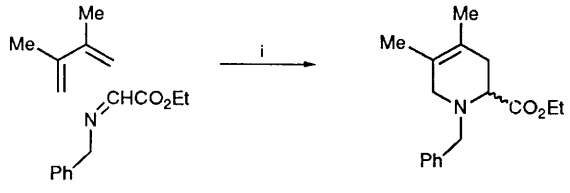
Enantio- and Diastereo-selective Synthesis of Pipecolic Acid Derivatives using the Aza-Diels–Alder Reaction of Imines with Dienes

Patrick D. Bailey,[a] Robert D. Wilson[a] and George R. Brown[b]
[a] *Department of Chemistry, University of York, Heslington, York YO1 5DD, UK*
[b] *ICI Pharmaceuticals, Mereside, Alderley Park, Macclesfield, Cheshire SK10 4TG, UK*

Optically active pipecolic acid derivatives can be prepared by the aza-Diels–Alder reaction of simple dienes with the imine derived from ethyl glyoxylate and chiral 1-phenylethylamine; the cycloadditions are regiospecific, highly diastereoselective within the heterocyclic ring (>92% *exo* with cyclic dienes, and 100% *endo* with acyclic dienes), and lead to high asymmetric induction in most cases (average d.e. = 72%).

The ubiquity of the piperidine ring system in natural products makes short, versatile, stereocontrolled routes to substituted piperidines of great value. One of the most attractive synthetic approaches is to use aza-Diels–Alder chemistry,[1,2] and we recently described the reaction of $PhCH_2N{=}CHCO_2Et$ with a range of dienes;[3] for example, in the presence of TFA (1 equiv.) and H_2O (catalytic), the adduct with 2,3-dimethylbutadiene could be obtained in 94% yield (Scheme 1), and reactions with

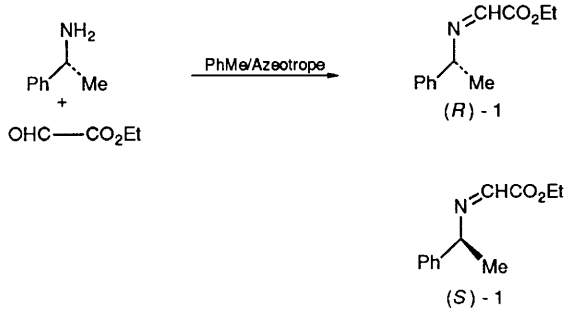


Scheme 1 Reaction between 2,3-dimethylbutadiene and $PhCH_2N{=}CHCO_2Et$. *Reagents and conditions:* i, DMF/TFA (1 equiv.)/H_2O (*ca.* 0.03 equiv.)/room temp./35 h (94% yield).

other dienes enabled us to show that the cycloadditions were regiospecific and highly diastereoselective.[3] To our knowledge, this is the only published example of aza-Diels–Alder chemistry between acyclic dienes and an imine of the type $RN{=}CHCO_2R'$ in which R is not a strong electron withdrawing group (*e.g.* acyl or tosyl) (*cf.* ref. 2).

A simple, yet important, extension of this chemistry was to replace the achiral benzyl group on the imine by a chiral 1-phenylethyl moiety, in order to generate optically active pipecolic acid derivatives. We were hopeful that high asymmetric induction might be observed because the chiral carbon of the auxiliary would be bonded directly to one of the atoms involved in the cycloaddition.

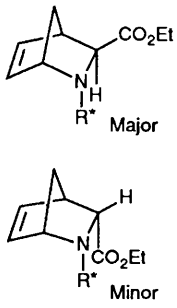
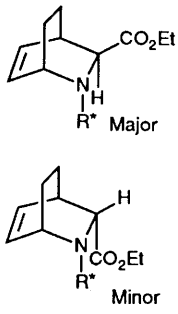
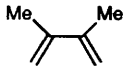
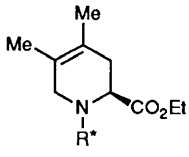
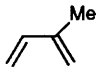
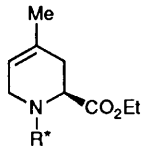
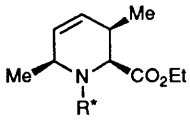
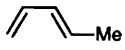
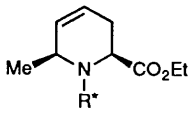
Formation of the chiral imine (*R*)-**1** was readily achieved by condensation of (*R*)-1-phenylethylamine with ethyl glyoxylate[4] (Scheme 2), and the Diels–Alder reactions were conducted using



Scheme 2 Formation of the chiral imine (*R*)-**1**

the standard conditions developed from the achiral work.[3] The cycloadducts were formed as single regioisomers in all cases,

