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Asymmetric Syntheses with a New Optically Active Perhydronaphthalene Based Chiral Auxiliary

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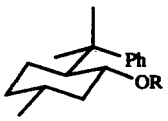
Abstract: (1*R*,4a*S*,8*S*,8a*S*)-8-(5'-Methoxy-2'-methylphenyl)-8-methyldecahydro-1-naphthalenol **3a** is a highly efficient chiral auxiliary in the Diels-Alder addition of its acrylate ester **5** and in the DIBAL-H and Grignard reactions of its phenylglyoxylate ester **7**.

One of the important developments in organic synthesis has been the use of chiral auxiliaries to control diastereofacial reactions. The most successful auxiliaries have structural features which influence rotamer populations so that selective approach of a reagent to one face of the prochiral carbon is preferred. 8-Phenylmenthol **1a** is remarkably effective in inducing diastereoselective reactions bearing in mind that rotation can occur around the C4-C8 bond. Various explanations[1-3] have been offered to rationalise this effective blocking of one diastereoface by the phenyl or other 8-aryl groups.

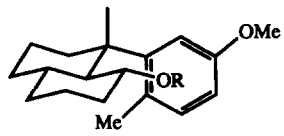
Whitesell[4] found that 8-phenylmenthol was slightly more effective than the more conformationally restricted racemic alcohol **2** as auxiliary in the ene reactions of their glyoxylate esters. The same authors also noted that the effectiveness of a chiral auxiliary in the ene reaction was usually related to the chemical shift of the aldehyde proton in the glyoxylate (the more shielded the proton, the higher the d.e.). However, this was not the case with the bicyclic auxiliary **2** in which the aldehyde proton in the ester was more shielded than the corresponding proton in 8-phenylmenthyl glyoxylate yet a decrease in diastereoselectivity was observed.

The optically active perhydronaphthalenol **3a** was considered to be a chiral auxiliary with features which would be expected to further restrict the conformation of the aryl group. In addition to the methyl group at C8, which is equivalent to that at C8 in 8-phenylmenthol **1a**, but which is not present in **2**, the aryl group contains the *ortho* methyl substituent which would be expected to further restrict the conformation of the aryl group. The methoxyl group might also assist π-π stacking[1-3] which would favour the desired conformation in which the aromatic ring and the π moiety of the ester occupy parallel planes. Although 8-(m-methoxyphenyl)menthyl glyoxylate has been used in the ene reaction[4] the effect of the methoxyl was not established with any accuracy because of the difficulty of analysis of the mixture of diastereoisomers.



1a R=H
1b R=$COCH_2COCH_3$

2

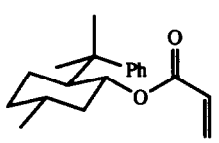


3a R=H
3b R=$COCH_2COCH_3$

Some results of the use of (1*R*,4a*S*,8*S*,8a*S*)-8-(5'-methoxy-2'-methylphenyl)-8-methyldecahydro-1-naphthalenol **3a**, prepared from podocarpic acid [5], as a chiral auxiliary in the Diels-Alder reaction of the acrylate ester **5** and the diisobutylaluminium hydride (DIBAL-H) reduction of the phenylglyoxylate ester **7**, have been described in a communication.[6] We present here full details of that work together with the results of the addition of methylmagnesium iodide to the phenylglyoxylate ester **7** and the catalytic hydrogenation of the enamido ester **9**. In each case the reaction of the corresponding 8-phenylmenthol derivative has been done under the same conditions for comparison. In addition, some chemical shift data of derivatives of **3a**, n.O.e. results and molecular modelling studies are discussed in relation to the efficiency of the alcohol **3a** as a chiral auxiliary.

The acrylate esters **4** and **5** were each prepared from the alcohols **1a** and **3a** as described for **1a**[2]. The ester **5** was obtained in 60% yield and the ^1H NMR and ^{13}C NMR spectra confirmed the structure; in particular, the alkene protons appeared as three well resolved signals instead of the complex second order multiplets found for **4** and the vinyl and ester carbonyl carbon resonances were present at δ 127.9, 129.0 and 165.3, respectively.

Reaction of the alcohols **1a** and **3a** with phenylglyoxyloyl chloride as described for **1a**[7] gave the phenylglyoxylates **6** and **7** (66%). The high resolution mass spectrum, ^{13}C and ^1H NMR spectra and carbonyl stretches at ν_{max} 1722, 1694 cm^{-1} all confirmed the structure **7**.



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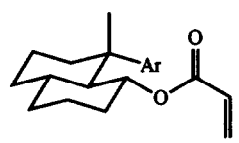
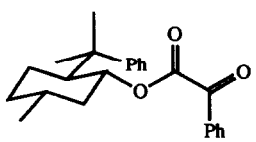
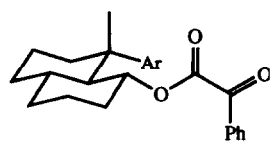


5

Ar = 5-methoxy-2-methylphenyl



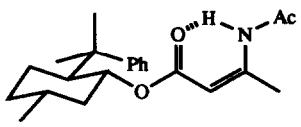
6



7

The enamido esters **8** and **9** were prepared from the esters **1b** and **3b**, by reaction with ammonia followed by acetylation of the resultant enamine with acetic anhydride, as described for 8-phenylmenthyl

acetoacetate.[8] In turn, the acetoacetates were synthesised from the alcohols **1a** and **3a** (82% yield) using the diketene/acetone adduct, 2,2,6-trimethyl-4H-1,3-dioxin-4-one.[9]



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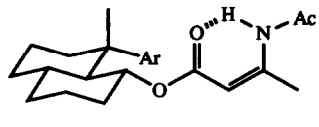


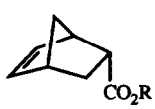
9

The ^{1}H NMR spectrum of **3b** provided confirmation of the structure, with doublets which were part of an AB quartet due to the H2 protons at δ 2.28 and 2.21, as well as a three proton singlet at δ 1.67 due to the H4 protons. The ^{13}C NMR spectrum supported the structure with carbonyl carbon resonances at δ 175 and 167, and the molecular formula of the product was confirmed by high resolution mass spectrometry.

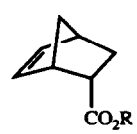
The enamido acetate **9** was then synthesised by saturating a methanolic solution of **3b** with ammonia and allowing the solution to stand for 3 days. The crude enamine, which was obtained upon work-up, was acetylated with acetic anhydride to give a 76% yield of the product **9** after chromatography. The ^{1}H NMR spectrum of **9** showed a broad singlet at δ 10.64 due to the NH proton as well as a one proton singlet at δ 3.52 due to H2. The resonance due to H2 occurred at an unusually high field, and this may indicate that the proton lies in the shielding zone of the aryl group.

Whitesell has reported[10] that 8-phenylmenthyl acrylate **4** reacts with cyclopentadiene in the presence of titanium tetrachloride to give the (2*R*)-bicycloheptenecarboxylate **10a** with a 90% d.e. In order to compare the efficiency of the new auxiliary with 8-phenylmenthol in this Diels-Alder reaction the result of Whitesell was first confirmed. Analysis of the product by 300 MHz ^{1}H NMR gave the same d.e.

