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SYNTHESIS OF DISODIUM PREPHENATE †

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Abstract - An efficient synthesis of disodium prephenate is described which illustrates the use of 5-ylidene-1,3-dioxalan-4-ones for the synthesis of acid labile α-keto acids.

The biosynthesis of the important α-amino acids, L-phenylalanine and L-tyrosine is accomplished in plants and micro-organisms by the shikimic acid pathway,[1] so named after the biosynthetic intermediate, shikimic acid (1) which was isolated first as a natural product in 1885.[2] The oxidation level and stereochemistry of (1) make this a challenging target for synthesis which was first realised by Raphael[3] and Smissman.[3] Subsequently the former route was modified to produce labelled shikimic acid for biosynthetic studies[4] designed to probe the stereochemistry of the later steps leading to chorismic acid (2) then prephenic acid (3) which is the final non-aromatic intermediate leading to L-phenylalanine (5) and L-tyrosine (6). Since the shikimic acid pathway is not utilised by mammals there is considerable potential for the design of modified shikimate intermediates as herbicides and antibacterial agents.[5] Although disodium prephenate (4) has been synthesised[6] it remains important to investigate routes which can be adapted to afford inhibitors of the enzymes *prephenate dehydratase* and *prephenate dehydrogenase* which mediate in the transformation of prephenic acid (3) to L-phenylalanine (5) and L-tyrosine (6).

Before embarking on the synthesis of a natural product it is mandatory to take account of the chemical characteristics of the target molecule. In the case of prephenic acid (3) this introduces remarkable constraints upon the strategy and protecting group selection. Prephenic acid (3) is decomposed rapidly under acid conditions to afford phenylpyruvic acid (7). However, it is decidedly more stable to aqueous alkaline treatment which requires prolonged standing, or heating, to convert prephenic acid (3) to *p*-hydroxyphenyllactic acid (8) by an intramolecular hydride transfer mechanism[7] which utilises the stereochemical features of (3). The *cis* stereochemistry of the hydroxyl and carboxylic acid functions follows from the stereochemistry of chorismic acid (2)[8] which is the immediate biosynthetic precursor of prephenic acid (3). These facts determine that the synthesis of prephenic acid (3) should lead to the relatively stable and isolable salt (4) and, further, that the uncovering of the functionality at the end of the synthesis should require mild alkaline

† **This paper is dedicated to Professor Ralph Raphael on his 65th birthday in grateful appreciation of his talents as a teacher and imaginative scientist.**

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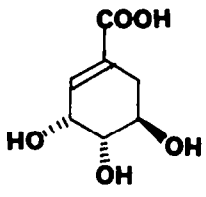
treatment. This policy was adopted by Danishefsky[6] in his synthesis of (3) which involved the final intermediate (9).



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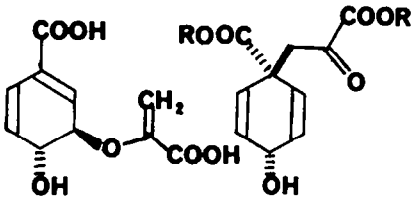

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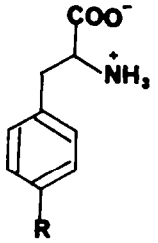
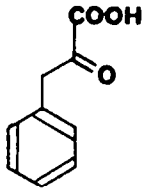
3, R=H
4, R=Na



5, R=H
6, R=OH



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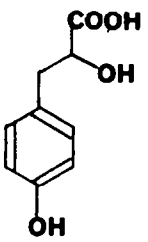

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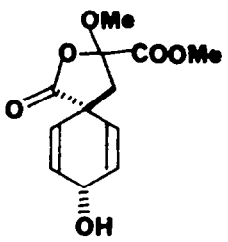

