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SYNTHESIS OF (+)-PODOCARP-8(14)-EN-13-ONE AND METHYL-(+)-13-OXO-PODOCARP-8(14)-EN-18-OATE FROM ABIETIC ACID

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Abstract - An efficient method for the preparation of (+)-podocarp-8(14)-en-13-one 6 and methyl-(+)-13-oxo-podocarp-8(14)-en-18-oate 8 from abietic acid is described.

The structure and distribution of the functional groups in (+)-podocarp-8-(14)-en-13-one 6 make this ketone a versatile starting material for the synthesis of diterpenes.[1] Compound 6 has previously been prepared by the degradation of natural diterpenes, e.g. isophyllocladene[2] and manool,[1b,3] by reduction of methyl-(+)-13-oxo-podocarp-8(14)-en-18-oate 8[1e] obtained from resin acids such as neoabietic,[4] levopimaric,[5] and dehydroabietic[6] acids, and more recently by total synthesis.[7] However, these methods tend towards sequences with many steps and low yields or a laborious isolation of the starting material. In this paper we describe the synthesis of (+)-podocarp-8-(14)-en-13-one 6 and methyl-(+)-13-oxo-podocarp-8(14)-en-18-oate 8, which latter can be transformed into the former, starting from easily available abietic acid.

RESULTS

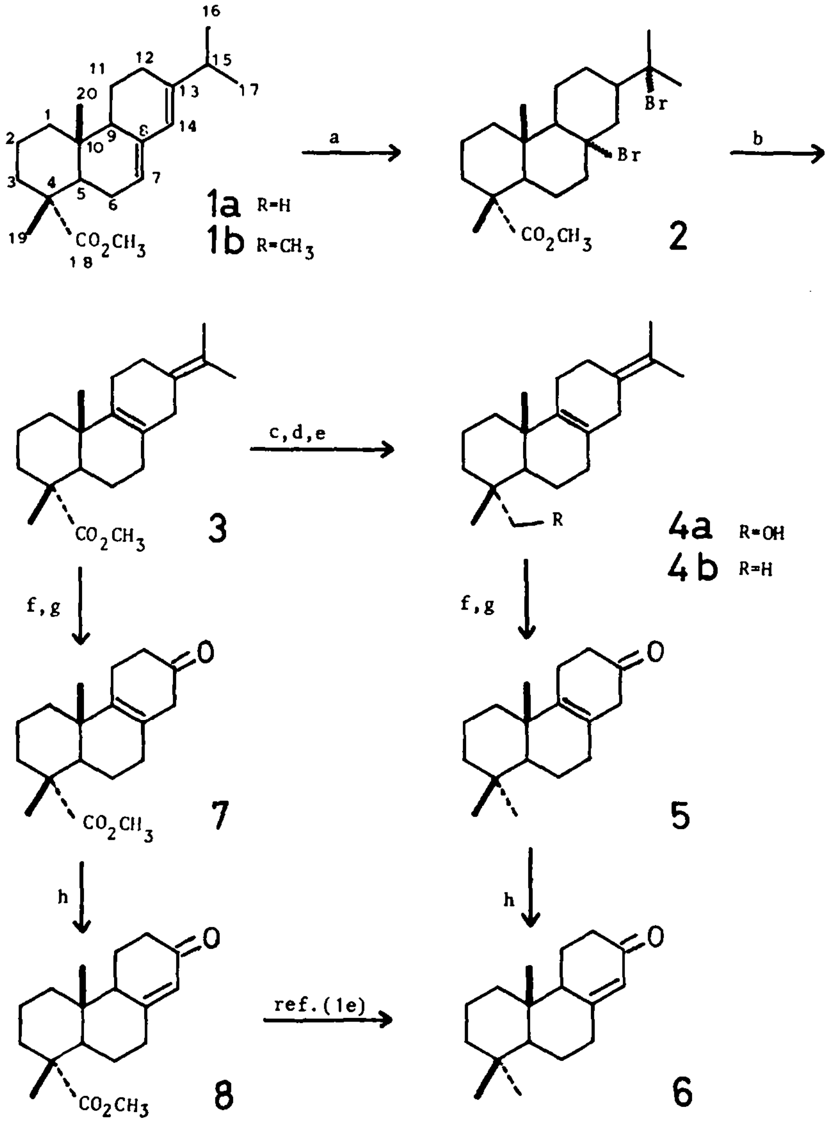
When abietic acid or its methyl ester is treated with a solution of hydrobromic acid in acetic acid a dibromo derivative is obtained.[8] At first it was thought that the bromine atoms would be found on the carbon atoms C_8 and C_{13},[9] however, Galt and Saksena[10] later observed that its ^{1}H-NMR spectrum and reactivity corresponded to a 8,15-dibromo derivative 2. We have confirmed this structure for the dibromo derivative 2 obtained from methyl abietate with a yield of 47%.

