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SHIKIMATE-DERIVED METABOLITES. 14.[1] CHIRAL SYNTHESIS OF 5-ENOLPYRUVYL-SHIKIMATE-3-PHOSPHATE

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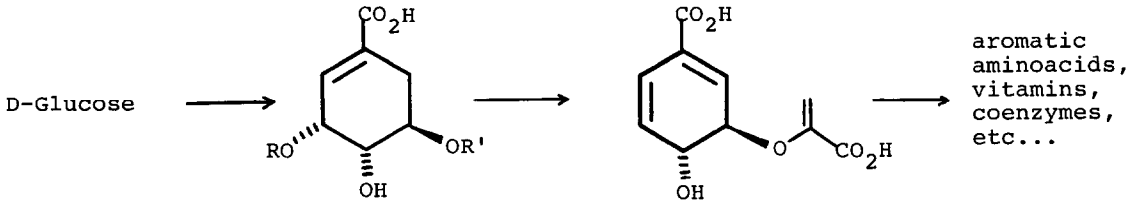
Summary: The title compound, a key biosynthetic intermediate in the shikimate metabolic pathway, has been synthesized in good yield from (-)-shikimic acid (1).

Plants and microorganisms use the shikimic acid biosynthetic pathway to make a host of important aromatic compounds from glucose.[2] Recently, the possibility of designing chemical inhibitors which may act as antibiotics or plant growth regulators has stimulated renewed research interest in this aspect of aromatic metabolism.[3] Through a combination of synthetic and mechanistic efforts, many intimate details of these enzyme-catalyzed reactions have now been illuminated.[4,5] In the late stages of the main pathway, phosphorylation of 1 at C3, then O-alkylation at C5 ultimately leads to the branch point metabolite chorismic acid (4). To our knowledge, all the main pathway intermediates have been successfully prepared by total synthesis except for phosphates 2 and 3, which are acid-labile and undergo facile 1,2-phosphate migrations. In this Letter we disclose the first chemical synthesis of 5-enolpyruvylshikimate--3-phosphate (EP-S-P, 3) in enantiomerically pure form.



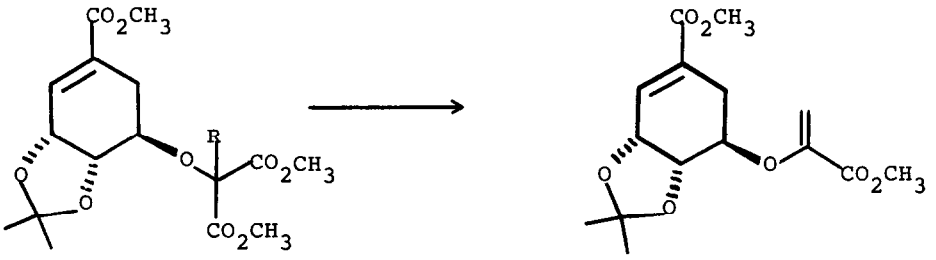
1 R, R'=H
2 R=PO_3H_2; R'=H
3 R=PO_3H_2; R'=$C(CH_2)CO_2H$

4

The known acetonide of methyl shikimate[6] was converted to alkoxymalonate 5 in 85% yield by the $Rh_2(OAc)_4$ catalyzed insertion of dimethyl diazomalonate (1.3 equiv, benzene, reflux).[7,8] Mannich condensation of 5 with Eschenmoser's reagent [1.2 equiv $CH_2=N(CH_3)_2I$, Et_3N-CH_2Cl_2] afforded 6 which was quaternized directly (CH_3I, CH_2Cl_2, rt) to ammonium salt 7 in 84% overall yield. Heating in DMSO (95°, 6h), transformed 7 into enolpyruvate 8 in 83% yield. The acetonide protecting group in 8 could be removed to afford 9 (90%) by careful treatment with 80% aqueous acetic acid (3h, 65-70°). However upon prolonged exposure to acid (>6h, 75°C), protonation of the enol pyruvate with participation of the C4-hydroxyl in 9 produced a diastereomeric mixture of 5-membered cyclic ketals (not shown). Diester 9 could be transformed by exhaustive saponification to "Compound Z_1" [(-)-5-enolpyruvylshikimic acid 10], a secondary metabolite of some historical significance[9] which has also been prepared by McGowan and Berchtold.[10]