The two *endo* diastereoisomers, **10b** and **11**, expected from the reaction of the acrylate **5** with cyclopentadiene were necessary for analysis and were prepared by esterification of the alcohol **3a** with the acid chloride from racemic *endo*-5-norbornene-2-carboxylic acid in the presence of 4-dimethylaminopyridine. The product (70% yield) was mainly a mixture of the two required isomers which were purified by HPLC, although base line separation could not be achieved. Several of the resonances were distinct for the two isomers including the protons of the aryl group in the chiral auxiliary (separated by about 0.4 ppm in each case), the alkene protons H5 and H6 (two dd in 2*S* isomer at δ 5.64 and 6.02; distorted dd in 2*R* isomer at δ 5.97 and 5.91) and the bridgehead protons H1 and H4. The aromatic methyls were well separated but overlapped other resonances.



10a R=1a
10b R=3a



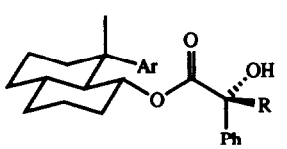
11 R=3a

Reaction of the acrylate **5** with cyclopentadiene under the conditions used with 8-phenylmenthyl acrylate gave the product in 64% yield. The dicyclopentadiene was removed by chromatography with care being taken to avoid fractionation of diastereoisomers. HPLC analysis of the product showed four

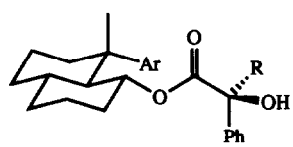
components. The two *exo* diastereoisomers (ratio 1:4) eluted first. The major component, the (2*R*) *endo* diastereoisomer **10b**, eluted next and finally some acrylate ester **5**. The 2*S* *endo* diastereoisomer could not be detected. The ratio of *endo* to *exo* isomers was 9:1, which is comparable with the ratios obtained in different systems[11]. Because base line separation of the authentic *endo* diastereoisomers could not be achieved the fraction containing *endo* isomers was analysed by 300 MHz ^{1}H NMR spectroscopy. Again, the (2*S*) diastereoisomer could not be detected, with a limit of <1% being established from the ^{13}C-H satellites. This d.e. of >98% is significantly higher than in the reaction of 8-phenylmenthyl acrylate. The configuration shown for **10b** was confirmed by its synthesis from optically enriched[12] *endo*-5-norbornene-2-carboxylic acid. The new chiral auxiliary **3a** and (-)-8-phenylmenthol induce the same configuration in the Diels-Alder reaction by approach from the *si* face with the acrylate moiety in the *anti* conformation.

The reduction of 8-phenylmenthyl phenylglyoxylate **6** with DIBAL-H at -78°C has been described[7]. Repetition of the DIBAL-H reduction gave a d.e. of 83%, higher than that reported (70%) and is probably due to our more accurate method of analysis. Direct integration of the hydroxyl and H2 resonances in the ^{1}H NMR spectrum, as described, is complicated because the H2 resonance overlaps another resonance in the major isomer. However, in D5 pyridine the H2 resonances of the two diastereoisomers are well separated and can be easily integrated.

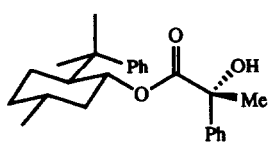
Reduction of the phenylglyoxylate **7** with DIBAL-H under the same conditions gave a product which was one diastereoisomer by 300 MHz ^{1}H NMR spectroscopy. The two authentic diastereoisomers **12** and **13** were prepared by the reduction of the phenylglyoxylate **7** with sodium borohydride at room temperature. Even at this temperature the reduction showed reasonably high diastereoselectivity (77% d.e.). The major and minor isomers showed singlets at δ 4.48 and 3.48 respectively in the NMR spectrum due to the proton on the newly introduced chiral centre. The isomers were also well separated by HPLC. Analysis of the product from the DIBAL-H reduction of **7** by HPLC showed a diastereoisomer ratio of 199:1, indicating a d.e. of 99%. This is significantly higher than the value (83%) found for the reduction of 8-phenylmenthyl phenylglyoxylate **6**. The configuration of the major isomer is the same as that observed when 8-phenylmenthol was used as the chiral auxiliary. It was established as (*R*) at C2 by the method of Solladié-Cavallo[7]. Thus amidolysis of the hydroxy ester followed by reduction with lithium aluminium hydride yielded the optically active amino alcohol, (*R*)-(-)-2-(N-isopropylamino)-1-phenylethanol. The *R* isomer in the DIBAL-H reduction therefore arises from hydride addition to the *si* face with the carbonyls of the phenylglyoxylate **7** in the *syn* conformation.



12 R=H
16 R=Me



13 R=H
17 R=Me



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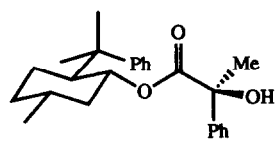
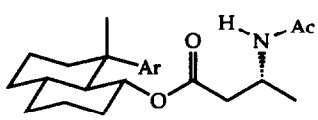


15

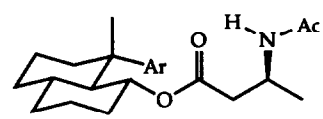
The third class of asymmetric synthesis which we investigated was the reaction of Grignard reagents with the phenylglyoxylates **6** and **7**. Whitesell[13] reported that the addition of one equivalent of methylmagnesium iodide to 8-phenylmenthyl phenylglyoxylate **6** gave the (*R*) atrolactate ester **14** with >90% d.e., based on a ^{13}C NMR method of analysis. Repetition of this reaction and analysis of the product by HPLC (major and minor isomers had retention times of 5.4 and 13.0 minutes, respectively) gave a d.e. of 91%. The authentic diastereoisomers **14** and **15** were prepared, in low yield, by esterification of racemic acetylatrolactic acid with 8-phenylmenthol, followed by hydrolysis of the acetate with potassium carbonate in methanol.

Reaction of the phenylglyoxylate **7** with methylmagnesium iodide under the conditions used for **6** gave a product in 92% yield. HPLC analysis showed that it contained only one diastereoisomer (>95% d.e.); in addition, starting material **7** and a trace of the chiral auxiliary were present. No evidence for the minor isomer could be found by 300 MHz NMR analysis of the HPLC fractions or of the crude product. An attempt to prepare a mixture of the authentic diastereoisomers **16** and **17** by the method used for the 8-phenylmenthol analogues was unsuccessful because esterification of the auxiliary **3a** with racemic acetylatrolactic acid did not proceed. It can be concluded that the addition of the Grignard reagent to the phenylglyoxylate **7** proceeded to give essentially only one diastereoisomer, presumably with the (*R*) configuration by analogy with the result when 8-phenylmenthol was used as chiral auxiliary.

The final reaction studied was the hetereogeneous catalytic hydrogenation of the enamido acetate **9**. This reaction is potentially useful for the asymmetric synthesis of β-amino acids and the results observed with several chiral auxiliaries were reported by d'Angelo[8]. Those authors found that the 8-phenylmenthol derivative **8** underwent hydrogenation over platinum oxide to give the (*R*)-β-acetylamino ester with 95% d.e. The successful outcome of this reaction was considered to be due to the preferred conformation resulting from intramolecular hydrogen bonding as shown in **8**.



