Amide Acetal Claisen Rearrangement in the Synthesis of Mesembrane Alkaloids

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The synthesis of primary and secondary allylic alcohols (differing in the degree of steric hindrance) and of amide acetals (achiral and chiral) is reported. These compounds were used as substrates in the amide acetal Claisen rearrangement, and the effect of Lewis acids on the stereoselectivity of the reaction was studied. The rearrangement products have been applied to the synthesis of the mesembrane alkaloids (−)-mesembranone, *rac*-*O*-methyljoubertiamine and joubertiamine.

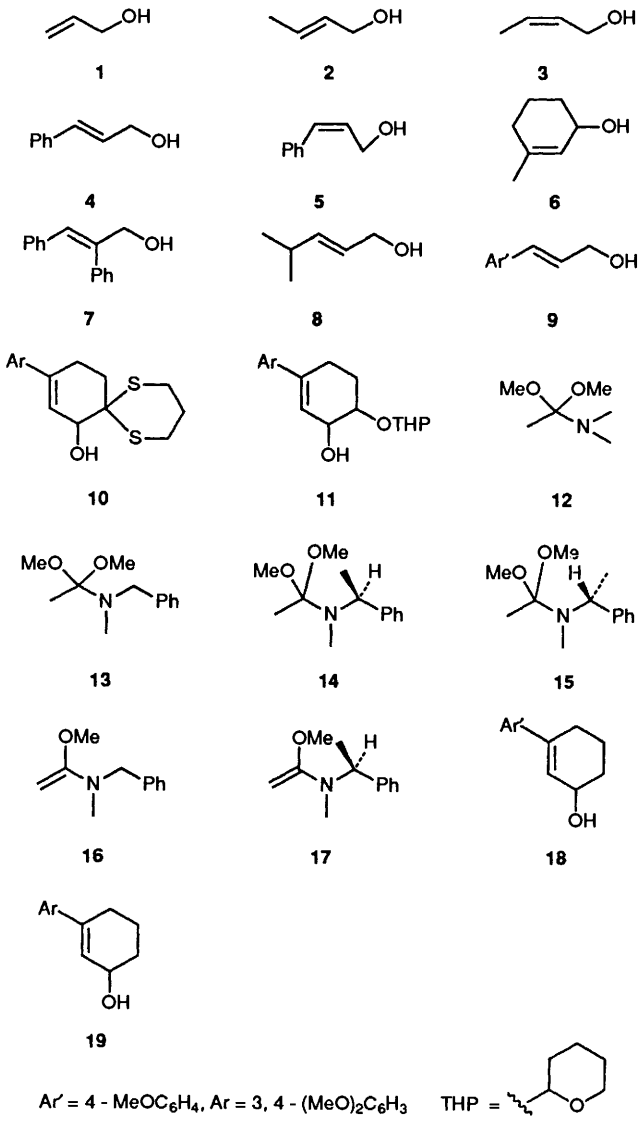
The amide acetal Claisen rearrangement[1-3] that follows the reaction of amide acetals with allylic alcohols has been applied to the synthesis of the mesembrane alkaloids (−)-mesembranone[4] **39**, *rac*-*O*-methyljoubertiamine[5] and joubertiamine.[6] In order to study this rearrangement and the scope of its synthetic applications, we synthesized a number of allylic alcohols (**1**–**11**) and achiral (**12**, **13**) as well as chiral (**14**, **15**) amide acetals, which we used as substrates in the amide acetal Claisen rearrangement.

Results and Discussion

Acetal **13** was prepared *via* modification of existing methods.[1,2] Of the two available methods in which either dry trimethyloxonium tetrafluoroborate is added to a highly concentrated solution of *N*-benzyl-*N*-methylacetamide in dichloromethane, or the dimethyl sulphate adduct of the corresponding amide is treated with two molecular equivalents of sodium methanolate in methanol, the latter gave more reproducible results. As expected,[1,2] the reaction yielded mixtures of starting amide, the acetal, and the ketene acetal **16** formed *via* elimination of methanol. Any attempts to separate the mixture by distillation increased the proportion of the ketene acetal. The crude mixture, however, could be successfully used in the Claisen rearrangement.

Products of the rearrangement were obtained after a neat mixture of the amide acetal (1.1–1.3 mol equiv.) and the corresponding alcohol was heated at 120 °C, with the continuous removal of methanol in a stream of nitrogen. Lower reaction temperatures and the presence of methanol brought about the formation of a mixture of products. The rearranged amides obtained and their yields are listed in Table 1. The rearrangement was also attempted using unstable alcohols **18** and **19**, but only the corresponding ethers were isolated in those cases.

