Tetrahedron: Asymmetry Vol. 2, No. 12, pp. 1343-1358, 1991
Printed in Great Britain

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

Development of Chiral Stabilised Azomethine Ylids: A Chiral Memory Relay System.

Amberley S. Anslow,[a] Laurence M. Harwood,[a]* Helen Phillips,[a] David Watkin[b] and Ling F. Wong[b]

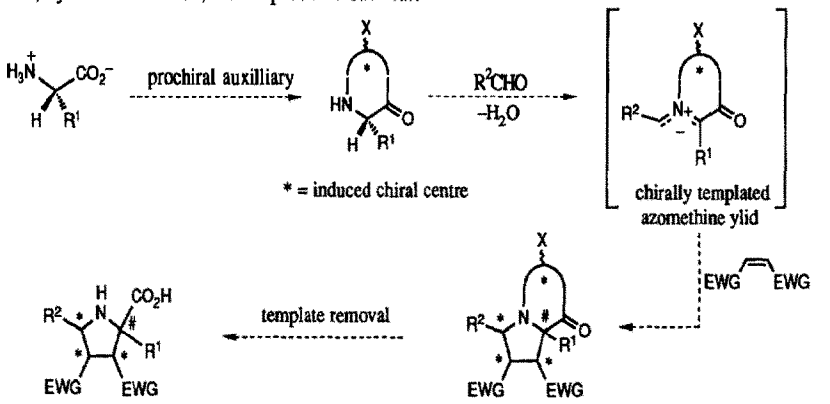
[a] *Dyson Perrins Laboratory, University of Oxford, South Parks Road, OXFORD OX1 3QY.*

[b] *Chemical Crystallography Laboratory, University of Oxford, Parks Road, OXFORD OX1 3PD.*

(*Received* 6 *November* 1991)

Abstract: Chiral, stabilised azomethine ylids incorporated in cyclic templates derived from (*R*)– or (*S*)–2–phenylglycinol and (*S*)–valine undergo enantioselective 1,3-dipolar cycloaddition reactions with a variety of dipolarophiles. Removal of the template in the case of adducts derived originally from (*S*)–valine furnishes enantiomerically pure α– substituted proline derivatives.

Azomethine ylids are readily accessible from α–amino acid precursors,[1] but the chiral information at the α–centre is necessarily lost in the process of ylid generation. We envisaged that incorporation of the amino acid into a chiral template and utilising its chirality to set up a new chiral centre, could permit [3+2] cycloadditions with good stereocontrol to furnish adducts from which enantiomerically pure proline derivatives could be derived after removal of the chiral template (**Scheme 1**).[2] Although template removal in the final step of such a sequence necessarily involves destruction of the chiral centre used as the stereodirecting element during cycloaddition, this involves no overall sacrifice of chirality since it was envisaged that the chiral template would be derived, by chiral induction, from a prochiral substrate.

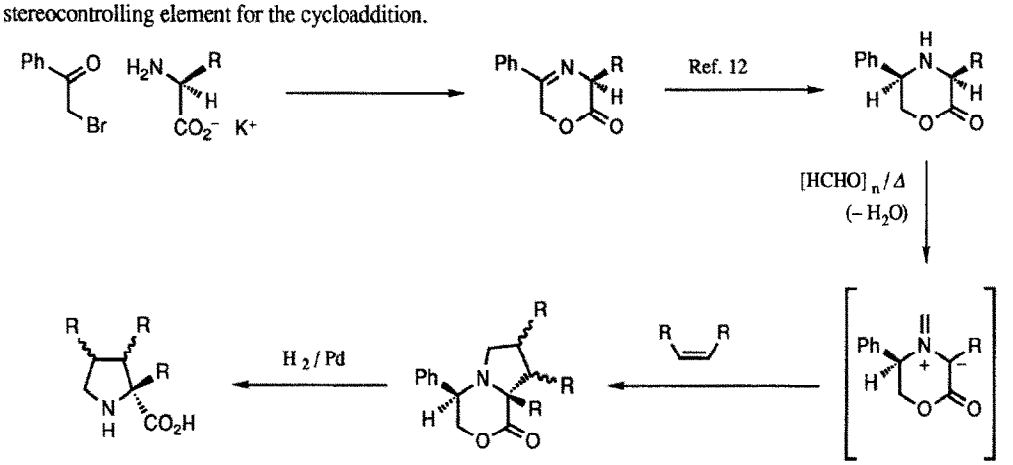


Scheme 1

This principle has been applied previously to deprotonation processes by Schmidt,[3] Seebach[4] and Schollkopf[5] and Seebach has coined the phrase "self replication of chirality" for such a process. Investigations into enantioselective cycloadditions with azomethine ylids have largely focussed upon the use of chiral auxiliaries on the dipolarophile[6] although attention has been paid to the dipole[7] and Grigg has recently presented work in which chiral catalysts have been used with achiral substrates.[8]

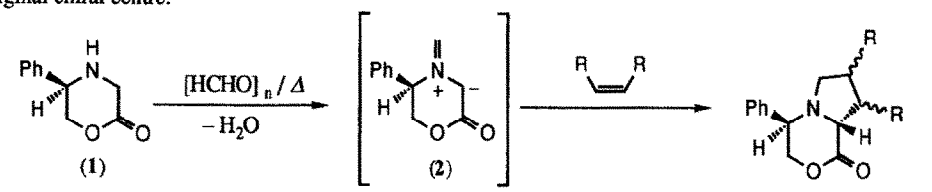
For our candidate system we decided to investigate the potential of the 3–substituted–5–phenylmorpholinone[9] template for generation and stereocontrolled trapping of azomethine ylids (**Scheme 2**).

Central to our decision was a brief report by Williams that 5(*R*)–6(*S*)–diphenylmorpholinone can act as an azomethine ylid precursor which undergoes stereocontrolled cycloaddition,[10] although such substrates could not be generated in a direct manner from α–amino acids.[11] Our choice of 5–phenylmorpholinone derived systems was governed by the demonstration by Caplar that hydrogenation of the cyclic condensation products derived from α–bromoacetophenone and α–amino acids occurs stereospecifically, forming homochiral 3–substituted–5–phenylmorpholinones with total 1,3–transfer of chirality from the α–amino acid centre to the newly formed benzylic centre.[12] In principle such a system could lead to the desired relay of the original amino acid chirality, with the stereocentre at C-5 of the template, generated as a consequence of the chiral centre at C-3, acting as the stereocontrolling element for the cycloaddition.