18



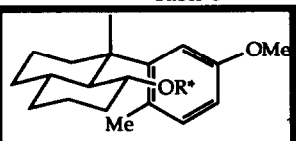
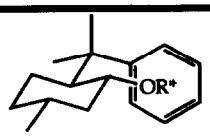
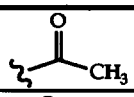
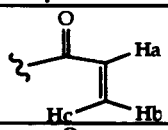
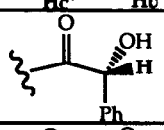
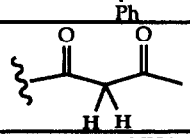
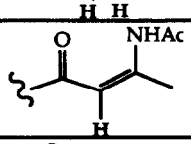
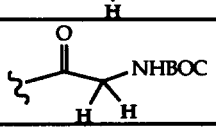
19

After confirmation of the value for the d.e. found by d'Angelo in the reduction of the 8-phenylmenthol derivative **8**, the hydrogenation of the analogue **9** was done under the same conditions. A mixture of the authentic diastereoisomers, **18** and **19**, was prepared in 79% yield by esterification of the chiral auxiliary **3a** with racemic 3-acetylaminobutanoic acid, using dicyclohexylcarbodiimide and 4-dimethylaminopyridine. HPLC analysis of this mixture showed incomplete separation of the two diastereoisomers and the ^1H NMR spectrum in $CDCl_3$ was unsatisfactory for the determination of the d.e. However, the ^1H NMR spectrum in C_6D_6 showed good separation of the signals for the two isomers. Integration of the methoxyl resonances (δ 3.36 and 3.48 for the major and minor isomers) of the reduction product showed that the d.e. was 90%. The d.e. found for the hydrogenation reaction is lower with alcohol **3a** than with 8-phenylmenthol as chiral auxiliary. The enamido ester appeared homogeneous (presumably the Z-isomer only) by HPLC and 300 MHz NMR spectroscopy and therefore it appears that the lower d.e. must arise from different conformational preferences in the transition states for the hydrogenation. Because the induced

configuration is the same in other reactions irrespective of whether the new auxiliary **3a** or 8-phenylmenthol was used, the stereochemistry of the major diastereoisomer **18** is tentatively assigned as (*R*).

The higher levels of diastereoselectivity observed with the auxiliary **3a** in the Diels-Alder, DIBAL-H reduction and the Grignard reaction suggest that the derivatives of **3a** are more conformationally restricted in comparison with their 8-phenylmenthol counterparts. Whitesell[4] noted that, for the asymmetric ene reaction between the glyoxylate esters of a variety of auxiliaries and 1-hexene, there is a relationship between the chemical shift of the aldehyde proton and the d.e. obtained in the reaction. A similar correlation was found between the chemical shift of the alkene protons in crotonate esters and the amount of asymmetric induction in the conjugate addition of amines[14]. In both of these cases it was found that the higher the field at which the protons resonated, the higher the d.e. obtained for the reaction. The chemical shifts reflect the degree of shielding by the aromatic ring resulting from different rotamer populations. It can be seen from Table 1 that the chemical shifts of the protons α to the carbonyl group are more shielded in all the derivatives of the alcohol **3a** than in those of 8-phenylmenthol.

Table 1

		
R*	δ (ppm)	δ (ppm)
	1.10	1.50
	Ha 5.04 Hb 5.31 Hc 5.70	Ha 5.99 Hb 5.56 Hc 5.56
	4.48	4.84
	2.28 / 2.21	2.74 / 2.61
	3.52	4.24
	3.07 / 2.56	3.28 / 3.05

In addition to the diequatorial arrangement of the ester moiety and the aryl group in derivatives of **3a**, the presence of the methoxyl and methyl groups should also favour conformations in which the ester moiety

and the aryl group occupy approximately parallel planes. Electron donation could favour orbital overlap and steric interactions clearly favour the conformation shown in which the aryl H6' hydrogen and the quaternary methyl groups are *syn* to each other. Support for this conformation comes from a series of n.O.e. difference spectra (Figure 1). Irradiation of the C8 methyl group of **3a** gave a 4.8% enhancement of the H1 proton. More importantly, a 4.5% enhancement of the H6' aromatic proton was observed. Irradiation of the aromatic methyl group caused an enhancement of the axial H7 and H8a protons, which again is consistent with the aryl group in the chiral auxiliary adopting the conformation shown.

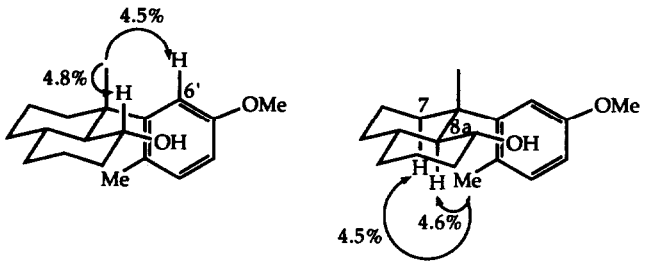


Figure 1

In addition, computer modelling studies, using the PC Model Program[15], show that the conformer depicted is the minimum energy conformation of auxiliary **3a**. The next lowest energy conformation, with the aryl group rotated through 180°, is 1.34 kcal/mol higher in energy. It is expected that similar results would be found with the derivatives of **3a** and that this preferred conformation is fundamental to the high d.e.'s observed.

EXPERIMENTAL

General

In addition to the general procedures already described[16], the following HPLC solvent systems were used:

Method A : 7% ethyl acetate in hexane at 1.5 ml/min.
Method B : 3% ethyl acetate in hexane at 1.5 ml/min.
Method C : 20% propan-2-ol in hexane at 1.5 ml/min.

(1'R,4a'S,8'S,8a'S)-8'-(5"-Methoxy-2"-methylphenyl)-8'-methyldecahydronaphthalen-1'-yl prop-2-enoate (5).

A solution of the alcohol[5] (3a) (135 mg, 0.47 mmol), triethylamine (0.13 mL, 0.94 mmol) and DMAP (6 mg) in dry CH_2Cl_2 (10 mL) was cooled to 0°C under N_2. Acryloyl chloride (85 mg, 0.94 mmol) was then added dropwise such that the temperature never rose above 5°C. The yellow solution was stirred for 1 h at 0°C and then at room temperature overnight. Water (10 mL) was added and the organic layer was washed with saturated $NaHCO_3$ solution and dried ($MgSO_4$). After removal of the solvent *in vacuo*, flash chromatography (hexane/ dichloromethane/ ethyl acetate, 18:1:1) gave the *title compound* (97 mg, 60%) as a colourless oil. M.S. 342 (M^+), 270 (A^+, M^+-CH_2=$CHCO_2H$), 255 (A^+-Me). Exact mass calculated for $C_{22}H_{30}O_3$ (M^+) 342.2195, found 342.2201. ^1H NMR (300 MHz, $CDCl_3$) δ: 6.99, d, *J* 8.2 Hz, 1H (H3"); 6.77, d, *J* 2.4 Hz, 1H (H6"); 6.52, dd, *J* 8.2 Hz, 2.4 Hz, 1H (H4"); 5.70, dd, *J* 17.3 , 1.4 Hz, 1H (CH_2=CH-); 5.31, dd, *J* 10.4, 1.4 Hz, 1H (CH_2=CH-); 5.04, dd, *J* 10.4, 17.3 Hz, 1H (CH_2=CH-); 4.79, dt, *J* 10.6, 4.4 Hz, 1H (H1'); 3.68, s, 3H (OMe); 2.62, s, 3H (ArMe); 1.41, s, 3H (C8'-Me), 2.2-0.8, complex, methylene envelope. ^{13}C NMR (75.5MHz, $CDCl_3$) δ: 165.5 (C=O); 157.7 (C5"); 150.8 (C1"); 133.6 (C3"); 129.2 (CH_2=CH-); 128.0 (CH_2=CH-); 127.0 (C2"); 112.8 (C6"); 109.3 (C4"); 73.6 (C1'); 55.0 (OMe); 49.0 (C8a'); 41.5 (C8'); 39.4 (C2'); 37.4 (C4a'); 34.5 (C3' or C6' or C7'); 33.6 (C6' or C3' or C7'); 33.2 (C7' or C3' or C6'); 23.6 (ArMe

overlapping with C4' or C5'); 22.1 (C5' or C4'); 20.5 (C8'-Me). ν_{max} (CH_2Cl_2) 1712, 1608, 1504 1048 cm^{-1}.

