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REACTIONS OF A NEW OPTICALLY ACTIVE ARYLPERHYDRONAPHTHALENOL BASED CHIRAL AUXILIARY

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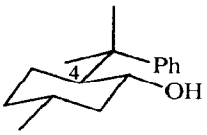
Abstract: (1R,4aS,8S,8aS)-8-(5'-methoxy-2'-methylphenyl)-8-methyldecahydro-1-naphthalenol is a chiral auxiliary more efficient than 8-phenylmenthol in the Diels-Alder reaction of its acrylate ester with cyclopentadiene and in the diisobutylaluminium hydride reduction of its phenylglyoxylate ester.

8-Phenylmenthol **1** is an effective chiral auxiliary which is capable of inducing highly diastereoselective reactions. A number of proposals[1-3] have been made in an attempt to explain the apparent restriction of rotation about the C4-C8 bond which results in the effective blocking of one diastereoface by the phenyl or other 8-aryl groups. Whitesell has prepared the conformationally restricted racemic perhydronaphthalenol **2**[4], and the results of that study indicated that **2** was marginally less effective than 8-phenylmenthol in the diastereoselective ene reaction of the corresponding glyoxylate derivatives.

In an attempt to gain further insight into the factors controlling the asymmetric induction in these auxiliaries we have prepared the optically active perhydronaphthalenol **3**†. In addition to the methyl group at C8, which is equivalent to that at C8 in 8-phenylmenthol **1**, but which is not present in **2**, the aryl group contains an ortho methyl substituent which would be expected to further restrict the conformation of the aryl group. Also, if the proposals regarding π-π stacking[1-3] have any validity then the methoxyl group might also favour the desired conformation in which the aromatic ring and the π moiety of the ester occupy parallel planes.

We report the results of a comparison of the chiral auxiliary **3** with 8-phenylmenthol in the Diels-Alder reaction of their acrylate esters with cyclopentadiene and also the reduction of their phenylglyoxylates with diisobutylaluminium hydride (DIBAL-H). The acrylate ester **4** was prepared using the same conditions[2] as those used in the formation of 8-phenylmenthyl acrylate **5**. The ester **4** was obtained in 60% yield as a viscous oil with ν_{max} 1712 cm^{-1}. The ^1H n.m.r. spectrum† showed three well resolved signals for the alkene protons. This contrasts with the complex, second order multiplets for the equivalent resonances of 8-phenylmenthyl acrylate **5**. Further confirmation of the structure came from the accurate mass measurement and resonances at δ 127.9, 129.0 and 165.3 in the ^{13}C n.m.r. spectrum for the vinyl and ester carbonyl carbons respectively.

The phenylglyoxylates **6** and **7** were each prepared by reaction of the alcohols with phenylglyoxyloyl chloride as described for **6**[5]. The new phenylglyoxylate **7** was obtained in 66% yield. The high resolution



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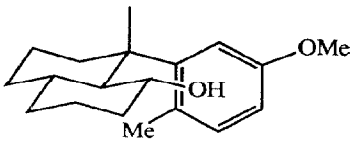

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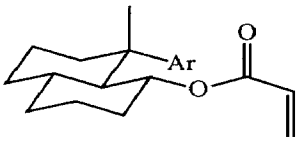

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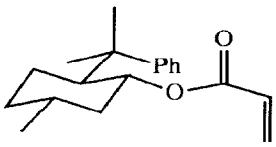

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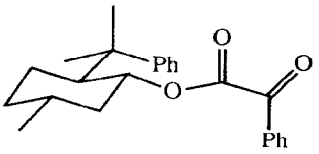

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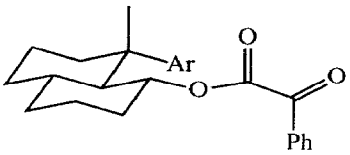

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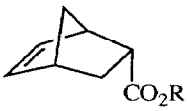
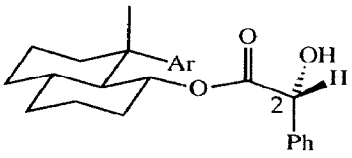