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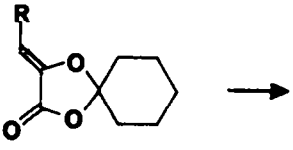
We have recently described[9] a method for the preparation of α-keto acids (11) which relies upon the synthesis and subsequent mild alkaline hydrolysis of 5-ylidene-1,3-dioxalan-4-ones (10). This hitherto relatively uninvestigated class of compounds[10] have been made by Wittig reaction of an aldehyde with the ylide (12) derived, *in situ*, from the phosphonium salt (13). Thus we sought to incorporate the system (10) into a synthetic strategy for disodium prephenate (4). Retrosynthetic considerations led to the structure (14) as the



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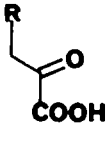

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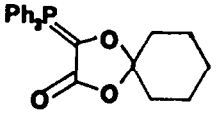

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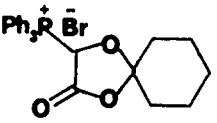

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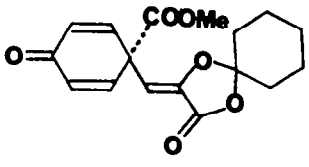

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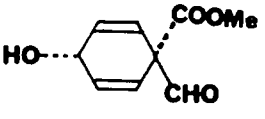

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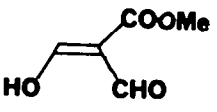

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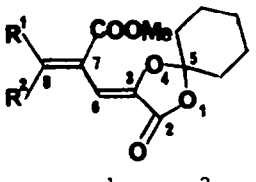
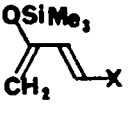
penultimate intermediate in the synthesis. Two possible routes to (14) immediately present themselves; namely Wittig reaction of the aldehyde (15) with the ylide (12), or Wittig reaction of the protected form of methyl diformylacetate (16)[11] followed by elaboration of the product (17/18) to the desired dienone (14) using Diels Alder methodology involving the diene (19/20).[12] The considerable steric restraints to the Wittig reaction, together with the likely instability of (15), decidedly favoured the second of these alternative strategies.

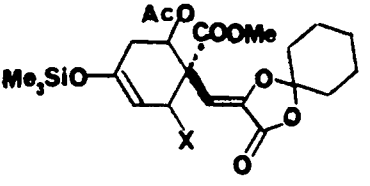
Acetylation of (16) afforded the unstable enolacetate as a mixture (1:1) of Z and E isomers which was reacted with the phosphorane (12), generated *in situ* from (13) by one equivalent of 1,4-diazabicyclo[2.2.2]octane (DABCO). This gave the 5-ylidene-1,3-dioxalan-2-one (18) as a mixture of two double bond isomers in 44% yield. Although it was not possible to separate these isomers by chromatography, the major isomer was obtained pure, m.p. 101°C, by fractional crystallisation from ether and it was determined by X-ray crystallographic analysis to be the E(7,8), Z(3,6) double bond isomer (18).[13] Interestingly the dienone system in (18) is twisted from planarity by rotation about the 6,7 bond isolating, to some extent, the acrylic ester function required for subsequent Diels Alder addition with a diene system. The enolacetate (18) was heated with the important diene (19), developed by Danishefsky,[12] for 46 h in refluxing benzene. After acid hydrolysis of the intermediate enolsilyl ether (21), followed by elimination of methanol, the acetoxycyclohexenone (23) could be isolated and characterised but, in practice, this intermediate was directly subjected to base-induced (Et_3N) elimination of acetic acid to produce the dienone (14) in 45% yield from (18). However this sequence of reactions starting from the methoxydiene (19) had the disadvantage that loss of methanol from (21) was not complete leading to methoxycyclohexenone by-products (24). Another disappointment was incurred when the minor isomer of (18), produced in the Wittig reaction with the enolacetate of (16), failed to undergo the Diels Alder reaction with (19). We attribute this to the minor isomer being the more sterically demanding E(7,8), E(3,6) double bond isomer of (18).