The dehydrobromation of 2 with different bases (sodium ethoxide,[10] triton B, potassium t-butoxide) gives a mixture of dienes in variable proportions. However, if the dibromo derivative is mixed with lithium hydroxide and treated in dimethylformamide at 80°C the main product is the diene 3 (83% in glc) which can be separated by crystallization from methanol (71% yield). Compound 3 can also be obtained by consecutive bromation and dehydrobromation of the methyl esters of the primary resinic acids[11] under the conditions stated (total yield 33% by weight).

In these types of compounds,[1e,12] reduction of the methoxycarbonyl group to methyl is usually carried out via the corresponding aldehyde with a Wolff-Kishner reduction. However, isomerization of the double bonds in 3 was caused by the basic medium at the high temperature required by Wolff-Kishner reduction. To avoid this, the reduction of 3 was carried out in three steps: Reduction of 3 to the alcohol 4a with sodium bis(2-ethoxymethoxy)aluminium hydride in toluene at 0°C, tosylation of this alcohol (tosyl chloride in pyridine, 0°C) and finally, reductive removal of the tosyloxy group with sodium iodide and zinc in hexamethylphosphorotriamide at 110°C.[13] Thus, diene 4b was obtained by column chromatography on silica gel from the gross product with a yield of 55% from 3.

Partial ozonolysis of 4b in ethyl acetate-dichloromethane at -78°C gave enone 5 with a yield of 79%. Finally, isomerization of enone 5 by refluxing with HCl in methanol gave (+)-podocarp-8(14)-en-13-one 6 (80% yield).

Enone 6 can also be obtained via an alternative pathway through compound 3. Partial ozonolysis of diene 3 under the same conditions as above gave enone 7 with a yield of 85%. Isomerization of enone 7 with HCl in methanol gave methyl (+)-13-oxo-podocarp-8(14)-en-18-oate 8 (85% yield). Reduction of the methoxycarbonyl group on 8 to methyl via a Wolf-Kishner reduction of the corresponding aldehyde, having previously protected the carbonyl group, is described in the literature[1e] but the total yield of 6 from diene 3 is inferior to that of the pathway given above.



a, HBr, AcOH; b, LiOH.2H_2O, DMF 80°C; c, SMEAH, toluene; d, TsCl, pyridine; e, NaI,Zn, HMPT; f, O_3,CH_2Cl_2-EtOAc,-78°C; g, Me_2S; h, HCl,MeOH.

EXPERIMENTAL

Mps are uncorrected. IR spectra were recorded on a Perkin-Elmer 281 spectrometer. ^{1}H-NMR spectra were determined on a Perkin-Elmer R12B (60-MHz) spectrometer in $CDCl_3$ solution with TMS as internal standard. Chemical shifts (δ) are expressed in ppm. Mass spectra were performed at 70 eV on a Varian 166 machine using the direct inlet system. Optical rotations were measured with a Carl Zeiss 77694 polarimeter. Ozone was generated with a laboratory ozonator (O_2 flow = 12 l/h, 7 mmol O_3/h). Tlc was carried out on Merck 0.25 mm silica gel 60 HF_{254} analytical aluminium plates. For column chromatographic separations of the products, silica gel Merck (0.063-0.200 mm) was used.

