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Marine Natural Products. XVII.[1] Nephtheoxydiol, a New Cytotoxic Hydroperoxy-Germacrane Sesquiterpene, and Related Sesquiterpenoids from an Okinawan Soft Coral of *Nephthea* sp. (Nephtheidae)

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A new cytotoxic hydroperoxy-germacrane sesquiterpene named nephtheoxydiol (**8**) and several related sesquiterpenoids, *ent*-oplopanone (**2**), nephthenol (**6**), and nephthediol (**9**), were isolated from an Okinawan soft coral of *Nephthea* sp. (Nephtheidae), together with a new cadinane-type sesquiterpene named nephthene (**17**). Based on chemical reactions and physical data analyses, the absolute stereostructures of *ent*-oplopanone (**2**), nephthenol (**6**), nephtheoxydiol (**8**), nephthediol (**9**), and nephthene (**17**) have been determined as (+)-oplopanone (**2**), (4*R*,7*S*)-germacra-1(10)*E*,5*E*-dien-4-ol (**6**), (1*S*,4*R*,7*S*)-1-hydroperoxygermacra-5*E*,10(15)-dien-4-ol (**8**), (1*S*,4*R*,7*S*)-germacra-5*E*,10(15)-diene-1,4-diol (**9**), and (1*S*,7*R*,10*S*)-cadina-4(14),5-diene (**17**), respectively.

Keywords——soft coral; *Nephthea* sp.; Nephtheidae; nephtheoxydiol; germacrane sesquiterpene hydroperoxylated; nephthenol; nephthediol; *ent*-oplopanone; nephthene; cytotoxic activity

During the course of our studies on bioactive constituents of marine organisms,[2] we isolated a trinorsesquiterpene named clavukerin C (**1**) from the Okinawan stoloniferan soft coral *Clavularia koellikeri* and determined the absolute stereostructure, which was characterized by the presence of a hydroperoxy function.[3] In a continuing study on chemical constituents of an Okinawan soft coral of *Nephthea* sp. (family: Nephtheidae, order: Alcyonacea), we have isolated a new cytotoxic germacrane-sesquiterpene named nephtheoxydiol (**8**) and several related sesquiterpenoids, *ent*-oplopanone (**2**), nephthenol (**6**), and nephthediol (**9**), together with a new cadinane-type sesquiterpene named nephthene (**17**). This paper deals with the structure elucidation of these sesquiterpenoids.[4]

The acetone extract of a fresh soft coral, collected in July 1984 at Iriomote-jima, Okinawa Prefecture, was partitioned into an ethyl acetate–water mixture. The ethyl acetate-soluble portion was subjected to silica gel column chromatography and high-performance liquid chromatography (HPLC) to furnish nephthene (**17**), nephthenol (**6**), nephtheoxydiol (**8**), *ent*-oplopanone (**2**), and nephthediol (**9**) in 11.0, 6.5, 1.5, 0.4, and 0.5% yields (from the ethyl acetate-soluble portion).

ent-Oplopanone (**2**) was obtained as colorless needles. The physicochemical properties of **2** except for the sign of its specific rotation were found to be identical with those reported for oplopanone (**3**), which was previously isolated from a terrestrial plant, *Oplopanax japonicus* (Araliaceae).[5] Furthermore, a dehydration product (**4**), which was prepared by phosphorus oxychloride treatment of *ent*-oplopanone (**2**), was found to be identical with (−)-anhydro-oplopanone (**5**), previously isolated from another terrestrial plant, *Rugelia nudicaulis* (Compositae),[6] in all respects except for the sign of the specific rotation. Therefore, we

concluded that *ent*-oplopanone (**2**) isolated from a soft coral of *Nephthea* sp. is an enantiomer of oplopanone (**3**) found in a terrestrial plant.

Nephthenol (**6**) is a sesquiterpene alcohol. The proton nuclear magnetic resonance (^{1}H-NMR) spectrum of **6** showed the presence of a *transoid* disubstituted double bond (δ 5.25, 1H, d, J=16.0 Hz; δ 5.18, 1H, dd, J=16.0, 9.5 Hz), a trisubstituted double bond (δ 4.95, 1H, br d, J=*ca.* 11.5 Hz), an olefinic methyl group (δ 1.54, 3H, s), a tertiary methyl group geminal to a hydroxyl group (δ 1.19, 3H, s), and an isopropyl moiety (δ 0.79, 0.83, both 3H, d, J= 7.0 Hz). In addition to these findings, detailed analysis of the carbon-13 nuclear magnetic resonance (^{13}C-NMR) spectrum of **6** led us to formulate nephthenol as **6**, except for its configuration.

Oxidation of nephthenol (**6**) with *m*-chloroperbenzoic acid (*m*-Cl-PBA) in chloroform provided *ent*-oplopanone (**2**). This conversion is considered to proceed successively *via*: i) epoxidation at the 1(10) double bond, ii) epoxide-ring opening concerted with the 1(6) bond formation, followed by another epoxide-ring formation, and iii) ring contraction constructing a five-membered ring with a methylketone moiety (*cf.* **i**, **ii**). Therefore, it has become clear that nephthenol (**6**) is a germacrane-type sesquiterpene having a 1(10)*E*,5*E*-dien-4-ol moiety and a 7*S* configuration.

In order to determine the C-4 configuration of nephthenol (**6**), **6** was oxidized with *tert*-butyl hydroperoxide in the presence of vanadium(IV) oxyacetylacetonate [$VO(acac)_2$][7] to afford an α-glycol derivative (**7**). The α-glycol (**7**) was presumably formed *via*: i) initial α-epoxidation at the 5(6) double bond, ii) epoxide-ring opening followed by 1(6) bond formation, and finally iii) deprotonation at C-15 to generate the 10(15) terminal methylene moiety (*cf.* **iii**).

In a nuclear Overhauser effect (NOE) experiment on **7**, irradiation of 4-CH_3 (δ 1.07) resulted in increased signal intensities of 1β-H (δ 1.40, dd-like, J=*ca.* 12.0, 10.0 Hz) (9%) and

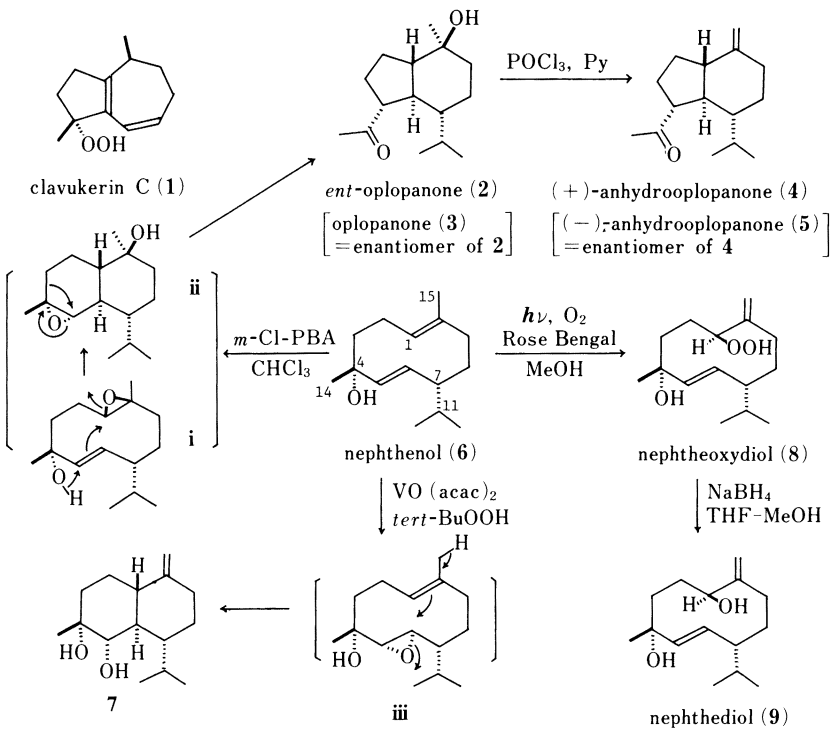


Chart 1

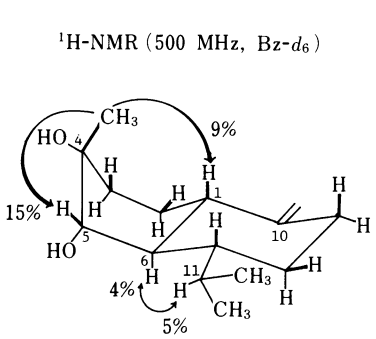


Fig. 1. NOE (%) of **7**
Bz = benzene.

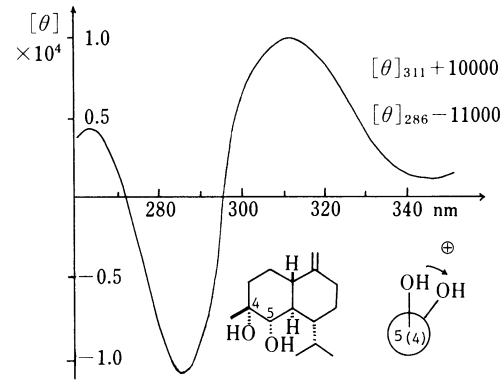


Fig. 2. The CD Curve of a Mixture of **7** (1.5×10^{-4} M) and Eu(fod)$_3$ (1.5×10^{-4} M)

5β-H (δ 2.85, br dd-like) (15%), whereas irradiation of 6α-H (δ 1.29, ddd, $J_{6,1} = J_{6,5} = 9.0$ Hz, $J_{6,7} = 10.5$ Hz) resulted in a 5% increase of 11-H (δ 2.67, m) and a 4% increase was observed for 6-H upon irradiation of 11-H (Fig. 1). These findings show that the A-ring with the α-glycol moiety in **7** takes a boat-like conformation in solution. The circular dichroism (CD) spectrum of **7** taken by the α-glycol chirality method[8] showed a positive first Cotton effect: $[\theta]_{311}$ +10000 (Fig. 2), indicating the 4*R* configuration in **7** and consequently in nephthenol (**6**). Thus, we concluded that the structure of nephthenol is 4*R*,7*S*-germacra-1(10)*E*, 5*E*-dien-4-ol (**6**).

