Tetrahedron. Asymmetry Vol. 2, No. 12, pp. 1263-1282, 1991
Printed in Great Britain

0957-4166/91 $3.00+.00
Pergamon Press plc

Asymmetric Synthesis of Pipecolic Acid Derivatives Using the Aza-Diels-Alder Reaction

Patrick D. Bailey[a*], George R. Brown[b], Fritjof Korber[c], Amanda Reed[c] and Robert D. Wilson[a]

[a]Department of Chemistry, University of York, Heslington, York YO1 5DD, U.K.

[b]ICI Pharmaceuticals, Mereside, Alderley Park, Macclesfield, Cheshire SK10 4TG, U.K.

[c]Department of Biophysics, Liverpool Polytechnic, Byrom Street, Liverpool L3 3AF, U.K.

(*Received* 1 *November* 1991)

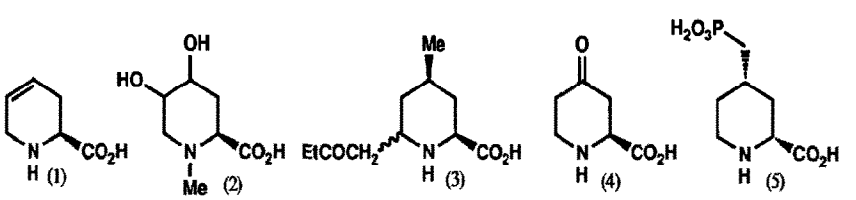
Abstract

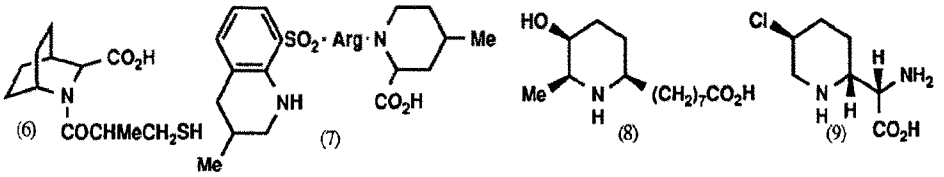
Imines of the type R-N=CHCO$_2$Et can be coerced into undergoing a (4+2) cycloaddition with substituted dienes if the reaction is carried out in DMF in the presence of both water and acid; these reactions show extremely high regio- and diastereoselectivity. Use of the 1-phenylethyl group as a chiral auxiliary leads to moderate asymmetric induction (typical d.e. ca. 70%); moreover, the diastereoisomers are surprisingly easy to separate, giving a short general route to optically pure substituted pipecolic acid derivatives.

Introduction

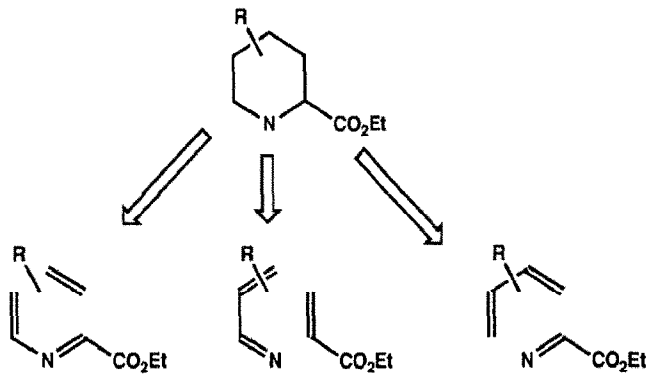
The work described herein was aimed at developing a general route to pipecolic acid derivatives that was simple, short and versatile, whilst also allowing control of regiochemistry, relative stereochemistry and absolute stereochemistry. The resultant asymmetric aza-Diels-Alder reaction is probably the most efficient method available for the synthesis of a wide range of optically active pipecolic acid derivatives, giving rapid access to products in which regio-, diastereo- and enantiocontrol have all been achieved in a predictable way.[1,2]

Our interest in the synthesis of substituted pipecolic acids was twofold. Firstly, there are many pipecolic acid derivatives that possess potent biological properties, including both natural (1-4)[3] and man-made [(5)[4a], (6)[4b,c] and (7)[5]] compounds. But secondly, as most piperidino natural products are substituted at the 2-position, the presence of an "ortho" carboxylic acid derivative would readily allow elaboration to a host of other targets. Of particular interest to us were carpamic acid (8)[6] and streptolutin(9)[7], for which Wittig or Strecker chemistry on the carboxaldehyde might reasonably be expected to introduce the key functionality at the 2-position.





For most 6-membered ring systems, it perhaps seems obvious to explore the use of the Diels-Alder reaction, with its reputation for high regio- and diastereo-control, as well as the convergent nature of the chemistry involved. For piperidine targets, we envisaged that the attachment of a chiral auxiliary onto the nitrogen might readily allow extension of the method to the preparation of optically active products. Although there are three types of aza-Diels-Alder reaction that might generate the desired heterocyclic products (Scheme 1), no general asymmetric methodology had been developed prior to our work.



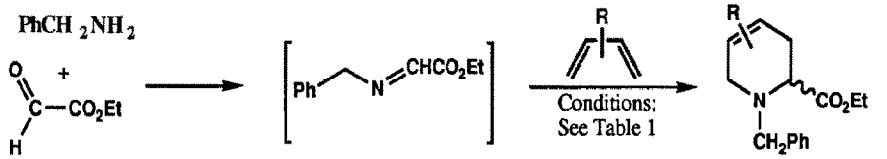
Scheme 1. Retro-synthetic analysis of pipecolic acid derivatives using Diels-Alder chemistry. Six such disconnections are possible, yielding pairs of 2-azadienes, 1-azadienes or imines as the "hetero" component; only one of each are shown. The attachment of a chiral auxiliary can be readily envisaged for structures possessing a "divalent" nitrogen.

The use of 2-azadienes as Diels-Alder dienes has been quite extensively studied, and they have been widely used for the preparation of piperidine/pyridine-based compounds.[8] However, from our point of view, this approach had one extremely serious drawback - the difficulty of attaching a removable chiral auxiliary to the tri-substituted nitrogen.

1-Azadienes, on the other hand, appear to have the potential for the attachment of a chiral auxiliary. The electron rich "1-amino-1-azadienes" (α,β-unsaturated hydrazones) react with electron deficient alkenes, but the range of dienes and dienophiles is rather limited.[9] The "2-alkoxy-1-aza-dienes" (trapped imino esters of α,β-unsaturated amides) will also react with electron deficient dienophiles, but only intramolecular reactions seem viable (*via* a non-concerted "double Michael" mechanism).[10] Finally, electron-deficient 1-azadienes possessing N-acyl[11] or N-sulphonyl[12] groups will undergo intramolecular (4+2) cyclo-additions with electron-rich alkenes. These examples notwithstanding, all of these reactions require specific derivatisation of the

nitrogen atom that severely limits the possibilities for the attachment of an effective chiral auxiliary, should an asymmetric version of the reaction be sought.

Imines have recently been found to undergo Diels-Alder reactions with a wide range of dienes, and several groups have extensively exploited this chemistry. The key to this reaction appears to be a result of making the imine nitrogen very electron deficient. This can sometimes be accomplished by simple protonation[13], but more general success has been achieved by the attachment of acyl[14] or, in particular, sulphonyl[15] groups to the nitrogen. When an alkyl group is attached to the imine nitrogen, the scope of the Diels-Alder reaction is considerably reduced; even in the presence of acid, intermolecular cyclo-additions were apparently only possible with very reactive dienes (typically cyclopentadiene).[13] These observations were discouraging for the development of an asymmetric version of the reaction, as we were hoping that a chiral alkyl group (specifically the 1-phenylethyl moiety) might be introduced onto the nitrogen of the imine, and that its close proximity to the reacting centres might lead to high asymmetric induction. Our first task was therefore to develop conditions in which N-alkylated C-alkoxycarbonylimines (i.e. $RN{=}CHCO_2R'$) would react with a range of dienes *via* an intermolecular Diels-Alder pathway.



Scheme 2. Formation of pipecolic acid derivatives *via* the achiral aza-Diels-Alder reaction

Development of the achiral aza-Diels-Alder chemistry[1] (Scheme 2)

Reaction conditions. The closest example to the reaction we sought had been reported by Fobare *et al,* who reacted $PhCH_2N{=}CHCO_2H$ (generated *in situ*) with cyclopentadiene under acidic aqueous conditions, isolating the Diels-Alder adduct in 80% yield.[13c] Although Diels-Alder reactions are often accelerated when carried out in water,[16] we suspected that the concommitant hydrolysis of the imine might be a serious problem, and we therefore decided to repeat the reaction with cyclopentadiene in a range of acidified non-aqueous solvents.

Because of problems in isolating the adducts (which are amino acids), we replaced glyoxylic acid by ethyl glyoxylate to generate amino ester adducts which could be readily chromatographed. The results, summarised in Table 1, confirm that the cyclo-addition takes place in water, albeit in moderate yield, whilst the less polar ethanol and THF gave progressively less cyclo-adduct. In contrast, DMF gave a satisfying 89% yield, indicating that polar non-aqueous solvents were a viable medium. Using these conditions, the reaction was also successful using 2,3-dimethylbutadiene as the diene, and this constituted the first example of an acyclic diene participating in a (4+2) cyclo-addition with an imine of the type $R\text{-}N{=}CHCO_2R'$. In further reactions with a series of methylated dienes, we were able to demonstrate the generality of the reaction, with yields varying from 36-47% (see Table 2). The modest yields are offset by the shortness of the method, its simplicity, and ease of product isolation.

Diene	Formation of imine	Reaction conditions			Yield of cyclo-adduct
		Solvent	Acid	Water	
	*In situ*	THF	HCl (1eq)	1eq(*in situ*)	0%
"	*In situ*	EtOH	HCl (1eq)	1eq(*in situ*)	17%
"	*In situ*	H_2O	HCl (1eq)	1eq(*in situ*)	52%
"	*In situ*	DMF	HCl (1eq)	1eq(*in situ*)	89%
	Pre-formed	DMF	TFA(1eq)	None	0%
"	Pre-formed	DMF	None	1eq	0%
"	Pre-formed	DMF	TFA(1eq)	0.01eq	94%
"	Pre-formed	DMF	TFA(1eq)	0.1eq	94%
"	Pre-formed	DMF	TFA(1eq)	1eq	29%
"	Pre-formed	DMF	TFA(1eq)	10eq	9%

Table 1. The effect of reaction conditions on the yield of Diels-Alder adduct from $PhCH_2N{=}CHCO_2Et$

Regiochemistry. The next question concerned the possibility of regiocontrol using unsymmetrical dienes (e.g. penta-1,3-diene and 2-methylbutadiene). In both cases, only a single regio-isomer was observed. With the penta-1,3-diene adduct, the pseudo-triplet (J = 5.6 Hz) for H(2) (i.e. the α-proton of the amino ester adduct - see note 17 concerning numbering) at δ3.46 indicated that the 2,6-disubstituted product had been formed, and that the ester group was occupying a pseudo-axial position [a conformational feature that was repeatedly seen in the NMR data, and also in an X-ray crystal structure (see below); c.f. ref. 18]. For the 2-methylbutadiene adducts, a series of proton decoupling experiments enabled us to show that the H(6) protons were vicinal to the alkenic proton; from this we inferred that the 2,4-disubstituted adduct had been formed. This would be consistent with the formation of "ortho/para" products (with respect to the nitrogen),[13a] and this might be expected from either a concerted (4+2) cyclo-addition or from a two-step polar process. If the latter were the case, then the diastereo-control characteristic of the Diels-Alder reaction would probably be lost.

