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A kinetic resolution route to the (*S*)-chromanmethanol intermediate for synthesis of the natural tocols

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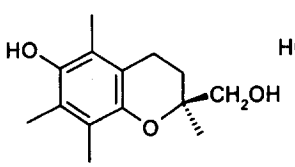
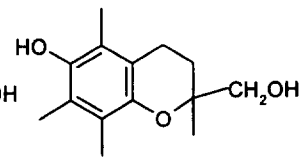
Abstract: Kinetic resolution of 2-hydroxymethyl-2,5,7,8-tetramethyl-6-chromanol was carried out by reaction with succinic anhydride catalysed by Amano PS-30 lipase. The (*S*)-enantiomer (which corresponds to the natural (2*R*)-configuration of the natural tocopherols and tocotrienols) was selectively acylated. An enantiomeric excess of 96.5% was achieved, and the absolute configuration was proven by conversion to known tocol intermediates. This work provides an example of the uncommon kinetic resolution of a primary neopentyl-type alcohol and provides a high-yield, chromatography-free route to a useful tocol intermediate. © 1997 Elsevier Science Ltd. All rights reserved.

Introduction

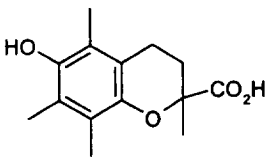
(*S*)-6-Hydroxy-2,5,7,8-tetramethyl-2-chromanmethanol (*S*)-**1** is an important intermediate for the synthesis of the natural tocols such as vitamin E and α-tocotrienol. A number of syntheses of (*S*)-**1** have been reported in which the sources of chirality are acyclic substances which were incorporated into the chroman ring in multistep sequences.[1] Since racemic chromanmethanol (*R,S*)-**1** is readily obtained by hydride reduction of the commercially available acid **2**,[2,3] it is surprising that little attention has been given to resolving this alcohol.



(*S*)-**1**



(*R,S*)-**1**



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In a pair of recent patent filings, Takahata, Torihara, and Tamai claim the lipase-catalysed kinetic resolution of (*R,S*)-**1** through selective acylation (benzoic anhydride was used) or selective ester hydrolysis.[4,5] However, these workers reported neither the optical rotation nor the absolute configuration of their products. We therefore are prompted to describe our work in this area, which provides a more convenient route to (*S*)-**1** and establishes the absolute configuration of the lipase-catalysed resolution.

Results and discussion

We found that while racemate (*R,S*)-**1** can be cleanly resolved by transesterification with vinyl acetate in the presence of Amano PS-30 lipase, the separation of the resulting (*S*)-acetate from the remaining (*R*)-alcohol required chromatography. A far superior preparative method consisted of reacting (*R,S*)-**1** with succinic anhydride in the presence of the lipase.[6] At the 15-gram scale, an overnight reaction followed by acid–base workup gave 94% of the theoretical yield of (*S*)-succinate **3** and an 84% recovery of the unreacted (*R*)-alcohol (*R*)-**1**. Chiral column HPLC established that succinate **3** was formed in 96.5% ee.

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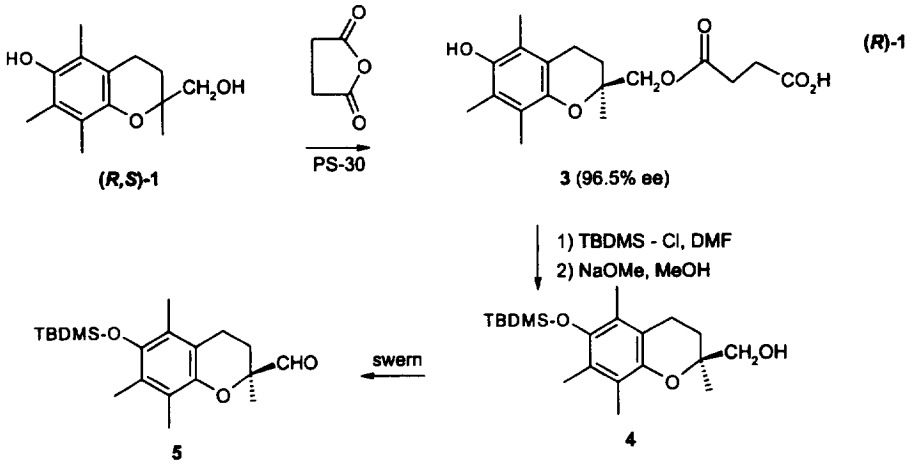
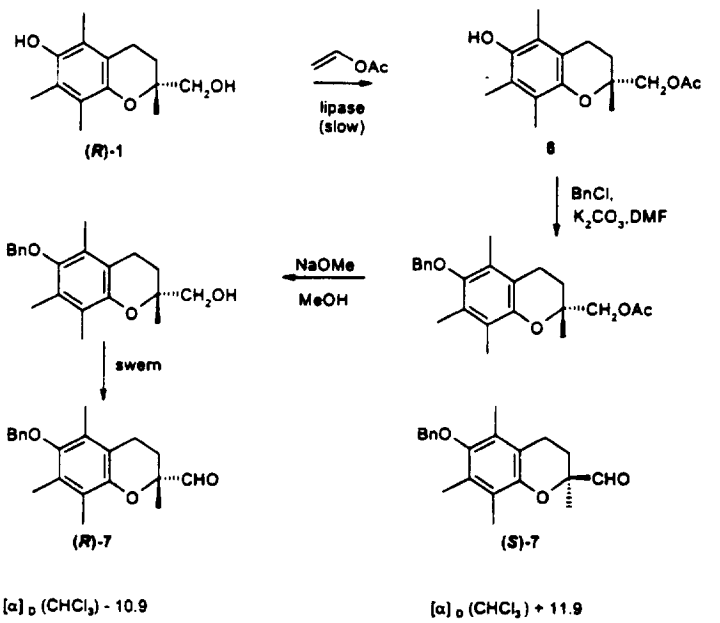
Although succinate **3** could be cleanly saponified to provide (*S*)-**1**, most applications of this intermediate require protection of the phenol group. A convenient protocol involved reaction of the succinate with *tert*-butyldimethylsilyl chloride; the crude TBDMS derivative could be transesterified in methanol to give protected alcohol **4**. We also noted that the crude **4** can be subjected to Swern oxidation to provide crystalline aldehyde **5**, which is functionally equivalent to the corresponding benzyl- and acetyl-protected aldehydes which have been used in tocol syntheses.[1e,f,7]



