DIASTEREOSELECTIVE SYNTHESIS OF CHROMAN-SULFOXIDES#

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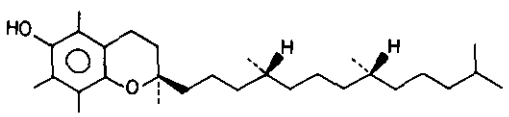
Abstract — Intramolecular addition of a phenolic hydroxy function to an α,β-unsaturated chiral sulfoxide led to the formation of a chiral chroman-sulfoxide in 22% optical yield. Subsequent conversions provided an α-tocopherol synthon in 12% enantiomeric excess.

The renewed interest in the biological role of α-tocopherol (vitamin E) in view of its applications in human health[2] has initiated new research[3] into the synthesis of the naturally occurring form, (2R,4'R,8'R)-α-tocopherol 1.



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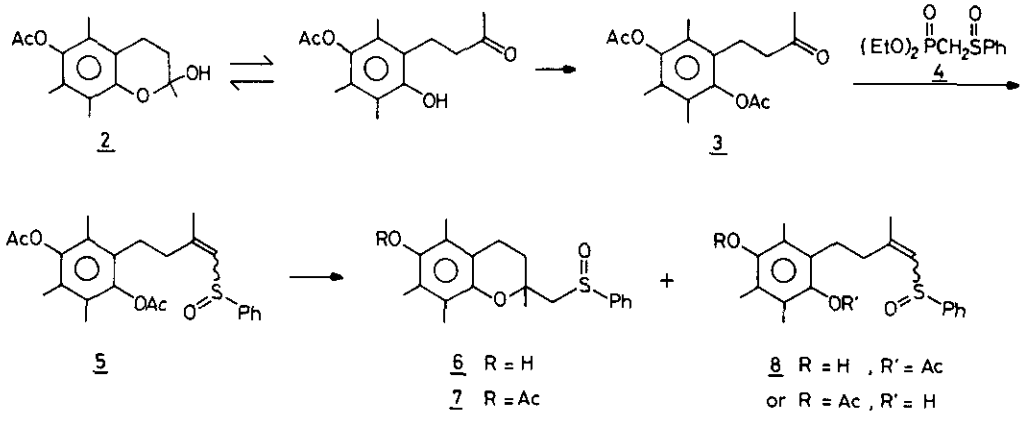
Recently we described the synthesis of rac.-α-tocopherol via chroman-sulfoxides[4], while the synthesis of nat.-α-tocopherol based on this work will be reported in due course[5]. We now wish to describe our investigations of an approach to optically active chroman-sulfoxides through base-catalyzed intramolecular addition of phenolic hydroxy functions to α,β-unsaturated sulfoxides (asymmetric β-induction by the chiral sulfoxide moiety).

#Dedicated to Professor Tetsuji Kametani on the occasion of his retirement from the Chair of Organic Chemistry at the Pharmaceutical Institute of Tohoku University.

The selectivity of the base-catalyzed cyclization of the α,β-unsaturated sulfoxides was first investigated in the racemic series. The magnitude of the β-induction by the sulfoxide function followed easily from the diastereoisomeric excess (d.e.), which could be calculated from the relative intensities of the C(2)-methyl protons in the n m r spectra.

Acetylation (Ac_2O in pyridine) of the hemiacetal 2[6] to the diacetate 3[7] [74% yield; mp 97-99°C; ir ($CHCl_3$) 1750, 1705 cm^{-1}; nmr δ ($CDCl_3$) 2.10 (aromatic CH_3), 2.30 (CH_3CO_2)] and subsequent Horner-Wittig reaction with the phosphonate 4 (slow addition of the carbanion of 4 - preformed in THF with 1.1 mol. equiv. of n-BuLi at -78°C for 1 h - to a solution of 3 in THF at 0°C), followed by column chromatography on silica gel, afforded the required vinyl-sulfoxide 5 as a mixture of geometric isomers[8] in 74% conversion [41% yield; ir ($CHCl_3$) 1030 cm^{-1}; nmr δ ($CDCl_3$) 6.08 (=CHSOPh); an E/Z ratio of 1:1 was calculated from nmr spectra in C_6D_6 (=CHSOPh at 5.89 and 6.02)] along with some hemiacetal 2 and chroman-sulfoxide 7[4] (0% d.e.). Horner-Wittig reaction of the carbanion of 4 (2 mol. equiv.) with hemiacetal 2 produced directly the chroman-sulfoxide 7 (32%), but with 0% d.e.