Diastereoselectivity. Initial results with cyclic dienes were not particularly encouraging, with the *exo* adduct predominating (ca. 2:1) from the reaction with cyclopentadiene, and the *endo* adduct being the major product (ca. 3:1) with cyclohexadiene. Nevertheless, when *trans*-penta-1,3-diene was employed, high diastereoselectivity was observed (ca. 13:1), with the NOE enhancement between the C(6)-methyl and ester-methyl groups providing strong evidence for a *cis* 2,6-relationship (assigned as diaxial - c.f. ref. 18).

Of more relevence to the reaction mechanism was the stereochemistry of the adduct derived from a 1,4-disubstituted butadiene. We were therefore delighted to observe that the adduct from *trans-trans*-hexa-2,4-diene was composed of a single diastereo-isomer, assigned as the all-*cis* product from a 2D-NOESY experiment. This was strongly indicative that the reaction had proceeded *via* a concerted pathway (although coulombic factors were probably driving the

regio-selectivity, with unsymmetrical dienes). It was reassuring to note that the adduct resulting from an *endo* transition state was again inferred for the reaction with an acyclic diene. The formation of significant amounts of *exo* adduct with cyclic dienes may be the result of thermodynamic control, as related Diels-Alder reactions have been shown to be reversible[13d]; this is supported by our observation that storage of the adduct from cyclopentadiene and $H_2C{=}NCH_2Ph$ led to formation of a cyclic imine trimer, presumably *via* retro-Diels-Alder chemistry.

Improving the yield. In order to increase the yield further, we attempted to remove the water generated during the *in situ* formation of the imine, by the addition of molecular sieves. To our amazement, no cyclo-adduct was observed (with 2,3-dimethylbutadiene), and the imine was recovered from the reaction mixture. By isolating the imine and specifically adding water to the reaction mixture, we were able to show that a catalytic amount of water (1-10 mol%) led to considerably enhanced yields, whilst an excess of water caused the yields to drop, presumably due to competing imine hydrolysis (see Table 1). The role of the water is hard to explain. With the amounts added being so small, it is highly unlikely that the "hydrophobic cavity" effect[16] is operating here. One possibility is that the water helps to increase the π-character of the iminium species (the presumed dienophile), by forming a cyclic intermediate *via* two hydrogen bonds (Figure 1); this should reduce the normally rapid rotation of iminium ions about the π-bond[19], thereby accelerating the reaction by increasing the effective concentration of the 2π-component, or by stabilising the 6π-transition state. (Direct intra-molecular hydrogen bonding of the iminium ester, to give a 5-membered "ring", is disfavoured for stereo-electronic reasons).[20] Evidence to support this hypothesis is that the addition of methanol in place of water led to a similar increase in the yield of cyclo-adduct (with 2,3-dimethylbutadiene), but that the use of formaldehyde in place of ethyl glyoxylate (cyclopentadiene/ benzylamine hydrochloride/ HCHO(aq)/ DMF) failed to give cyclo-adduct with DMF as solvent (c.f. successful reaction in water - see ref.13a). The presence of acid was also shown to be essential (see Table 1).

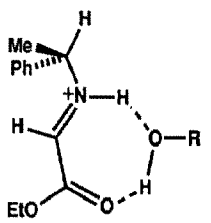


Figure 1. Possible role of water in catalysing the Diels-Alder reaction between imines of the type $RN{=}CHCO_2Et$ and dienes under acidic conditions. For the (R)-1-phenylethyl auxiliary depicted here, the diene approaches from the *si* face in all cases where the relevant stereochemistry has been determined. For acyclic dienes, the products result from an *endo* transition state, whilst cyclic dienes yield mainly the *exo* adducts.

The asymmetric aza-Diels-Alder reaction[2]

Reaction conditions and regiochemistry. Having developed suitable conditions for the achiral aza-Diels-Alder chemistry, it was relatively simple to use optically active 1-phenylethylamine in place of benzylamine. The imine itself was isolated prior to carrying out the reaction ($PhMeCHNH_2$/ $OHC\text{-}CO_2Et$/ PhMe/ azeotrope), and it in fact proved to be considerably more stable than the ethyl

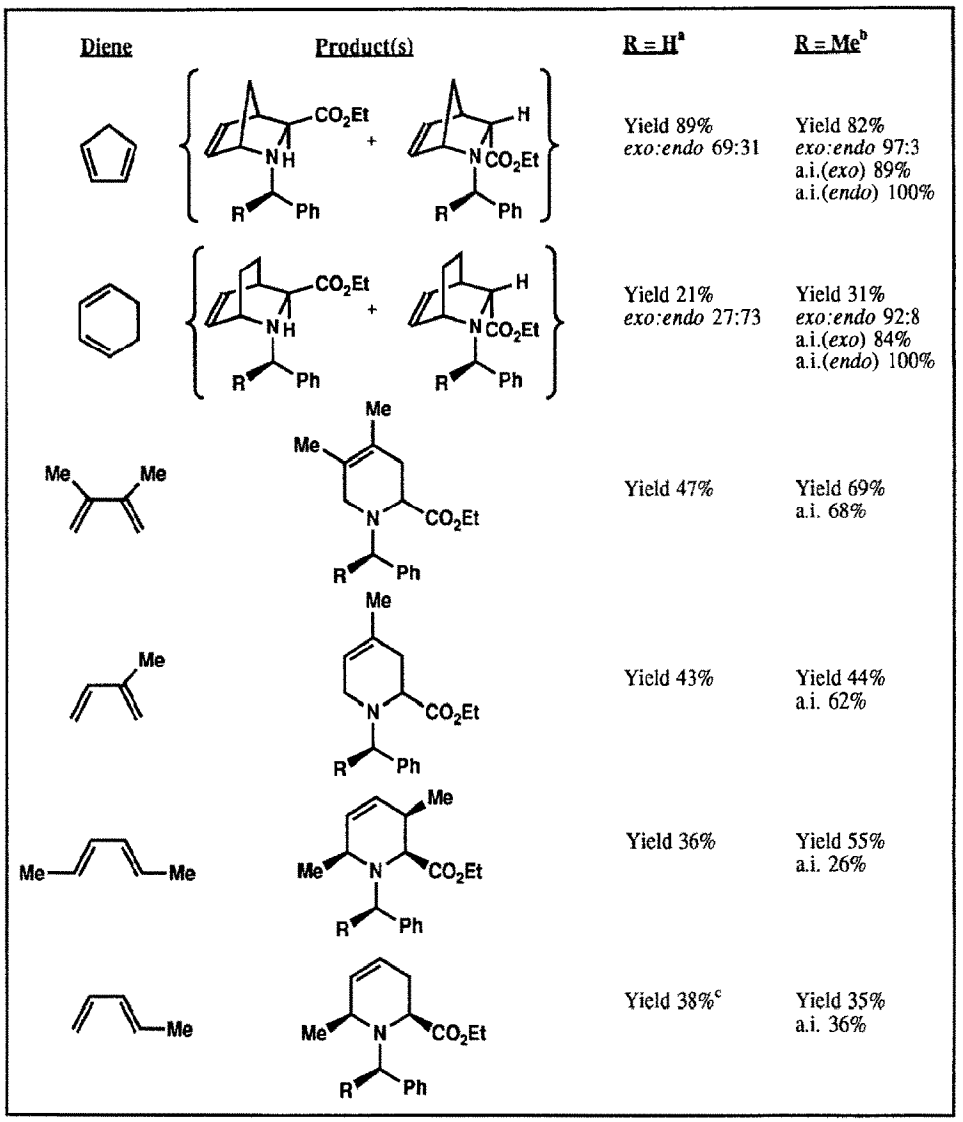


Table 2. Outcome of the aza-Diels-Alder reactions of imines of the type R'-N=CHCO$_2$Et with a range of dienes. [a] Reaction conditions for the achiral imine (R' = PhCH$_2$) used method A (see "Experimental" section); [b] Reaction conditions for the chiral imine [R' = (R)-PhMeCH] used method B (see "Experimental" section) - a.i. refers to asymmetric induction, equivalent to e.e. after removal of the chiral auxiliary; [c] Product was a 13:1 *cis:trans* mixture.

glyoxylate precursor (imine stable for 1-2 weeks at 0°C under argon). The cyclo-additions were carried out with the same dienes (2 mol eq.) as in the achiral series; with DMF as the solvent, and the addition of TFA (1 mol eq.) and water (0.03 mol eq.), the yields averaged about 55%. As

before, complete control of regiochemistry was observed, generating the "ortho/para" adducts (with respect to the nitrogen) (see Table 2).

Diastereoselectivity. The simple addition of the methyl group to the auxiliary had a surprisingly large (and wholly desirable) effect on the diastereoselectivity. For the cyclic dienes, a dramatic preference for the *exo* adducts was observed (ca. 32:1 for cyclopentadiene and 11.5:1 for cyclohexadiene). Presumably the bulkier auxiliary is directed away from the bridging $(CH2)_n$ group into the axial *endo* position, forcing the ester into the considerably less hindered *exo* stereochemistry.

For acylic dienes, 100% control of diastereochemistry was observed within the piperidine ring, and the all-*cis* adducts resulting from an *endo* transition state were inferred by analogy with the acylic cases. In general, the diastereo-control using the bulkier auxiliary was extremely good with all dienes, and would have justified its use even in the absence of any asymmetric induction.

Enantioselectivity. For the reactions using cyclic dienes, the asymmetric induction for both the *exo* and *endo* isomers were determined, and we were able to detect only a single *endo* isomer. However, it is clearly the major *exo* adducts that are of greatest synthetic interest, and the asymmetric induction in these cases was pleasingly high - 89% d.e. for cyclopentadiene and 84% for cyclohexadiene.

Moving on to the acyclic dienes, the 2,3-dimethylbutadiene and 2-methylbutadiene adducts were both obtained with about 65% asymmetric induction. We were surprised that the effect of the auxiliary should have been so great; not only is it freely rotating, but the presumed *endo* transition state (with respect to the ester group) for the cyclo-addition would force the auxiliary away from the reacting centres. These results were therefore particularly pleasing.