(1'R,4a'S,8'S,8a'S)-8'-(5"-Methoxy-2"-methylphenyl)-8'-methyldecahydronaphthale (R)-endo-2-bicyclo[2.2.1]hept-5-enecarboxylate (10b).

Freshly distilled titanium tetrachloride (83 mg, 48 μL, 0.44 mmol, 1.5 eq) was added dropwise to a solution of the acrylate (5) (100 mg, 0.29 mmol) in dry CH_2Cl_2 (4 mL) under N_2 at 0°C[10]. The s turned brown and after 45 min freshly distilled cyclopentadiene (97 mg, 120 μL, 1.5 mmol, 5 eq) wa dropwise via syringe. The solution was stirred at 0°C for 4 h before more cyclopentadiene (19 mg, 24 mmol) was added. After stirring for a further 1 h at 0°C water (5 mL) was added to the solution mixture was stirred for 5 min before the organic layer was separated and the aqueous layer was extract ether (3x 10 mL). The organic layers were combined and centrifuged to remove insoluble Ti^{III} salts supernatant liquid was washed with water (10 mL), brine and dried (Na_2SO_4). Removal of the so *vacuo* yielded a brown oil. Tlc analysis of the product revealed it was a mixture of four components, dicyclopentadiene, *exo* product, *endo* product, and starting acrylate ester. The dicyclopentadiene was r from the mixture by flash chromatography (ethyl acetate/hexane, 1:9) to yield 77 mg (64%) of a colou HPLC analysis (method A) showed this product contained four components, namely two *exo* diastereo (t_R 6.93, 9% and t_R 7.09, 2%, 64% d.e.), one *endo* diastereoisomer (t_R 9.22, 86%) and starting acryl (t_R 10.96%, 3%). A small amount of the major *endo* diastereoisomer was purified by HPLC to colourless oil which crystallised on standing, m.p. 83-85°C. Microanalysis: found C 79.29%, H $C_{27}H_{36}O_3$ requires C 79.37%, H 8.88%. M.S. 408 (M^+), 330 (M^+-C_6H_6). ^1H NMR (300 MHz, CD 6.99, d, *J* 8.3 Hz, 1H (H3"); 6.87, d, *J* 2.5 Hz, 1H (H6"); 6.56, dd, *J* 8.3, 2.5 Hz, 1H (H4"); 5.9 each distorted dd, each 1H (H5 and H6); 4.66, dt, *J* 10.6, 4.2 Hz, 1H (H1'); 3.74, s, 3H (OMe); 2.7 each br s, each 1H (H1 and H4); 2.59, t, *J* 10.6 Hz, 1H (H8a'); 2.58, s, 3H (ArMe); 2.05, m, 1H (H s, 3H (C8'-Me); 1.7-0.6, complex, methylene envelope. ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 174.2 157.7 (C5"); 151.2, (C5 or C6); 149.4, (C1"); 136.4 (C5 or C6); 133.7 (C3"); 127.6 (C2"); 113. 108.4 (C4"); 73.0 (C1'); 55.1 (OMe); 48.9 (C8a'); 44.4 (C2); 43.0 (C1 or C4); 42.1 (C4 or C1); 41. 39.9 (C2'); 37.3 (C4a'); 34.6 (C3' or C6' or C7'); 33.7 (C6' or C3' or C7'); 33.4 (C7' or C3' or C (C3); 29.9 (C7); 23.8 (ArMe); 23.6 (C4' or C5'); 22.1 (C5' or C4'); 20.5 (C8'-Me). $[\alpha]_D$ +30.9 ($CHCl_3$). ν_{max} (CH_2Cl_2) 1720, 1042 cm^{-1}.

The acrylate[10] from 8-phenylmenthol, (1'*R*, 2'*S*, 5'*R*)-2'-(1-methyl-1-phenylethyl)-5'-methylcyclohex 2-enoate (4), was subjected to the Diels-Alder conditions above with cyclopentadiene. The major (2*R* was obtained with a d.e. of 90% in agreement with that reported (90% d.e.).

Authentic mixture of *(1'R,4a'S,8'S,8a'S)-8'-(5"-methoxy-2"-methylphenyl)-8'-methyldecahydronaphthalen-1'-yl (R)-endo-2-bicyclo[2.2.1]hept-5-enecarboxylate (1* and *(1'R,4a'S,8'S,8a'S)-8'-(5"-methoxy-2"-methylphenyl)-8'-methyldecahydronapht 1'-yl (S)-endo-2-bicyclo[2.2.1]hept-5-enecarboxylate (11).*

A solution of racemic *endo*-5-norbornene-2-carboxylic acid (5 mg, 0.036 mmol) in oxalyl chloride (2 r refluxed under dry conditions for 1 h. The solution was then cooled and the excess of oxalyl chlo removed *in vacuo*. A solution of the alcohol (3a) (10 mg; 0.035 mmol) and DMAP (0.5 mg) in dry CH mL) was then added to the residue and the mixture was stirred at room temperature for 2 days. Wate was added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2x 5 mL) organic layers were combined and washed with saturated $NaHCO_3$ solution, water and dried (M Removal of the solvent *in vacuo* yielded a colourless oil which was purified by flash chromat (hexane/dichloromethane/ethyl acetate, 85:10:5) to yield 10 mg (70%) of the mixture of diastereoison colourless oil. HPLC analysis (method A) of the purified product showed it was a mixture of five com namely two *exo* diastereoisomers (t_R 6.28 and 6.59, 3%) in a 1:1 ratio, two *endo* diastereoismers (t_R 9.59, 95%) in a 1:1 ratio and acrylate ester (5) (t_R 10.83, 2%). A small amount of the tw diastereoisomers was purified by HPLC. ^1H NMR (300 MHz, $CDCl_3$) resonances as for (10b) above as δ: 7.03, d, *J* 8.3 Hz, 1H (H3"); 6.84, d, *J* 2.6 Hz, 1H (H6"), 6.56, dd, *J* 8.3, 2.6 Hz, 1H (H4"); 6 *J* 5.5, 3.1 Hz, 1H (H5 or H6); 5.64, dd, *J* 5.5, 2.7 Hz, 1H (H5 or H6); 4.64, dt, *J* 10.6, 4.2 Hz, 1H 3.73, s, 3H (OMe); 2.72 and 2.45, each br s, 1H (H1 and H4); 2.65, s, 3H (ArMe); 1.40, s, 3H (C8'-

Partially resolved[12] *endo*-5-norbornenecarboxylic acid was esterified with the alcohol (3a) in the man with racemic *endo*-5-norbornenecarboxylic acid to give the title compound (10b) in 83% yield. The ma diastereoisomer corresponded to the major product from the Diels-Alder reaction, thereby establis configuration of the major product as (2*R*).

