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SYNTHETIC STUDIES ON TERPENIC COMPOUNDS—XV[1]

SYNTHESIS OF METHYL 14β-HYDROXY-7β:8β,9β:11β,12α:13α-TRIEPOXYABIETAN-18-OATE, COMPLETE B/C RING MODEL OF ANTILEUKEMIC TRIPTOLIDES, FROM LEVOPIMARIC ACID[2]

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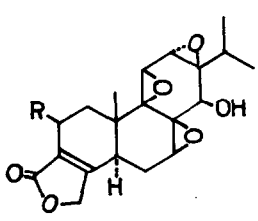
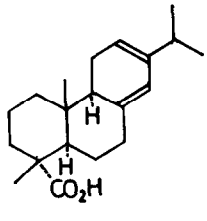
Abstract—Stereospecific construction of the hydroxytriepoxide system present in triptolide **1** and tripdiolide **2** has been explored starting from levopimaric acid **3**. 8α:14α,12α:13α-Diepoxide **9** derived from **3** was converted to the epoxy dienone **16** by four steps process. The 9,11-epoxide group was introduced stereospecifically by oxidation with m-chloroperbenzoic acid to produce diepoxide **20**. Epoxidation of the 14β-hydroxy derivative **33** with m-chloroperbenzoic acid or by a photochemical method afforded the title compound **36** which possesses the complete B/C ring functionality of **1** and **2**. The stereochemistry of the epoxy rings in **36** was confirmed by X-ray crystallographic analysis of the isomeric triepoxide **37**. The result of antitumor tests of the stereoisomeric epoxides obtained in this study is described.

Triptolide **1** and tripdiolide **2** are diterpenes which have been isolated from *Tripterygium wilfordii* (Celastraceae) in the course of the systematic survey of antitumor plant constituents by Kupchan *et al.*[3] They are distinguished for their potent antileukemic activity and counted among several substances surviving for clinical test. The compounds **1** and **2** are structurally characterized by the complex oxygen functionalities present in novel 18(4→3)-abeo-abietan skeleton.[4] It is also a point of interest that the alkylation through the selective opening of 9,11-epoxy group assisted by the hydrogen bonding with 14β-hydroxy group is claimed as a mechanism for the exertion of their biological activity.[5] The stereospecific elaboration of the oxygen functions on the B/C ring of **1** and **2** are thus intriguing both from synthetic and biological points of view. The resin acids with abietan skeleton were selected as the starting material because of a close similarity in structure and ready availability. We report here the full account of the first successful synthesis[6] of a 14β-hydroxy-7β:8β,9β:11β,12α:13α-triepoxide, which has the complete B/C ring moiety of **1** and **2** from levopimaric acid **3**. At the same time, mention will be made on physico-chemical studies (^{13}C NMR and X-ray crystallographic analysis) and results of antitumor screening tests on the stereoisomeric epoxides obtained.



1 R = H
2 R = OH



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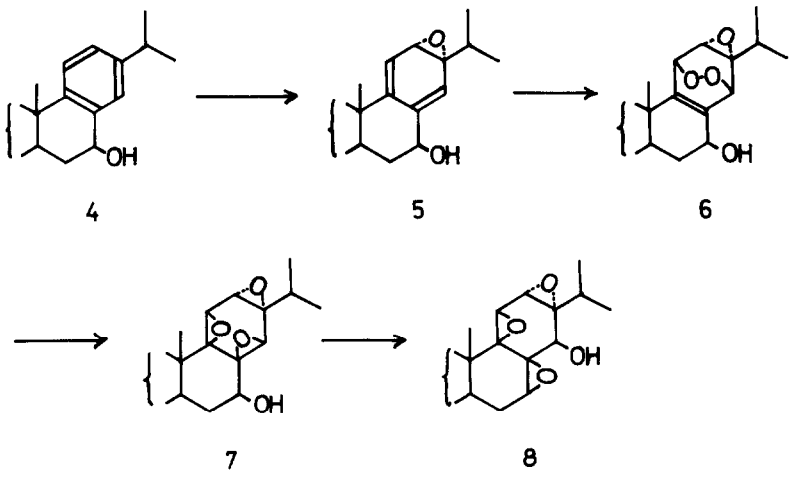
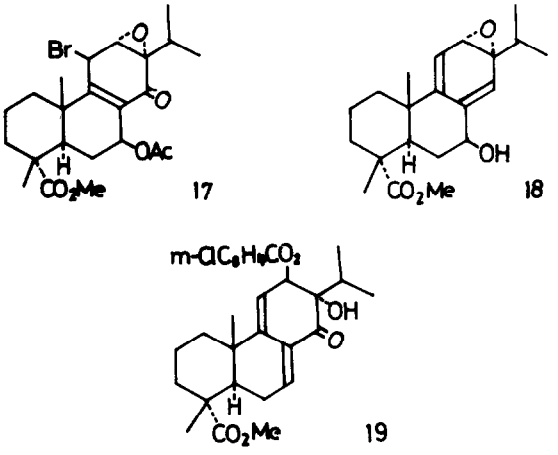
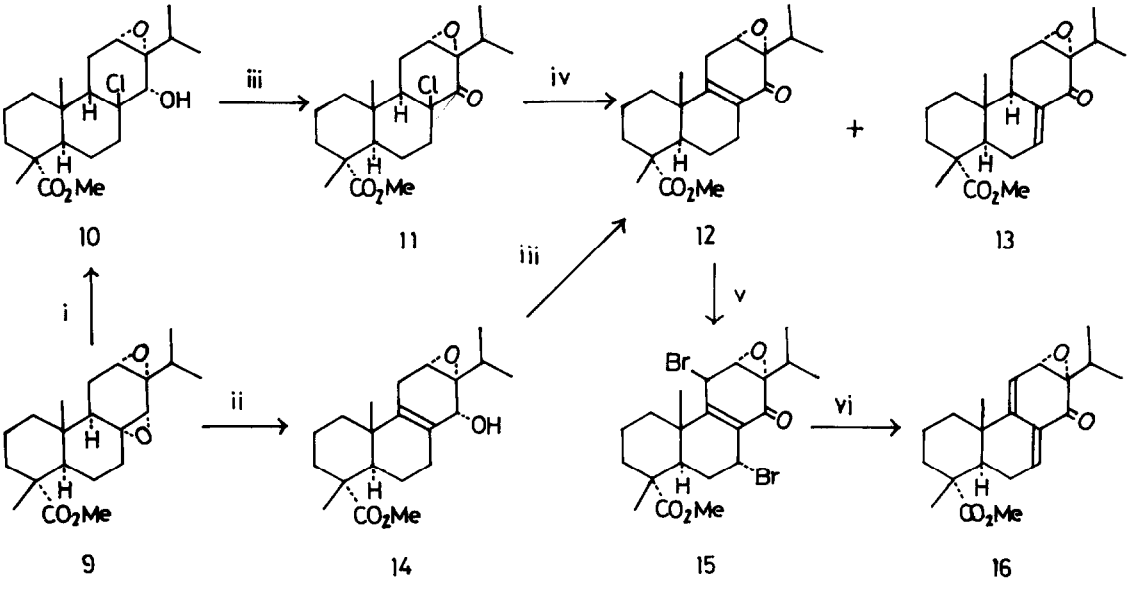
Synthetic studies. In connection with the consideration of synthetic strategy it would be pertinent to speculate on the biosynthetic pathway for the formation of oxygen functionalities on B/C rings of **1** and **2**. A precursor like **4** with aromatic C ring would be first oxygenated at C-12–C-13 from less hindered side giving an arene oxide **5**. Subsequent addition of oxygen molecule from the side opposite to the epoxide ring and the rearrangement of the endoperoxide **6**, thus formed, give the hydroxytriepoxide **7** which might rearrange[7] further to produce finally **8**. We envisaged that the intermediates such as **5** would be useful in view of reactivity and functionality. From this consideration our synthesis started from the chlorohydrin epoxide **10**, which had previously been obtained from levopimaric acid **3** by the reactions involving sensitized photooxygenation.[8–10] Oxidation of **10** with Jones reagent gave smoothly the chloroketon **11** which was dehydrochlorinated by treatment with $LiCO_3$, LiCl and DMF at 100° affording a mixture (5:1 ratio) of the isomeric conjugated enones **12** and **13**. The transoid enone **12** and cisoid **13** were discriminated in their IR spectra by the C=O frequencies (1660 and 1690 cm^{-1}, respectively) and the stronger absorption of the C=C stretching band (1620 cm^{-1}) in the latter. The desired enone **12** could be secured more efficiently by the following way. When **9** was treated with catalytic amount of hydrogen chloride in ether, a mixture of **10** and allylic alcohol **14** in approximately 1:1 ratio was obtained. This mixture was subjected successively to Jones oxidation and dehydrohalogenation reaction ($LiCO_3$, LiCl and DMF), giving the enone **12** in an overall yield of 77.4% from **9**. The reaction of the enone **12** with N-bromosuccinimide proceeded cleanly, affording crystalline dibromide **15** in 70% yield. The configuration of the introduced bromine atoms was assigned on the basis of ^1H NMR evidences. The signal of the angular methyl group was observed at a deshielded position (δ 1.42) as compared with that of **12** (δ 1.10) and this would be ascribed to the diamagnetic anisotropy of the 11β-standing bromine as reported in the case of androstane derivatives.[11] On the other hand the bromine atom at C-7 was determined to have α configuration since the C-7



