N-Alkyl oxazolidines as stereocontrol elements in asymmetric Diels–Alder cycloadditions of 9-substituted anthracene derivatives†

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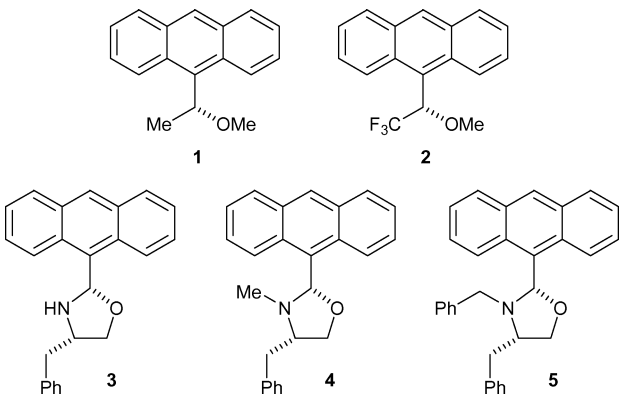
Chiral 9-oxazolidinyl anthracene derivatives have been prepared as single diastereoisomers by condensation of 9-anthraldehyde with the appropriate *N*-alkyl amino alcohol. Asymmetric Diels–Alder cycloadditions of these with *N*-methyl maleimide proceeds in good yield and in good diastereoselectivity, the sense of which may be controlled by judicious choice of the *N*-alkyl group.

Introduction

The use of chiral auxiliaries for achieving stereocontrol has been popularised through the work of groups such as Evans and Oppolzer, and is now widely used in the academic and industrial organic chemistry communities.[1] The plethora of synthetic transformations that may be performed on the auxiliary–substrate adduct is primarily determined by the group that is attached to the auxiliary. Thus, Evans' auxiliary is usually attached to an acid chloride through formation of an acyl bond and the range of synthetic transformations that can be performed may then be considered as being dependant upon formation of this type of bond. Thus, enolate alkylation, aldol addition and conjugate addition can all be performed in excellent diastereoselectivity and good yield.[2] However, addition of Grignard or alkyl lithium reagents can often result in complex mixtures, including addition at the oxazolidinone carbonyl group.[3] If a different attachment strategy could be employed that makes a different type of bond, then other synthetic transformations not normally amenable to regular auxiliaries would become available.

Based on this approach, research by this group and others has described the use of chiral 9-substituted anthracenes such as 9-methoxyethyl anthracene **1** and 9-trifluoromethoxyethyl anthracene **2** as a new class of chiral auxiliary.[4] Here diastereoselective addition of an alkene occurs across the 9 and 10 positions of the anthracene moiety, the selectivity of which is controlled by the stereogenic centre pendant from the anthracene. Cleavage of the auxiliary from the substrate can then be achieved through photolysis and/or flash vacuum pyrolysis. In previous studies we and others had to resort to introduction of the stereogenic centre of the anthracene moiety by asymmetric synthesis. Although this method gave the desired targets in good enantiomeric excess, we were interested in developing methods to install stereogenic elements directly. This should greatly simplify the preparation of a suitable auxiliary, however the stereogenic elements should be able to control the diastereoselectivity of the alkene cycloaddition with comparable levels of diastereoselectivity to those as previously observed. Previous attempts at using the 2-(anthr-9-yl)oxazolinyl anthracene have shown that the stereogenic centre in this species lies too far away from the reactive centre to exert any degree of stereocontrol in the Diels–Alder cycloaddition.[5] Therefore, it was proposed that if another stereogenic centre was installed closer to the anthracene ring, it should enhance the selectivity. Thus, the 2-(anthr-9-yl)oxazolidine derivatives **3**, **4** and **5** were proposed as appropriate candidates for investigating this aspect. Each of these would allow us to probe the role of the nitrogen substituent in this reaction, with oxazolidine **3** having the potential for hydrogen bonding, while the other analogues **4** and **5** have protecting groups with very different steric properties.



There is good precedent for 1,3-oxazolidines controlling stereoselective transformations of adjacent sp^2 hybridised atoms. 1,3-Oxazolidines were first used for stereoselective functionalization of alkenes by Abdallah *et al.* in the palladium-catalysed cyclopropanation of an ephedrine-derived oxazolidine in good yield and excellent diastereoselectivity (>90%).[6] Since then, other stereoselective transformations include conjugate addition of cuprates,[7] dihydroxylation,[8] and intra-molecular bromolactonisation.[9] However, the use of chiral oxazolidines to control the stereochemistry in Diels–Alder cycloadditions is rather limited. While chiral dienophiles bearing oxazolidines have been used as stereocontrol elements in Diels–Alder cycloadditions showing high levels of diastereoselectivity,[10] only a single report of the use of chiral oxazolidinyl dienes has been reported in the synthesis of hydroxylated piperidines, although the stereoselectivity observed was rather modest.[11]

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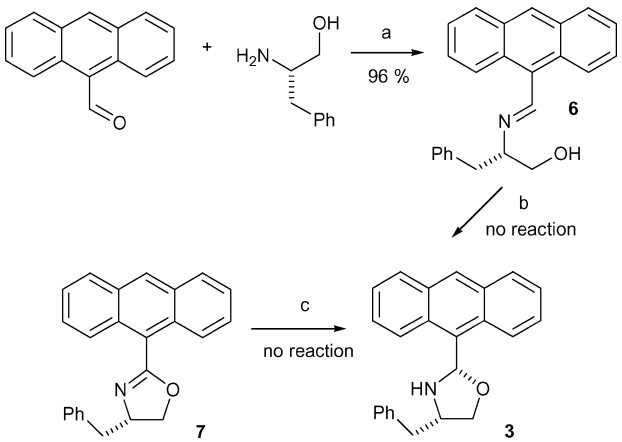
In this work we report the approaches to the synthesis of oxazolidines **3–5** and evaluation in Diels–Alder reactions with *N*-methyl maleimide.

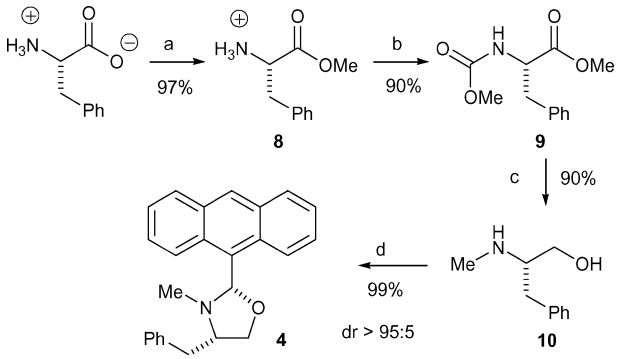
Results

Condensation between anthracene 9-carboxaldehyde and (*S*)-phenylalaninol furnished the 9-anthrylimino alcohol **6** in an excellent yield of 96% (Scheme 1). This imino alcohol did not cyclise to form the desired oxazolidine **3** using a range of acidic catalysts including Amberlyst, $ZnCl_2$, $AlCl_3$, TMSCl and HCl. In all cases, starting material was returned and in some cases 9-anthraldehyde was also observed. This probably results from a series of competing reactions, whereby the rate of cyclisation is slow compared to the rate of hydrolysis and/or iminium ion formation. As an alternative approach, 9-[4-(*S*)-benzyloxazolinyl] anthracene **7**, prepared using a previously reported procedure,[5] was subjected to catalytic hydrogenation to reduce the double bond to obtain the target oxazolidine. However, only starting material was obtained. Attempts to hydrogenate oxazolidine **5** (see later) also proved unsuccessful.



