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A TOTAL SYNTHESIS OF ENANTIOMERICALLY PURE VITAMIN E SIDE CHAIN USING A CHIRAL PROPIONATE SYNTHON[1]

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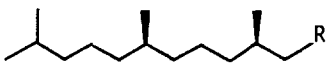
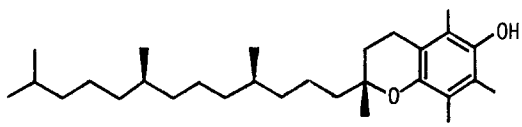
Summary: Alcohol 1a, representing the side chain of α-tocopherol, has been synthesized in 58 % overall yield via 9 steps. Key reactions of the synthesis are asymmetric alkylations of the chiral propionate 3 (ds ≥ 97 %) and chain elongation with t-butyl α-trimethylsilylacetate.

The development of methods for control of stereochemistry in acyclic systems is an area of fruitful and challenging current research[2]. Among the touchstones for demonstation of new methods the side chain, as represented by alcohols 1a or 1b, of α-tocopherol (vitamin E, 2) appears particularly interesting because of its model character for a variety of methyl branched natural products (i.e. vitamin K_1 [3a], pheromones[3b], membrane lipids[3c], and antibiotics[3d]).



1a R = OH
1b R = CH_2OH



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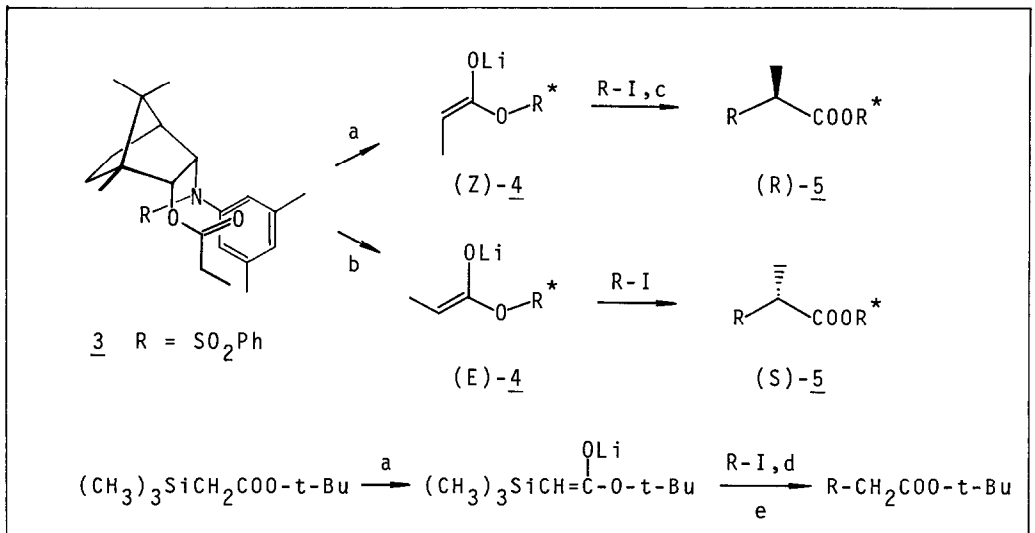
We wish to report an approach towards 1a, different from others presented so far[4], which is based on assembling according to the following scheme propionate (—●—o) and acetate (●—o) units[5]:

