Shikimate-derived Metabolites. Total Synthesis of Nor-chorismic Acid[1]

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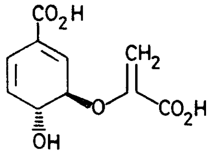
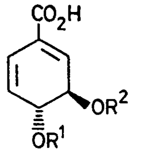
Summary The mild *O*-alkylation of a β-methoxyethoxymethyl-protected precursor for chorismic acid leads to nor-chorismic acid in good yield.

FOR some time we have been interested in the chemistry of chorismic acid (**1**) and in processes which regulate its metabolism at the branch point of the shikimic acid pathway. Recently we completed a stereospecific synthesis of the bacterial natural product (**2**) and outlined a strategy for preparing chorismic acid from the readily available family of monoprotected diols (**3**)[2] Since the target structure (**1**) is a thermally unstable, acid and base-labile substance, the choice of protecting group R^1 and the final alkylation and deprotection procedures for elaborating the sidechain are critical. We now describe the synthesis of (**4**), an analogue of (**1**) lacking the methylene carbon, which illustrates the feasibility of this approach.

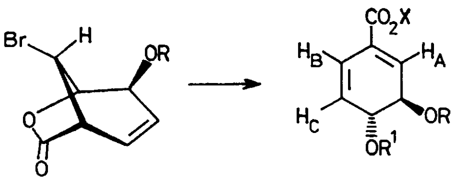


(1)

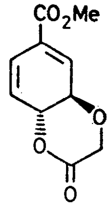


(2) $R^1=R^2=H$
(3) R^1 = protecting group, R^2 = H
(4) R^1 = H, $R^2=CH_2CO_2H$

The bicyclic β-methoxyethoxymethyl ether (**6**), prepared from (**5**)[2] using $MeOCH_2CH_2OCH_2NEt_3^+Cl^-$ (reflux; MeCN; 12h; 90%),[3] was saponified with KOH (2·0 equiv.; tetrahydrofuran–H_2O) to produce the dienol (**7**) [84%, m.p. 63—64 °C; $\delta(CDCl_3)$ 7·07 (s, 1H, H_A), 6·30 (m, 1H, H_B), 5·87 (m, 1H, H_C), 4·73 and 4·47 (ring >CH–), and 4·85, 3·40 (s), and 3·45—4·0 ($MeOCH_2CH_2OCH_2$); i.r. λ_{max} ($CHCl_3$) 2·85 and 5·89 μm; u.v. λ_{max} (EtOH) 277 nm (ε 2200)]. Exposure of (**7**) to MeI–hexamethylphosphoramide furnished the corresponding methyl ester (**8**) (85%; n.m.r. δ 3·78).[4] When treated with ethyl diazoacetate (1·6 equiv.; CH_2Cl_2) and a catalytic quantity of fluoboric acid at 0 °C, (**8**) furnished the oily *O*-alkyl derivative (**9**) in 34% yield [70% based on recovered (**8**); i.r. λ_{max} 5·70 and 5·80 μm]. The acetal protecting group in (**9**) proved to be completely inert to the Lewis acids which customarily effect β-methoxyethoxymethyl ether cleavage ($ZnBr_2$ or $TiCl_4$); however, fluoboric acid in CH_2Cl_2 (*ca.* 1·5 M; 0 °C; 3 h) effectively transformed (**9**) to (**10**) which was contaminated with only traces of aromatized by-products. Nearly pure (**10**) could be obtained by silica gel column chromatography [50—60% yield; i.r. λ_{max} 2·81, 5·73, and 5·80 μm; mass spectrum *m/e* 256 (M^+) and 238 $(M - 18)^+$].



(5) R = H
(6) R = $CH_2OCH_2CH_2OMe$
(7) $R^1=CH_2OCH_2CH_2OMe$, R^2 = H, X = H
(8) $R^1=CH_2OCH_2CH_2OMe$, R^2 = H, X = Me
(9) $R^1=CH_2OCH_2CH_2OMe$, $R^2=CH_2CO_2Et$, X = Me
(10) R^1 = H, $R^2=CH_2CO_2Et$, X = Me
(12) R^1 = H, $R^2=CH_2CO_2H$, X = Me



(11)

Basic hydrolysis of the diester (**10**) produced mostly aromatic acids and only a small amount of (**4**). A much more useful route involved cyclization of (**10**) to the crystalline bicyclic compound (**11**) [*p*-$MeC_6H_4SO_3H$; C_6H_6; reflux, 6 h; 50%; m.p. 135 °C; *m/e* 210 (M^+)] followed by acidic hydrolysis of its δ-lactone ring (10% H_2SO_4–tetrahydrofuran). The resulting monoester (**12**) [85%; m.p. 109—110 °C; *m/e* 228 (M^+)] underwent saponification with 1 equiv. of NaOH at 0 °C to nor-chorismic acid (**4**), m.p. 143—145 °C (acetone–ether–hexane)† [69%; R_f 0·38 on silica gel (MeOH–Bu^nOH–C_6H_6–H_2O, 6:5:4:3); $\delta(CD_3COCD_3)$ 6·99, 6·27, and 5·93 (m, each 1H, vinyl), 4·47 and 4·63 (m, each 1H, CH), and 4·37 (d, 2H, OCH_2CO_2); i.r. λ_{max} (KBr) 5·75 and 5·88 μm; u.v. λ_{max} (H_2O) 273 nm (ε 2200); *m/e* 214 (M^+), 196 $(M - 18)^+$, and 138 (100%; *p*-hydroxybenzoate)].

Some of these intermediates, notably (**11**), hold promise as synthetic precursors to (**1**) and their chemistry is being explored.

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† Upon repeated precipitation from acetone–ether–hexane, the m.p. of solid (**4**) became 225—235 °C (decomp.) but the n.m.r., i.r., u.v., mass spectral, and t.l.c. properties of this sample remained identical with the lower-melting (hydrated ?) form.

[1] For previous paper in the series Shikimate-derived Metabolites, see B. Ganem, *Tetrahedron Reports*, **1978**,

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[3] E. J. Corey, J. L. Gras, and P. Ulrich, *Tetrahedron Letters*, **1976**, 809.

[4] J. E. Shaw, D. C. Kunerth, and J. J. Sherry, *Tetrahedron Letters*, **1973**, 689.