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ENANTIOSPECIFIC SYNTHESIS OF OPTICALLY ACTIVE CYCLOHEXYLIDENE BROMOMETHANES

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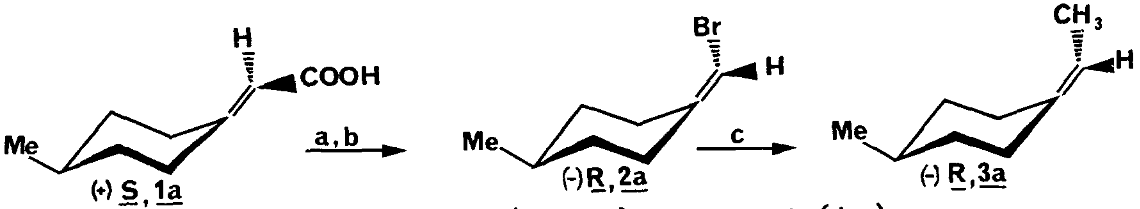
Abstract. Optically pure cyclohexylidene bromomethanes were prepared by stereospecific bromination alpha to a chiral sulfoxide, followed by the stereospecific pyrolytic elimination of the sulfoxide moiety.

Optically active cyclohexylidene bromomethanes 2 are important intermediates in the synthesis of chiral alkylidenecyclohexanes 3. As a matter of fact, Walborsky[1,2] showed that (-)R (4-methylcyclohexylidene) ethane 3a could be obtained from the corresponding vinylic bromide 2a with 92% of retention of configuration by a coupling reaction with methyllithium in the presence of a catalyst, dichloro [1,2 bis-(diphenylphosphino)ethane] Nickel II. Till now the only way to obtain the optically active vinylic bromide 2a was from resolved 4-methylcyclohexylidene acetic 1a by stereospecific bromination followed by stereospecific bromodecarboxylation leading to overall inversion of configuration[3,4] (Scheme 1).



a) Br_2, $CHCl_3$ - b) Na_2CO_3, H_2O, Δ - c) CH_3Li, $NiCl_2(dpe)_2$

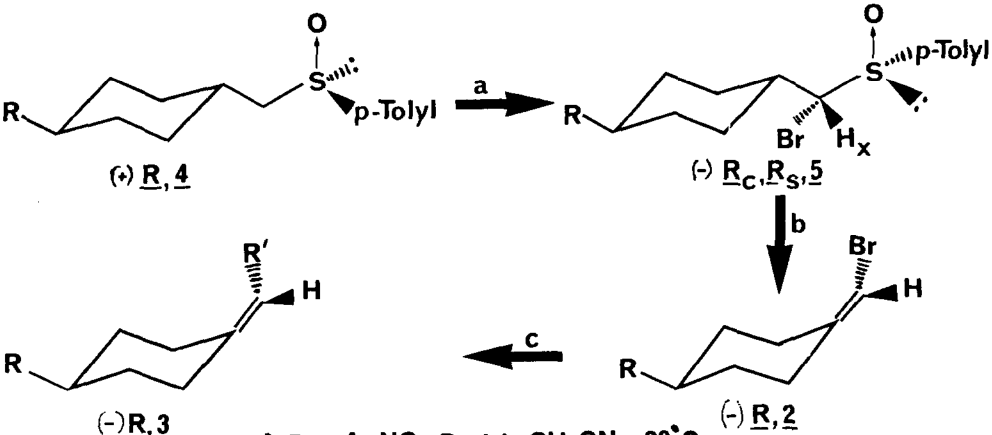
Scheme 1

We recently reported an enantiospecific synthesis of chiral 4-substituted cyclohexylidene acetic acid[7].

We now report a new enantiospecific synthesis of cyclohexylidene bromomethanes by stereospecific bromination of chiral sulfoxides.

Although it was known, from the work of Montanari, Colonna and Cinquini[5], that bromination of p-Tolylmethylsulfoxide with bromine in the presence of silver nitrate proceeded with complete inversion of configuration at sulfur, very little was known about the stereochemistry of the brominated carbon atom[6].

Our study started from sulfoxide <u>4</u>[7].



a) Br_2, $AgNO_3$, Pyrid., CH_3CN, -20°C
b) 250°, Na_2CO_3
c) R'MgX, $NiCl_2(dpe)_2$

Scheme 2

Sulfoxide <u>4</u> was brominated in acetonitrile with bromine in presence of silver nitrate and pyridine[5] at -20°C. The reaction was totally stereospecific since only one diastereoisomer[8], <u>RR</u> <u>5</u>, could be detected by NMR at 200 MHz.