Scheme 2

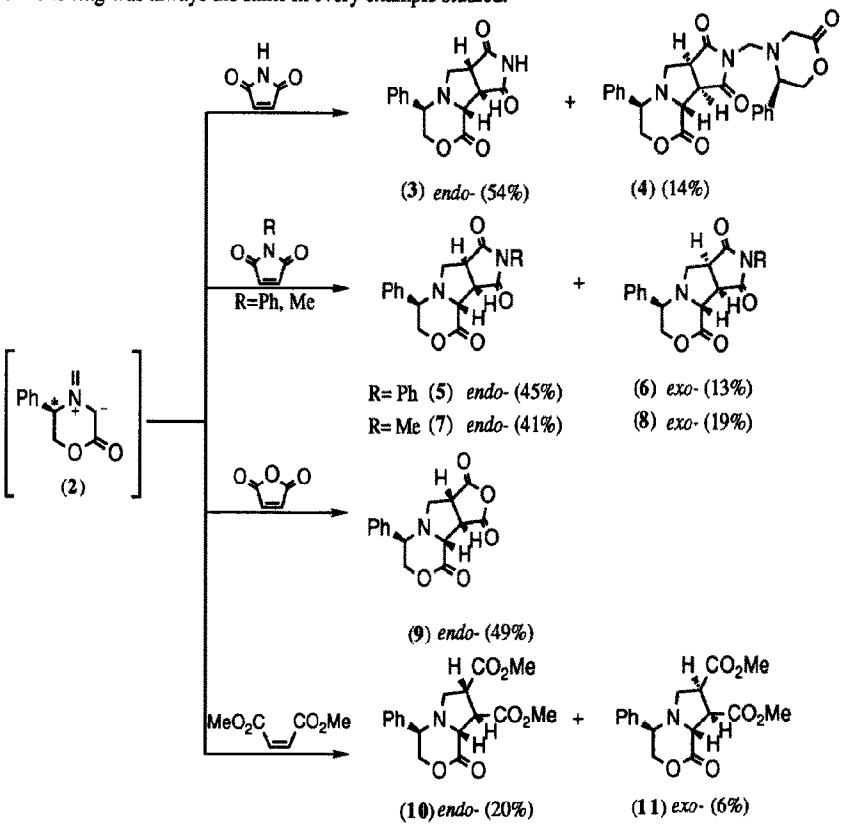
Initially, we carried out a model study using 5–(*R*)– and 5–(*S*)–phenylmorpholinone template (**1**) as a chiral glycine equivalent This was readily prepared by reaction of (*R*)– or (*S*)–phenylglycinol with phenyl bromoacetate using the method of Dellaria.[13] Such a substrate would permit us to test the overall viability and stereoselectivity of the sequence of ylid formation followed by *in situ* trapping [**Scheme 3**, (*R*)– series only shown], although *N*–debenzylation of the cycloadducts resulting from this sequence would result in destruction of the original chiral centre.[14]



Scheme 3

Due to the propensity of the morpholinone (**1**) to dimerise[13] it was stored at 0 °C prior to use and the ylid (**2**) generated under high–dilution conditions by dropwise addition to refluxing benzene containing paraformaldehyde and the dipolarophile, following a modified method of that used by Tsuge.[15] *In situ* trapping of the ylid with a variety of different alkene dipolarophiles led to the desired adducts, usually as *endo*– *exo*– mixtures in the yields indicated in **Scheme 4**. Reaction of **2** with maleimide yielded the *endo*– adduct (**3**) in 54% yield whilst the *exo*– adduct was found to have reacted with a further molecule of **2** to yield the *bis*– adduct **4** in 14% yield. Presumably the *endo*– analogue of compound **4** was not obtained due to greater steric hindrance to approach to the NH in this case. In all instances the *endo*– adducts were formed predominantly and, with

maleic anhydride as dipolarophile, no *exo*–adduct could be isolated, possibly due to the reduced steric bulk of the anhydride compared to *N*–substituted maleimides. Gratifyingly however, the stereochemistry at C–3 of the morpholinone ring was always the same in every example studied.



Scheme 4

The stereochemical control can be rationalised by envisaging an axial approach of the dipolarophile to the least–hindered face of the ylid held in a chair conformation in which the phenyl group is equatorial (**Figure 1**).

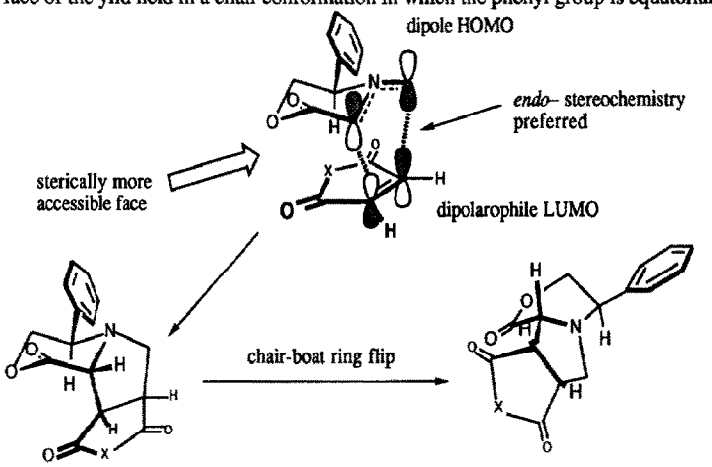
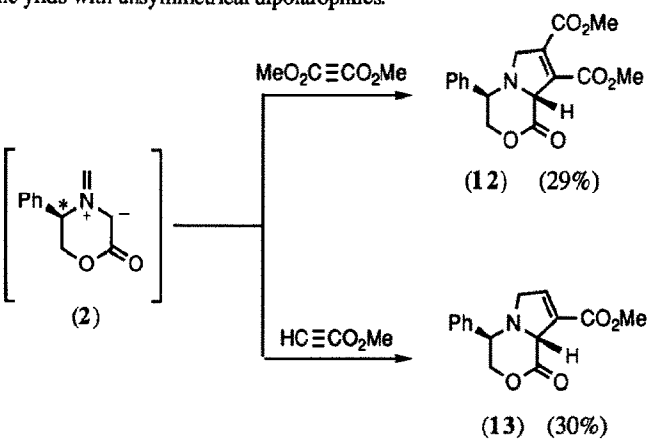


Figure 1

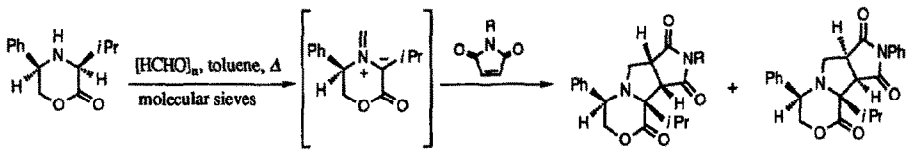
Subsequent to cycloaddition, flipping the morpholinone ring to a boat conformation results in all substituents lying in the sterically least demanding environments. X–ray structure determination of **5** together with n.O.e. difference studies confirmed both the boat conformation of the morpholinone ring and the *total stereochemical integrity* achieved at the newly formed ring junction of all products **3–11**.[2a]