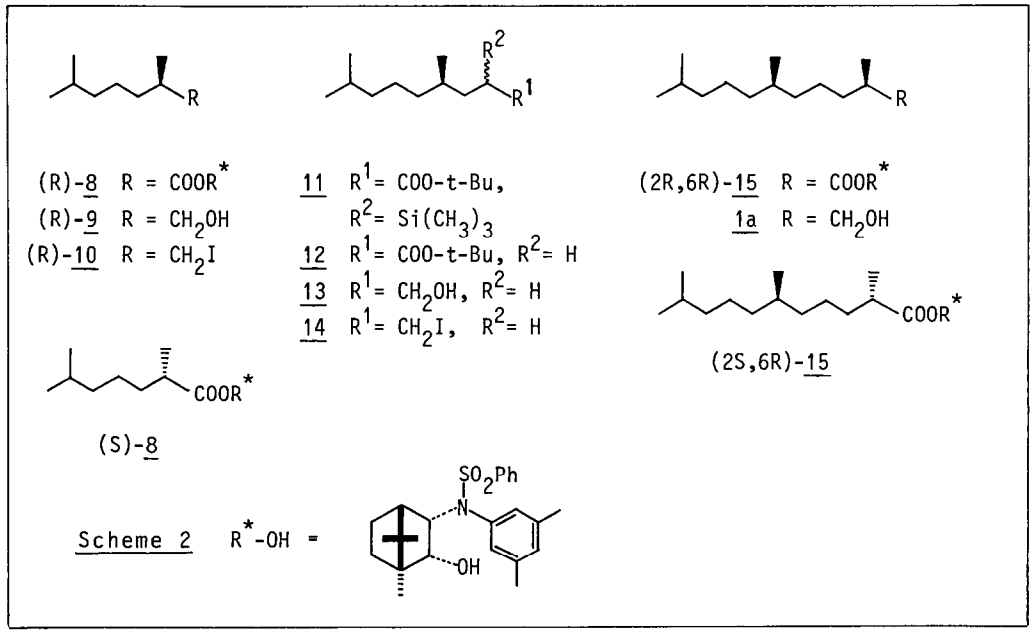
● electron donor center

o electron acceptor center

Highly stereoselective CC bond formation can generally be achieved by alkylation of the propionate 3 (Scheme 1). 3 is a unique reagent. It allows to construct both (R)- and (S)-α-alkylpropionates (5) with ds ≥ 95 %[6] via solvent controlled generation of either the (Z)- or (E)-lithium enolate, (Z)-4 or (E)-4, respectively, in conjunction with a high level of diastereoface-differentiation in the alkylation step. An acetate equivalent was provided by t-butyl α-trimethylsilylacetate (6) which was used as shown in Scheme 1. The lithium enolates of esters 3 and 6 are excellent chain elongation reagents as they are cleanly monoalkylated and, under proper



Scheme 1 a Lithium cyclohexylisopropylamide (LICA), THF, -80 °C; b LICA, THF-HMPT (23 %), -80 °C; c DMEU (2 eq.); d TMEDA (2 eq.); e THF-H_2O, NBu_4F (cat.), r.t.



Scheme 2

reaction conditions, do not induce elimination in the alkylating agent R-X[7]. The reactions described in Scheme 1 were used to construct the alcohol 1a via the intermediates whose formulas are shown in Scheme 2[8].

Alkylation of 3 with isohexyl iodide (7) via (Z)-4 [- 80 → - 40 °C, 2 eq. of N,N-dimethylimidazolidinone (DMEU) added together with 7] proceeded with high diastereoselectivity [ds = 98 %, i. e. (R)-8 : (S)-8 = 98 : 2, analysis by HPLC[9]]. Diastereoisomerically pure (R)-8 was obtained by crystallization or medium pressure liquid chromatography (MPLC)[9] (88 %, mp = 106 - 106.5 °C). For reference pure (S)-8 (oil) was prepared from 3 and 7 via (E)-4 [90 %, ds = 94 %, i. e. (R)-8 : (S)-8 = 6 : 94, MPLC purification]. (R)-8 was reduced ($LiAlH_4$, THF, MPLC purification[10]) to give (R)-9 [86 %, bp_{12} = 90 °C, $[\alpha]_D^{25}$ = + 10.8° (c = 2.1, benzene), Lit.[11]: $[\alpha]_D^{25}$ = + 10.14° (c = 2.01, benzene)].

(R)-9 was converted [aq. HI (56 %), reflux] into the iodide (R)-10 (93 %, bp_{12} = 100 °C). Chain elongation was effected by adding (R)-10, admixed with 2 eq. of TMEDA, to a THF solution of the lithium enolate of t-butyl α-trimethylsilylacetate at - 80 °C. The solution was allowed to warm to 0 °C whereupon standard work-up gave an epimer mixture of silylated esters 11 (oil) in 78 % yield (100 %, based on recovered iodide 10). Desilylation (2 eq. H_2O, THF, n-$Bu_4N^+F^-$ catalytic amount) yielded the ester (R)-12 (94 %, bp_{12} = 123 °C) reduction of which ($LiAlH_4$, THF) afforded the alcohol (R)-13 (99 %, $[\alpha]_D^{20}$ = + 2.86° (neat, d_4^{20} = 0.8269)[12]).