17, R^1=OAc, R^2=H
18, R^1=H, R^2=OAc



19, X=OMe
20, X=OAc

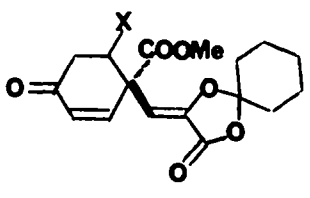


21, X=OMe
22, X=OAc

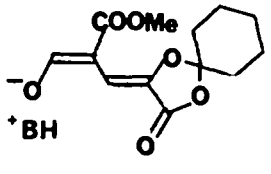
These problems could be resolved easily resulting in the efficient preparation of (14) from (12). The yield loss due to the formation of the unreactive E(3,6) isomer of (18) was avoided by the simple expedient of using the anion of (16) for the Wittig reaction. The phosphorane (12) was generated from the salt (13) in the usual manner using DABCO but, in this instance, 2 molar equivalents of the base was used. Addition of methyl diformylacetate (16) resulted in enolate formation with the remaining equivalent of DABCO followed by Wittig reaction indicated by the loss of the orange colour of the

ylid. The resonance stabilised enolate product (25) was quenched with acetyl chloride to afford the mixture of dienes (17) and (18) in 59% yield as a 1:4 mixture of isomers in which the latter was favoured. In this case the minor product of the Wittig reaction was not the same as the unreactive minor isomer obtained in the previous Diels Alder reaction. It has previously been found[10] that resonance stabilised aldehydes favour the formation of the Z(3,6) double bond isomer in the Wittig reactions leading to the series (10). In contrast to previous experience it was found that both isomers (17) and (18) reacted smoothly in the Diels Alder reaction with 1-acetoxy-3-trimethylsilyloxybutadiene (20), which was prepared readily from 4-acetoxybutenone[14]. Reaction of this diene (20) with the mixture of (17) and (18) gave the adduct (22) which was found to eliminate efficiently two molar equivalents of acetic acid to give the desired dienone (14) in 72% yield.

Having thus established a convenient and efficient two stage preparation of the key dienone intermediate (14) from the readily available starting reagents (13) and (16), reduction to the dienol (26) was undertaken. After experimentation with different reagents we opted for 9-borabicyclo[3.3.1]nonane (9-BBN)[15] in THF which reduced (14) to a mixture of two epimeric dienols which were separated by chromatography. The major product (53%, m.p. 74-77°C) was assigned the structure (28) resulting from attack of 9-BBN from the least hindered face of the dienone; the lesser product (31%, m.p. 73-74°C) (26) has the same relative configuration as prephenic acid (3). Neither of the dienols gave crystals suitable for X-ray studies. However, the relative configurations could be assigned unambiguously by a Mitsunobu[16] inversion of the major product (28) which afforded the formate ester (27) which fulfilled two purposes. Firstly, X-ray structure determination[13] clearly showed the *cis* relationship of the methoxycarbonyl and formate functions and, secondly, the formate (27) could be solvolysed in methanol, containing triethylamine, to give the desired dienol (26). This recycling sequence brought the overall yield of (26) from the dienone (14) to 46%.



23, X=OAc
24, X=OMe



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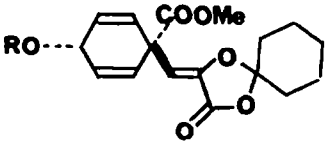
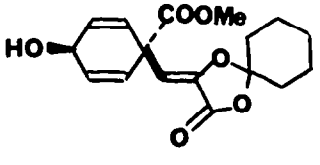


26, R=H
27, R=CHO



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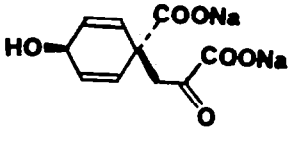