Scheme 1.

proton signal appeared as a doublet of doublets with the coupling constants of 2 and 5 Hz. The attack of the bromine at C-7 from α-side is in accord with expectations. On the other hand the introduction of bromine atom at C-11 from β-side might indicate the encumbering effect of the $12\alpha:13\alpha$-epoxide group is more significant than the steric hindrance by the angular methyl group. Treatment of the dibromide **15** with zinc dust in refluxing THF afforded in a good yield (91%) the dienone **16**, while the reaction of the dibromide **15** with one equivalent of silver acetate produced the acetate **17** in 87% yield, only the bromine atom at C-7 being substituted. Initial numerous attempts for derivation of **18** corresponding to the intermediate **5** from **15**, **16** or **17** (mostly involving the reduction of 14-keto group) uniformly failed due to an unusual propensity to 12,13-epoxide ring cleavage and the aromatization of C ring.





Scheme 2. (i) HCl–Et_2O, (ii) HCl(cat. amount)–Et_2O, (iii) CrO_3–H_2SO_4–Me_2CO, (iv) $LiCO_3$–LiCl–DMF, (v) NBS–CCl_4, (vi) Zn–THF.

Next our attention was turned to the direct epoxidation of **16** by per acid. Exposure of **16** to m-chloroperbenzoic acid (MCPBA) in methylene chloride at buffered conditions[12,13] afforded diepoxide **20** contaminated by variable amounts of 12,13-epoxy cleaved product **19** which was hard to remove, depending on the buffering methods. Although the use of the two layer system with aq. 0.1 M $NaHCO_3$ solution gave exclusively **20**, the yield was low (31%). A better result was obtained by the reaction at the presence of stronger bases such as solid Na_2CO_3, where **20** containing *ca.* 10% of **19** was obtained in the yield more than 50%. The introduction of an epoxy group between C-9 and C-11 in **20** was revealed by the presence of an intense absorption due to C=C stretching vibration (1640 cm^{-1}) in the IR spectrum, characteristic[14] for the cisoid conjugated enone, and by the appearance of its β-proton signal at δ 6.76 in the NMR spectrum. As for steric course of the epoxidation, two opposing effects would be considered *a priori*; namely those of the 12,13-epoxy ring at α-side and the angular methyl group at β-side. Acidic treatment of **20** afforded the ene-diol **21** through S_N2'-type opening of the 9,11-epoxide ring. In the NMR spectrum **21** exhibited the signals due to C-7 proton as triplet (J = 8 Hz) at δ 4.68. Therefore, the β-pseudo-equatorial configuration was assigned to C-7 hydroxyl group. Since the signal due to the angular methyl group appeared at the field (δ 1.45) deshielded by 0.35 ppm than that of **12**, β-configuration of C-11 hydroxyl group was suggested. Thus it was indicated that the 9,11-epoxide in **20** might have the desired stereochemistry (β). In order to confirm unequivocally this crucial assignment, the other sets of investigation have been carried out. Catalytic reduction of **20** at the presence of Pd-on-charcoal furnished a hydrogenolysis product **22** (37% yield) accompanying the ethyl ether **25** (31% yield) which were characterized as crystalline acetate **26**. In the NMR spectra both compounds **25** and **26** exhibited the methine proton resonances of the ethoxyl-bearing carbon atoms as doublets with relatively small coupling constants (J = 2 and 3 Hz) at δ 4.38 and 4.42, respectively. Therefore the 7-ethoxyl group of **25** has α-configuration opposite to that of 7-hydroxyl group in **21**. The product **25** would be formed probably through Pd-assisted solvolytic opening of the α,β-ethylenic epoxide ring. The configuration of 11-hydroxyl group in the alcohol **22**, which retains one of the C–O bonds of the epoxide group in **20**, was investigated. The treatment of the mesylate **23** derived from **22** with tetraethylammonium acetate gave the acetate **28** which on hydrolysis produced the alcohol **27** with the inverted configuration. Acetate **24** was also prepared from **22**. A close comparison of NMR spectra between the pairs of alcohols **22** and **27** or acetates **24** and **28** led to the conclusion that the newly introduced epoxide ring in **20** had the desired β-configuration as depicted. Firstly, when the chemical shifts of 20-methyl proton signal in **22** and **27** in the ^1H NMR spectra are compared with that of the 11-deoxy compound **12**, the deshielding effect of 11-hydroxyl group is more prominent in the case of **22** ($\Delta\delta = 0.20$) than in **27** ($\Delta\delta = 0.06$). The 1,3-diplanar C ring of **22** would be in a flattened boat conformation **29** which is concaved in β-side. Then the syn relationship of the pseudo-axial hydroxyl group at C-11 and the angular methyl group in **22** will explain the observed larger NMR shift. Secondly in the ^1H NMR spectra measured in the presence of added $Eu(dpm)_3$, the 20-methyl protons of **22** show markedly larger shifts than those of **27**, which

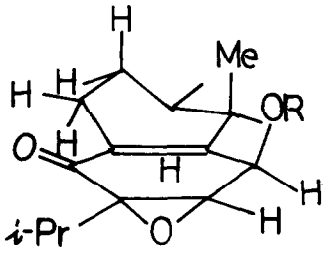


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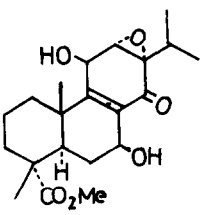
exhibit LIS values comparative to those of 19-methyl protons of **27** and **22**. Thirdly the C-11 proton signal of the acetate **28** appears as a doublet of doublets with the coupling constants of J = 2 and 4 Hz, whereas that of the epimeric acetate **24** splits only to a doublet (J = 2 Hz). The vicinal coupling constant of **28** larger than **24** (4 Hz vs 2 Hz) are in accordance with dihedral angle relationship observed in models (viz. *ca.* 30° vs 60° for **28** and **24**, respectively). The coupling constant of the epoxide proton is known to be considerably smaller than the value calculated from the Karplus equation.[15] Moreover the presence of the additional splitting (J = 2 Hz) in **28** provides a good support for the assignment of the conformation, since it is reasonably ascribed to a homoallylic coupling between $C_{11\beta}$ and $C_{7\alpha}$ pseudo-axial protons.[16] Fourthly the ^1H NMR behavior of C-11 and hydroxyl protons of the epimeric alcohols **22** and **27** is interesting in connection with their stereochemistry. The alcohol **27** displays a doublet with J = 11 Hz due to hydroxyl proton at δ 2.23 and a doublet of doublets with J = 2 and 11 Hz due to C-11 proton at δ 4.56 whereas the corresponding signals of **22** appear as a doublet with J = 8 Hz at δ 1.69 and a doublet of doublets with J = 2 and 8 Hz at δ 4.94 respectively. The large J_{CH-OH} (11 Hz) in **27** is interpretable on the basis of the frozen conformation[17] with the dihedral angle of 180°, owing to the hydrogen bonding with 12α,13α-epoxy group. The OH bond fixation to lesser extent is indicated also in the NMR spectrum of **22** (J_{CH-OH} = 8 Hz) and might be traced to the hydrogen bonding with 14-keto group. Finally the correlation of the configurations in **22** and **27** with ^{13}C NMR is not sufficiently distinctive, reflecting the pseudo nature of their hydroxyl groups. ^{13}C NMR chemical shift for C-20 carbon of **22** reported in the preliminary communication[2] is erroneous and should be corrected (see Experimental). However more deshielding in the β- and γ-carbon shifts of **27** as compared with those of **22** was observed, a result which conforms with the general tendencies in the effect of equatorial and axial substituents in cyclohexane ring.[18] The correctness of the stereochemical assignment of **20** has been ascertained ultimately by X-ray crystallographic analysis described later. With β-configuration of 9,11-epoxide ring in **20** established, the preferential attack of the peracid molecule from β-side of **16** remains a problem to be explained. The result may indicate that the influence due to 12α,13α-epoxide ring outweigh the effect of C-20 methyl group. However the reported conversion of **30** to **31** by MCPBA is worthy of note in this connection.[6a] The other dynamic conformational factors would also be important[19] and the clarification of the problem awaits further experimentation.

