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A New Synthesis of Methyl 13-Hydroxypodocarpa-8,11,13-trien-18-oate *via* Nitrodeisopropylation of Methyl 12-Acetylabieta-8,11,13-trien-18-oate

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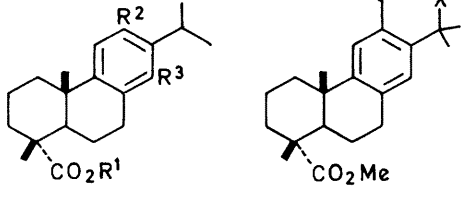
Summary Nitration of methyl 12-acetylabieta-8,11,13-trien-18-oate (Ij) has given the products (Ik) and (IIIa), and the latter has been converted into methyl 13-hydroxypodocarpa-8,11,13-trien-18-oate (IIIf) in 26% overall yield from methyl abieta-8,11,13-trien-18-oate (Ib).

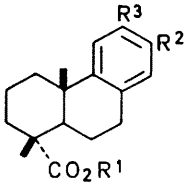
We have reported functionalisation of the isopropyl group of abieta-8,11,13-trien-18-oic acid (Ia; dehydroabietic acid) by intramolecular cyclisations in which the aromatic acid (Ic) was converted into the γ-lactone (IIa) by lead tetra-acetate oxidation, and the diazomethyl ketone (Id) was converted into the indanone (IIb) by thermolysis.[1] The possibility of direct replacement of the isopropyl group by a nitro-group[2] has also been examined. Previous nitration experiments have shown that abieta-8,11,13-trien-18-oic acid (Ia) gives the dinitro-acid (Ie),[3] the sulphonic acid (If) gives the dinitro-acid (Ie) (resulting from nitrodesulphonation), and the nitro-sulphonic acid (Ig),[4] and the C-12-amine (Ih) gives the nitro-amine (Ii).[5]

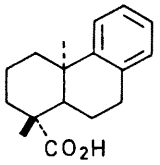
We have found that nitration of methyl 12-acetylabieta-8,11,13-trien-18-oate (Ij) with a mixture of fuming nitric acid–sulphuric acid[6] effects a remarkably clean conversion into the dinitro-ester (Ik) in 10% yield, and the nitro-ketone (IIIa) in 85% yield. Reduction of the nitro-ketone (IIIa) with tin(II) chloride–hydrochloric acid in acetic acid,[7] followed by hydrolysis of the tin(IV) chloride addition compound with aqueous sodium hydroxide, gave the amino-ketone (IIIb) in 68% yield. Diazotisation of the amine (IIIb) in 10% aqueous hydrochloric acid with aqueous sodium nitrite,[8] and decomposition of the diazonium salt with hot aqueous sulphuric acid, gave the phenol (IIIc) in 84% yield. Methylation of the latter compound with



		R^1	R^2	R^3
(I)	a;	H	H	H
	b;	Me	H	H
	c;	Me	CO_2H	H
	d;	Me	$COCHN_2$	H
	e;	H	NO_2	NO_2
	f;	H	SO_3H	H
	g;	H	SO_3H	NO_2
	h;	H	NH_2	H
	i;	H	NH_2	NO_2
	j;	Me	COMe	H
	k;	Me	NO_2	NO_2
	l;	Me	COMe	NO_2

(II) a; X = O
b; X = CH_2





		R^1	R^2	R^3
(III)	a;	Me	NO_2	COMe
	b;	Me	NH_2	COMe
	c;	Me	OH	COMe
	d;	Me	OMe	COMe
	e;	Me	OMe	CO_2H
	f;	Me	OH	H
	g;	H	H	H

(IV)

sodium hydroxide–dimethyl sulphate[9] gave the methyl ether (IIId) (82% yield).

Reaction of the keto-ester (IIId) with iodine in pyridine, followed by cleavage of the *N*-pyridinium iodide salt with ethanolic sodium hydroxide[10] gave, after acidification, the aromatic acid (IIIe) in 78% yield. By treating the carboxylic acid (IIIe) with basic copper carbonate in boiling quinoline,[11] decarboxylation, with concomitant demethylation of the 13-methoxy-group occurred. The ring-A ester was also partially hydrolysed during this reaction, and by treating the crude decarboxylation product with diazomethane in ether, the phenol (IIIf) was obtained in almost quantitative yield.

The phenol (IIIf) prepared in this way had identical properties with that prepared by Wenkert *et al.*[8] and by Dev *et al.*[12] which showed that no inversion of configuration of the angular methyl group at C-10 had occurred during the nitrodeisopropylation reaction. This is in contrast to the aluminium chloride-catalysed deisopropylation of abieta-8,11,13-trien-18-oic acid (Ia) which has been shown to give podocarpa-8,11,13-trien-18-oic acid (IIIg) in 6% yield, and 10α-podocarpa-8,11,13-trien-18-oic acid (IV) in 44% yield.[13] The present sequence for replacing the isopropyl group of methyl abieta-8,11,13-trien-18-oate (Ib) with an hydroxy-group appears to be the most efficient yet reported,[8,12,14] and is easily conducted on both large and small scales.

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[1] R. C. Cambie and R. A. Franich, *Chem. Comm.*, 1969, 725.
[2] For a review of nitration reactions other than nitrodeprotonation, see D. V. Nightingale, *Chem. Rev.*, 1947, **47**, 117.
[3] L. F. Fieser and W. P. Campbell, *J. Amer. Chem. Soc.*, 1938, **60**, 159.
[4] L. F. Fieser and W. P. Campbell, *J. Amer. Chem. Soc.*, 1939, **61**, 258.
[5] W. P. Campbell and M. Morgana, *J. Amer. Chem. Soc.*, 1941, **63**, 1838.
[6] E. L. Martin, *J. Amer. Chem. Soc.*, 1936, **58**, 1438.
[7] L. I. Smith, *Org. Synth. Coll. Vol.* **2**, 1943, 254.
[8] E. Wenkert, R. W. J. Carney, and C. Kaneko, *J. Amer. Chem. Soc.*, 1961, **83**, 4440.
[9] G. N. Vyas and N. M. Shah, *Org. Synth. Coll. Vol.* **4**, 1963, 837.
[10] Y. T. Pratt, *J. Amer. Chem. Soc.*, 1951, **73**, 3805.
[11] E. B. Herschberg and L. F. Fieser, *J. Amer. Chem. Soc.*, 1941, **63**, 2561.
[12] D. K. Banerjee, S. Dev, T. R. Kasturi, and E. Raghavan, *Indian J. Chem.*, 1968, **6**, 409.
[13] M. Ohta and L. Ohmori, *Chem. and Pharm. Bull. (Japan)*, 1957, **5**, 91, 96.
[14] A. W. Burgstahler and L. R. Worden, *J. Amer. Chem. Soc.*, 1961, **83**, 2587.