Attention was then turned to the use of alkyne dipolarophiles, as the resultant cycloadducts would be free of stereochemical complications resulting from *exo*– or *endo*– attack. Generation of **2** followed by reaction with the symmetrical dipolarophile dimethyl acetylenedicarboxylate furnished, as expected, only one cycloadduct (**12**) in 29% yield (**Scheme 5**). In order to evaluate the regiocontrol possible with this system, ylid (**2**) was also reacted with methyl propynoate and was found to furnish a single product (**13**) in 30% isolated yield. In both instances no other monomeric products could be identified and the low yields presumably reflect reduced reactivity of the dipolarophiles. The regio– and stereochemistry of **13** were established by COSY and n.O.e. difference studies,[2a] the regioselectivity being the inverse of that usually observed for cycloadditions of stabilised azomethine ylids with unsymmetrical dipolarophiles.[16]



Scheme 5

Having demonstrated that stereochemical control at the ring junction in the cycloaddition reactions of ylid (**2**) was uniformly excellent and the material yields ranged from moderate to good, we were encouraged to extend our studies towards the development of a chiral relay system utilising 3,5–disubstituted morpholinone templates in which the 3–substituent is derived from an α–amino acid. As our initial candidate we decided to utilise the known 3(*S*)–isopropyl–5(*R*)–phenylmorpholinone (**14**) prepared from *N*–Boc valine following the method of Caplar.[12] Substrate (**14**) appeared resistant to the troublesome dimerisation side–reaction shown by **1** on storage. The ylid generation and trapping procedure utilising **14** was carried out in a similar manner to that described for substrate (**1**) except that the generally lower reactivity exhibited by **14** meant that it was beneficial to perform this series of reactions in toluene to improve the yields of cycloadducts obtained (**Scheme 6**). Under these conditions, reaction with *N*–phenyl maleimide furnished *ca.* 5 : 1 mixture of *endo*– and *exo*– cycloadducts; whereas *N*–methyl maleimide gave only the *endo*– cycloadduct. Once again, only a single stereochemistry was observed at the regenerated chiral centre at C–3 of the morpholinone ring. Full characterisation of compounds **16–18** included n.O.e difference studies and an X–ray structure determination of **17**.[2b]



(14) (15) (16) R = Ph 34% (17) R = Me 46% (18) 7%

Scheme 6

The stereochemistries observed for adducts (**16**) – (**18**) can be explained by our rationale of sterically directed approach in the same manner as with ylid (**2**). In this case, the isopropyl substituent on the ylid (**15**) appears to favour *endo*– approach of the dipolarophile slightly compared to the unsubstituted ylid (**2**) and may also explain the lower reactivity of (**14**) (**Figure 2**).

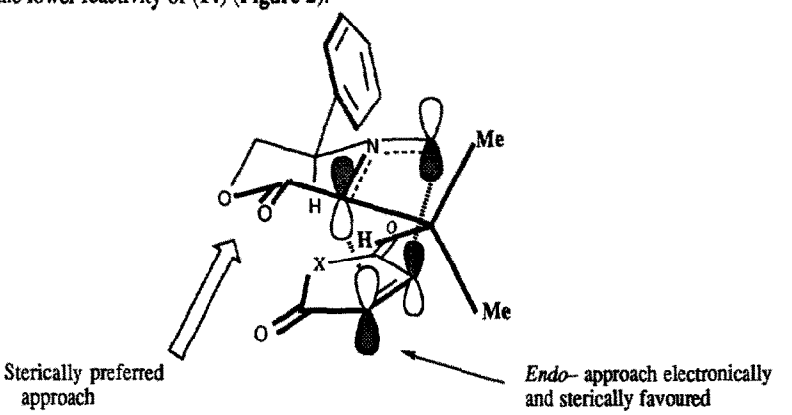
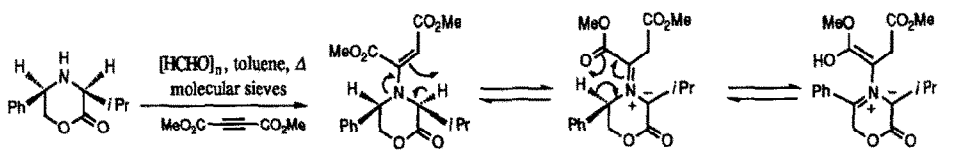


Figure 2

Disappointingly the lower reactivity of morpholinone (**14**) was reflected in the fact that attempted trapping of the derived ylid with dimethyl maleate gave no identifiable products; whilst dimethyl acetylenedicarboxylate gave the Michael adduct (**19**) in 39% yield after chromatography as the only isolable monomeric material. Adduct (**19**) was found to show no optical rotation at a series of wavelengths, and we rationalise this result by invoking racemisation under the conditions of thermolysis *via* a sequence such as that shown in **Scheme 7** involving a series of prototropic shifts.



(14) 3(*S*,*R*),5(*S*,*R*)-(**19**) 39%

Scheme 7

In order to demonstrate the feasibility of our overall strategy of chiral relay it simply remained to carry out template removal by benzylic deprotection of adducts (**16**) – (**18**) followed by hydrolysis to yield proline derivatives. In practice, benzylic hydrogenolysis (methanol, Pearlman's Catalyst, H_2,trifluoroacetic acid[17]) occurred with concomitant hydrolysis of the ester linkage to yield the free proline derivatives (**20**) – (**22**) in good yields (**Figure 3**).

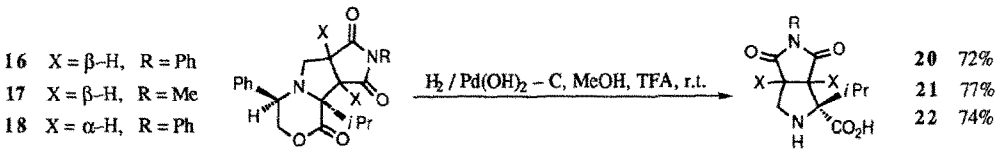
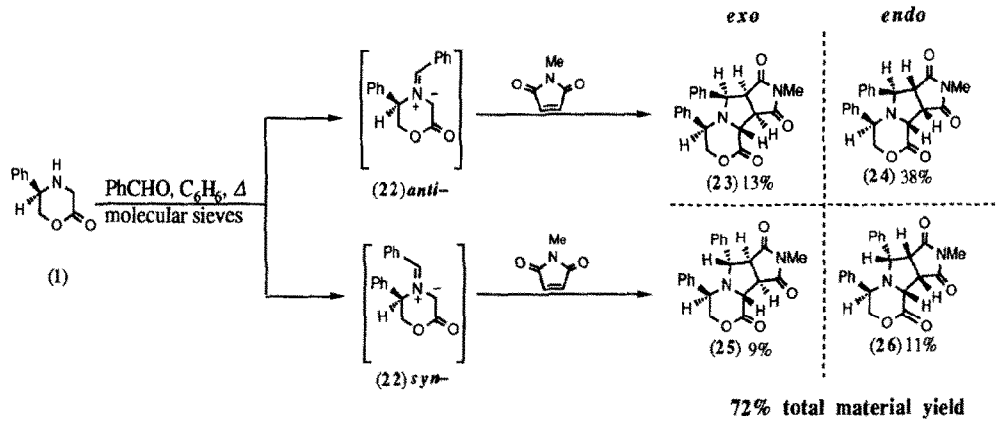


