Rearrangement of methyl 11,12-di-*O*-methyl-6,7-didehydrocarnosate in basic medium. Easy hemisynthesis of miltirone

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Methyl 11,12-di-*O*-methyl-6,7-didehydrocarnosate 3, obtained from the abundant natural product carnosol 1, undergoes an interesting rearrangement when treated with potassium *tert*-butoxide in dimethyl sulfoxide to give 11,12-dimethoxy-20(10→7)*abeo*-abieta-5(10),8,11,13-tetraen-20-oic acid 4, in which an additional double bond is formed between C-5 and C-10 and the carboxylic acid group has migrated from C-10 to C-7. Deprotection of the two methyl ether moieties in 4 with BBr_3 allows spontaneous air oxidation and decarboxylation of the catechol derivative to give the potent benzodiazepine agonist miltirone 10. The structure of 6 has been unequivocally elucidated by X-ray diffraction analysis and indirect chemical correlation between 4 and 6 has been established.

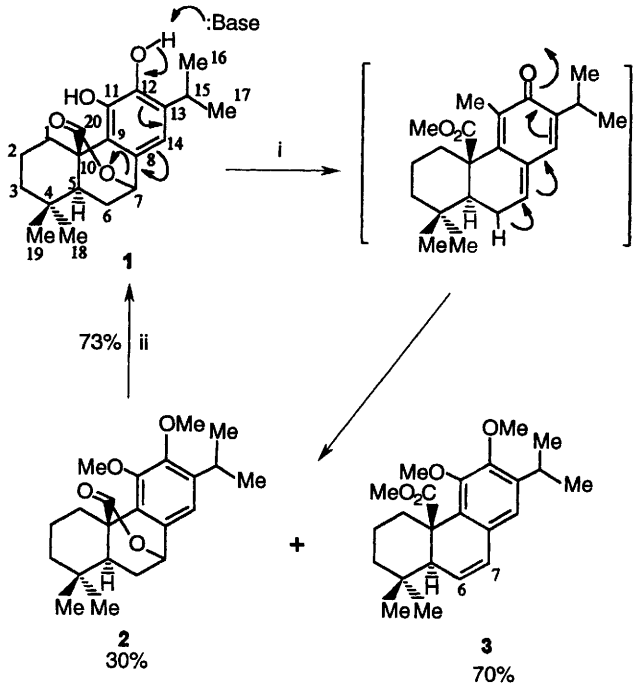
A member of the Labiatae family, the genus *Salvia* consists of some five hundred species found worldwide. Since ancient times, many species of this genus have been credited with medicinal properties [1,2,3] and thus reward investigation.

In previous papers [4,5] and on the basis of the isolation and chemical behaviour [6] of a large number of abietane diterpenes from the *Salvia* species, we have postulated a biosynthetic pathway to highly oxidized abietatrienes in which enzymatic dehydrogenation processes and the participation of singlet oxygen appear to play an important role.

In such a pathway, 6,7-didehydrocarnosic acid was postulated to have a key role.[4] In order to obtain further chemical evidence for the postulated process *via* the possible participation of a perepoxide intermediate in the reaction of the double bond of 6,7-didehydrocarnosic acid derivatives with singlet oxygen,[7] a certain amount of 6,7-didehydrocarnosic acid dimethyl ether **7** was required. Methyl 11,12-di-*O*-methyl-6,7-didehydrocarnosate **3** was obtained from carnosol **1**, an abundant natural product of the *Salvia* species, which can also be obtained by oxidation of carnosic acid, another abundant natural product, as indicated in Scheme 1.[8] A 90% yield of **3** was achieved by recycling **2**, which when treated with boron tribromide gave **1** (73%) after purification.

