Inversion of the C-4 Substituents in Dehydroabietic Acid: Synthesis of (+)-Callitrisic Acid[1]

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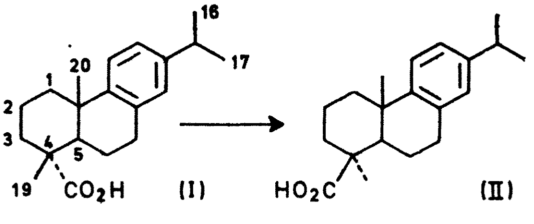
Summary A simple five-step sequence for the inversion of the C-4 substituents of dehydroabietic acid to yield (+)-callitrisic acid is reported.

AN important problem encountered in di- and tri-terpene chemistry is the difficulty in inverting the stereochemical configuration of substituents attached to a quaternary carbon atom. Of particular interest is the problem of inverting the configuration at C-4 of the diterpene resin acids. Because of the ready availability of resin acids from pine rosin, these compounds could serve as useful, inexpensive starting materials in the synthesis of other, closely related, but less readily available natural products containing C-4 substituents of opposite stereochemical configuration, provided that a simple synthetic scheme could be devised for first inverting the substituents at C-4 of the diterpene resin acids. Wenkert and co-workers[2] have recently described a reaction sequence which partially accomplishes this goal. However, the low yield and number of steps required seriously impair the utility of this method for such synthetic purposes. We report here a simple five-step sequence for the inversion of the C-4 substituents of one of the most common diterpene resin acids, *i.e.*, dehydroabietic acid (I), to yield (+)-callitrisic acid (II), a diterpene acid recently isolated from natural sources.[3]



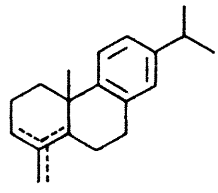
(I) (II)

Oxidative decarboxylation[4] of (I) with lead tetra-acetate in benzene–pyridine resulted in the formation of a mixture of isomeric olefins (IIIa-c). Pure (IIIc)[4a,b] was isolated in a

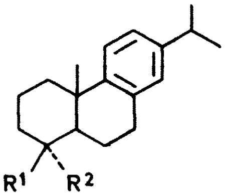
40% yield† *via* chromatography over 10% silver nitrate impregnated silica gel.[4a,5] Epoxidation of (IIIc) with *m*-chloroperbenzoic acid in methylene chloride afforded (IV),[6] m.p. 63·5—65·0° (sublimed); $[\alpha]_D^{25} + 121°$ (*c* 0·23, EtOH); i.r. (neat): 3020, 1250, 980, and 915 cm^{-1} (epoxide); n.m.r.‡ (CCl_4): δ1·12 (3H, s, 20-H_3), 1·21 (6H, d, *J* 7 Hz, 16-H_3 and 17-H_3), 2·54 (2H, AB quartet, *J* 5·5 Hz, 19-H_2), 2·65—3·05 (3H, m, benzylic protons), and 6·95—7·25 (3H, m, aromatic protons). Rearrangement of crude (IV) with BF_3 etherate in benzene afforded a mixture of epimeric aldehydes (Va) and (Vb)[4b] [62% isolated yield based on (IIIc)], i.r. (neat): 2720 (-CHO) and 1725 cm^{-1} (>C=O); n.m.r. (CCl_4: δ0·98 and 1·08 (3H, singlets, 20-H_3 of Va and Vb), 1·20 (6H, d, *J* 7 Hz, 16-H_3 and 17-H_3), 9·52 and 10·00 (1H, doublets, *J* 3 Hz and 0·5 Hz, respectively, C*H*O protons of Va and Vb).

Methylation of the mixture of (Va) and (Vb) proceeded with predictable stereochemistry[7] and, most readily accomplished by titration of a dimethylformamide solution of the aldehyde mixture with tritylsodium[8] and subsequent treatment of the anion thus generated with an excess of methyl iodide for 24 h at 50°, afforded callitrisaldehyde[3a] (VI) (66% isolated yield), i.r. (neat): 2710 (CHO) and 1720 cm^{-1} (>C=O); n.m.r. (CCl_4): δ1·03 (3H, s, 18-H_3), 1·06 (3H, s, 20-H_3), 1·20 (6H, d, *J* 7 Hz, 16-H_3 and 17-H_3), and 9·78 (1H, d, *J* 1 Hz, C*H*O[9])], as well as one of the two possible geometrically isomeric enol ethers, (VIII) (14% yield), i.r. (neat): 3050 (=CH-), 1680 cm^{-1} (C=C), 1225 and 1130 cm^{-1} (=COMe); n.m.r. (CCl_4): δ0·98 (3H, s, 20-H_3) 1·22 (6H d, *J* 7 Hz, 16-H_3 and 17-H_3), 3·55 (3H, s, OCH_3), 5·57 (1H, broad singlet, -C=C-*H*), and 6·75—7·30 (3H, m, aromatic). Alkylation, using either potassium t-butoxide or sodium hydride as the base, proved less satisfactory, resulting either in incomplete reaction or formation of undesirable side-products.

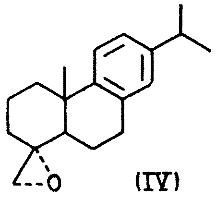
Oxidation of callitrisaldehyde (VI) with silver oxide in aqueous methanol *or* with Jones reagent[10] provided callitrisic acid (II) (80% crude yield) which was purified as its methyl ester (VII)[3] [76% isolated yield based on (VI)], m.p. 79·0—79·5° (MeOH); $[\alpha]_D^{25} + 137°$ (*c* 0·642, EtOH); i.r. (KBr): 1720 (>C=O) and 1495, 1240, 1232, 1193, 1157, 1138, 887, and 835 cm^{-1}; n.m.r. (CCl_4): δ0·99 (3H, s, 18H_3) 1·27 (3H, s, 20-H_3), 1·21 (6H, d, *J* 7 Hz, 16-H_3 and 17-H_3), 1·40—2·50 (9H, m, methylene and methine protons), 2·50—3·10 (3H, m, benzylic protons), 3·64 (3H, s, CO_2CH_3), and 6·73—7·39 (3H, m, aromatic protons). The i.r. and mass spectra of the synthetic material were superimposable upon those of an authentic sample of (+)-methyl callitrisate. The overall yield of methyl callitrisate based on dehydroabietic acid is 12·5—15·5%.



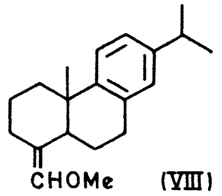
(III) a; $\Delta^{3(4)}$
b; $\Delta^{4(5)}$
c; $\Delta^{4(18)}$



(Va) R^1 = H, R^2 = CHO
(Vb) R^1 = CHO, R^2 = H
(VI) R^1 = CHO, R^2 = Me
(VII) R^1 = CO_2Me, R^2 = Me



(IV)



(VIII)

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† The partial conversion of olefin (IIIa) (formed in a 39% yield) into (IIIc) *via* a hydrobromination (HBr, pentane, −10°)-dehydrobromination (potassium t-butoxide, $HCONMe_2$, 25°) sequence provided additional quantities of the exocyclic olefin, raising the overall yield of (IIIc) to 50%.

‡ All n.m.r. spectra were recorded at 60 MHz and are measured in p.p.m. relative to $SiMe_4$ as an internal standard.

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