Figure 3

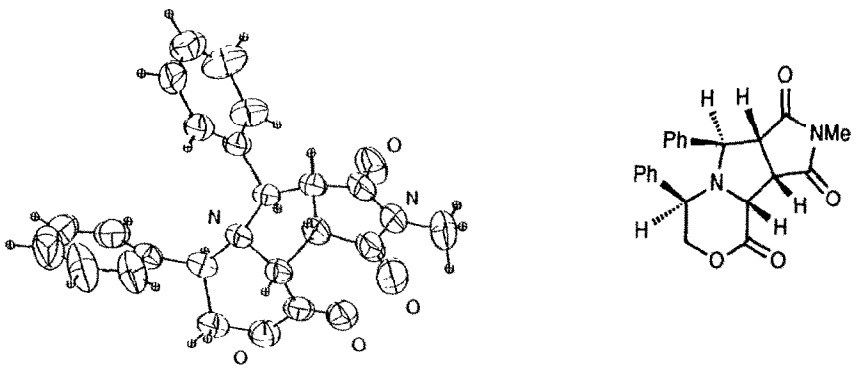
Isolation of the pure amino acids **19–21** from the crude hydrogenolysis mixtures was achieved by means of the recently reported reverse-phase variant[18] of dry flash chromatography,[19] eluting with 1 : 1 methanol / water.

In an extension of this methodology, it was decided to investigate the outcome of trapping ylids generated by reaction of morpholinone (**1**) with aldehydes other than formaldehyde, in order to synthesize derivatives with functionality at the off–template α'–amino centre and to study the degree of stereocontrol possible at this centre. Williams has previously observed formation of mixtures of stereoisomers at this new centre using the ylid derived from 5(*R*),6(*S*)–diphenylmorpholinone and benzaldehyde.[10] Following the method used to prepare adducts (**3**) – (**13**), compounds (**23**) – (**26**) were obtained in good total material yield by reacting morpholinone (**1**) with benzaldehyde in the presence of *N*–methyl maleimide.(**Scheme 8**)



Scheme 8

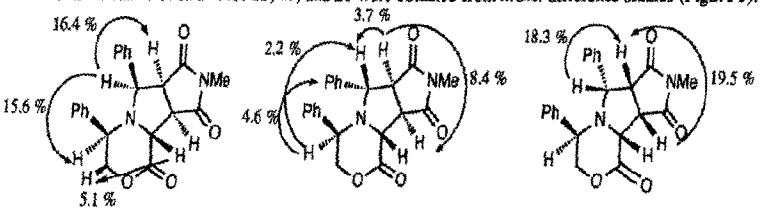
The structure of the major adduct (**24**) was confirmed by X–ray crystallographic analysis (**Figure 4**).[20]



X–ray crystal structure of *endo*–adduct(**24**)

Figure 4

Confirmations of structures **23**, **25**, and **26** were obtained from n.O.e. difference studies (**Figure 5**).



(23) (25) (26)

Figure 5

The stereochemical outcome can be rationalised by envisaging *exo*– or *endo*– attack of the dipolarophile on the ylid (**22**) in either the *syn*– or *anti*– configuration (**Figure 6**).

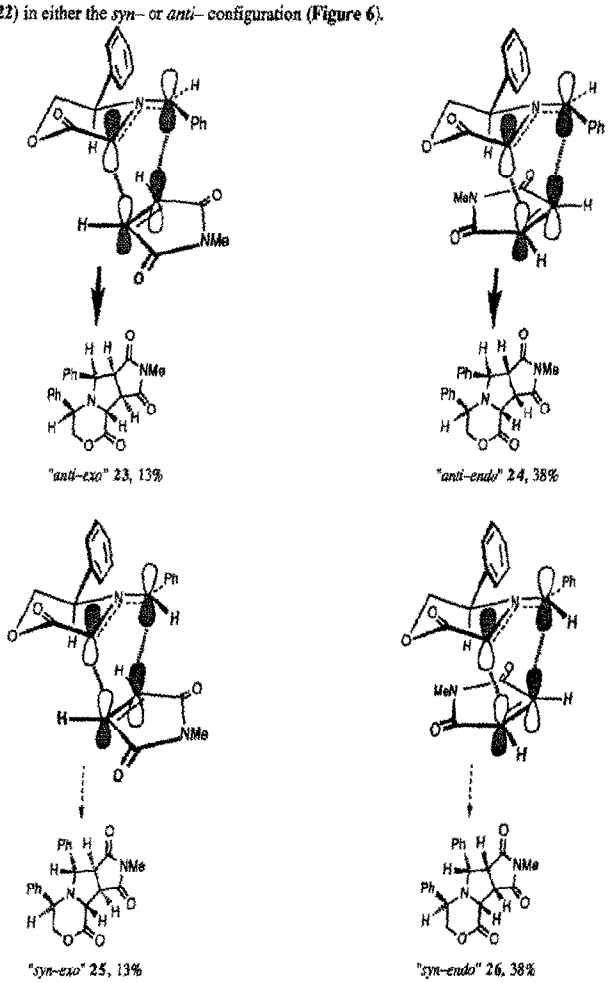
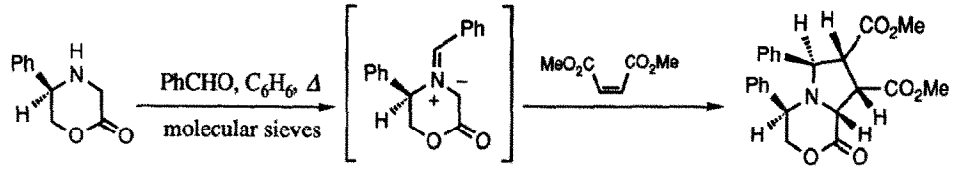


Figure 6

It can be seen from the relative yields of the adducts that the favoured cycloaddition pathway occurs *via* the ylid possessing the *anti*– configuration. This may be due either to preferential formation (lower steric interaction of the two phenyl groups) or greater reactivity of *anti*– **22**. It is important to note once again that total stereochemical integrity at C–3 of the morpholinone ring is achieved for all of the adducts.

Morpholinone **1**, when reacted with benzaldehyde and dimethyl maleate in refluxing benzene, furnished the *endo*– adduct (**27**) as the only isolable material, but in a disappointingly low 8% yield (**Scheme 9**). Since the yield of this reaction was low, it is possible that other adducts were formed but in quantities too small to detect in the crude reaction mixture.



(**1**) (**22**) *anti*– (**27**) 8 %

Scheme 9

Currently work is being carried out on extensions of these studies towards the synthesis of substituted pyrrolidines and amino acids and will be reported in due course.