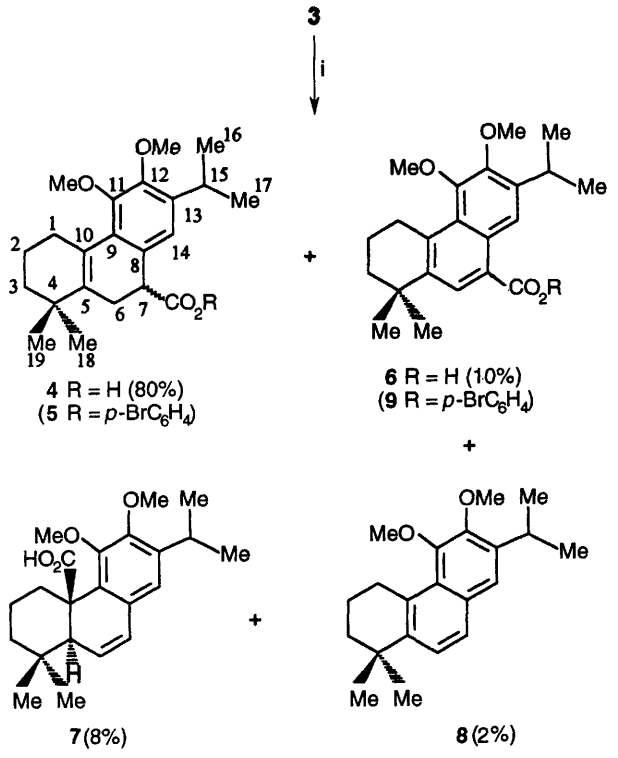
Our previous experience of this type of abietane diterpenes indicated that the C-20 methoxycarbonyl group is very difficult to saponify except with Bu^{t}OK in dimethyl sulfoxide (DMSO). Nevertheless attempts were made to saponify **3** using the following conditions: KOH–H_2O (20%), MeOH, 50 °C; LiOH, THF, H_2O reflux; AcOH, quinolein, 120 °C. In all the cases the starting material **3** was recovered. When the saponification was carried out with potassium *tert*-butoxide (Scheme 2), compound **3** gave a mixture of four products which were separated by silica gel chromatography. The major product (80% yield) was characterized by its spectroscopic data and those of its methyl ester derivative and also by chemical and spectroscopic correlation with **6**, as the rearranged substance 11,12-dimethoxy-20(10→7)*abeo*-abieta-5(10),8,11,13-tetraen-20-oic acid **4**.

Product **4**, which did not give crystals good enough for X-ray diffraction analysis, had the same molecular ion ($C_{22}H_{30}O_4$ by HRMS) as the expected hydrolysis product **7** and it also presented bands for a carboxylic group in its IR spectrum.



Scheme 1 *Reagents and conditions:* i, MeI, K_2CO_3, acetone, room temp., 1 d; ii, BBr_3, CH_2Cl_2, room temp., 2 h

Nevertheless, its ^{1}H NMR spectrum showed clear differences as compared with that of **7**, the most remarkable being the lack of the ABX system assignable to protons H-5 (δ 2.74, dd, ^1J 2.1, ^2J 3.8 Hz), H-6 (δ 5.98, dd, ^1J 3.8, ^2J 10.0 Hz) and H-7 (δ 6.40, dd, ^1J 2.1, ^2J 10.0 Hz) present in the latter and the lower chemical shift of the H-14 proton (δ 6.77) as compared with the same proton in the ^{1}H NMR spectrum of **7** (δ 6.64). On the other hand, the ^{13}C NMR spectrum of **4** shows, in addition to the signals corresponding to the six carbon atoms of the aromatic ring, two singlets at δ 150.82 and 150.37, demonstrating the existence of a tetrasubstituted C-5/C-10 double bond in the molecule. Finally, a carbon doublet at δ 44.89 is also observed in this spectrum which, taken in conjunction with the low chemical shift of the H-14 aromatic proton (δ 6.77) and with the



Scheme 2 *Reagents and conditions:* i, Bu^{t}OK, DMSO, 40 °C, 4 h

presence of a proton triplet at δ 3.55 (J 5.5 Hz) in the ^{1}H NMR spectrum, places the carboxylic group at C-7. All these data and those of its methyl derivative agree with the structure proposed for this compound. The derivative **5** ($C_{28}H_{33}O_4Br$ by HRMS), prepared by treatment of **4** with *p*-bromophenol, failed to provide a suitable crystal for X-ray diffraction analysis.

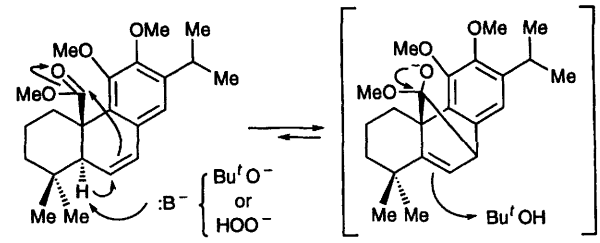
Nevertheless when **5** was left for a month in air without solvent, oxidation occurred to give some of the corresponding 6,7-didehydro derivative **9**, which in its ^{1}H NMR spectrum shows singlet signals for the H-6 and H-14 protons at similar chemical shifts to those observed for the same protons in the ^{1}H NMR spectrum of **6**.