Nephtheoxydiol (**8**) has a hydroperoxy residue in its molecule as shown by its positive responses to the *N*,*N*-dimethyl-*p*-phenylenediammonium dichloride reagent[3,9] and the ferrous thiocyanate reagent.[3,10] The chemical ionization mass spectrum (CI-MS) of **8** gave the ($M^+ + H$) ion peak at *m*/*z* 255, which shows that **8** is a sesquiterpene having one hydroxyl group and one hydroperoxyl group.

The ^{1}H-NMR spectrum of nephtheoxydiol (**8**) showed the presence of a *transoid* disubstituted double bond (δ 5.38, 1H, d, $J = 15.5$ Hz; δ 5.70, 1H, dd, $J = 15.5$, 10.0 Hz), a tertiary methyl residue geminal to a hydroxyl group (δ 1.47, 3H, s), an isopropyl residue (δ 0.83, 0.87, both 3H, d, $J = 6.5$ Hz), a terminal methylene moiety (δ 5.14, 5.42, both 1H, s), and a secondary hydroperoxyl residue (δ 4.55, 1H, br d, $J = ca.$ 6.5 Hz). The ^{13}C-NMR spectrum of **8** also showed signals due to a carbon bearing a secondary hydroperoxyl residue [δ_c 93.0 (d)].[3] It was presumed therefore that nephtheoxydiol (**8**) is an oxygenated derivative of nephthenol (**6**). In order to verify this presumption, nephthenol (**6**) was subjected to photosensitized oxygenation in the presence of Rose Bengal in a Pyrex tube.[3,11] The product obtained in high yield was shown to be identical with nephtheoxydiol (**8**). Thus, it has become clear that the structure of nephtheoxydiol corresponds to **8** having a 1-hydroperoxy-10(15)-ene moiety, except for its C-1 configuration.

Nephthediol (**9**) is a sesquiterpene diol. The ^{1}H- and ^{13}C-NMR spectra of **9** were very similar to those of nephtheoxydiol (**8**) except that the former showed signals due to H-1 and C-1 at δ 3.93 (1H, dd, $J = 9.0$, 3.0 Hz) and δ_c 78.7 (d), respectively. Therefore, nephthediol (**9**) appears to be the 1-hydroxy counterpart of nephtheoxydiol (**8**). In fact, sodium borohydride reduction of **8** afforded **9** quantitatively. Thus, the structure of nephthediol can be formulated as **9**, except for the C-1 configuration. This formulation of **9** was further supported by the fact that oxidation of nephthediol under Moffatt conditions[12] provided **4**, the anhydro derivative of *ent*-oplopanone (**2**). The conversion from nephthediol (**9**) to **4** is considered to proceed *via*: i) initial elimination of the 1-OH group followed by 1(6) bond formation and epoxide-ring

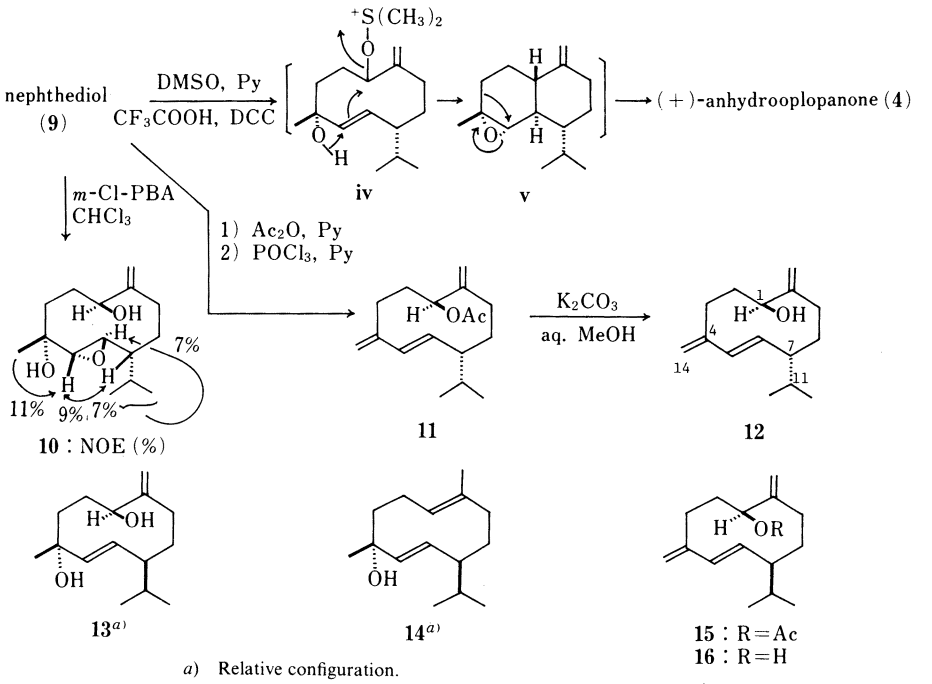
formation, and ii) ring contraction constructing a five-membered ring with a methylketone moiety (*cf.* **iv**, **v**).

In order to determine the C-4 configuration of nephthediol (**9**), **9** was epoxidized with *m*-Cl-PBA to afford the 5,6-epoxide (**10**). In the NOE experiments on **10**, irradiation of 4-CH_3 (δ 1.27) increased by 11% the signal intensity of 5-H (δ 2.54, d, J=2.0 Hz) whereas irradiation of 5-H increased by 7% the signal intensity of 7-H (δ 1.18, m). Furthermore, irradiation of 7-H resulted in 9% NOE for 5-H while irradiation of the two 11-CH_3 signals (δ 0.97, 3H, d, J= 6.5 Hz; δ 0.98, 3H, d, J=7.0 Hz) caused 7% NOE for 6-H (δ 2.93, dd, J=9.5, 2.0 Hz). These results substantiate the 4*R* configuration in nephthediol (**9**) and consequently in nephthenol (**6**) and nephtheoxydiol (**8**).

Next, the C-1 configuration in nephtheoxydiol (**8**) and nephthediol (**9**) was investigated. Acetylation of nephthediol (**9**) followed by dehydration with phosphorus oxychloride afforded a trienol acetate (**11**). Deacetylation of **11** furnished the trienol (**12**). Examination in detail of the ^{1}H-NMR spectrum of **12** allowed us to assign all the proton signals (see Experimental). Furthermore, in the NOE experiments on **12**, irradiation of 1-H (δ 4.08, dd, J=11.5, 4.0 Hz) caused 5% increases of 5-H (δ 6.01, d, J=16.0 Hz) and 9-Hb (δ 1.79, ddd, J= 14.0, 12.0, *ca.* 2.0 Hz), whereas irradiation of 5-H increased signals due to 1-H (3%), 14-Ha (δ 4.96, s) (5%), and 7-H (δ 1.67, dddd, J=10.5, 10.5, 6.5, 4.5 Hz) (8%). Further detailed NOE experiments on **12**, indicated that the conformation of **12** is as shown in Fig. 3, and consequently the 1*S* configuration has been determined. This conclusion was further supported by applying Horeau's method[13] to nephthediol (**9**) and **12**, where recovered α-phenylbutyric acid showed $[\alpha]_D$ $-13.5°$ (from **9**) and $[\alpha]_D$ $-2.5°$ (from **12**).

Based on the above evidence, the absolute stereostructures of nephtheoxydiol and nephthediol were concluded to be (1*S*,4*R*,7*S*)-1-hydroperoxygermacra-5*E*,10(15)-dien-4-ol (**8**) and (1*S*,4*R*,7*S*)-germacra-5*E*,10(15)-diene-1,4-diol (**9**), respectively.

A sesquiterpene dienediol (**13**) was isolated from the red alga *Laurencia subopposita*[14]



a) Relative configuration.

Chart 2

^{1}H-NMR [500 MHz, Bz-d_6-Py-d_5 (1 : 1)]

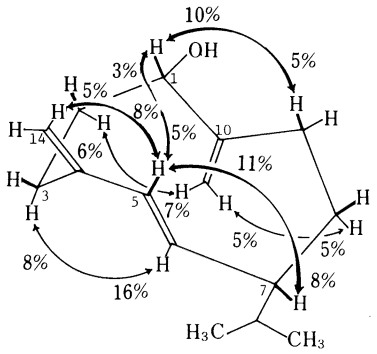


Fig. 3. NOE (%) of **12**
Py = pyridine

^{1}H-NMR (500 MHz, Bz-d_6 or Py-d_5)

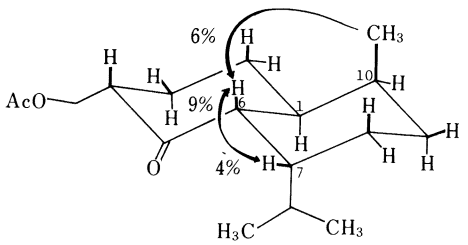


Fig. 4. NOE (%) of **21**

and a sesquiterpene dienol (**14**) was isolated from the soft coral *Lemnalia africana*,[15] and their relative configurations were proposed to be as shown.[14,15] Physical data reported for **13** and **14** including the signs of $[\alpha]_D$ values were found to be identical with those of present nephthediol (**9**) and nephthenol (**6**), respectively. Therefore, re-examination of the structures proposed for **13** and **14** seems to be necessary. Furthermore, there was a report on the structure elucidation of a germacrane-type trienol acetate (**15**), which was isolated from the brown alga *Dilophus fasciola*.[16] The structures proposed for **15** and its deacetylated product (**16**) are diastereomeric to the present trienol acetate (**11**) and its deacetylated product (**12**), respectively. Since there is some ambiguity in the presentation[16] and the reported data for **15** and **16** are similar to those for **11** and **12** except for the sign of the specific rotation, re-examination of the structure proposed for **15** also seems to be appropriate.