Hydroxyl participation under basic conditions made it possible to saponify diester 9 selectively (1.1 equiv NaOH, THF-H_2O, 0°, 3h) to monoacid 11 needed for the synthesis of EP-S-P. Cyclization of 11 using water-soluble carbodiimide (1.1 equiv, THF-DMAP, rt, 3h) furnished α-methylene lactone 12 in 48% yield from 9 — $[\alpha]_D^{23}$ -129° (c 0.25, $CHCl_3$); mp >240°C; 300 MHz ^{1}H-NMR 6.90 (dd, 1H, J=5.3, 2.7), 5.64, 5.07 (2d's, each 1H, J=1.4), 4.59 (dd, 1H, J=5.4, 3.5), 4.35 (m, 2H), 3.75 (s, 3H); CIMS m/e 241 (100%, M+), 242 (13%). This lactonization was designed to target phosphate construction selectively at the C3 hydroxyl group. Several methods of direct phosphorylation were investigated, however the Letsinger phosphite ester approach proved by far the most successful.[11] Treatment of 12 with PCl_3 (10 equiv, C_5H_5N-THF, -78°) then with 2.3 equiv of p-nitrophenethanol presumably furnished an intermediate mixed phosphite ester which, without workup, was oxidized (I_2-H_2O, -78 to 0°C) to the bis-p-nitrophenethyl phosphate 13 (50% from 12).[12] A one-pot deprotection of 13 was achieved first by treatment with diazabicyclo[5.4.0]undec-7-ene (5 equiv, C_5H_5N, rt, 72h), then with aqueous NaOH (10 equiv, 5h, 0°). The crude product was extracted with $CHCl_3$, acidified with Amberlite IR-120H resin and lyophilized. The product was purified on a column of DEAE Sephadex A-25. Pure EP-S-P 3 was thus obtained as its tetrasodium salt in 70% yield from 13. The 300 MHz ^{1}H-NMR spectrum of synthetic 3 was identical with that of an authentic sample kindly provided by Professor J.R. Knowles (Harvard Univ.).

Several aspects of this new chemistry may find use in the synthesis of specific inhibitors of chorismate synthase.

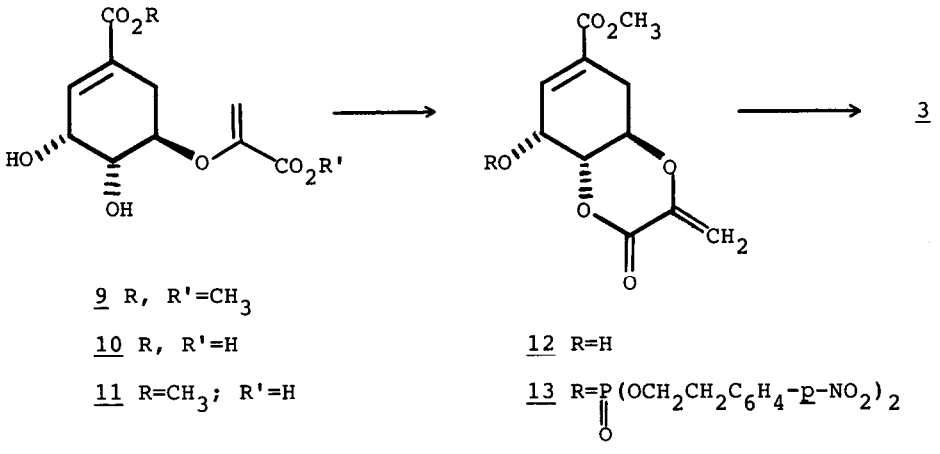


5 R=H

6 R=$CH_2N(CH_3)_2$

7 R=$CH_2N(CH_3)_3I$

8



9 R, R'=CH_3

10 R, R'=H

11 R=CH_3; R'=H

12 R=H

13 R=$P(OCH_2CH_2C_6H_4\text{-}p\text{-}NO_2)_2$ (=O)

3

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