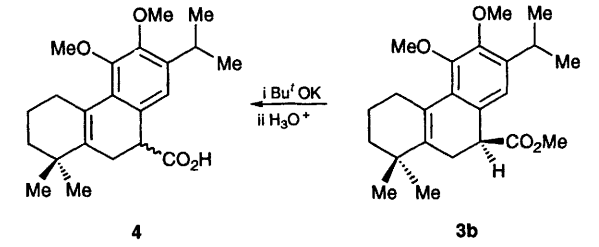
From the mechanistic point of view, we suggest that the rearrangement from **3** to **4** follows a mechanism such as that indicated in Scheme 3. Because of the high steric hindrance in **3a**, the molecule must collapse to **3b**, which is less strained. Racemization from **3b** to **4** under the strong basic conditions accounts for the near-zero optical activity of **4**.

Chemical proof of the structure **4** for the rearranged product comes from its clean transformation in a one-pot reaction to the potent benzodiazepine agonist miltirone **10**[9-12] when treated with boron tribromide, in a process which can be rationalized as indicated in Scheme 4. Some of **4a** could also be isolated and its ^{1}H NMR spectrum recorded. The product **4a** was converted into **10** when it was left in a solution open to the air, or when it was treated with silver oxide.

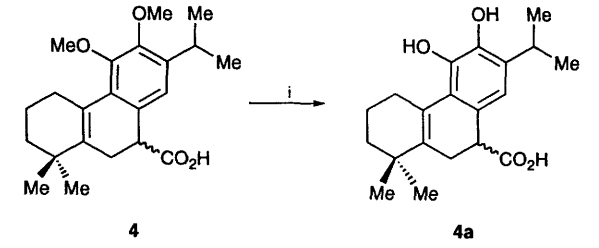
Taken in conjunction, the reactions summarized in Schemes 1, 2 and 4 represent an efficient hemisynthesis of miltirone from an abundant natural product such as carnosol or carnosic acid.

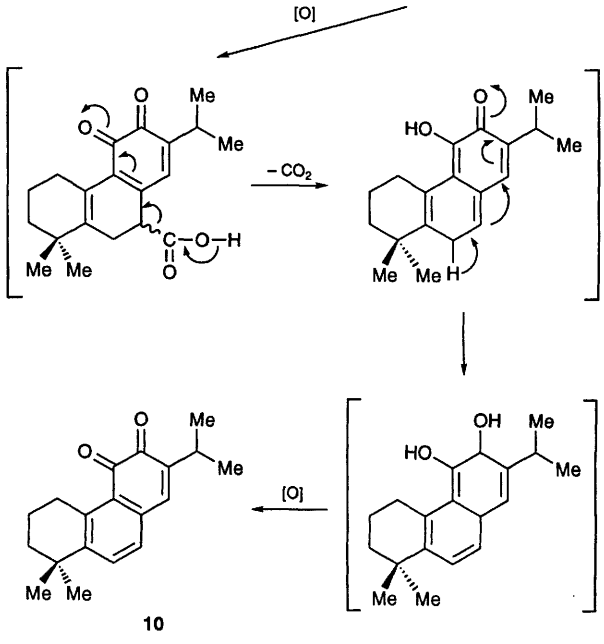
The minor products **6** and **8** formed in the basic treatment of **3** (Scheme 2) were also characterized from their spectroscopic data. Compound **6** shows the molecular ion $[M]^+$ at m/z 356 and the IR spectrum presents bands consistent with an aromatic carboxylic acid. In the ^{1}H NMR spectrum, the lack of the H-5 proton and the low chemical shift for two aromatic protons [δ 8.23 (s) and 8.62 (s)] revealed the presence of a carboxy group at C-7. These data and those of the methyl ester derivative agree with the structure of 11,12-dimethoxy-20(10→7)*abeo*-abieta-5(10),6,8,11,13-pentaen-20-oic acid for **6**. Unlike **4**, compound





Scheme 3





Scheme 4 *Reagents and conditions:* i, BBr_3, CH_2Cl_2, room temp., 5 min

6 gave good crystals from hexane–AcOEt and its structure was confirmed by X-ray diffraction analysis (Fig. 1).