Table I : α-bromosulfoxides <u>RR</u>, <u>5</u>

	R	$[\alpha]_D^{20}$ (acetone)	Rf*	NMR δ_{HX}	Yield %
<u>5a</u>	CH_3	-152° (C 1.2)	0.58	4.36 (J = 6)	62
<u>5b</u>	CH_2OCH_3	-138° (C 2.4)	0.44	4.36 (J = 6)	50
<u>5c</u>	n-C_5H_{11}	-121° (C 1.4)	0.68	4.35 (J = 6)	73
<u>5d</u>	t-Bu	-118° (C 1.0)	0.66	4.35 (J = 6)	43

* CH_2Cl_2/ether/n-hexane = 50/25/25

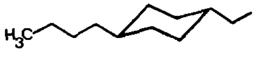
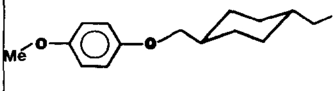
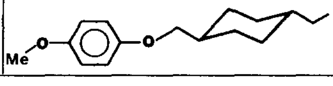
The pyrolytic elimination of the sulfoxide group was conducted without solvent in the presence of sodium carbonate at 250°C for 15 min. In the case of sulfoxide 5a (R = CH_3), the known methyl-4-cyclohexylidene bromomethane 2a was obtained : $[\alpha]_D$ = -50.3° (Lit.[3] $[\alpha]_D$-50.4°). Comparison of the optical rotations showed that the enantiomeric purity of the product was higher than 99%. Therefore the pyrolysis was completely stereospecific, no racemization of the sulfoxide occuring at this temperature. Finally the known absolute configuration[4](-)R of the vinylic bromide 2a allowed us to assign the configuration RR to the diastereoisomer 5a. The similarity of the NMR characteristics[8], Rf and optical rotations of compounds 5, as well as the negative rotations of all the vinylic bromides 2, are fully consistent with the absolute configuration being RR for all the α-bromosulfoxides 5.

Table II : Cyclohexylidene bromomethanes 2, R

	R	$[\alpha]_D^{20}$ (EtOH)	NMR vinylic H	Yield %
2a	CH_3	-50.3 (C 4.7)	5.88	70
2b	CH_2OCH_3	-50.0 (C 1.8)	5.93	78
2c	n-C_5H_{11}	-17.0 (C 3.5)	5.87	50
2d	t-Bu	-17.0 (C 1.1)	5.90	40

Finally these vinylic bromides 2 were coupled with Grignard reagents at room temperature in presence of $NiCl_2(dpe)_2$ and afforded optically active cyclohexylidene cyclohexanes 3. The unusual nature of ligands R' is due to the fact that these molecules were involved in our studies dealing with liquid crystals[9].

Table III : Alkylidene cyclohexanes 3, R

R	R'	m.p.	$[\alpha]_D$ ($CHCl_3$)	Yield %
CH_2OCH_3	n-C_4H_9	liquid	-3.2 (C 4.8)	70
CH_2OCH_3		liquid	-2.0 (C 1.4)	90
CH_2OCH_3		68-71	-1.8 (C 3.3)	70
n-C_5H_{11}		41-2	-0.5 (C 0.8)	30

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8) The complete inversion of configuration at sulfur during the bromination step was demonstrated by reductive debromination of diastereoisomer 5b with $Zn/MeOH/H_2SO_4$, affording the enantiomer of the starting sulfoxide 4b ($[\alpha]_D$ -182°, C 1.6, acetone, Lit.[7] $[\alpha]_D$ + 182°). The two diastereoisomers 5b S_cS_s and 5b R_cS_s were made for identification by another route : reaction of carbanion of sulfoxide 4 R with dibromoethane giving a diastereoisomeric ratio SS/RR = 32/68. These two diastereoisomers showed very sharp differences in NMR for the proton H_X (δ = 4.36, J = 6Hz for the SS series and δ = 4.41 , J = 2.4 Hz for the RS series) and in TLC (Rf = 0.44 (SS), 0.42 (RS), solvent : CH_2Cl_2/ether/hexane : 50/25/25). The absolute configuration of diastereoisomer 5 was determined after pyrolytic elimination of the sulfoxide.

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