Nephthene (**17**) is a cadinane-type sesquiterpene having a conjugated diene chromophore, as shown by its ultraviolet (UV) maximum at 240 nm ($\varepsilon = 20000$). The ^{1}H-NMR spectrum of nephthene (**17**) showed the presence of a terminal methylene moiety (δ 4.63, 4.68, both 1H, s), a trisubstituted double bond (δ 5.99, 1H, s), an isopropyl residue (δ 0.76, 0.93, both 3H, d, $J = 6.5$ Hz), and a secondary methyl residue (δ 0.87, 3H, d, $J = 6.0$ Hz). Thus, nephthene (**17**) has a bicarbocyclic skeleton.

Dehydrogenation of nephthene (**17**) with 10% palladium–carbon in boiling diethyleneglycol dimethyl ether provided cadalene (**18**).[17] Oxidation of nephthene (**17**) with osmium tetroxide–sodium periodate yielded the norenone (**19**). In the ^{1}H-NMR spectrum of **19**, irradiation of 1α-H (δ 2.59, dddd, $J = 5.0$, 5.0, 5.0, 2.0 Hz) resulted in 5% NOE for 10α-H (δ 2.17, m) whereas irradiation of 10α-H caused 7% NOE for 1α-H. Thus, the relative configurations of 1α-H and 10α-H were determined.

Hydroboration-oxidation of nephthene (**17**) furnished a diol (**20**). In the ^{1}H-NMR spectrum of **20**, both $J_{4,5}$ and $J_{5,6}$ were observed at 9.5 Hz, so that the *trans*-diaxial correlations of 4-H/5-H and 5-H/6-H were established. Mild acetylation of **20** followed by pyridinium chlorochromate (PCC) oxidation yielded a keto-alcohol acetate (**21**). In the ^{1}H-NMR spectrum of **21**, the coupling constant between 6β-H and 1α-H was 12.5 Hz whereas the J value between 6β-H and 7β-H was 3.5 Hz, so that the *trans*-diaxial correlation of 1α-H and 6β-H and the axial-equatorial correlation of 6β-H and 7β-H were proven. Furthermore, irradiation of 6β-H caused 4% NOE for 7β-H and irradiation of 7β-H resulted in 9% NOE for 6β-H (in benzene-d_6). Irradiation of 10β-CH_3 (δ 0.80, d, $J = 7.0$ Hz) caused 6% NOE for 6β-H (δ 2.18, dd, $J = 12.5$, 3.5 Hz) in pyridine-d_5 (Fig. 4). The CD spectrum of **21** showed

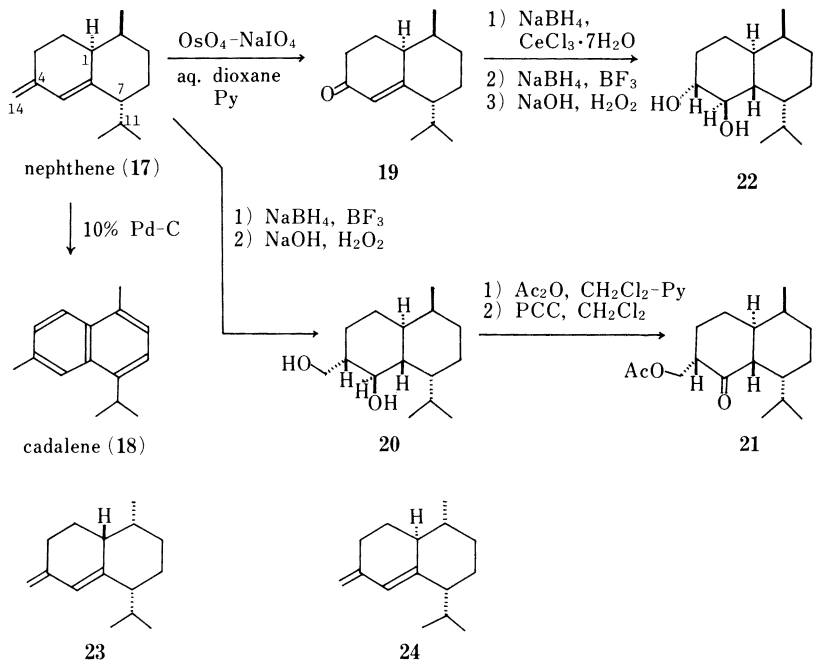


Chart 3

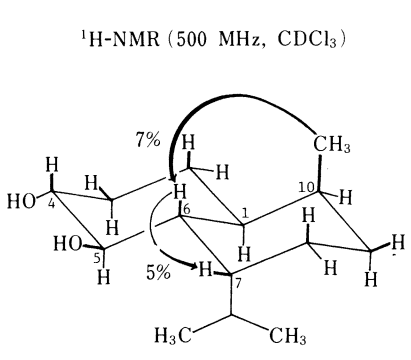


Fig. 5. NOE (%) of **22**

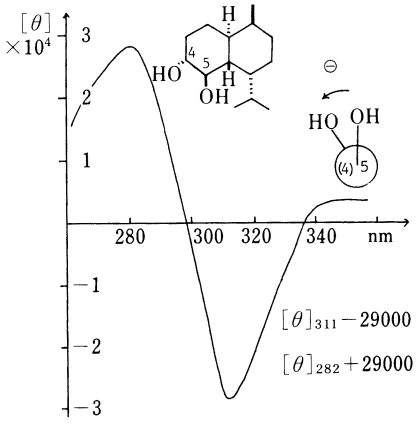


Fig. 6. The CD Curve of a Mixture of **22** (1.5×10^{-4} M) and Eu(fod)$_3$ (1.5×10^{-4} M)

a positive maximum: $[\theta]_{297}$ +4000 due to the 5-CO moiety. These results established the 1*S*, 4*S*, 6*S*, 7*R*, and 10*S* configurations in **21**.

Reduction of the norenone (**19**) with sodium borohydride in the presence of cerous chloride hydrate and subsequent hydroboration-oxidation, provided the nor-*trans*-α-glycol (**22**). The ^{1}H-NMR spectrum of **22** showed signals due to 1α-H (δ 1.63, ddd, J=12.0, 10.5, 4.5 Hz), 4β-H (δ 3.34, ddd, J=11.0, 10.0, 4.5 Hz), 5α-H (δ 3.40, dd, J=10.0, 9.0 Hz), 6β-H (δ 1.54, ddd, J=12.0, 9.0, 5.0 Hz), and 7β-H (δ 1.79, m). The coupling constants between 4-H and 5-H (10.0 Hz), between 5-H and 6-H (9.0 Hz), between 1-H and 6-H (12.0 Hz), and between 6-H and 7-H (5.0 Hz), indicated *trans*-diaxial correlations of 4-H/5-H, 5-H/6-H, and

1-H/6-H, and the axial-equatorial correlation of 6-H/7-H. Furthermore, irradiation of 10-CH_3 (δ 0.87, d, J=7.0 Hz) caused 7% NOE for 6-H (Fig. 5). The CD spectrum of **22** taken by the α-glycol chirality method[8] showed a negative first Cotton effect ($[\theta]_{311}$ −29000) (Fig. 6). Thus, **22** has 1*S*, 4*R*, 5*R*, 6*S*, 7*R*, and 10*S* configurations, and consequently, the absolute configuration of **21** has been further substantiated.

Based on the above evidence, the absolute stereostructure of nephthene is 1*S*,7*R*,10*S*-cadina-4(14),5-diene (**17**).

Several examples of naturally occurring sesquiterpenes having a cadina-4(14),5-diene structure are known: *e.g.* bicyclosesquiphellandrene (**23**)[18] from the terrestrial plant *Piper cubeba* (Piperaceae)[19] and 1-*epi*-bicyclosesquiphellandrene (**24**)[18] from the terrestrial plant *Ocimum basilicum* (Labiatae)[19] and from the brown alga *Dilophus fasciola*.[20] It should be pointed out here that nephtheoxydiol (**8**) having a hydroperoxyl function was found to exhibit a significant growth-inhibitory effect on B-16 melanoma cells (IC_{50} 0.1 μg/ml). However, the other four sesquiterpenes described in this paper did not exhibit such an effect, so that the physiological function of the hydroperoxyl residue may be an interesting subject for future study.

