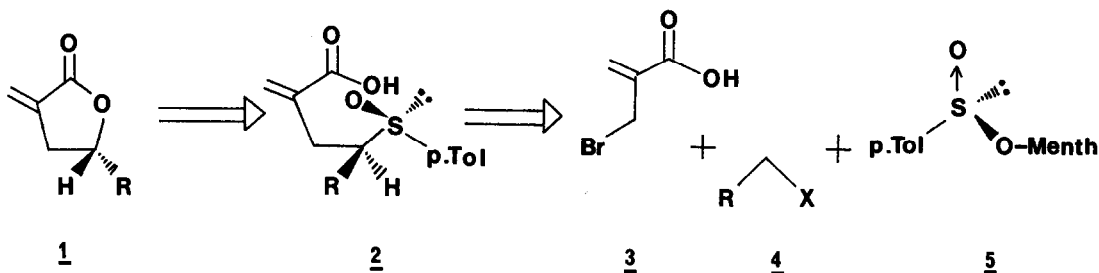


SYNTHESIS OF OPTICALLY PURE α -METHYLENE- γ -LACTONES FROM (+)-R-(4-METHYLPHENYL)-ALKYLSULPHOXIDES

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Abstract: Optically pure (+)-R-(4-methylphenyl)sulphoxides were lithiated and alkylated with lithium α -bromomethyl acrylate with medium to high diastereoselection; condensation products gave in two steps optically pure α -methylene- γ -lactones.

Many natural compounds showing varied and interesting biological properties contain the α -methylene- γ -lactone moiety¹ and this fact has stimulated numerous groups to search for new and efficient synthesis of this functional array. The target structure (1) was obtained in optically active form either through the methylenation of preformed lactones,^{2,3} or through metal induced carbonylation of alkenyl alcohols,⁴ or through the addition of methacrylic amide dianion to aldehydes.⁵ We thought that easily available starting materials for the carbon skeleton of α -methylene- γ -lactones (1) could be α -bromomethyl acrylic acid (3) and alkyl halides (4) according to the retrosynthetic scheme reported below. A proper functionality was needed which could first allow the asymmetric C-C bond formation between the two carbon fragments (3) and (4) and could then be removed to give stereospecifically the target structure (1).



The sulphinyl moiety was chosen as it can be introduced on an alkyl chain through an Andersen type reaction⁶ starting from the corresponding alkyl halide and (-)-S-menthyl-p-toluene

sulphinates (5), it allows an easy alkylation of the α position and it can be removed stereospecifically by a nucleophile⁷ after being transformed into a sulphonium salt. In our case the entering group would be the carboxylic one and its intramolecular attack on the sulphonium salt would give the desired product. Here we describe our preliminary results relative to the synthetic sequence above described.

(+)-R-(4-methylphenyl)sulphoxides (6a-e),⁸ obtained in almost quantitative yields⁹ starting from corresponding alkyl halides (4a-e) and (-)-S-menthyl-p-toluene-sulphinate (5), were first lithiated in tetrahydrofuran solution at -75°C and a separately prepared suspension of lithium α -bromomethyl acrylate was immediately added at the same temperature. Alkylation occurred almost instantaneously and α -methylene- γ -sulphinyl acids (7a-e) were formed¹⁰ in good yields (Scheme 1). When deprotonation was made by using lithium diisopropyl amide (LDA) chemical yields were higher than when a more hindered base such as lithium tetramethylpiperidine (LTMP) was employed (Table), but with this last metallating agent a more diastereoselective process occurred¹¹ and a $S_{C4} : R_{C4}$ ratio up to 95 : 5 was obtained for sulphinyl acids 7b. The two diastereoisomeric α -methylene- γ -sulphinyl carboxylic acids could be separated through chromatography (7b-d) or crystallization (7e) and optically pure compounds were reduced to γ -tolylthio acids¹² 8b-e with sodium iodide and trifluoro acetic anhydride in acetone at -40°C . Successive methylation with a slight excess of trimethylxonium tetrafluoroborate in a 1 : 1 mixture of methylene chloride / nitromethane at -5°C to 20°C affected only the sulphur atom and γ -sulphonium carboxylic acids (9b-e) were formed. Solvent was removed in the vacuum at 0°C and crude sulphonium salts (9b-e) were dissolved in dimethylformamide (0.05 molar solution) and at -45°C solid potassium tert-butoxide was added. The temperature was left to reach 0°C in