Scheme 1 Attempted preparation of oxazolidine **3**. *Reagents and conditions*: (a) $MgSO_4$, THF, rt, 4 h; (b) see text; (c) H_2, Pd/C, EtOAc or H_2, Pd/C, HOAc, rt, 8–24 h.

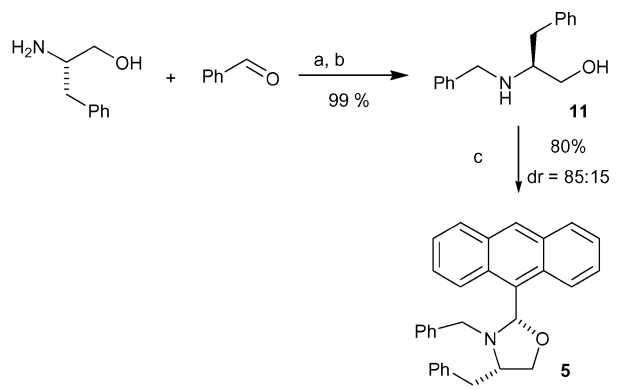
Attention was then turned to the *N*-alkyl oxazolidines and in the first instance the *N*-methyl derivative. It was envisioned that the use of these compounds would lead to the *in situ* formation of an iminium ion, increasing the electrophilicity of the carbon centre, thus facilitating nucleophilic addition of the alcohol. *N*-Methyl-(*S*)-phenylalaninol **10** required for this synthesis was prepared in a three-step synthetic route starting with treatment of (*S*)-phenylalanine with thionyl chloride in dry methanol to form (*S*)-phenylalanine methyl ester hydrochloride **8** in excellent yield (97%). This was reacted with methyl chloroformate forming the *N*-methoxyformyl-(*S*)-phenylalanine methyl ester **9**, which was further reduced to the *N*-methyl-(*S*)-phenylalaninol, both steps proceeding once again in excellent yield (90%). The target oxazoline **4** was then easily prepared *via* a condensation reaction between anthracene 9-carboxaldehyde and *N*-methyl-(*S*)-phenylalaninol giving a single diastereoisomer of the target compound in excellent yield (Scheme 2).



Scheme 2 Preparation of oxazolidine **4**. *Reagents and conditions*: (a) $SOCl_2$, MeOH, rt, overnight; (b) $ClCO_2Me$, $NaHCO_3$, H_2O, 0 °C→rt, overnight; (c) $LiAlH_4$, THF, reflux, overnight; (d) anthracene 9-carboxaldehyde, $MgSO_4$, THF, rt, 6 h.

The relative stereochemistry around C2 of the oxazolidine ring was confirmed by single crystal structure and ^{1}H NMR studies (see below) showing that the ring closure led to the *syn* isomer with the anthryl, benzyl and methyl groups all adopting equatorial positions. This preference is the same as has been previously observed,[8,9] being attributed to the greater thermodynamic stability of the *cis* isomer in such five-membered systems.[12]

The corresponding *N*-benzyl derivative **5** was prepared *via* a similar procedure. Condensation of benzaldehyde with (*S*)-phenylalaninol in dry methanol followed by reduction using sodium borohydride formed the target aminoalcohol **11** in excellent yield (99%). This was then reacted with anthracene 9-carboxaldehyde in dry THF in the presence of $MgSO_4$ as before, however, only 30% conversion was observed after 48 h stirring at rt, probably due to the increased steric hindrance caused by the benzyl group. Thus, this reaction was repeated using a Lewis acid, $Mg(OTf)_2$, in dry CH_2Cl_2, reaching completion within 48 h at rt yielding an 85 : 15 mixture of diastereoisomers that was recrystallised to provide the target oxazolidine **5** in 80% yield as a single diastereoisomer (Scheme 3).

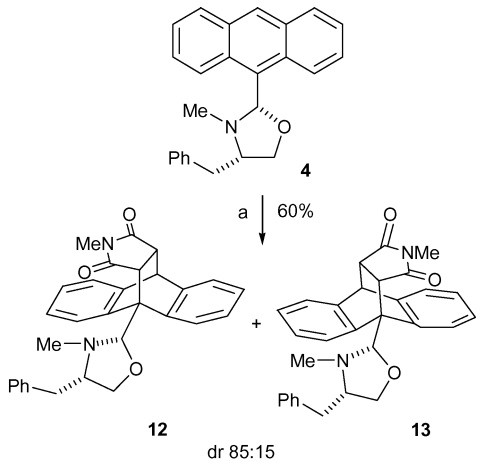


Scheme 3 Preparation of oxazolidine **5**. *Reagents and conditions*: (a) MeOH, rt, 1 h; (b) $NaBH_4$, 0 °C→rt, 2 h; (c) anthracene 9-carboxaldehyde, $Mg(OTf)_2$, CH_2Cl_2, rt, 48 h.

The relative stereochemistry of the major isomer around the C2 of the oxazolidine ring was confirmed by single crystal structure, again revealing that ring closure took place to provide the *syn* isomer as in the case of the formation of *N*-methyloxazolidine **4**. As before, all of the substituents adopt equatorial positions

minimising 1,3-diaxial interactions, however, the *N*-benzyl group now occupied a position over the plane of the anthracene ring probably as a result of π–π interactions. The slightly reduced diastereomeric ratio probably results from increased steric interactions of the close proximity of two benzyl groups and the anthracene ring system.

The *N*-methyl oxazolidine **4** showed slightly reduced reactivity in the Diels–Alder cycloaddition with 1 eq. of *N*-methyl maleimide in toluene at 80–85 °C, giving 60% conversion after 2 h, compared to 9-methoxyethyl anthracene **1**, which gave 100% conversion under the same conditions. The cycloaddition gave a mixture of two diastereoisomers in a ratio of 85 : 15, the ratio of which did not vary with either time or temperature (Scheme 4).



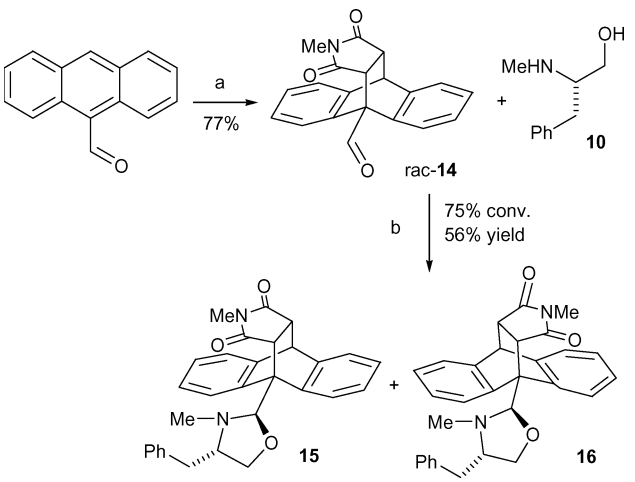
Scheme 4 Diels–Alder addition of *N*-methyl oxazolidine **4**. *Reagents and conditions*: (a) 1.0 eq., *N*-methyl maleimide, toluene, 80–85 °C.