Methyl abietate (1b)

A solution of abietic acid 1a (160 g, 0.53 mol) and lithium hydroxide monohydrate (44.5 g, 1.0 mol) in dimethylformamide (640 ml) was stirred for 4 h at room temperature and then cooled in an ice-water bath. After addition of dimethyl sulfate (150 ml) stirring was continued for 15 min. The mixture was poured into water and extracted with hexane. The combined extracts were washed with 5% HCl solution, 10% $NaHCO_3$ solution and brine. After drying and concentration *in vacuo* 164 g (98%) of methyl abietate 1b, as an oil, was obtained.

Methyl 8,15-dibromoabietan-18-oate (2)

A solution of methyl abietate 1b (164 g, 0.52 mol) in acetic acid (490 ml) was added to a solution of 33% HBr in acetic acid (490 ml) and stirred for 6 h at room temperature. The precipitated solid was collected by vacuum filtration, the filtrate separated, and the solid washed with acetic acid and water. After drying *in vacuo* over P_2O_5 116.6 g (42%) of 2 was obtained. From the filtrate a second crop of 12.4 g (5%) of 2 was obtained after standing overnight. Mp 146-148°C (lit.,[8] 148°C); IR (KBr): 1722 (CO_2CH_3) cm^{-1}; ^{1}H-NMR: δ 3.60 (s, 3H, CO_2CH_3), 1.73 (bs, 6H, 2 C_{15}-CH_3), 1.17 (s, 3H, C_4-CH_3), 1.03 (s, 3H, C_{10}-CH_3).

Methyl abieta-8,13(15)-dien-18-oate (3)

An intimate mixture of 2 (110 g, 0.23 mol) and powdered lithium hydroxide monohydrate (24.3 g, 0.58 mol) in dimethylformamide (960 ml) was stirred while the temperature was raised over 30 min to 80°C. The resulting solution was stirred for 3 h 30 min at the same temperature and the reaction mixture was then poured into water and extracted with hexane. The hexane extract was washed with 5% HCl solution, 10% $NaHCO_3$ solution and brine. Removal of the solvent after drying gave a white residue (71.3 g) that was shown by glc (5% EGA over Chromosorb W AW, 210°C) to be essentially one component (86% purity). Crystallization from methanol (625 ml) gave 3 (48.7 g); a second crop (2.9 g) was obtained from the mother liquor giving a total of 51.6 g of 3 (71%). Mp 104-105°C (lit.,[9b] 104.5-106°C); $[\alpha]_D^{24}$ +173° (c 1.45, $CHCl_3$); IR(KBr): 1720 (CO_2CH_3) cm^{-1}; ^{1}H-NMR: δ 3.58 (s, 3H, CO_2CH_3), 1.62 (s, 6H, 2 C_{15}-CH_3), 1.14 (s, 3H, C_4-CH_3), 0.98 (s, 3H, C_{10}-CH_3); MS: m/z 316 (M^+, 46.6%), 301(18.1%), 257(8.0%), 241(28.2%), 135(100%).

Abieta-8,13(15)-diene (4b)

To a solution of 3 (1.50 g, 4.75 mmol) in toluene (8 ml), under argon at 0°C, a solution 70% sodium bis(2-methoxyethoxy)aluminium hydride in toluene (2 ml) was added. The mixture was stirred for 1 h 30 min at the same temperature and poured into sodium potassium tartrate (aq. soln.). The combined extracts were washed with brine, dried, and concentrated. The crude alcohol 4a obtained (1.36 g) was dissolved in dry pyridine (8 ml) and stirred with tosyl chloride (1.46 g, 7.70 mmol) at 0°C. After 24 h 85% lactic acid (0.3 ml) was added and the mixture further stirred for 30 min., poured into water and extracted with ether. The ether extract was washed with cold 5% HCl solution, 10% $NaHCO_3$ solution and brine. Removal of the solvent after drying gave the tosylate as an oil (2.0 g). A mixture of this tosylate (2.0 g, 4.52 mmol), sodium iodide (3.4 g, 22.6 mmol), zinc powder (2.9 g, 45.2 mmol) and hexamethylphosphorotriamide (23 ml) was stirred, under argon, for 20 h at 105-110°C. The reaction mixture was filtered to remove excess sodium iodide and zinc powder. The filtrate was poured into water and extracted with n-pentane. The combined extracts were washed with brine, dried, concentrated and chromatographed on silica gel with hexane, giving 4b (0.71 g, 55% yield). IR(NaCl): 1369, 1378, 1390 (CH_3) cm^{-1}; ^{1}H-NMR: δ 1.63 (s, 6H, 2 C_{15}-CH_3), 0.95 (s, 3H, C_{10}-CH_3), 0.87 (s, 3H, C_4-CH_3), 0.84 (s, 3H, C_4-CH_3); MS: m/z 272 (M^+, 5.0%), 187(2.4%), 148(7.4%), 135(33.4%), 41(100%).