Experimental

The instruments used to obtain physical data and the experimental conditions for chromatography were the same as described in our previous paper.[1]

Isolation of Nephthene (17), Nephthenol (6), Nephtheoxydiol (8), *ent*-Oplopanone (2), and Nephthediol (9)——The fresh, soft coral (360 g) of *Nephthea* sp. (Neph-84-IRI-1),[21] which was collected at Iriomote-jima, Okinawa Prefecture, in July 1984, was cut finely and immersed in acetone at room temperature (25 °C). The acetone solution was concentrated under reduced pressure at below 30 °C. The acetone extract thus obtained was partitioned into an AcOEt–H_2O mixture. Removal of the solvent under reduced pressure from the AcOEt-soluble portion afforded the AcOEt extract (4 g). Column chromatography (SiO_2 200 g, 60—230 mesh, Merck) of the AcOEt extract furnished a nephthene fraction (600 mg) (by eluting with *n*-hexane), a nephthenol fraction (300 mg) (by eluting with *n*-hexane–AcOEt=20:1), a nephtheoxydiol fraction (100 mg) and an *ent*-oplopanone fraction (80 mg) (by eluting with *n*-hexane–AcOEt=2:1), and a nephthediol fraction (60 mg) (by eluting with *n*-hexane–AcOEt=1:1). The fraction containing nephthene (600 mg) was purified with a Lobar column [LiChroprep Si 60 (40—63 μm), *n*-hexane] to furnish nephthene (**17**) (460 mg). The nephthenol containing fraction (300 mg) was purified by HPLC (Semi Prep Zorbax SIL, *n*-hexane–AcOEt=20:1) to furnish nephthenol (**6**) (270 mg). The fraction containing nephtheoxydiol (100 mg) was purified by column chromatography (SiO_2 40 g, *n*-hexane–AcOEt=2:1) again and then by HPLC (Semi Prep Zorbax ODS, MeOH–H_2O=8:1) to afford nephtheoxydiol (**8**) (60 mg). The *ent*-oplopanone fraction (80 mg) was also purified by column chromatography (SiO_2 30 g, *n*-hexane–AcOEt=2:1) again and then by HPLC (Semi Prep Zorbax ODS, MeOH–H_2O=6:1) to afford *ent*-oplopanone (**2**) (14 mg). The nephthediol fraction (60 mg) was purified again by column chromatography (SiO_2 20 g, *n*-hexane–AcOEt=1:1) and then by HPLC (Semi Prep Zorbax SIL, *n*-hexane–AcOEt=1:1) to furnish nephthediol (**9**) (20 mg). Nephthene (**17**), colorless oil, $[\alpha]_D^{20}$ −9° (c=5.3, $CHCl_3$). High-resolution MS: Found 204.188. Calcd for $C_{15}H_{24}$ (M^+)=204.188. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1637, 1600, 893. UV λ_{max}^{MeOH} nm (ε): 240 (20000). CD ($c=3.3\times10^{-2}$, MeOH): $[\theta]_{265}$ 0, $[\theta]_{240}$ −17000 (neg. max.), $[\theta]_{215}$ 0, $[\theta]_{200}$ +21000! ^{1}H-NMR (500 MHz, $CDCl_3$, δ): 2.33 (2H, overlapped, 1,7-H), 5.99 (1H, s, 5-H), 1.96 (1H, m, 10-H), 0.76, 0.93 [both 3H, d, J=6.5 Hz, 11-$(CH_3)_2$], 0.87 (3H, d, J=6.0 Hz, 10-CH_3), 4.63, 4.68 (both 1H, s, 14-H_2). ^{13}C-NMR (22.5 MHz, $CDCl_3$, δ_c): 144.2 (s), 144.0 (s), 126.8 (d), 51.3 (d), 37.2 (d), 34.9 (d), 27.4 (d), 108.1 (t), 29.7 (t), 29.5 (t), 27.3 (t), 22.9 (t), 21.8 (q), 21.3 (q), 14.8 (q). MS m/z (%): 204 (M^+, 18), 161 ($M^+-C_3H_7$, 100). Nephthenol (**6**), colorless oil, $[\alpha]_D^{20}$ +184° (c=3.1, $CHCl_3$). High-resolution MS: Found 222.196. Calcd for $C_{15}H_{26}O$ (M^+)=222.198. IR ν_{max}^{film} cm^{-1}: 3470. CD ($c=3.7\times10^{-2}$, MeOH): $[\theta]_{265}$ 0, $[\theta]_{229}$ +48000 (pos. max.), $[\theta]_{200}$ +10000! ^{1}H-NMR (500 MHz, $CDCl_3$, δ): 4.95 (1H, br d, J=11.5 Hz, 1-H), 5.25 (1H, d, J=16.0 Hz, 5-H), 5.18 (1H, dd, J=16.0, 9.5 Hz, 6-H), 1.19 (3H, s, 4-CH_3), 1.54 (3H, s, 10-CH_3), 0.79, 0.83 [both 3H, d, J=7.0 Hz, 11-$(CH_3)_2$]. ^{13}C-NMR (22.5 MHz, $CDCl_3$, δ_c): 129.0 (d, C-1), 23.7 (t, C-2), 41.3 (t, C-3), 72.9 (s, C-4), 140.0 (d, C-5), 125.9 (d, C-6), 52.9 (d, C-7), 39.7 (t, C-8), 26.1 (t, C-9), 132.3 (s, C-10), 33.0 (d, C-11), 19.0 (q, C-12), 20.6 (q, C-13), 30.9 (q, C-14), 16.6 (q, C-15). MS m/z (%): 222 (M^+, 4), 207 (M^+-CH_3, 16), 204 (M^+-H_2O, 11), 179 ($M^+-C_3H_7$, 5), 161 ($M^+-H_2O-C_3H_7$, 30), 81 (100). Nephtheoxydiol (**8**), colorless amorphous, $[\alpha]_D^{21}$ +14° (c=1.2, $CHCl_3$). High-resolution MS: Found 236.180. Calcd for $C_{15}H_{24}O_2$ (M^+-H_2O)=236.178. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3600, 3530, 3312 (br). CD ($c=2.9\times10^{-2}$, MeOH): $[\theta]_{248}$ 0, $[\theta]_{215}$ −21000 (neg. max.), $[\theta]_{208}$ 0. ^{1}H-NMR (500 MHz, pyridine-d_5, δ): 4.55 (1H, br d, J=*ca.* 6.5 Hz, 1-H), 5.38 (1H, d, J=15.5 Hz, 5-H), 5.70 (1H, dd, J=15.5, 10.0 Hz, 6-H), 5.14, 5.42 (both 1H, s, 15-H_2), 0.83, 0.87 [both 3H, d,

J=6.5 Hz, 11-$(CH_3)_2$], 1.47 (3H, s, 4-CH_3). ^{13}C-NMR (22.5 MHz, $CDCl_3$, δ_c): 149.1 (s, C-10), 72.5 (s, C-4), 137.0, 131.3 (both d, C-5, 6), 93.0 (d, C-1), 50.9 (d, C-7), 32.3 (d, C-11), 114.8 (t, C-15), 40.3, 33.0, 32.3, 25.5 (all t, C-2, 3, 8, 9), 29.8 (q, C-14), 20.7, 20.3 (both q, C-12, 13). CI-MS (isobutane) m/z (%): 255 (M^++H, 2), 237 (255−H_2O, 17), 221 (255−H_2O_2, 22), 219 (255−$2H_2O$, 35). *ent*-Oplopanone (**2**), colorless needles (from petr. ether), mp 83—84 °C, $[\alpha]_D^{22}$ +19° (c=0.8, dioxane). High-resolution MS: Found 238.195. Calcd for $C_{15}H_{26}O_2$ (M^+)=238.193. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3600, 1700. CD ($c=1.3\times10^{-1}$, dioxane): $[\theta]_{286}$ +3400 (pos. max.), $[\theta]_{237}$ 0. ^{1}H-NMR (500 MHz, $CDCl_3$, δ): 2.65 (1H, ddd, J=10.5, 10.5, 5.5 Hz, 3-H), 2.19 (3H, s, 4-CH_3), 1.20 (3H, s, 9-CH_3), 0.69, 0.89 [both 3H, d, J=7.0 Hz, 11-$(CH_3)_2$]. ^{13}C-NMR (22.5 MHz, $CDCl_3$, δ_c): 211.2 (s, C-4), 73.0 (s, C-9), 57.2, 55.9, 46.8 (all d, C-3, 5, 10), 49.6 (d, C-6), 29.6 (d, C-11), 42.2, 28.7, 25.4, 23.1 (all t, C-1, 2, 7, 8), 29.5 (q, C-14), 22.0, 15.7 (both q, C-12, 13), 20.4 (q, C-15). MS m/z (%): 238 (M^+, 8), 223 (M^+-CH_3), 220 (M^+-H_2O, 2), 205 ($M^+-CH_3-H_2O$, 2), 177 ($M^+-C_3H_7-H_2O$, 7), 153 (100). Nephthediol (**9**), colorless amorphous, $[\alpha]_D^{21}$ +82° (c=1.2, $CHCl_3$). High-resolution MS: Found 238.195. Calcd for $C_{15}H_{26}O_2$ (M^+)=238.193. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3600, 3440 (br). CD ($c=2.7\times10^{-2}$, MeOH): $[\theta]_{230}$ 0, $[\theta]_{218}$ −5000 (neg. max.), $[\theta]_{212}$ 0. ^{1}H-NMR (500 MHz, $CDCl_3$, δ): 3.93 (1H, dd, J=9.0, 3.0 Hz, 1-H), 5.21 (1H, d, J=15.5 Hz, 5-H), 5.29 (1H, dd, J=15.5, 10.0 Hz, 6-H), 4.89, 5.12 (both 1H, s, 15-H_2), 1.26 (3H, s, 4-CH_3), 0.84, 0.89 [both 3H, d, J=6.5 Hz, 11-$(CH_3)_2$]. ^{13}C-NMR (22.5 MHz, $CDCl_3$, δ_c): 151.1 (s, C-10), 72.3 (s, C-4), 137.7, 129.9 (both d, C-5, 6), 78.7 (d, C-1), 49.9 (d, C-7), 32.4 (d, C-11), 111.4 (t, C-15), 38.7, 30.0, 28.4, 28.4 (all t, C-2, 3, 8, 9), 29.5 (q, C-14), 20.6, 20.6 (both q, C-12, 13). MS m/z (%): 238 (M^+, 2), 220 (M^+-H_2O, 10), 205 ($M^+-H_2O-CH_3$, 9), 202 (M^+-2H_2O, 7), 177 ($M^+-C_3H_7-H_2O$, 49), 81 (100).