8; R = **1**
9; R = **3**

10; R = **3**



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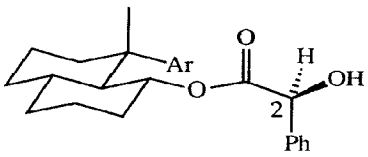

12

Ar = 5-methoxy-2-methylphenyl

mass spectrum, ^{13}C and ^{1}H n.m.r.† spectra and carbonyl stretches at ν_{max} 1722, 1694 cm^{-1} all confirmed the structure **7**.

Whitesell[6] has reported that the reaction between 8-phenylmenthyl acrylate **5** and cyclopentadiene in the presence of 1.5 equivalents of titanium tetrachloride gave the (2R)-bicycloheptenecarboxylate **8** with a 90% d.e. After confirmation of this result, the acrylate **4** was subjected to the same reaction conditions with cyclopentadiene to give the product in 64% yield (8:1 endo:exo ratio).

The authentic endo diastereomers, **9** and **10**, were synthesised by reaction of the alcohol **3** with the acid chloride prepared from racemic endo-5-norbornene-2-carboxylic acid and oxalyl chloride. The two endo diastereomers were inseparable by HPLC and therefore HPLC separation of the crude product from the asymmetric synthesis was used to give the endo isomer fraction in, with care being taken to avoid any fractionation of the isomers. Analysis by ^{1}H n.m.r. spectroscopy showed the presence of only one isomer with a detection limit of < 1% being established from the ^{13}C-H satellites. This d.e. of > 98% is significantly higher than that for the analogous reaction with 8-phenylmenthol as the chiral auxiliary and is comparable with the level of induction for the reaction using cis-3-hydroxyisonorbornyl ethers as auxiliaries[7]. The d.e. for the exo by-product was 64%. Confirmation of the structure of the endo diastereomer came from microanalysis, high resolution mass determination and ^{1}H† and ^{13}C n.m.r. spectra. The configuration was established as **9** by synthesis of the diastereomers from optically enriched[8] endo-5-norbornene-2-carboxylic acid. The result is consistent with reaction of cyclopentadiene from the si face of the acrylate **4** with the acrylate moiety in the anti conformation (analogous to 8-phenylmenthyl acrylate).

The diastereoselective reduction of 8-phenylmenthyl phenylglyoxylate **6** with a variety of reagents, including DIBAL-H at -78°C (70% d.e.) has been reported[5]. Repetition of the DIBAL-H reduction gave a somewhat higher d.e. (83%) which probably arose from a more accurate method of assessment. Solladié-Cavallo[5] determined the d.e. by integration of the hydroxyl and H2 resonances in the ^{1}H n.m.r. spectrum, but the H2 resonance was overlapping with another in the major isomer. In D_5-pyridine the H2 resonances of the two diastereomers are well separated and this allows a more accurate method of integration.

DIBAL-H reduction of the phenylglyoxylate ester **7** at -78°C, under conditions identical with those used with **6** gave a quantitative yield of a product which consisted of essentially one diastereomer by 300 MHz ^{1}H n.m.r. spectroscopy and HPLC. The two authentic diastereomers, **11** and **12**, were prepared by reduction at room temperature with sodium borohydride, a much less selective reducing agent with 8-phenylmenthyl phenylglyoxylate[9] (33% d.e. at -78°C). Even at room temperature this reduction was quite selective with a 77% d.e. The major and minor isomers showed singlets at δ 4.48 and 3.48, respectively, in the ^{1}H n.m.r spectrum and were well separated by HPLC. Integration of the HPLC trace showed a ratio of 199:1, indicating a d.e. of 99%. The configuration of the major isomer **11** was established as (R) at C2 by the method of Solladié-Cavallo[5]. This configuration is the same as that observed with 8-phenylmenthol as auxiliary[5] and it is consistent with hydride addition having occurred from the si face with the carbonyls of the phenylglyoxylate **7** in the syn conformation. The structure of the major product **11** has been established by full spectral† and microanalytical data.