(1'R,4a'S,8'S,8a'S)-8'-(5"-Methoxy-2"-methylphenyl)-8'-methyldecahydronaphthalen-1'-yl 2-oxophenylacetate (7).

Phenylglyoxyloyl chloride (36 mg, 0.215 mmol) was added to a solution of the alcohol (3a) (62 mg, 0.215 mmol) in dry benzene (3 mL) containing dry pyridine (17 mg, 0.215 mmol) and the solution was stirred under N_2 for 3 h. The solution was filtered through Kenite (diatomaceous earth) and the filtrate was washed with water (2x 1 mL) and dried ($MgSO_4$). The solvent was removed *in vacuo* to give a yellow solid which was purified by flash chromatography (ethyl acetate/hexane, 1:4) to yield 60 mg (66%) of the *title compound* as a white solid, m.p. 126-128°C. M.S. 420 (M^+), 149. Exact mass calculated for $C_{27}H_{32}O_4$ 420.2301, found 420.2316. ^1H NMR (300 MHz, $CDCl_3$) δ: 7.80, d, *J* 8 Hz, 2H (oPhCO); 7.58, t, *J* 8 Hz, 1H (pPhCO); 7.42, t, *J* 8 Hz, 2H (mPhCO); 6.71, d, *J* 2.7 Hz, 1H (H6"); 6.70, d, *J* 8.3 Hz, 1H (H3"); 6.08, dd, *J* 8.3, 2.7 Hz, 1H (H4"); 4.97, dt, *J* 10.5, 4.5 Hz, 1H (H1'); 3.26, s, 3H (OMe); 2.77, t, *J* 10.5 Hz, 1H (H8a'); 2.52, s, 3H (ArMe); 1.48, s, 3H (C8'-Me); 2.2-1.0, complex, methylene envelope. ν_{max} (CCl_4) 1722, 1694, 1608, 1494, 1048 cm^{-1}.

(1'R,4a'S,8'S,8a'S)-8'-(5"-Methoxy-2"-methylphenyl)-8'-methyldecahydronaphthalen-1'-yl (R)-2-hydroxyphenylacetate (12).

A solution of the phenylglyoxylate (7) (5 mg, 0.012 mmol) in dry THF (1 mL) was cooled to -78°C under N_2. DIBAL-H (2.4 μL, 0.013 mmol, 1.1 eq) was then added dropwise[7]. After 15 min, methanol (1 mL) and saturated NH_4Cl solution (1 mL) were added and the solution was allowed to warm slowly to room temperature overnight. Water (5 mL) was added and the solution was extracted with ethyl acetate (4x 5 mL). The combined organic layers were washed with brine and dried (Na_2SO_4). The solvent was removed *in vacuo* to give 5 mg (100%) of a brown oil which was analysed prior to purification. HPLC analysis (method B) showed 3 peaks, namely starting phenylglyoxylate ester (t_R 6.08, 3.74%), the major (2*R*) diastereoisomer (t_R 9.90, 91.73%) and the minor (2*S*) diastereoisomer (t_R 21.00, 0.46%). The major and minor diastereoismers were present in a ratio of 99.5:0.5 i.e. a 99% d.e. ^1H NMR (300 MHz, $CDCl_3$) δ: 7.28, complex, 5H (PhH); 7.12, d, *J* 8.3 Hz, 1H (H3"); 6.97, d, *J* 2.7 Hz, 1H (H6"); 6.71, dd, *J* 8.3, 2.7 Hz, 1H (H4"); 4.84, dt, *J* 10.3, 4.4 Hz, 1H (H1'); 4.48, s, 1H (H2); 3.80, s, 3H (OMe); 2.75, t, *J* 10.3 Hz, 1H (H8a'); 2.62, s, 3H (ArMe); 1.48, s, 3H (C8'-Me); 2.15-0.99, complex, methylene envelope. A small amount of the major diastereoisomer was purified by HPLC. Microanalysis: found C 76.97%, H 8.23%. $C_{27}H_{34}O_4$ requires C 76.75%, H 8.23%. ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 170.5 (C=O); 157.9 (C5"); 149.4 (C1"); 137.9 (qPhC); 133.9 (C3"); 128.2 (pPhC); 128.1 (2xoPhC); 126.5 (2xmPhC); 116.1 (C2"); 113.5 (C6"); 109.2 (C4"); 75.5 (C1'); 74.1 (C2); 55.2 (OMe); 48.9 (C8a'); 41.7 (C8'); 39.4 (C2'); 37.5 (C4a'); 34.4 (C3' or C6' or C7'); 33.5 (C6' or C3' or C7'); 32.9 (C7' or C3' or C6'); 23.6 (C4' or C5'); 23.5 (ArMe); 22.0 (C5' or C4'); 20.5 (C8'-Me). ν_{max} (CH_2Cl_2) 3552, 1728, 1604, 1490, 1042 cm^{-1}.

(1'*R*,2'*S*,5'*R*)-2'-(1-Methyl-1-phenylethyl)-5'-methylcyclohexyl 2-oxophenylacetate (6) was prepared and reduced with DIBAL-H as above. The product (90%) had a d.e. of 83% by integration of the HCO protons.

Authentic mixture of *(1'R,4a'S,8'S,8a'S)-8'-(5"-methoxy-2"-methylphenyl)-8'-methyldecahydronaphthalen-1'-yl (R)-2-hydroxyphenylacetate (12)* and *(1'R,4a'S,8'S,8a'S)-8'-(5"-methoxy-2"-methylphenyl)-8'-methyldecahydronaphthalen-1'-yl (S)-2-hydroxyphenylacetate (13).*

Sodium borohydride (1 mg, 0.026 mmol) was added to a solution of the phenylglyoxylate (7) (5.5 mg, 0.013 mmol) in dry methanol (1 mL) and the mixture was stirred at room temperature for 15 min. Dilute HCl (2 mL) was added followed by water (10 mL) and the solution was extracted with ethyl acetate (2x 10 mL). The combined organic phases were washed with brine and dried ($MgSO_4$). The solvent was removed *in vacuo* to yield 5mg (100%) of a yellow oil. HPLC analysis (method B) showed 2 peaks, namely the major (2*R*) diastereoisomer (t_R10.77, 86%) and the minor (2*S*) diastereoisomer (t_R23.89, 11%). The major (2*R*) and minor (2*S*) diastereoisomers were present in a ratio of 7.8:1. ^1H NMR (300MHz, $CDCl_3$) for the major (2*R*) diastereoisomer δ: 4.48, s, 0.825H (H2) and the minor (2*S*) diastereoisomer δ: 3.48, s, 0.175H (H2).

Amidolysis and reduction of (12) to (*R*)-(-)-2([N-Isopropyl]-amino)-1-phenylethanol.