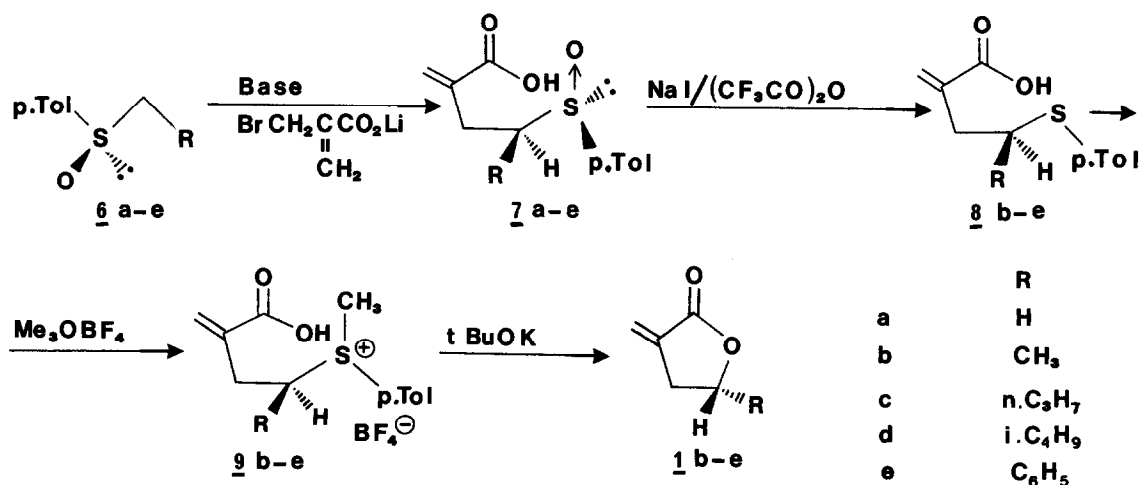


Table - Yields, optical rotations^{a)}, and absolute configurations of prevailing diastereoisomer of sulphanyl acids 7, γ -tolylthio acids 8, and α -methylene- γ -lactones 1.

R	Base ^{b)}	7			8			1		
		Yields % (S _{C4} :R _{C4})	Abs. config.	$ \alpha _D^{15}$	Yields %	Abs. config.	$ \alpha _D^{15}$	Yields %	Abs. config.	$ \alpha _D^{15}$
b CH ₃	LDA	88(82:18)	S _{C4} R _S	+111(1.0)	84	S _{C4}	+12.2(2.0)	74	R	+33.8(1.8) ^{c)}
	LTMP	81(95:5)								
c n-C ₃ H ₇	LDA	82(79:21)	S _{C4} R _S	+102(1.0)	91	S _{C4}	-4.7(1.0)	95	R	+54.4(1.8)
	LTMP	75(84:16)								
d i-C ₄ H ₉	LDA	85(78:22)	S _{C4} R _S	+109(1.0)	94	S _{C4}	-8.85(1.1)	93	R	+67.0(1.8) ^{d)}
	LTMP	73(82:18)								
e C ₆ H ₅	LDA	65(61:39)	S _{C4} R _S	-54.0(0.7)	96	S _{C4}	-169(3.0)	96	R	-19.0(1.0)
	LTMP	55(64:36)								

a) All measurements were made in CHCl₃, except for 1d for which EtOH was used as solvent; concentrations are given in parenthesis. b) Both lithium amides were generated by adding the proper volume of 2.5 molar solution of n-BuLi in n-hexane (Aldrich-Chemie) to a cooled solution of the amine in tetrahydrofurane. c) $|\alpha|_D^{15} +33.8$ (5.82, CH₂Cl₂) ref. 4; $|\alpha|_D^{20} +34$ (89, CHCl₃) ref. 2. d) $|\alpha|_D^{25} +67.0$ (1.44, EtOH) ref. 3.

one hour and usual work up gave final lactones 1b-e in high yields and optical pure form¹³. This fact means that reduction of sulphoxides 7 to sulphides 8 and their transformation into sulphonium salts 9 occurred with retention of chirality at C₄ carbon atom, an inversion of configuration occurring^{6,14} when the in situ formed potassium carboxylate attacked intramolecularly the sulphonium group. Absolute configuration of unknown lactones 1c,e was tentatively assigned through Cotton effect in circular dichroism spectra¹⁵.