For *trans* -penta-1,3-diene and *trans-trans* -hexa-2,4-diene, the asymmetric induction was reduced to 36% and 26% respectively. This could be due to the additional substituent at the 1-position of the diene also interacting with the auxiliary. If this were so, then *cis* -penta-1,3-diene might be expected to yield the *trans* -2,6-disubstituted piperidine with very high asymmetric induction (c.f. ref. 21). However, when this reaction was attempted, no cyclo-adduct was formed. This observation does have a practical benefit, which we have used to advantage - a mixture of *cis*- and *trans*- dienes can be used in the aza-Diels-Alder reactions, as only the *trans* isomer will react. In view of the difficulties often encountered when trying to obtain stereochemically pure alkenes, this feature is extremely valuable (see below).

Assessment of optical purity. Overall, the average asymmetric induction for the eight Diels-Alder adducts was about 70%. However, a far more important practical consideration is pertinant to the adducts - it was possible to separate ALL of the diastereoisomers by column chromatography. This was helped by the fact that the monocyclic adducts were the highest R_f compounds (excluding volatile excess diene) from the crude reaction mixtures by silica gel chromatography, and using hexane plus a trace of ethyl acetate as eluant resulted in complete resolution of the

diastereomeric components. In all cases where we attempted to obtain the major adduct as a single stereoisomer, purification by flash chromatography proved successful.

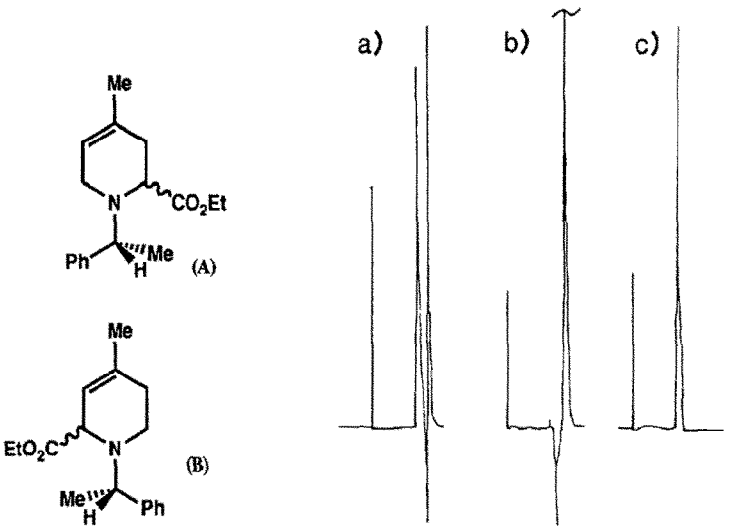
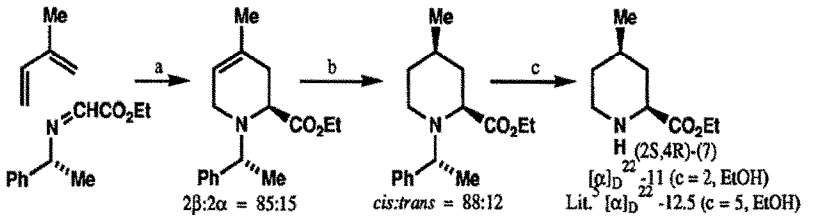


Figure 2. Chiral HPLC of: a) 50:50 mixture of (A) [(R)-auxiliary] and (B) [(S)-auxiliary]; b) (A); c) (B). See note 22 for the conditions used for the chiral HPLC.

Confirmation that no racemisation of the auxiliary had occurred (e.g. by imine tautomerism) was obtained by chiral HPLC of the 2-methylbutadiene adducts on a Pirkle column[22]. It turned out that it was unnecessary to separate the diastereoisomers for assessment of the optical purity, because the absolute stereochemistry at C(2) (where the ester is attached) had no effect on the retention time [i.e. the 1:6 diastereomeric mixture of adducts using the (R)-auxiliary were not resolved by chiral HPLC, and neither were those resulting from use of the (S)-auxiliary]. However, there was a large decrease in the retention time when the (R)-auxiliary was replaced by the (S)-auxiliary, giving fully resolved peaks (see Figure 2). We were able to conclude that the enantiomeric excess was > 97% for the (R)-auxiliary, and >99% for the (S)-auxiliary; indeed, the (R)- and (S)-1-phenylethylamines were not purified before use, and their estimated optical purities correlated very closely to those of the adducts.[23] We are therefore confident that the auxiliary is configurationally stable during the aza-Diels-Alder reactions. Importantly, this not only means that diastereomerically pure products will be homochiral (assuming that homochiral auxiliary is employed), but also that the diastereomeric excess is a measure of the e.e. in the final product (assuming that one chose to continue with a diastereomeric mixture); indeed, it would be quite superfluous to removal the auxiliary prior to assessment of the e.e., as optical purity is often determined by the specific introduction of a chiral auxiliary. It is important, however, that removal of 1-phenylethyl auxiliaries from nitrogen by hydrogenolysis should proceed without loss of optical integrity; this is indeed the case from literature examples, including many that are closely related to the substrates described herein.[24]

Synthetic of MQPA thrombin inhibitors using the asymmetric aza-Diels-Alder chemistry

The MQPA derivatives (7) are important because of their action as thrombin inhibitors.[5] The key feature that controls their biological activity is the stereochemistry of the piperidine ring[5], the synthesis of which was ideally suited to our newly developed chemistry. The reaction sequence that we followed is depicted in Scheme 3, for which the key Diels-Alder reaction has already been described above.



Scheme 3. Formation of ethyl (2S,4R)-4-methylpipecolate. Reagents: a, DMF/ TFA (1eq)/ H_2O (cat.)/ RT (44%), then flash chromatography (F.C.); b, H_2/ 3% Pt-C/ EtOAc/ RT (78%), then F.C.; c) H_2/ $Pd(OH)_2$/ EtOH (72%).

Of importance is that we could carry out the reaction using the cheap E/Z mixture of penta-1,3-dienes (see above), and that the reaction could be conducted out on a multi-gram scale (including the chromatography), from which only the major isomer was taken forward. The optical purity of the adduct was confirmed by chiral HPLC, as discussed above. Although we could probably have reduced the double bond and removed the auxiliary in a single step, we chose to carry out these steps separately in order to facilitate detailed monitoring of the reactions. Thus, hydrogenation over a platinum catalyst in ethyl acetate gave mainly the *cis* disubstitued piperidine by reduction from the least hindered face[25], and removal of the auxiliary was easily achieved using H_2 over Pearlman's catalyst in ethanol, giving (2S,4R)-(7). Similarly, the minor hydrogenation product was deprotected to give (2S,4S)-(7). These esters were the intermediates previously used in the synthesis of the MQPA thrombin inhibitors[5], and our work therefore constitutes a formal synthesis of these compounds. Moreover, by comparison with the literature optical rotations, we were able to deduce the absolute stereochemistry of our products (although assessment of e.e. from the optical rotation of free amines is notoriously unreliable because traces of acid can have such a dramatic effect). Access to the remaining two stereoisomers of MQPA could have been achieved by simply using the equally cheap (S)-auxiliary, or by using the minor diastereo-isomer resulting from the initial Diels-Alder reaction.

The absolute stereochemistry induced by the auxiliary.

The synthesis of the MQPA thrombin inhibitors allowed us to determine the direction of asymmetric induction with 2-methylbutadiene. We were also able to determine the sense of asymmetric induction from the 2,3-dimethylbutadiene adduct, by X-ray crystallography of the major diastereoisomer (see Figure 3). The solid state structure closely resembled that inferred from the NMR data, with the C(2)-ester group occupying a pseudo-axial position on the half-chair

didehydro-piperidine ring. Moreover, it was again observed that the (R)-auxiliary had induced the (S)-stereochemistry at the C(2)-position.

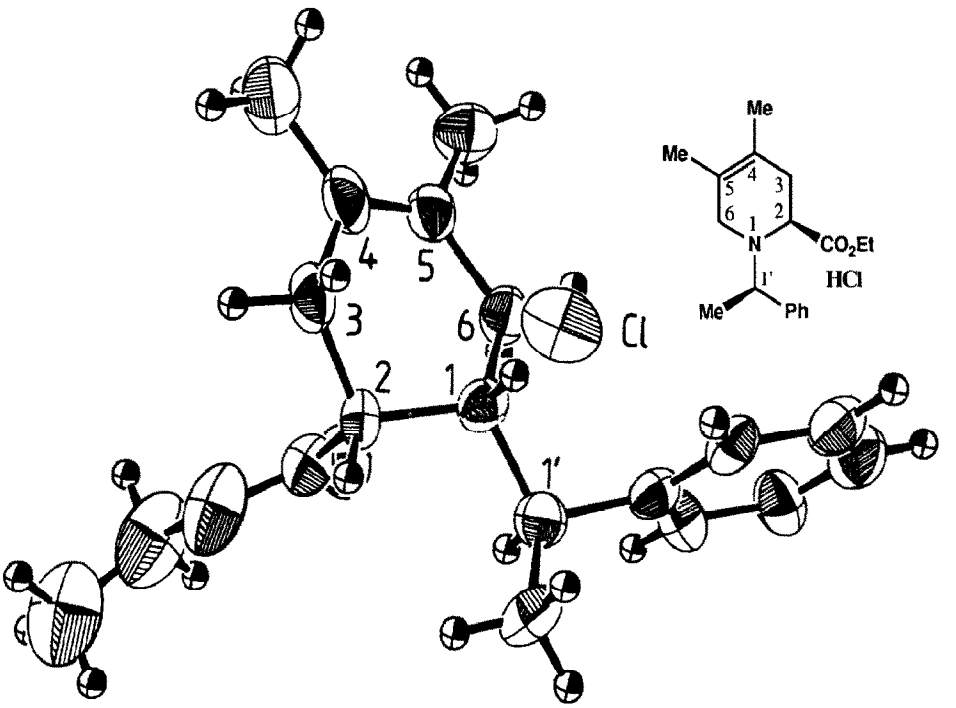


Figure 3. X-Ray crystal structure of the major adduct from the aza-Diels-Alder reaction of (R)-PhMeCH-N=$CHCO_2Et$ and 2,3-dimethylbutadiene, indicating the relative stereochemistry of the chiral centres. Full data has been deposited with the Cambridge Crystallographic Data Base.