The crystal structure of **6** shows a tricyclic system with two phenyl rings (rings B and C) and a six-membered ring (A). The endocyclic torsion angles of the fused phenyl rings are small, showing that it is essentially planar; the same planarity is observed in the individual aromatic rings, the greater deviation from the least-squares plane is 0.040 (4) Å for C-9 in rings B and C. The angle between both rings is 5°. Ring A has an envelope conformation with the flap at C-2; the angle between ring A and

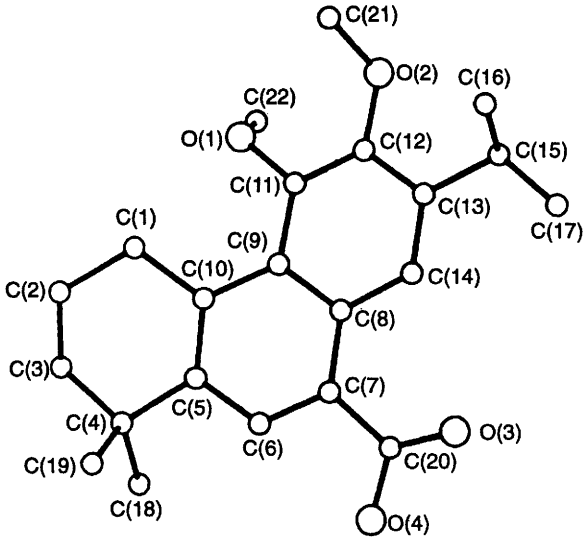


Fig. 1 PLUTO drawing of the molecule **6** with the atomic numbering (ref. 13)

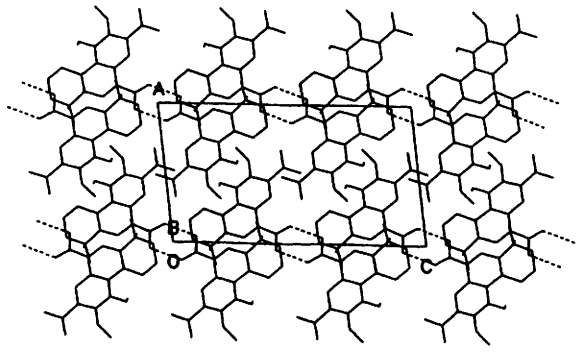


Fig. 2 A PLUTO crystal packing diagram of **6**, viewed along the *b* axis illustrating the hydrogen-bonding chain along the *c* axis

ring B is 164.6(1)°. Neither of the methoxy groups are coplanar with the ring, as revealed by the torsion angles C-22–O-1–C-11–C-9 = −103.8(5)°, and C-21–O-2–C-12–C-13 = −123.3(5)°; both methoxy groups point in the same direction. The carboxylic group at C-7 is essentially planar with the greater deviation of 0.007(5)° at C-20. Fig. 2 shows the packing of the molecules in the crystal. There is one intermolecular hydrogen bond: O-4 · · · H · · · O-3 (i) (*y* = *x*, 1 − *y*, 1 − *z*); O-4 · · · H = 1.03 (7) Å; O-4 · · · O-3 = 2.656 (6) Å; H · · · O-3 = 1.63 (8) Å; O-4 · · · H · · · O-3 = 172(7)°. There are no other intermolecular contacts less than 3.30 Å.

Compound **8** had the molecular ion $[M]^+$ at *m*/*z* 312. No band for a carboxylic acid was observed in the IR spectrum, and in the ^{1}H NMR spectrum the lack of the H-5 proton and the presence of two proton doublets at δ 7.36 and 7.52 belonging to an AB system are indicative of the existence of an aromatized ring B in the molecule. The above data are in accordance with the structure of 11,12-dimethoxy-20-*nor*-abieta-5(10),6,8,11,13-pentaene for **8**.

When oxygen was completely eliminated from the medium, no traces of compounds **4** or **6** were observed and the major product proved to be the normal hydrolysis product **7**. These results seem to indicate that the rearrangement occurrs with the participation of a hydroperoxy anion.

Experimental

General

^{1}H and ^{13}C NMR spectra were recorded on Bruker AMX400 and WP200SY spectrometers. Chemical shifts (δ) are given in ppm and *J* values in Hz. IR spectra were taken on a Perkin-Elmer 1600 (FTIR) spectrometer and UV spectra on a Perkin-Elmer 550SE. High resolution mass spectra were run on a VG-Micromass ZAB-2F at 70 eV. Low resolution mass spectra were run on a Hewlett-Packard, model 5995.

For the numbering schemes for the various polycyclic ring systems, see Schemes 1 and 2.