Podocarp-8-en-13-one (5)

A stream of ozone (2.57 mmol) was passed through a solution of 4b (0.70 g, 2.57 mmol) in dichloromethane-ethyl acetate (1:1) (40 ml) for approximately 22 min at -78°C. Nitrogen was bubbled through the mixture which was then treated with dimethyl sulfide (3.4 ml) and removed from the cooling bath. The resulting mixture was stirred at room temperature for 48 hrs. Dimethylsulfide and the solvent were removed *in vacuo* and the residue dissolved in ether. The ether phase was washed with brine, dried, concentrated and chromatographed on silica gel (hexane-ether, 8:2), giving 5 (0.50 g, 79% yield) as an oil. $[\alpha]_D^{30}$ +176° (c 2.28, $CHCl_3$); IR (NaCl): 1715 (CO)cm^{-1}; ^{1}H-NMR: δ 2.67 (bs, 2H, H-C_{14}), 2.37 (bs, 4H, H-C_{11} and H-C_{12}), 1.01 (s, 3H, C_{10}-CH_3), 0.87 (s, 3H, C_4-CH_3), 0.85 (s, 3H, C_4-CH_3); MS: m/z 246 (M^+, 3.6%), 231(3.0%), 161(3.9%), 41(100%).

(+)-Podocarp-8(14)-en-13-one (6)

A solution of 5 (0.45 g, 1.83 mmol) and conc. HCl (5.9 ml) in methanol (15 ml) was refluxed, under argon, for 40 min. The mixture was diluted with water and extracted with ether. The organic phase was washed with 10% $NaHCO_3$ solution and brine. After drying and concentration the residue was chromatographed on silica gel (hexane-ether, 7:3) affording 6 (0.36 g, 80% yield). Mp 59-61°C (ether petroleum) (lit.,[7] 61.5-62.5°C); $[\alpha]_D^{26}$ +39° (c 1.10, $CHCl_3$); IR (KBr): 1616(C=C), 1656(CO)cm^{-1}; ^{1}H-NMR: δ 5.75 (bs, 1H, H-C_{14}), 0.93 (s, 3H, C_{10}-CH_3), 0.88 (s, 3H, C_4-CH_3), 0.81 (s, 3H, C_4-CH_3); MS: m/z 246 (M^+, 2.4%), 231(1.23%), 137(19.0%), 41(100%).

Methyl 13-oxo-podocarp-8-en-18-oate (7)

A stream of ozone (50.63 mmol) was passed through a solution of 3 (16 g, 50.63 mmol) in dichloromethane-ethyl acetate (1:1) (400 ml) for approximately 7 h 13 min at -78°C. The mixture was processed as described for the preparation of 5 with 70 ml of dimethyl sulfide. After chromatographic separation 7 (12.5 g 85% yield) was obtained. MP 108-110°C (petroleum ether); $[\alpha]_D^{25}$ +154° (c 1.81, $CHCl_3$); IR (KBr): 1715 (CO and CO_2CH_3) cm^{-1}; ^{1}H-NMR: δ 3.65 (s, 3H, CO_2CH_3), 2.71 (bs, 2H, H-C_{14}), 2.39 (bs, 4H, H-C_{11} and H-C_{12}), 1.21 (s, 3H, C_4-CH_3), 1.16 (s, 3H, C_{10}-CH_3); MS: m/z 290 (M^+, 4.9%), 275(2.1%), 231(4.7%), 215(28.2%), 41(100%).