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Finally, the chemistry of the 5-ylidene-1,3-dioxalan-4-one system was brought into effect and the dienol (26) was subjected to mild alkaline hydrolysis with two equivalents of NaOH in aqueous methanol to give disodium prephenate (4) in 97% yield having 360 MHz n.m.r. data consistent with that derived from natural sources (with the exception that the "natural" material was contaminated with aromatic species). Similarly, hydrolysis of the dienol (28) gave disodium epiprephenate (29) which was isolated in 89% yield and was found to have similar n.m.r. data to disodium prephenate but clearly different in detail as reported by others.[6] Thus we have succeeded in designing and executing a short synthesis of the salt of prephenic acid involving only three isolated intermediates (17/18), (14) and (26) and which is capable of modification in order to probe the specificity of the final stage in the biosynthesis of L-phenylalanine and L-tyrosine by the shikimate pathway.

Acknowledgment

We thank SERC for financial support, the Royal Society for an equipment grant, Dr G.J. Griffiths for preliminary studies and Dr I.H. Sadler for n.m.r. measurements at 360 MHz.

Experimental

M.p.s were measured using a Buchi 510 immersion melting point apparatus and were uncorrected. ^{1}H N.M.R. were measured on Perkin Elmer R34 and Bruker-AM360 instruments and chemical shifts are expressed in ppm downfield from TMS. IR spectra were obtained using Perkin Elmer 197 or 298 instruments and UV spectra recorded on Pye Unicam SP8-100 and Cary118X instruments. Mass spectra were measured on a Kratos MS 45 instrument.

Wittig Reaction of Phosphorane (12)with Enolacetate of Aldehyde (16). - An aqueous solution of sodium bicarbonate (5.10 g, 60.7 mmol in 50 ml H_2O) was added slowly to a stirred solution of methyl diformylacetate (16) (7.87 g, 60.7 mmol) in acetone (100 ml). When evolution of CO_2 had ceased, the acetone was removed under reduced pressure then the remaining aqueous solution was washed with ether (20 ml) and freeze dried to give the sodium salt of methyl diformylacetate (9.05 g, 98%). The white powdered salt (5.09 g, 33.5 mmol) was suspended in dry CH_2Cl_2 (50 ml) to which was added acetyl chloride (3.8 ml, 53.2 mmol) dropwise with stirring over 15 min. After 30 min the volatiles were removed under reduced pressure and the residue dissolved in ether, filtered and concentrated to give the *Enolacetate* as an oil which was a 1:1 mixture of Z and E isomers (1.5 g, 26%), ν_{max} (CH_2Cl_2) 1 795 (enolacetate), 1 742-1 700 (several bands, aldehyde and ester) and 1 610 cm^{-1} (C=C) δ($CDCl_3$) (60 MHz) 2.41 (3H, s, Ac), 3.88 (3H, 2 lines, OMe), 8.45 (s) and 8.77 (d, J 2 Hz) total 1H (C*H*OAc), 9.78 (s) and 10.10 (d, J 2 Hz) total 1H(CHO). Due to the instability of this material, which was *ca* 90% pure (from nmr), it was used immediately without purification.

To the phosphorane (12), generated from phosphonium salt (13) (4.2 g, 8.4 mmol) and DABCO (0.93 g, 8.3 mmol) in dry toluene (10 ml) under nitrogen, was added the enolacetate of aldehyde (16) dropwise with stirring. After 15 min, the reaction mixture was poured onto a column of silica gel which was eluted with an ether - light petroleum gradient. This gave an oil from which the *E/Z dioxolanone* (18) (544 mg, 21%) could be obtained by fractional crystallisation mpt 100.5-101°C (ether) (Found: C, 57.9; H, 5.8 $C_{15}H_{18}O_7$ requires C, 57.9; H, 5.8); ν_{max} (CH_2Cl_2) 1 790 (dioxolanone and enolacetate), 1 720 (ester) and 1 635 cm^{-1} (C=C); λ_{max} (EtOH) 288 nm (ε 16 100) and 222 nm (ε 13 760); δ ($CDCl_3$) (220 MHz) 1.4-1.9 (1H, m, cyclohexyl), 2.25 (3H, s, Ac), 3.83 (3H, s, OMe), 6.22 (1H,s, 6-H) and 8.29 (1H, s, 8-*H*). The mother liquors on concentration gave an oil which was a mixture of geometrical isomers (590 mg, 23%, 90% pure by nmr), δ($CDCl_3$) (220 MHz) 1.4-1.9 (10H,m), 2.13 and 2.25 (3H, 2s), 3.78 and 3.82 (3H, 2s), 5.98 (d, J 2 Hz) and 6.22 (s) total 1H, 7.50 (d, J 2 Hz) and 8.28(s) total 1H.