Experimental

Infra red spectra were recorded on Perkin-Elmer 297 or 781 instruments. Proton n.m.r. spectra were recorded on Varian Gemini (200 MHz), Bruker WH300 (300 MHz) or Bruker AM500 (500 MHz) spectrometers. Carbon-13 n.m.r. spectra were recorded on a Varian Gemini (50 MHz) spectrometer. Melting points were recorded on a Kofler hot stage and are uncorrected. Mass spectra (*m/z*) were recorded on Masslab 20-250, V.G. micromass 30F, ZAB 1F or Trio-1 GCMS (DB-5 column) spectrometers, using desorption chemical ionisation (NH_3 D.C.I.). N.O.e. difference data are quoted in the format: irradiation position (δ), ***irradiated proton***–enhanced proton (% enhancement). Microanalyses were carried out an a Carlo Erba 1106 elemental analyser. Flash column chromatography was carried out using Sorbsil C60 40/60 or Merck Kieselgel 60 (0.40-0.063 mm diameter) silica.

General method for the preparation of compounds (3) – (13)

Paraformaldehyde (10 equiv.) was added to a solution of dipolarophile (5–7 equiv.) in sodium-dried benzene (300 ml). The flask was fitted with a condenser and Soxhlet extractor containing activated 3Å sieves, and the mixture heated with stirring to reflux under nitrogen. Morpholinone (**1**) (1 equiv., 5 mmol) was dissolved in benzene (10 ml) and the solution added dropwise *via* a cannula to by–pass the Soxhlet extractor. After 2h, the reaction mixture was allowed to cool to room temperature and filtered to remove excess paraformaldehyde. Removal of solvent *in vacuo* yielded the crude mixture of products along with excess dipolarophile. Column chromatography using gradient elution, typically 3:1 hexane / ethyl acetate to 1:1 hexane / ethyl acetate, yielded the pure cycloadducts:

2(R),6(R),7(S),8(R) 2–phenyl–1–aza–4–oxa[4.3.0^{1,6}]bicyclononan–5–one–7,8–dicarboximide (**3**)

Colourless needles (0.7 g, 54 %) m.p. 150-153°C; R_f = 0.12, 2:1 ethyl acetate-hexane; (Found C, 62.9; H, 5.2; N, 9.8; $C_{15}H_{14}N_2O_4$ requires C, 62.9; H, 4.9; N, 9.8 %); ν_{max} ($CHCl_3$) 1 745 and 1 710 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.40-7.26, 5H, m, -Ph; 5.11, 2H, m, 3α/β–H; 4.29, 1H, s, -NH; 4.17, 1H, d, J=8.0 Hz,

6β–H; 3.80, 1H, t, J=8.2 Hz, 7β–H; 3.56, 1H, bt, J=8.0 Hz, 2α–H; 3.32, 1H, dd, J=2.1, J'=11.9 Hz, 9α/β–H; 3.29, 1H, dd, J=2.2, J'=8.7, 8α–H; 3.15, 1H, dd, J=9.4, J'=13.1 Hz, 9α/β–H; δ_C (50 MHz, $CDCl_3$) 177.5, 175.8, 165.7, 135.1, 129.2, 129.1, 128.1, 73.6, 63.4, 62.8, 59.0, 53.8, 48.8, 44.2, 30.9; m/z (DCI+, NH_3) 304, 287 (100 %, M+1), 104 (85%); $[\alpha]_D^{20}$ +45.3 (c 1.0, $CHCl_3$), *ent*–**3** $[\alpha]_D^{20}$ –44.8 (c 1.0, $CHCl_3$).

2(R),6(R),7(R),8(S)–N–(5'(R)–phenylmorpholin–2–onyl)methyl2–phenyl–1–aza–4–oxa[4.3.0^{1,6}]–bicyclo nonan–5–one–7,8–dicarboximide (**4**)

Colourless solid. (0.3 g, 14 %) m.p. 122-125 °C; R_f = 0.29, 2:1 ethyl acetate-hexane; (Found C, 65.7; H, 5.8; N, 8.3; $C_{26}H_{25}N_3O_6$ requires C, 65.7; H, 5.3; N, 8.8 %); ν_{max} ($CHCl_3$) 1 750 and 1 710 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.49-7.25, 10H, m, -Ph; 4.61, 1H, dd, J=4.4, J'=11.5 Hz, 3α/β–H; 4.52, 1H, d, J=13.5 Hz, 9'β/9'α–H; 4.46, 1H, dd, J=6.3, J'=11.5 Hz, 3α/β–H; 4.31, 1H, d, J=13.6 Hz, 9'α/9'β–H; 4.31, 2H, m, 3'α/3'β and 2'α–H; 4.20, 1H, dd, J=10.7, J'=12.6 Hz, 3'α/3'β–H; 3.96, 1H, d, J=17.1 Hz, 6'α/6'β–H; 3.96, 1H, dd, J=4.4, J'=6.3 Hz, 2α–H; 3.79, 1H, d, J=7.3 Hz, 6β–H; 3.76, 1H, d, J=17.1 Hz, 6'α/6'β–H; 3.61, 1H, dd, J=7.6, J'=8.2 Hz, 7α–H; 3.24, 1H, dd, J=3.0, J'=10.7 Hz, 9α/9β–H; 3.19, 1H, dt, J=3.0, J'=8.6 Hz, 8α–H; 2.92, 1H, dd, J=8.9, J'=10.7 Hz, 9α/9β–H; δ_C (50 MHz, $CDCl_3$) 178.4, 176.3, 169.1, 165.8, 137.4, 134.3, 129.0, 128.9, 128.7, 128.0, 73.2, 71.6, 61.2, 59.8, 59.0, 57.2, 53.4, 50.3, 46.4, 43.2; m/z (DCI+, NH_3) 476 (25 %, M+1), 304, 287 (100%), 190, 178, 118, 104 (100%); $[\alpha]_D^{20}$ +13.0 (c 1.0, $CHCl_3$), *ent*–**4** $[\alpha]_D^{20}$ –14.2 (c 0.98, $CHCl_3$).