Dehydration of *ent*-Oplopanone (2) Giving (+)-Anhydrooplopanone (4)——An ice-cooled solution of **2** (13 mg) in dry pyridine (1 ml) was treated with $POCl_3$ (3 drops) under a nitrogen atmosphere and stirred for 30 min. The reaction mixture was stirred at room temperature (15 °C) for a further 8 h, then poured into water. The whole was extracted with AcOEt. The AcOEt extract was washed with aq. sat. NaCl and dried over $MgSO_4$. Removal of the solvent under reduced pressure from the AcOEt extract afforded a product, which was purified by column chromatography (SiO_2 2 g, *n*-hexane–AcOEt=8:1) to furnish (+)-anhydrooplopanone (**4**) (9 mg). **4**, colorless needles (from petr. ether), mp 70—71 °C, $[\alpha]_D^{18}$ +14° (c=0.5, $CHCl_3$). High-resolution MS: Found 220.182. Calcd for $C_{15}H_{24}O$ (M^+)=220.183. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3075, 1711, 1651, 891. ^{1}H-NMR (500 MHz, $CDCl_3$, δ): 4.56, 4.67 (both 1H, d, J=2.0 Hz, 15-H_2), 2.19 (3H, s, 4-CH_3), 0.91 (3H, d, J=7.0 Hz, 11-CH_3), 0.66 (3H, d, J=6.5 Hz, 11-CH_3). ^{13}C-NMR (22.5 MHz, $CDCl_3$, δ_c): 211.6 (s, C-4), 150.9 (s, C-9), 56.2 (d, C-3), 52.2 (d, C-5), 52.0 (d, C-10), 49.5 (d, C-6), 29.7 (d, C-11), 103.6 (t, C-15), 35.4 (t, C-8), 28.6 (t, C-2), 27.4 (t, C-1), 26.7 (t, C-7), 28.9 (q, C-14), 22.0, 15.8 (both q, C-12, 13). MS m/z (%): 220 (M^+, 12), 205 (M^+-CH_3, 7), 187 ($M^+-CH_3-H_2O$), 177 ($M^+-C_3H_7$, 85), 43 (100).

Oxidation of Nephthenol (6) with *m*-Cl-PBA Giving *ent*-Oplopanone (2)——An ice-cooled solution of **6** (40 mg) in $CHCl_3$ (1 ml) was treated with *m*-Cl-PBA (118 mg, 1.5 eq) and stirred for 2 h. The reaction mixture was poured into ice-water and the whole was extracted with AcOEt. The AcOEt extract was washed with aq. sat. NaCl and dried over $MgSO_4$. Removal of the solvent under reduced pressure from the AcOEt extract gave a product, which was purified first by column chromatography (SiO_2 5 g, *n*-hexane–AcOEt=2:1) and then with a Lobar column (LiChroprep Si 60, *n*-hexane–AcOEt=2:1) to furnish *ent*-oplopanone (**2**) (8 mg). **2** thus obtained was shown to be identical with an authentic sample by mixed melting point determination and $[\alpha]_D$, ^{1}H-NMR (90 MHz, $CDCl_3$), and ^{13}C-NMR (22.5 MHz, $CDCl_3$) comparisons.

Oxidation of Nephthenol (6) with $VO(acac)_2$-*tert*-BuOOH Giving 7——A solution of **6** (50 mg) in benzene (1 ml) was treated with $VO(acac)_2$ (0.6 mg, 0.01 eq) and then with a solution of aq. 70% *tert*-BuOOH (32 mg, 1.1 eq) in benzene (1 ml) and the whole mixture was stirred at room temperature (25 °C) for 3 h. Work-up of the reaction mixture as described above for *m*-Cl-PBA oxidation yielded a product, which was purified by column chromatography (SiO_2 6 g, *n*-hexane–AcOEt=7:1) and HPLC (Semi Prep Zorbax ODS, MeOH–H_2O=10:1) to furnish the α-glycol (**7**) (15 mg). **7**, colorless amorphous, $[\alpha]_D^{25}$ +4.5° (c=0.9, $CHCl_3$). High-resolution MS: Found 220.184. Calcd for $C_{15}H_{24}O$ (M^+-H_2O)=220.183. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3620, 3560 (br), 3457 (br), 1644, 893. ^{1}H-NMR (500 MHz, benzene-d_6, δ): 1.40 (1H, dd-like, J=*ca*. 12.0, 10.0 Hz, 1-H), 2.85 (1H, br dd-like, 5-H), 1.29 (1H, ddd, J=10.5, 9.0, 9.0 Hz, 6-H), 1.22 (1H, dddd, J=10.5, 10.5, 3.0, 3.0 Hz, 7-H), 2.67 (1H, m, 11-H), 0.98 (3H, d, J=7.0 Hz, 11-CH_3), 0.86 (3H, d, J=6.5 Hz, 11-CH_3), 4.69, 4.77 (both 1H, d, J=1.5 Hz, 15-H_2), 1.07 (3H, s, 4-CH_3). ^{1}H-NMR (500 MHz, $CDCl_3$, δ): 1.64 (2H overlapped, 1-H), 3.22 (1H, dd, J=9.0, 8.5 Hz, 5-H), 2.15 (1H, d, J=8.5 Hz, 5-OH). ^{13}C-NMR (22.5 MHz, $CDCl_3$, δ_c): 152.2 (s), 72.3 (s), 79.2 (d), 49.3 (d), 48.4 (d), 45.5 (d), 28.6 (d), 104.5 (t), 37.2 (t), 35.5 (t), 26.0 (t), 23.2 (t), 28.0 (q), 22.3 (q), 16.8 (q). MS m/z (%): 220 (M^+-H_2O, 100), 202 (M^+-2H_2O, 25), 177 ($M^+-H_2O-C_3H_7$, 25), 159 ($M^+-2H_2O-C_3H_7$, 51).

CD Spectrum of 7 Taken by the α-Glycol Chirality Method——**7** (0.357 mg, 1.5×10^{-4} M) was dissolved in a solution of tris(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octane-dionato)europium [Eu(fod)$_3$] (1.5×10^{-4} M) in CCl_4 (10 ml) [prepared from Eu(fod)$_3$ (155 mg) and dry CCl_4 (10 ml)]. After 30 min, the CD spectrum of the solution was measured. CD ($c=1.6\times10^{-1}$, CCl_4): $[\theta]_{311}$ +10000 (pos. max.), $[\theta]_{295}$ 0, $[\theta]_{286}$ −11000 (neg. max.), $[\theta]_{272}$ 0.

Photosensitized Oxygenation of Nephthenol (6) Giving Nephtheoxydiol (8)——A solution of **6** (20 mg) and Rose Bengal (5 mg) in MeOH (5 ml) was put in a Pyrex tube and cooled (0 °C). While bubbling with a stream of oxygen, the cooled solution was irradiated with a 100 W high-pressure Hg lamp for 10 min. The residue, obtained by removal of the solvent, was purified by column chromatography (SiO_2 5 g, *n*-hexane–AcOEt=2:1) and then with a Lobar

column [LiChroprep Si 60 (40—63 μm), *n*-hexane–AcOEt = 3 : 1) to furnish nephtheoxydiol (**8**) (20 mg). Nephtheoxydiol (**8**) thus obtained was shown to be identical with an authentic sample by $[\alpha]_D$, MS, ^{1}H-NMR (90 MHz, $CDCl_3$), and ^{13}C-NMR (22.5 MHz, $CDCl_3$) comparisons.

$NaBH_4$ Reduction of Nephtheoxydiol (8) Giving Nephthediol (9)——An ice-cooled solution of **8** (20 mg) in tetrahydrofuran (THF)–MeOH (2 : 1) (1 ml) was treated under a nitrogen atmosphere with $NaBH_4$ (10 mg) and stirred for 30 min. The reaction mixture was poured into ice-water and the whole was extracted with AcOEt. The AcOEt extract was washed with aq. sat. NaCl and dried over $MgSO_4$. Removal of the solvent under reduced pressure from the AcOEt extract gave a product, which was purified by column chromatography (SiO_2 5 g, *n*-hexane–AcOEt = 1 : 1) to furnish nephthediol (**9**) (14 mg). Nephthediol (**9**) obtained here was shown to be identical with an authentic sample by $[\alpha]_D$, MS, ^{1}H-NMR (90 MHz, $CDCl_3$), and ^{13}C-NMR (22.5 MHz, $CDCl_3$) comparisons.

