JOURNAL OF THE CHEMICAL SOCIETY

Chemical Communications

Number 4
1982

Synthesis of the C_{14} Chromanyl Moiety of Natural α-Tocopherol (Vitamin E)

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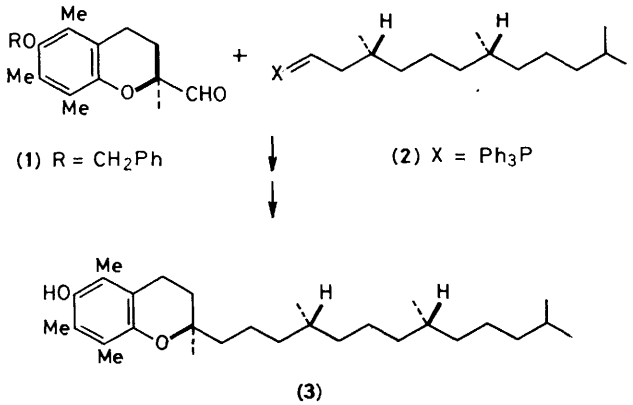
The synthesis of the C_{14} (2*S*) aldehyde (**1**) from the C_5 ketone (**7**) *via* the C_{16} adduct (**10**) is reported.

One approach to the total synthesis of natural α-tocopherol (vitamin E) (**3**) is based on chiral synthons obtained by microbial transformations as starting materials. By this method, the two C_{14} and C_{15} key building blocks (**1**) and (**2**) have been prepared from (+)-(*S*)-citramalic acid[1] (**4**) and from a variety of C_4 and C_5 intermediates,[2–4] respectively. The synthesis of the C_{14} chromanyl aldehyde (**1**) from (**4**) involves the direct incorporation of the chirality present in (**4**) through C–C bond formation between a suitable C_5 unit derived from (**4**) and a C_9 aromatic fragment, followed by ring closure.

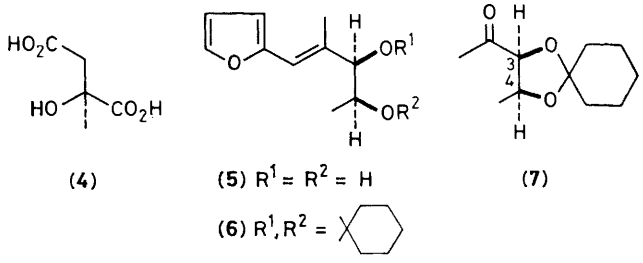
We present now a synthesis of enantiomerically pure (**1**) based on the use as optically active starting material of the C_5 ketone (**7**), obtained from the diol (**5**), prepared, in turn, from α-methyl-β-(2-furyl)acrolein and fermenting bakers' yeast.[5]

To this end, the (2*S*,3*R*)-diol (**5**), prepared in 15—20% yield in fermenting bakers' yeast from α-methyl-β-(2-furyl)acrolein,†

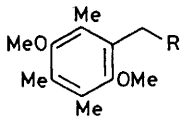


(1) R = CH_2Ph (2) X = Ph_3P

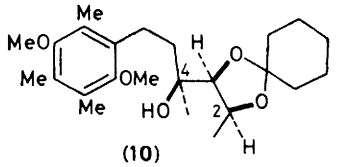
(3)



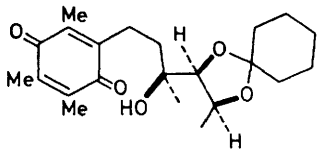
(4) (5) $R^1 = R^2 = H$ (6) R^1, R^2 = (7)



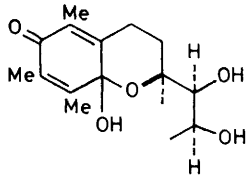
(8) R = CO_2H
(9) R = CH_2MgBr



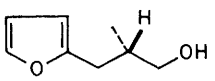
(10)



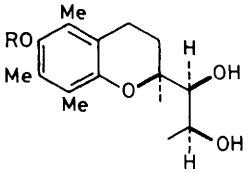
(11)