N–phenyl 2(R),6(R),7(S),8(R) 2–phenyl–1–aza–4–oxa[4.3.0^{1,6}]bicyclononan–5–one–7,8–dicarboximide (**5**)

Colourless rods (1.76 g, 45 %) m.p. 222-224 °C; R_f = 0.31, 2:1 ethyl acetate-hexane; (Found C, 69.3; H, 4.7; N, 8.0; $C_{21}H_{18}N_2O_4$ requires C, 69.6; H, 5.0; N, 7.7 %); ν_{max} ($CHCl_3$) 1 753 and 1 716 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.54-7.27, 10H, m, -Ph; 4.34, 1H, dd, J=11.5, J'=13.2 Hz, 3α/β–H; 4.33, 1H, dd, J=11.5, J'=26.7 Hz, 3α/β–H; 4.27, 1H, d, J=7.8 Hz, 6β–H; 3.93, 1H, dd, J=7.8, J'=8.7 Hz, 7β–H; 3.86, 1H, dd, J=4.4, J'=9.1 Hz, 2α–H; 3.46, 1H, m, 8β–H; 3.35, 1H, dd, J=3.3, J'=12.6 Hz, 9α/β–H; 3.30, 1H, dd, J=9.1, J'=12.6 Hz, 9α/β–H; δ_C (50 MHz, $CDCl_3$) 176.7, 174.4, 165.9, 135.4, 132.0, 129.4, 129.2, 129.1, 128.8, 127.9, 125.9, 73.3, 62.9, 60.07, 54.4, 48.3, 44.1, m/z (DCI+, NH_3) 380, 363 (50 %, M+1), 104 (100%); $[\alpha]_D^{20}$ -42.3 (c 0.6, $CHCl_3$), *ent*–**5** $[\alpha]_D^{20}$ +38.9 (c 0.6, $CHCl_3$).

N–phenyl 2(R),6(R),7(R),8(S) 2–phenyl–1–aza–4–oxa[4.3.0^{1,6}]bicyclononan–5–one–7,8–dicarboximide (**6**)

Colourless filaments, (0.51 g, 13 %) m.p. 220-222 °C; R_f = 0.59, 2:1 ethyl acetate-hexane; (Found C, 69.3; H, 4.5; N, 8.3; $C_{21}H_{18}N_2O_4$ requires C, 69.6; H, 5.0; N, 7.7 %); ν_{max} ($CHCl_3$) 1 759 and 1 718 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.55-7.25, 10H, m, -Ph; 4.50, 1H, d, J=0.9 Hz, 6β–H; 4.46, 1H, dd, J=5.2, J'=12.3 Hz, 3α/β–H; 4.23, 1H, dd, J=1.3, J'=8.5 Hz, 7α–H; 4.21, 1H, t, J=12.0, 3α/β–H; 3.95, 1H, dd, J=5.2, J'=11.7 Hz, 2α–H; 3.69, 1H, dd, J=0.9, J'=9.9 Hz, 9α–H; 3.53, 1H, dt, J=0.9, J'=8.3 Hz, 8α–H; 2.96, 1H, dd, J=8.0, J'=9.9 Hz, 9β–H; n.O.e. expt: 4.50, ***6β–H***–7α-H (15.9%); 4.44, ***3α–H***–2α-H (10.5%), –3β-H (32.3%); 3.95, ***2α–H***–9β-H (8.2%), –3α-H (9.1%); 3.68, ***9α–H***–9β-H (27.2%), –8α-H (2%), –2α-H (1.7%); 3.52, ***8α–H***–9β-H (7.8%), –7α-H (11.5%); 2.9, ***9β–H***–8α-H (13.3%), –9α-H (30.2%), –2α-H (10.2%); δ_C (50 MHz, $CDCl_3$) 176.9, 176.7, 169.6, 137.0, 132.0, 129.3, 129.0, 128.9, 128.5, 126.5, 126.4, 71.0, 62.6, 62.2, 57.2, 45.2, 43.9, m/z (DCI+, NH_3) 380, 363 (65 %, M+1), 104 (100%); $[\alpha]_D^{20}$ +88.0 (c 0.25, $CHCl_3$), *ent*–**6** $[\alpha]_D^{20}$ –86.2 (c 0.25, $CHCl_3$).

N–methyl 2(R),6(R),7(S),8(R) 2–phenyl–1–aza–4–oxa[4.3.0^{1,6}]bicyclononan–5–one–7,8–dicarboximide (**7**)

Colourless foam, unstable in the presence of air, (0.96 g, 41 %) m.p. 115-117 °C; R_f = 0.25, 2:1 ethyl acetate-hexane; (Found C, 64.2; H, 5.1; N, 9.0; $C_{16}H_{16}N_2O_4$ requires C, 64.0; H, 5.34; N, 9.3 %); ν_{max} ($CHCl_3$) 1 752 and 1 708 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 7.5-7.2, 5H, m, -Ph; 4.35, 2H, m, 3α/β–H; 4.08, 1H, d, J=7.8 Hz, 6β–H; 3.75, 1H, t, J=7.8, 8β–H; 3.67, 1H, t, J=6.3, 7β–H; 3.3, 1H, m, 2α–H; 3.25, 1H, d, J=1.96, 9α/β–H; 3.08, 1H, dd, J=9.4, J'=12.7, 9α/β–H; 3.08, 3H, s, -NMe; δ_C (50 MHz, $CDCl_3$) 178.4, 176.0, 166.1, 134.9, 129.3, 129.2, 128.1, 73.3, 62.5, 59.3, 53.5, 48.0, 43.7, 25.5; m/z (DCI+, NH_3) 318, 301 (85%, M+1), 256, 104 (100%); $[\alpha]_D^{20}$ +45.0 (c 1.0, $CHCl_3$), *ent*–**7** $[\alpha]_D^{20}$ –45.9 (c 1.0, $CHCl_3$).

N–methyl 2(R),6(R),7(R),8(S) 2–phenyl–1–aza–4–oxa[4.3.0^{1,6}]bicyclononan–5–one–7,8–dicarboximide (**8**)

Colourless foam, (0.45 g, 19 %) m.p. 110–112 °C; R_f = 0.52, 2:1 ethyl acetate-hexane; (Found C, 64.2; H, 5.34; N, 9.48; $C_{16}H_{16}N_2O_4$ requires C, 64.0; H, 5.34; N, 9.3 %); ν_{max} ($CHCl_3$) 1 757 and 1 705 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.38-7.26, 5H, m, -Ph; 4.4, 1H, dd, J=5, J'=12.3 Hz, 3α/β–H; 4.38, 1H, d, J=1.2 Hz, 6β–H; 4.19, 1H, t, J=11.9 Hz, 3α/β–H; 4.07, 1H, dd, J=1.2, J'=8.4 Hz, 7α–H; 3,87, 1H, dd, J=5.0, J'=11.7 Hz, 2α–H; 3.56, 1H, dd, J=1.0, J'=9.9 Hz, 9α–H; 3.38, 1H, t, J=8.1 Hz, 8α–H; 3.08, 3H, s, -NMe; 2.85, 1H, dd, J=8.1, J'=9.9 Hz, 9β–H; δ_C (50 MHz, $CDCl_3$) 178.3, 178.0, 170.2, 137.0, 129.0, 128.6, 126.8, 70.9, 62.8, 61.5, 56.6, 44.9, 43.7, 25.4; m/z (DCI+, NH_3) 318, 301 (85 %, M+1), 256, 104 (100%); $[\alpha]_D^{20}$ +30.9 (c 1.0, $CHCl_3$), *ent*–**8** $[\alpha]_D^{20}$ –31.4 (c 1.0, $CHCl_3$).