Methylation of carnosol 1

Carnosol **1** (300.0 mg) was dissolved in dry acetone and treated with 2 ml of MeI and 250 mg of K_2CO_3. The reaction mixture was stirred under an inert atmosphere in the absence of light for 48 h. Filtration, washing with acetone, evaporation of the solvent and chromatographic purification yielded two products: 11,12-di-*O*-methylcarnosol **2** (97 mg) and methyl 11,12-di-*O*-methyl-6,7-didehydrocarnosate **3** (236 mg).

11,12-Di-*O*-methylcarnosol 2. (Found: C, 74.17; H, 8.73. $C_{22}H_{30}O_4$ requires C, 73.71; H, 8.44%); λ_{max}(EtOH)/nm 273, 241; ν_{max}($CHCl_3$)/cm^{-1} 2945, 1740, 1270, 850; δ_H(200 MHz, $CDCl_3$) 0.86 (3 H, s, Me-19), 0.90 (3 H, s, Me-18), 1.17, 1.19 (each 3 H, d, *J* 7.0, Me-16 and Me-17), 2.41 (1 H, td, ^1J 4.5, ^2J 14.0, H-1α), 2.75 (1 H, br d, *J* 14.0, H-1β), 3.28 (1 H, sept, *J* 7.0, H-15), 3.78 (3 H, s, Ar-OCH_3), 3.80 (3 H, s, Ar-OCH_3), 5.40 (1 H, dd, ^1J 1.4, ^2J 4.0, H-7), 6.81 (1 H, s, H-14); *m*/*z* 358 (M^+, 15%), 314 (100), 299 (23), 284 (4), 271 (5), 245 (12), 243 (10), 232 (17), 229 (13), 215 (10), 201 (9), 189 (12).

Methyl 11,12-di-*O*-methyl-6,7-didehydrocarnosate 3. (HRMS: found, 372.2287. Calc. for $C_{23}H_{32}O_4$, 372.2301); λ_{max}(EtOH)/nm 310, 280, 240; ν_{max}($CHCl_3$)/cm^{-1} 2940, 1735, 1220, 1050, 950, 885, 853; δ_H(200 MHz, $CDCl_3$) 0.87 (3 H, s, Me-19), 1.01 (3 H, s, Me-18), 1.18, 1.21 (each 3 H, d, *J* 7.0, Me-16 and Me-17), 2.55 (1 H, t, *J* 2.8, H-5), 3.24 (1 H, sept, *J* 7.0, H-15), 3.52 (3 H, s, CO_2CH_3), 3.59 (1 H, br d, *J* 14.0, H-1β), 3.75 (3 H, s, Ar-OCH_3), 3.78 (3 H, s, Ar-OCH_3), 6.03 (1 H, dd, ^1J 2.8, ^2J 9.6, H-6), 6.36 (1 H, dd, ^1J 2.8, ^2J 9.6, H-7), 6.67 (1 H, s, H-14); *m*/*z* 372 (M^+, 59%), 327 (8), 313 (100), 271 (90), 256 (30), 243 (77), 228 (26), 201 (44), 149 (19), 84 (64), 55 (28).

Reaction of 2 with BBr_3

Compound **2** (130 mg) dissolved in dry CH_2Cl_2 (5 ml) was treated and stirred with 10 drops of freshly distilled BBr_3 at room temperature for 2 h. The solution was then diluted by careful addition of distilled water and extracted with $CHCl_3$. The dried organic layer was evaporated under reduced pressure and the crude residue was purified by preparative silica gel TLC (hexane–AcOEt 3:2). After purification carnosol **1** (87 mg) was obtained.

Saponification of 3

Compound **3** (50.1 mg) was dissolved in dry DMSO, Bu^{t}OK (35 mg) was added and then the reaction mixture was heated at 40–60 °C for 4 h. The reaction was neutralized with 5% aqueous HCl, water was added and the mixture extracted with AcOEt. The organic layers were dried over Na_2SO_4, filtered and the solvent evaporated in the rotary evaporator. The crude product was purified by preparative silica gel TLC (hexane–AcOEt 4:1) to give four products: 11,12-dimethoxy-20(10→7)*abeo*-abieta-5(10),8,11,13-tetraen-20-oic acid **4** (38.7 mg), 11,12-dimethoxy-20(10→7)*abeo*-abieta-5(10),6,8,11,13-pentaen-20-oic acid **6** (4.8 mg), 11,12-di-*O*-methyl-6,7-didehydrocarnosic acid **7** (3.7 mg) and 11,12-dimethoxy-20-*nor*-abieta-5(10),6,8,11,13-pentaene **8** (1 mg).