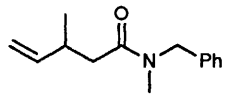
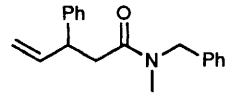
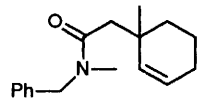
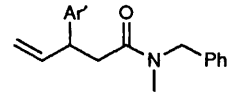
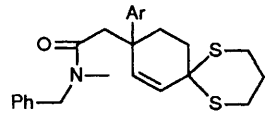
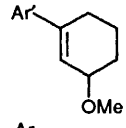
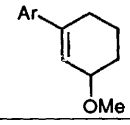
It is possible, in the case of a chiral allylic alcohol, to form a new carbon–carbon bond at an asymmetric centre in high optical yield and with predictable absolute configuration.[3] We have investigated the possibility of inducing chirality during the rearrangement with the chirality already existing, not in the allylic alcohol, but rather in the amide acetal. The reason for that change was that alcohols **10** and **11** needed for the synthesis of the natural products[4] [prepared *via* lithium aluminium hydride (LAH) reduction of the corresponding enones] were unstable, and any attempted resolution thereof brought about their decomposition. The chiral acetal **14** was prepared in a similar manner as was acetal **13**, the difference being that a suspension of potassium methanolate in tetrahydrofuran (THF) was used with the dimethyl sulphate adduct of the corresponding chiral amide. As expected, a mixture, consisting of the starting amide, acetal **14** and ketene acetal **17**, was obtained, and was subsequently used for the rearrangement.

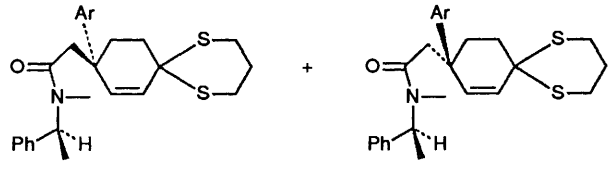


The rearrangement was first attempted using alcohol **10**—a substrate in the synthesis of (−)-mesembranone.[4] An equimolar mixture of the diastereoisomers **27** and **28** was obtained with no indication of any stereoselectivity in the reaction. Amide **28** was eventually converted into (−)-mesembranone.[4]

In the Claisen rearrangement (3,3-sigmatropic rearrangement) different factors control the stereochemical outcome of the reaction and the formation of new chiral centres. The geometry of the alkene influences the rate of the rearrangement.[8]

Table 1 Rearranged amides **20–26**

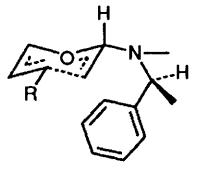
Alcohol	Acetal	Product		Yield (%)
2	**13**		**20**	**82**
4	**13**		**21**	**93**
6	**13**		**22**	**91**
9	**13**		**23**	**52**[7]
10	**13**		**24**	**43**[7]
18	**13**		**25**	**13**
19	**13**		**26**	**37**



27 **28**

There exists a high preference for the chair conformation of the intermediate (formed during the ester enolate Claisen rearrangement) but the rearrangement can also be achieved (partially or totally) *via* a boat conformation of the intermediate.[9] The reaction medium has an effect on the rearrangement,[10] and inversion of configuration of the already existing chiral centres during the Claisen amide rearrangement has been observed.[3]

In order to test for possible stereoselectivity in the Claisen rearrangement, different alcohols (**2–5**, **7** and **8**) were synthesized and their reaction with acetal **14** or its enantiomer **15** was studied. A possible transition state occurring in these reactions can be represented as structure **29**.

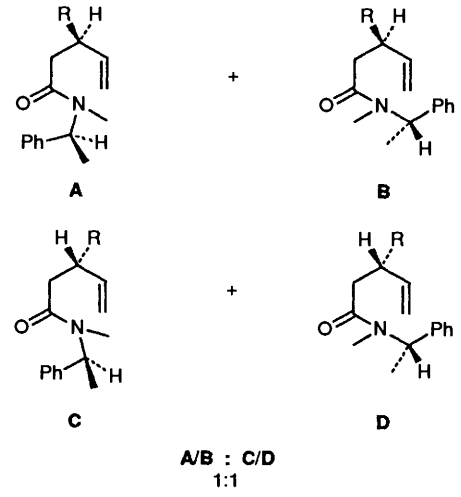


29

Relatively non-bulky (**2**, **3**) as well as sterically more hindered primary allylic alcohols (**4**, **5**, **7** and **8**) were used in the hope of inducing a diastereoisomerical enrichment of the product.

The existing chiral centre in acetals **14** and **15** was too far away from the newly formed chiral centre to have any influence on the stereochemistry of the reaction product—usually 1:1 mixtures of diastereoisomers were obtained.

For example, for alcohol **4**, the 1:1 mixture of the diastereoisomers **A**/**B** and **C**/**D** (R = Ph) was isolated. Structures **A**/**B** and **C**/**D** result from restricted rotation around the amide C–N bond.[11] Results of the rearrangements are listed in Table 2.