The remaining task is the reduction of C-14 ketone to a



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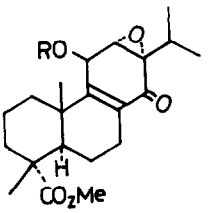
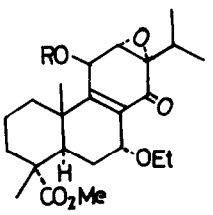
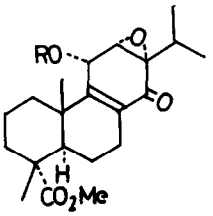


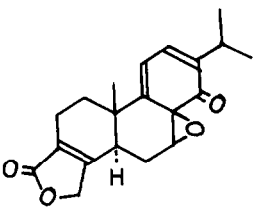
22 R = H
23 R = Ms
24 R = Ac



25 R = H
26 R = Ac



27 R = H
28 R = Ac



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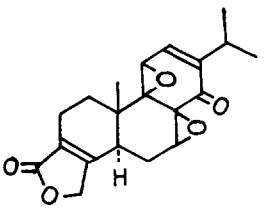

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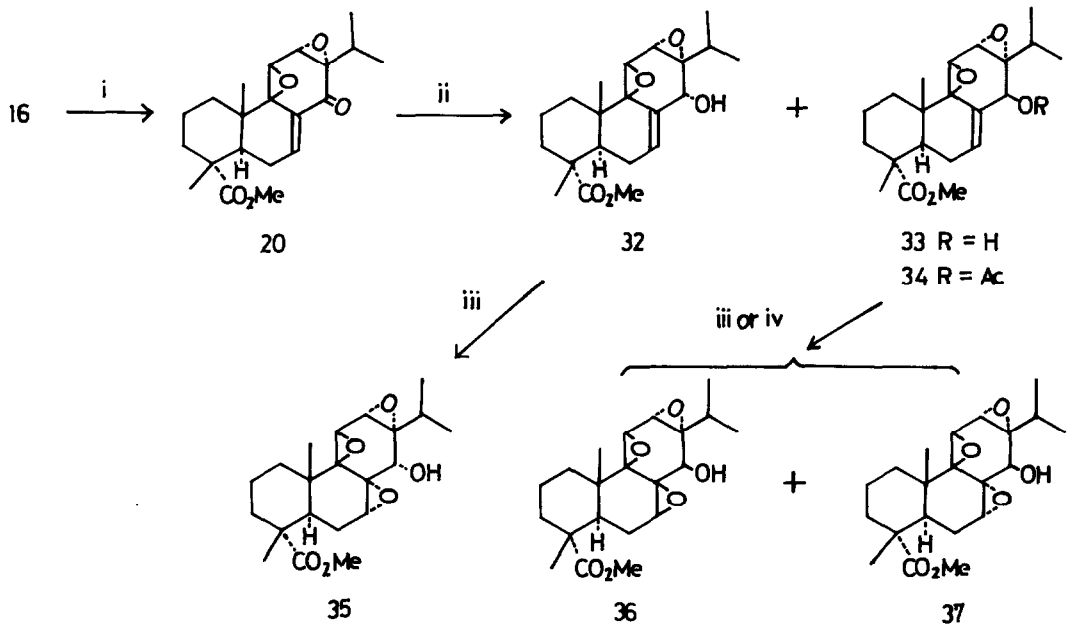
14β-hydroxyl group and the introduction of 7β,8β-epoxide group, both of which should be preferably stereospecific. The treatment of **20** with alkaline hydrogen peroxide failed to effect the epoxidation of $\Delta^{7,8}$ double bond. Then the attention was turned to the initial reduction of 14-keto group and subsequent stereospecific epoxidation, taking advantage of the directing effect of resulted 14-hydroxyl group.[20] Reduction of the ketodiepoxide **20** with sodium borohydride in methanol at $-10°$ produced approximately equal amounts of the epimeric alcohols **32**, low melting crystals, and **33**, m.p. 162–165°, readily separable by silica gel chromatography. Assignment of the configuration of their hydroxyl groups was possible on the basis of ^{1}H NMR evidences. Firstly the spectrum of **33** displays resonances at δ 2.92 (doublet, J = 12 Hz, C_{14}–OH, disappears upon D_2O addition) and 4.36 (doublet, J = 12 Hz, C_{14}–H, collapses to a singlet upon D_2O addition). The highly distinctive coupling constant (12 Hz) between the hydroxyl and C-14 protons, which are also observed in the case of triptolide **1** and tripdiolide **2**,[3,5] is attributable to the rigid trans orientation of the coupled protons resulting from strong hydrogen bonding between the 14-hydroxyl and 9,11-epoxide group[17] and thus the 14-hydroxyl group of **33** must be disposed in the β-direction. The C-14 proton of **32** also show a somewhat larger coupling constant (8 Hz) with the hydroxyl proton than expected from free rotation.[21] This may indicate restricted rotation of the hydroxyl C–O bond by the weaker hydrogen bonding with the 12α,13α-epoxide group. The α-orientation of the 14-hydroxyl group in the epimeric counterpart **32** is supported by the observation of an allylic coupling (J = 3 Hz) between C-7 and C-14 protons, which are in conformity with the pseudo-equatorial nature of the hydroxyl group.[16]

Next we proceeded to the epoxidation reaction of **33**. The reaction by the Sharpless method[22] resulted only in the formation of a complex mixture. Although the oxidation of **33** with MCPBA in methylene chloride solution buffered with sodium hydrogenphosphate occurred only very slowly, the reaction for two weeks at ambient temperature afforded two kinds of triepoxide **36** and **37** in yields of 3% and 22%, respectively. The comparison of the coupling pattern of C-7 proton resonances with that of triptolide **1**[3] allowed the assignment of the configuration of the newly introduced 7,8-epoxide rings in both compounds and the desired one was the minor product. As seen in Table 1, the other signals due to the protons of the hydroxy-triepoxide system in **36** also show excellent agreement to those of triptolide **1**. The stereochemistry of **36** has been unequivocally determined by the X-ray crystallographic analysis of the stereoisomeric triepoxide **37** (see later section). Thus the construction of 14β-hydroxy-7β:8β,9β:11β,12α:13α-triepoxide system, which is believed to be responsible for antileukemic activity of triptolides,[5] has been first[2] accomplished. In contrast to **33**, the oxidation of **32** with MCPBA proceeded in normal rate and in the direction as expected from syn-directing effect of C-14 hydroxyl group. Thus the exposure of **32** to the same condition as the case of **33** led to the stereospecific formation of **35**. The vivid difference observed in the reactivity of the epimers **32** and **33** to the per acid should be ascribed to the extent of hydrogen bonding. The relatively free C-14 hydroxyl group in **32** would contribute normally to the

Table 1. Comparison of ^{1}H NMR data† of the triepoxides **36** and **37** with those of triptolide **1**[3]

	C_7-H	C_{11}-H	C_{12}-H	C_{14}-H	C_{14}OH
triptolide **1**	3.46 (d, J = 5)	4.00 (d, J = 3)	3.60 (dd, J = 1,3)	3.52 (dd, J = 1,11)	2.83 (d, J = 11)
36	3.23 (d, J = 5)	4.04 (d, J = 4)	3.50 (dd, J = 1,4)	3.36 (dd, J = 1,11)	2.77 (d, J = 11)
37	3.31 (m)	3.90 (d, J = 3)	3.54 (dd, J = 1,3)	3.38 (dd, J = 1,12)	2.93 (d, J = 12)

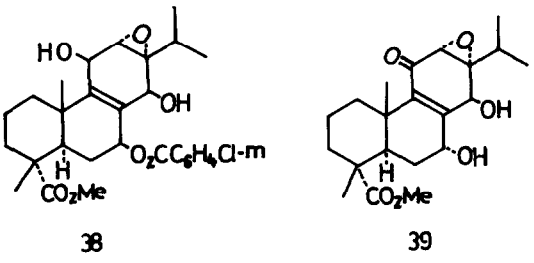
†Chemical shifts, δ (multiplicity, J = Hz).



