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INVESTIGATION OF A CHIRAL MASKED KETENE SYNTHON SYNTHESIS OF THE (+)-(1R,4R) and (-)-1S,4S) ENANTIOMERS OF DEHYDRONORCAMPHOR†

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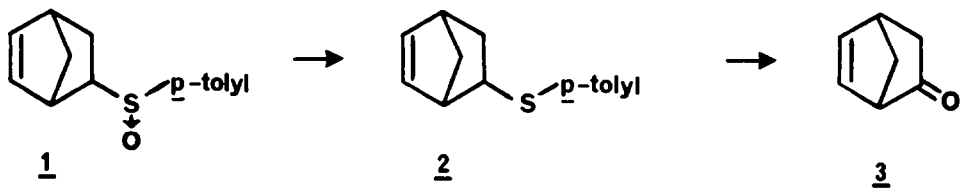
Abstract - The Diels-Alder reaction between (+)-(R)-p-tolyl vinyl sulphoxide and cyclopentadiene gives four separable diastereoisomers. The two most abundant were transformed by a two-step procedure into the two enantiomers of dehydronorcamphor (bicyclo[2,2,1]hept-5-en-one) possessing very high enantiomeric purity.

It is well known that the interaction of conjugated dienes and ketenes results in a $_{\pi}2_{a} + _{\pi}2_{s}$ cycloaddition to yield cyclobutanones.[1] To obtain cyclohexenones an indirect Diels-Alder approach must be envisaged employing a dienophile possessing latent functionality which is readily transformable into a carbonyl group at the adduct stage (e.g. α-acetoxy or α-chloroacrylonitriles).[2] Another useful aspect of the Diels-Alder synthesis is its convenient utilisation for asymmetric induction, with the chiral vector versatilely residing in the dienophile,[3] the diene[4] or a Lewis acid catalyst.[5]

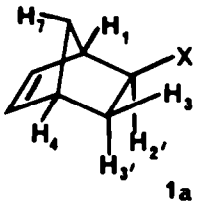
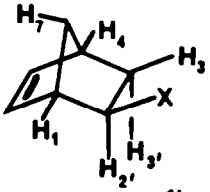
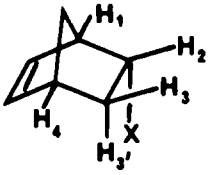
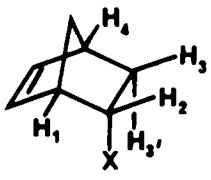
We sought to unite the above two aspects of the Diels-Alder process by studying the asymmetry transfer of a chiral dienophile capable of behaving as a ketene surrogate. To this end we have examined the reaction of cyclopentadiene with the readily obtainable (+)-(R)-p-tolyl vinyl sulphoxide.[6] Racemic conjugated sulphoxides have occasionally been employed as dienophiles[7] but, to our knowledge, no optically active sulphoxide has been so used. Heating the above two components neat in a sealed tube gave a high yield of an adduct mixture of gross structure (1). Analytical chromatography on silica gel showed the presence of four isomeric adducts, readily separable by HPLC, shown in order of elution in

† Dedicated with warm affection to Professor E Lederer on the occasion of his 75th birthday



1 2 3

TABLE 1

Adducts	Yield	^{1}H N.M.R. (δ ppm) H_2 or H_2'	Optical activities $[\alpha]_{acetone}^{25}$ c=1 (nm)
 1a	8%	LP 2,45 (8 lines) $J_{2'-3'}$ = 7 Hz $J_{2'-3}$ = 4 Hz $J_{2'-1*}$ = 2 Hz	 + 118.6° (589) + 124° (578) + 144° (546)
 1b	28%	O 2,65 (8 lines) $J_{2'-3'}$ = 7 Hz $J_{2'-3}$ = 4 Hz $J_{2'-1*}$ = 2 Hz	 + 101.6° (589) + 106.5° (578) + 125.1° (546)
 1c	42%	O 3,36 (5 lines) J_{2-1} = 3.8 Hz $J_{2-3'}$ = 3.8 Hz J_{2-3} = 9 Hz	 + 180.4° (589) + 189.2° (578) + 221.4° (546)
 1d	22%	LP 3,30 (5 lines) J_{2-1} = 3.8 Hz $J_{2-3'}$ = 3.8 Hz J_{2-3} = 9 Hz	 + 25.7° (589) + 28° (578) + 34° (546)