Methyl-(+)-13-oxo-podocarp-8(14)-en-18-oate (8)

A solution of 7 (37 g, 0.127 mol) and conc. HCl (400 ml) in methanol (1000 ml) was refluxed, under argon, for 40 min. 500 ml Of methanol were distilled at reduced pressure and the reaction mixture diluted with water and extracted with ether. The organic phase was washed with 10% $NaHCO_3$ solution and brine. After drying the ether was concentrated to 300 ml and 650 ml of hexane were added and the ether left to distil until a slight turbidness appeared. After cooling the crystals were collected by filtration giving 25.8 g of 8 (70% yield). The mother liquor was concentrated and the residue chromatographed on silica gel (hexane-ether 8:2) affording a further 5.4 g (14.6%) of 8. Mp 125-127°C (lit.,[5] 126-127°C, lit.,[4] 126-128°C); $[\alpha]_D^{24}$ +57° (c 1.10, $CHCl_3$): IR (KBr): 1615 (C=C), 1660 (C=O), 1720 (CO_2CH_3) cm^{-1}; ^{1}H-NMR: δ 5.9 (bs, 1H, H-C_{14}), 3.65 (s, 3H, CO_2CH_3), 1.21 (s, 3H, C_4-CH_3), 0.84 (s, 3H, C_{10}-CH_3); MS: m/z 290 (M^+, 3.4%), 275(1.6%), 231(2.2%), 41(100%).

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REFERENCES

1 a) G. Ohloff, C. Vial, H.R. Wolf, K. Job, E. Jegou, J. Polonsky and E. Ledever Helv. Chim. Acta., 63, 1932 (1980).
b) D.D.K. Manh, M. Fetizon and J.P. Flament, Tetrahedron, 31, 1897 (1975); ibid, 31, 1903 (1975).
c) D.K.M. Duc, M. Fetizon and S. Lazare, J. Chem. Soc., Chem. Commun., 282 (1975).
d) R.C. Cambie, K.N. Joblin and A.F. Preston, Aust. J. Chem., 24, 2365 (1971).
e) E. Wenkert, J.R. Mahajan, M. Nussim and F. Schenker, Can. J. Chem., 44, 2575 (1966).
2 P.K. Grant and R. Hodges, Tetrahedron, 8, 261 (1960).
3 J.A. Barltrop, D. Giles, J.R. Hanson and N.A.J. Rogers, J. Chem. Soc., 2534 (1962).
4 S.W. Pelletier, K.N. Iyer and C.W.J. Chang, J. Org. Chem., 35, 3535 (1970).
5 W. Herz and V. Baburao, J. Org. Chem., 36, 3271 (1971).
6 A.W. Burgstahler and L.R. Worden, J. Am. Chem. Soc., 86, 96 (1964).
7 T. Matsumoto and S. Usui, Bull. Chem. Soc., Japan, 52, 212 (1979).
8 P. Levy, Ber., 64, 2441 (1931).
9 a) Sir J. Simonsen, "The Terpenes", Cambridge University Press, Vol. III, pp. 384 (1951).
b) A.W. Burgstahler, J.N. Marx and D.F. Zinkel, J. Org. Chem., 34, 1550 (1969)
10 R.H.B. Galt and A.K. Saksena, J. Chem. Soc., C, 1033 (1969).
11 G.C. Harris and T.F. Sanderson, J. Am. Chem. Soc., 70, 334 (1948).
12 a) A. Tahara, M. Shimagaki, S. Ohara and T. Nakata, Tetrahedron Letters, 1701 (1973).
b) T. Matsumoto, Y. Ohsuga, S. Harada and K. Fukui, Bull. Chem. Soc., Japan, 50, 266 (1977).
c) H. Okawara, H. Nakai and M. Ohno, Tetrahedron Letters, 1087 (1982).
13 Y. Fujimoto and T. Tatsuno, Tetrahedron Letters, 3325 (1976).