Lithium aluminium hydride (45 mg, 1.19 mmol) in dry ether (4.5 mL) was refluxed for 90 min and allowed to cool. A solution of isopropylamine (0.54 mL, 6.34 mmol) in dry ether (2.3 mL) was added dropwise and the solution was stirred for 30 min. The hydroxy ester (12) (21 mg, 0.05 mmol, 88% d.e.) in dry ether (1 mL) was added dropwise and the solution was stirred overnight under N_2. Water (50 μL) was then carefully added followed by 10% NaOH solution (50 μL) and water (0.14 mL). The solution turned from grey to white then brown and after this time the ether was decanted from the solid residue. The residue was refluxed with ether (5 mL) and decanted (x3) and the combined solutions were evaporated *in vacuo* to yield a brown oil. The crude product in dry THF (0.5 mL) was added dropwise to lithium aluminium hydride (45 mg, 1.19 mmol) in dry THF (2.25 mL) and the mixture was refluxed under N_2 for 17 h. Water (50 μL), 10% NaOH solution (50 μL)

and water (0.14 mL) were then added successively with stirring. The white precipitate was filtered off and then refluxed with ether (3x5 mL) as before. The ether solutions were combined and the solvent was evaporated *in vacuo* to yield a brown oil. Dilute HCl (5 mL) was added to the crude product and the solution was extracted with ether (3x10 mL). The ether phases were combined and dried ($MgSO_4$). The solvent was removed *in vacuo* to yield 10.5 mg (73%) of the alcohol (3a).

The acidic aqueous layer from above was neutralised with saturated $NaHCO_3$ solution (20 mL) and the solution was extracted with CH_2Cl_2 (3x 5 mL). The extracts were dried ($MgSO_4$) and the solvent was removed *in vacuo* to yield 3.5 mg of a brown solid which was purified by squat column chromatography (ethyl acetate/hexane gradient) to yield 3 mg (33%) of the known amino alcohol, (*R*)-(-)-2([N-Isopropyl]-amino)-1-phenylethanol[7] as a yellow solid. $[\alpha]_D$=-52.0° (c=0.3, EtOH).^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.37-7.24, complex, 5H (PhH); 4.74, dd, 1H (CHOH); 3.48, br s, (NH or OH); 2.84-2.75, complex, 2H (CH^iPr and CH_2CHOH); 2.65, dd, *J* 11.8, 9.3 Hz, 1H (CH_2CHOH); 1.03, dd, *J* 2.1, 6.2 Hz, 6H ($(CH_3)_2CH$).

(1'R,2'S,5'R)-2'-(1-Methyl-1-phenylethyl)-5'-methylcyclohexyl (R)-2-hydroxy-2-phenylpropanoate (14).

A solution of the phenylglyoxylate (6) (15 mg,0.041 mmol) in dry ether was cooled to 0°C under N_2. A solution of MeMgI in ether (1.99 M , 21 mL , 0.041 mmol) was then added dropwise. After stirring for 15 min at 0°C, saturated NH_4Cl (2 mL) was added and the solution was allowed to warm slowly to room temperature overnight. Ether (10 mL) was then added and the layers separated. The aqueous layer was extracted with ether (3x 5 mL) and the ether layers were combined. The ether extracts were washed with water (5 mL) , brine (5 mL), and dried (Na_2SO_4) and the solvent was evaporated *in vacuo* to yield 13 mg (83%) of a colourless oil. ^{1}H NMR (300 MHz,$CDCl_3$) δ: 7.45-7.19, complex, 5H (PhH); 4.80, dt, *J* 10.7, 4.4 Hz, 1H (H1'); 1.25, s, 3H (CH_3COH); 1.07, s, 3H (CH_3CPh); 0.98, s, 3H (CH_3CPh); 0.82, d, *J* 6.5 Hz, 3H (C5'-Me); 2.0-0.8, complex, methylene envelope. HPLC analysis (method B) showed the major (2*R*) diastereoisomer (t_R5.35) and the minor (2*S*) diastereoisomers (t_R13.04) were present in a 21:1 ratio, which correponds to a 91% d.e.

Authentic mixture of *(1'R,2'S,5'R)-2'-(1-methyl-1-phenylethyl)-5'-methylcyclohexyl (R)-2-hydroxy-2-phenylpropanoate (14)* and *(1'R,2'S,5'R)-2'-(1-methyl-1-phenylethyl)-5'-methylcyclohexyl (S)-2-hydroxy-2-phenylpropanoate (15).*

A solution of 8-phenylmenthol (1a) (34 mg; 0.15 mmol), racemic acetylatrolactic acid[15] (30 mg; 0.15 mmol), DCC (33 mg; 0.16 mmol) and DMAP (1 mg) in dry CH_2Cl_2 (1 mL) was stirred under anhydrous conditions for 2 days. The reaction mixture was then cooled in ice, filtered through Kenite and the solvent was removed to give 43 mg of a colourless oil. Flash chromatography (ethyl acetate/hexane, 1:9) gave starting material and esterified product (5mg). The product was refluxed in methanol (10 mL) containing water (5 mL) and K_2CO_3 (353 mg) for 3 days. The methanol was removed *in vacuo*, water (10 mL) was added and the residue was extracted with CH_2Cl_2 (3x 10 mL). The organic layers were combined, dried ($MgSO_4$) and the solvent was removed in *vacuo* to give 4mg of the title compounds. HPLC analysis (method B) showed peaks for the (2*R*) diastereoisomer (t_R5.41) and the (2*S*) diastereoisomer (t_R13.03) in a 1:1 ratio.

(1'R,4a'S,8'S,8a'S)-8'-(5"-methoxy-2"-methylphenyl)-8'-methyldecahydronaphthalen-1'-yl (R)-2-hydroxy-2-phenylpropanoate (16).

A solution of the phenylglyoxylate (7) (21 mg , 0.05 mol) in dry ether (2 mL) was cooled to 0°C under N_2. MeMgI in ether (2.0 M , 25 mL , 0.05 mol) was then added and the reaction mixture was stirred at 0°C. After 40 min, saturated NH_4Cl solution (2 mL) was added and the mixture was allowed to warm to room temperature overnight. The layers were separated and the aqueous phase was extracted with ether (3x 5 mL). The combined ether phases were washed with brine and dried (Na_2SO_4). Removal of the solvent *in vacuo* yielded 20 mg (92%) of a yellow oil which was analysed prior to purification. HPLC analysis (method A) showed 5 peaks , namely starting phenylglyoxylate ester (t_R 13.52 , 9.5%), the major (2*R*) diastereoisomer (16) (t_R 16.18 , 85%) , starting auxiliary (3a) (t_R 27.07), unknown (t_R 30.85 , 0.5%) and an unknown impurity (t_R 35.86 , 3%). The (2*R*) diastereoisomer (16) was isolated by HPLC. Microanalysis: found C 77.34%, H 8.45%. $C_{28}H_{36}O_4$ requires C 77.03%, H 8.31%. M.S. 436 (M^+), 421 (M^+-Me). ^{1}H NMR (300 MHz , $CDCl_3$) δ: 7.92, d, *J* 8.0 Hz, 2H (o-PhH); 7.49-7.25, complex, 7H (ArH, H3" and H6"); 6.87, dd, *J* 8.2, 2.3 Hz, 1H (H4"); 5.08, dt, *J* 10.4, 4.1 Hz, 1H (H1'); 4.49, s, 1H (OH); 3.67, s, 3H (OMe); 2.81, t, *J* 10.4 Hz, 1H (H8a'); 2.72, s, 3H (ArMe); 1.97, s, 3H (CH_3COH); 1.56, s, 3H (C8'-Me); 2.2-0.5, complex, methylene envelope. ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 172.3 (C=O); 158.0 (C5"); 151.5 (C1"); 142.8 (qPhC); 134.1 (C3"); 127.9 (2x o-PhC); 127.2 (p-PhC); 127.0m (C2"); 124.7 (2x m-PhC); 113.6 (C6"); 109.0 (C4"); 75.8 (C1'); 55.0 (OMe); 48.6 (C8a'); 41.6 (C8'); 40.0 (C2'); 37.5 (C4a'); 34.4 (C3' or C6' or C7'); 33.5 (C6' or C3' or C7'); 32.4 (C7' or C3' or C6'); 29.6 (COH); 26.7 (CH_3COH); 23.7 (C4' or C5'); 23.4 (C5' or C4'); 22.0 (ArMe); 20.5 (C8'-Me). ν_{max} (CH_2Cl_2) 3552, 1726, 1606, 1042 cm^{-1}.