X = (R)-S(O)-p-tolyl

* or $J_{2'-7}$ (W coupling) if $J_{2'-1}$ = 0

TABLE 2

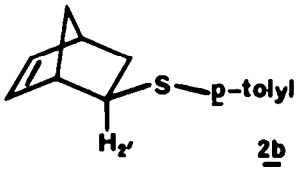
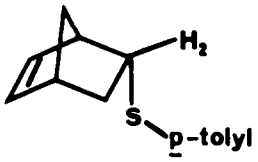
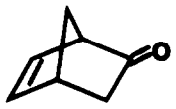
	Yield	Optical activities $[\alpha]_{acetone}^{25}$ (nm)
 2b	69%	- 3,3° (589) (c=0,012) - 3,5° (578) - 5,5° (546)
 2c	75%	+ 123,3° (589)(c=0,015) + 128° (578) + 147° (546)
 1S,4S 3b	41%	- 1051° (589)(c=0,030) - 1109° (578) - 1316° (546) - 2959° (436)
 1R,4R 3c	50%	+ 1032° (589)(c=0,025) + 1091° (578) + 1296° (546) + 2913° (436)

Table 1. The structures were assigned by n.m.r. spectroscopy; the chemical shifts and the coupling constants of H-2' in the exo products (1a and 1b) and of H-2 in the endo products (1c and 1d) shown in Table 1 were used as the diagnostic characteristics.[8] The absolute configurations shown were assigned a posteriori from the conversions described below. The sulphoxide chirality was reckoned to be unchanged by the Diels-Alder process. This was supported by subjecting the starting vinyl sulphoxide alone to the conditions of the reaction whereby the optical rotation remained unchanged.

Originally it was intended to convert the most abundant adducts 1b and 1c to the enantiomeric dehydronorcamphors by means of a Pummerer rearrangement.[9] Although the initial process did lead to the corresponding 2,2-acetoxy sulphides the conversion of these products to ketones was un-

expectedly troublesome and no procedure proved fruitful. As a very effective alternative the sulphoxides 1b and 1c were individually reduced by 2-chloro-1,3,2-benzodioxaphosphole in pyridine[10] to the corresponding sulphides 2b and 2c followed by chlorination (N-chlorosuccinimide) and oxidative hydrolysis ($CuCl_2/CuO$).[11] The resulting enantiomers of dehydronorcamphor 3b and 3c were purified by preparative g.l.c. and possessed spectroscopic properties identical to those recorded for the racemic ketone. The optical rotations for the enantiomers thus obtained were very high (Table 2), well above those recorded for the preparation of the enantiomers from norbornadiene[12] and closely comparable to the (+)-enantiomer synthesised from bicyclo-[2,2,1]hept-5-ene-2-carboxylic acid.[13] The known[12] absolute configurations of 3b and 3c establish the cognate configurations for the sulphoxides (1a to 1d) and the sulphides (2b,2c).

Although chirality transfer has been demonstrated in this process the production of four diastereoisomers in the initial cycloaddition makes the procedure inefficient. Studies are in hand to obtain more reactive chiral ethylenic sulphoxides which would allow milder conditions for the Diels-Alder reaction and thus favour the formation of the endo-isomers.

We thank Roche Products Limited for their support.

EXPERIMENTAL

Infrared spectra were run on a Perkin-Elmer 297. N.m.r. spectra were recorded on a Varian EM 390 in $CDCl_3$ with TMS as internal standard. Optical rotations were measured on Perkin-Elmer 240 and Jobin et Yvon polarimeters. Mass spectra were obtained on a Varian-MAT 311 instrument. Preparative gas chromatography was carried out on a Varian Aerograph 90-P.

Interaction of cyclopentadiene and (+)-(R)-p-tolyl vinyl sulphoxide. Cyclopentadiene (2g), (+)-(R)-p-tolyl vinyl sulphoxide (1.66 g; $[\alpha]_{589}^{25}$ + 400°; c=1; acetone) and hydroquinone (10 mg) were heated in a sealed pyrex tube at 115°C for 15 hr. The cooled mixture showed no trace of the starting sulphoxide. The excess cyclopentadiene was removed under reduced pressure and the residue dissolved in ether and filtered. Evaporation and distillation gave the mixture of adducts as a viscous oil (2.2 g; 95%) b.p. 140 - 145°C/0.05 mm. (Found : C, 72.15; H, 7.10; S, 13.60. $C_{14}H_{16}OS$ requires C, 72.35; H, 6.95; S, 13.80%).

