Efficient Stereoselective Synthesis of Natural α-Tocopherol (Vitamin E)

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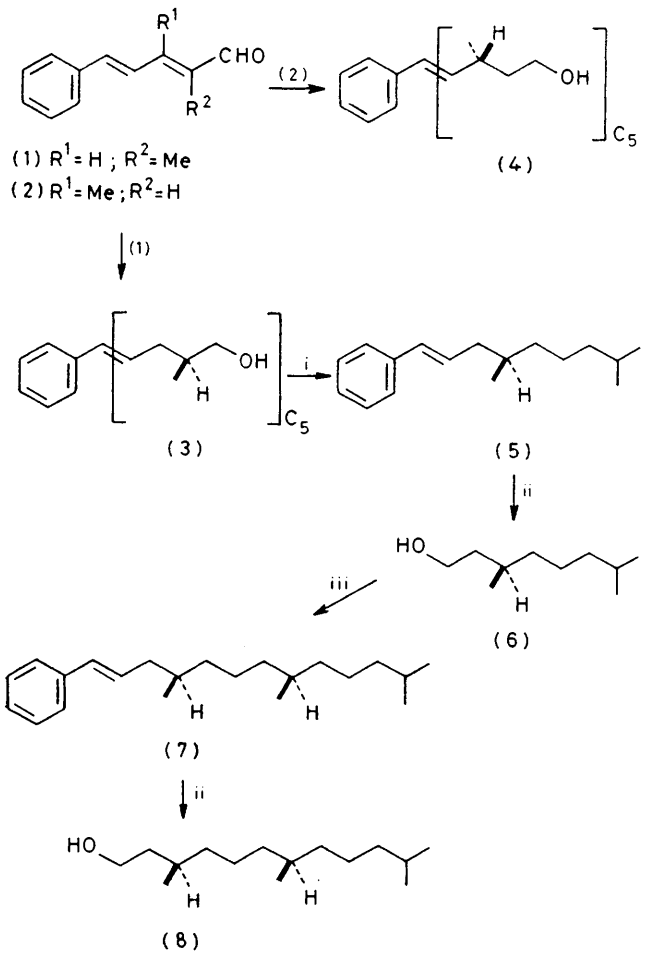
Summary Reduction by bakers' yeast of the aldehyde (**1**) gives 2-methyl-5-phenylpent-4-en-1-ol, containing *ca.* 87% of the (2*S*)-isomer (**3**), which is converted into (3*R*,7*R*)-3,7,11-trimethyldodecan-1-ol (**8**), a key intermediate in the synthesis of natural α-tocopherol (**19**); the same alcohol (**8**) and its lower homologue (**16**), which is also an intermediate in the same synthesis, are both obtained in optically pure form from the acid (**9**).

THERE has been considerable interest[1] in efficient syntheses of the natural form of α-tocopherol (vitamin E) (**19**), whose C_{29} chiral framework has been built up *via* C–C bond formation between a C_{14} or C_{15} optically active chromanyl group, *e.g.* (**17**) or (**18**), and a chiral C_{15} or C_{14} acyclic terpenoid chain, derived from the alcohols (**8**) and (**16**), respectively. Compounds (**17**) and (**18**) may be derived by classical optical resolution of the racemic materials and the alcohols (**8**) and (**16**) have been prepared by degradation of natural phytol, a compound which is not readily accessible. Accordingly, most efforts have been devoted to efficient stereoselective[2,3] syntheses of compounds (**8**) and (**16**). There are two ways of synthesising (**8**) and (**16**). (i) C_4 or C_5 chiral synthons[4,5] possessing appropriate functional groups, obtained by asymmetric transformation(s) of non-conventional substrates by micro-organisms, may be converted into (**8**) and (**16**), *via* C_9 and C_{10} intermediates. (ii) Classical optical resolution of racemic mixtures, followed by conversion of *both* enantiomers *via* different routes, also gives the chiral molecule (**19**).[6]