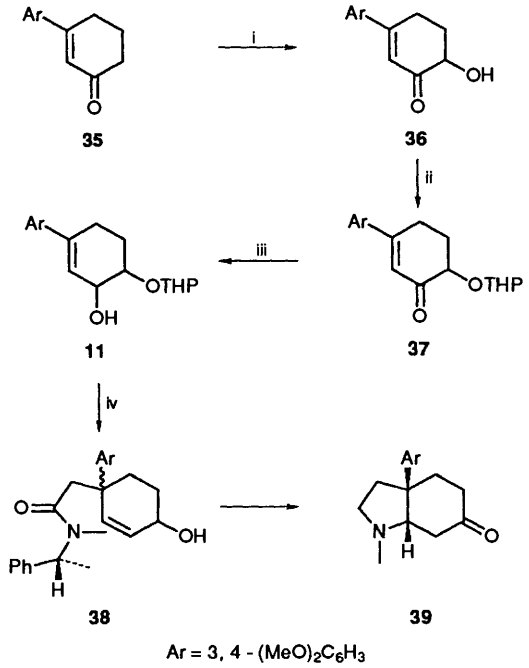
A **B**

C **D**

A/B : C/D
1:1

In order to investigate the possibility of altering the stereochemistry of the rearrangement, either *via* complexation[12] or by lowering the reaction temperature,[13] the effects of Lewis acids were next investigated. As a model reaction, the rearrangement involving substrates **4** and **14** was studied in the presence of catalytic, or equimolar, quantities of such catalysts as $BF_3{\cdot}OEt_2$, $AlCl_3$, or $ZnCl_2$. With the last mentioned catalyst, total decomposition of the acetal resulted, with no rearrangement taking place. With the first one, partial decomposition of the acetal resulted in the isolation of the usual rearranged products, in lower yields, and with no apparent stereoselectivity.

The alcohol **11** was also used, since it is involved in the synthesis of (−)-mesembranone **39** (Scheme 1).

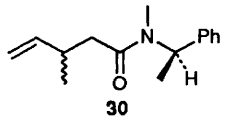
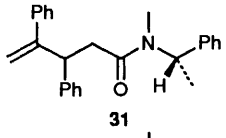
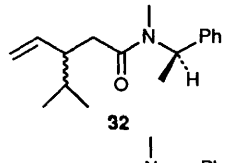
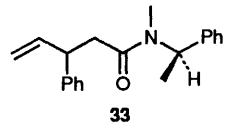
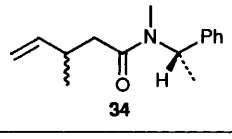


35 **36** **11** **37** **38** **39**

Ar = 3, 4 - $(MeO)_2C_6H_3$

Scheme 1 *Reagents and conditions:* i, $KOBu^t$, $PhSO_2N^{-}C(H)Ph$ or better LDA, Me_3SiCl, MCPBA, Br_4NF; ii, dihydropyran, TsOH; iii, LAH; iv, (*R*)-**15**, heat, N_2-stream

Table 2 Amide acetal Claisen rearrangement

Alcohol	Amide acetal	Conditions: Toluene, T/°C; t/h * rt = room temperature	Product	Yield (%)	Method used to ascertain diastereoisomeric ratio
3	(+)-**15**	rt, 0.5 h; 60 °C, 0.75 h; 90 °C, overnight; 100 °C, 1.5 days	 **30**	27	^{1}H NMR (80 MHz)
7	(−)-**14**	60 °C, 2 h; 110 °C, 2 h	 **31**	77	^{1}H NMR (80 MHz)
8	(+)-**15**	rt, 0.75 h; 60 °C, 0.92 h; 90 °C, 2 h; 110 °C, 2.25 h	 **32**	50	^{1}H NMR (80 MHz)
5	(+)-**15**	rt, 0.3 h; 60–75 °C, 3.5 h; 90 °C, 1.5 h; 110 °C, overnight	 **33**	91	^{1}H NMR (80 MHz)
2	(−)-**14**	70 °C, 18 h	 **34**	95	^{1}H NMR (300 MHz), HPLC

α-Hydroxylation of the enone **35** was attempted by direct oxidation with 3-phenyl-2-phenylsulphonyloxaziridine,[14] but only 18% of the alcohol **36** could be isolated. It was decided therefore to apply the method of Rubottom[15] in which the trimethylsilyl ether of the dienolate [formed by treatment of enone **35** with lithium diisopropylamide (LDA), followed by trimethylsilyl chloride], was oxidized with *m*-chloroperbenzoic acid (MCPBA) and desilylated with tetrabutylammonium fluoride. The α-hydroxy enone **36** was isolated by column chromatography in 60% yield. Protection of the alcohol **37** and reduction of the carbonyl group with LAH gave an unstable allylic alcohol **11**, which, upon being heated with the chiral acetal **15**, gave, after deprotection, the known allylic alcohol[4] **38**. The natural product **39** has been synthesized[4] from this alcohol. Again, unfortunately, no diastereoisomeric enrichment was found during the amide acetal Claisen rearrangement.