Although the conversion to product could be improved by heating at 90–95 °C for 4 h (89%) with no change in diastereoselectivity, no improvement in yield or selectivity was obtained at room temperature with or without Lewis acid-catalysis using $Cu(OTf)_2$–BEN (*N*,*N*-dibenzylidene ethylene diamine).

The major diastereoisomer **12** was isolated by diffusion recrystallisation from CH_2Cl_2–petroleum ether 40–60 °C and its structure was determined by single crystal X-ray diffraction and ^{1}H NMR studies (see later). As in the case of the parent oxazolidine **4**, all ring substituents occupied equatorial positions. After recrystallisation, the mother liquor was found to be enriched with the minor isomer **13** and was thus stirred with an excess of *N*-methyl maleimide in toluene for 2 h at 80–85 °C showing no change in the diastereomeric ratio demonstrating that the Diels–Alder reaction between the *N*-methyl oxazolidine **4** and *N*-methyl maleimide was irreversible and thus kinetically controlled.

The preferred conformation of the oxazolidine **4** would most likely be such that the aminal hydrogen atom lies parallel to the anthracene ring system, thus avoiding *peri*-interactions of the nitrogen and oxygen substituents of the oxazolidine with the anthracene ring (Fig. 1). Approach of the dienophile to either face occurs such as to minimise electrostatic repulsion between the carbonyl of the *N*-methyl maleimide and either nitrogen or oxygen atom in an analogous fashion to the model already generally accepted for this type of cycloaddition.[4c,e,i] Approach A is then favoured since the other face experiences greater steric repulsion from the large *N*-methyl group compared to the electrostatic repulsion from the oxygen atom (Fig. 1).

In order to elucidate the structure of diastereisomer **13**, attempts were made to prepare both cycloadducts **12** and **13** *via* another synthetic route. The product of the Diels–Alder reaction between anthracene 9-carboxaldehyde and *N*-methyl maleimide *rac*-**14** was condensed with *N*-methyl-(*S*)-phenylalaninol **10** in the presence of $MgSO_4$ leading to the formation of a mixture of oxazolidines (Scheme 5). However, the ^{1}H NMR spectrum of the crude product revealed the formation of two diastereoisomers **15** and **16** in a 60 : 40 ratio, which were not the same as those observed when the *N*-methyl oxazolidine **4** was reacted with *N*-methyl maleimide in toluene, implying the formation of a product with different stereochemistry around C2 of the oxazolidine ring. The sensitivity



Scheme 5 Preparation of diastereoisomers **15** and **16**. *Reagents and conditions*: (a) *N*-Methyl maleimide, toluene, 80–85 °C, 24 h; (b) $MgSO_4$, THF, rt, 19 h.

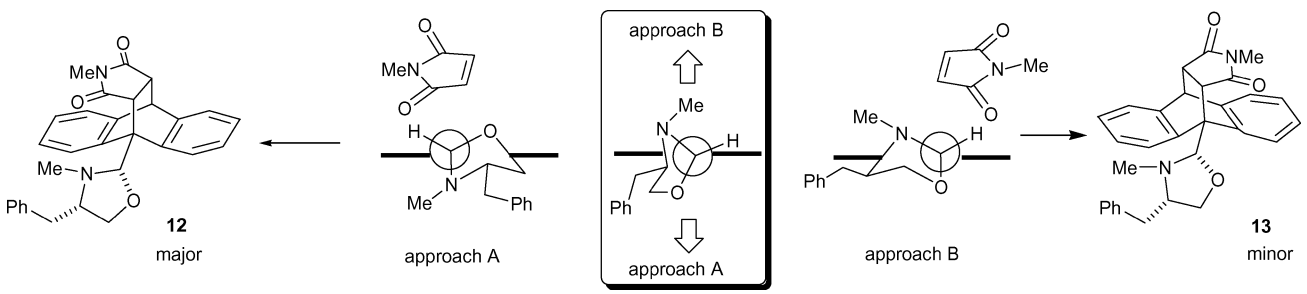


Fig. 1 Rationale for the selectivity observed in the Diels–Alder cycloaddition of *N*-methyl oxazolidine **4** with *N*-methyl maleimide.

Table 1 Interconversion of diastereoisomers **15** and **16** to diastereoisomers **12** and **13**

		Ratio (%)[a]			
Entry	Time (day)	**12**	**13**	**15**	**16**
1	0	0	0	60	40
2	7	16	16	49	19
3	9	16	22	46	16
4	13	29	32	28	10
5	15	37	35	21	7
6	21	45	37	13	5
7	24	48	38	9	4
8	33	53	38	7	2

[a] Ratio was calculated from the integrals of appropriate signals in the ^{1}H NMR spectrum.

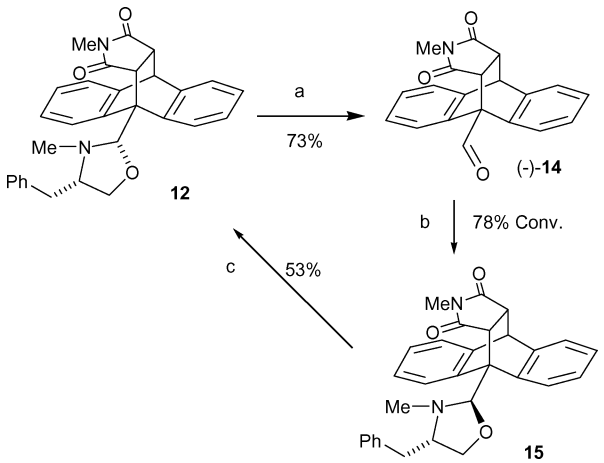
of the crude product to silica gel chromatography prevented the isolation of these diastereoisomers as it decomposed to form the starting aldehyde *rac*-**14**. Deactivating the silica gel using triethylamine also led to decomposition. However, attempted separation of these isomers by recrystallisation from CH_2Cl_2–petroleum ether 40–60 °C at rt gave the thermodynamically favoured diastereoisomer **12**.

This interconversion was studied further using *in situ* NMR studies. The mixture of diastereoisomers **15** and **16** from the reaction between *rac*-**14** and *N*-methyl-(*S*)-phenylalaninol were left in a $CDCl_3$ solution and analysed over a period of time (Table 1). Isomers **15** and **16** slowly reverted to a 1 : 1 mixture of isomers **12** and **13**, supporting the thought that the outcome of the reaction between the adduct *rac*-**14** and *N*-methyl-(*S*)-phenylalaninol **10** was kinetically controlled, forming the *trans* oxazolidine adducts **15** and **16**, which slowly interconverted to the thermodynamically more stable *cis* cycloadducts **12** and **13** over a prolonged period of time.