We here describe our studies of two syntheses of (**19**). Firstly it was thought possible to obtain optically active compounds containing a 'masked' C_5 chiral unit [see structures (**3**) and (**4**)], by reduction of the carbonyl-activated α-double bond of the aldehydes (**1**) and (**2**) with bakers' yeast. This would occur if the reduction showed the same stereochemistry and degree of stereospecificity as in the conversion of cinnamaldehyde into 3-phenylpropanol.[7] Indeed, (**1**) gave the alcohol (**3**) on reduction at pH 8·5, which was converted into the chiral hydrocarbon (**5**) {oil[α]$_D^{20}$ 1° (neat)} in 100% yield (see Scheme 1). The latter, upon ozonolysis and reductive work up, gave benzyl alcohol (which was eliminated from the crude mixture upon hydrogenolysis as toluene) and 3,7-dimethyloctan-1-ol in 70% yield, present mainly as the (3*R*)-isomer (**6**) {oil [α]$_D^{20}$ 2·5° (neat) (lit.[5] 4°)}. Compound (**6**) was coupled with the *p*-$MeC_6H_4SO_2$–derivative of the alcohol (**3**) to give the hydrocarbon (**7**) {oil, [α]$_D^{20}$ 1·3° (neat)} in 80% yield, incorporating two C_5 chiral synthons derived from (**3**). Compound (**7**) gave, under the same conditions as for the conversion of (**5**) into (**6**), 3,7,11-trimethyldodecan-1-ol, as

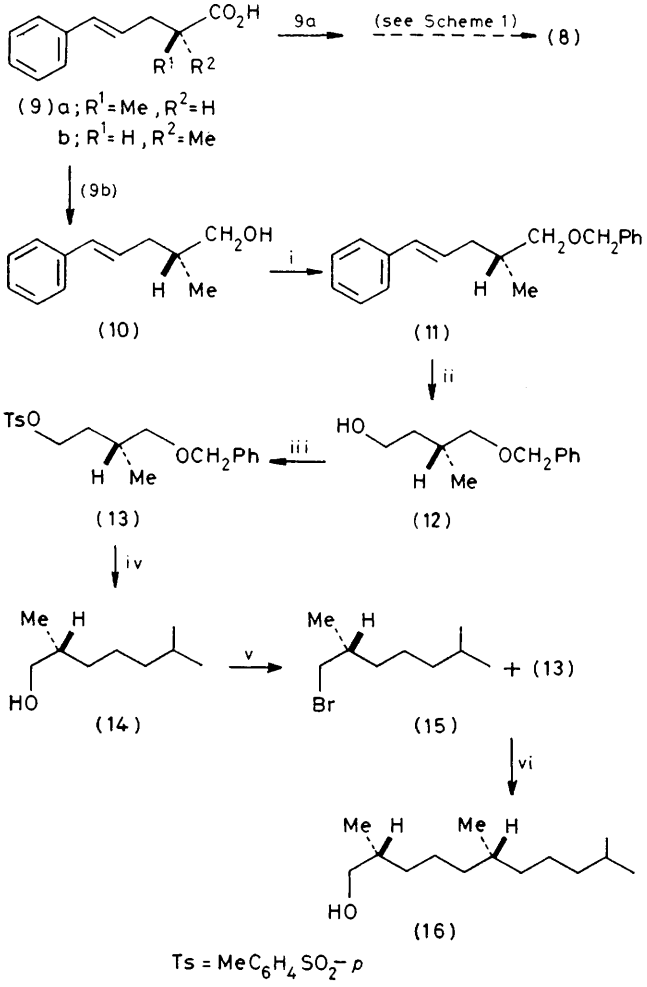
expected, in 70% yield, which was shown by its optical properties and by comparison with an authentic sample,[5] to contain 85—90% of the (3*R*, 7*R*)-isomer (**8**) {oil, $[\alpha]_D^{20}$ 3·2° (*c*, 4·23 in octane) (lit.[5] 4·1°)}. The aldehyde (**2**) gave a mixture of optically active (**4**)† and 3-methyl-5-phenylpenta-2,4-dien-1-ol, which could not be separated by conventional procedures.



SCHEME 1. i, *p*-$MeC_6H_4SO_2Cl$–pyridine then $BrMgCH_2CH_2$-$CHMe_2$, Et_2O–tetrahydrofuran (THF), Li_2CuCl_4; ii, O_3–hexane, −30 °C, then $LiAlH_4$–Et_2O at −30 °C; iii, *N*-Bromosuccinimide (NBS)–Ph_3P, CH_2Cl_2, then Mg,Et_2O, then *p*-$MeC_6H_4SO_2$-derivative of (**3**).