11,12-Dimethoxy-20(10→7)*abeo*-abieta-5(10),8,11,13-tetraen-20-oic acid 4. (HRMS: found, 358.21452. Calc. for $C_{22}H_{30}O_4$, 358.21441); ν_{max}(film)/cm^{-1} 3600–3100, 2940, 2860, 1750, 1440, 1360, 1330, 1310, 1210, 1160, 1130, 1060, 1050, 1000, 990, 870; δ_H(200 MHz, $CDCl_3$) 1.04 (3 H, s, Me-19), 1.08 (3 H, s, Me-18), 1.20 (6 H, d, *J* 7.0, Me-16 and Me-17), 1.56 (4 H, m, H-2 and H-3), 2.37 (1 H, br d, H-1β), 2.60 (2 H, m, H-6), 3.28 (1 H, sept, *J* 7.0, H-15), 3.55 (1 H, t, *J* 5.5, H-7), 3.78 (3 H, s, Ar-OCH_3), 3.83 (3 H, s, Ar-OCH_3), 6.77 (1 H, s, H-14); δ_C(50 MHz, $CDCl_3$) 20.15 (t, C-2), 23.37 (q, C-17), 23.44 (q, C-16),

26.68 (d, C-15), 27.17 (t, C-1), 27.38 (q, C-19), 28.11 (q, C-18), 29.90 (t, C-6), 34.78 (s, C-4), 39.31 (t, C-3), 44.89 (d, C-7), 60.27 (q, OCH_3), 60.56 (q, OCH_3), 120.27 (d, C-14), 127.79 (s, C-9), 129.05 (s, C-8), 129.20 (s, C-13), 138.97 (s, C-12), 140.19 (s, C-11), 150.32 (s, C-5), 150.37 (s, C-10), 179.07 (s, C-20); *m/z* 358 (M^+, 64%), *343 (100)*, 313 (10), 271 (11), 255 (16), 243 (10), 228 (6), 201 (14), 179 (8), 165 (14), 153 (9), 141 (8), 115 (8), 91 (5), 55 (21).

11,12-Dimethoxy-20(10→7)*abeo*-abieta-5(10),6,8,11,13-pentaen-20-oic acid 6. Mp 165 °C (from hexane–AcOEt) (Found C, 74.52; H, 8.17. $C_{22}H_{28}O_4$ requires C, 74.13; H, 7.92%. HRMS: found, 356.19675. Calc. for $C_{22}H_{28}O_4$, 356.19876); $\nu_{max}(CHCl_3)/cm^{-1}$ 3500–3000, 2960, 2920, 2860, 1690, 1680, 1590, 1550, 1480, 1460, 1400, 1340, 1270, 1160, 1140, 1120, 1080, 1060, 1030, 1010; δ_H(200 MHz, $CDCl_3$) 1.33 (6 H, d, *J* 7.0, Me-16 and Me-17), 1.37 (6 H, s, Me-18 and Me-19), 3.44 (1 H, sept, *J* 7.0, H-15), 3.84 (3 H, s, Ar-OCH_3), 3.96 (3 H, s, Ar-OCH_3), 8.23 (1 H, s, H-14), 8.62 (1 H, s, H-6); *m/z* 356 (M^+, 92%), 344 (16), 341 (68), 315 (14), 312 (95), 287 (20), 297 (100), 284 (34), 259 (42), 256 (45), 241 (29), 223 (36), 185 (27), 167 (23), 149 (91), 129 (40), 111 (30), 97 (40), 83 (48), 57 (89).