Since the optical rotations of chromanols such as **1** are low, we chose to establish the absolute stereochemistry of our products through conversion to a known compound in the aldehyde series. Thus, the supposed unnatural series recovered alcohol (*R*)-**1** was subjected to acetyl transfer from vinyl acetate using lipase catalysis; conversion to monoacetate **6** was complete after 10 days. Compound **6** was then benzylated, deacetylated, and oxidized to give benzyl aldehyde (*R*)-**7**. Our sample of (*R*)-**7** had an absolute rotation of -10.9. Since Cohen *et al.*[1f] have shown that natural-series (*S*)-aldehyde (*S*)-**7** has a rotation of +11.9, we conclude that the absolute stereochemistries of **3** and (*R*)-**1** are as depicted above.



Experimental

Melting points were determined on a Thomas–Hoover apparatus and are uncorrected. NMR spectra were recorded with a Varian Gemini instrument at 300 Mhz. Optical rotations were determined with a Rudolf Autopol II polarimeter using a 1 dm tube and chloroform as solvent. HPLC analyses utilized Perkin-Elmer equipment and a Daicel OJ column operated at 35 deg C and a 0.3 mL/min flow of 20% isopropanol in heptane. Detection was by UV absorption at 270 nm.

Kinetic resolution of alcohol (R,S)-*1*

Alcohol (*R,S*)-**1** was prepared by hydride reduction of commercial acid **2**.[2,3] Amano PS-30 lipase was supported on Celite according to the procedure of Panza *et al.*[8] A mixture of 15.0 grams of alcohol (*R,S*)-**1**, 10.0 grams of Celite-supported PS-30 lipase, 9.0 grams of succinic anhydride, and 250 ml of *tert*-butyl methyl ether was stirred at room temperature for 20 hours, at which time TLC analysis indicated formation of equal amounts of a polar product and unreacted alcohol. The mixture was diluted with ethyl acetate, filtered (Celite), and extracted 5 times with 5% aq. sodium bicarbonate solution. The aqueous phase was then acidified carefully with dilute HCl and extracted with ethyl acetate. The extract was dried and stripped of solvent to give crude succinate **3** which weighed 10.1 grams (94% of theory) after recrystallization from ether–hexane. Compound **3** had mp 97–100°C, $[\alpha]_D$ +0.48, (C=0.50), FD mass spec m/e 336 (calc. 336), NMR ($CDCl_3$): 4.14 (q, J=12 Hz, 2H), 2.69 (s, 4H), 2.63 (m, 2H), 2.15 (s, 3H), 2.12 (s, 3H), 2.10 (s, 3H), 1.97-1.72 (m, 2H), 1.29 (s, 3H). Analysis: Calc. for $C_{18}H_{24}O_6$: C, 67.3, H, 7.19%. Found: C, 67.7, H, 7.22%.

The ethyl acetate phase remaining from the bicarbonate extraction was worked up in the usual manner to give 6.0 grams of recrystallized (*R*)-chromanmethanol (*R*)-**1**. This material was reserved for conversion to benzyl aldehyde (*R*)-**7** (see below).

A sample of succinate **3** was saponified with excess sodium methoxide in methanol (rt, 4 hours) to give a 88% yield of (*S*)-chromanmethanol (*S*)-**1** which had physical properties in agreement with literature values.[1] Chiral-column HPLC analysis as described above was capable of giving baseline resolution of the enantiomers of **1** and demonstrated that the sample of (*S*)-**1**, and hence the succinate **3**, was formed in 96.5% ee.

