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

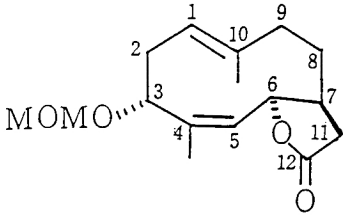
Takayoshi NAKAMURA, Hiroshi HIROTA,* Chiaki KURODA, and Takeyoshi TAKAHASHI*
Department of Chemistry, Faculty of Science, The University of Tokyo,
Hongo, Bunkyo-ku, Tokyo 113

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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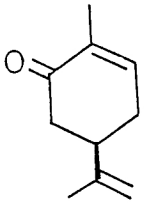
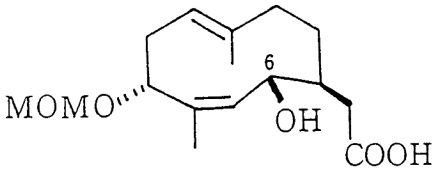


2

2' : Enantiomer of 2



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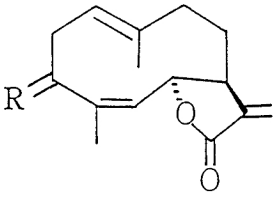
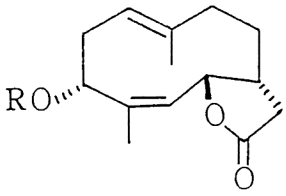
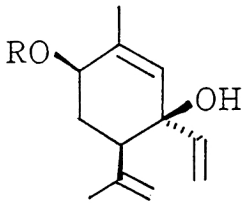


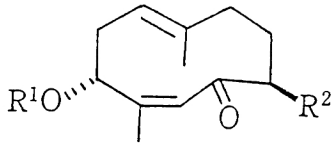
4a : R = β-OH, α-H
4a': Enantiomer of 4a
4b : R = β-OAc, α-H
4c : R = O



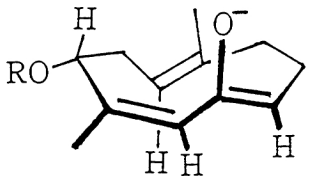
5a : R = CH_2Ph
5b : R = TBDMS
5b': Enantiomer of 5b



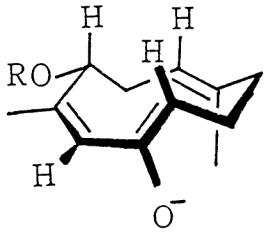
6a : R = MOM
6b : R = H
6b': Enantiomer of 6b
6c : R = CH_2Ph
6d : R = TBDMS
6d': Enantiomer of 6d



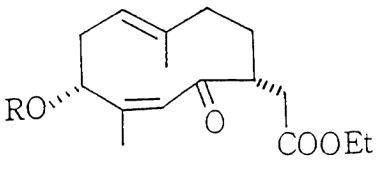
7 : R^1 = MOM, R^2 = H
9a : R^1 = MOM, R^2 = CH_2COOEt
9b : R^1 = CH_2Ph, R^2 = CH_2COOEt



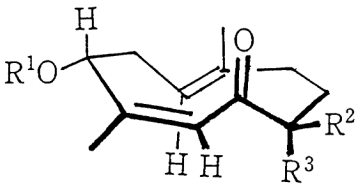
8a : R = MOM
8b : R = CH_2Ph



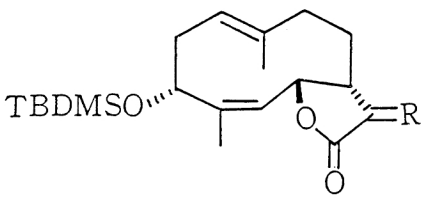
10a : R = MOM
10b : R = CH_2Ph
10c : R = TBDMS
10c' : Enantiomer of 10c



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

1) a) C. Kuroda, H. Hirota, and T. Takahashi, Chem. Lett., 1982, 249; C. Kuroda, T. Nakamura, H. Hirota, K. Enomoto, and T. Takahashi, Bull. Chem. Soc. Jpn., 58, 146 (1985); b) W. C. Still, S. Murata, G. Revial, and K. Yoshihara, J. Am. Chem. Soc., 105, 625 (1983). Literatures of other synthetic works on germacranolides are listed in their references.
2) F. Bohlmann, A. Suwita, A. A. Natu, H. Czerson, and A. Suwita, Chem. Ber., 110, 3572 (1977).
3) J. de Pascual-T., M. S. González, M. A. Moreno Valle, and T. S. Bellido, Phytochemistry, 22, 1985 (1983).
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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