In the literature, there is now an additional single example of an aza-Diels-Alder reaction using PhMeCHN=$CHCO_2R$ as the dienophile; Stella *et al* carried out such a reaction with cyclopentadiene, although under very different conditions to those developed by us (-78°C/ CH_2Cl_2/ TFA/ $BF_3.OEt_2$).[26] Using a racemic auxiliary, they were able to crystallise the major *exo* adduct and carry out X-ray diffraction; they observed that the (R/S)-auxiliary gave rise to the (S/R)-stereochemistry at the C(2)-position. Because their *exo* selectivity and high asymmetric induction were so similar to those observed by us, it seems probable that our conditions also lead to the same relationship between the stereochemistry of the auxiliary and the piperidine ring; thus, out (R)-auxiliary would again generate predominently (S)-stereo-chemistry at the 2-position of the adduct.

We therefore expect that the (R)-auxiliary will, in general, lead to attack on the *si* face of the imine, thereby inducing (S)-stereochemistry at the C(2)-position in the aza-Diels-Alder reaction; the (S)-auxiliary would, of course, give access to the antipodal series.

Summary

The following observations summarise our results concerning the asymmetric aza-Diels-Alder reactions:

a) The reaction is a simple one pot cycloaddition between (R)- or (S)-PhMeCHN=CHCO$_2$Et and an alkylated diene. The reaction takes place at room temperature in DMF, with TFA (1 eq.) and water (catalytic) being essential additives.

b) Material yields are typically around 50-60%.

c) Complete control of regiochemistry is observed, with ortho/para products (with respect to the piperidine nitrogen) being generated.

d) Good to excellent diastereoselectivity is observed within the piperidine ring, with cyclic dienes giving mainly *exo* adducts, and acyclic dienes reacting *via* an *endo* transition state.

e) Asymmetric induction is high for cyclic dienes (> 84%), and moderate for acyclic dienes (>62%) except for those substituted in the 1-position (ca. 30%).

f) In all cases, chromatographic separation of the diastereomeric products is relatively straightforward.

g) The auxiliary is configurationally stable to the reaction conditions, can be used to assess the optical purity of the piperidine moiety, and is readily removed by hydrogenolysis over Pd(OH)$_2$-C.

h) The (R)-auxiliary induces (S)-stereochemistry at the C(2)-position in all three cases for which relevant data is available. The equally cheap (S)-auxiliary should lead to the antipodal series.

Acknowledgements

We thank Dr. G.K. Barlow, Mrs. B. Chamberlain, Dr. T.A. Dransfield, Mr. B.R. Glennie, Dr. N.R. McLay and Mr. B. Wright for NMR & mass spectra. Thanks are also due to ICI and the Yorkshire Cancer Research Campaign for financial support.

Experimental

Apparatus. The NMR spectra reported below were run on a Bruker MSL300 spectrometer (^{1}H at 300MHz and ^{13}C at 75MHz), or on a JEOL FX 90Q spectrometer (^{1}H at 90MHz and ^{13}C at 22.5MHz), and are measured in ppm downfield from TMS. IR spectra were all run as thin films on a Perkin-Elmer 197 spectrophotometer. Mass spectra were obtained by electron impact at 70eV on an AEI MS-3074 spectrometer. Optical rotations were measured using a Perkin-Elmer 141 Polarimeter. Melting points were determined on a Reichert microscope hot-stage apparatus; products were colourless oils, unless otherwise stated.

Chemicals. Dimethylformamide was obtained anhydrous from Aldrich ("anhydrous" or "gold label" grade), and was stored under dry argon. Trifluoroacetic acid (TFA) was distilled before use. Cyclopentadiene was prepared from its dimer, and used immediately. All other reagents were

used as supplied. Flash chromatography[27] utilised silica gel 60 from Camlab as the stationary phase.

General procedures for the aza-Diels-Alder reactions

Method A (benzyl auxiliary). In a typical procedure, benzylamine hydrochloride (360mg, 2.5mmol) was dissolved in DMF (10ml), to which freshly prepared ethyl glyoxylate[28] (360mg, 3.5mmol) and 2-methylbutadiene (310mg, 5.0mmol) were added. The mixture was stirred at room temperature until TLC indicated no further accumulation of adduct (35h). After removal of the solvent *in vacuo*, the residue was taken up in chloroform, and was washed with sodium bicarbonate solution (5%) and with saturated brine. After drying the solution over potassium carbonate, the solvent was removed *in vacuo*, and the pure adduct was isolated after flash chromatography.

Method B [(R)-1-phenylethyl auxiliary]. The chiral imine was pre-formed from (R)-1-phenylethylamine (10g, 82.7mmol) and freshly prepared ethyl glyoxylate[28] (8.43g, 82.7mmol) in refluxing toluene (30ml), by removal of water using a Dean-Stark apparatus. After 20 minutes, removal of the solvent *in vacuo* gave the chiral imine {ethyl [(R)-1-phenylethyl]iminoethanoate} as an orange oil (16.9g, 100%): $[\alpha]_D^{24}$ +45 (c=1.00, $CHCl_3$); δ_H(90MHz, $CDCl_3$) 1.32 (3H, t, J=7.0Hz), 1.60 (1H, d, J=6.9Hz), 4.31 (2H, q, J=7.0Hz), 4.58 (1H, q, J=6.9Hz), 7.31 (5H, brs), 7.72 (1H, s); δ_C 13.9 (q), 23.6 (q), 61.5 (t), 69.4 (d), 126.7 (d), 127.3 (d), 128.5 (d), 142.5 (s), 152.1 (d), 163.0 (s); IR ν_{max} cm^{-1}: 700, 770, 1035, 1200, 1300, 1380, 1450, 1490, 1600, 1650, 1720, 1745, 2980; MS m/e 205 (M^+, 2%), 176 (8%), 160 (7%), 131 (9%), 105 (100%), 77 (20%); HRMS calcd. for $C_{12}H_{15}NO_2$: 205.1064. Found: 205.1065.

The use of (S)-1-phenylethylamine in place of (R)-1-phenylethylamine gave ethyl [(S)-1-phenylethyl]iminoethanoate, which was identical to the (R)-imine above in all respects except the sign of the optical rotation: $[\alpha]_D^{24}$ -45 (c=1.00, $CHCl_3$).

In a typical cyclo-addition reaction, the (R)-chiral imine {ethyl [(R)-1-phenylethyl]imino-ethanoate} (3.75g, 18.3mmol) was dissolved in DMF (13ml) with TFA (2.1g, 18.3mmol), 2-methylbutadiene (2.49g, 36.6mmol) and water (10µL, 0.56mmol). The reaction was stirred at room temperature until TLC indicated no further accumulation of adduct (30h). Work up and product isolation were the same as for Method A above.

The aza-Diels-Alder adducts. (N.B. See note 17 concerning numbering)

2-Aza-2-benzyl-3-ethoxycarbonyl-[2.2.1]-bicyclohept-5-ene. Prepared by method A (15h) from cyclo-pentadiene (89% yield). The *exo* and *endo* isomers (ratio 69:31) were separated by flash chromatography.

Exo-isomer. R_f [PhMe/EtOAc/EtOH/NH_3(aq) 95:1:2:2] 0.3; δ_H(300MHz, $CDCl_3$) 1.12 (3H, t, J=7Hz), 1.36 (1H, d, J=8.3Hz), 1.98 (1H, d, J=8.3Hz), 2.80 (1H, s), 3.08 (1H, s), 3.39-3.60 (2H, ABq, J=12.7Hz), 3.86 (1H, s), 4.00 (2H, q, J=7.0Hz), 6.21-6.24 (1H, dd, J=5.4, 1.7Hz), 6.44-6.47 (1H, m), 7.20-7.34 (5H, m); δ_C(22.5MHz, $CHCl_3$) 14.1 (q), 46.5 (t), 48.4 (d), 58.9 (t), 60.5 (t), 64.3 (d), 64.9 (d), 126.9 (d), 129.0 (d), 133.5 (d), 136.5 (d), 139.1 (s), 174.0 (s); IR ν_{max} cm^{-1}: 715, 750, 850, 1040,

1100, 1180, 1240, 1325, 1370, 1460, 1500, 1740, 2800, 2880, 2980, 3015; MS m/e 257 (M^+, 28%), 184 (48%), 117 (9%), 91 (100%), 76 (15%); HRMS calcd. for $C_{16}H_{19}NO_2$: 257.1411. Found: 257.1412.

Endo-isomer. R_f [PhMe/EtOAc/EtOH/NH_3(aq) 95:1:2:2] 0.16; δ_H(300MHz, $CDCl_3$)1.15 (3H, t, J=7Hz), 158 (1H, d, J=8.3Hz), 1.88 (1H, d, J=8.3Hz), 3.37 (2H, m), 3.72 (1H, s), 3.80-3.90 (2H, ABq, J=13.9Hz), 4.02 (2H, ABqq, J=7.0, 3.5 Hz), 6.12-6.15 (1H, dd, J=5.6, 2.8Hz), 6.45-6.50 (1H, dd, J=5.6, 2.8Hz), 7.20-7.40 (5H, m); δ_C(22.5MHz, $CHCl_3$) 14.2 (q), 45.3 (t), 47.9 (t), 60.3 (t), 60.9 (t), 65.0 (d), 66.1 (d), 127.0 (d), 128.2 (d), 129.2 (d), 135.0 (d), 139.3 (s), 173.0 (s); IR ν_{max} cm^{-1}: 715, 750, 850, 1040, 1100, 1180, 1240, 1325, 1370, 1460, 1500, 1740, 2840, 2905, 3060; MS m/e 257 (M^+, 28%), 184 (48%), 117 (9%), 91 (100%), 76 (15%); HRMS calcd. for $C_{16}H_{19}NO_2$: 257.1411. Found: 257.1412.

2-Aza-2-benzyl-3-ethoxycarbonyl-[2.2.2]-bicyclooct-5-ene. Prepared by method A (32h) from cyclo-hexadiene (21% yield). The *exo* and *endo* isomers (ratio 27:73) were separated by flash chromatography.

Exo-isomer. R_f (EtOAc/hexane 1:9) 0.32; δ_H(300MHz, $CDCl_3$) 0.83-1.42 (2H, m), 1.19 (3H, t, J=7.2Hz), 1.59 (1H, dddd, J=12.0, 9.4, 3.75, 3.3Hz), 2.00 (1H, dddd, J=12.0, 9.4, 3.75 and 3.3Hz), 2.75 (1H, dd, J=2.2, 1.8Hz), 2.83 (1H, m), 3.40 (1H, m), 3.39-3.59 (2H, ABq, J=13.4Hz), 4.08 (2H, q, J=7.0Hz), 6.23-6.33 (1H, dd, J=8.3, 5.3Hz), 6.46-6.51 (1H, m), 7.19-7.40 (5H, m); δ_C(22.5MHz, $CHCl_3$) 14.3 (q), 18.0 (t), 26.7 (t), 33.8 (d), 51.0 (d), 60.4 (t), 61.9 (t), 66.7 (d), 127.0 (d), 128.1 (d), 129.3 (d), 132.5 (d), 133.3 (d), 139.3 (s), 173.6 (s); IR ν_{max} cm^{-1}: 700, 760, 860, 1040, 1120, 1160, 1180, 1380, 1440, 1460, 1720, 2860, 2940; MS m/e 271 (M^+, 6%), 198 (100%), 170 (91%), 117 (4%), 91 (68%), 79 (12%); HRMS calcd. for $C_{17}H_{21}NO_2$: 271.1572. Found: 271.1574.