Table 1 The aza-Diels–Alder reactions between the chiral imine (*R*)-**1** and various dienes

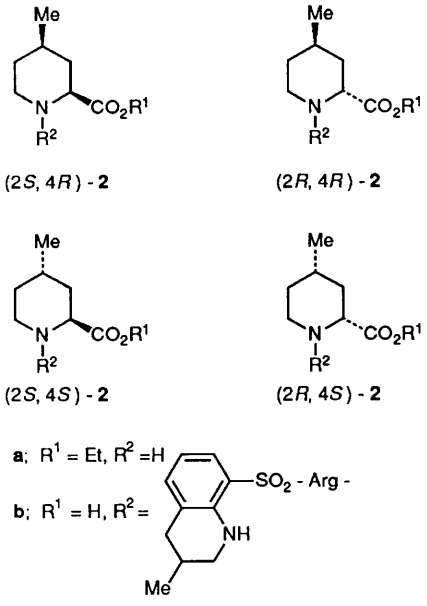
Entry	Diene	Time (h)	Product(s)[a]	D.e.[b] (%)	*endo*:*exo*[c]	Yield (%)
1		24	 Major Minor	89 100	3:97	82
2		60	 Major Minor	84 100	8:92	31
3		24		72	N.a.	69
4		30		70	N.a.	44
5		36		24	100:0	55
6		36		38	100:0	35

* R* = (*R*)-PhCHMe. Conditions: 2 equiv. diene/TFA (1 equiv.)/H_2O (0.03 equiv.)/DMF/room temp. [a] Isolated yields; all the adducts are new compounds, and gave satisfactory IR, ^1H NMR, ^{13}C NMR and high resolution mass spectra; the absolute stereochemistries of the major diastereoisomers are depicted as (2*S*) throughout, and were assigned from literature precedent[5] (entry 1), from X-ray crystal structure determination (entry 3) or by transformation to known compounds (entry 4). [b] The diastereoisomeric excesses (d.e.) are a measure of the asymmetric induction,† and were determined from the ^1H NMR integrations (entries 1, 4, 5 and 6) or by careful quantification of ^{13}C NMR spectra (entries 2 and 3). [c] The *endo*:*exo* ratios were determined by separation and isolation of these diastereoisomers during purification; the *endo* selectivity for entries 5 and 6 was inferred by analogy with the achiral work.[3]

and were isolated in moderate to high yields (average 53%, non-optimised), confirming the ease and efficiency of this procedure.

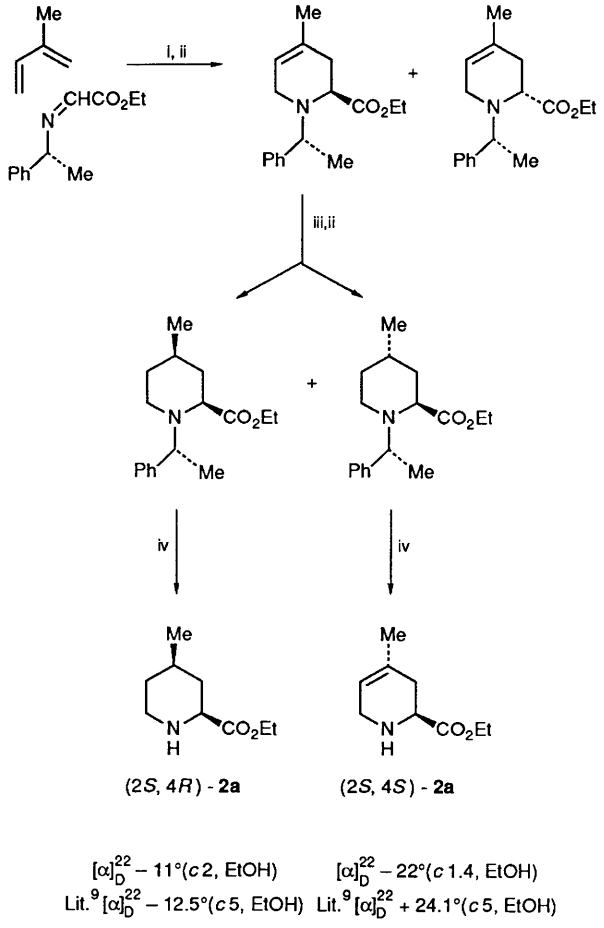
We were delighted to discover that the reactions had proceeded with excellent diastereoselectivity within the hetero-cyclic ring. For cyclic dienes, the *exo* adducts were favoured (92–97% *exo*), whilst acyclic dienes yielded products resulting exclusively from an *endo* transition state. Moreover, the chiral auxiliary had effected high asymmetric induction in most cases,

giving ready access to a range of optically active pipecolic acid derivatives* [average diastereoisomeric excess (d.e.) = 72%]—see Table 1. Particularly noteworthy were the cyclopentadiene adducts, which were obtained in 82% yield; the major *exo* product (preferred over the *endo* isomer by a ratio of 30:1) was formed with a d.e. of 89% (*cf.* ref. 5).



