Synthesis of Disodium Prephenate

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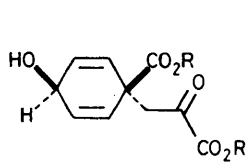
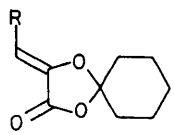
An efficient synthesis of disodium prephenate has been achieved utilising a 5-ylidene-1,3-dioxolan-4-one intermediate as a protected α-keto acid.

Prephenic acid (**1**) occupies a crucial position in the biosynthetic scheme used by higher plants and micro-organisms for the synthesis of phenylalanine and tyrosine.[1] Although disodium prephenate (**2**) has been synthesised by Danishefsky[2] and Plieninger[3] there remains a need for a shorter route to (**2**) that can be adapted to afford analogues designed to inhibit the enzymes *prephenate dehydratase* and *prephenate dehydrogenase,* which mediate in the transformation of prephenic acid (**1**) to phenylalanine and tyrosine and which are absent in mammalian systems.

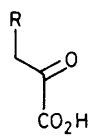
Prephenic acid (**1**) is unstable to acid conditions owing to the easy decarboxylative dehydration which leads to phenylpyruvic acid. Thus a successful strategy for synthesis must involve alkaline deprotection conditions in the final stage leading to the salt of prephenic acid, *e.g.* (**2**). We have recently described a method[4] for the preparation of α-keto acids (**4**), which relies on the synthesis and subsequent mild alkaline hydrolysis of 5-ylidene-1,3-dioxolan-4-ones (**3**). This latter class of compounds have been made by Wittig reaction



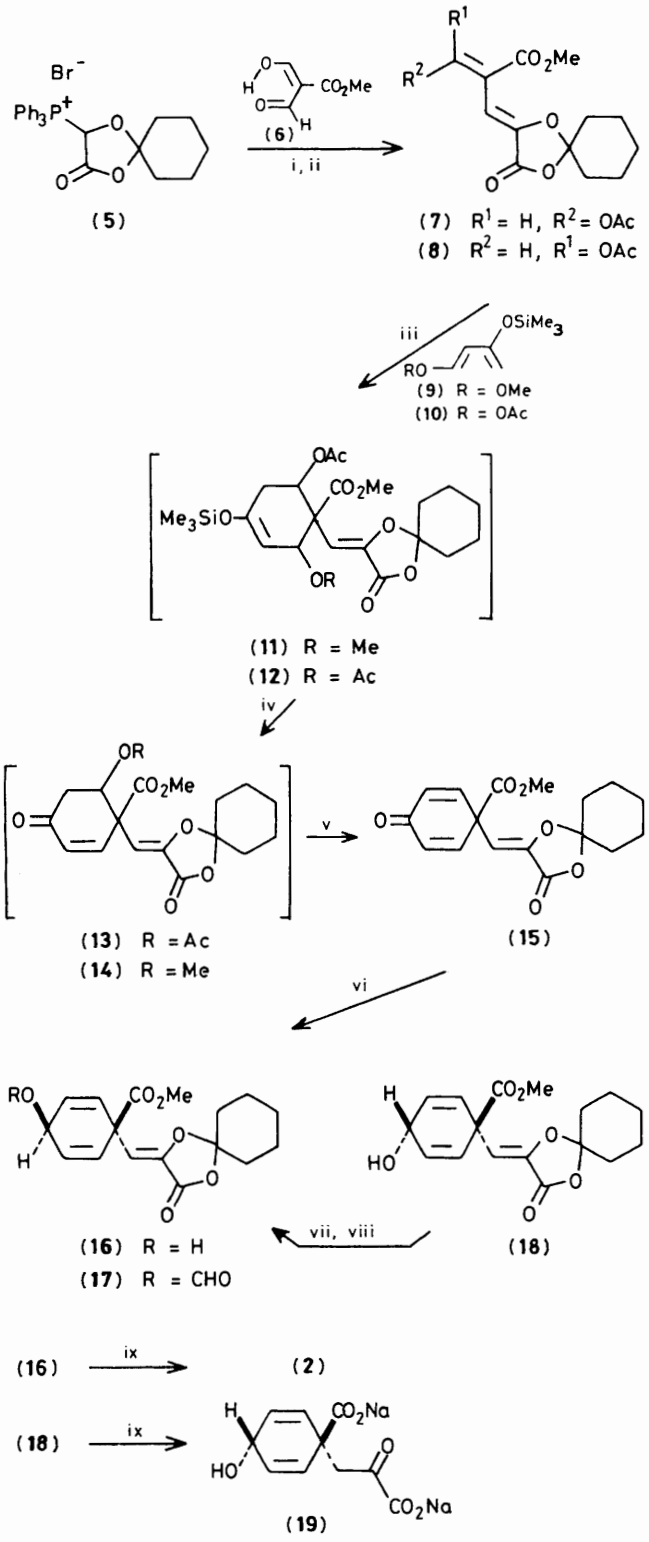
(**1**) R = H
(**2**) R = Na



(**3**)



(**4**)



Scheme 1. i, DABCO (2 equiv.); ii, AcCl, 59%; iii, heat, 70 °C; iv, H_3O^+; v, Et_3N, 72% from (**7**)/(**8**); vi, 9-BBN, (**16**) 31%, (**18**) 53%; vii, $Ph_3P/EtO_2C{\cdot}N{=}N{\cdot}CO_2Et/HCO_2H$; viii, Et_3N–MeOH, 25% from (**18**); ix, NaOH (2 equiv.)–MeOH.

involving the ylide derived from the phosphonium salt (**5**) and an aldehyde.