Endo-isomer. Rf (EtOAc/hexane 1:9) 0.13; δ_H(300MHz, $CDCl_3$) 1.13 (3H, t, J=7.0Hz), 1.21-1.45 (2H, m), 1.68 (1H, m), 2.19 (1H, m), 2.89 (1H, m), 3.05 (1H, d, J-1.6Hz), 3.39 (1H, m), 3.70-3.85 (2H, ABq, J=12.8Hz), 3.92-4.05 (2H, ABqq, J=7.0, 3.5Hz), 6.17 (1H, dd, J=7.3, 6.2Hz), 6.53 (1H, m), 7.17-7.41 (5H, m); δ_C(22.5MHz, $CHCl_3$) 14.2 (q), 18.3 (t), 24.0 (t), 33.5 (d), 49.9 (d), 58.2(t), 60.4 (t), 66.0 (d), 127.1 (d), 128.2 (d), 129.4 (d), 130.5 (d), 136.7 (d), 139.0 (s), 173.5 (s); IR ν_{max} cm^{-1}: 700, 725, 750, 1040, 1120, 1180, 1260, 1380, 1440, 1460, 1720, 2860, 2940; MS m/e 271 (M^+, 1%), 198 (43%), 170 (88%), 117 (3%), 91 (100%), 79 (10%); HRMS calcd. for $C_{17}H_{21}NO_2$: 271.1572. Found: 271.1574.

(6R/S)-1-Benzyl-6-ethoxycarbonyl-3,4-dimethyl-3,4-didehydropiperidine. Prepared by method A (35h) from 2,3-dimethylbutadiene in 47% yield.

R_f (EtOAc/hexane 1:9) 0.55; δ_H(90MHz, $CDCl_3$) 1.25 (3H, t, J=7.0Hz), 1.53 (3H, s), 1.61 (3H, s), 2.32 (2H, broad s), 3.10 (2H, broad q, J=18.0Hz), 3.48 (1H, t, J=4.9Hz), 3.63-3.98 (2H, ABq, J=13.0Hz), 4.14 (2H, q, J=7.0Hz), 7.19-7.30 (5H, m); δ_C(22.5MHz, $CHCl_3$) 14.4 (q), 16.3 (q), 18.4 (q), 34.3 (t), 53.9 (t), 52.9 (t), 59.3 (d), 59.9 (t), 121.9 (s), 123.9 (s), 127.0 (d), 128.2 (d), 128.9 (d), 138.6 (s), 173.0 (s); IR ν_{max} cm^{-1}: 700, 740, 980, 1025, 1040, 1090, 1130, 1150, 1180, 1360, 1450, 1490, 1730, 2860, 2900, 2980, 3010; MS m/e 273 (M^+, 8%), 200 (100%), 182 (8%), 108 (5%), 91 (47%); HRMS calcd. for $C_{17}H_{23}NO_2$: 273.1729. Found: 273.1732.

(6R/S)-1-Benzyl-6-ethoxycarbonyl-4-methyl-3,4-didehydropiperidine. Prepared by method A (35h) from 2-methylbutadiene in 43% yield.
R_f (EtOAc/hexane 1:9) 0.48; δ_H(300MHz, $CDCl_3$) 1.28 (3H, t, J=7.0Hz), 1.68 (3H, s), 2.25-2.45 (2H, m), 3.06-3.39 (2H, ABq, J=16.0Hz), 3.53 (1H, dd, J=5.6, 3.7Hz), 3.75-3.90 (2H, ABq, J=13.0Hz), 4.17 (2H, q, J=7.0Hz), 5.36 (1H, s), 7.23-7.36 (5H, m); δ_C(22.5MHz, $CHCl_3$) 14.3 (q), 22.8 (q), 32.9 (t), 48.7 (t), 58.6 (t), 59.1 (d), 59.9 (t), 119.3 (d), 126.9 (d), 128.1 (d), 128.8 (d), 129.9 (s), 138.6 (s), 172.8 (s); IR ν_{max} cm^{-1}: 700, 740, 1030, 1050, 1160, 1190, 1370, 1450, 1490, 1730, 2860, 2920, 2980, 3020; MS m/e 259 (M^+, 3%), 186 (100%), 168 (3%), 91 (51%); HRMS calcd. for $C_{16}H_{21}NO_2$: 259.1568. Found: 259.1569.

(2R/S,5S/R,6R/S)-1-Benzyl-6-ethoxycarbonyl-2,5-dimethyl-3,4-didehydropiperidine. Prepared by method A (48h) from *trans,trans*-hexa-2,4-diene in 36% yield, as a single diastereoisomer.
R_f (EtOAc/hexane 1:9) 0.43; δ_H(300MHz, $CDCl_3$) 1.04 (3H, td J=7.0Hz), 1.08 (3H, d, J=6.9Hz), 1.2 (3H, t, J=7.1Hz), 2.54 (1H, m), 3.37 (1H, m), 3.46 (1H, d, J=4.7Hz), 3.90-4.01 (2H, ABq, "J_{AB}"=14.8Hz), 4.10-4.22 (2H, ABqq, J=7.0 and "J_{AB}"=3.8Hz), 5.51 (1H, dt, J=9.9 and 2.2Hz), 5.64 (1H, ddd, J=9.9, 3.5 and 2.5Hz), 7.20-7.37 (5H, m, Ph); δ_C(22.5MHz, $CHCl_3$) 14.3 (q), 16.8 (q), 18.6 (q), 32.8 (d), 53.9 (d), 56.8 (t), 59.9 (t), 62.6 (d), 126.8 (d), 128.0 (d), 128.8 (d), 130.0 (d), 139.2 (s), 172.4 (s); IR ν_{max} cm^{-1}: 715, 750, 1040, 1120, 1140, 1170, 1380, 1470, 1750, 2900, 2960, 3000, 3060; MS m/e 273 (M^+, 1%), 200 (69%), 108 (8%), 91 (100%), 65 (13%); HRMS calcd. for $C_{17}H_{23}NO_2$: 273.1729. Found: 273.1730.

(2R/S,6R/S)-1-Benzyl-6-ethoxycarbonyl-2-methyl-3,4-didehydropiperidine. Prepared by method A (45h) from *trans*-penta-1,3-diene in 38% yield, as a mixture of *cis* [(2R,6R)/(2S,6S)] and *trans* [(2R,6S)/(2S/6R)] isomers in a ratio of 93:7. (The ^{13}C data in brackets refers to the minor isomer).
R_f (EtOAc/hexane 1:9) 0.27; δ_H(300MHz, $CDCl_3$) 1.08 (3H, d, J=6.9Hz), 1.23 (3H, t, J=7.2Hz), 2.23 (1H, dddd, J=17.0, 5.6, 5.5 and 2.8Hz), 2.45 (1H, dddd, J=17.0, 6.3, 4.2 and 2.0Hz), 3.31-3.39 (1H, m), 3.46 (1H, t, J=5.6Hz), 3.90-4.00 (2H, ABq, "J_{AB}"=14.7Hz), 3.94-4.14 (2H, qABq, J=7.2 and "J_{AB}"=3.5Hz), 5.54 (1H, dddd, J=10.0, 2.8, 1.8 and 1.8Hz), 5.72 (1H, dddd, J=10.0, 3.85, 3.85 and 2.3Hz), 7.18-7.38 (5H, m); δ_C(22.5MHz, $CHCl_3$) 14.1 (14.3) (q), 18.4 (21.0) (q), 27.6 (t), 53.7 (52.3) (d), 56.4 (54.8) (t), 58.6 (56.1) (d), 60.4 (59.8) (t), 122.2 (121.5) (d), 126.9 (d), 128.1 (128.3) (d), 128.5 (128.8 (d), 131.1 (132.4) (d), 139.3 (140.0) (s), 174.3 (173.7) (s); IR ν_{max} cm^{-1}: 700, 730, 1030, 1180, 1260, 1290, 1370, 1450, 1490, 1730, 2860, 2940, 2980, 3040; MS m/e 259 (M^+, 3%), 244 (4%), 200 (12%), 186 (100%), 170 (8%), 91 (80%); HRMS calcd. for $C_{16}H_{21}NO_2$: 259.1568. Found: 259.1568.

2-Aza-2-[(R)-1-phenylethyl]-3-ethoxycarbonyl-[2.2.1]-bicyclohept-5-ene. Prepared by method B (24h) from cyclopentadiene (82% yield). The *exo* and *endo* isomers (ratio 97:3) were separated by flash chromatography.
Exo-isomers (ratio 94.5:5.5; ^{13}C data on minor isomer given in brackets). R_f (EtOAc/hexane 1:9) 0.51; δ_H(300MHz, $CDCl_3$) 0.95 (3H, t, J=7.2Hz), 1.40 (4H, d, J=6.5Hz), 2.12 (1H, d, J=6.9Hz), 2.19

(1H, s), 2.89 (1H, broad s), 3.02 (1H, q, J=6.5Hz), 3.81 (2H, m), 4.30 (1H, d, J=1.5Hz), 6.25-6.28 (1H, dd, J=5.6, 1.9Hz), 6.40-6.43 (1H, m), 7.13-7.41 (5H, m); δ_C(75MHz, $CHCl_3$) 14.1 (14.2) (q), 22.6 (24.3) (q), 45.4 (44.9) (t), 49.0 (48.4) (d), 60.2 (60.4) (t), 62.6 (d), 63.9 (63.7) (d), 65.0 (64.7) (d), 126.9 (127.4) (d), 127.9 (d), 128.0 (128.4) (d), 132.9 (134.3) (d), 136.4 (139.0) (d), 145.0 (s), 174.3 (s); IR ν_{max} cm^{-1}: 700, 730, 770, 840, 890, 920, 950, 970, 1030, 1060, 1080, 1110, 1160, 1190, 1240, 1320, 1370, 1450, 1490, 1740, 2820, 2900,2980, 3030; MS m/e 271 (M^+, 10%), 256 (11%), 198 (70%), 131 (8%), 105 (100%), 94 (28%); HRMS calcd. for $C_{17}H_{21}NO_2$: 271.1572. Found: 271.1572.