(12)



(15)



(13) R = H
(14) R = CH_2Ph

† Typically, 60 g of α-methyl-β-(2-furyl)acrolein in 30 l of tap water, containing 2.5 kg of commercial bakers' yeast, 0.8 kg of D-glucose, and 0.1 kg of Na_2HPO_4, under stirring at room temperature gave within 6—8 h, after extraction with ethyl acetate and SiO_2 column chromatography, 40—45 g of (**15**), containing some α-methyl-β-(2-furyl)prop-2-en-1-ol, and *ca.* 10 g of (**5**).

was quantitatively converted (cyclohexanone, toluene-*p*-sulphonic acid, benzene) into (**6**). Ozonolysis of (**6**) at −30 °C in CH_2Cl_2, followed by treatment with 1 mol. equiv. of Ph_3P, gave the ketone (**7**), b.p. 70 °C at 20 mmHg, $[\alpha]_D^{20}$ −51° (*c* 1, $CHCl_3$), *in ca.* 70% yield. The (3*R*,4*S*) absolute configuration of (**7**) is based on its conversion into *N*-benzoyl-2,3,6-trideoxy-3-*C*-methyl-3-amino-L-*arabino*hexose.[6] The C_9–C_2 Grignard reagent (**9**), prepared from the acid (**8**)[7] by standard methods, added in tetrahydrofuran at −30 °C to the ketone (**7**) to give[8] in *ca.* 75% yield the C_{16} adduct (**10**), $[\alpha]_D^{20}$ −20° (*c* 1, $CHCl_3$). The conversion of (**10**) into the chromanyl moiety (**14**) was achieved by known methods.[1,9] Thus, compound (**10**), upon oxidation with $Ce(NH_4)_2(NO_3)_6$ in MeCN–water (1 : 1), yielded the quinone (**11**), $[\alpha]_D^{20}$ −20° (*c* 1, $CHCl_3$), the ^1H n.m.r. spectrum (90 MHz; $CDCl_3$) of which showed a signal due to the C-4 methyl group at δ 1.50. Upon acid treatment, compound (**11**) gave rise to (**12**), $[\alpha]_D^{20}$ −80° (*c* 1, $CHCl_3$), in *ca.* 70% overall yield from (**10**). Hydrogenation of (**12**) over 10% Pd–C at room temperature gave quantitatively the vicinal diol (**13**), which, following benzylation to (**14**) ($PhCH_2Br$; Me_2NCHO; K_2CO_3) and HIO_4 oxidation in dry tetrahydrofuran (85%), yielded the required C_{14} aldehyde (**1**), $[\alpha]_D^{20}$ 12.3° (*c* 5, MeOH), in good agreement with the literature[1] value. In this last step, the two chiral centres of (**7**) which induced the chirality at C-4 in (**10**) are destroyed.

The significance of the present result is further supported by the fact that compound (**5**) is accompanied by the chiral alcohol (**15**) in the yeast fermentation of α-methyl-β-(2-furyl)-acrolein. The alcohol (**15**) obtained was optically pure since on ozonolysis and oxidative work-up it gave (*S*)-3-methyl-γ-butyrolactone, $[\alpha]_D^{20}$ −24.5° (*c* 4, MeOH) (lit.[3] −24.7°), and, on chain elongation through a procedure similar to that previously described[4] for the (2*S*)-2-methyl-5-phenylpent-4-en-1-ol, it gave optically pure (**2**). In this way, the two key intermediates (**1**) and (**2**) for the synthesis of enantiomerically pure (**3**) can be prepared from the optically active products (**5**) and (**15**), easily obtained from α-methyl-β-(2-furyl)acrolein in a single microbial transformation using inexpensive commercial bakers' yeast, in 15—20 and 40—60% yields, respectively.

We thank DE.BI, Derivati Biologici International (gruppo ENI), Cassina de'Pecchi, for financial support.

Received, 25th September 1981; Com. 1133

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