Since the poor selectivity observed in this reaction is likely to be a consequence of the *N*-methyl phenylalaninol **10** effectively acting as a resolving agent, a single diastereoisomer of product would probably be obtained if enantiomerically pure aldehyde **14** was used. Therefore, pure diastereoisomer **12** was stirred for 18 h with silica gel in CH_2Cl_2–H_2O (9 : 1; v/v). This produced the enantiomerically pure aldehyde adduct (−)-**14** in 73% yield that was involved in a condensation reaction with *N*-methyl-(*S*)-phenylalaninol **10** in dry THF in the presence of $MgSO_4$ giving 78% conversion to the corresponding oxazolidine adduct **15** (Scheme 6).

The ^{1}H NMR spectrum of the crude material revealed that a single diastereoisomer was formed which was the same as the major isomer formed when the *rac*-**14** was reacted with *N*-methyl-(*S*)-phenylalaninol **10**. This diastereoisomer **15** interconverted to isomer **12** after 14 days standing in $CDCl_3$ and diffusion recrystallisation from CH_2Cl_2–petroleum ether 40–60 °C gave a 53% yield of this isomer.

Further confirmation of the *cis* configuration of the oxazolidine ring came from comparison of the observed and calcuated dihedral angles with the predicted magnitude of the coupling constants. Thus, when both aldehydes *rac*-**14** and (−)-**14** were condensed with *N*-methyl-(*S*)-phenylalaninol **10**, the ^{1}H NMR spectrum of the crude diastereoisomers in both cases revealed the appearance of the two protons H^{5a} and H^{5b} (Fig. 2), as two double doublet



Scheme 6 Formation of aldehyde (−)-**14** and condensation with *N*-methyl phenylalaninol. *Reagents and conditions*: (a) SiO_2, CH_2Cl_2–H_2O (9 : 1; v/v), rt, 18 h; (b) *N*-methyl-(*S*)-phenylalaninol **10**, $MgSO_4$, THF, rt, 19 h; (c) 12 days, $CDCl_3$.

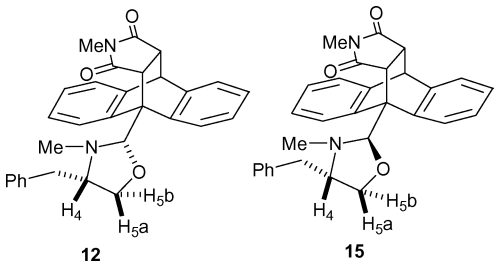


Fig. 2 Structures depicting *N*-methyl oxazolidine NMR spin system.

signals with large and small coupling constants. However, in the case of the major isomer **12**, the protons H^{5a} and H^{5b} were seen in the ^{1}H NMR spectrum as two apparent triplets or double doublets with large coupling constants. A molecular modelling study was carried out on the adducts **12** and **15** to measure the dihedral angles between hydrogen atoms (H^4 and H^{5a}; H^{5b} in both systems) (Fig. 2, Table 2).[13]

The molecular modelling on adduct **15** revealed that the dihedral angle between H^4 and H^{5b} was 117.2°, whereas between H^4 and H^{5a} was 7.3°. According to the Karplus correlation, the corresponding coupling constants for such angles should be small and big respectively (Table 2). This is in fact what was observed in the ^{1}H NMR spectrum of the crude material. Likewise, according to the data obtained from the single crystal structure of the major isomer **12**, the dihedral angle between H^4 and H^{5b} was found to be 142.3°, whereas between H^4 and H^{5a} was 21.8°. These values

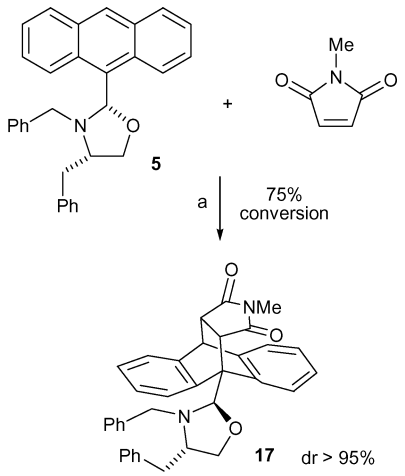
Table 2 Observed and calculated bond angles and coupling constants for diastereoisomers **12** and **15**

Isomer	HC–CH_2	θ_{calc}/°[a]	θ_{obs}/°[b]	J_{pred}/Hz[c]	J_{obs}/Hz[d]
12	H^4–H^{5a}	11.9	21.8	7–9	7.8
	H^4–H^{5b}	135.9	142.3	4–6	7.8
15	H^4–H^{5a}	7.3	—	8–9	13.4
	H^4–H^{5b}	117.2	—	1–2	1.2

[a] Calculated using molecular modelling. [b] Measured from crystal structure. [c] Predicted range from the Karplus correlation. [d] Observed values from the ^{1}H NMR spectra.

correlated well with the calculated ones and correspond to large coupling constants according to the Karplus prediction.

Likewise, the *N*-benzyl oxazolidine **5** was involved in a thermal Diels–Alder reaction with *N*-methyl maleimide in toluene, showing slightly increased reactivity towards the Diels–Alder cycloaddition with *N*-methyl maleimide (81% conversion) after 2 h stirring at 80–85 °C, when compared to the reactivity of the *N*-methyl counterpart **4** (60% conversion) under the same conditions. However, this time formation of a single diastereoisomer **17** was observed with the opposite sense of stereoselection as the *N*-methyl counterpart, as confirmed by single crystal X-ray analysis (Scheme 7).



Scheme 7 Diels–Alder cycloaddition of *N*-benzyl oxazolidine **5** with *N*-methyl maleimide. *Reagents and conditions*: (a) toluene, 90–95 °C, 4 h.

Both the anthryl moiety and *N*-benzyl group adopted equatorial conformations to the oxazolidine ring, while the other benzyl group was enforced to orientate axially to the oxazolidine ring. Most importantly, the stereochemistry around C2 changed from *S* to *R* configuration, which was rather unusual in such ring systems as the *cis* configuration is usually more thermodynamically stable. Additionally, the coupling constants for the oxazolidine ring system followed that of the minor isomer formed in the cycloadditions of *N*-methyl oxazolidine **4** (Fig. 3, Table 3).

The stereoselectivity of this reaction was believed to follow the same model as for the *N*-methyl oxazolidine (Fig. 4), but since the *N*-benzyl group is much larger it effectively shuts off cycloaddition *via* approach B, exposing only one face to react, the stereochemistry of which was once again determined using an electrostatic repulsion model. However, a consequence of this mode of approach is that the pseudo axial *N*-benzyl group now suffers severe steric interaction with the deforming anthracene

Table 3 Observed and calculated bond angles and coupling constants for diastereoisomer **17**

Isomer	HC–CH_2	θ_{calc}/°[a]	θ_{obs}/°[b]	J_{pred}/Hz[c]	J_{obs}/Hz[d]
17	H^4–H^{5a}	10.0	22.5	7–9	6.4
	H^4–H^{5b}	114.2	98.2	0–2	4.2

[a] Calculated using molecular modelling. [b] Measured from crystal structure. [c] Predicted range from the Karplus correlation. [d] Observed values from the ^{1}H NMR spectra.