Experimental

IR spectra were recorded on a Beckman Acculab 2, Beckman 4250, Bruker IFS 45 FT, or Bohmem Michelson 100 spectrophotometer for samples in the stated solvent, or neat (NaCl windows), or as a suspension in KBr. ^{1}H NMR spectra were determined with a Bruker WP 80, Bruker AM 300 MHz, or Bruker AC 300 MHz spectrometer for solutions in $CDCl_3$ with $SiMe_4$ as internal standard; *J*-values are given in Hz. Mass spectra were determined with a Varian MAT-212 double-focusing direct-insertion probe with an ionizing potential of 70 eV. M.p.s were obtained from a Kofler micro hot stage or a Gallankamp digital melting point apparatus and are uncorrected. Solvents were dried according to standard procedures. Light petroleum refers to the fraction boiling in the range 40–60 °C.

N-*Benzyl*-N-*methylacetamide Dimethyl Acetal* **13**.—*Method 1*. While the reaction mixture was kept at room temperature under argon, a solution of *N*-benzyl-*N*-methylacetamide (3.00 g, 18.40 mmol) in dry CH_2Cl_2 (3 cm^3) was added in one portion to solid Me_3OBF_4 (3.00 g, 20.30 mmol). After 2 h, the viscous oil that had formed was added dropwise (0.5 h) to a solution of NaOMe (0.49 g Na) in methanol (13 cm^3). After an additional one hour, the mixture was centrifuged with exclusion of air, the clear solution was concentrated, the residue was redissolved in dry CH_2Cl_2 (3 cm^3), and the solution was filtered and concentrated. A 7:1 amide acetal:amide mixture (2.90 g) was isolated, δ_H(acetal) 1.23 (3 H, s, Me), 2.11 (3 H, s, NMe), 3.18 (6 H, s, 2 × OMe), 3.6 (2 H, s, CH_2) and 7.04–7.36 (5 H, m, Ph).

Method 2. *N*-Benzyl-*N*-methylacetamide (8.00 g, 49.00 mmol) and dimethyl sulphate (6.70 g, 53.00 mmol, stored over anhydrous K_2CO_3) were mixed and kept at 80 °C (under N_2) for 1 h. The viscous oil which formed was added (15 min) to a solution of NaOMe (1.25 g Na) in methanol while the reaction mixture was kept at ambient temperature. After 0.5 h the mixture was filtered, diluted with light petroleum, filtered again, and concentrated to give an oily 9:2 acetal:amide mixture. Distillation afforded the ketene acetal **16**, b.p. 51 °C/0.05 mmHg; δ_H(neat) 2.97 and 3.09 (2 H, AB dd, olefinic H), 3.47 (2 H, s, CH_2), 4.15 (3 H, s, OMe) and 7.03–7.40 (5 H, m, Ph).

N-*Benzyl*-N,3-*dimethylpent*-4-*enamide* **20**.—But-2-en-1-ol **2** (0.83 g, 11.60 mmol) and *N*-benzyl-*N*-methylacetamide dimethyl acetal **13** (3.26 g, 15.60 mmol) were heated (110 °C) while a stream of N_2 was directed over the surface of the reaction mixture. After 0.5 h the mixture was cooled and chromatographed (SiO_2; light petroleum–acetone, 9:1). The amide **20** (2.00 g) was isolated as a clear oil in 82% yield, ν_{max}/cm^{-1} 1645 (amide CO); δ_H 1.06 (3 H, br d, *J* 7, CMe), 2.15–2.34 (2 H, m, CH_2CO), 2.78 and 2.81 (4 H, br q and s, *J* 7, CH and NMe), 4.49 (2 H, br s, CH_2Ph), 4.76 and 5.10 (2 H, m, $=CH_2$), 5.56–6.01 (1 H, m, CH=) and 7.19 (5 H, br s, Ph) (Found: N, 6.4. $C_{14}H_{19}NO$ requires N, 6.45%).

N-*Benzyl*-N-*methyl*-3-*phenylpent*-4-*enamide* **21**.—3-Phenylprop-2-enol **4** (1.34 g, 10.0 mmol) and the acetal **13** (2.71 g, 13.00 mmol) were heated in a similar manner as above. After 2 h at 110 °C, the reaction mixture was cooled and chromatographed

(SiO_2; light petroleum–acetone, 17:3) to give the amide **21** as a viscous liquid (2.58 g, 93%), ν_{max}/cm^{-1} 1650 (amide CO); δ_H 2.56–2.83 (5 H, m, NMe and CH_2CO), 3.90–4.09 (1 H, m, methine H), 4.23–4.51 (2 H, m, CH_2Ph), 4.83–5.11 (2 H, m, $=CH_2$), 5.80–6.17 (1 H, m, CH=) and 6.83–7.32 (10 H, m, Ph) (Found: N, 5.0. $C_{19}H_{21}NO$ requires N, 5.02%).

