Synthesis of the Lichen Depsidones Notatic Acid and 4-*O*-Methylhypoprotocetraric Acid

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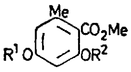
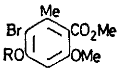
Summary The lichen depsidones notatic acid (**14**) and 4-*O*-methylhypoprotocetraric acid (**18**) were synthesised by different routes.

Although the depsidones have been known for many years[1] only the simplest member, diploicin, has been totally synthesised.[2] Recently we reported the isolation and structural determination of the lichen depsidones notatic acid (**14**) and 4-*O*-methylhypoprotocetraric acid (**18**),[3] and we now report the synthesis of these metabolites by different routes.

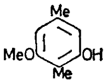
Selective benzylation[4] of methyl orsellinate (**1**) gave the benzyl ether (**2**) m.p. 64—66°, which on methylation gave the oily ether (**3**). Bromination of (**3**) gave the bromo-compound (**4**), m.p. 101—104°, and hydrogenation to the phenol (**5**), m.p. 122—123°, followed by methylation gave the known methyl ether (**6**).[5] Ullmann reaction of the bromo-compound (**4**) with the phenol (**7**)[6] under a modification of the conditions of Tomita,[7] then gave the diaryl ether (**8**) (38%), m.p. 117—119°.



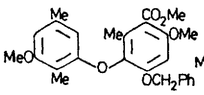
(1) $R^1 = R^2 = H$
(2) $R^1 = CH_2Ph, R^2 = H$
(3) $R^1 = CH_2Ph, R^2 = Me$



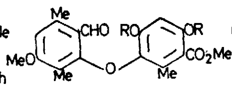
(4) $R = CH_2Ph$
(5) $R = H$
(6) $R = Me$



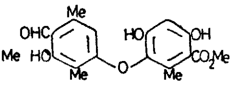
(7)



(8)



(9) R = H
(10) R = Ac



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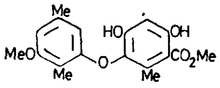

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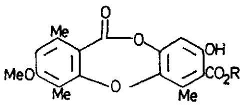
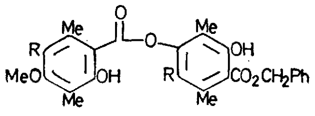
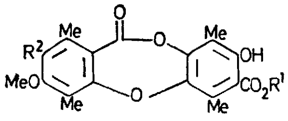


(13) R = Me
(14) R = H

Formylation[4] of compound (**8**) with an excess of dichloromethyl methyl ether and titanium(IV) chloride at −70° followed by boron trichloride demethylation[8] gave the required aldehyde (**9**) (21%), m.p. 241—242° (decomp.), the aldehyde (**11**) (47%), m.p. 118—120°, and the *o*-hydroxy-ester (**12**) (31%), m.p. 146—148°. Acetylation of the aldehyde (**9**) gave the oily acetate (**10**) which on permanganate oxidation and subsequent base hydrolysis and lactonisation with trifluoroacetic anhydride in toluene at room temperature[9] gave methyl notatate (**13**) [29% overall from (**10**)], identical with an authentic sample.[3] Mild hydrolysis of ester (**13**) followed by relactonisation then gave notatic acid (**14**), identical with an authentic sample.[3]



(**15**) R = H
(**16**) R = Br



(**17**) $R^1 = CH_2Ph, R^2 = Br$
(**18**) $R^1 = R^2 = H$

For the synthesis of 4-*O*-methylhypoprotocetraric acid (**18**) benzyl barbatate (**15**), which had been synthesised previously,[10] was chosen as starting material. Bromination of this compound gave the dibromo-compound (**16**), m.p. 171°. This on treatment with copper bronze in pyridine at 37° for 7 days[11] underwent lactonisation and gave the bromodepsidone (**17**) (13%), m.p. 173°. Hydrogenolysis of (**17**) then gave 4-*O*-methylhypoprotocetraric acid (**18**), identical with an authentic sample.[3]

These methods are currently being applied to the synthesis of other depsidones.

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