5a was treated with H_2/Pd-C, hydrogenation of the double bond in the ten-membered ring took place. Treatment of 5a with TMSI/CCl_4 resulted in the formation of complex by-products.
6) P. A. Grieco, G. F. Majetich, and Y. Ohfune, J. Am. Chem. Soc., 104, 4226 (1982).

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