Oxidation of Nephthediol (9) under Moffatt Conditions Giving (+)-Anhydrooplopanone (4)——Under a nitrogen atmosphere, **9** (50 mg) was dissolved in dry CH_2Cl_2 (850 μl) and the solution was treated successively with dimethyl sulfoxide (distilled before use, 850 μl), pyridine (distilled before use, 15 μl), CF_3COOH (10 μl), and dicyclohexylcarbodiimide (DCC) (125 mg). The whole was stirred at room temperature (25 °C) for 10 h. The reaction mixture was concentrated under reduced pressure, and the resulting product was purified by column chromatography (SiO_2 10 g, *n*-hexane–AcOEt = 10 : 1) and then with a Lobar column (LiChroprep Si 60, *n*-hexane–AcOEt = 10 : 1) to furnish (+)-anhydrooplopanone (**4**) (33 mg). **4** thus obtained was shown to be identical with an authentic sample (prepared above) by mixed melting point determination and by $[\alpha]_D$, MS, ^{1}H-NMR (90 MHz, $CDCl_3$), and ^{13}C-NMR (22.5 MHz, $CDCl_3$) comparisons.

Epoxidation of Nephthediol (9) Giving 10——A solution of **9** (60 mg) in $CHCl_3$ (2 ml) was treated with *m*-Cl-PBA (86 mg) and the whole mixture was stirred at room temperature (24 °C) for 6 h. Work-up of the reaction mixture as described above for *m*-Cl-PBA oxidation of nephthenol (**6**) gave a product, which was purified by column chromatography (SiO_2 10 g, *n*-hexane–AcOEt = 1 : 1) and HPLC (Semi Prep Zorbax ODS, MeOH–H_2O = 3 : 1) and then with a Lobar column (LiChroprep Si 60, *n*-hexane–AcOEt = 2 : 1) to furnish the 5,6-epoxide (**10**) (16 mg). **10**, colorless amorphous, $[\alpha]_D^{25}$ +48 (c = 0.7, $CHCl_3$). High-resolution MS: Found 236.180. Calcd for $C_{15}H_{24}O_2$ ($M^+ - H_2O$) = 236.178. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3410 (br), 900. ^{1}H-NMR (500 MHz, $CDCl_3$, δ): 4.15 (1H, dd, J = 9.0, 3.5 Hz, 1-H), 2.54 (1H, d, J = 2.0 Hz, 5-H), 2.93 (1H, dd, J = 9.5, 2.0 Hz, 6-H), 1.18 (1H, m, 7-H), 5.08, 4.98 (both 1H, s, 15-H_2), 1.27 (3H, s, 4-CH_3), 0.98 (3H, d, J = 7.0 Hz, 11-CH_3), 0.97 (3H, d, J = 6.5 Hz, 11-CH_3). ^{13}C-NMR (22.5 MHz, $CDCl_3$, δ_c): 149.8 (s), 69.0 (s), 77.2 (d), 65.4 (d), 57.3 (d), 45.5 (d), 30.6 (d), 111.3 (t), 33.5 (t), 27.7 (t), 27.7 (t), 23.1 (t), 28.4 (q), 20.1 (q), 18.2 (q). MS m/z (%): 236 ($M^+ - H_2O$, 1), 221 ($M^+ - H_2O - CH_3$, 3), 203 ($M^+ - 2H_2O - CH_3$, 3), 81 (100).

Acetylation of Nephthediol (9) Followed by Dehydration Giving the Trienol Acetate (11)——A solution of **9** (11 mg) in pyridine (1 ml) was treated with Ac_2O (2 drops) and the whole mixture was stirred at room temperature (20 °C) for 6 h. Work-up of the reaction mixture in the usual manner gave a product which was purified by column chromatography (SiO_2 2 g, *n*-hexane–AcOEt = 5 : 1) to furnish the monoacetate (8 mg) and **4** (recovered, 3 mg). The monoacetate (8 mg) was dissolved in dry pyridine (1 ml) and under a nitrogen atmosphere, the ice-cooled solution was treated with $POCl_3$ (2 drops). The whole was stirred at room temperature for 3 h. The reaction mixture was poured into water and the whole was extracted with AcOEt. Work-up of the AcOEt extract in the usual manner gave a product, which was purified by column chromatography (SiO_2 2 g, *n*-hexane–AcOEt = 10 : 1) to furnish the trienol acetate (**11**) (2 mg). **11**, colorless oil, $[\alpha]_D^{21}$ +102 (c = 0.35, $CHCl_3$). High-resolution MS: Found 262.194. Calcd for $C_{17}H_{26}O_2$ (M^+) = 262.193. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1720, 1243 (br). UV λ_{max}^{MeOH} nm (ε): 237 (17000). ^{1}H-NMR (500 MHz, $CDCl_3$, δ): 5.05 (1H, dd, J = 12.0, 4.0 Hz, 1-H), 6.10 (1H, d, J = 16.0 Hz, 5-H), 5.44 (1H, dd, J = 16.0, 10.5 Hz, 6-H), 0.82, 0.90 [both 3H, d, J = 6.5 Hz, 11-$(CH_3)_2$], 4.89, 5.14 (both 1H, s, 15-H_2), 4.93, 5.36 (both 1H, s, 14-H_2), 1.97 (3H, s, $OCOCH_3$). ^{13}C-NMR (22.5 MHz, $CDCl_3$, δ_c): 170.4 (s, $OCOCH_3$), 149.3 (s, C-10), 146.1 (s, C-4), 138.2 (d, C-6), 129.6 (d, C-5), 77.5 (d, C-1), 52.5 (d, C-7), 31.8 (d, C-11), 113.9, 113.3 (both t, C-14, 15), 35.9, 34.5, 33.0, 29.7 (all t, C-2, 3, 8, 9), 21.4, 20.7, 20.5 (all q, C-12, 13, $OCOCH_3$). MS m/z (%): 262 (M^+, 1), 202 (M^+ – AcOH, 29), 187 (M^+ – AcOH–CH_3, 13), 159 (M^+–AcOH–C_3H_7, 100).

Deacetylation of Trienol Acetate (11) Giving the Trienol (12)——A solution of **11** (18 mg) in 0.1 M K_2CO_3 (aq. 85% MeOH) (1 ml) was stirred at room temperature (20 °C) for 3 h. The reaction mixture was poured into water and the whole was extracted with AcOEt. The AcOEt extract was washed with aq. sat. NaCl and dried over $MgSO_4$. A product, obtained by evaporation of the solvent under reduced pressure, was purified by column chromatography (SiO_2 5 g, *n*-hexane–AcOEt = 3 : 1) to furnish the trienol (**12**) (13 mg). **12**, colorless solid, $[\alpha]_D^{20}$ +200 (c = 0.5, $CHCl_3$). High-resolution MS: Found 220.182. Calcd for $C_{15}H_{24}O$ (M^+) = 220.182. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3600, 3425 (br). UV λ_{max}^{MeOH} nm (ε): 238 (16000). ^{1}H-NMR (500 MHz, benzene-d_6, δ): 3.71 (1H, dd, J = 11.5, 4.0 Hz, 1-H), 1.86 (1H, dddd, J = 13.0, 11.5, 5.0, 3.0 Hz, 2-H_a), 1.68 (1H, dddd, J = 13.0, 13.0, 5.5, 4.0 Hz, 2-H_b), 2.34 (1H, ddd, J = 13.0, 13.0, 5.0 Hz, 3-H_a), 2.04 (1H, ddd, J = 13.0, 5.5, 3.0 Hz, 3-H_b), 5.87 (1H, d, J = 16.0 Hz, 5-H), 5.37 (1H, dd, J = 16.0, 10.5 Hz, 6-H), 1.55 (2H, overlapped, 7-H, 9-H_b), 1.77 (1H, dddd, J = 13.0, 6.5, 4.5, 2.0 Hz, 8-H_a), 1.42 (1H, dddd, J = 13.0, 12.0, 10.5, 2.0 Hz, 8-H_b), 2.47 (1H, ddd, J = 14.0, 6.5, 2.0 Hz, 9-H_a), 1.33 (1H, oct, J = 6.5 Hz, 11-H), 0.80, 0.83 [both 3H, d, J = 6.5 Hz, 11-$(CH_3)_2$], 4.84, 4.88 (both 1H, s, 14-H_2), 4.77, 5.03 (both 1H, s, 15-H_2). ^{1}H-NMR [500 MHz, benzene-d_6–pyridine-d_5 (1 : 1), δ]: 4.08 (1H, dd, J = 11.5, 4.0 Hz, 1-H), 2.31 (1H, dddd, J = 13.0, 11.5, 5.0, 3.0 Hz, 2-H_a), 1.98 (1H, dddd, J = 13.0, 13.0, 5.5, 4.0 Hz, 2-H_b), 2.54 (1H, ddd, J = 13.0, 13.0, 5.0 Hz, 3-H_a), 2.20 (1H, ddd, J = 13.0, 5.5,

3.0 Hz, 3-H_b), 6.01 (1H, d, J = 16.0 Hz, 5-H), 5.56 (1H, dd, J = 16.0, 10.5 Hz, 6-H), 1.67 (1H, dddd, J = 10.5, 10.5, 6.5, 4.5 Hz, 7-H), 1.87 (1H, dddd, J = 13.0, 6.5, 4.5, 2.0 Hz, 8-H_a), 1.58 (1H, dddd, J = 13.0, 12.0, 10.5, 2.0 Hz, 8-H_b), 2.66 (1H, ddd, J = 14.0, 6.5, 2.0 Hz, 9-H_a), 1.79 (1H, ddd, J = 14.0, 12.0, *ca.* 2.0 Hz, 9-H_b), 1.39 (1H, oct, J = 6.5 Hz, 11-H), 0.81, 0.85 [both 3H, d, J = 6.5 Hz, 11-$(CH_3)_2$], 4.96, 4.90 (both 1H, s, 14-H_2), 5.37, 5.02 (both 1H, s, 15-H_2). ^{13}C-NMR (22.5 MHz, $CDCl_3$, δ_c): 153.6 (s, C-10), 146.8 (s, C-4), 137.9 (d, C-6), 129.7 (d, C-5), 76.0 (d, C-1), 52.6 (d, C-7), 31.8 (d, C-11), 112.8, 110.5 (both t, C-14, 15), 36.2, 36.2, 34.5, 30.0 (all t, C-2, 3, 8, 9), 20.7, 20.5 (both q, C-12, 13). MS m/z (%): 220 (M^+, 7), 202 ($M^+ - H_2O$, 25), 177 ($M^+ - C_3H_7$, 29), 159 ($M^+ - C_3H_7 - H_2O$, 51), 109 (100).