Wittig Reaction of Phosphorane (12) with Methyl Diformylacetate (16).- Methyl diformylacetate (490 mg, 3.77 mmol) was added dropwise under nitrogen to a stirred solution of phosphorane (12) generated *in situ* from phosphonium salt (13) (1.90 g, 3.82 mmol) and DABCO (940 mg, 8.38 mmol) in dry benzene (5 ml). After 25 min acetyl chloride (300 µl, 4.20 mmol) was added and the reaction mixture stirred a further 10 min, then diluted with ether, filtered and concentrated. Chromatography on silica gel followed by crystallisation from ether - light petroleum gave the dioxolanone (698 mg, 59%) as a 4:1 mixture of E/Z (18) and Z/Z (17) isomers, $\delta(CDCl_3)$(220 MHz) 1.4-1.9 (10H, m), 2.25 and 2.29 (3H, 2s), 3.83 and 3.86 (3H, 2s), 6.23 and 6.34 (1H, 2s), 8.29 and 8.44 (1H, 2s). Some E/Z isomer identical with that described above could be obtained by fractional crystallisation from ether but this was not necessary in practice. The ratio of isomers obtained varied with the temperature at which the reaction was quenched with acetyl chloride (*eg* E:Z ratio 1:2 when quenched at 60°C).

Preparation of Dienone (14) using Diene (19). - A solution of the E/Z dioxolanone (18) (507 mg, 1.63 mmol) and the diene (19) (600 mg, 3.48 mmol) in dry benzene (1 ml) was heated at 77°C. After 46 h, the solvent was removed and the remaining oil dissolved in THF (8 ml) to which was added 0.5M HCl (1 ml). The solution was stirred for 30 min then diluted with ether, washed successively with saturated sodium bicarbonate solution and brine, dried and concentrated. In initial studies of this preparation, the reaction mixture was purified at this stage by chromatography on silica gel eluting with ether-light petroleum (4:1) to give the *Acetoxycyclohexenone* (23) as a colourless oil, $\nu_{max}(CH_2Cl_2)$ 1 790 (dioxolanone), 1 745 (acetate), 1 690 (enone) and 1 605 cm^{-1} (C=C); λ_{max} (95% EtOH) 248 nm (ε8 188) and 224 nm (ε 8 061); $\delta(CDCl_3)$ (220 MHz) 1.5-1.9 (10H, m, cyclohexyl), 2.04 (3H, s, OAc), 2.68 (1H, dd, J 17 and 8 Hz, CH*H*CHOAc), 2.86 (1H, dd, J 17 and 4.5 Hz, C*H*HCHOAc), 3.77 (3H, s, OMe), 5.80 (1H, dd, J 8 Hz and 4.5 Hz, C*H*OAc), 5.81 (1H, s, 11-H), 6.15 (1H, d, J 10 Hz, CHCO), 7.02 (1H, d, J 10 Hz, C*H*CHCO). Found: M^+378.1311. $C_{19}H_{22}O_8$ requires M^+ 378.1315.