N-*Benzyl*-N-*methyl*-(1-*methylcyclohex*-2-*enyl*)*ethanamide* **22**.—3-Methylcyclohex-2-enol **6** (0.34 g, 3.00 mmol) and the acetal **13** were heated (as above) at 100 °C (0.75 h) and then at 120 °C (0.3 h). After chromatography (SiO_2; light petroleum–acetone, 15:1), the amide **22** (0.70 g, 91%) was isolated as an oil, ν_{max}/cm^{-1} 1650 (amide CO); δ_H 1.13 (3 H, s, Me), 1.42–2.02 (6 H, m, ring CH_2), 2.19–2.34 (2 H, m, CH_2CO), 2.84 (3 H, s, NMe), 4.50 (2 H, br s, CH_2Ph), 5.48–5.60 (2 H, m, CH=CH) and 7.19 (5 H, br s, Ph); *m/z* 257 (M^+).

(S)-(−) *and* (R)-(+)-N-*Methyl*-N-(1-*phenylethyl*)*acetamide Dimethyl Acetal* **14** *and* **15**.—*N*-Methyl-*N*-(1-phenylethyl)acetamide (5.00 g, 28.34 mmol) and dimethyl sulphate (3.69 g, 29.32 mmol, stored over anhydrous Na_2CO_3 or K_2CO_3) were mixed under N_2 and heated (80 °C) for 3 h. The dark brown viscous oil was cooled, transferred to a dropping funnel (under N_2), and added dropwise (0.5 h) to a suspension of potassium methanolate [1.13 g K in MeOH (2.3 cm^3)] in dry THF (70 cm^3), while the reaction mixture was kept at ambient temperature. After being stirred for an additional 0.5 h the mixture was filtered under a filter aid and the filtrate was concentrated to give a light brown oil (3.70 g) as a 2.5:1 mixture of acetal:amide, the amide diastereoisomers in a 1:1 ratio, and some of the ketene acetal, ν_{max}(neat)/cm^{-1} 2880 (OMe); δ_H 1.32 (3 H, s, CMe), 1.39 (3 H, d, *J* 7.08, NCMe), 2.18 (3 H, s, NMe), 3.20 (6 H, 2 s, 2 × OMe), 4.52 (1 H, q, *J* 7.08, NCH) and 7.15–7.51 (5 H, m, Ph); and ketene acetal, δ_H 1.42 (3 H, *J* 7.08, NCMe), 2.33 (3 H, s, NMe), 2.97 and 3.18 (2 H, 2 d, *J* 3.00, $H_2C=$), 3.65 (3 H, s, OMe), 5.05 (1 H, q, *J* 7.01, NCH) and 7.15–7.51 (5 H, m, Ph); and amide, δ_H 1.47 and 1.58 (3 H, 2 d, *J* 7.08, NCMe), 2.62 and 2.66 (3 H, 2 s, NMe), 2.11 and 2.22 (3 H, 2 s, COMe), 5.05 and 6.02 (1 H, 2 q, *J* 7.01, NCH) and 7.15–7.51 (5 H, m, Ph).

N-*Methyl*-3-*phenyl*-N-[(R)-1-*phenylethyl*]*pent*-4-*enamide* **33**.—(*Z*)-3-Phenylprop-2-en-1-ol **5** (0.07 g, 0.54 mmol) and the acetal **15** were dissolved in dry toluene and the solution was stirred (20 min) while a stream of N_2 was directed over its surface. The reaction mixture was additionally stirred at 60–75 °C (3.5 h), at 90 °C (1.5 h) and at 110 °C (overnight). At 60–75 °C more of the acetal (0.17 g, 0.74 mmol) was added. The mixture was concentrated and chromatographed (SiO_2; hexane–acetone, 3:2) to give a diastereoisomeric mixture of the *amide* **33** in a 1:1 ratio (0.15 g, 91%), $\nu_{max}(CCl_4)/cm^{-1}$ 1635 (amide CO); $\delta_H(CD_3OD)$ 1.22–1.61 (3 H, m, NCMe), 2.53 and 2.54 (3 H, 2 s, NMe), 2.64–3.02 (2 H, m, CH_2CO), 3.82–4.12 (1 H, m, =CHCHPh), 4.94–5.21 (2 H, m, $H_2C=$), 4.94–5.21 and 5.71–6.31 (1 H, 2 m, NCH), 5.71–6.31 (1 H, m, =CH) and 6.85–7.40 (10 H, m, Ph); *m/z* 293 (M^+, 100) (Found: M^+, 293.1779. $C_{20}H_{23}NO$ requires M, 293.1790).