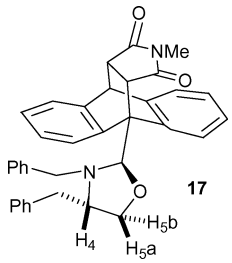


Fig. 3 Structure depicting *N*-benzyl oxazolidine NMR spin system.

ring. This effect is relayed to the benzyl stereodirecting group through 1,2-tortional interactions, ultimately leading to a high energy transition state. Unable to react *via* this mode of approach, the oxazolidine ring undergoes a ring opening–closure process to generate the much less stable *trans*-oxazolidine. This once again has one face of the anthracene blocked by the *N*-benzyl group and incurs interaction of this group with the deforming anthracene ring, but now does not suffer the same 1,2 tortional interactions since the benzyl stereodirecting group is axial. Cycloaddition followed by epimerisation of the oxazolidine ring cannot occur since this would lead to the opposite sense of stereochemistry of the cycloaddition reaction.

Unfortunately it was not possible to access the stereoisomers of this reaction by condensation of anthracene 9-carboxaldehyde cycloadduct *rac*-**14** and *N*-benzyl-(*S*)-phenylalaninol **11** in the presence of $Mg(OTf)_2$, presumably due to the steric effects due to the bulky amino alcohol being used.

Conclusion

We have demonstrated that chiral oxazolidines may be quickly and selectively prepared from readily available *N*-alkyl amino alcohols and that this class of compound undergoes highly stereoselective cycloadditions. The sense of diastereoselection of this reaction depends critically upon the *N*-alkyl group employed. Although the level of diastereocontrol is excellent and shows that oxazolidines may be used effectively to control the outcome of Diels–Alder cycloadditions, their use in our auxiliary chemistry is limited, since they appear to easily decompose to afford the corresponding aldehydes.

Experimental

All solvents used were freshly dried over sodium except CH_2Cl_2 which was dried over $LiAlH_4$. Et_3N was distilled over KOH. Glassware was flame dried and cooled *in vacuo* before use and all reactions were carried out under nitrogen unless otherwise stated. TLC was carried out using Merk aluminium TLC sheets (silica gel 60 F_{254}). Visualisation of the TLC plates was carried out using a UV lamp or by dipping in $KMnO_4$ then exposure by heating. Flash column chromatography was carried out with Fluorochem Limited Silica Gel 40–63u 60A.

Melting points were measured on a Gallenkamp apparatus and are uncorrected. Specific rotations were performed on an Optical Activity LTD. AA-10 automatic polarimeter at 589 nm (Na D-line) and measured at 20 °C unless otherwise stated. $[\alpha]_D$ values are given in 10^{-1} deg cm^2 g^{-1}. All infrared spectra were recorded on a Perkin Elmer Spectrum RX/FT-IR system with a DuraSampl*IR* II ATR

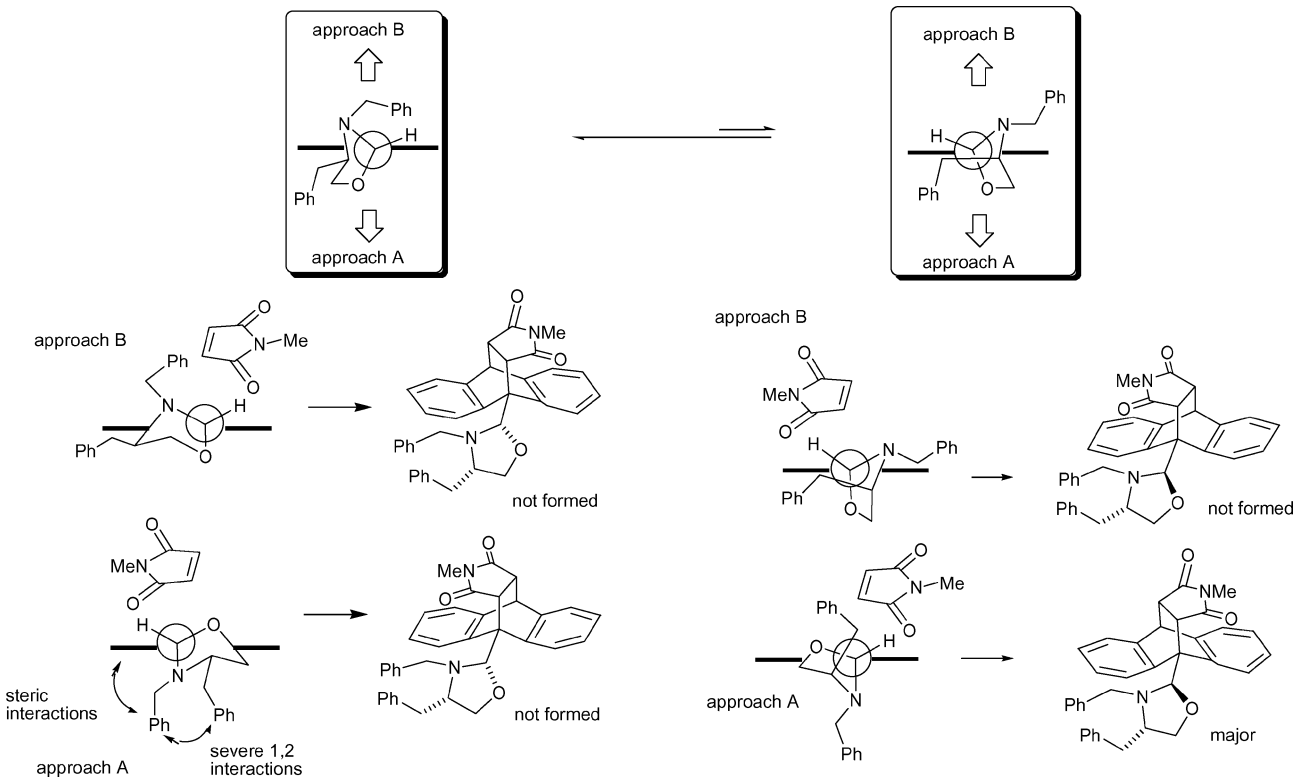


Fig. 4 Model for the diastereoselectivity of oxazolidine **5**.

accessory. 250 MHz ^{1}H NMR and 62.5 MHz ^{13}C NMR were carried out on an AC-250 supported by an Aspect 200 data system. Residual proton signals from the deuteriated solvents were used as references [chloroform (^{1}H 7.25 ppm, ^{13}C 77 ppm)]. Coupling constants were measured in Hz. Mass spectra were recorded on a Micromass Autospec M spectrometer. Elemental microanalysis was performed using a Perkin Elmer 2400 CHNS/0 Series II elemental analyzer.