The crude acetoxycyclohexenone (23) was treated with Et_3N (350 µl, 2.52 mmol) in CH_2Cl_2 for 21 h at room temperature. The solution was filtered through florisil, concentrated, and the residue purified by chromatography on silica gel (gradient elution with ether - light petroleum). Crystallisation from ether gave the *Dienone* (14) (235 mg, 45%), mpt 90-91°C (Found: C, 63.9; H, 5.7. $C_{17}H_{18}O_8$ requires C, 64.1; H, 5.7%); ν_{max} (CH_2Cl_2) 1 790 (dioxolanone), 1 740 (ester), 1 680 (sh, exocyclic C=C), 1 670 (dienone) and 1 630 cm^{-1} (dienone C=C); λ_{max} (95% EtOH) 243nm (ε 22 180); $\delta(CDCl_3)$ (220 MHz) 1.4-1.9 (10H, m, cyclohexyl), 3.82 (3H, s Me), 5.78 (1H, s, 11-H), 6.41 (2H, d, J 10 Hz, $(CHCH)_2CO$), 7.02 (2H, d J 10 Hz, $(CHCH)_2CO$).

The major by-products also obtained were the *Methoxycyclohexenones* (24) higher Rf isomer (32 mg, 6%), colourless oil *ca* 90% pure by nmr, ν_{max} (CH_2Cl_2) 1 785 (dioxolanone), 1 735 (ester), and 1 680 cm^{-1} (enone); $\delta(CDCl_3)$ (220 MHz) 1.4-1.9 (10H, m, cyclohexyl), 2.56 (1H, dd, J 17 and 9 Hz, C*H*HCHOMe), 2.73 (1H, dd, J 17 and 4 Hz, CH*H*CHOMe), 3.33 (3H, s, OMe), 3.75 (3H, s, CO_2Me), 4.15 (1H, dd J 9 and 4 Hz, C*H*OMe), 5.92 (1H, s, 11-H), 6.07 (2H, dd, J 11 Hz, $(CHCH)_2CO$) and 6.93 (1H, d, J 11 Hz, $(CHCH)_2CO$); lower Rf isomer (155 mg, 27%), colourless oil, ν_{max} (CH_2Cl_2) 1 790 (dioxolanone), 1 742 (ester), and 1 690 cm^{-1} (enone); λ_{max} (EtOH) 254 and 227 nm; $\delta(CDCl_3)$ (220MHz) 1.4-1.8 (10H, m, cyclohexyl), 2.64 (1H, dd, J 17 and 3 Hz, CH*H*CO), 2.84 (1H, dd, J 17 and 4 Hz, C*H*HCO), 3.30 (3H, s OMe), 3.79 (3H, s, CO_2Me) 4.15 (1H, bm, C*H*OMe), 5.65 (1H,s, 11-H), 6.18 (1H, d, J 10 Hz, CHCO) and 7.20 (1H, dd, J 10 and 2 Hz, C*H*CHCO). Found: M^+ 350.1364. $C_{18}H_{22}O_7$ requires M^+ 350.1366.

Preparation of 1-Acetoxy-3-trimethylsilyloxybutadiene (20). - To a suspension of zinc chloride (590 mg, 4.3 mmol) in dry benzene (10 ml) and Et_3N (25 ml, 182 mmol) was added 4-acetoxybutenone (10.5 g, 82 mmol) in benzene (10 ml). Chlorotrimethylsilane (17 g, 157 mmol) was added dropwise and the solution was stirred for 48 h then poured onto ether - light petroleum (1:1, 175 ml) which was filtered and concentrated. Distillation of the resulting oil gave *1-Acetoxy-3-trimethylsilyoxybutadiene* (20) (12.05 g, 73%) as a colourless oil, bpt 115°C at 30 mmHg; ν_{max} (CH_2Cl_2) 1 750 (C=O), and 1 655 cm^{-1} (C=C); $\delta(CDCl_3)$ (220 MHz) 0.01 (9H, s, $SiMe_3$), 2.00 (3H,s Ac), 4.13 (2H, s, $C=CH_2$), 5.73 (1H, d J 12 Hz, C*H*=CHO) and 7.42 (1H, d J 12 Hz, C*H*OAc).