Crystal data for 6.—$C_{22}H_{28}O_4$, M_r = 356.46, monoclinic, space group $P2_1/c$, a = 10.307(1), b = 10.311(1), c = 18.689(2) Å, β = 97.579(6)°, V = 1968.8(3) Å, Z = 4, D_c = 1.2026 mg m^{-3}, λ(Cu-Kα) = 1.5418 Å, μ = 6.526 cm^{-1}, $F(000)$ = 768.00. A colourless crystal of approximate dimensions 0.23 × 0.20 × 0.17 mm was chosen for data collection. The lattice parameters were determined by least-squares from 31 reflections with 10° < θ < 31. The data were collected on a SEIFER four-circle diffractometer controlled under the CRYSOM[14] program. The intensities measurement was performed up θ = 65°, $\omega/2\theta$ scan technique, scan width = 2.00°, scan speed 0.10° s^{-1}. The total reflections collected were 3384, reduced to 2047 independent reflections, 1337 observed reflections with $I > 2\sigma(I)$, the range of the indices was: $-12 \leqslant h \leqslant 12$, $0 \leqslant k \leqslant 12$, $0 \leqslant l \leqslant 22$. Two reflections (3 0 6) and (−3 0 −6) monitored every 100 measured reflections showed no significant intensity decay; the intensities were corrected for Lorentz and polarization effects but no absorption correction was applied. The structure was solved by direct methods (SIR88)[15] and subsequent difference Fourier maps. During the initial isotropic refinement the isopropyl group at C-15 showed high thermal parameters and an additional peak appeared in this area which represented an alternative atomic site. Attempts were made to refine various models of the disordered area with partial occupation of atomic sites. These methyl groups continued to show large thermal parameters and unsatisfactory geometry indicating a conformational disorder; as a consequence the methyl C-17 has to be assigned two positions with the same occupancies and refined under geometrical constrains. The present geometry assigned to this part of the molecule is assumed to be the best one. The non-H atoms were refined with anisotropic thermal parameters and after several cycles the methyl groups at C-15 were not refined. The H-atoms were located from difference Fourier maps, with the exception of the H-atoms associated with the disordered methyl groups, which were held in fixed idealized positions with C–H = 1.00 Å. An empirical weighting scheme was applied to just avoid dependence in $\langle w\Delta^2F\rangle$ *vs.* $\langle F_o\rangle$ and $\langle \sin\theta/\lambda\rangle$.[16] The largest peak in the resulting difference map was 0.47(2) e $Å^{-3}$. The final R and R_w values are 6.1 and 6.9%, respectively. All calculations were performed on a VAX 6410 computer, with the X-Ray SYSTEM[17] and several local programs using literature scattering factors.[18]

Atomic coordinates, thermal parameters and bond lengths and angles have been deposited at the Cambridge Crystallographic Data Centre (CCDC). See Instructions for Authors, *J. Chem. Soc., Perkin Trans. 1*, 1996, Issue 1. Any request to the CCDC for this material should quote the full literature citation and the reference number 207/41.

11,12-Di-*O*-methyl-6,7-dehydrocarnosic acid 7. (HRMS: found, 358.2133. Calc. for $C_{22}H_{30}O_4$, 358.2122); λ_{max}(EtOH)/nm 266, 222; ν_{max}(film)/cm^{-1} 3420, 2960, 2860, 2620, 1690, 1450, 1380, 1360, 1330, 1310, 1270, 1220, 1110, 1090, 1080, 1060, 1040, 1000, 880, 750; δ_H(200 MHz, $CDCl_3$) 0.80 (3 H, s, Me-19), 1.06 (3 H, s, Me-18), 1.18 and 1.20 (each 3 H, d, *J* 7.0, Me-16 and Me-17), 2.74 (1 H, dd, ^1J 2.1, ^2J 3.8, H-5), 3.25 (1 H, sept, *J* 7.0, H-15), 3.76 (3 H, s, Ar-OCH_3), 3.80 (3 H, s, Ar-OCH_3), 3.85 (1 H, br d, *J* 14.0, H-1β), 5.98 (1 H, dd, ^1J 3.8, ^2J 10.0, H-6), 6.40 (1 H, dd, ^1J 2.1, ^2J 10.0, H-7), 6.64 (1 H, s, H-14); *m/z* 358 (M^+, 100%), 343 (21), 341 (19), 313 (87), 297 (25), 257 (63), 243 (46), 228 (29), 201 (38), 183 (14), 165 (22), 154 (8), 141 (18), 128 (22), 115 (18), 83 (31).

11,12-Dimethoxy-20-*nor*-abieta-5(10),6,8,11,13-pentaene 8. δ_H(200 MHz, $CDCl_3$) 1.30 (6 H, d, *J* 7.0, Me-16 and Me-17), 1.35 (6 H, s, Me-18 and Me-19), 3.43 (2 H, overlapping signals H-15 and H-1β), 3.86 (3 H, s, Ar-OCH_3), 3.94 (3 H, s, Ar-OCH_3), 7.34 (1 H, s, H-14), 7.36 (1 H, d, *J* 8.7, H-6), 7.52 (1 H, d, *J* 8.7, H-7); *m/z* 312 (M^+, 100%), 297 (83), 282 (8), 269 (7), 254 (9), 239 (6), 223 (8), 206 (5), 178 (3), 165 (6).