Scheme 3. (i) MCPBA–Na_2CO_3–CH_2Cl_2, (ii) $NaBH_4$–MeOH, −10°. (iii) MCPBA–MeCN, (iv) biacetyl–benzene–O_2–$h\nu$.

stabilization of the transition state leading to syn-epoxidation, whereas the strongly hydrogen-bonded hydroxyl group in **33** is no longer capable of such effect and rather would hinder the approach of the reagent from β-side.

Finally investigations have been carried out to increase the formation ratio of **36** to **37** in two directions. One of these was the examination of solvent effect. Change of the solvent in the per acid oxidation from methylene chloride to benzene or acetonitrile showed some improvement but still the undesired **37** predominated (Table 2). The continuation of the reaction in acetonitrile solution for a month did not result in the increased yield of **36** and, instead, led to the formation of 9,11-epoxy-cleaved product **38** and 9,11-epoxy isomerized product **39**, which would be derived from **33** and **37**, respectively. The other approach was the application of photoepoxidation developed by Bartlett.[23] When a solution of



33 and a large excess of biacetyl in benzene contained in a quartz vessel was irradiated with high pressure mercury lamp under oxygen atmosphere, **36** and **37** were obtained in yields of 19% and 13%, respectively. The formation ratio reversed from the case of the per acid oxidation.

Table 2. Epoxidation reactions of the diepoxide **33**

Reaction conditions	yields (%)		
	36	37	recovery of 33
MCPBA, CH_2Cl_2[a,c]	3	22	2
" , benzene[b,d]	16	54	23
" , CH_3CN[b,d]	11	19	42
O_2, biacetyl, hν[d]	19	13	--

[a]Reaction at room temp. for 2 weeks with 4.4 molar equiv. of MCPBA.
[b]Reaction at room temp. for 8 days with 10 molar equiv. of MCPBA.
[c]Isolated yields.
[d]The products were separated firstly to the recovery of **33** and the mixture of **36** and **37** by silica gel chromatography, and then the formation ratios of the latter two were estimated by ^1H NMR integration.

Table 3. ^{13}C NMR data of triptolide analogs

carbon number	32	33	35	36	37
1	37.1	37.1	36.4	37.6	36.4
2	17.5	17.4	17.4	18.6	17.4
3	32.6	32.5	34.2	33.1	34.1
4	46.7	46.7	46.4	46.8	46.4
5	43.0	43.0	34.9	43.7	34.7
6	24.8	25.0	24.3	23.6	24.7
7	125.9	132.5	56.1	60.5	56.8
8	133.4	132.2	58.9	60.4	57.2
9	69.1	70.2	68.2	69.5	66.4
10	35.6	35.3	35.4	36.5	35.3
11	57.7	59.3	57.6	58.2	59.1
12	55.5	56.7	53.2	55.0	56.2
13	67.8	66.0	65.6	65.6	65.6
14	68.7	73.8	65.2	74.1	74.1
15	27.5	28.5	27.5	28.3	28.8
16	17.8	17.8†	18.4	18.0	18.1
17	19.4	18.1	19.3	18.6	18.6
18	178.3	178.1	178.1	177.9	178.1
19	16.6†	17.4†	17.6	17.0†	17.3†
20	16.2†	16.6	16.0	16.9†	17.4†
ester Me	52.2	52.2	52.2	52.3	52.3

†Assignments may be interchanged.

^{13}C NMR studies of triptolide analogs. The ^{13}C NMR spectra of the stereoisomeric di- and tri-epoxides synthesized in this study were measured and the assignments were made by the aid of off-resonance and selective decoupling techniques. To provide further evidences for the assigned structures, the result is listed in Table 3. Distinct differences in the chemical shifts of the relevant carbon atom signals are observed between the pair of the stereoisomers as for 7,8-epoxide ring and 14-hydroxyl group and this may serve to the stereochemical argument of triptolide analogs.

X-Ray crystallographic analysis of the triepoxide **37**. Preliminary X-ray photographs revealed that the triepoxide **37** crystallized from a mixture of petroleum ether and ethyl ether belongs to the orthorhombic crystal class. Systematic absences conformed to the space group $P2_12_12_1$ with accurate lattice constants of $a = 27.976(9)$ Å, $b = 11.482(3)$ Å, $c = 5.939(2)$ Å, and $Z = 4$. All unique diffraction maxima with $2\theta < 50°$ were recorded on a computer-controlled four circle diffractometer using graphite monochromated MoKα radiation. Of the 1997 reflections surveyed, 928 were judged observed ($I > 3\sigma(I)$) after correction for Lorenz, polarization, and background effects.

The structure was solved by direct methods using a multisolution weighted tangent formula approach.[24] Full matrix least-squares refinement with anisotropic temperature factors for the nonhydrogen atoms and isotropic temperature factors for hydrogen atoms have converged to a standard crystallographic residual of 0.043 for the observed reflections.[25]† Figure 1 is a perspective drawing of the final X-ray model.[27] The X-ray experiment did not define the absolute configuration.

In general all bond distances and angles agree well with generally accepted values for given bond types. The ring A is in a chair conformation. Since the tortional angles about the C7–C8 and C8–C9 bonds are 0.8° and 0.4° respectively, the ring B has a 1,2-diplanar conformation. The ring C is in the same unusual 1,3-diplanar conformation as that of the ring C in triptolide itself[28] and has an approximate two-fold axis which bisects the C-11–C-12 and C8-C14 bonds. An intramolecular hydrogen bond appears to exist between O4 and O2 with a distance of 2.905 Å (O4-H—O2 = 2.26 Å), as well as an intermolecular hydrogen bond between O4 and O3 with a distance of 2.849 Å (O4-H—O3).

Antitumor screening tests of triptolide analogs. Several triptolide analogs obtained in this study were submitted to two kinds of antitumor screening tests, viz cytotoxicity (ED_{50}) against KB cell culture‡ and antileukemic

†Additional crystallographic details have been deposited with the Cambridge Crystallographic Data Centre.[26]

‡The tests have been carried out by the auspice of Drs. K. Sakurai and T. Tsuruo, Cancer Chemotherapy Center.

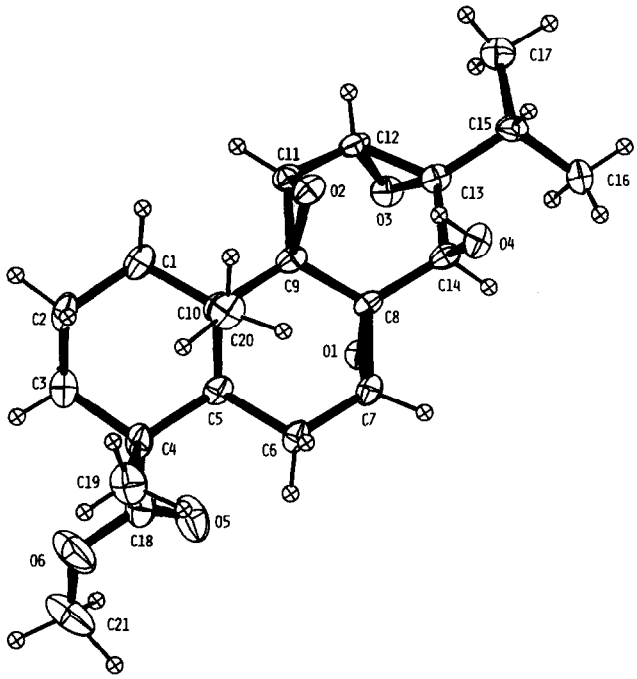


Fig. 1. The molecular structure of triepoxide **37**. The molecule is drawn with 30% probability ellipsoids for the heavier atoms and arbitrary spheres for hydrogen.