However, it is the adducts from acyclic dienes that are likely to be of more synthetic value; for example, we have been able to show that our methodology can be applied to the synthesis of all 4 stereoisomers of ethyl 4-methylpipecolate **2a**, which are key components for the preparation of the MQPA **2b** thrombin inhibitors.[6] Thus, the Diels–Alder reaction of (*R*)-**1** with 2-methylbutadiene could be conveniently conducted on a multi-gram scale (see Table 1, entry 4), and (in common with all these reactions) the highest R_F components from flash chromatography[7] were the desired adducts. The first eluted compound was the major isomer,* and hydrogenation over a platinum catalyst in ethyl acetate[8] gave the *cis* and *trans* pipecolic acid derivatives in a ratio of 88:12. Removal of the chiral auxiliaries was effected by hydrogenation over Pearlman's catalyst, giving ethyl (2*S*,4*R*)-4-methylpipecolate and the corresponding (2*S*,4*S*)-isomer (see Scheme 3); the absolute stereochemistries were assigned by comparison of their optical rotations with those of the authentic compounds[9] (which were, in turn, assigned from single crystal X-ray structure determinations[9]). The remaining 2 isomers of ethyl 4-methylpipecolate **2a** [(2*R*,4*R*) and (2*R*,4*S*)] are accessible either from the minor Diels–Alder adduct, or by repeating the sequence in Scheme 3 using the (*S*)-**1** for the initial cycloaddition.

The asymmetric induction in the above example corresponds to attack of the diene predominantly on the *Si* face of the (*R*)-imine (*R*)-**1**. Single crystal X-ray structure determination



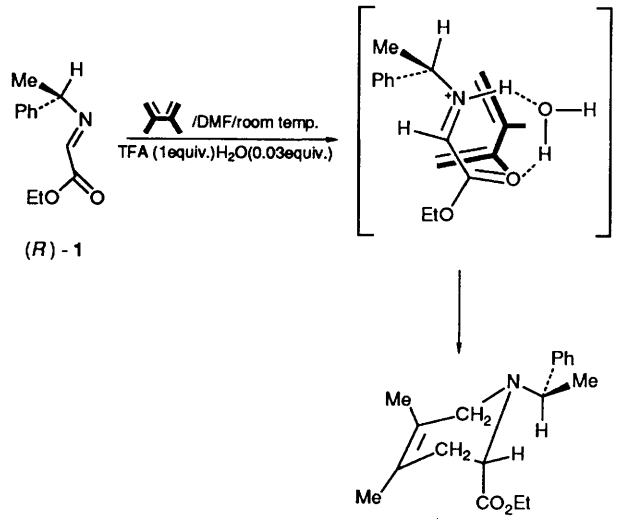
Scheme 3 *Reagents and conditions:* i, TFA (1 equiv.)/H_2O (0.03 equiv.)/DMF/room temp./30 h (44%); ii, flash chromatography;[7] iii, H_2/3% Pt–C/EtOAc/1 atm/room temp./16 h (78%); iv, H_2/$Pd(OH)_2$–C/EtOH/1 atm/room temp. [72% for (2*S*,4*R*)-**2a** and 51% for (2*S*,4*S*)-**2a**].

(to be reported subsequently in full) of the major adduct of (*R*)-**1** with 2,3-dimethylbutadiene (see Table 1, entry 3) similarly revealed that the *R*-auxiliary led to *S*-stereochemistry at the 2-position of the resulting pipecolate; the stereoselectivity for this reaction is depicted in Scheme 4, in which the role of the catalytic water is possibly to minimise rotation[10] of the iminium dienophile *via* 7-membered-ring hydrogen-bonding (5-ring hydrogen-bonding being disfavoured in similar systems[11]). In the only other published example of this type of cycloaddition (although under very different conditions), the *Si* face of the imine derived from methyl glyoxylate and (*R*)-1-phenylethylamine was the preferred directon of approach of cyclopentadiene,[5] suggesting that selection of an *R*- and *S*-auxiliary might, in general, lead to a predominance of *Si* or *Re* face attack respectively.