The iodide (R)-14, obtained (99 %) from (R)-13 in the same way as 10 from 9, was subjected to an asymmetric alkylation reaction with 3 (2 eq.) in essentially the same way as isohexyl iodide (7). Again, excellent diastereoselectivity (ds = 97 %, analysis by HPLC) was observed. Purification by MPLC afforded stereochemically homogeneous (HPLC control) (R,R)-15 (90 %, mp = 56 - 57.5 °C) which was reduced ($LiAlH_4$, THF) to give the target compound 1a (99 %, bp_{12} = 143 °C). The optical rotation of the synthetic specimen, $[\alpha]_D^{25}$ = + 9.25° (c = 1.96, n-hexane), is in excellent agreement with that of material derived from natural phytol, $[\alpha]_D^{25}$ = + 9.36° (c = 2.02, n-hexane)[13].

The methods described above are fairly efficient. This may be assessed by the following observations. 1) The synthesis requires 9 steps (from isohexyl iodide) and produces 1a in 58 % overall yield. This compares favourably with that achieved in other total syntheses of 1a or 1b[4c,d]. 2) The preparation of ester (S)-8 in addition to (R)-8 demonstrates that all of the stereoisomers of 1a can be obtained via routes similar to that described above. Use of the cis-exo isomer of 3 as reagent also allows build-up of (S)-α-alkyl esters. 3) The strategy described herein has been successfully applied to total syntheses of the four stereoisomers of 15,19,23-trimethylheptatriacontane (sex pheromone of the tsetse fly Glossina morsitans) and (S,S)-2,4,6-trimethyl--2-docosenoic acid (mycolipenic acid)[14].

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(5) This synthon pattern does not correspond to that of the biosynthesis of α-tocopherol which is derived from mevalonate. Interestingly, however, the biosynthesis of 1,5 methyl branched cuticular hydrocarbons of insects seems to proceed according to such a scheme: G.J.Blomquist, R.W.Howard, C.A.McDaniel, Insect Biochem. 9, 371 (1979).

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(7) Successful alkylations of α-trimethylsilylacetates via lithium enolates are documented: (a) P.F.Hudrlik, D.Peterson, D.Chou, Synth.Commun. 5, 359 (1975), (b) P.A.Grieco, C.-L.Wang, S.D.Burke, J.Chem.Soc.Chem.Commun. 1975, 537. However, the usefulness of α-trimethylsilyl acetates for preparation of α-trimethylsilylalkanoates or for 2-carbon chain elongation does not seem to have been appreciated: (c) G.L.Larson, L.M.Fuentes, J.Am.Chem.Soc. 103, 2418 (1981), (d) W.Bos, H.J.J.Pabon, Rec.Trav.Chim.Pays-Bas 99, 141 (1980).

(8) All new compounds described herein gave correct elemental analyses and spectra.

(9) For all chromatographic separations silica gel was used as the adsorbent and petroleum ether (l.b.)-ethyl acetate mixtures of appropriate eluotropicity as eluents.

(10) The reagent R*-OH (Scheme 2) was obtained back in near quantitative yield.

(11) N.Cohen, W.F.Eichel, R.J.Lopresti, C.Neukom, G.Saucy, J.Org.Chem. 41, 3505 (1976). For the enantiomer, (S)-9, a slightly better value is documented[4a]: bp 100-105 °C, $[\alpha]_{589}^{25}$ = - 10.97° (c = 2, benzene). For the neat compound we found $[\alpha]_{578}^{25}$ = + 11.18°, $[\alpha]_{546}^{25}$ = + 12.66° (1 dm, no normalization with respect to density).

(12) $[\alpha]_{589}$ = + 2.05° (neat, d_{20}^{4} = 0.8269) has been recorded for (R)-13 prepared from optically impure citronellal with $[\alpha]_{589}$ = + 11.70 (neat): D.Hauser, K.Schaffner, O.Jeger, Helv. Chim.Acta 47, 1883 (1964). On the basis of $[\alpha]_{589}^{20}$ = + 16.50°(neat, d_{20}^{4} = 0.851) of optically pure citronellal [B.D.Sully, P.L.Williams, Perfum.Essent.Oil Rec. 59, 365 (1968)] the value $[\alpha]_{589}$ = + 2.89° (neat) is calculated for optically pure (R)-13.

(13) J.W.Scott, F.T.Bizzarro, D.R.Parrish, G.Saucy, Helv.Chim.Acta 59, 290 (1976). For the neat compound we found: $[\alpha]_{589}^{25}$ = + 7.741°(1 dm, no normalization with respect to density).

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