The first stage in this synthesis of disodium prephenate (**2**) (Scheme 1) involved the Wittig reaction between the phosphorane derived from (**5**) and the enolate of methyl diformylacetate (**6**).[5] After generation of the phosphorane from the salt (**5**) using 1,4-diazabicyclo[2.2.2]octane (DABCO) (2 equiv.), followed by addition of (**6**), the reaction was quenched with acetyl chloride. This afforded the desired product as a mixture (4 : 1) of geometrical isomers (**7**) and (**8**).‡ The structure of (**7**) [m.p. 101 °C; $\nu_{max}(CH_2Cl_2)$ 1790, 1720, and 1635 cm^{-1}; λ_{max} (EtOH) 288 (ε 16 100) and 222 nm (ε 13 760)] was assigned unambiguously by *X*-ray crystallographic determination† which showed the enol acetate double bond to be 45° out of planarity with the ylidene dioxolanone system. It was found that (**7**) underwent a Diels–Alder reaction with the important diene (**9**),[6] followed by mild hydrolysis of the adduct (**11**) to afford the cyclohexenone (**13**) [$\nu_{max}(CH_2Cl_2)$ 1790, 1745, 1690, and 1605 cm^{-1}; λ_{max} (EtOH) 248 (ε 8188) and 224 nm (ε 8061)]. Subsequent elimination of acetic acid by Et_3N gave the required dienone (**15**) (45%). However it was found that this sequence of reactions produced the major by-product (**14**) (33%) resulting from inefficient loss of methanol during the initial hydrolysis of the [4 + 2] adduct (**11**). Consequently, in order to insert a better leaving group in the diene, 1-acetoxy-3-trimethylsilyloxybuta-1,3-diene (**10**) was prepared (73%) from the known 4-acetoxybut-3-en-2-one[7] using trimethylsilyl chloride ($ZnCl_2$–Et_3N–benzene).

It was gratifying to find that separation of the isomers (**7**) and (**8**) was unnecessary since both reacted with (**10**) at 70 °C to give the [4 + 2] adduct (**12**) which was immediately hydrolysed to (**13**) and then treated with Et_3N to afford the dienone (**15**) [m.p. 90—91 °C; ν_{max} (CH_2Cl_2) 1790, 1740, 1685(sh), 1670, and 1630(w) cm^{-1}; λ_{max} (EtOH) 242 nm (ε 22 130); δ ($CDCl_3$, 220 MHz) 1.4—1.9 (m, 10H), 3.82 (s, 3H), 5.78 (s, 1H), 6.41 (d, *J* 10 Hz, 2H), and 7.02 (d, *J* 10 Hz, 2H)]. In practice the intermediates (**12**) and (**13**) are not isolated and the dienone (**15**) is produced from the mixture of (**7**) and (**8**) in 72% overall yield.

Reduction of dienone (**15**) with 9-borabicyclo[3.3.1]nonane (9-BBN)[8] gave the separable epimeric dienols (**16**) [m.p. 73—74 °C; ν_{max} (CH_2CL_2) 3580, 1788, 1736, 1687(w), and 1605(w) cm^{-1}; 31%] and (**18**) [m.p. 74—77 °C, ν_{max} (CH_2Cl_2) 3580, 1788, 1735, 1687(w), and 1630(w) cm^{-1}, 53%]. This lack of stereospecificity during the reduction stage was not deleterious since the undesired dienol (**18**) could be converted into the formate (**17**) with inversion of stereochemistry using the Mitsunobu reaction.[9] The stereochemistry of (**17**), and hence (**16**) and (**18**), was established unambiguously by *X*-ray structure determination.† Mild solvolytic treatment of (**17**) then afforded the required dienol (**16**). At the final stage of conversion of (**16**) into disodium prephenate (**2**) the chemistry of the ylidene dioxolan-4-one system was brought into effect. Hydrolysis of the dienol (**16**) using NaOH (2 equiv.) in methanol for 16 h gave disodium prephenate (**2**) isolated as the hemihydrate in 97% yield. Similarly, hydrolysis of the epimer (**18**) produced disodium epiprephenate (**19**) which was isolated as the dihydrate. Comparison of (**2**) and (**19**) by n.m.r. spectroscopy (300 MHz) with authentic disodium prephenate (**2**) was made after ion exchange of the commercial barium salt.

‡ All known compounds were characterised by comparison with literature data. All new compounds were fully characterised by full spectral and analytical data.

† *X*-Ray crystallographic studies performed by R. G. Pritchard and will be reported separately.

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