N,3-*Dimethyl*-N-[(S)-1-*phenylethyl*]*pent*-4-*enamide* **34**.—(*E*)-But-2-en-1-ol **2** (0.10 g, 1.40 mmol, 0.12 cm^3) and (*S*)-(−)-*N*-methyl-*N*-(1-phenylethyl)acetamide dimethyl acetal **14** were dissolved in toluene and the solution was heated at 70 °C for 18 h while a N_2 stream was directed over its surface. After column chromatography (SiO_2; heptane–acetone, 2:1) the oily *amide* **34** in a 1:1 ratio of isomers (0.30 g, 95%) was isolated, ν_{max}(neat)/cm^{-1} 1630 (amide CO); δ_H(300.133 MHz) 1.08–1.12 (3 H, m, =CHC*Me*), 1.47, 1.48, 1.60 and 1.61 (3 H, 4d, *J* 7.00, NCMe), 2.18–2.58 (2 H, m, CH_2CO), 2.64, 2.65, 2.66 and 2.68 (3 H, 4 s, NMe), 2.83 (1 H, quin, *J* 6.80, =CHC*H*), 4.95–5.09 (2 H, m, $H_2C=$), 5.12–5.21 (1 H, m, NCH), 5.78–5.92 (1 H, m, =CH), 6.11 (1 H, q, *J* 7.00, NCH) and 7.18–7.42 (5 H, m, Ph); couplings were also studied by the COSY 45-technique: δ_H 2.83 with =CHCMe; 1.08–1.12, CH_2CO; 2.18–2.58, $H_2C=$; 4.95–5.09 and =CH; 5.78–5.92, NCH; 6.11 with NCMe; 1.47, 1.48, 1.60 and 1.61 also $H_2C=$; 4.95–5.09 with =CH and 5.78–5.92; δ_C(75.539 MHz) 40.57 (CH_2CO), 113.00 ($CH_2=$), 126.00–128.67 (phenyl C), 143.00 (=CH) and 171.67 (CO); *m/z* 231 (M^+, 56%) and 105 (100) (Found: M^+, 231.1623. $C_{15}H_{21}NO$ requires M, 231.1617).

N,3-*Dimethyl*-N-[(R)-1-*phenylethyl*]*pent*-4-*enamide* **30**.—(*Z*)-But-2-en-1-ol **3** and (*R*)-(+)-*N*-methyl-*N*-(1-phenylethyl)-acetamide dimethyl acetal **15** (0.44 g, 2.00 mmol) were dissolved in toluene, the solution was stirred at ambient temperature (0.5 h) at 60 °C (0.75 h), at 90 °C (overnight) and at 100 °C for a further 1.5 days. Concentration and chromatography gave the oily diastereoisomeric *amide* **30** in a 1.1:1 ratio (0.01 g, 27%) as an oil, $\nu_{max}(CCl_4)/cm^{-1}$ 1635 (amide CO); $\delta_H(CD_3OD$; 80.130 MHz) 1.03–1.13 (3 H, m, =CHC*Me*), 1.44–1.66 (3 H, m, NCMe), 2.35–2.47 (2 H, m, CH_2CO), 2.65 and 2.71 (3 H, 2 s, NMe), 2.75–2.93 (1 H, m, =CHC*H*), 4.88–5.35 (2 H, m, $H_2C=$), 4.88–5.35 and 5.65–6.12 (1 H, 2 m, NCH), 5.65–6.12 (1 H, m, =CH) and 7.19–7.42 (5 H, m, Ph); *m/z* 231 (M^+, 4%) and 105 (100) (Found: M^+, 231.1621. $C_{15}H_{21}NO$ requires M, 231.1617).

N-*Methyl*-3,4-*diphenyl*-N-[(S)-1-*phenylethyl*]*pent*-4-*enamide* **31**.—2,3-Diphenylprop-2-en-1-ol **7** (0.10 g, 0.48 mmol) and (*S*)-(−)-*N*-methyl-*N*-(1-phenylethyl)acetamide dimethyl acetal **14** (0.14 g, 0.65 mmol) were heated, as above in toluene, at 60 °C (2 h) and at 110 °C (2 h). After concentration and chromatography (SiO_2; benzene–acetone, 9:1), the oily diastereoisomeric *amides* **31** in a 1.1:1 ratio (0.14 g, 77%) were isolated, $\nu_{max}(CHCl_3)/cm^{-1}$ 1615 (amide CO); $\delta_H(CD_3OD)$ 1.12, 1.25, 1.36 and 1.50 (3 H, 4 d, *J* 6.96, NCMe), 2.38, 2.43, 2.50 and 2.55 (3 H, 4 s, NMe), 2.85–3.18 (2 H, m, CH_2CO), 4.59 (1 H, t, *J* 7.57, H_2CCH), 5.12–5.41 (2 H, m, $H_2C=$), 5.72–6.03 (1 H, m, NCH) and 6.80–7.43 (15 H, m, Ph); *m/z* 369 (M^+, 100) (Found: M^+, 369.2093. $C_{26}H_{27}NO$ requires M, 369.2097).

