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ACYCLIC STEREOSELECTION. 15. SEQUENTIAL ALDOL-CLAISEN AS A METHOD FOR 1,5-STEREOSELECTION. TOTAL SYNTHESIS OF THE VITAMIN-E SIDE CHAIN

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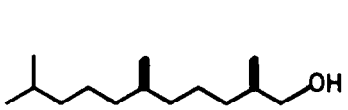
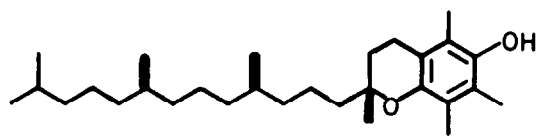
Summary: *Alcohol* **1**, *the side chain of* α*-tocopherol, has been synthesized in a stereoselective route involving an aldol condensation-Claisen rearrangement sequence. The synthesis requires 11 steps and produces* **1** *in 17% overall yield. A complementary sequence employing reagent* **14** *provides isomer* **18**.

The aldol condensation has been established to be an effective tool for achieving 1,2-stereoselection in the synthesis of acyclic compounds.[2] In this communication we demonstrate that this versatile reaction may also be used in conjunction with the Claisen rearrangement to achieve overall 1,5-stereoselection. The strategy is illustrated with a total synthesis of the C_{14} alcohol **1**, which has been converted into vitamin-E (**2**)[3]

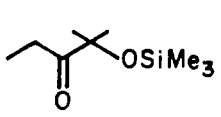


1



2

The lithium enolate of ketone **3** reacts with acrolein to give aldol **4** in 80% yield.[5] Oxidation of **4** with periodic acid in tetrahydrofuran (THF)[6] gives β-hydroxy acid **5** (100%),[5] which is reduced by lithium aluminum hydride in refluxing THF to obtain diol **6** (90%).[5] Selective protection[6] of the primary hydroxyl is achieved by treatment of **6** with *t*-butyldimethylsilyl chloride, triethylamine and 4-(N,N,dimethylamino)pryidine in methylene chloride; hydroxy ether **7**[5] is obtained in quantitative yield. Propionate ester **8**[5] obtained by reaction of **7** with propionyl chloride in methylene chloride (73%), is subjected to Ireland's conditions for the enolate Claisen rearrangement[8](1. LDA, THF, -78°C; 2. *t*-$BuMe_2SiCl$, -78°C; 3. 25°C, 5.5 hr) to obtain unsaturated acid **9**[5] (58%). Catalytic hydrogenation of this material (H_2, PtO_2, EtOAc) affords saturated acid **10** (100%)[5] which is reduced (diborane, THF, 25°C) to obtain the monoprotected diol **11** (83%).[5] Tosylate **12**[5] obtained from **11** in the normal manner (*p*-TsCl, C_5H_5N, CH_2Cl_2, 86%), is allowed to react with two equivalents of 3-methyl-1-butylmagnesium bromide and Li_2CuCl_4 in THF at 0°C for 1 hr, then at 25°C for 30 hr[3a, 9] to obtain ether **13**[5] (85%). Deprotection of this compound (*n*-$Bu_4N^+F^-$, THF 25° C) gives alcohol **1** (80%). Alcohol **1** was shown by ^{13}C-NMR spectroscopy to be identical with an authentic sample of enantiomerically homogeneous **1**.[3, 10]



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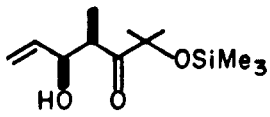

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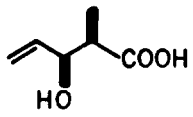

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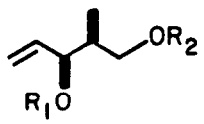
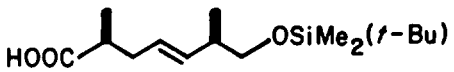


6: $R_1 = R_2 = H$
7: $R_1 = H$, $R_2 = t\text{-}BuMe_2Si$
8: $R_1 = COEt$, $R_2 = t\text{-}BuMe_2Si$



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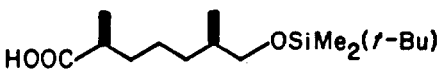

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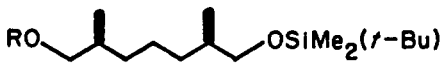
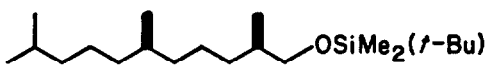
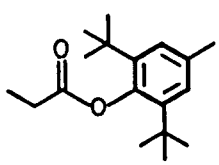


11: R = H
12: R = Ts

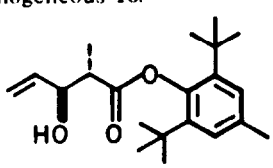


13

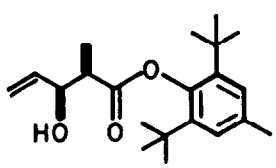
In a complementary sequence of reactions ester **14**[11] is condensed with acrolein to provide an 86:14 mixture of β-hydroxy esters **15** and **16** (88%) which is reduced ($LiAlH_4$, refluxing THF) to a similar mixture of alcohols **17** and **6**. This mixture of diastereomers is converted by the same sequence outlined above to an 86:14 mixture of alcohols **18** and **1**. The major isomer was identified by comparison (^{13}C-NMR)[10] with an authentic sample of enantiomerically homogeneous **18**.[3]