Endo-isomer. R_f (EtOAc/hexane, 1:9) 0.17; δ_H(300MHz, $CDCl_3$) 1.04 (3H, t, J=7.1Hz), 1.47 (3H, d, J=6.4Hz), 1.51 (1H, d, J=9.6Hz), 1.64 (1H, d, J=9.6Hz), 3.23 (1H, broad s), 3.30 (1H, d, J=3.3Hz), 3.64 (1H, q, J=6.5Hz), 3.85-3.94 (2H, ABqq, J=7.1, 2.5Hz), 4.05 (1H, broad s), 6.05-6.08 (1H, dd, J=5.6, 2.7Hz), 6.57-6.60 (1H, dd, J=5.5, 3.1Hz), 7.16-7.35 (5H, m); δ_C(22.5MHz, $CHCl_3$) 14.1 (q), 22.9 (q), 45.5 (t), 48.3 (d), 60.1 (t), 63.3 (d), 64.2 (d), 64.3 (d), 127.1 (d), 128.1 (d), 128.2 (d), 135.1 (d), 138.7 (d), 144.4 (s), 173.4 (s); IR ν_{max} cm^{-1}: 700, 730, 770, 900, 920, 1040, 1050, 1110, 1170, 1290, 1330, 1450, 1740, 2860, 2940, 2980, 3040; MS m/e 271 (M^+, 11%), 256 (12%), 198 (80%), 131 (40%), 105 (100%), 94 (18%); HRMS calcd. for $C_{17}H_{21}NO_2$: 271.1572. Found: 271.1570.

2-Aza-2-[(R)-1-phenylethyl]-3-ethoxycarbonyl-[2.2.2]-bicyclooct-5-ene. Prepared by method B (60h) from cyclohexadiene (31% yield). The *exo* and *endo* isomers (ratio 92:8) were separated by flash chromatography.

Exo-isomers (ratio 92:8; ^{13}C data on minor isomer given in brackets). R_f (EtOAc/hexane, 1:9) 0.51; δ_H(300MHz, $CDCl_3$) 0.92-1.37 (2H, m), 1.06 (3H, t, J=7.1Hz), 1.30 (3H, d, J=6.7Hz), 1.54-1.64 (1H, m), 2.02-2.19 (1H, m), 2.72 (1H, m), 2.89 (1H, dd, J=2.2, 1.8Hz), 3.43 (1H, q, J=6.6Hz), 3.64 (1H, m), 3.96 (2H, q, J=7.2Hz), 6.22-6.28 (1H, m), 6.36-6.41 (1H, td, J=6.7, 1.0Hz), 7.10-7.40 (5H, m); δ_C(75MHz, $CHCl_3$) 14.1 (q), 18.5 (18.3) (t), 19.0 (q), 26.4 (t), 33.8 (34.3) (d), 47.6 (49.0) (d), 60.1 (60.2) (t), 63.0 (63.9) (d), 65.1 (65.0) (d), 126.4 (127.3) (d), 127.8 (128.3) (d), 128.1 (128.8) (d), 132.2 (d), 132.7 (132.9) (d), 144.3 (s), 173.7 (s); IR ν_{max} cm^{-1}: 700, 730, 770, 820, 920, 1030, 1040, 1070, 1180, 1260, 1280, 1300, 1370, 1450, 1490, 1740, 2860, 2900, 2960, 3020; MS m/e 285 (M^+, 2%), 270 (1%), 212 (70%), 184 (45%), 105 (100%), 80 (95%); HRMS calcd. for $C_{18}H_{23}NO_2$: 285.1727. Found: 285.1728.

Endo-isomer. Rf (EtOAc/hexane, 1:9) 0.17; δ_H(300MHz, $CDCl_3$) 1.08-1.44 (2H, m), 0.92 (3H, t, J=7.1Hz), 1.40 (3H, d, J=6.6Hz), 1.63 (1H, m), 2.12 (1H, m), 2.67 (1H, m),3.02 (1H, d, J=1.8Hz), 3.62 (1H, q, J=6.6Hz), 3.71 (2H, q, J=7.1Hz), 3.94 (1H, m), 6.11-6.16 (1H, t, J=7.1Hz), 6.64-6.70 (1H, td, J=8.2, 1.6Hz), 7.13-7.34 (5H, m); δ_C(75MHz, $CHCl_3$) 14.0 (q), 18.6 (t), 22.1 (q), 23.8 (t), 34.3 (d), 47.4 (d), 59.9 (t), 63.4 (d), 66.4 (d), 127.1 (d), 128.0 (d), 128.4 (d), 130.8 (d), 136.6 (d), 145.0 (s), 173.6 (s); IR ν_{max} cm^{-1}: 700, 770, 1040, 1060, 1100, 1160, 1180, 1280, 1380, 1460, 1500, 1750, 2860, 2940, 3030; MS m/e 285 (M^+, 2%), 270 (1%), 212 (70%), 185 (45%), 105 (100%), 80 (95%); HRMS calcd. for $C_{18}H_{23}NO_2$: 285.1727. Found: 285.1728.

(6S/R)-1-[(R)-1-Phenylethyl]-6-ethoxycarbonyl-3,4-dimethyl-3,4-didehydropiperidine. Prepared by method B (24h) from 2,3-dimethylbutadiene (69% yield) as a mixture of 6S/R-isomers (ratio 84:16).

(The ^{13}C data in brackets refers to the minor isomer).
R_f (EtOAc/hexane 1:9) 0.43; δ_H(300MHz, $CDCl_3$) 1.25 (1.19) (3H, t, J=7.0Hz), 1.32 (1.26) (3H, d, J=6.8Hz), 1.43 (3H, s), 1.62 (3H, s), 2.29-2.59 (2H, broad m), 2.75-3.17 (2H, broad ABq, J=16.4Hz), 3.94-4.04 (2H, m and q, J=6.8Hz), 4.14 (2H, q, J=7.0Hz), 7.17-7.38 (5H, m); δ_C(75MHz, $CHCl_3$) 14.4 (14.2) (q), 16.3 (16.6) (q), 18.4 (q), 21.0 (22.2) (q), 34.8 (t), 52.2 (50.6) (t), 55.1 (56.2) (d), 59.8 (60.4) (t), 61.8 (61.5) (d), 121.4 (122.1) (s), 124.4 (124.3) (s), 126.7 (d), 127.2 (127.4) (d), 128.3 (128.5) (d), 146.1 (145.0) (s), 173.6 (173.1) (s); IR ν_{max} cm^{-1}: 700, 760, 1040, 1100, 1140, 1180, 1240, 1370, 1450, 1490, 1730, 2910, 2980, 3020, 3060; MS m/e 287 (M^+, 18%), 214 (100%), 182 (18%), 110 (75%), 105 (69%), 77 (10%); HRMS calcd. for $C_{18}H_{25}NO_2$: 287.1899. Found: 287.1899.
The major (6S)-isomer could be isolated by flash chromatography (EtOAc/hexane 1:249), and was converted to its hydrochloride salt: m.p. 162-164°C, $[\alpha]_D^{20}$ -7.5 (c=1.00, MeOH). Crystallisation from EtOAc/hexane yielded crystals suitable for structure determination by X-ray diffraction.

(6S/R)-1-[(R)-1-Phenylethyl]-6-ethoxycarbonyl-4-methyl-3,4-didehydropiperidine. Prepared by method B (30h) from 2-methylbutadiene (44% yield) as a mixture of 6S/R-isomers (ratio 81:19). (The NMR data in brackets refers to the minor isomer).
R_f (EtOAc/hexane 1:9) 0.48; δ_H(300MHz, $CDCl_3$) 1.27 (1.21) (3H, t, J=7.2Hz), 1.34 (1.38) (3H, d, J=6.7Hz), 1.67 (3H, s), 2.29-2.59 (2H, m), 2.91-3.19 (2H, m), 3.96 (1H, q, J=6.7Hz), 4.05 (3.39) (1H, dd, J=6.5 and2.2Hz), 4.17 (2H, q, J=7.2Hz), 5.26 (5.45) (1H, brs), 7.17-7.64 (5H, m); δ_C(75MHz, $CHCl_3$) 14.4 (14.2) (q), 21.1 (q), 22.9 (22.2) (q), 33.6 (t), 47.2 (45.6) (t), 54.7 (55.9) (d), 59.9 (59.7) (t), 61.8 (61.6) (d), 119.8 (d), 126.7 (127.1) (d), 127.2 (127.3) (d), 128.3 (128.5) (d), 129.4 (130.1) (s), 146.0 (145.3) (s), 173.4 (173.1) (s); IR ν_{max} cm^{-1}: 700, 750, 770, 1030, 1050, 1160, 1180, 1370, 1450, 1490, 1730, 2940, 2980, 3040, 3060; MS m/e 273 (M^+, 3%), 200 (100%), 168 (32%), 105 (67%), 96 (67%), 77 (11%); HRMS calcd. for $C_{17}H_{23}NO_2$: 273.1729. Found: 273.1738.
The diastereoisomers could be separated by flash chromatography (EtOAc/hexane 1:249), giving the major (6S)-isomer {$[\alpha]_D^{22}$ +7.5 (c=1.00, CHCl3)} and the minor (6R)-isomer {$[\alpha]_D^{22}$ +65 (c=2.00, CHCl3)}.
Using the (S)-imine in the aza-Diels-Alder reaction generated the antipodal adducts, which were used as a diastereomeric mixture for assessment of optical purity by chiral HPLC (see Figure 2 and note 22).

(2S/R,5R/S,6S/R)-1-[(R)-1-Phenylethyl]-6-ethoxycarbonyl-2,5-dimethyl-3,4-didehydropiperidine. Prepared by method B (36h) from *trans,trans*-hexa-2,4-diene (55% yield) as a mixture of (2S,5R,6S)- and (2R,5S,6R)-isomers (ratio 63:37). (The NMR data in brackets refers to the minor isomer).
R_f (EtOAc/hexane 1:9) 0.55; δ_H(300MHz, $CDCl_3$) 1.08 (0.94) (3H, d, J=7.6Hz), 1.01 (1.14) (3H, d, J=7.0Hz), 1.28 (1.25) (3H, t, J=7.1Hz), 1.45 (1.38) (3H, d, J=6.7Hz), 2.41-2.60 (1H, m), 3.43 (3.79) (1H, m), 3.76 (3.23) (1H, d, J=5.5Hz), 3.95 (4.00) (1H, q, J=7.0Hz), 4.19 (4.20) (2H, m), 5.53-5.69 (2H, m), 7.17-7.40 (5H, m); δ_C(75MHz, $CHCl_3$) 14.3 (q), 17.2 (16.6) (q), 17.4 (17.0) (q), 21.0 (q), 32.0 (31.9) (d), 50.4 (49.5) (d), 57.3 (57.7) (d), 58.7 (59.3) (d), 59.7 (59.5) (t), 126.7 (126.9) (d),

127.2 (127.4) (d). 127.5 (d), 128.2 (128.3) (d), 130.4 (129.8) (d), 145.5 (s), 173.5 (172.8) (s); IR ν_{max} cm^{-1}: 700, 770, 1030, 1150, 1240, 1300, 1320, 1450, 1490, 1730, 2880, 2940, 2980, 3020, 3060; MS m/e 287 (M^+, 8%), 214 (78%), 168 (19%), 110 (78%), 105 (100%), 77 (8%); HRMS calcd. for $C_{18}H_{25}NO_2$: 287.1899. Found: 287.1899.