The cycloadducts from the Diels–Alder reactions contain a number of valuable features for further elaboration. In particular, the carboxylic ester gives access either to pipecolic acid derivatives, or to the enormous range of naturally occurring 2-alkylated piperidines, whilst regio- and stereo-controlled reactions on 4,5-didehydro derivatives of piperidine[12] and pipecolic acid[13] are well documented. Finally, the chiral auxiliary allows continuous monitoring of optical integrity,* but can be readily removed by hydrogenolysis (H_2/$Pd(OH)_2$–C).

In summary, the chiral imine derived from optically active 1-phenylethylamine and ethyl glyoxylate is an effective dienophile in the aza-Diels–Alder reaction; in the presence of TFA (1 equiv.) and water (catalytic), the cycloadducts can be

* The d.e. corresponds to enantiomeric excess (e.e.) after removal of the chiral auxiliary, assuming that no racemisation of the auxiliary occurs during the cycloaddition (*e.g. via* imine tautomerisation) or during its removal. When the 2-methylbutadiene adducts (see Table, entry 4) were analysed by chiral HPLC (Pirkle column), the products were enantiomerically pure within the detection limits (>95% e.e.), indicating that the auxiliary is stereochemically stable under the reaction conditions. Removal of *N*-benzyl type groups using catalytic hydrogenation proceeds without loss of optical integrity in similar systems (*e.g.* see ref. 14).



Scheme 4 Stereochemical outcome of the reaction of chiral imine (*R*)-**1** with 2,3-dimethylbutadiene. The adduct is depicted in the conformation found from the X-ray crystal structure determination.

obtained in a single step in moderate to high yields, with complete control of regiochemistry, and with excellent diastereoselectivity. Moreover, high asymmetric induction is observed in most cases (average 72% d.e.) and, as both enantiomers of 1-phenylethylamine are readily available, the method is applicable to the synthesis of either (*R*)- or (*S*)-pipecolic acid derivatives.

Experimental

Typical Procedure for Aza-Diels–Alder Reactions: Ethyl (2*S*/R)-1-[(*R*)-1-*Phenylethyl*]-4,5-*dimethyl*-1,2,3,6-*tetrahydropyridine*-2-*carboxylate* (*see Table* 1, *entry* 3).—(*R*)-1-Phenylethylamine (10.0 g, 82.6 mmol) and freshly prepared ethyl glyoxylate[4] (8.43 g, 82.6 mmol) were dissolved in dry toluene (30 ml), and the water was removed using a Dean–Stark apparatus by refluxing the mixture for 20 min. Removal of the solvent under reduced pressure gave the chiral imine (*R*)-**2** as an orange oil (16.93 g, 100%), which was fully characterised. A portion of (*R*)-**2** (3.75 g, 18.3 mmol) was dissolved in DMF (12 ml), and TFA (2.1 g, 18.3 mmol), 2,3-dimethylbutadiene (3.0 g, 36.6 mmol) and water (10 μl) were added. The mixture was stirred at room temperature for 24 h under argon, and the solvent was then removed under reduced pressure. A solution of the residue in chloroform (20 ml) was washed with $NaHCO_3$ (aq.) and brine, dried (K_2CO_3) and evaporated under reduced pressure to give a residue which was purified by flash chromatography[7] (hexane–ethyl acetate 98:2) to give the title compound (3.6 g, 69%) as a 84:16 mixture of diastereoisomers. Further flash chromatography (hexane–ethyl acetate 99.6:0.4) allowed isolation of the major (6*S*)-diastereoisomer, which could be recrystallised as its hydrochloride salt from ethyl acetate–hexane to give white crystals suitable for X-ray diffraction; m.p. 162–164 °C; $[\alpha]_D^{20}$ −7.5° (*c* 1.00, MeOH); ν_{max}(thin film)/cm^{-1} 3060, 3020, 2980, 2910 and 1730; δ_H(300 MHz, $CDCl_3$) 1.25 (3 H, t, *J* 7.0), 1.32 (3 H, d, *J* 6.8), 1.43 (3 H, s), 1.62 (3 H, s), 2.29–2.59 (m, 2 H), 2.75–3.17 (2 H, AB system, *J* 16.4), 3.94–4.04 (1 H, m), 3.99 (1 H, q, *J* 7.0) and 7.17–7.38 (5 H, m); δ_C(75.5 MHz) 14.4(q), 16.3(q), 18.4(q), 21.0(q), 34.8(t), 52.2(t), 55.1(d), 59.8(t), 61.8(d), 121.4(s), 124.4(s), 126.7(d), 127.2(d), 128.3(d), 146.1(s) and 173.6(s) (Found: M^+, 287.1860. $C_{18}H_{25}NO_2$ requires 287.1860).

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