Application of Horeau's Method to Nephthediol (9)——A solution of **9** (29 mg) in pyridine (1 ml) was treated with (±)-α-phenylbutyric anhydride (42 mg) and the whole mixture was stirred under a nitrogen atmosphre at room temperature (21 C) for 14 h. The reaction mixture was then treated with H_2O (1 ml) and stirred further for 1 h. The whole mixture was partitioned into an AcOEt–aq. sat. $NaHCO_3$ mixture. The AcOEt phase was washed with aq. sat. NaCl and dried over $MgSO_4$. A product, obtained after work-up in the usual manner, was purified by column chromatography (SiO_2 5 g, *n*-hexane–AcOEt = 5 : 1) to furnish the ester (28 mg) and **9** (recovered, 12 mg). The aq. $NaHCO_3$ phase was acidified with aq. 2 N HCl and the whole was extracted with AcOEt. Work-up of the AcOEt extract in the usual manner afforded the recovered acid, which was purified by HPLC (Semi Prep Cosmosil $5C_{18}$, MeOH = H_2O–8 : 1) to furnish α-phenylbutyric acid (26 mg) of $[\alpha]_D^{22}$ −13.5° (c = 0.8, benzene). The ester, colorless oil. High-resolution MS: Found 384.267. Calcd for $C_{25}H_{36}O_3$ (M^+) = 384.266. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3600, 1720, 1265. ^{1}H-NMR (90 MHz, $CDCl_3$, δ): 5.07 (3H, overlapped, 1-H, 15-H_2), 5.30 (2H, overlapped, 5, 6-H), 1.27 (3H, s, 4-CH_3), 0.86 (9H, overlapped), 7.26 (5H, s), 3.38 (1H, t, J = 7.5 Hz). MS m/z (%): 384 (M^+, 0.4), 341 ($M^+ - C_3H_7$, 0.4), 91 (100).

Application of Horeau's Method to the Trienol (12)——A solution of **12** (13 mg) in pyridine (1 ml) was treated with (±)-α-phenylbutyric anhydride (21 mg) and the whole mixture was stirred under a nitrogen atmosphere at room temperature (19 C) for 19 h. Work-up of the reaction mixture as described above furnished the ester (10 mg), **12** (recovered, 5 mg) and α-phenylbutyric acid (15 mg). α-Phenylbutyric acid: $[\alpha]_D^{20}$ −2.5° (c = 0.4, benzene). The ester, colorless oil. High-resolution MS: Found 366.254. Calcd for $C_{25}H_{34}O_2$ (M^+) = 366.256. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1718, 1264. ^{1}H-NMR (90 MHz, $CDCl_3$, δ): 5.00 (1H, m, 1-H), 5.49 (1H, d, J = 9.0 Hz, 5-H), 5.31 (1H, dd, J = 9.0, *ca.* 3.0 Hz, 6-H), 0.80, 0.88 [both 3H, d, J = 7.0 Hz, 11-$(CH_3)_2$], 5.99, 6.16 (both 1H, s, 14-H_2), 4.87, 5.14 (both 1H, s, 15-H_2), 3.36 (1H, t, J = 7.5 Hz), 0.85 (3H, t, J = 7.5 Hz), 7.26 (5H, s). MS m/z (%): 366 (M^+, 3), 323 ($M^+ - C_3H_7$, 0.5), 159 (100).

Dehydrogenation of Nephthene (17)——A solution of **17** (50 mg) in diethyleneglycol dimethyl ether (3 ml) was treated with 10% Pd–C (10 mg) and the whole mixture was heated under reflux for 25 h. After cooling to room temperature (25 C), the reaction mixture was filtered. The filtrate was poured into water and the whole was extracted with AcOEt. The AcOEt extract was washed with water several times and with aq. sat. NaCl, then dried over $MgSO_4$. A product, obtained after removal of the solvent under reduced pressure, was purified by column chromatography (SiO_2 5 g, *n*-hexane) to furnish cadalene (**18**) (9 mg). **18**, colorless oil. High-resolution MS: Found 198.143. Calcd for $C_{15}H_{18}$ (M^+) = 198.141. IR ν_{max}^{film} cm^{-1}: 1625, 1600, 1508. UV λ_{max}^{EtOH} nm (ε): 231 (45000), 290 (6000), 325 (800). ^{1}H-NMR (90 MHz, CCl_4, δ): 2.54 (3H, s), 2.61 (3H, s), 1.36 (6H, d, J = 7.0 Hz), 7.81 (2H, overlapped), 7.20 (3H, overlapped). ^{13}C-NMR (22.5 MHz, $CDCl_3$, δ_c): 142.2 (s), 134.7 (s), 131.9 (s), 131.6 (s), 131.2 (s), 127.2 (d), 125.6 (d), 124.8 (d), 123.0 (d), 121.5 (d), 28.3 (d), 23.7 (q), 23.7 (q), 22.0 (q), 19.4 (q). MS m/z (%): 198 (M^+, 33), 183 ($M^+ - CH_3$, 100), 168 ($M^+ - 2CH_3$, 42), 155 ($M^+ - C_3H_7$, 12), 153 ($M^+ - 3CH_3$, 30).

Oxidation of Nephthene (17) with OsO_4–$NaIO_4$ Giving the Norenone (19)——A solution of **17** (30 mg) in dioxane–H_2O (1.8 : 0.5) (2.3 ml) was treated with a solution of OsO_4 (12 mg) in pyridine–H_2O (1 : 1) (0.5 ml) and the whole mixture was stirred at room temperature (20 C) for 10 min. The reaction mixture was then treated with $NaIO_4$ (190 mg) in small portions over a period of 10 min and stirred at room temperature for further 2 h. The reaction mixture was poured into water and the whole was extracted with AcOEt. The AcOEt extract was washed with aq. sat. NaCl and worked up in the usual manner. A product thus obtained was purified by column chromatography (SiO_2 7 g, *n*-hexane–AcOEt = 5 : 1) to furnish the norenone (**19**) (15 mg). **19**, colorless oil, $[\alpha]_D^{18}$ +45° (c = 1.5, $CHCl_3$). High-resolution MS: Found 206.166. Calcd for $C_{14}H_{22}O$ (M^+) = 206.167. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1675, 1611. UV λ_{max}^{MeOH} nm (ε): 244 (15000). CD (c = 1.8 × 10^{-2}, MeOH): $[\theta]_{320}$ +3000 (pos. max.), $[\theta]_{268}$ 0, $[\theta]_{241}$ −15000 (neg. max.), $[\theta]_{226}$ 0, $[\theta]_{208}$ +30000 (pos. max.), $[\theta]_{200}$ +20000! ^{1}H-NMR (500 MHz, $CDCl_3$, δ): 2.59 (1H, dddd, J = 5.0, 5.0, 5.0, 2.0 Hz, 1-H), 5.92 (1H, d, J = 2.0 Hz, 5-H), 2.17 (1H, m, 10-H), 0.95 (3H, d, J = 7.5 Hz, 10-CH_3), 0.76, 0.98 [both 3H, d, J = 6.0 Hz, 11-$(CH_3)_2$]. ^{13}C-NMR (22.5 MHz, $CDCl_3$, δ_c): 199.7 (s), 167.8 (s), 127.6 (d), 52.0 (d), 37.7 (d), 36.0 (d), 27.8 (d), 36.0 (t), 29.0 (t), 25.5 (t), 23.1 (t), 21.6 (q), 21.1 (q), 14.9 (q). MS m/z (%): 206 (M^+, 49), 191 ($M^+ - CH_3$, 11), 164 ($M^+ - C_3H_6$, 100), 163 ($M^+ - C_3H_7$, 46), 149 ($M^+ + 1 - C_3H_7 - CH_3$, 49).