Table 4. Antitumor screening tests of triptolide analogs

Compounds	KB cell (ED_{50} μg/ml)	L-1210 leukemia	
		dose, mg/kg/day	T/C (%)
32	32	12	100
		3	125
		0.75	133
33	100	12	117
		3	108
		0.75	117
35	60	12	100
		3	108
		0.75	117
36	100	6	125
		1.5	117
		0.375	108
37	100	12	117
		3	117
		0.75	117

activity against the L-1210 afflicted mice.† As shown in the Table 4, all of the epoxide derivatives examined were found not to be effective in the KB test. In the life-prolonging effects in mice afflicted with the L-1210 lymphoid leukemia, our triptolide analogs were only marginally active. However the compounds **33**, **36** and **37** tend to show a distinct effect throughout the different levels of the dose compared to **32** and **35**. This result seems to accord with the proposal[5] that the ring opening reaction of 9,11-epoxide assisted by the hydrogen bonding with 14β-hydroxyl group would be responsible to the antileukemic activity of triptolides. Nevertheless our results suggest that not only the hydroxytriepoxide system on B/C ring but also A ring functionalities may take part in the exertion of the biological activity of triptolides.

†The tests have been done at Bristol Laboratories by Dr. R. L. Buchanan.

EXPERIMENTAL

Mps were determined on a Yanagimoto micro hot-stage apparatus MP-S2 and are uncorrected. IR spectra were recorded on a JASCO IRA-1 spectrometer. ^1H and ^{13}C NMR spectra were

taken, unless otherwise stated, in $CDCl_3$ on a JEOL PS-100 and a JEOL FX-100 spectrometers, respectively. Microanalyses were carried out at the microanalytical laboratory, Faculty of Science, Osaka City University.

Treatment of methyl 9α:14α,12α:13α-diepoxyabietan-18-oate **9** *with a catalytic amount of HCl.* To a soln of **9** (5.40 g) in absolute ether was added a saturated ether soln of dry HCl (5 ml) at −20° under stirring. After the mixture was allowed to react for 1.5 h, it was washed with brine and dried with anhyd $MgSO_4$. Evaporation of the soln left semi-crystalline residue which was chromatographed on a column of SiO_2 giving the chlorohydrin **10** as crystals[9] (benzene: AcOEt = 20:1, 2.53 g, 42.5% yield) and methyl 12α:13α-epoxy-14α-hydroxyabiet-8-en-18-oate **14** as an oil (EtOH, 2.97 g, 55% yield): IR (CCl_4) 3560, 3480, 1725, 1690, 1613, 1235, 1180, 872 cm^{-1}; ^1H NMR δ 0.90, 1.08 (each 3H d, J = 7 Hz, 16- and 17-H), 1.05 (3H, s, 20-H), 1.18 (3H, s, 19-H), 3.24 (1H, dd, J = 1,4 Hz, 11-H), 3.45 (3H, s, ester Me), 3.97 (1H, broad s, 14-H).

Methyl 8-chloro-12α:13α-epoxy-14-oxoabietan-18-oate **11**. Jones reagent (268 mg CrO_3/ml, 5 ml) was added dropwise to a stirred soln of the chlorohydrin **10** (595 mg) in acetone (40 ml) at ambient temp. and the reaction was continued for 7 h. After addition of MeOH to destroy the excess of the reagent, the precipitate was removed by filtration with the aid of Celite and the filtrate was neutralized by the addition of $NaHCO_3$, then dried with anhyd $MgSO_4$. Evaporation of the solvent afforded a crystalline product (536 mg) which was purified by SiO_2 chromatography to give **11** as prisms (436 mg, 74% yield), m.p. 162–164° (from MeOH): IR (CCl_4) 1725, 1250, 900 cm^{-1}; ^1H NMR δ 0.88, 1.05 (each 3H d, J = 7 Hz, 16- and 17-H), 1.15 (3H, s, 20-H), 1.23 (3H, s, 19-H), 3.49 (1H, t, J = 3 Hz, 12-H), 3.71 (1H, s, ester Me). (Found: C, 65.89; H, 8.26. $C_{21}H_{31}O_4Cl$ requires: C, 65.87; H, 8.16%).

Methyl 12α:13α-epoxy-14-oxoabiet-8-en-18-oate **12**

(a) *From the chloroketone* **11**. A soln of **11** (164 mg) in anhyd DMF (16 ml) was mixed with $LiCO_3$ (156 mg) and LiCl (90 mg), and the mixture was heated at 100° under stirring for 2.5 h. It was poured into water and the product was extracted with ether. The organic layer was washed thoroughly with water and then dried. The oily product (151 mg) was chromatographed on a column of SiO_2 (23 g, benzene) to afford successively methyl 12α:13α-epoxy-14-oxoabiet-7-en-18-oate **13** as a glass (17 mg, 15.4% yield): IR (CCl_4) 1725, 1690, 1620, 1240 cm^{-1}; ^1H NMR (CCl_4) δ 0.78 (3H, s, 20-H), 0.81 (6H, d, J = 7 Hz, 16- and 17-H), 1.22 (3H, s, 19-H), 3.37 (1H, m, 12-H), 3.61 (3H, s, ester Me), 6.89 (1H, s, 7-H) and **12** as a glass (81 mg, 73.1% yield): IR (CCl_4) 1725, 1665, 1620, 1248 cm^{-1}; ^1H NMR (CCl_4) δ 0.89, 0.96 (each 3H d, J = 7 Hz, 16- and 17-H), 1.10 (3H, s, 20-H), 1.18 (3H, s, 19-H), 3.42 (1H, dd, J = 2, 3 Hz, 12-H), 3.60 (3H, s, ester Me), ^{13}C NMR δ 16.5 (C-19),[a] 16.6 (C-20),[a] 18.3 (C-2), 18.7 (C-16), 20.5 (C-6), 20.7 (C-17), 23.6 (C-11), 24.5 (C-7), 26.0 (C-15), 36.2 (C-3),[b] 36.6 (C-1),[b] 38.2 (C-10), 44.3 (C-5), 47.7 (C-4), 52.0 (ester Me), 55.2 (C-12), 62.8 (C-13), 128.3 (C-8), 155.8 (C-9), 178.5 (C-18), 195.6 (C-14) ppm.

(b) *From the allylic alcohol* **14**. To a soln of **14** (1.10 g) in acetone (58 ml) was added dropwise Jones reagent (1.5 ml) at 0° under stirring. The ice bath was removed and the mixture was allowed to react for 1.5 h. After addition of MeOH, it was concentrated and diluted with water. Isolation of the product by ether extraction gave **12** as crystalline mass (989 mg, 90.4% yield).

(c) *From the mixture of* **10** *and* **14**. A mixture of **10** and **14** (approximately 1:1 ratio, 4.335 g), obtained by the reaction of **9** (4.33 g) in absolute ether (90 ml) containing saturated HCl–ether soln (1 ml) at 0° for 4 h, was dissolved in acetone (100 ml) and oxidized with Jones reagent (10 ml). The product (4.049 g) dissolved in DMF (200 ml) was treated with $LiCO_3$ (3.6 g), LiCl (2.0 g) as described to furnish the enone **12** as yellow crystals (3.373 g, 77.4% yield).

Methyl 7α,11β-dibromo-12α:13α-epoxy-14-oxoabiet-8-en-18-oate **15**. A mixture of enones **12** and **13** (approximately 5:1 ratio, 1.72 g) obtained by dehydrochlorination of **11** was dissolved in CCl_4 (90 ml) and heated under refluxing with NBS (1.78 g), $CaCO_3$ (1.78 g) and dibenzoyl peroxide (50 mg) for 4 h. The solid material was filtered off and evaporation of the solvent from the filtrate left crystalline residue (3.4 g) which was recrystallized from MeOH to afford **15** as prisms (1.82 g, 73% yield), m.p. 180–182°: IR (CCl_4)1731, 1695, 1605, 1245, 920 cm^{-1}; ^1H NMR δ 0.98, 1.06 (each 3H d, J = 7 Hz, 16- and 17-H), 1.24 (3H, s, 19-H), 1.42 (3H, s, 20-H), 3.88 (1H, d, J = 3 Hz, 12-H), 5.08 (1H, d, J = 3 Hz, 11-H), 5.30 (1H, dd, J = 2.5 Hz, 7-H). (Found: C, 49.89; H, 5.55. $C_{21}H_{28}O_4Br_2$ requires: C, 50.01; H, 5.61%).