2(R),6(R),7(S),8(R) 2–phenyl–1–aza–4–oxa[4.3.0^{1,6}]bicyclononan–5–one–7,8–dicarboxylic anhydride (**9**)

Colourless plates, (0.40 g, 49 %) m.p. 190-192 °C; R_f = 0.51, 2:1 ethyl acetate-hexane; (Found C, 62.7; H, 4.47; N, 4.8 %; $C_{15}H_{13}NO_5$ requires C, 62.7; H, 4.52; N, 4.9 %); ν_{max} ($CHCl_3$) 1 785, 1 774 and 1 748 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.42-7.27, 5H, m, -Ph; 4.38-4.43, 2H, m, 3α/β–H; 4.12, 1H, d, J=7.9 Hz, 6β–H; 4.02, 1H, dd, J=7.9, J'=9.1 Hz, 7β–H; 3.86, 1H, dd, J=4.4, J'=7.7 Hz, 2α–H; 3.54, 1H, dt, J=2.0, J'=9.1 Hz, 8β–H; 3.46, 1H, dd, J=2.0, J'=12.8 Hz, 9α/β–H; 3.15, 1H, dd, J=9.2/12.8 Hz, 9α/β–H; δ_C (50 MHz, $CDCl_3$) 172.1, 169.8, 164.6, 134.2, 129.4, 129.3, 128.1, 73.5, 63.9, 58.7, 54.7, 48.6, 44.0; m/z (DCI+, NH_3) 305 (100 %), 288 (30 %, M+1), 104 (65 %); $[\alpha]_D^{20}$ +66.1 (c 0.58, $CHCl_3$), *ent*–**9** $[\alpha]_D^{20}$ –65.8 (c 0.60, $CHCl_3$).

2(R),6(R),7(S),8(R) dimethyl 2–phenyl–1–aza–4–oxa[4.3.0^{1,5}]bicyclononan–5–one–7,8–dicarboxylate (**10**)

Colourless filaments, (0.30 g, 20 %) m.p. 168-169 °C; R_f = 0.51, 2:1 ethyl acetate-hexane; (Found C, 61.5; H, 5.86; N, 4.3; $C_{17}H_{19}NO_6$ requires C, 61.3; H, 5.71; N, 4.2 %); ν_{max} ($CHCl_3$) 1 747 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.40-7.26, 5H, m, -Ph; 4.65, 1H, d, J=7.3 Hz, 6β–H; 4.26, 2H, d, J=2.3 Hz, 3α/β–H; 3.79, 1H, dd, J=4.8, J'=10 Hz, 2α–H; 3.77, 3H, s, -CO_2Me; 3.72, 3H, s, -CO_2Me; 3.69, 1H, t, J=7.3 Hz, 7β–H; 3.42, 1H, dt, J=1.4, J'=5.5 Hz, 8β–H; 3.29, 1H, dd, J=1.4, J'=9.5 Hz, 9α/β–H; 2.76, 1H, dd, J=5.5, J'=9.5 Hz, 9α/β–H; δ_C (50 MHz, $CDCl_3$) 172.1, 170.8, 137.3, 128.9, 128.5, 127.1,.71.9, 63.8, 58.9, 55.9, 52.4, 52.3, 47.5, 45.6; m/z (DCI+, NH_3) 334 (100 %, M+1), 104 (60%); $[\alpha]_D^{20}$ +6.0 (c 0.73, $CHCl_3$), *ent*–**10** $[\alpha]_D^{20}$ –6.2 (c 0.75, $CHCl_3$).

2(R),6(R),7(R),8(S) 2–phenyl–dimethyl 1–aza–4–oxa[4.3.0^{1,5}]bicyclononan–5–one–7,8–dicarboxylate (**11**)

Colourless needles, (0.09 g, 6 %); m.p. 139–141 °C; R_f = 0.45, 2:1 ethyl acetate-hexane; (Found C, 61.4; H, 5.79; N, 4.1; $C_{17}H_{19}NO_6$ requires C, 61.3; H, 5.71; N, 4.2 %); ν_{max} ($CHCl_3$) 1 736 and 1 700 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.43-7.27, 5H, m, -Ph; 4.45, 1H, d, J=6.2 Hz, 6β–H; 4.23-4.30, 3H, m, 2α and 3α/β–H; 3.74, 1H, m, 7α–H; 3.73, 3H, s, -CO_2Me; 3.67, 3H, s, -CO_2Me; 3.35, 1H, dt, J=7.0, J'=11.8 Hz, 8α–H; 3.22, 1H, dd, J=7.1, J'=9.3 Hz, 9α/β–H; 3.08, 1H, dd, J=9.3, J'=11.8 Hz, 9α/β–H; δ_C (50 MHz,

$CDCl_3$) 172.2, 170.4, 170.3, 137.7, 129.3, 128.8, 128.5, 127.7, 127.4, 73.2, 63.0, 62.5, 54.1, 52.3, 52.1, 49.8, 45.2; m/z (DCI+, NH_3) 334 (100 %, M+1), 289, 104 (40%); $[\alpha]_D^{20}$ –14.7 (c 0.87, $CHCl_3$), *ent*–**11** $[\alpha]_D^{20}$ +14.3 (c 0.85, $CHCl_3$).

2(R),6(R) dimethyl 2–phenyl–1–aza–4–oxa[4.3.0^{1,6}]bicyclononan–7–en–5–one–7,8–dicarboxylate (**12**)

Pale yellow foam, (0.37 g, 18 %) m.p. 52-55 °C; R_f = 0.35, 2:1 ethyl acetate-hexane; (Found C, 61.4; H, 5.28; N, 4.46; $C_{17}H_{17}NO_6$ requires C, 61.6; H, 5.13; N, 4.2 %); ν_{max} ($CHCl_3$) 1 741, 1 700 and 1593 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.43-7.21, 5H, m, -Ph; 4.76, 1H, t, J=4 Hz, 2α–H; 4.72, 1H, dd, J=4, J'=12 Hz, 3β–H_B; 4.68, 1H, s, 6β–H; 4.55, 1H, dd, J=4, J'=12 Hz, 3α–H; 4.16, 2H, d, J=4 Hz, 9α/β–H; 3.83, 3H, s, -CO_2Me; 3.61, 3H, s, -CO_2Me; δ_C (50 MHz, $CDCl_3$) 166.9, 165.4, 164.8, 151.6, 135.0, 129.4, 129.1, 128.8, 126.1, 90.1, 69.9, 56.8, 53.1, 51.1, 47.6; m/z (DCI+, NH_3) 332 (20 %, M+1), 320 (100%), 104 (18%); $[\alpha]_D^{20}$ –76 (c 0.82, $CHCl_3$), *ent*–**12** $[\alpha]_D^{20}$ +74.8 (c 0.80, $CHCl_3$).