Data collected were measured on a Bruker Smart CCD area detector with Oxford Cryosystems low temperature system. Single crystals of compounds **4**, **5**, **12** and **17** were grown as described, mounted in inert oil and transferred to the cold gas stream of the diffractometer. In all cases, the relative stereochemistry of the compounds was recorded and cross referenced to the known stereogenic centre.

[*N*-(9-Anthracenylmethylene)-(*S*)-phenylalaninol 6

A solution of anthracene-9-carboxaldehyde (0.567 g, 2.75 mmol) in dry THF (20 cm^3) was added dropwise at room temperature to a stirred mixture of (*S*)-phenylalaninol[14] (0.415 g, 2.75 mmol) and $MgSO_4$ (0.5 g, 4.86 mmol) in dry THF (10 cm^3). The resulting mixture was stirred for 4 h at room temperature, filtered through Celite and the solvent was removed to obtain a yellow solid of the title compound **6** (0.896 g, 96%). A sample of the hydroxyl imine was recrystallised from EtOAc for analytical purposes. Mp 178–180 °C (from EtOAc); (found: C, 84.7; H, 6.2; N, 4.01. $C_{24}H_{21}NO$ requires C, 84.9; H, 6.2; N, 4.1%); $[\alpha]_D^{25}$ −70.0 (*c* 0.5 in $CHCl_3$); ν_{max}/cm^{-1} 1642 (C=N); δ_H(250 MHz; $CDCl_3$; Me_4Si) 2.14 (1H, br s, O*H*), 3.05 (1H, dd, *J* 13.6 and 9.3, C*H*HPh), 3.18 (1H, dd, *J* 13.6 and 4.3, C*H*HPh), 3.46–3.97 (1H, m, C*H*N), 4.02 (2H, br s, CH_2OH), 7.28–7.47 (9H, m, ArC*H*), 7.89–8.00 (4H, m, ArC*H*), 8.43 (1H, s, ArC*H*), 9.03 (1H, s, N=C*H*); δ_C(62.5 MHz; $CDCl_3$; Me_4Si) 38.8 (*C*H$_2$), 66.4 (*C*H$_2$O), 76.0 (*C*H), 124.9 (*C*H), 125.2 (*C*H), 126.4 (*C*H), 126.5 (*C*H), 128.6 (*C*), 128.7 (*C*H), 128.8 (*C*H), 129.1 (*C*H), 129.8 (*C*H), 131.2 (*C*), 138.7 (*C*), 162.2 (*C*); *m*/*z* (EI) 339.1620 (M$^+$. $C_{24}H_{21}NO$ requires 339.1623), 248 (100%), 191 (17), 178 (18), 91 (74), 77 (12).

(2*S*,4*S*)-2-(9-Anthracenyl)-3-methyl-4-benzyl oxazolidine 4

A solution of (*S*)-*N*-methylphenylalaninol **10**[15] (0.627 g, 3.8 mmol) in dry THF (30 cm^3) was added dropwise at room temperature to a stirred mixture of anthracene-9-carboxaldehyde (0.782 g, 3.8 mmol) and $MgSO_4$ (0.5 g, 4.86 mmol) in dry THF (20 cm^3). The resulting mixture was stirred for a further 6 h at rt, filtered through Celite and the solvent was removed to give a yellow solid of the target oxazolidine **4** (1.325 g, 99%). A sample was recrystallised from toluene for analytical purposes. Mp 204–209 °C (from toluene); (found: C, 84.9; H, 6.45; N, 3.85. $C_{25}H_{23}NO$ requires C, 84.95; H, 6.6; N, 4.0%); $[\alpha]_D^{26}$ +18.0 (*c* 0.5 in $CHCl_3$); ν_{max}/cm^{-1} 1624 (C=C); δ_H(250 MHz; $CDCl_3$; Me_4Si) 2.23 (3H, s, CH_3), 2.98–3.26 (3H, m, PhCH_2 and C*H*N), 4.15–4.26 (2H, m, CH_2O), 6.24 (1H, s, NC*H*O), 7.30–7.49 (9H, m, ArC*H*), 7.99–8.03 (2H, m, ArC*H*), 8.49 (1H, s, ArC*H*), 8.75–8.79 (2H, m, ArC*H*); δ_C(62.5 MHz; $CDCl_3$; Me_4Si) 36.1 (*C*H$_3$), 37.9 (*C*H$_2$), 66.6 (*C*H), 70.9 (*C*H$_2$), 94.7 (*C*H), 124.8 (*C*H), 124.9 (*C*H), 125.6 (*C*H), 126.7 (*C*H), 126.9 (*C*), 128.6 (*C*H), 129.1 (*C*H), 129.5 (*C*H), 129.8 (*C*H), 131.5 (*C*), 138.1 (*C*); *m*/*z* (EI) 354.1851 (M$^+$. $C_{25}H_{23}NO$ requires 354.1858), 353 (10%), 262 (100), 232 (25), 178 (35), 91 (30).

Crystal structure determination of compound 4‡

Crystal data. $C_{25}H_{23}NO$, $M = 353.44$, monoclinic, $a = 18.188(3)$, $b = 7.0490(10)$, $c = 17.257(2)$ Å, $U = 1891.7(5)$ Å^3, $T = 150(2)$ K, space group $C2$, $Z = 4$, μ(Mo–Kα) = 0.075 mm^{-1}, 10741 reflections measured, 2328 unique ($R_{int} = 0.0406$) which were used in all calculations. The final $wR(F_2)$ was 0.0943 (all data).