Preparation of Dienone (14) using Diene (20). - The E/Z dioxolanone (18) (500 mg, 1.67 mmol) was heated with 1-acetoxy-3-trimethylsilyloxybutadiene (810 mg, 4.05 mmol) at 80°C for 64 h. the excess diene was removed under reduced pressure then THF (8 ml) and 0.1M HCl solution (1 ml) were added. After stirring for 35 min, the reaction mixture was diluted with ether, washed with sodium bicarbonate solution and brine, dried and concentrated. The residue was treated with Et_3N (450 µl, 3.23 mmol) in CH_2Cl_2 (10 ml) for 23 h then

filtered through florisil which was washed with ether. Activated charcoal was added to the organic solution which was then filtered through celite and concentrated to give a residue which, on crystallisation from ether - light petroleum, yielded the dienone (14) (235 mg) identical with that described above. The mother liquors were purified on silica gel to give, after crystallisation, a further 163 mg (total 77%) of dienone. When the reaction was repeated using a mixture of the Z (17) and E (18) enolacetates (2:1), both isomers reacted to give the same dienone (14) (72%).

Reduction of Dienone (14). - To a solution of dienone (14) (343 mg, 1.07 mmol) in THF (5 ml) under N_2, with cooling from an ice bath, was added a 0.5M solution of 9-BBN in THF (5 ml, 1.5 mmol) dropwise with stirring. The solution was allowed to warm slowly to room temperature then stirred for 2.5 h. MeOH (3 ml)was added and, after 5 min, the solution was poured onto water (50 ml) which was then extracted three times with CH_2Cl_2. The combined organic extracts were dried, concentrated, and the residue purified by chromatography (twice) on silica gel (gradient elution with ether-toluene). The less polar isomer (28) (Rf 0.40, ether-light petroleum 4:1) was obtained as pure white amorphous solid from ether-light petroleum (182 mg, 53%), mpt 74-77°C (Found: C, 63.7; H, 6.4. $C_{17}H_{20}O_6$ requires C, 63.7; H, 6.3); ν_{max} (CH_2Cl_2) 3 580 (OH), 1 787 (dioxolanone), 1735 (ester), 1 687 (w, exocyclic C=C) and 1 630 cm^{-1} (w, C=C). λ_{max} (EtOH) 249 nm (ε 17 000); δ($CDCl_3$) (300 MHz) 1.4-1.8 (10H, m, cyclohexyl), 3.69 (3H,s, Me), 4.50 (1H, m, CHOH), 5.74 (1H, s, 11-H), 5.98 (2H, dd, J 10 and 1.5 Hz, (CHCH)$_2$OH) and 6.08 (2H, dd, J 10 and 3 Hz, (CHCH)$_2$OH). The more polar isomer (26) (Rf 0.37) was obtained as fine needles from ether-light petroleum (108 mg, 31%), mpt 73-74°C (Found: C, 63.4; H, 6.3. $C_{17}H_{20}O_6$ requires C, 63.7; H, 6.3); ν_{max} (CH_2Cl_2) 3 580 (OH), 1 788 (dioxolanone), 1 736 (ester), 1 687 (exocyclic C=C) and 1 605 cm^{-1} (C=C); λ_{max} (EtOH) 252 nm (ε14 700). δ($CDCl_3$) (300 MHz) 1.4-1.8 (10H, m, cyclohexyl), 3.71 (3H, s, Me), 4.48 (1H, m, CHOH), 5.68 (1H, s, 11-H), 5.97 (2H, dd, J 10 and 1.5Hz, (CHCH)$_2$OH) and 6.08 (1H, dd, J 10 and 3Hz, 2H (CHCH)$_2$OH).