3-*Isopropyl*-N-*Methyl*-N-[(R)-1-*phenyl*]*pent*-4-*enamide* **32**.—4-Methylpent-2-en-1-ol **8** (0.11 g, 1.10 mmol) and (*R*)-(+)-*N*-methyl-*N*-(1-phenylethyl)acetamide dimethyl acetal **15** (0.30 g, 1.30 mmol) were dissolved in toluene and the solution was stirred as above, at ambient temperature (0.75 h), 60 °C (55 min), 90 °C (2 h) and at 110 °C (2.5 h). Concentration and chromatography (SiO_2; hexane–acetone, 2:1) gave the oily diastereoisomeric *amides* **32** in a 1.1:1 ratio (0.14 g, 50%), $\nu_{max}(CCl_4)/cm^{-1}$ 1633 (amide CO); δ_H 0.86 and 0.95 (6 H, 2 d, *J* 3.64, Me_2CH), 1.45 and 1.51 (3 H, 2 d, *J* 7.26, NCMe), 2.35–2.60 (2 H, m, CH_2CO), 2.35–2.60 (1 H, m, Me_2CH), 2.61 and 2.65 (3 H, 2 s, NMe), 4.89–5.12 (2 H, m, $H_2C=$), 4.89–5.12 and 5.52–6.23 (1 H, 2 m, NCH), 5.42–6.23 (1 H, m, =CH) and 7.30 (5 H, s, Ph); *m/z* 259 (M^+, 9%) and 105 (100) (Found: M^+, 259.1936. $C_{17}H_{25}NO$ requires M, 259.1937.

3-(3′,4′-*Dimethoxyphenyl*)-6-*hydroxycyclohex*-2-*enone* **36**.—*Method* 1. Potassium t-butoxide (0.15 g, 1.29 mmol) was added in one portion to a cooled solution (−78 °C) of 3-(3,4-dimethoxyphenyl)cyclohex-2-enone **35** in dry THF (10 cm^3). A solution of 3-phenyl-2-phenylsulphonyloxaziridine (0.45 g, 1.72 mmol) in THF (10 cm^3) was added after 0.5 h to the stirred solution. The reaction was quenched with saturated aq. NH_4Cl after another 0.5 h and was then allowed to reach ambient temperature. Water (10 cm^3) was added and the reaction mixture was extracted with diethyl ether (3 × 10 cm^3), dried ($MgSO_4$), filtered and concentrated. After chromatography on SiO_2 (hexane–acetone, 2:1), compound **36** was isolated in 18% yield.

Method 2. LDA was generated by stirring together diisopropylamine (2 cm^3, 14.27 mmol) and BuLi (4 cm^3 of a 15% solution) in dry THF (50 cm^3) at −78 °C. After a solution of 3-(3,4-dimethoxyphenyl)cyclohex-2-enone **35**, (1.30 g, 5.59 mmol) in THF (15 cm^3) had been added, the mixture was stirred for an additional 0.75 h. A solution of triethylamine (2.2 cm^3, 15.57 mmol) and chlorotrimethylsilane (2 cm^3, 15.30 mmol) in dry THF (15 cm^3) was added in one portion. The reaction mixture was allowed to reach ambient temperature and after 2 h pentane (40 cm^3) was added, and the solution was washed with water (3 × 20 cm^3), dried ($MgSO_4$), filtered and concentrated. To a solution of the silyl enol ether (1.28 g, 4.20 mmol) in THF (80 cm^3 was added MCPBA (85%; 0.86 g, 4.20 mmol) in one portion. After 1 h the mixture was concentrated and redissolved in CH_2Cl_2 (80 cm^3). Tetrabutylammonium fluoride (2.00 g, 6.30 mmol) was added in one portion and after 0.25 h the mixture was washed successively with aq. $NaHCO_3$ (30 cm^3), 0.5 mol dm^{-3} HCl (30 cm^3) and aq. $NaHCO_3$ (30 cm^3), dried ($MgSO_4$), filtered and concentrated. After chromatography on SiO_2 (light petroleum–acetone, 2:1), the α-hydroxy enone **36** (0.88 g, 60%) was isolated as reddish crystals, m.p. 143–144 °C (from diethyl ether–acetone); $\nu_{max}(CHCl_3)/cm^{-1}$ 1664 (enone CO) and 3504br (OH); δ_H 1.93–1.99 (1 H, m, 5-H_{ax}), 2.49–2.56 (1 H, m, 5-H_{eq}), 2.86–2.94 (2 H, m, 4-H_2), 3.75 (1 H, br s, OH), 3.98 and 3.90 (6 H, 2 s, 2 × OMe), 4.22 (1 H, dd, *J* 13.50 and 5.40, 6-H), 6.44 (1 H, d, *J* 2.00, 2-H), 6.87 (1 H, d, *J* 8.4, 5′-H), 7.04 (1 H, d, *J* 2.00, 2′-H) and 7.15 (1 H, dd, *J* 8.4 and 2, 6′-H). With decoupling of the multiplet at δ 2.86–2.94, the signal at δ 1.93 (dd) appeared as (1 H, br t, H_a, J_{gem} 13.80, $J_{a,a'}$ 12.00, that at δ 2.48 (1 H, dd, H_e, J_{gem} 12.00, $J_{a,e}$ 4.80) and that at δ 6.44 (1 H, s, 2-H); *m/z* 248 (M^+, 36%), 204 (100) and 176 (41) (Found: C, 67.8; H, 6.6. $C_{14}H_{18}O_4$ requires C, 67.73; H, 6.49%).