The key step of the synthetic sequence here described is the alkylation of sulphoxides 6a-e and it occurs with medium to high diastereoselection. This alkylation represents an exploitation of 1,2-chirality transfer from sulphur to carbon and parallels the more studied 1,3-transfer¹⁶.

Acknowledgements: financial support by National Research Council, P.f. "Chimica Fine e Secondaria" is gratefully acknowledged

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 8. 6c: $|\alpha|_D^{20} + 200$ (1.0, acetone), $|\alpha|_D + 187$ (acetone ref. 9; 6d: $|\alpha|_D^{20} + 150$ (1.0, CHCl_3).
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 10. Selected spectroscopic data: (+)- $\text{R}_S\text{-7a}$: $^1\text{H NMR}$ (CDCl_3): 2.42(s, CH_3), 2.61 and 2.77(m, 1H each, CH_2SO), 3.03(bt, $\text{CH}_2\text{-C-SO}$), 5.77 and 6.35(bs, 1H each, $\text{H}_2\text{C=}$), 7.33(d, 2H, CH arom.), 7.54 (d, 2H, CH arom.). (+)- $\text{S}_{\text{C}_4\text{R}_S\text{-7b}}$: $^{13}\text{C NMR}$ (CDCl_3): 9.72, 21.25, 33.83, 57.22, 124.57, 129.76, 136.13, 141.22, 169.30. (+)- $\text{S}_{\text{C}_4\text{R}_S\text{-7c}}$: $^1\text{H NMR}$ (CDCl_3): 0.70(bt, CH_3), 1.2-1.7(m, $(\text{CH}_2)_2$), 2.40(s, CH_3), 5.76 and 7.40(bs, 1H each, $\text{H}_2\text{C=}$). (+)- $\text{S}_{\text{C}_4\text{R}_S\text{-7e}}$ (higher R_f compound on silica gel TLC with $\text{CHCl}_3/\text{AcOEt}/\text{AcOH} = 60/20/1$ as eluent): $^{13}\text{C NMR}$ (CDCl_3): 21.36, 31.02, 67.94, 128.10, 124.72, 127.78, 128.10, 129.04, 128.42, 130.72, 131.31, 135.60, 137.03, 141.25, 170.70.
 11. Diastereoisomer ratios were determined either through integration of vinyl proton signals in $^1\text{H NMR}$ spectra of row mixture of acids 7 or through the $|\alpha|_D^{20}$ value of lactones 1 obtained starting from crude condensation products of (3) and (4).
 12. Selected spectroscopic data: $\text{S}_{\text{C}_4\text{-8b}}$: $^1\text{H NMR}$ (CDCl_3): 1.21(d, CH_3), 2.30(s, CH_3), 2.25-2.77 (m, CH_2), 3.33(m, CH), 5.68 and 6.32(bs, 1H each, $\text{H}_2\text{C=}$), 7.00 - 7.45(q, CH arom.). $\text{S}_{\text{C}_4\text{-8d}}$: $^1\text{H NMR}$ (CDCl_3): 0.89 and 0.91(d each, $(\text{CH}_3)_2\text{C}$), 1.25 - 1.50(m, CH_2), 1.95(m, $\text{CH}(\text{CH}_3)_2$), 2.30 (s, CH_3), 2.54(m, $\text{H}_2\text{C-C=}$), 3.32(m, CHS), 5.70 and 6.38(bs, 1H each, $\text{H}_2\text{C=}$), 7.05 - 7.45(q, CHar).
 13. For unknown compounds 1c,e optical purity was verified by $^1\text{H NMR}$ with $\text{Eu}(\text{hfc})_3$.
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 15. 1b-d showed a positive Cotton effect at 205-210 nm and a negative one at 254 nm ca.; 1e showed maxima at similar wavelengths, but with opposite signs.
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(Received in UK 28 March 1985)