The results of the diastereoselective ring-closure upon treatment of 5 with base are compiled in Table I. Two equiv. of base might be consumed for saponification of the ester functions. Preliminary experiments with 1.05 and 3.5 mol. equiv. of 5% aqueous NaOH in ethanol indeed showed incomplete reaction and severe deterioration, respectively, while the best results were obtained with 2.1 mol. equiv. of base. It appears from Table I that most of the reactions furnished chroman derivatives with d.e. 20-30%, though in variable yields on account of formation of

decomposition products. Unfortunately the highest d.e. (40%; run 5) was attended by a low yield. The best results were obtained with 7.5% KOH in ethanol at 20°C (run 9). In all of the reactions with d.e.>0%, the chroman-sulfoxides contained as major component the isomer with the C(2)-methyl protons absorbing at relatively low field, indicating predominant formation of the (R,S)/(S,R) racemate[9]. Consequently use of the (S)-enantiomer of the sulfoxide as starting material would result in predominant formation of the (2S)-chroman-(R)-sulfoxide.

Table I. Cyclizations of 5.

Run	Base	Mol. equiv.	Solvent	Temp. (°C)	Time[a] (days)	Yield (%) 6	7	d.e.[b]	8	5
1	5% aq. NaOH	2.1	EtOH	20	1	49	—	25	—	10
2	"	2.1	"	15	3	16	—	24	—	17
3	"	2.1	"	4	7	—	—	—	—	13
4	"	2.1	t-BuOH	20	5	56	—	23	—	3
5	"	2.1	"	15	14	—	9	40	22	—
6	"	2.1	dioxane	20	14	25[d]	25[d]	30	12	12
7	"	2.1	"	60	14	—	23	26	22	22
8	5% aq. KOH	2.1	EtOH	20	1	63	—	20	—	—
9	7.5% aq. KOH	2.1	"	20	1	77	—	25	—	—
10	5% aq. NaOH[c]	∞	CH_2Cl_2	20	1	46	—	0	—	21
11	imidazole	0.7	i-PrOH/H_2O	88	5	—	10	25	7	30
12	10% aq. Na_2CO_3	∞	EtOH	50	3	8	—	23	5	—

[a]The reaction was followed on tlc until no significant changes occurred

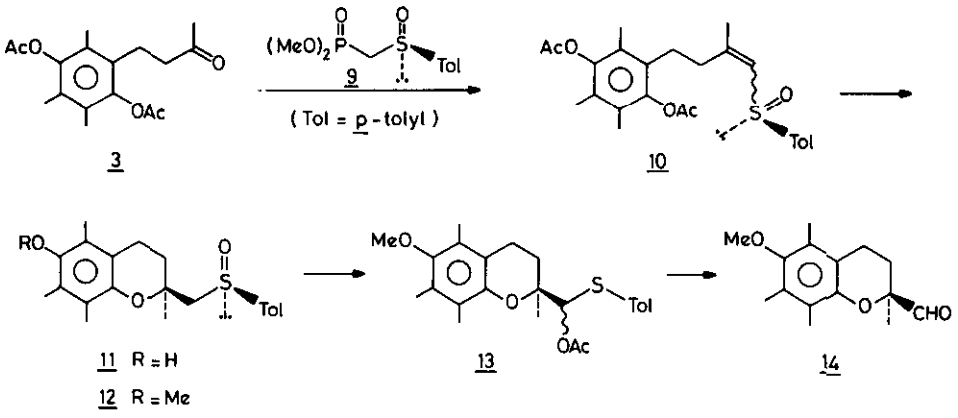
[b]Absorption of the C(2)-methyl protons at δ 1.66 always larger than at δ 1.45