(2S/R,6S/R)-1-[(R)-1-Phenylethyl]-6-ethoxycarbonyl-2-methyl-3,4-didehydropiperidine. Prepared by method B 36h) from *trans*-penta-1,3-diene (35% yield) as a mixture of (2S,6S)- and (2R,6R)-isomers (ratio 68:32). (The NMR data in brackets refers to the minor isomer).
R_f (EtOAc/hexane 1:9) 0.47; δ_H(300MHz, $CDCl_3$) 0.92 (1.08) (3H, d, J=6.9Hz), (1.30 (1.29) (3H, t, J=7.1Hz), 1.42 (1.38) (3H, d, J=6.6Hz), 2.03-2.58 (2H, m), 3.29-3.38 (3.75-3.85) (1H, m), 3.96 (3.33) (1H, dd, J=6.2 and 1.7Hz), 4.14 (4.07) (2H, q, J=7.1Hz), 5.50-5.78 (2H, m), 7.17-7.43 (5H, m); δ_C(22.5MHz, $CHCl_3$) 14.1 (q), 16.5 (15.9) (q), 21.5 (21.7) (q), 26.7 (26.5) (t), 49.5 (49.3) (d), 52.2 (52.6) (d), 58.8 (59.0) (d), 60.2 (60.0) (t), 121.9 (122.6) (d), 126.6 (126.8) (d), 127.1 (127.5) (d), 128.2 (128.3 (d), 131.2 (130.7) (d), 145.9 (145.7) (s), 175.2 (s); IR ν_{max} cm^{-1}: 700, 770, 1030, 1180, 1370, 1450, 1490, 1730, 2900, 2940, 2980, 3020; MS m/e 273 (M^+, 17%), 258 (53%), 200 (100%), 154 (13%), 105 (100%), 96 (92%); HRMS calcd. for $C_{17}H_{23}NO_2$: 273.1729. Found: 273.1727.

Further transformations of Diels-Alder adducts. (N.B. See note 17 concerning numbering)

Ethyl (2S,4R/S)-1-[(R)-1-phenylethyl]-4-methylpipecolate. (6S)-1-[(R)-1-Phenylethyl]-6-ethoxycarbonyl-4-methyl-3,4-didehydropiperidine (125mg, 0.46 mmol) was dissolved in degassed ethyl acetate (10ml), and 3% platinum on charcoal (31mg) was added. After hydrogenation for 16h at atmospheric pressure, the catalyst was filtered off through a short kieselguhr column, and the solvent was removed *in vacuo*. Flash chromatography (ethyl acetate/hexane 1:99) gave the *cis* (2S,4R) and *trans* (2S,4S) isomers (88:12 ratio), in a combined yield of 78%.
Cis-isomer (2S,4R). R_f (EtOAc/hexane 1:9) 0.43; $[\alpha]_D^{24}$ -17.5 (c=1.00, $CHCl_3$); δ_H(300MHz, $CDCl_3$) 0.89 (3H, d, J=6.0Hz), 1.09 (1H, qd, J=11.9 and 3.8Hz), 1.29 (3H, t, J=7.1Hz), 1.31 (3H, d, J=6.9Hz), 1.34-1.53 (3H, m), 1.85 (1H, m), 2.13 (1H, td, 11.2 and 2.2Hz), 2.48 (1H, dt, J=11.3 and 3.3Hz), 3.36 (1H, dd, J=10.4 and 2.8Hz), 3.94 (1H, q, J=6.9Hz), 4.16-4.26 (2H, qABq, J=7.1 and "J_{AB}"=3.4Hz), 7.18-7.53 (5H, m); δ_C(75MHz, $CHCl_3$) 9.0 (q), 14.3 (q), 21.7 (q), 30.6 (d), 33.7 (t), 38.6 (t), 43.5 (t), 57.7 (d), 60.6 (t), 64.1 (d), 126.5 (d), 127.8 (d), 127.9 (d), 143.4 (s), 174.4 (s); IR ν_{max} cm^{-1}: 700, 740, 780, 1035, 1100, 1130, 1170, 1240, 1260, 1280, 1370, 1450, 1490, 1740, 2880, 2930, 2960, 3030; MS m/e 275 (M^+, 2%), 260 (8%), 202 (73%), 105 (52%), 98 (100%), 77 (10%); HRMS calcd. for $C_{17}H_{25}NO_2$: 275.1916. Found: 275.1916.
Trans-isomer (2S,4S). R_f (EtOAc/hexane 1:9) 0.54; $[\alpha]_D^{24}$ +32.5 (c=1.00, $CHCl_3$); δ_H(300MHz, $CDCl_3$) 0.88 (3H, d, J=5.8Hz), 0.99-1.12 (1H, m), 1.22 (3H, d, J=6.7Hz), 1.29 (3H, t, J=7.1Hz), 1.44-1.55 (3H, m), 2.05 (1H, m), 2.48 (1H, m), 2.83 (1H, td, J=12.0 and 2.7Hz), 3.95 (2H, q and d), 4.14-4.22 (2H, qABq, J=7.1 and "J_{AB}"=3.4Hz), 7.17-7.37 (5H, m); δ_C(22.5MHz, $CHCl_3$) 14.4 (q), 21.9 (q), 22.0 (q), 27.1 (d), 34.2 (t), 36.9 (t), 43.8 (t), 57.0 (d), 59.8 (t), 61.7 (d), 126.6 (d), 127.0 (d), 128.2 (d), 147.2 (s), 174.0 (s); IR ν_{max} cm^{-1}: 700, 750, 770, 900, 1030, 1060, 1090, 1160, 1370, 1450, 1490,

1730, 2850, 2880, 2920, 2960, 3030; MS m/e 275 (M^+, 1%), 260 (1%), 202 (100%), 105 (35%), 98 (63%), 79 (3%); HRMS calcd. for $C_{17}H_{25}NO_2$: 275.1916. Found: 275.1916.

Ethyl (2S,4R)-4-methylpipecolate. Ethyl (2S,4R)-1-[(R)-1-phenylethyl]-4-methylpipecolate (200mg, 0.72 mmol) was dissolved in ethanol (5ml); Pearlman's catalyst (10% palladium hydroxide on charcoal, 22mg) was added, and the mixture was hydrogenated for 8h at atmospheric pressure. The catalyst was filtered off through a short kieselguhr column, the solvent was removed *in vacuo,* and the residue was purified by flash chromatography (ethyl acetate/hexane 3:7) to give the desired product in 72% yield.
$[\alpha]_D^{22}$ -10.5 (c=2.00, EtOH) {Lit. $[\alpha]_D^{22}$ -12.5 (c=5.00, EtOH); δ_H(300MHz, $CDCl_3$) 0.95 (3H, d, J=6.4Hz), 0.99-1.13 (1H, qd, J=12.3 and 3.2Hz), 1.27 (4H, t + m, J=7.1Hz), 1.49-1.60 (2H, m), 2.00 (1H, m), 2.09 (1H, brs), 2.62 (1H, td, J=12.2 and 2.3 Hz), 3.15 (1H, ddd, J=12.2, 3.8 and 1.6Hz), 3.30 (1H, dd, J=11.6 and 2.7Hz), 4.17 (2H, q, J=7.1Hz); δ_C(75MHz, $CHCl_3$) 14.2 (q), 22.4 (q), 31.3 (d), 34.6 (t), 37.9 (t), 45.8 (t), 59.0 (d), 60.7 (t), 173.4 (s); IR ν_{max} cm^{-1}: 750, 1030, 1100, 1130, 1180, 1220, 1270, 1375, 1450, 1730, 2880, 2940, 2960, 3020; MS m/e 171 (M^+, 1%), 98 (100%), 56 (35%), 42 (9%), 41(10%); HRMS calcd. for $C_9H_{17}NO_2$: 171.1263. Found: 171.1267.

Ethyl (2S,4S)-4-methylpipecolate. Ethyl (2S,4S)-1-[(R)-1-phenylethyl]-4-methylpipecolate (100mg, 0.36 mmol) was dissolved in ethanol (5ml); Pearlman's catalyst (10% palladium hydroxide on charcoal, 11mg) was added, and the mixture was hydrogenated for 8h at atmospheric pressure. The catalyst was filtered off through a short kieselguhr column, the solvent was removed *in vacuo,* and the residue was purified by flash chromatography (ethyl acetate/hexane 3:7) to give the desired product in 51% yield.
$[\alpha]_D^{22}$ +22 (c=1.40, EtOH) {Lit. $[\alpha]_D^{22}$ +24.1 (c=5.00, EtOH); δ_H(300MHz, $CDCl_3$) 0.94 (3H, d, J=6.4Hz), 1.02-1.15 (1H, qd, J=12.3 and 3.2Hz), 1.25 (4H, t+m, J=7.1Hz), 1.59-1.65 (2H, m), 2.10 (1H, brs), 2.20 (1H, m), 2.98 (1H, td, J=12.2 and 2.3 Hz), 3.46 (1H, ddd, J=12.2, 3.8 and 1.6Hz), 4.01 (1H, dd, J=11.6 and 2.7Hz), 4.21 (2H, q, J=7.1Hz); δ_C(22.5MHz, $CHCl_3$) 14.3 (q), 22.7 (q), 27.8 (d), 35.1 (t), 36.2 (t), 48.1 (t), 58.3 (d), 59.9 (t), 173.0 (s); IR ν_{max} cm^{-1}: 760, 1025, 1100, 1130, 1150, 1220, 1270, 1385, 1450, 1740, 2880, 2930, 2960, 3020; MS m/e 171 (M^+, 1%), 98 (100%), 56 (35%), 42 (9%), 41(10%); HRMS calcd. for $C_9H_{17}NO_2$: 171.1263. Found: 171.1267.

References

1) For preliminary communication on the achiral aza-Diels-Alder reaction, see P.D. Bailey, R.D. Wilson and G.R. Brown, **Tetrahedron Lett.**, 1989, **30**, 6781.

2) For preliminary communication on the chiral aza-Diels-Alder reaction, see P.D. Bailey, R.D. Wilson and G.R. Brown, **J. Chem. Soc., Perkin Transactins 1**, 1991, 1337.