(1'R,4a'S,8'S,8a'S)-8'-(5"-Methoxy-2"-methylphenyl)-8'-methyldecahydronaphthalen-1'-yl 3-oxobutanoate (3b).

A solution of the alcohol (3a) (93 mg, 0.32 mmol) and 2,2,6-trimethyl-4H-1,3-dioxin-4-one (91.5 mg, 0.64 mmol) in xylene (1 mL) was added to a vial containing a magnetic stirring bar, and the vial was immersed in an oil bath which had been preheated to 160°C. The solution was stirred vigorously for 30 min and then cooled. The solvent was removed *in vacuo* and the residue was purified by flash chromatography (ethyl acetate/hexane, 1:4) to yield 98 mg (82%) of the *title compound* as a colourless oil. M.S. 372 (M^+). Exact mass calculated for $C_{23}H_{32}O_4$ 372.2301, found 372.2285. $[\alpha]_D$=+21.4° (C=0.7, CHCl3). ^1H NMR (300 MHz, $CDCl_3$) δ: 6.99, d, *J* 8.3 Hz, 1H (H3"); 6.83, d, *J* 2.6 Hz, 1H (H6"); 6.56, dd, *J* 8.3, 2.6 Hz, 1H (H4"); 4.72, dt, *J* 10.5, 4.5 Hz, 1H (H1'); 3.69, s, 3H (OMe); 2.53, s, 3H (ArMe); 2.28, d, *J* 12.5 Hz, 1H (H2); 2.21, d, *J* 11.2 Hz, 1H (H2); 1.67, s, 3H (CH_3C=O); 1.38, s, 3H (C8'-Me); 2.0-0.5, complex, methylene envelope. ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 175.0 (ketone C=O); 166.7 (ester C=O); 157.1 (C5"); 150.9 (C1"); 133.7 (C3"); 127.6 (C2"); 113.0 (C6"); 108.6 (C4"); 74.1 (C1'); 55.0 (OMe); 50.3 (C2); 50.0 (C8a'); 41.6 (C8'); 39.4 (C2'); 37.1 (C4a'); 34.3 (C3' or C6' or C7'); 33.6 (C6' or C3' or C7'); 33.0 (C7' or C3' or C6'); 29.7 (C4); 23.6 (ArMe); 23.4 (C4' or C5'); 21.9 (C5' or C4'); 20.4 (C8'-Me). ν_{max} (CCl_4) 1720, 1606, 1500, 1048 cm^{-1}.

(1'R,4a'S,8'S,8a'S)-8'-(5"-Methoxy-2"-methylphenyl)-8'-methyldecahydronaphthalen-1'-yl (Z)-3-acetamido-2-butenoate (9).

A solution of the keto ester (3b) (70 mg, 0.19 mmol) in dry methanol (10 mL) was cooled to 0°C and the solution was saturated with gaseous NH_3 and left standing for 3 days before the solvent was removed *in vacuo* and the residue was taken up into dry THF (10 mL). Dry pyridine (50 μL, 0.62 mmol) and acetic anhydride (0.15 mL) were added and the solution was refluxed under N_2 for 17 h. The solvent was removed *in vacuo* and the residue was purified by flash chromatography (ethyl acetate/hexane, 3:17) to yield 59 mg (76%) of the *title compound* as a colourless oil. ^1H NMR (300MHz, $CDCl_3$) δ: 10.64, br s, 1H (NH); 7.01, d, *J* 8.3 Hz, 1H (H3"); 6.76, d, *J* 2.6 Hz, 1H (H6"); 6.55, dd, *J* 8.3, 2.6 Hz, 1H (H4"); 4.67, dt, *J* 10.3, 4.2 Hz, 1H (H1'); 3.68, s, 3H (OMe); 3.52, s, 1H (H2); 2.60, s, 3H (ArMe); 2.13, s, 3H (H4); 2.10, s, 3H (CH_3CO); 1.40, s, 3H (C8'-Me); 1.9-0.9, complex, methylene envelope.

Authentic mixture of *(1'R,4a'S,8'S,8a'S)-8'-(5"-methoxy-2"-methylphenyl)-8'-methyldecahydronaphthalen-1'-yl (R)-3-acetamidobutanoate (18)* and *(1'R,4a'S,8'S,8a'S)-8'-(5"-methoxy-2"-methylphenyl)-8'-methyldecahydronaphthalen-1'-yl (S)-3-acetamidobutanoate (19).*

A solution of the alcohol (3a) (30 mg, 0.1 mmol), racemic 3-acetylaminobutyric acid[18] (17 mg, 0.11 mmol), DCC (24 mg, 0.11 mmol) and DMAP (6 mg) in dry CH_2Cl_2 (2 mL) was stirred at 0°C for 15min and then overnight at room temperature. The solution was filtered through Kenite and the filtrate was washed with saturated $NaHCO_3$ solution and dried ($MgSO_4$). The solvent was removed *in vacuo* to give a white solid which was purified by flash chromatography (ethyl acetate/hexane, 7:3) to give 2 fractions, one being 16 mg of the starting chiral auxiliary (3a) and the other being 16 mg (37% or 79% based on recovered starting material) of the *title compounds* as a white solid. HPLC (method C) analysis revealed two overlapping peaks, namely the (3*R*) diastereoisomer (18) (t_R5.54) and the (3*S*) diastereoisomer (19) (t_R5.98) in a 1:1 ratio. ^1H NMR (300MHz, C_6D_6) for the (3*R*) diastereoisomer δ: 7.06, d, *J* 2.6 Hz, 1H (H6"); 6.98, d, *J* 8.3 Hz, 1H (H3"); 6.43, dd, *J* 8.3, 2.6 Hz, 1H (H4"); 5.46, br d, *J* 8.6 Hz, 1H (NH); 4.83, dt, *J* 10.6, 4.4 Hz, 1H (H1'); 4.29, m, 1H (H3); 3.36, s, 3H (OMe); 2.58, s, 3H (ArMe superimposed on resonance for H8a'); 1.62, s, 3H (CH_3CO); 1.32, s, 3H (C8'-Me), 0.96, d, 3H (H4). For the (3*S*) diastereoisomer δ: 7.07, d, *J* 2.5 Hz, 1H (H6"); 6.99, *J* 8.3 Hz, 1H (H3"); 6.50, dd, *J* 8.3, 2.5 Hz, 1H (H4"); 5.70, br d, *J* 8.0 Hz, 1H (NH); 4.90, dt, *J* 10.5, 4.3 Hz, 1H (H1'); 4.18, m, 1H (H3); 3.48, s, 3H (OMe); 2.56, s, 3H (ArMe superimposed on resonance for H8a'); 1.58, s, 3H (CH_3CO); 1.22, s, 3H (C8'-Me); 0.95, d, 3H (H4).

