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SYNTHESIS OF POTENTIALLY ALLERGENIC CHIRAL α-(HYDROXYALKYL)ACRYLATES.

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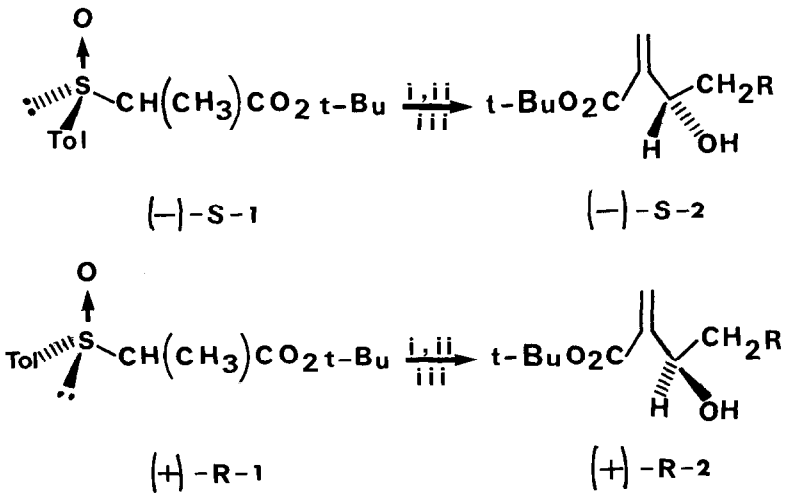
Abstract : The title compounds have been synthesized with 75% enantiomeric excess from chiral p-tolylsulfoxides 1 and aldehydes, followed by thermal elimination of the sulfoxide.

Because of their recent introduction in new printing processes, acrylates constitute one of the major problems in occupational allergic contact dermatitis (ACD)[1]. Their excellent Michael-acceptor potential make them ideal targets for skin proteins, with which they can form covalent bonds[2]. As part of continuing efforts to understand molecular aspects of ACD, we have recently shown that induction of ACD was enantiospecific with (+)- and (-)-frullanolides, two sensitizing sesquiterpene lactones[3]. In need of optically active contact sensitizers, we thought of applying our recently developed methods for the synthesis of β-hydroxy-α-methylene-γ-butyrolactones[4,5] using this time optically active sulfoxides.

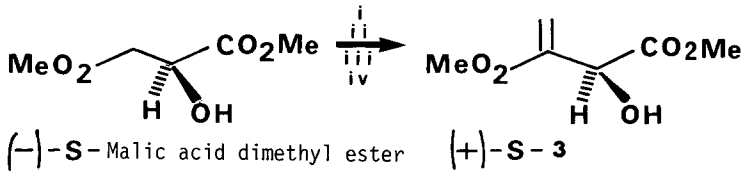
The synthesis is outlined in Scheme I.



i) t-BuMgBr, ii) RCH_2CHO, iii) Δ, $CaCO_3$

SCHEME I.

Reaction of tolylsulfoxides 1 [6] with t-BuMgBr and aldehydes RCH_2CHO gave, after thermal elimination of tolylsulfenic acid, the allylic alcohols 2 with a 25% overall yield [7] and an enantiomeric excess of 75% [8]. In order to establish the absolute configuration of the major enantiomer 2 obtained from each sulfoxide 1, analogous allylic alcohols 3 [9], were prepared from malic acids of known absolute configuration, according to Scheme II. The overall yield was 10% [10] (80% of the starting material was recovered).



i) LDA 2 eq, ii) $CH_2=\overset{+}{N}(CH_3)_2I^-$, iii) CH_3I, iv) $NaHCO_3$

SCHEME II

(-)-R-3 was prepared, using the same sequence, from (+)-R-malic acid dimethyl ester.

A comparison of the CD spectra of (+)-S-3 and of (+)-R-2 on the one hand, of (-)-R-3 and (-)-S-2 on the other, seems to establish the absolute configuration of the major (>87.5%) enantiomer 2. Table I summarizes physical data . Furthermore, use of Mioskowski-Solladié model for condensation of chiral sulfoxides with aldehydes [11] also predicts our assigned configurations.