Esterification of 4

Compound **4** (30 mg) was dissolved in dry CH_2Cl_2 and treated with dicyclohexylcarbodiimide (DCC) (52 mg), *p*-bromophenol (22 mg) and 4-dimethylaminopyridine (DMAP) (5 mg) at room temperature for 3 h. The reaction mixture was purified by preparative silica gel TLC ($CHCl_3$) to give **5** (19.6 mg).

***p*-Bromophenyl 11,12-dimethoxy-20(10→7)*abeo*-abieta-5(10),8,11,13-tetraen-20-oate 5.** Mp 51 °C (from acetone); $[\alpha]_D^{22}$ +5.25 (*c* 0.17, $CHCl_3$) (HRMS: found, 514.15384. Calc. for $C_{28}H_{33}O_4Br$, 514.15417); δ_H(400 MHz, $CDCl_3$) 1.10 (3 H, s, Me-19), 1.12 (3 H, s, Me-18), 1.23 (6 H, d, *J* 6.7, Me-16 and Me-17), 1.59 (4 H, m, H-2 and H-3), 2.46 (1 H, br d, *J* = 14.0, H-1β), 2.74 (2 H, m, H-6), 3.31 (1 H, sept, *J* 6.7, H-15), 3.77 (1 H, t, *J* 5.5, H-7), 3.81 (3 H, s, Ar-OCH_3), 3.85 (3 H, s, Ar-OCH_3), 6.84 (1 H, s, H-14), 6.97 (2 H, d, *J* 8.7, H-2′ and H-6′), 7.48 (2 H, d, *J* 8.7, H-3′ and H-5′); δ_C(100 MHz, $CDCl_3$) 18.16 (q, C-18), 22.22 (t, C-2), 23.51 (q, C-17), 23.56 (q, C-16), 26.75 (d, C-15), 27.20 (t, C-1), 27.71 (q, C-19), 29.96 (t, C-6), 34.90 (s, C-4), 39.16 (t, C-3), 45.30 (d, C-7), 60.38 (q, OCH_3), 60.65 (q, OCH_3), 118.69 (s, C-1′), 120.05 (s, C-14), 123.21 (d, C-2′ and C-6′), 127.95 (s, C-9), 129.00 (s, C-8), 129.13 (s, C-13), 132.38 (d, C-3′ and C-5′), 138.91 (s, C-12), 140.26 (s, C-11), 150.34 (s, C-5), 150.77 (s, C-10), 172.07 (s, C-20); *m/z* 243 (M^+, 62%), 228 (11), 201 (14).

Reaction of 4 with BBr_3

Compound **4** (51.2 mg) was dissolved in 8 ml of dry CH_2Cl_2 and treated with 15 drops of BBr_3, then stirred for 10 min at room temperature. The medium was diluted by careful addition of distilled water and extracted with $CHCl_3$. The crude reaction product (49.2 mg) was purified by preparative silica gel TLC (hexane–AcOEt 4:1) to give two products: miltirone **10** (10.9 mg) and 11,12-dihydroxy-20-(10→7)*abeo*-abieta-5(10),8,11,13-tetraen-20-oic acid **4a** (26.1 mg). Spontaneous oxidation of product **4a** occurred in the NMR tube to form miltirone **10** (30.2 mg in total) which was found to be identical with natural miltirone.

11,12-Dihydroxy-20(10→7)*abeo*-abeita-5(10),8,11,13-tetraen-20-oic acid 4a. δ_H(200 MHz, $CDCl_3$) 1.04 (3 H, s, Me-19), 1.08 (3 H, s, Me-18), 1.25 (6 H, d, *J* 7.0, Me-16 and Me-17), 2.35 (1 H, br d, *J* 14.0, H-1β), 2.63 (2 H, m, H-6), 3.12 (1 H, sept, *J* 7.0, H-15), 3.55 (1 H, t, *J* 5.5, H-7), 6.58 (1 H, s, H-14).

Miltirone 10. δ_H(200 MHz, $CDCl_3$) 1.16 (6 H, d, *J* 7.0, Me-16 and Me-17), 1.30 (6 H, s, Me-19 and Me-18), 1.67 (2 H, m, H-2), 1.77 (2 H, m, H-3), 3.03 (1 H, sept, *J* 7.0, H-15), 3.18 (2 H, t, *J* 6.4, H-1), 7.07 (1 H, s, H-14), 7.11 (1 H, d, *J* 8.0, H-6), 7.60 (1 H, d, *J* 8.0, H-7); *m/z* 282 (M^+, 3%), 269 (2), 254 (46), 240 (100), 165 (25), 152 (19).

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