3-(3′,4′-*Dimethoxyphenyl*)-6-(*tetrahydropyran-2″-yloxy*)-*cyclohex-2-enone* **37**.—3-(3,4-Dimethoxyphenyl)-6-hydroxycyclohex-2-enone **36**, (0.17 g, 0.68 mmol), 3,4-dihydro-2*H*-pyran (0.40 cm^3, 4.00 mmol) and TsOH (7.00 mg) were dissolved in dry 1,4-dioxane (20 cm^3) and the solution was stirred for 3 h at ambient temperature. Saturated aq. $NaHCO_3$ (6 cm^3) and water (10 cm^3) were added, and the mixture was extracted with $CHCl_3$ (4 × 20 cm^3); the extracts were washed with water (20 cm^3), dried (K_2CO_3), filtered and concentrated. Chromatography (SiO_2; light petroleum–acetone, 5:3) afforded the unstable diastereoisomeric mixture **37** in a 1:1 ratio (0.16 g, 71%) as an oil, ν_{max}(neat)/cm^{-1}, 1255 (C–O), 1516 (C=C) and 1672 (C=O); δ_H 1.48–2.00 (6 H, m, 3″-, 4″-, 5″-H_2), 2.10–2.13 (1 H, m, 5-H_{ax}), 2.32–2.41 (1 H, m, 5-H_{eq}), 2.78–2.98 (2 H, m, 4-H_2), 3.44–3.55 (1 H, m, 6″-H), 3.88 and 3.89 (6 H, 2 s, 2 × OMe), 4.00–4.12 (1 H, m, 6″-H), 4.32 and 4.33 (1 H, 2 dd, *J* 6.0, 3.75, 9.0, 6-H), 4.86 and 4.96 (1 H, s, dd, *J* 3.0; 6.0, 3.0, 2″-H), 6.35 and 6.40 (1 H, 2 d, *J* 1.5, 2-H), 6.86 (1 H, d, *J* 8.5, 5′-H), 7.04 (1 H, d, *J* 2.0, 2′-H) and 7.13 (1 H, dd, *J* 8.5, 2.0, 6′-H); *m/z* 332 (M^+, 0.6%), 232 (99), 205 (52) and 85 (100) (Found: C, 67.8; H, 7.0. $C_{19}H_{24}O_5$ requires C, 68.6; H, 7.3%).

3-(3′,4′-*Dimethoxyphenyl*)-6-(*tetrahydropyran-2″-yloxy*)-*cyclohex-2-enol* **11**.—A solution of 3-(3,4-dimethoxyphenyl)-6-(tetrahydropyran-2-yloxy)cyclohex-2-enone **37** (0.10 g, 0.30 mmol) in dry THF (10 cm^3) was added dropwise during 0.5 h to a suspension of LAH (0.30 g, 0.79 mmol) in THF (10 cm^3). After 2 h addition of a few drops of ethyl acetate destroyed the excess of LAH and the mixture was filtered through a filter aid and concentrated. Chromatography (SiO_2; light petroleum–acetone, 5:3) gave the diastereoisomeric mixture in a 1:1 ratio (0.09 g, 90%) as an unstable oil, ν_{max}(neat)/cm^{-1} 1251 (C–O), 1515 (C=C) and 3403 (OH); *m/z* 334 (M^+, 31%), 232 (87), 203 (35) and 85 (100).

2-[1-(3′,4′-*Dimethoxyphenyl*)-4-*hydroxycyclohex-2-enyl*]-N-*methyl*-N-[(R)-1-*phenylethyl*]*acetamide* **38**.—Freshly prepared 3-(3,4-dimethoxyphenyl)-6-(tetrahydropyran-2-yloxy)cyclo-2-enol **11** (0.06 g, 0.14 mmol) and (*R*)-(+)-*N*-methyl-*N*-(1-phenylethyl)acetamide dimethyl acetal **15** (0.43 g, 0.92 mmol) were heated together (130 °C) while a stream of N_2 was directed over the surface of the mixture. After 3 h the reaction mixture was dissolved in diethyl ether (8 cm^3), washed successively with 3.50% aq. HCl (8 cm^3) and aq. $NaHCO_3$, dried (K_2CO_3), filtered and concentrated. Chromatography (SiO_2; benzene–ethyl acetate, 7:3) gave the oily product as a diastereoisomeric mixture in a 1:1 ratio (0.05 g, 85%), ν_{max}(neat)/cm^{-1} 1624 (C=O) and 3426 (OH); δ_H 1.22–2.10 and 2.50–2.88 (8 H, 3 m, OH, CMe, 5- and 6-H_2), 2.13 (2 H, s, $COCH_2$), 2.46 (3 H, s, NMe), 3.81 and 3.82 (6 H, 2 s, 2 × OMe), 4.08–4.10 and 4.25–4.27 (1 H, 2 m, 4-H), 4.96–5.08 (1 H, m, PhC*H*), 5.88–6.35 (2 H, m, 2- and 3-H) and 6.71–6.90 and 6.99–7.30 (8 H, m, ArH); *m/z* 409 (M^+, 24%), 233 (45), 177 (100) and 105 (65).

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