The conformationally restricted chiral auxiliary **3** has been shown to be highly efficient in stereoselective reactions. Its preparation in optically active form will be reported elsewhere.

† 300 MHz ^{1}H n.m.r. data (excluding methylene envelope):

(1R,4aS,8S,8aS)-8-(5'-Methoxy-2'-methylphenyl)-8-methyldecahydro-1-naphthalenol **3** δ ($CDCl_3$): 7.06, d, 8.3Hz, (H3'); 7.05, d, 2.7Hz, (H6'); 6.65, dd, 8.3Hz and 2.7Hz, (H4'); 3.76, s, (OMe); 3.53, dt, 10.0Hz and 4.2Hz, (H1); 2.62, s, (ArMe); 1.53, s, (C8-Me).

(1'R,4a'S,8'S,8a'S)-8'-(5"-Methoxy-2"-methylphenyl)-8'-methyldecahydronaphthalen-1'-yl prop-2-enoate **4** δ ($CDCl_3$): 6.99, d, =8.2Hz, (H3"); 6.77, d, 2.4Hz, (H6"); 6.52, dd, 8.2Hz and 2.4Hz, (H4"); 5.70, dd, 17.3Hz and 1.4Hz, (CH_2=CH-); 5.31, dd, 10.4Hz and 1.4Hz, (CH_2=CH-); 5.04, dd, 17.3Hz and 10.4Hz, (CH_2=C**H**-); 4.79, dt, 10.6Hz and 4.4Hz, (H1'); 3.68, s, (OMe); 2.62, s, (ArMe); 1.41, s, (C8'-Me).

(1'R,4a'S,8'S,8a'S)-8'-(5"-Methoxy-2'-methylphenyl)-8'-methyldecahydronaphthalen-1'-yl 2-oxophenylacetate **7** δ ($CDCl_3$): 7.80, d, 8Hz, (oPhCO); 7.58, t, 8Hz, (pPHCO); 7.42, t, 8Hz, (mPhCO); 6.71, d, 2.7Hz, (H6"); 6.70, d, 8.3Hz, (H3"); 6.08, dd, 8.3Hz and 2.7Hz, (H4"); 4.97, dt, 10.5Hz and 4.5Hz, (H1'); 3.26, s, (OMe); 2.77, t, 10.5Hz, (H8a'); 2.52, s, (ArMe); 1.49, s, (C8'-Me).

(1'R,4a'S,8'S,8a'S,2R)-8'-(5"-Methoxy-2"-methylphenyl)-8'-methyldecahydronaphthalen-1'-yl endo-2-bicyclo[2.2.1]hept-5-ene carboxylate **9** δ ($CDCl_3$): 6.99, d, 8.3Hz, (H3"); 6.87, d, 2.5Hz, (H6"); 6.56, dd, 8.3Hz and 2.5Hz, (H4"); 5.97 and 5.91, both distorted dd, (H5 and H6); 4.66, dt, 10.6Hz and 4.2Hz, (H1'); 3.74, s, (OMe); 2.76 and 2.64, both br s, (H1 and H4); 2.59, t, 10.6Hz, (H8a'), 2.58, s, (ArMe); 2.05, m, (H2); 1.42, s, (C8'-Me).

(1'R,4a'S,8'S,8a'S,2R)-8'-(5"-Methoxy-2"-methylphenyl)-8'-methyldecahydronaphthalen-1'-yl 2-hydroxyphenylacetate **11** δ ($CDCl_3$): 7.28, complex, (PhH); 7.12, d, 8.3Hz, (H3"); 6.97, d, 2.7Hz, (H6"); 6.71, dd, 8.3Hz and 2.7Hz, (H4"); 4.84, dt, 10.3Hz and 4.4Hz, (H1'); 4.48, s, (H2); 3.80, s, (OMe); 2.75, t, 10.3Hz, (H8a'); 2.62, s, (ArMe); 1.48, s, (C8'-Me).

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