3) a) C.E. Aiman and A.W. Burgstahler, **J. Org. Chem.**, 1960, **25**, 489; b) G.J. Hanson and M.A. Russell, **Tetrahedron Lett.**, 1989, **30**, 5751; c) V.V.S. Murti, P.S.S. Kumar and T.R. Seshadri, **Tetrahedron Lett.**, 1971, 4451; d) I. Arita, K. Fuji, E. Fujita, T. Fujita, N. Hiratsuka, M. Komatsu, A. Okamura, Y. Takaishi, **J. Chem. Soc., Chem. Commun.**, 1981, 585; e) P. Crooy and R. De Neys, **J. Antibiot.**, 1972, **25**, 371; f) A. Boit, F. Gossele, D.G.I. Kingston, M.B. Purvis

and J.W. Reed, **J. Org. Chem.**, 1989, **54**, 1161; g) S.R. Angle and D.O. Arnaiz, **Tetrahedron Lett.**, 1989, 515 (and references therein).

4) a) C. Angst, P.S. Bernard, L. Blanchard, T. Campbell, R. De Jesus, W. Guida, A.J. Hutchison, R.H. Jackson, D.E. Murphy, M.A. Stills, M. Williams and E. Wilusz, **J. Med. Chem.**, 1989, **32**, 2171; b) M. Laubie, G. Remond and M. Vincent, **Chem. Abstr.**, 1982, **97**, 144792; c) D. Gaitanopoulos and J. Weinstock, **Chem. Abstr.**, 1984, **100**, 22583; d) R. Becker, R. Henning and H. Urbach, **Chem. Abstr.**, 1985, **103**, 6713.

5) a) S. Okamoto, A. Hijikata, R. Kikumoto, S. Tonomura, H. Hara, K. Ninomiya, A. Maruyama, M. Sugano and Y. Tamao, **Biochem. Biophys. Res. Commun.**, 1981, **101**, 440; b) H. Hara, A. Hijikata, R. Kikumoto, K. Ninomiya, S. Okamoto, Y. Tamao, T. Tezuka and S. Tonomura, **Biochemistry**, 1984, **23**, 85.

6) a) E. Brown, P.F. Casals and R. Dahl, **Tetrahedron**, 1972, **28**, 5607; b) R. Frenette and S. Hanessian, **Tetrahedron Lett.**, 1979, 3391; c) M. Natsume and M. Ogawa, **Heterocycles**, 1980, **14**, 169; d) M. Natsume and M. Ogawa, **Heterocycles**, 1980, **14**, 615; e) A.B. Holmes, C. Swithenbank and S.F. Williams, **J. Chem. Soc., Chem. Commun.**, 1986, 265.

7) a) C.O. Gitterman, E.L. Rickes, D.E. Wolf, J. Madas, S.B. Zimmerman, T.H. Stoudt and T.C. Demny, **J. Antibiot.**, 1970, **23**, 305; b) B.H. Arison and J.L. Beck, **Tetrahedron**, 1973, **29**, 2743; c) C. Herdeis and U. Nagel, **Heterocycles**, 1983, **20**, 2163 and ref. 9 therein.

8) A. Demoulin, L. Ghosez, H. Gorissen and A.M. Hesbain-Frisque, **J. Amer. Chem. Soc.**, 1975, **97**, 4409; b) L. Ghosez, A.M. Hesbain-Frisque, F. Sainte and B. Serckx-Poncin, **J. Amer. Chem. Soc.**, 1982, **104**, 1428; c) P. Bayard and L. Ghosez, **Tetrahedron Lett.**, 1988, 6115; d) H.L. Ammon, Y.S. Cheng, E. Ho and P.S. Mariano, **J. Org. Chem.**, 1985, **50**, 5678; e) Y.S. Cheng, E. Ho and P.S. Mariano, **Tetrahedron Lett.**, 1988, 4799.

9) a) L. Ghosez, A.M. Hesbain-Frisque and B. Serckx-Poncin, **Tetrahedron Lett.**, 1982, 3261; b) P. Bayard, C. Bernard-Henriet, A. Demoulin, L. Ghosez, A.M. Hesbain-Frisque, A. Mockel, L. Munoz, M. Rivera, F. Sainte and B. Serckx-Poncin, **Lect. Heterocycl. Chem.**, 1985, **8**, 69.

10) a) K. Fukumoto, M. Ihara, T. Kametani, A. Kawaguchi and T. Kirihara, **Tetrahedron Lett.**, 1984, 4541; b) K. Fukumoto, M. Ihara, T. Kametani and T. Kirihara, **Heterocycles**, 1985, **23**, 1097; c) K. Fukumoto, M. Ihara, T. Kametani and M. Tsuruta, **J. Chem. Soc., Chem. Commun.**, 1985, 1159.

11) a) Y.S. Cheng, F.W. Fowler and A.T. Lupo, **J. Amer. Chem. Soc.**, 1981, **103**, 2090; b) Y.S. Cheng, F.W. Fowler and A.T. Lupo, **J. Amer. Chem. Soc.**, 1983, **105**, 7696; c) Y.C. Hwang and F.W. Fowler, **J. Org. Chem.**, 1985, **50**, 2719; d) F.W. Fowler and M. Teng, **Tetrahedron Lett.**, 1989, 2481; e) F.W. Fowler and M. Teng, **J. Org. Chem.**, 1990, **55**, 5646.

12) a) D.L. Boger and A.M. Kasper, **J. Amer. Chem. Soc.**, 1989, **111**, 1517; b) D.L. Boger, W.L. Corbett and J.M. Wiggins, **J. Org. Chem.**, 1990, **55**, 2999; c) D.L. Boger, W.L. Corbett, T.T. Curran and A.M. Kasper, **J. Amer. Chem. Soc.**, 1991, **113**, 1713; d) D.L. Boger and S. Nakahara, **J. Org. Chem.**, 1991, **56**, 880; e) D.L. Boger, **Bull. Soc. Chim. Belg.**, 1990, **99**, 599.

13) a) P.A. Grieco and S.D. Larsen, **J. Amer. Chem. Soc.**, 1985, **107**, 1768; b) P.A. Grieco and S.D. Larsen, **J. Org. Chem.**, 1986, **51**, 3553; c) W.F. Fobare, P.A. Grieco and S.D. Larsen, **Tetrahedron Lett.**, 1986, 1975; d) A. Bahsas and P.A. Grieco, **J. Org. Chem.**, 1987, **52**, 5746; e) P.A. Grieco and D.T. Parker, **J. Org. Chem.**, 1988, **53**, 3658; f) H. Waldmann, **Angew. Chem. Int. Ed.**, 1988, **27**, 274; g) H. Waldmann, **Liebigs Ann. Chem.**, 1989, 231.

14) S.M. Weinreb, **Acc. Chem. Res.**, 1985, **18**, 16.

15) a) R.P. Loven, W.N. Speckamp and W.A. Zunnebeld, **Tetrahedron**, 1975, 31, 1717; b) A.J.G. Baxter, J. Dixon, A.B. Holmes and J. Thompson, **J. Chem. Soc., Chem. Commun.**, 1985, 37; c) M. Maggini, M. Prato and G. Scorrano, **Tetrahedron Lett.**, 1990, 6243; d) J. Sisko and S.M. Weinreb, **Tetrahedron Lett.**, 1989, 3037.

16) a) R. Breslow and D.C. Rideout, **J. Amer. Chem. Soc.**, 1980, **102**, 7816; b) R. Breslow, U. Maitra and D.C. Rideout, **Tetrahedron Lett.**, 1983, 1901; c) R. Breslow and U. Maitra, **Tetrahedron Lett.**, 1984, 1239.

17) Within the main text, the numbering around the piperidine ring (including for didehydro-derivatives) has been consistently quoted w.r.t. pipecolic acid [i.e. nitrogen (1), α-carbon (2) etc]. The UIPAC nomenclature requires that the didehydro-derivatives are quoted as being unsaturated at the 3,4-positions, meaning that the α-position is now C(6); this latter numbering has only been used in the experimental section.

18) M. Bonin, J.R. Romero, D.S. Grierson and H.-P. Husson, **J. Org. Chem.**, 1984, **49**, 2392.

19) R.F. Childs and M. Pankratz, **J. Org. Chem.**, 1985, **50**, 4553.

20) H.S. Aaron, "Topics in Stereochemistry" (N.L. Allinger and E.L. Eliel, eds.), Vol. 11, Wiley, 1979 (see p.34, and references therein).

21) For example, see S. Masamune, W. Choy, J.S. Peterson and L.R. Sita, **Angew. Chem. Int. Ed. Engl.**, 1985, **24**, 1.

22) The stationary phase for the chiral HPLC was a covalently bound Pirkle column derived from the 3,5-dinitrobenzamide of (R)-phenylglycine (Technicol), and hexane/EtOAc/NEt_3 (99:0.5:0.5) was used as eluant, with product detection by absorption at 254nm. See W.H. Pirkle and M.H. Hyun, **J. Org. Chem.**, 1984, **49**, 3043.

23) The commercial (R)- and (S)-1-phenylethylamines employed (Aldrich) had optical rotations of $[\alpha]^D$ +38 (neat) and $[\alpha]^D$ -39 (neat), respectively. If the (S)-isomer were optically pure, this indicated that the (R)-isomer had an e.e. of about 97.4%. Optically active 1-phenylethylamines are usually obtained by resolution of the racemic amine (e.g. crystallisation of the tartrate: A. Ault, **J. Chem. Ed.**, 1965, **42**, 269), although this rarely yields optically pure products {e.g. the tartrate resolution method (*loc. cit.*) yields products with $[\alpha]^D$ ca. 38 (neat), which corresponds to an e.e. of ca. 95%, by comparison with literature $[\alpha]^D$ ca. 40.5 (neat) (W. Theilaker and H.-G. Winkler, **Chem. Ber.**, 1954, **87**, 691}. Therefore, it seems reasonable to infer that the e.e.s of the aza-Diels-Alder adducts [>97% for the (R)-auxiliary and >99% for the (S)-auxiliary], determined by chiral HPLC, reflect the optical purity of the starting amines, and that the cycloadditions are racemisation-free.

24) For example, see W.A. Szabo and H.T. Lee, **Aldrichimica Acta**, 1980, **13**, 13 and refs. 107-113 therein.

25) B.L. Lences, E. McPherson and H.W. Thompson, **J. Org. Chem.**, 1976, **41**, 2903; b) G. Fels, J.S. Petersen and H. Rapport, **J. Amer. Chem. Soc.**, 1984, **106**, 4539; c) M. Ghiaci and A.M.P. Koskinen, **Tetrahedron Lett.**, 1990, 3209.

26) L. Stella, H. Abraham, J. Feneau-Dupont, B. Tinant and J.P. Declercq, **Tetrahedron Lett.**, 1990, 2603.

27) W.C. Still, M. Kahn and A. Mitra, **J. Org. Chem.**, 1978, **43**, 2923.

28) J.M. Hook, **Synthetic Communications**, 1984, **14**, 83.