Hydroboration-Oxidation of Nephthene (17) Giving the Diol (20)——Under a nitrogen atmosphere, a solution of **17** (40 mg) in dry THF (1 ml) was treated with $NaBH_4$ (23 mg) and then cooled to −25 °C. The cooled mixture was then treated with a solution of BF_3-etherate (0.5 ml) in THF (1 ml) over a period of 10 min. The reaction mixture was stirred at room temperature (20 °C) for a further 1.5 h, then treated with H_2O (0.5 ml). After adjusting weakly alkaline with aq. 2 N NaOH (1.5 ml), the reaction mixture was treated with aq. 30% H_2O_2 (0.5 ml) and the whole mixture was stirred at room temperature for 1 h, then poured into water. The whole was extracted with AcOEt and work-up of the AcOEt extract in the usual manner gave a product. Purification of the product by column

chromatography (SiO_2 10 g, *n*-hexane–AcOEt = 2 : 1) and HPLC (Semi Prep Zorbax SIL, *n*-hexane–AcOEt = 2 : 1) gave the diol (**20**) (11 mg). **20**, colorless solid, $[\alpha]_D^{18}$ +66° (c = 0.6, $CHCl_3$). High-resolution MS: Found 222.200. Calcd for $C_{15}H_{26}O$ ($M^+ - H_2O$) = 222.198. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3455 (br). ^{1}H-NMR (500 MHz, $CDCl_3$, δ): 3.58 (1H, dd, J = 9.5, 9.5 Hz, 5-H), 2.02 (1H, m, 11-H), 0.89 (3H, d, J = 7.0 Hz, 10-CH_3), 1.05, 1.01 [both 3H, d, J = 6.5 Hz, 11-$(CH_3)_2$], 3.68 (2H, overlapped, 14-H_2). ^{13}C-NMR (22.5 MHz, $CDCl_3$, δ_c): 76.9 (d), 46.5 (d), 45.6 (d), 37.9 (d), 37.3 (d), 32.0 (d), 26.3 (d), 69.0 (t), 30.6 (t), 30.3 (t), 26.4 (t), 21.3 (t), 25.0 (q), 22.1 (q), 13.2 (q). MS m/z (%): 222 ($M^+ - H_2O$, 16), 191 ($222 - CH_2OH$, 21), 179 ($222 - C_3H_7$, 33), 161 ($222 - C_3H_7 - H_2O$, 36).

Acetylation of the Diol (20) Followed by Oxidation Giving 21——Under a nitrogen atmosphere, a solution of **20** (30 mg) in CH_2Cl_2–pyridine (2 : 1) (3 ml) was treated with Ac_2O (5 drops) at −20 °C.

The mixture was stirred for 3 h while the reaction temperature was raised from −20 °C to room temperature (25 °C). The reaction mixture was poured into water and the whole was extracted with AcOEt. Work-up of the AcOEt extract in the usual manner gave a product, which was purified by column chromatography (SiO_2 7 g, *n*-hexane–AcOEt = 4 : 1) to furnish the monoacetate (22 mg) and **20** (recovered, 5 mg). The monoacetate (22 mg) was dissolved in CH_2Cl_2 (2 ml) and the solution was treated with PCC (30 mg). The mixture was stirred at room temperature for 30 h and filtered. The filtrate was poured into water and the whole was extracted with AcOEt. Work-up of the AcOEt extract in the usual manner gave a product, which was purified by column chromatography (SiO_2 7 g, *n*-hexane–AcOEt = 7 : 1→5 : 1) to furnish the keto-alcohol acetate (**21**) (5 mg) and the monoacetate (recovered, 14 mg). **21**, colorless oil, $[\alpha]_D^{29}$ +112° (c = 0.9, $CHCl_3$). High-resolution MS: Found 280.205. Calcd for $C_{17}H_{28}O_3$ (M^+) = 280.204. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1737 (sh), 1725, 1250 (br). CD ($c = 4.0 \times 10^{-1}$, MeOH): $[\theta]_{331}$ 0, $[\theta]_{297}$ +4000 (pos. max.), $[\theta]_{225}$ 0. ^{1}H-NMR (500 MHz, benzene-d_6, δ): 1.65 (1H, overlapped, 1-H), 2.57 (1H, dddd, J = 7.0, 7.0, 6.0, 5.5 Hz, 4-H), 1.96 (1H, dd, J = 12.5, 3.5 Hz, 6-H), 2.26 (1H, dddd, J = 10.0, 3.5, 3.0, 2.5 Hz, 7-H), 4.30 (A in ABX, J_{AB} = 11.0, J_{AX} = 6.0 Hz, 14-H_a), 4.15 (B in ABX, J_{AB} = 11.0, J_{BX} = 7.0 Hz, 14-H_b), 0.66 (3H, d, J = 7.0 Hz, 10-CH_3), 0.76, 0.89 [both 3H, d, J = 6.5 Hz, 11-$(CH_3)_2$], 1.67 (3H, s, $OCOCH_3$). ^{1}H-NMR (500 MHz, pyridine-d_5, δ): 1.91 (1H, dddd, J = 12.5, 11.5, 4.5, 4.5 Hz, 1-H), 2.83 (1H, dddd, J = 7.0, 7.0, 6.0, 5.5 Hz, 4-H), 2.18 (1H, dd, J = 12.5, 3.5 Hz, 6-H), 2.23 (1H, dddd, J = 10.0, 3.5, 3.0, 2.5 Hz, 7-H), 4.43 (A in ABX, J_{AB} = 11.0, J_{AX} = 6.0 Hz, 14-H_a), 4.29 (B in ABX, J_{AB} = 11.0, J_{BX} = 7.0 Hz, 14-H_b), 0.80 (3H, d, J = 7.0 Hz, 10-CH_3), 0.76, 0.88 [both 3H, d, J = 6.5 Hz, 11-$(CH_3)_2$], 2.00 (3H, s, $OCOCH_3$). ^{13}C-NMR (22.5 MHz, $CDCl_3$, δ_c): 213.7 (s), 170.9 (s), 51.2 (d), 46.5 (d), 41.9 (d), 36.5 (d), 32.3 (d), 26.0 (d), 65.1 (t), 28.2 (t), 25.2 (t), 24.8 (t), 24.2 (t), 23.6 (q), 22.0 (q), 20.9 (q), 12.5 (q). MS m/z (%): 280 (M^+, 10), 220 ($M^+ - AcOH$, 80), 177 ($M^+ - AcOH - C_3H_7$, 14), 109 (100).

Synthesis of the Nor-*trans*-α-Glycol (22) from the Norenone (19)——Under a nitrogen atmosphere, a solution of **19** (100 mg) in dry THF–MeOH (2 : 1) (2 ml) was treated with $CeCl_3 \cdot 7H_2O$ (181 mg) and $NaBH_4$ (30 mg) and the mixture was stirred at room temperature (22 °C) for 1 h. The reaction mixture was poured into water and the whole was extracted with AcOEt. Work-up of the AcOEt extract in the usual manner gave a mixture of 4-ol-5-ene derivatives (100 mg). The product (100 mg) was dissolved in dry THF (2 ml) and the solution was treated under a nitrogen atmosphere with $NaBH_4$ (28 mg) and then with a solution of BF_3-etherate (0.3 ml) in THF (2 ml) at −70 C. The reaction mixture was stirred for 4 h while the reaction temperature was raised from −70 °C to room temperature (25 °C), then treated with H_2O (1 ml). The reaction mixture was made weakly alkaline with aq. 2 N NaOH, and treated with aq. 30% H_2O_2 (0.5 ml). The whole mixture was stirred at room temperature for 4 h and poured into water. The whole was then extracted with AcOEt and the AcOEt extract was worked up in the usual manner. The product was purified by column chromatography (SiO_2 30 g, *n*-hexane–AcOEt = 2 : 1) and HPLC (Semi Prep Zorbax ODS, MeOH–H_2O = 7 : 1) to furnish the nor-*trans*-α-glycol (**22**) (10 mg). **22**, colorless oil, $[\alpha]_D^{22}$ +43° (c = 0.7, $CHCl_3$). High-resolution MS: Found 208.183. Calcd for $C_{14}H_{24}O$ ($M^+ - H_2O$) = 208.183. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3586, 3425 (br). CD ($c = 1.6 \times 10^{-1}$, CCl_4): $[\theta]_{311}$ −29000 (neg. max.), $[\theta]_{297}$ 0, $[\theta]_{282}$ +29000 (pos. max.). ^{1}H-NMR (500 MHz, $CDCl_3$, δ): 1.63 (1H, ddd, J = 12.0, 10.5, 4.5 Hz, 1-H), 3.34 (1H, ddd, J = 11.0, 10.0, 4.5 Hz, 4-H), 3.40 (1H, dd, J = 10.0, 9.0 Hz, 5-H), 1.54 (1H, ddd, J = 12.0, 9.0, 5.0 Hz, 6-H), 1.79 (1H, m, 7-H), 1.82 (1H, m, 10-H), 2.01 (1H, m, 11-H), 0.87 (3H, d, J = 7.0 Hz, 10-CH_3), 1.00, 1.04 [both 3H, d, J = 7.0 Hz, 11-$(CH_3)_2$]. ^{13}C-NMR (22.5 MHz, $CDCl_3$, δ_c): 76.4 (d), 76.3 (d), 43.2 (d), 37.9 (d), 37.8 (d), 31.8 (d), 26.4 (d), 31.8 (t), 30.2 (t), 28.9 (t), 21.1 (t), 25.0 (q), 22.2 (q), 13.2 (q). CI-MS (isobutane) m/z (%): 227 ($M^+ + H$, 0.3), 209 ($227 - H_2O$, 43), 191 ($227 - 2H_2O$, 47).

CD Spectrum of 22 Measured by the α-Glycol Chirality Method——**22** (0.339 mg) was dissolved in a 1.5×10^{-4} M solution of $Eu(fod)_3$ in CCl_4 (10 ml) [prepared from $Eu(fod)_3$ 1.55 mg in CCl_4 10 ml] and after 30 min, the CD spectrum of the solution (1.5×10^{-4} M **22**) was measured. CD ($c = 1.6 \times 10^{-1}$, CCl_4): $[\theta]_{311}$ −29000 (neg. max.), $[\theta]_{297}$ 0, $[\theta]_{282}$ +29000 (pos. max.).

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