Methyl 12α:13α-epoxy-14-oxoabiet-7,9-dien-18-oate **16**. A soln of the dibromide **15** (1.0 g) in THF (140 ml) was treated with Zn dust (400 mg, freshly washed with 1M HCl, water and THF) under refluxing and vigorous stirring (slower stirring resulted in marked lowering in the yield of **16**) for 10 min. Zn was removed by filtration and the filtrate was extracted with ether (×3). The combined organic layers were washed thoroughly with water until $AgNO_3$ test became negative and, after drying with $MgSO_4$, the solvent was evaporated giving a yellow oil (800 mg). Purification by SiO_2 chromatography (30 g, benzene: AcOEt = 20:1) furnished the dienone **16** as yellow glass (623 mg, 91% yield). This compound is rather unstable when absorbed on SiO_2 and due precautions are necessary for chromatography. IR (CCl_4) 1725, 1692, 1625, 1600, 1240, 1180, 1125, 1100, 910, 890 cm^{-1}; ^1H NMR δ 0.91, 0.95 (each 3H d, J = 7 Hz, 16- and 17-H), 1.00 (3H, s, 20-H), 1.25 (3H, s, 12-H), 2.40 (1H, septet, 15-H), 3.42 (1H, d, J = 4 Hz, 12-H), 3.60 (3H, s, ester Me), 5.70 (1H, broad d, J = 4 Hz, 11-H), 6.94 (1H, m, 7-H).

Methyl 7β-acetoxy-11β-bromo-12α:13α-epoxy-14-oxoabiet-8-en-18-oate **17**. A soln of the dibromide **15** (30 mg) in AcOH (5 ml) was stirred with silver acetate (10 ml) at room temp. White precipitate appeared after 15 min and the reaction was continued for further 2 h. The precipitate was filtered off and the filtrate diluted with ether was washed successively with sat. $NaHCO_3$, water and brine, then dried. Evaporation of the solvent afforded crystalline product (25 mg, 87% yield), which was recrystallized twice from MeOH to furnish pure **17** as prisms, m.p. 150–153°: IR (CCl_4) 1735, 1685, 1610, 1230, 1008, 960, 925 cm^{-1}; ^1H NMR (CCl_4) δ 0.93, 1.06 (each 3H d, J = 7 Hz, 16- and 17-H), 1.24 (3H, s, 19-H), 1.52 (3H, s, 20-H), 2.03 (3H, s, acetyl Me), 2.44 (1H, septet, 15-H), 3.66 (3H, s, ester Me), 3.77 (1H, d, J = 3 Hz, 12-H), 5.18 (1H, dd, J = 1, 3 Hz, 11-H), 5.63 (1H, ddd, J = 1, 7, 10 Hz, H-7). (Found: C, 57.19; H, 6.46. $C_{23}H_{31}O_6Br$ requires: C, 57.15; H, 6.46%).

Methyl 9β:11β,12α:13α-diepoxy-14-oxoabiet-7-en-18-oate **20**. A mixture of the crude dienone **16** (508 mg), MCPBA (300 mg, purified, 97%), Na_2CO_3 (300 mg) in CH_2Cl_2 (50 ml) was stirred at room temp. for 17 h. Water was added and the product was extracted with ether. The ether layer was washed successively with *10%* $NaHCO_3$, *10%* Na_2CO_3 and brine, and dried with $MgSO_4$. The crude product left after evaporation of the solvent was chromatographed on a column of SiO_2 (15 g, benzene: AcOEt = 50:1) afforded **20** as a glass (264 mg, 48% yield), which contained *ca.* 10% of **19** as shown by the analysis of the integral of ^1H NMR. The same reaction at the presence of solid Na_2HPO_4 gave **20** in 50–70% yield which contaminated by more amounts of **19** (*ca.* 20–40%). Two-phase reaction with 0.5 M $NaHCO_3$ soln[12] furnished **20**, uncontaminated with **19**, in 31% yield. **20**: IR (CCl_4) 1730, 1710, 1640, 1240, 930, 900 cm^{-1}; ^1H NMR δ 0.87, 0.99 (each 3H, s, J = 7 Hz, 16- and 17-H), 1.04 (3H, s, 20-H), 1.28 (3H, s, 19-H), 3.64 (3H, s, ester Me), 3.75 (1H, d, J = 3 Hz, H-12), 4.00 (1h, d, J = 3 Hz, H-11), 6.68 (1H, m, H-7). Treatment of **16** (6.5 mg) in CH_2Cl_2 (4 ml) with m-chlorobenzoic acid (8 mg) at room temp. for two days gave quantitatively methyl 12β-(3'-chlorobenzoyloxy)-13α-hydroxy-14-oxoabiet-7,9-dien-18-oate **19** as crystals: IR (CCl_4) 3520, 3410, 1732, 1703, 1635, 1255 cm^{-1}; ^1H NMR δ 0.69, 1.01 (each 3H, d, J = 7 Hz, 16- and 17-H), 1.08 (3H, s, 20-H), 1.28 (3H, s, 19-H), 3.61 (3H, s, ester Me), 5.53 (1H, d, J = 6.5 Hz, 12-H), 5.96 (1H, broad d, J = 6.5 Hz, 11-H), 6.96 (1H, m, 7-H), 7.25 (1H, dt, J = 0.7, 7 Hz, 5'-H), 7.43 (1H, dt, J = 2, 7 Hz, 4'-H), 7.73 (1H, dt, J = 1.5, 7 Hz, 6'-H), 7.83 (1H, t, J = 1.5 Hz, 2'-H).

Methyl 12α:13α-epoxy-7β:11β-dihydroxy-14-oxoabiet-8-en-

[a,b] The assignments are interconvertible.

18-*oat* **21**. A soln of **20** (15 mg) in dioxane (4 ml) was treated with 1M H_2SO_4 (3 ml) at 40° for 3 h. The reaction mixture was extracted with ether and the ether layer was washed with sat. $NaHCO_3$ and brine, then dried. Evaporation of the solvent left a crystalline product (15 mg, 95% yield), which was recrystallized to give **21** as needles, m.p. 201–204° (from MeOH). IR (CCl_4) 3400, 1735, 1660, 1615, 1250 cm^{-1}; ^1H NMR δ 0.97, 1.05 (each 3H d, J = 7 Hz, 16- and 17-H), 1.30 (3H, s, 19-H), 1.45 (3H, s, 20-H), 3.69 (3H, s, ester Me), 4.35 (1H, d, J = 1 Hz, 12-H), 4.68 (1H, t, J = 8 Hz, H-7), 4.96 (1H, dd, J = 1, 9 Hz, 11-H).