The four isomeric constituents of this mixture as shown by t.l.c. were separated by chromatography on silica gel (ratio 40:1) using ether-ethyl acetate (8:2) as eluent. In order of elution they were:

Diasteroisomer 1a (Found: M^+ 232.0920. $C_{14}H_{16}OS$ requires M 232.0922) ^1H NMR δ 7.39 (4H, dd, Ar-H), 6.1 (2H, two symmetrical m from 6.2 to 5.9, -CH=CH-), 2.95 (2H, br s, H-1 and H-4), 2.45 (1H, m, details as in Table 1, H-2') 2.38 (3H, s, Ar-CH_3), 2.2 to 1.0 (4H, m, 2 x CH_2).

Diastereoisomer 1b (Found: M^+ 232.0920). ^1H NMR δ 7.37 (4H, dd, Ar-H), 6.12 (2H, sharp m, -CH=CH-), 3.44 (1H, br s, H-1), 2.65 (1H, m, details as in Table 1, H-2'), 2.38 (3H, s, Ar-CH_3), 1.8 to 1.0 (4H, m, 2 x CH_2).

Diastereoisomer 1c (Found: M^+ 232.0922). ^1H NMR 7.39 (4H, dd, Ar-H), 6.32 (2H, sharp m, -CH=CH-), 3.43 (1H, br s, H-1), 3.36 (1H, m, details as in Table 1, H-2), 2.9 (1H, br s, H-4), 2.38 (3H, s, Ar-CH_3), 1.7 to 0.7 (4H, m, 2 x CH_2).

Diastereoisomer 1d (Found: M^+ 232.0921). ^1H NMR δ 7.39 (4H, dd, Ar-H), 6.15 (2H, two symmetrical m from 6.37 to 5.9, -CH=CH-), 3.3 (1H, m, details as in Table 1, H-2), 2.98 (1H, br s, H-4), 2.58 (1H, br s, H-1), 2.38 (3H, s, Ar-CH_3), 2.2 to 1.1 (4H, m, 2 x CH_2).

Sulphides 2b and 2c

To a stirred solution of 1b or 1c (1.16g) and pyridine (0.4g) in benzene (7 ml) was slowly added 2-chloro-1,3,2-benzodioxaphosphole (0.87g); a precipitate formed almost immediately. After one hour 2N sodium hydroxide (5 ml) was added and the benzene layer washed several times with aqueous NaOH and finally with water. The benzene solution was dried ($MgSO_4$), the solvent evaporated and the residue purified by chromatography on silica gel (hexane-ether, 6:4, as eluent) to give a pale yellow oil showing no sulphoxide band in the IR spectrum.

Sulphide 2b (0.74g; 69%) (Found: M^+ 216.0975. $C_{14}H_{16}S$ requires M^+ 216.0973). ^1H NMR δ 7.3 (4H, dd, Ar-H), 6.15 (2H, sharp m, -CH=CH-), 3.0 (1H, m, H-2'), 2.87 (2H, br s, H-1 and H-4), 2.32 (3H, s, Ar-CH_3), 1.8 to 1.3 (4H, m, 2 x CH_2).

Sulphide 2c (0.82g; 75%) (Found: M^+ 216.0973). ^1H NMR δ 7.3 (4H, dd, Ar-H), 6.3 (2H, symm. m from 6.45 to 6.1; -CH=CH-), 3.67 (1H, m, H-2), 3.1 (1H, br s, H-1), 2.9 (1H, br s, H-4), 2.32 (3H, s, Ar-CH_3), 1.7 to 0.8 (4H, m, 2 x CH_2).

(1S,4R)-(-)- and (1R,4S)-(+)-Dehydronorcamphor

A mixture of sulphide 2b or 2c (1.51g), N-chlorosuccinimide (0.93g) and CCl_4 (10 ml) was heated under reflux under nitrogen for one hour. Cooling, filtration and evaporation furnished a residue which was immediately treated with acetone (30 ml), water (1 ml), $CuCl_2$ (2g) and CuO (2g) and the mixture heated under reflux for 30 min. It was then cooled, filtered, diluted with water (10 ml) and extracted with ether. Drying ($MgSO_4$) and evaporation of the ether under reduced pressure at 15°C gave a residue which was purified by preparative g.l.c. (3m Carbowax column, 110°C). From 2b there was obtained (-)-dehydronorcamphor (310 mg; 41%) and 2c produced (+)-dehydronorcamphor (330 mg; 49%). The optical rotations of the two enantiomers are shown in Table 2. They are close to those estimated by extrapolation[12] from less enantiomerically pure samples (calculated values $[\alpha]_{598}$ in isooctane, - 1160° and + 1140°).

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