COMPOUNDS	$[\alpha]_D^{20}$	c [a](EtOH)	λ^b_{max} (nm)	$\Delta\varepsilon$ [b]
(+)-2 (R = CH_3)	+6.0	2.00	233	+3.8
(-)-2 (R = CH_3)	-5.9	1.85	233	-4.0
(+)-2 (R = $(CH_2)_3CH_3$)	+5.5	2.30	232	+0.9
(-)-2 (R = $(CH_2)_3CH_3$)	-5.5	2.30	232	-1.1
(+)-2 (R = $(CH_2)_7CH_3$)	+3.0	2.20	232	+2.0
(-)-2 (R = $(CH_2)_7CH_3$)	-3.1	1.90	232	-2.2
(+)-3	+11.0	1.00	228	+8.7
(-)-3	-10.0	1.77	228	-8.1

[a] g/100 mL [b] CD spectra recorded in CH_3CN

TABLE I. PHYSICAL DATA OF COMPOUNDS 2 AND 3.

All compounds gave satisfactory NMR, IR and Mass Spectra.

Biological assays to test the sensitizing power of the acrylates 1 are in progress.

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2. G.Dupuis, C.Benezra. Allergic Contact Dermatitis to Simple Chemicals, Marcel Dekker, New York, 1982.
3. P.Barbier, C.Benezra. *Naturwissenschaften*, 69, 296-297 (1982).
4. J.P.Corbet, C.Benezra. *J.Org.Chem.*, 46, 1141-1147 (1981).
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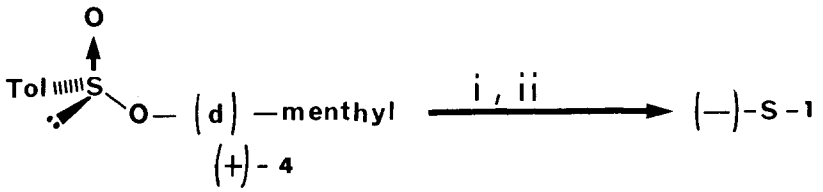
6. Sulfoxide (+)-1 has been described $[\alpha]_D^{20} = +148$ and the (R) configuration at sulfur atoms established (see M.Matloubi, Thèse de Doctorat d'Etat, Université de Strasbourg, 1981 ; C.Mioskowski, G.Solladié, *Tetrahedron Letters*, 3341 , (1975) ; G.Solladié, *Synthesis*, 185-196 (1983)).We have synthesized its enantiomer, sulfoxide (-)-1 $[\alpha]_D^{20} = -148°$ c = 2 acetone, using the same approach, from p-toluenesulfinyl chloride and d-menthol. Sulfinate 4 obtained in this way had an $[\alpha]_D^{20} = +203°$, c = 1,8 acetone, thus establishing the (S)-configuration ((+)-sulfinate 4 had an $[\alpha]_D^{20} = -202°$).



i = $(i\text{-}Pr)_2NMgBr$ ii = $CH_3CH_2CO_2t\text{-}Bu$

7. The condensation reaction was carried in THF at -78°C. After quenching with aqueous sodium bicarbonate, the unreacted aldehyde was separated by chromatography on a silica gel column. (eluted with a 1:1 ethyl ether-hexane mixture). The crude, unreacted 1 and the condensation product, Tol S(O) $C(CH_3)(CHOHCH_2R)CO_2t\text{-}Bu$) were heated in refluxing toluene for 2 hours in the presence of solid calcium carbonate. The suspension was then washed with water and the crude chromatographed on a silica gel column. In a typical run, from 1.0g (3.7 mmole) of sulfoxide 1,172 mg(0.92 mmole) of allylic alcohol 2 ($R = CH_3$) were obtained. IR (cm^{-1}) : 3570 (OH), 1700 (CO), 1630 (C = C) ; NMR ($CDCl_3$) :

1.08 (t, 3H), 1.54 (s, 9H), 1.4-1.9 (m, 2H), 2.81 (d, 1H), 4.28 (dt,1H), 5.69 (m, 1H), 6.12 (d, 1H).

8. Calculated from the ^{1}H-NMR spectra in the presence of Eu $(TFC)_3$ with a 1:1 shift reagent-compound 2 ratio.

9. (+)-S-3 : IR : 3512(OH), 1742 (C = O), 1630 (C = C) ; NMR ($CDCl_3$) : 3.86 (s,6H), 5.00 (broad s, 1H), 6.07 (s, 1H), 6.48 (s, 1H).

10. Protection of the hydroxyl function as a THP ether did not increase the yield. See also : S.Danishefsky, T.Kitahara, R.McKee, P.F.Schuda, *J.Amer.Chem.Soc.*, 98, 6715-6717 (1976).

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