Catalytic reduction of the diepoxide **20**. A soln of **20** (180 mg) in EtOH (20 ml) was stirred under atmosphere of hydrogen at the presence of 10% Pd–C for 2.5 h. After removal of the catalyst by filtration, the solvent was evaporated from the filtrate to yield a colorless oil (161 mg) which was chromatographed on a column of SiO_2 (30 g, benzene: AcOEt = 10:1). From the earlier fractions methyl 12α:13α-epoxy-11β-hydroxy-14-oxoabiet-8-en-18-oate **22** was obtained as a glass: IR (CCl_4) 3480, 1730, 1675, 1620, 1250, cm^{-1}; ^1H NMR δ 0.96, 1.03 (each 3H d, J = 7 Hz, 16- and 17-H), 1.24 (3H, s, 19-H), 1.30 (3H, s, 20-H), 3.66 (4H, s, ester Me and 12-H), 4.89 (1H, broad d, J = 8 Hz, collapse to a broad s upon D_2O addition, 11-H); ^{13}C NMR δ 16.8 (C-19, C-20), 18.3 (C-2), 18.7 (C-16), 20.3 (C-6), 22.1 (C-17), 23.6 (C-7), 25.5 (C-15), 36.3 (C-3),† 36.5 (C-1),† 38.1 (C-10), 44.2 (C-5), 47.7 (C-4), 52.2 (ester Me), 58.7 (C-12), 62.2 (C-13), 63.0 (C-11), 131.7 (C-8), 156.2 (C-9), 178.7 (C-18), 195.7 (C-14). Acetylation with Ac_2O and pyridine at room temp. afforded the corresponding acetate **24** as a glass: IR (CCl_4) 1740, 1680, 1620, 1220 cm^{-1}; ^1H NMR δ 0.91, 0.98 (each 3H d, J = 7 Hz, 16- and 17-H), 1.10 (3H, s, H-20), 1.22 (3H, s, H-19), 2.12 (3H, s, acetyl Me), 3.53 (1H, d, J = 2 Hz, H-12), 3.67 (3H, s, ester Me), 6.26 (1H, broad d, J = 2 Hz, H-11). Further elution on the chromatography above furnished methyl 12α:13α-epoxy-7α-ethoxy-11β-hydroxyabiet-8-en-18-oate **25** as a glass: IR (CCl_4) 3590, 3460, 1730, 1680, 1620, 1245, 1180 cm^{-1}; ^1H NMR δ 0.94, 0.96 (each 3H, d, J = 7 Hz, 16- and 17-H), 1.09 (3H, t, J = 7 Hz, $-CH_2CH_3$), 1.24, 1.26 (each 3H s, 19- and 20-H), 3.50 (2H, m, $-CH_2CH_3$), 3.67 (4H, s, ester Me and 12-H), 4.38 (1H, dd, J = 2, 3 Hz, 7-H), 4.94 (1H, dd, J = 2, 8 Hz, collapse to d, J = 2 Hz, upon D_2O addition, 11-H). Acetylation as above gave an acetate **26** as crystals, m.p. 214–216°, IR (CCl_4) 1740, 1685, 1620, 1215 cm^{-1}; ^1H NMR δ 0.95, 0.98 (each 3H d, J = 7 Hz, 16- and 17-H), 1.04 (3H, s, 20-H), 1.12 (3H, d, J = 7 Hz, $-OCH_2CH_3$), 1.23 (3H, s, 19-H), 2.10 (3H, s, acetyl Me), 2.54 (1H, septet, 15-H), 3.47 (2H, dq, J = 2, 7 Hz, $-OCH_2CH_3$), 4.42 (1H, dd, J = 2, 3 Hz, H-7), 6.18 (1H, d, J = 2 Hz, 11-H). (Found: C, 67.01; H, 8.20. $C_{25}H_{36}O_7$ requires: C, 66.94; H, 8.09%).

Conversion of **22** *to the epimeric alcohol* **27**. To a soln of **22** (70 mg) in CH_2Cl_2 (10 ml) cooled to 0° was added ethylamine (0.11 ml) and MsCl (0.05 ml), and the mixture was allowed to react for 1.5 h. After addition of ice, it was stirred for 30 min and then the product was extracted with ether. The organic layer was washed successively with 1 M HCl and brine, and dried. Crude product (103 mg) obtained by evaporation of the solvent was purified by chromatography (SiO_2 3 g, benzene: AcOEt = 10:1) giving methyl 12α:13α-epoxy-11β-mesyloxy-14-oxoabiet-8-en-18-oate **23** as prisms (80 mg, 94% yield), m.p. 135–137° (from benzene–CH_2Cl_2): IR (CCl_4) 1675, 1615, 1345, 1175 cm^{-1}; ^1H NMR δ 0.94, 1.02 (each 3H, d, J = 7 Hz, 16- and 17-H), 1.19 (3H, s, 20-H), 1.23 (3H, s, 19-H), 3.08 (3H, s, mesyl Me), 3.65 (3H, s, ester Me), 3.91 (1H, d, J = 2.5 Hz, 12-H), 6.00 (1H, d, J = 2.5 Hz, 11-H). (Found: C, 59.91; H, 7.36. $C_{22}H_{32}O_7S$ requires: C, 59.98; H, 7.32%). This mesylate **23** (27 mg) and tetraethylammonium acetate (26 mg) was dissolved in anhyd acetone (10 ml) and the mixture was refluxed under N_2 atmosphere for 17 h. The reaction mixture was extracted with ether and the extract soln was washed with sat. $NaHCO_3$ and brine, dried with $MgSO_4$. Evaporation of the solvent left a crude product (23 mg) which was chromatographed on a column of SiO_2 (5 g, benzene: AcOEt = 20:1) to afford methyl 11α-acetoxy-12α:13α-epoxy-14-oxoabiet-8-en-18-oate **28** as a glass (13 mg, 52% yield): IR (CCl_4) 1730, 1675, 1620, 1225 cm^{-1}; ^1H NMR δ 0.87, 0.95 (each 3H d, J = 7 Hz, 16- and 17-H), 1.15 (3H, s, 20-H), 1.22 (3H, s, 19-H), 2.20 (3H, s, acetyl Me), 3.68 (3H, s, ester Me), 3.75 (1H, d, J = 4 Hz, H-12), 5.77 (1H, dd, J = 2, 4 Hz, 11-H). The acetate **28** (13 mg) dissolved in a mixture of EtOH (5 ml) and water (3 ml) was hydrolyzed by allowing to react with 10% Na_2CO_3 at room temp. for 16 h. The crude product isolated by ether extraction was purified by chromatography (SiO_2 5 g, benzene: AcOEt = 20:1) giving methyl 12α:13α-epoxy-11α-hydroxy-14-oxoabiet-8-en-18-oate **27** as a glass (7 mg, 60% yield): IR (CCl_4) 3550, 1722, 1665, 1610, 1245 cm^{-1}; ^1H NMR δ 0.89, 0.96 (each 3H s, J = 7 Hz, 16- and 17-H), 1.15 (3H, s, H-20), 1.24 (3H, s, H-19), 2.23 (1H, d, J = 11 Hz, disappears upon D_2O addition, –OH), 3.69 (3H, s, ester Me), 3.76 (1H, d, J = 5 Hz, 11-H), 4.56 (1H, dd, J = 5, 11 Hz, collapses to d upon D_2O addition); ^{13}C NMR δ 15.7 (C-19), 17.6 (C-20), 18.3 (C-2), 18.8 (C-16), 20.8 (C-6), 22.1 (C-17), 23.7 (C-7), 25.8 (C-15), 36.1 (C-3),‡ 36.7 (C-1)‡ 39.6 (C-10), 44.2 (C-5), 47.8 (C-4), 52.2 (ester Me), 59.4 (C-12), 61.7 (C-11), 65.1 (C-13), 130.3 (C-8), 158.0 (C-9), 178.7 (ester CO), 192.9 (C-14).

$NABH_4$ reduction of **20**. To a soln of the crude diepoxide **20** (3.92 g) in MeOH (300 ml) cooled at −10° was added $NaBH_4$ (6.0 g) and the mixture was allowed to react for 2 h. Further amounts of $NaBH_4$ (2.0 g) was added and the reaction was continued for another 2 h. The mixture was quenched by the addition of dil. AcOH and extracted with ether. The organic layer was washed with water, dried and the solvent was evaporated. The residue (3.90 g) was chromatographed on a column of SiO_2 (250 g, benzene: AcOEt = 20:1–10:1) giving the epimeric alcohols, methyl 9β:11β,12α:13α-diepoxy-14α-hydroxyabiet-7-en-18-oate **33** and methyl 9β:11β,12α:13α-diepoxy-14β-hydroxyabiet-7-en-18-oate **32** in this sequence. **33**, needles (from petroleum ether–ether), m.p. 161.5–162.5°; IR (CCl_4) 3510, 3400, 1725, 1235, 1115, 1015, 925, 860 cm^{-1}; ^1H NMR δ 0.91, 1.05 (each 3H, J = 7 Hz, 16- and 17-H), 1.11 (3H, s, 20-H), 1.30 (3H, s, 19-H), 2.92 (1H, d, J = 12 Hz, disappears upon D_2O addition, –OH), 3.51 (1H, d, J = 3 Hz, H-13), 3.69 (3H, s, ester Me), 3.95 (1H, d, J = 3 Hz, H-11), 4.30 (1H, d, J = 12 Hz, collapses to broad s with $W_{1/2}$ = 3 Hz upon D_2O addition), 6.00 (1H, m, H-7); ^{13}C NMR, see Table 3. (Found: C, 69.69; H, 8.47. $C_{21}H_{30}O_5$ requires: C, 69.59; H, 8.34%). **32**, needles (from petroleum ether–ether), m.p. 151–152°; IR (CCl_4) 3569, 3420, 1722, 1240, 1128, 910 cm^{-1}; ^1H NMR δ 0.83, 1.14 (each 3H, s, 16- and 17-H), 1.08 (3H, s, H-20), 1.31 (3H, s, H-19), 3.45 (1H, d, J = 3 Hz, H-12), 3.70 (3H, s, ester Me), 3.80 (1H, d, J = 3 Hz, H-11), 4.67 (1H, broad d, J = 10 Hz, H-14, collapses to a broad s with W = 7 Hz upon D_2O addition), 6.11 (1H, m, H-7); ^{13}C NMR, see Table 3. (Found: C, 69.67; H, 8.43. $C_{21}H_{30}O_5$ requires: C, 69.59; H, 8.34%).