(2*S*,4*S*)-2-(9-Anthracenyl)-3,4-dibenzyl oxazolidine 5

A solution of *N*-benzylphenylalaninol **11**[16] (0.76 g, 3.15 mmol) in dry CH_2Cl_2 (10 cm^3) was added dropwise at room temperature to a stirred mixture of anthracene-9-carboxaldehyde (0.5 g, 2.43 mmol) and $Mg(OTf)_2$ (0.08 g, 0.248 mmol) in dry CH_2Cl_2 (10 cm^3). The resulting mixture was stirred for 48 h at room temperature, filtered through Celite and the solvent was removed to give a yellow solid as a mixture of diastereoisomers (85 : 15) which was recrystallised from CH_2Cl_2–petroleum ether 40–60 °C to provide a single isomer of the desired oxazolidine **5** (0.91 g, 85%). Mp 101–103 °C (from CH_2Cl_2–petroleum ether 40–60 °C); (found: C, 86.8; H, 6.6; N, 3.2. $C_{31}H_{27}NO$ requires C, 86.7; H, 6.3; N, 3.3%); $[\alpha]_D^{25}$ −22.0 (*c* 1 in $CHCl_3$); ν_{max}/cm^{-1} 1491 and 1452 (C=C); δ_H(250 MHz; $CDCl_3$; Me_4Si) 2.79 (1H, dd, *J* 13.4 and 9.5, C*H*HPh), 2.89 (1H, dd, *J* 13.4 and 4.3, C*H*HPh), 3.36–3.50 (1H, m, C*H*N), 3.62 (1H, d, *J* 13.7, C*H*HPh), 3.75 (1H, d, *J* 13.7, C*H*HPh), 4.15 (1H, app t, *J* 7.7, C*H*HO), 4.22 (1H, app t, *J* 7.7, C*H*HO), 6.48 (1H, s, NC*H*O), 6.86–6.99 (4H, m, ArC*H*), 7.12–7.76 (10H, m, ArC*H*), 7.97 (2H, d, *J* 7.9, ArC*H*), 8.42 (1H, s, ArC*H*), 8.91 (2H, d, *J* 8.2, ArC*H*); δ_C(62.5 MHz; $CDCl_3$; Me_4Si) 40.2 (*C*H$_2$), 55.1 (*C*H$_2$), 65.6 (*C*H), 71.5 (*C*H$_2$), 93.5 (*C*H), 124.7 (*C*H), 124.8 (*C*H), 125.1 (*C*H), 125.3 (*C*H), 125.5 (*C*H), 125.8 (*C*H), 126.4 (*C*H), 126.7 (*C*H), 127.6 (*C*H), 128.0 (*C*H), 128.6 (*C*H), 128.7 (*C*H), 129.0 (*C*H), 129.1 (*C*H), 129.3 (*C*H), 129.9 (*C*H), 131.5 (*C*), 131.6 (*C*), 138.2 (*C*), 138.7 (*C*); *m*/*z* (EI) 429.2091 (M$^+$. $C_{31}H_{27}NO$ requires 429.2093), 429 (9%), 338 (93), 269 (6), 252 (7), 206 (8), 178 (28), 157 (8), 91 (100).

Selected ^{1}H NMR signals for the minor diastereoisomer. δ_H(250 MHz; $CDCl_3$; Me_4Si) 3.14 (1H, dd, *J* 12.2 and 4, C*H*HPh), 3.92 (1H, dd, *J* 8.5 and 3.6, C*H*HO), 4.40 (1H, dd, *J* 8.5 and 6.4, C*H*HO), 6.87 (1H, s, NC*H*O), 8.50 (1H, s, ArC*H*).

Crystal structure determination of compound 5‡

Crystal data. $C_{31}H_{27}NO$, $M = 429.54$, triclinic, $a = 7.284(3)$, $b = 9.462(3)$, $c = 18.426(6)$ Å, $U = 1144.2(7)$ Å^3, $T = 293(2)$ K, space group $P1$, $Z = 2$, μ(Mo–Kα) = 0.074 mm^{-1}, 12849 reflections measured, 5114 unique ($R_{int} = 0.0593$) which were used in all calculations. The final $wR(F_2)$ was 0.1422 (all data).

(3a*R*,9a*R*)-3a,4,9,9a-Tetrahydro-4-[(2*S*,4*S*)-5-benzyl-3-methyl-2-oxazolidinyl]-2-methyl-4,9[1′,2′]-benzeno-1*H*-benz[*f*]isoindole-1,3(2*H*)-dione 12

N-Methyl maleimide (0.083 g, 0.75 mmol) was added in one portion as a solid at 90–95 °C to a stirred solution of oxazolidine **4** (0.177 g, 0.5 mmol) in toluene (3 cm^3). The resulting mixture was left stirring for a further 4 h at 90–95 °C, cooled to room temperature and the solvent was removed under reduced pressure to give the target compound as two diastereoisomers in a ratio of (85 : 15) (0.246 g, 89% conversion). A sample was recrystallised from CH_2Cl_2–petroleum ether 40–60 °C (diffusion recrystallisation) to afford a white solid of the major diastereoisomer **12**. Mp 215–217 °C (from CH_2Cl_2–petroleum ether 40–60 °C); $[\alpha]_D^{25}$ +25.0 (*c* 1 in $CHCl_3$); ν_{max}/cm^{-1} 1692 (C=O); δ_H(250 MHz; $CDCl_3$; Me_4Si) 2.41 (3H, s, C*H*$_3$), 2.54 (3H, s, C*H*$_3$), 2.93 (1H, dd, *J* 13.5 and 8.2, C*H*HPh), 3.05 (1H, dd, *J* 8.4 and 3.3, C*H*HPh), 3.15–3.33 (2H, m, PhCHC(O)C*H* and C*H*N), 3.72 (1H, d, *J* 8.4, C(O)C*H*), 3.92 (1H, app t, *J* 7.8, C*H*HO), 4.15 (1H, app t, *J* 7.8, C*H*HO), 4.69 (1H, d, *J* 3.3, PhC*H*CH), 5.84 (1H, s, NC*H*O), 7.03–7.39 (11H, m, ArC*H*), 7.53–7.60 (1H, m, ArC*H*), 8.61 (1H, d, *J* 7.9, ArC*H*); δ_C(62.5 MHz; $CDCl_3$; Me_4Si) 24.1 (*C*H$_3$), 37.4 (*C*H$_2$), 37.6 (*C*H$_3$), 46.8 (*C*H), 48.0 (*C*H), 49.2 (*C*H), 49.8 (*C*), 66.4 (*C*H), 69.3 (*C*H$_2$), 94.0 (*C*H), 123.4 (*C*H), 124.1 (*C*H), 125.1 (*C*H), 125.9 (*C*H), 126.1 (*C*H), 126.3 (*C*H), 126.6 (*C*H), 126.8 (*C*H), 128.1 (*C*H), 128.5 (*C*H), 128.7 (*C*), 129.4 (*C*H), 137.8 (*C*), 138.4 (*C*), 138.9 (*C*), 141.9 (*C*), 175.8 (*C*), 176.7 (*C*); *m*/*z* (ES) 465.2168 (MH$^+$. $C_{30}H_{29}N_2O_3$ requires 465.2178).

Selected ^{1}H NMR signals for the minor diastereoisomer **13**. δ_H(250 MHz; $CDCl_3$; Me_4Si) 3.66 (1H, d, *J* 7.9, C(O)C*H*), 4.66 (1H, d, *J* 3.4, PhC*H*CH), 5.82 (s, 1H).

Crystal structure determination of compound 12‡

Crystal data. $C_{31}H_{30}Cl_2N_2O_3$, $M = 549.47$, monoclinic, $a = 7.6834(10)$, $b = 10.5554(14)$, $c = 16.299(2)$ Å, $U = 1319.4(3)$ Å^3, $T = 150(2)$ K, space group $P2_1$, $Z = 2$, μ(Mo–Kα) = 0.283 mm^{-1}, 11779 reflections measured, 3123 unique ($R_{int} = 0.0224$) which were used in all calculations. The final $wR(F_2)$ was 0.0766 (all data).