Reduction of (9).

A mixture of the (Z)-3-acetamido-2-butenoate (9) (17 mg, 0.041 mmol), acetic acid (0.6 mL) and acetic anhydride (0.2 mL) in ethyl acetate (2 mL) was hydrogenated over platinum oxide (1.6 mg) at 60psi for 3 h. The mixture was filtered through Kenite and the solvent was removed *in vacuo* to yield a colourless oil which was analysed prior to purification. HPLC analysis (method C) revealed two peaks, namely the major (3*R*) diastereoisomer (t_R5.37) and the minor (3*S*) diastereoisomer as a shoulder to the main peak (t_R5.92). ^1H NMR (300 MHz, C_6D_6) for the major (3*R*) diastereoisomer (18) δ: 7.06, d, *J* 2.6 Hz, 1H (H6"); 6.98, d, *J* 8.3 Hz, 1H (H3"); 6.43, dd, *J* 8.3, 2.6 Hz, 1H (H4"); 5.42, br d, *J* 8.5 Hz, 1H (NH); 4.83, dt, *J* 10.5, 4.2 Hz, 1H (H1'); 4.27, m, 1H (H3); 3.36, s, 2.85H (OMe); 2.58, s, 3H (ArMe); 2.56, t, J 10.5 Hz, 1H (H8a'); 1.61, s, 3H (CH_3CO); 1.32, s, 3H (C8'-Me); 0.96, d, *J* 6.7 Hz, 3H (H4); 2.1-0.6, complex, methylene envelope. For the minor (3*S*) diastereoisomer (19): as above except δ: 3.48, s, 0.15H (OMe). Integration of the methoxy peak for both diastereoisomers indicated a ratio of 19:1. The crude product was then purified by flash

chromatography (ethyl acetate/hexane, 1:1) to yield 15 mg (88%) of the *title compound* as a white solid, m.p. 119-120°C. M.S. 415 (M^+), 381, 270 (A^+, M^+-$CH_3CH(NHAc)CH_2CO_2H$), 255 (A^+-Me). Exact mass calculated for $C_{25}H_{37}NO_4$ 415.2723, found 415.2733. ^{13}C NMR (75.5 MHz, C_6D_6) δ: 171.0 (amide C=O); 168.8 (ester C=O); 157.4 (C5"); 151.4 (C1"); 133.9 (C3"); 127.9 (C2"); 113.5 (C6"); 107.9 (C4"); 73.7 (C1'); 54.9 (OMe); 48.6 (C8a'); 41.5 (C8); 41.2 (C3); 39.6 (C2'); 39.0 (C2); 37.3 (C4a'); 34.4 (C3' or C6' or C7'); 33.6 (C6' or C3' or C7'); 33.0 (C7' or C3' or C6'); 23.7 (ArMe); 23.5 (C4' or C5'); 23.3 (CH_3CO); 22.0 (C5' or C4'); 20.5 (C4); 20.2 (C8'-Me). ν_{max} (CH_2Cl_2) 3432, 1722, 1672, 1606, 1514, 1044 cm^{-1}.

Reduction of (1'*R*,2'*S*,5'*R*)-2'-(1-methyl-1-phenylethyl)-5'-methylcyclohexyl (Z)-3-acetamido-2-butenoate (8) gave the same ratio of diastereoisomers as described[8].

(1R,4aS,8S,8aS)-8-(5'-Methoxy-2'-methylphenyl)-8-methyldecahydronaphthalen-1-yl [(tert-butoxycarbonyl)amino]acetate.

A solution of the alcohol (3a) (86 mg; 0.3 mmol), N-Boc-glycine (55 mg; 0.32 mmol), DCC (66 mg; 0.32 mmol) and DMAP (3 mg) in dry ether (5 ml) was stirred overnight. The reaction mixture was cooled in ice and then filtered through Kenite. The filtrate was washed with dilute HCl, water and saturated $NaHCO_3$ solution. The organic layer was dried (Na_2SO_4) and the solvent evaporated *in vacuo* to yield a colourless oil which was purified by flash chromatography (ethyl acetate/hexane, 3:17) to yield 106 mg (80%) of the *title compound* as a colourless oil. M.S. 445 (M^+), 389 (M^+-$(CH_3)_2C=CH_2$), 270 (M^+-NtBOCgly). Exact mass calculated for $C_{26}H_{34}NO_5$ 445.2828, found 445.2815. ^1H NMR (300 MHz, $CDCl_3$) δ: 7.05, d, *J* 8.2 Hz, 1H (H3'); 6.84, d, *J* 2.6 Hz, 1H (H6'); 6.61, dd, *J* 8.2, 2.6 Hz, 1H (H4'); 4.85, dt, *J* 10.4, 4.5 Hz, 1H (H1); 4.19, br t, 1H (NH); 3.75, s, 3H (OMe); 3.09, dd, *J* 18.2, 5.6 Hz, 1H (αCH); 2.61, s, 4H (ArMe superimposed with αCH); 1.43, s, 12H (tBu superimposed with C8-Me). ^1H NMR (300MHz, C_6D_6) δ: 7.06, d, *J* 2.5 Hz, 1H (H6'); 6.96, d, *J* 8.1 Hz, 1H (H3'); 6.50, dd, *J* 2.5, 8.1 Hz, 1H (H4'); 4.92,dt, *J* 10.6, 4.4 Hz, 1H (H1); 4.42, br t, *J* 5.9 Hz, 1H (NH); 3.45, s, 3H (OMe); 3.31, dd, *J* 5.9, 18.1 Hz, 1H (αCH); 2.84, dd, *J* 5.8, 18.1 Hz, 1H (αCH); 2.53, s, 3H (ArMe superimposed on an unassigned resonance); 1.40, s, 9H (tBu); 1.33, s, 3H (C8-Me). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 169.3 (esterC=O); 157.5 (C5'); 155.7 (carbamate C=O); 150.9 (C1'); 133.9 (C3'); 127.7 (C2'); 113.4 (C6'); 108.4 (C4'); 79.2 (-$C(CH_3)_3$); 73.9 (C1); 55.0 (OMe); 49.0 (C8a); 42.0 (αC); 41.6 (C8); 39.3 (C2); 37.2 (C4a); 34.3 (CH_2); 33.6 (CH_2); 33.3 (CH_2); 28.3 ($C(CH_3)_3$); 23.6 (ArMe); 23.5 (CH_2); 21.9 (CH_2); 20.4 (C8-Me). ν_{max} (CH_2Cl_2) 3420, 1714, 1606, 1504, 1044 cm^{-1}.

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