Epoxidation of the allylic alcohol **32** *with MCPBA*. A soln of **32** (200 mg) in CH_2Cl_2 (120 ml) was stirred at room temp. with MCPBA (100 mg) and Na_2HPO_3 (1.1 g) for 19 h. Water and ether were added and the organic layer was washed successively with 10% $NaHSO_3$, 10% Na_2CO_3 and brine, then dried. The crystalline product (189 mg, 91% yield) left after evaporation of the solvent was recrystallized from petroleum ether–ether giving pure methyl 7α:8α,9β:11β,12α:13α-triepoxy-14α-hydroxyabietan-18-oate **35** as needles, m.p. 211–213°; IR ($CHCl_3$) 3535, 1720, 1242, 1152, 1090, 1070, 900 cm^{-1}; ^1H NMR δ 0.81, 1.09 (each 3H d, J = 7 Hz, 16- and 17-H), 1.02 (3H, s, H-20), 1.27 (3H, s, H-19), 3.43 (1H, m, $W_{1/2}$ = 6 Hz, H-7), 3.50 (1H, d, J = 3 Hz, 12-H), 3.70 (4H, s, ester Me and H-11), 4.27 (1H, broad s, sharpens upon addition of D_2O, 14-H); ^{13}C NMR, see Table 3. (Found: C, 66.70; H, 8.06. $C_{21}H_{30}O_6$ requires: C, 66.63; H, 8.00%).

Epoxidation of the allylic alcohol **33**

(a) *With MCPBA (analytical run)*. A soln of **33** (166 mg) in CH_2Cl_2 (20 ml) was stirred at room temp. with MCPBA (70%, 350 mg) and Na_2HPO_4 (500 mg) for 2 weeks. The reaction mixture was treated as above and crude products (224 mg) obtained were separated by repeated chromatography on SiO_2 columns (twice, benzene: EtOAc = 20:1) giving the starting material **33** (4 mg, 2% yield), methyl 7β:8β,9β:11β,12α:13α - triepoxy - 14β - hydroxyabietan - 18 - oate **36** (7 mg, 3%) and methyl 7α:8α,9β:11β,12α:13α - triepoxy - 14β - hydroxyabietan - 18 - oate **37** (38 mg, 22%). Authentic samples of the triepoxides were

†The assignments may be interconvertible.

‡The assignments are interchangeable.

prepared by recrystallization from petroleum ether–ether. **36**, needles, m.p. 183.5–185.5°; IR ($CHCl_3$) 3510, 1720, 1250, 1215, 1085, 1035 cm^{-1}; ^1H NMR δ 0.89, 1.01 (each 3H d, J = 7 Hz, 16- and 17-H), 1.20 (6H, s, 19- and 20-H), 2.77 (1H, d, J = 11 Hz, disappears on D_2O addition, OH), 3.23 (1H, d, J = 5 Hz, H-7), 3.36 (1H, dd, J = 1, 11 Hz, collapses to a broad singlet upon D_2O addition, H-14), 3.50 (1H, dd, J = 1, 4 Hz, 12-H), 3.67 (3H, s, ester Me), 4.04 (1H, d, J = 4 Hz, H-11); ^{13}C NMR, see Table 3. (Found: C, 66.63; H, 8.02. $C_{21}H_{30}O_6$ requires: C, 66.63; H, 8.00%). **37**, plates, m.p. 181.5–182.5°; IR ($CHCl_3$) 3510, 1715, 1245, 1215, 1190, 1152, 1052 cm^{-1}; ^1H NMR δ 0.90, 1.01 (each 3H s, 16- and 17-H), 1.05 (3H, s, H-20), 1.25 (3H, s, H-19), 2.93 (1H, d, J = 12 Hz, disappears upon D_2O addition, OH), 3.31 (1H, m, H-7), 3.38 (1H, dd, J = 1, 11 Hz, collapses to s, H-14), 3.54 (1H, dd, J = 1, 3Hz, H-12), 3.65 (3H, s, ester Me), 3.90 (1H, d, J = 3 Hz, H-11); ^{13}C NMR, see Table 3. (Found: C, 66.72; H, 8.03. $C_{21}H_{30}O_6$ requires: C, 66.63; H, 8.00%). The reactions using benzene and MeCN as solvents (Table 2) were performed by stirring a mixture of **33** (30 mg), MCPBA (150 mg) and the solvent (3 ml) at room temp. for 8 days. The crude products were separated into the starting material and mixtures of **36** and **37** by SiO_2 chromatography (3 g). The ratio of **36** and **37** was estimated from the integration of ^1H NMR spectra with reference to the signals due to C_{11}–H.

(b) *With MCPBA (preparative run).* A soln of **33** (500 mg) in MeCN (150 ml) was stirred at room temp. with MCPBA (2.45 g) and Na_2HPO_4 (3.0 g) for a month. The crystalline crude products (649 mg) obtained after usual work-up was roughly separated by SiO_2 chromatography (18 g, benzene: AcOEt = 20:1) to give successively the starting material **33** (131 mg), a mixture mainly containing **36** and **37** (239 mg), a mixture of **38** and **39** (31 mg), and pure **39** (45 mg). Further separation of **36** and **37** was conveniently performed on a Lobar column (Merck, Lichroprep Si 60) using mixtures of petroleum ether and ether (3:1–2:1) as the eluting solvent. The total yields of products thus obtained were: **33** (145 mg, 29%), **36** (40.5 mg, 7.8%, 11.0% based on the reacted material), **37** (90 mg, 17%), **38** (40 mg) and **39** (64 mg). **38**: IR ($CHCl_3$) 3480, 1720, 1240, 1120, 985 cm^{-1}; ^1H NMR δ 0.91, 1.03 (each 3H d, J = 7 Hz, 16- and 17-H), 1.21 (3H, s, H-19), 1.35 (3H, s, H-20), 3.43 (1H, dd, J = 2, 4 Hz, H-12), 3.70 (3H, s, ester Me), 4.37 (1H, broad singlet, H-14), 4.67 (1H, dd, J = 4, 10 Hz, H-11), 5.69 (1H, t, J = 8 Hz, H-7), 7.3–7.9 (4H, m, Ar). **39**: IR ($CHCl_3$) 3590, 3400, 1720, 1680, 1250, 1095, 1068 cm^{-1}; ^1H NMR δ 0.95, 1.15 (each 3H d, J = 7 Hz, 16- and 17-H), 1.23 (3H, s, H-19), 1.27 (3H, s, H-12), 3.41 (1H, s, H-12), 4.33 (1H, broad s, H-14), 4.90 (1H, dd, J = 2, 4 Hz, H-7).

(c) *By sensitized photooxygenation.* A soln of **33** (50 mg) and biacetyl (1 g) in anhyd. benzene (100 ml) was charged in a photochemical quartz vessel and internally irradiated by a high pressure Hg-lamp (100 W) under continuous bubbling of oxygen. Tlc monitoring showed the disappearance of the starting material after 8 h. The soln was washed successively with sat. $NaHCO_3$, water (×2) and brine, then dried. Evaporation of the solvent left a yellow oil (110 mg) which was separated by chromatography on a SiO_2 column (petroleum ether–ether = 2:1) and then on a Lobar column (Merck, Lichroprep Si 60) to furnish **36** (10 mg, 19% yield) and **37** (5 mg, 10%) with some recovery of **33** (4 mg).

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