(3a*S*,9a*S*)-3a,4,9,9a-Tetrahydro-4-[(2*R*,4*S*)-3,5-dibenzyl-2-oxazolidinyl]-2-methyl-4,9[1′,2′]-benzeno-1*H*-benz[*f*]isoindole-1,3(2*H*)-dione 17

N-Methyl maleimide (0.129 g, 1.160 mmol) was added in one portion as a solid at 90–95 °C to a stirred solution of oxazolidine **5** (0.5 g, 1.16 mmol) in toluene (10 cm^3). The resulting mixture was left stirring for 4 h at 90–95 °C, cooled to room temperature and the solvent was removed under reduced pressure to give a single diastereoisomer of the target cycloadduct (0.47 g, 75%). A sample was recrystallised from CH_2Cl_2–petroleum ether 40–60 °C (diffusion recrystallisation) to afford a white solid of the title compound **17**. Mp 204–207 °C from CH_2Cl_2–petroleum ether 40–60 °C); (found: C, 79.7; H, 5.9; N, 5.1. $C_{36}H_{32}N_2O_3$ requires C, 80.0; H, 6.0; N, 5.2%); $[\alpha]_D^{25}$ +66.1 (*c* 1 in $CHCl_3$); ν_{max}/cm^{-1} 1688 (C=O), 1454, 1428 and 1376 (C=C); δ_H(250 MHz; $CDCl_3$; Me_4Si) 2.50 (3H, s, C*H*$_3$), 2.81 (1H, dd, *J* 13.4 and 10.0, C*H*HPh), 3.01 (1H, dd, *J* 13.4 and 5.1, C*H*HPh), 3.10 (1H, dd, *J* 8.3 and 3.1, PhCHC(O)C*H*), 3.60 (1H, d, *J* 8.3, C(O)C*H*), 3.63–3.71 (3H, m, C*H*$_2$Ph and C*H*N), 3.83 (1H, dd, *J* 8.3 and 4.2, C*H*HO), 4.15 (1H, dd, *J* 8.3 and 6.4, C*H*HO), 4.77 (1H, d, *J* 3.1, PhC*H*CH), 6.55 (1H, s, NC*H*O), 7.00–7.04 (2H, m, ArC*H*), 7.06–7.46 (14H, m, ArC*H*), 8.10 (1H, dd, *J* 7.0 and 1.8, ArC*H*), 8.17 (1H, dd, *J* 6.7 and 2.2, ArC*H*); δ_C(62.5 MHz; $CDCl_3$; Me_4Si) 24.3 (*C*H$_3$), 38.4 (*C*H$_2$), 46.6 (*C*H), 48.3 (*C*H), 49.8 (*C*H), 50.3 (*C*H$_2$), 56.6 (*C*H$_2$),

‡ CCDC reference numbers 614833 (**4**), 614834 (**5**), 614835 (**12**) and 614836 (**17**). For crystallographic data in CIF or other electronic format see DOI: 10.1039/b610055d

64.5 (*C*H), 67.8 (*C*H$_2$), 90.9 (*C*H), 123.5 (*C*H), 125.0 (*C*H), 125.1 (*C*H), 125.7 (*C*H), 126.2 (*C*H), 126.7 (*C*H), 127.0 (*C*H), 127.3 (*C*H), 128.0 (*C*H), 128.2 (*C*H), 128.4 (*C*H), 128.6 (*C*H), 129.2 (*C*H), 137.1 (*C*), 137.9 (*C*), 138.8 (*C*), 139.1 (*C*), 139.4 (*C*), 141.9 (*C*), 175.7 (*C*), 176.3 (*C*); *m*/*z* (ES) 541.2508 (MH^+. $C_{36}H_{33}N_2O_3$ requires 541.2491).

Crystal structure determination of compound 17

Crystal data. $C_{36}H_{32}N_2O_3$, M = 540.64, monoclinic, a = 10.3383(14), b = 9.6773(13), c = 14.613(2) Å, U = 1390.0(3) Å^3, T = 150(2) K, space group $P2(1)$, $Z = 2$, μ(Mo–Kα) = 0.082 mm^{-1}, 15882 reflections measured, 3373 unique (R_{int} = 0.0471) which were used in all calculations. The final $wR(F_2)$ was 0.0935 (all data).

3a,4,9,9a-Tetrahydro-4-carboxaldehyde-2-methyl-4,9[1′,2′]-benzeno-1*H*-benz[*f*]isoindole-1,3(2*H*)-dione 14

N-Methyl maleimide (1.621 g, 14.60 mmol) was added in one portion as a solid at 80–85 °C to a stirred solution of 9-anthraldehyde (2 g, 9.7 mmol) in toluene (20 cm^3). The resulting mixture was left stirring for 24 h at 80–85 °C, cooled to room temperature and the solvent was removed under reduced pressure to give the target compound. The crude was purified by column chromatography (20% EtOAc–petroleum ether 40–60 °C) to afford a white solid of the title compound **14** 2.356 g (77%); mp 243–248 °C; (found: C, 75.9; H, 4.7; N, 4.3. $C_{20}H_{15}NO_3$ requires C, 75.70; H, 4.8; N, 4.4%); ν_{max}/cm^{-1} 1772 (C=O), 1724 (C=O), 1691 (C=O), 1457 and 1432 (C=C); δ_H(250 MHz; $CDCl_3$; Me_4Si) 2.44 (3H, s, C*H*$_3$), 3.26 (1H, dd, *J* 8.6 and 3.4, PhCHC(O)C*H*), 3.67 (1H, d, *J* 8.6, C(O)C*H*), 4.72 (1H, d, *J* 3.4, PhC*H*CH), 7.05–7.27 (6H, m, ArC*H*), 7.35–7.40 (1H, m, ArC*H*), 7.54–7.61 (1H, m, ArC*H*), 10.81 (1H, s, C*H*O); δ_C(62.5 MHz; $CDCl_3$; Me_4Si) 24.4 (*C*H$_3$), 45.9 (*C*H), 47.5 (*C*H), 48.0 (*C*H), 57.7 (*C*), 122.9 (*C*H), 123.4 (*C*H), 124.7 (*C*H), 125.4 (*C*H), 126.8 (*C*H), 127.2 (*C*H), 127.5 (*C*H), 136.4 (*C*), 138.2 (*C*), 139.1 (*C*), 141.2 (*C*), 175.7 (*C*), 176.2 (*C*), 200 (*C*); *m*/*z* (ES) 318.1125 (MH^+. $C_{20}H_{16}NO_3$ requires 318.1130).

(3a*R*,9a*R*)-3a,4,9,9a-Tetrahydro-4-carboxaldehyde-2-methyl-4,9[1′,2′]-benzeno-1*H*-benz[*f*]isoindole-1,3(2*H*)-dione 14

The title compound was obtained by stirring cycloadduct **12** (0.100 g, 0.216 mmol) in a solution of CH_2Cl_2–H_2O (5 cm^3; 9 : 1, v/v) for 18 h at rt in the presence of silica gel (approx. 50 mg). The reaction was filtered, evaporated and purified by column chromatography (20% EtOAc–petroleum ether 40–60 °C) to afford a white solid of the title compound **14** (0.050 g, 73%). $[a]_D^{25}$ −48.0 (*c* 0.5 in $CHCl_3$).

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