[c]With 0.15 eq. phase-transfer catalyst 18-crown-6

[d]Ratio 6:7 calculated from nmr spectra

Horner-Wittig reaction of the phosphoryl-(S)-sulfoxide 9[10] {$[\alpha]_D$ +142°, acetone, c 1.0; enantiomeric excess (e.e.) 95%} with the ketone 3 provided the (R)-sulfoxide 10[8] in 53% conversion (28% yield; $[\alpha]_D$ -112.2°, acetone, c 2.0; ir and nmr spectra comparable with those of 5), which upon subsequent treatment with 2.1 mol. equiv. of 7% aqueous KOH in ethanol at 20°C cyclized to give the mixture of isomeric chromans ($[\alpha]_D$ +56.8°, acetone, c 1.38) in 74% yield. According to the nmr

spectrum, the mixture contained the (2S)-chroman-(R)-sulfoxide 11 in 22% d.e. (so the optical yield was 22%) and consequently the e.e. at C(2), important for the synthesis of the nat.-α-tocopherol, would be 21%. The C(6)-hydroxy function was then protected by methylation of the mixture (n-BuLi in THF, MeI) to give the (2S)-chroman-(R)-sulfoxide methyl ether 12 {56% yield; $[\alpha]_D$ +83.9°, acetone, c 1.04; ir and nmr spectra comparable with those of 7[4]; relative intensity of the C(2)-CH_3 absorption at δ 1.68 higher than at δ 1.48 with d.e. 22%}.



Pummerer reaction of 12 (Ac_2O, AcONa, 135°, cf. ref. 4) gave the (2S)-chroman-monothioacetal 13 {83% yield; $[\alpha]_D$ -3.5°, acetone, c 3.4; ir ($CHCl_3$) 1750 and 1020 cm^{-1}; nmr δ ($CDCl_3$) 1.40 and 1.44 (ratio 1:1, C(2)-CH_3), 3.63 (OCH_3), 6.33 and 6.42 (ratio 1:1, AcOCHS)}, which was hydrolyzed with aqueous ethanolic sodium hydroxide to furnish the (2S)-chroman-aldehyde 14 {81% yield; $[\alpha]_D$ +1.6°, $CHCl_3$, c 3.0; ir ($CHCl_3$) 1730 cm^{-1}; nmr δ ($CDCl_3$) 1.39 (C(2)-CH_3), 3.62 (OCH_3), and 9.62 (CHO)} in 12% e.e. (as determined by nmr spectroscopy with chiral europium shift reagent). The optical yield over the last three steps amounted to 57%. Because Pummerer reaction and hydrolysis with analogous optically active chroman-sulfoxides proceeded in high optical yield[5], considerable racemization must have occurred in the methylation step, presumably by reaction of n-butyllithium with 11. Aldehyde 14 can easily be converted into α-tocopherol according to the procedure of Mayer[7], but because of the low e.e. of 14 these final steps were not completed.

Notes and References

1. Part of the forthcoming doctorate thesis of J.M. Akkerman, University of Amsterdam.
2. "Vitamin E", L.J. Machlin, Ed., Marcel Dekker, Inc., New York, 1979.
3. See G.L. Olsen, H.-C. Cheung, K. Morgan, and G. Saucy, J. Org. Chem., 1980, 45, 803 and references cited in there.
4. J.M. Akkerman, H. de Koning, and H.O. Huisman, J. Chem. Soc., Perkin Trans. 1, 1979, 2124. In the discussion the word "respectively" (p. 2125, 1st column, line 19) should be deleted, because the relative configurations were not known at that time, as may correctly be concluded from the experimental part on p. 2127. Configurational assignment of the isomers will be discussed in ref. 5. See also ref. 9 below.
5. J.M. Akkerman, H. de Koning, and H.O. Huisman, to be published.
6. J.W. Scott, F.T. Bizzarro, D.R. Parrish, and G. Saucy, Helv. Chim. Acta, 1976, 59, 290.
7. H. Mayer, P. Schudel, R. Rüegg, and O. Isler, Helv. Chim. Acta, 1963, 46, 650.
8. The isomers could not be separated easily; so cyclization of the individual isomers could not be investigated.
9. Independent synthesis[5] of the (+)-(2S)-chromanaldehyde 14, and subsequently (2R,4'R,8'R)-α-tocopherol, from the optically active chroman-(S)-sulfoxide with the C(2)-methyl protons absorbing at relatively high field, proved the (2S)-chroman configuration for the latter compound. Consequently the RS/SR configuration can be assigned to the isomer in which the C(2)-methyl protons absorb at relatively low field.
10. M. Mikołajczyk, W. Midura, S. Grzejszczak, A. Zatorski, and A. Chefczyńska, J. Org. Chem., 1978, 43, 473. Though these authors give the correct configuration of 9 in the figure, the assignment should be (S). We are grateful to Professor Mikołajczyk for a generous gift of this compound.

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