The relative simplicity of the conversion of (**3**) into (**8**), induced us to study as a second method an enantioconvergent synthesis of (**19**) from the acid (**9**) making use of the reaction sequence of Scheme 1. The acid (**9**) was resolved into its components (**9a**) and (**9b**) *via* salt formation with (+)- and (−)-α-phenylethylamine. The (2*S*)-isomer (**9a**) {$[\alpha]_D^{20}$ 20·2° (*c* 1·1, EtOH)} upon reduction with $LiAlH_4$ gave alcohol (**3**) {$[\alpha]_D^{20}$ — 13·3° (*c* 1·1, EtOH)} in *ca.* 85% yield. Compound (**3**) was converted (Scheme 1) into optically pure (**6**) which was coupled with the tosyl derivative of (**3**) {$[\alpha]_D^{20}$ 9·6° (*c* 1·19, $CHCl_3$)} to give (**7**), then (**8**). The $[\alpha]_D^{20}$ values obtained for (**5**)—(**8**) were 1·5, 4·1, 1·41, and 4·4, respectively.

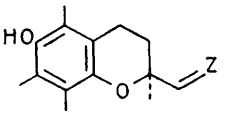
The (2*R*)-isomer (**9b**) {$[\alpha]_D^{20}$ — 20·3° (*c* 1·04, EtOH)} was reduced to the alcohol (**10**) {$[\alpha]_D^{20}$ 12·7° (*c* 1·06, EtOH)} and transformed into the benzyl ether (**11**) {oil, $[\alpha]_D^{20}$ — 7·6° (*c* 1·02, EtOH)} (Scheme 2) in 90% yield, which, upon



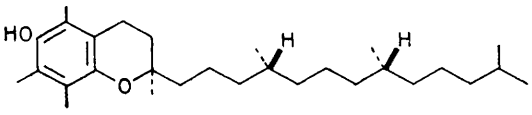
SCHEME 2. i, NaH–THF, $PhCH_2Cl$, reflux; ii, O_3–hexane, −30 °C then $LiAlH_4$–Et_2O, −30 °C, distillation at 133 °C, 1 mmHg; iii, *p*-$MeC_6H_4SO_2Cl$–pyridine; iv, $BrMgBu^t$, Et_2O–THF, Li_2CuCl_4, then H_2–Pd/C 10%, H_3O^+, EtOH; v, NBS–PPh_3, CH_2Cl_2; vi, Mg, Et_2O–THF, Li_2CuCl_4, (**13**), then as for iv.

ozonolysis and reductive work up gave the alcohol (**12**) {$[\alpha]_D^{20}$ — 2·8° (*c* 1·07, EtOH)} in 73% yield. Compound (**12**) was converted into the tosyl derivative (**13**) {$[\alpha]_D^{20}$ — 1·3° (*c* 1·37, $CHCl_3$)} in 100% yield, and was coupled with $BrMgBu^t$ to give, after removal of the protecting group, optically pure (2*R*)-2,6-dimethylheptan-1-ol (**14**) {oil, $[\alpha]_D^{20}$ 10·0° (*c* 2,C_6H_6) (lit.[4] 10·14°)} in 95% yield.[4] The alcohol (**14**) was converted into the bromide (**15**) {$[\alpha]_D^{20}$ — 0·62° (neat)} in 95% yield, and *via* the Grignard derivative, was coupled with (**13**) to give, eventually, optically pure

† The stereochemistry depicted in (**4**) is conjectural, and based only on analogous results obtained with cinnamaldehyde (see ref. 7).



(17) Z = O
(18) Z = H, CH_2OH



(19)

(2*R*,6*R*)-2,6,10-trimethylundecan-1-ol (**16**) {$[\alpha]_D^{20}$ 8·76° (*c* 2·06, hexane) (lit.[4] 9·13 and 8·16°)} in 85% yield,[4] incorporating two C_5 chiral units derived from the alcohol (**10**).

Since the chromanyl derivative (**17**) has been obtained from the intermediate(s) leading to (**18**),[1] and both (**17**) and (**18**) can be coupled with the C_{15} and C_{14} chains, (**8**) and (**16**), respectively, the above results represent an enantioconvergent synthesis of natural (2*R*,4′*R*,8′*R*)-α-tocopherol (**19**).

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