Conversion of succinate 3 to aldehyde 5

A solution of 7.9 grams of succinate **3** in 80 mL of dry DMF was treated with 12 grams of imidazole and 12 grams of TBDMS chloride. After stirring overnight at rt, the mixture was poured into water, neutralized with acetic acid, and extracted with ethyl acetate. The organic phase was washed, dried, and stripped of solvent to give, as a syrup, crude silyl ether–ester. This material was dissolved in about 50 mL of dry methanol and treated with 4 mL of 25% sodium methoxide in methanol. After 4 hours at rt the mixture was neutralized with acetic acid, poured into water, and extracted with ethyl acetate. The organic phase was washed, dried, and evaporated (excess silyl by-products were removed under high vacuum) to give 8.1 grams of the crude TBDMS ether–alcohol **4**. A small sample of **4** was purified by preparative TLC and analysed. The syrupy substance had NMR: 3.61 (m, 2H), 2.62 (m, 2H), 2.10 (s, 3H), 2.08 (br s, 6H), 1.95–1.70 (m, 2H), 1.22 (s, 3H), 1.04 (s, 9H), and 0.13 (s, 6H) ppm. FD mass spec: m/e 350 (calc. 350).

The crude **4** was oxidized as follows: A mixture of 15 mL of dry dichloromethane and 0.33 mL of oxalyl chloride was cooled below −50°C under argon. There was added 0.53 mL of dry DMSO, followed by a solution of 1.1 grams of alcohol **4** in 5 mL of dichloromethane. After about 20 min, the mix was allowed to warm to rt and 2.2 mL of dry triethylamine was added. Workup afforded 1.0 grams (91%) of TBDMS aldehyde **5** as a solid of mp 60–65°C. Recrystallization from pentane gave mp 66–69°C. $[\alpha]_D$ +14.7 (C=0.42). NMR ($CDCl_3$): 9.62 (d, J=1.4 Hz, 1H), 2.51 (m, 2H), 2.3–2.2 (m, 1H), 2.17 (s, 3H), 2.11 (s, 3H), 2.02 (s, 3H), 1.8 (m, 1H), 1.38 (s, 3H), 1.02 (s, 9H), and 0.12 (s, 6H). FD mass spec: m/e 348 (calc, 348). Analysis: Calc. for $C_{20}H_{32}SiO_3$: C, 68.9, H, 9.26%. Found: C, 69.1, H, 9.40%.

Proof of absolute configuration

A mixture of 21 grams of (*R*)-chromanmethanol (*R*)-**1** (combined lots of recovered unsuccinoylated material from the kinetic resolutions described above; 88% ee by HPLC), 11 grams of Celite-supported lipase PS-30, 50 grams of 4A molecular seive, and 500 mL of vinyl acetate was stirred at rt for 10 days, by which time TLC analysis indicated completion of the very slow conversion to (*R*)-2-acetoxymethyl-2,5,7,8-tetramethyl-6-chromanol **6** (no formation of diacetate was detected even at this reaction time). Workup as described above gave 20 grams (81%) of **6**, mp 86–88°C, $[\alpha]_D$ +0.30 (C=0.47). mA mixture of 0.278 grams of this acetate, 5 mL of dry DMF, 0.40 grams of potassium carbonate, and 0.15 grams of benzyl chloride was stirred at rt overnight. Aqueous workup followed by product isolation by preparative TLC afforded 0.21 grams (57%) of benzyl ether–acetate as a colorless syrup which was not further characterized.

A mixture of 0.76 grams of material prepared in this way was dissolved in 20 mL of dry methanol and treated with 5 drops of freshly prepared 2% sodium methoxide in methanol. After 2 hours at rt, TLC analysis disclosed the conversion of benzyl ether–acetate to a single more polar product. Aqueous workup of this reaction gave 0.63 grams of the benzyl ether–alcohol as a clear syrup, which was oxidized as follows: 15 mL of dry dichloromethane containing 0.23 mL of oxalyl chloride was cooled to below −50°C. DMSO (0.45 mL) was added, followed by 0.63 grams of the alcohol as a solution in 3 mL of dichloromethane. The reaction was allowed to warm to 0°C and 2.5 mL of triethylamine was added. Aqueous workup followed by flash chromatographic purification (5% acetone in hexane elution) gave 0.44 grams of benzyl ether–aldehyde (*R*)-**7** whose NMR spectrum was in agreement with that reported for the corresponding (*S*)-benzyl ether aldehyde (*S*)-**7**[8]. Our product had $[\alpha]_D$ −10.9 (C=0.39). Since Cohen *et al.*[8] reported the opposite rotation for aldehyde later converted to natural-series tocopherol, we conclude that the unreacted alcohol (*R*)-**1** is of the unnatural (*R*)-configuration and that the succinate (*S*)-**3** must be (*S*).

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