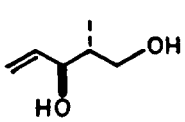
14



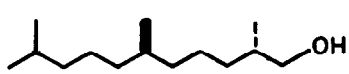
15



16



17



18

The foregoing investigations have been carried out entirely with racemic intermediates. However, by taking advantage of one of the enantioselective aldol reagents that are now available,[12] alcohols **1** and **18** could easily be prepared in enantiomerically homogeneous form. It should be noted that the Roche group have also employed the Claisen rearrangement of optically active allylic alcohols for construction of the α-tocopherol side chain.[13]

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References and Notes

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5. Compounds were characterized by elemental analysis and/or ^{1}H-NMR. ^{1}H-NMR data are expressed as δ (number of protons, multiplicity, coupling constant). **4**: δ 0.22 (9 H, s), 1.12 (3 H, d, J = 7), 1.38 (3 H, s), 1.39 (3 H, s), 3.08 (1 H, d, J = 2), 3.47 (1 H, qd, J = 4, 7), 4.37 (1 H, m), 5.17 (1 H, dt, J = 2, 11), 5.29 (1 H, d of t, J = 2, 17), 5.79 (1 H, ddd, J = 4, 11, 17); **5**: δ 1.15 (3 H, d, J = 7), 2.68 (1 H, qd, J = 4, 7), 4.42 (1 H, m), 5.05-5.30 (2 H, m), 5.70 (1 H, ddd, J = 2, 11, 17); **6**: δ 0.85 (3 H, d, J = 7), 1.90 (1 H, m), 3.7-3.9 (2 H, m), 4.40 (1 H, m), 5.25-5.50 (2 H, m), 6.00 (1 H, ddd, J = 4, 11, 7); **7**: δ 0.07 (6 H, s), 0.86 (3 H, d, J = 7), 0.90 (9 H, s), 1.94 (1 H, m), 3.33 (1 H, d, J = 5), 3.64-3.74 (2 H, m), 4.27 (1 H, m), 5.18 (1 H, d, J = 11), 5.29 (1 H, d, J = 17), 5.88 (1 H, ddd, J = 5, 11, 17); ^{13}C-NMR ($CDCl_3$): δ -5.6, 11.0, 25.9, 40.2, 66.7, 74.8, 114.6, 139.3; **8**: δ 0.02 (6 H, s), 0.88 (9 H, s), 0.91 (3 H, d, J = 7), 1.15 (3 H, t, J = 7), 1.86 (1 H, quintet, J = 5), 2.35 (2 H, q, J = 7), 3.44 (1 H, dd, J = 6, 10), 3.53 (1 H, dd, J = 6, 10), 5.13-5.38 (3 H, m), 5.78 (1 H, ddd, J = 6, 10, 18); ^{13}C-NMR ($CDCl_3$): δ -5.6, 9.0, 11.6, 18.1, 25.8, 27.7, 39.9, 64.5, 74.8, 116.3, 135.6, 173.0; **9**: δ 0.03 (6 H, s), 0.88 (9 H, s), 0.96 (3 H, d, J = 7), 1.15 (3 H, d, J = 7), 2.13-2.52 (4 H, m); 3.35 (1 H, dd, J = 7.10), 3.46 (1 H, dd, J = 7, 10), 5.40 (1 H, t, J = 4), 5.40 (1 H, t, J = 5); **10**: δ 0.02 (6 H, s), 0.88 (3 H, d, J = 7), 0.91 (9 H, s), 1.19 (3 H, d, J = 7), 1.24-1.70 (6 H, m), 2.45 (1 H, m), 3.37-3.55 (2 H, m); **11**: δ 0.03 (6 H, s), 0.86 (3 H, d, J = 7), 0.89 (9 H, s), 0.91 (3 H, d, J = 7), 1.0-1.7 (6 H, m), 3.35-3.54 (4 H, m); **12**: δ 0.05 (6 H, s), 0.89-0.90 (6 H, m), 0.90 (9 H, s), 1.0-1.7 (6 H, m), 2.45 (3 H, s), 3.35 (2 H, d, J = 7), 3.90 (2 H, d, J = 7), 7.40 (2 H, m), 7.80 (2 H, m); **13**: δ 0.04 (6 H, s), 0.83-0.90 (12 H, m), 0.90 (9 H, s), 1.0-1.65 (15 H, m), 3.35-3.55 (2 H, m).
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10. The ^{13}C-NMR spectra of alcohols **1** and **18** are almost identical. The following resonances are observed at 0.56 *M* in $CDCl_3$ (ppm downstream from TMS): **1**, 16.60, 19.65, 22.56, 22.66, 24.38, 24.75, 27.90, 32.71, 33.46, 35.70, 37.20, 37.33, 39.31, 68.14; **2**, 16.53, 19.68, 22.56, 22.66, 24.38, 24.75, 27.90, 32.71, 33.45, 35.70, 37.21, 37.33, 39.31, 68.20. A mixture 0.23 *M* each in **1** and **18** examined at 63.07 MHz showed distinct doubling of the resonances due to the carbinol carbon (68.15 and 68.20 ppm) and the two methyl carbons (16.53 and 16.60 ppm, 19.58 and 19.66 ppm). All other signals are coincident under these conditions. A similar 1:1 mixture of synthetic **1** and authentic **1**, supplied by Dr. Cohen, showed exact coincidence of all 14 resonances.
11. C. H. Heathcock, M. C. Pirrung, S. H. Montgomery, and J. Lampe, *Tetrahedron*, **37**, 4087 (1981).

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