Inversion of Dienol (28). - To a stirred solution of dienol (28) (70 mg, 0.218 mmol) and triphenylphosphine (203 mg, 0.774 mmol) in dry benzene (0.5 ml) under nitrogen was added formic acid (36 mg, 0.782 mmol) in benzene (0.5 ml). This was followed by the dropwise addition of diethyl azodicarboxylate (149 mg, 0.856 mmol) in benzene (0.5 ml). After 15 min the reaction was diluted with ether, washed with sodium bicarbonate solution, dried and concentrated. The residue was partially purified by chromatography on silica gel eluting with ether-light petroleum. A pure sample of the *Formate* (27) could be obtained by crystallisation from ether-light petroleum, mpt 79°C (Found: C, 62.0; H, 5.8. $C_{18}H_{20}O_7$ requires C, 62.1; H, 5.8); ν_{max} (CH_2Cl_2) 1 790 (dioxolanone), 1 735 (methyl ester), 1 725 (formate) and 1 692 cm^{-1} (exocyclic C=C); λ_{max} (EtOH) 250 nm (ε 15 100); δ($CDCl_3$) (200 MHz) 1.4-1.8 (10H, m, cyclohexyl), 3.73 (3H, s, OMe), 5.67 (1H, s, 11-H), 5.78 (1H, m, CHOCHO), 5.96 (2H, dd, J 10 and 3 Hz, (CHCH)$_2$CH), 6.13 (2H, dd J 10 and 1.5 Hz, (CHCH)$_2$CH) and 8.10 (1H, d, J 1 Hz).

The partially purified formate from above was treated with Et_3N (3 µl, 0.0216 mmol) in methanol (5 ml) for 24 h at room temperature after which time the solution was concentrated under reduced pressure. Chromatography on silica gel gave the dienol (26) (20 mg, 28%) identical with that described above.

Preparation of Disodium Prephenate (4). - To a solution of the dienol (26) (72 mg, 0.225 mmol) in MeOH (1 ml) was added 2N NaOH solution (228 µl, 0.456 mmol). After stirring for 16 h at room temperature the reaction mixture was concentrated under reduced pressure. The residue was triturated with MeOH (2 x 0.5 ml) to leave a pure white solid which was combined with that obtained on centrifugation of the cooled (0°C) MeOH solution. There was thus obtained *Disodium Prephenate* (4) (61 mg, 97%) (Found: C, 42.9; H, 3.0. $C_{10}H_8O_6Na_2.\frac{1}{2}H_2O$ requires C, 43.0; H, 3.2); ν_{max} (KBr) 3520 and 3 450 (br), 1 690, 1 645 and 1 570 cm^{-1}; δ(D_2O) (360 MHz) 3.22 (2H, s, CH_2), 4.60 (1H, m, CHOH), 6.02 (2H, dd, J 10.4 and 3.2 Hz, (CHCH)$_2$CH) and 6.11 (2H, dd, J 10.4 and 1.5 Hz, (CHCH)$_2$CH). This nmr was consistent with one of disodium prephenate obtained by ion exchange of the commercially available barium salt with the exception that the natural material was contaminated with aromatic species.

Preparation of Disodium Epiprephenate (29). - In a similar manner, hydrolysis of dienol (28) with 2molar equivalents of NaOH gave *Disodium Epiprephenate* (29) (89%) (Found: C, 38.3; H, 4.3. $C_{10}H_8O_6Na_2.2H_2O$ requires C, 39.2; H, 3.95); ν_{max} (KBr) 3 400, 1 695, 1 625 and 1 570 cm^{-1}; δ(D_2O) (360 MHz) 3.27 (2H, s, CH_2), 4.64 (1H, m, CHOH), 5.99 (2H, dd, J 10.3and 3.2 Hz, (CHCH)$_2$CH) and 6.09 (1H, dd, J 10.3 and 1.6 Hz, (CHCH)$_2$CH).

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