2(R),6(R) methyl 2–phenyl–1–aza–4–oxa[4.3.0^{1,6}]bicyclononan–7–en–5–one–7–carboxylate (**13**)

Colourless needles,.(0.20 g, 17 %) m.p. 167-169 °C; R_f = 0.56, 2:1 ethyl acetate-hexane; (Found C, 65.6; H, 5.45; N, 4.9; $C_{15}H_{15}NO_4$ requires C, 65.9; H, 5.50; N, 5.1 %); ν_{max} ($CHCl_3$) 1 744 and 1 726 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.46-7.32, 5H, m, -Ph; 6.92, 1H, dd, J=1.7, J'=4.1 Hz, 8–H; 5.09, 1H, dt, J=1.7, J'=6.3 Hz, 6β–H; 4.31, 1H, dd, J=4.0, J'=11.8 Hz, 3α/β–H; 4.25, 1H, t, J=10.8 Hz, 3α/β–H; 4.03, 1H, dt, J=2.2, J'=16.7 Hz, 9α–H; 3.94, 1H, dd, J=4.0, J'=10.8 Hz, 2α–H; 3.84, 3H, s, -CO_2Me; 3.53, 1H, ddd, J=1.9, J'=6.3, J''=16.7 Hz, 9β–H; n.O.e. expt: 6.90, ***8–H***–9β-H (3.6%), –9α-H (5.7%); 5.10, ***6β–H***–3α-H (6.2%); 4.03, ***9α–H***–9β-H_F (23.8%), –8-H (10.9%), –Ph (2%); 3.95, ***2α–H***–9β-H (7.6%), –3β-H (6.9%), –Ph (3%); 3.53, ***9β–H***–2α-H (10.2%), –9α-H (25.7%), –8-H (7%); δ_C (50 MHz, $CDCl_3$) 140.5, 129.9, 129.6, 128.6,.127.5, 127.1, 71.8, 65.2, 64.4, 60.9, 51.9; m/z (DCI+, NH_3) 291, 274 (100 %, M+1), 229, 104 (30%); $[\alpha]_D^{20}$ –32.8 (c 0.83, $CHCl_3$), *ent*–**13** $[\alpha]_D^{20}$ +33.6 (c 0.83, $CHCl_3$).

General method for the preparation of compounds (16) – (18)

Paraformaldehyde (10 equiv.) was added to a solution of dipolarophile (5–7 equiv.) in sodium-dried toluene (300 ml for 1 equiv. of **14**). The flask was fitted with a condenser and a Soxhlet extractor containing activated 3Å, and the mixture heated to reflux with stirring under nitrogen. Morpholinone (**14**) (5 mmol, 1 equiv.) dissolved in toluene (10 ml) was added dropwise *via* a cannula to by–pass the Soxhlet extractor. After 2h, the reaction mixture was allowed to cool to room temperature and filtered to remove excess paraformaldehyde. Removal of solvent *in vacuo* yielded the crude mixture of products along with excess dipolarophile. Column chromatography using gradient elution, typically 3:1 hexane / ethyl acetate to 1:1 hexane / ethyl acetate, furnished the pure compounds:

N–phenyl 2(R),6(R),7(S),8(R) 6–isopropyl–2–phenyl–1–aza–4–oxa[4.3.0^{1,6}]bicyclononan–5–one–7,8–dicarboximide (**16**)

Colourless needles. (1.25 g, 34 %) m.p. 220-222 °C; R_f = 0.50, 2:1 ethyl acetate-hexane; (Found C, 71.33; H, 6.17; N, 7.0; $C_{24}H_{24}N_2O_4$ requires C, 71.29; H, 5.94; N, 6.9 %); ν_{max} ($CHCl_3$) 1 784, 1 738, 1 703 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.53-7.27, 10H, m, -Ph; 4.20, 1H, t, J=10.4 Hz, 3α/β–H; 4.13, 1H, dd, J=3.4, J'=11.3 Hz, 3α/β–H; 3.97, 1H, d, J=8.0 Hz, 7β–H; 3.87, 1H, dd, J=3.4, J'=10.4 Hz, 2α–H; 3.60, 1H, dd, J=9.8, J'=14.1 Hz, 9β–H; 3.40, 1H, dt, J=3.0, J'=8.0 Hz, 8β–H; 3.25, 1H, dd, J=3.0, J'=14.2 Hz, 9α–H; 2.18, 1H, m, -*i*Pr-CH; 1.32, 3H, d, J=6.8 Hz, *i*Pr-Me; 1.23, 3H, d, J=6.8 Hz, *i*Pr-Me; n.O.e. expt: 4.20, ***3β–H***–*i*Pr-Me (4 %), –Ph (8.6 %); 4.15, ***3α–H***–2α-H (9 %), –3β-H (8 %); 3.97, ***7β–H***–*i*Pr-Me (2.2, 7.3 %), *i*Pr-CH (5.6 %); –8β-H (9 %); 3.87, ***2α–H***–9α-H (3.8 %), –3α-H (5 %), –Ph (15 %); 3.60, ***9β–H***–

*i*Pr-CH (3.8 %), –9a-H_G (32 %), –8β-H (10 %); 3.40, ***8β-H***–*i*Pr-CH (3.2 %), –9b-H_F (5 %), –7b-H_D (9 %); 3.25, ***9α-H***–9β-H (24.4 %), –2α-H (5.8 %); δ_C (50 MHz, $CDCl_3$) 176.8, 175.0, 166.8, 137.1, 132.0, 129.3, 129.1,.128.7, 127.8, 125.8, 72.6, 61.9, 54.8, 53.5, 44.4, 37.0, 18.5, 18.1; m/z (DCI+, NH_3) 422, 405 (50 %, M+1), 361 (100 %), 104 (20 %); $[\alpha]_D^{20}$ –42.8 (c 1.29, $CHCl_3$).

N–methyl 2(R),6(R),7(S),8(R) 6–isopropyl–2–phenyl–1–aza–4–oxa[4.3.0^{1,6}]bicyclononan–5–one–7,8–dicarboximide (**17**)

Colourless rhombs. (1.44 g, 46 %) m.p. 215-216 °C; R_f = 0.42, 2:1 ethyl acetate-hexane; (Found C, 66.7; H, 6.63; N, 8.4; $C_{19}H_{22}N_2O_4$ requires C, 66.7; H, 6.43; N, 8.2 %); ν_{max} ($CHCl_3$) 1 785, 1 751 and 1 699 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.37-7.22, 5H, m, -Ph; 4.14, 1H, t, J=10.8 Hz, 3α/β–H; 4.08, 1H, dd, J=3.4, J'=11.3 Hz, 3α/β–H; 3.77, 1H, d, J=7.9 Hz, 7β–H; 3.63, 1H, dd, J=3.4, J'=10.4 Hz, 2α–H; 3.46, 1H, dd, J=9.8, J'=14.1 Hz, 9β–H; 3.23, 1H, ddd, J=3.0, J'=7.9, J''=10.4 Hz, 8β–H; 3.08, 1H, dd, J=3.0, J'=14.1 Hz, 9α–H; 3.01, 3H, s, -NMe; 2.13, 1H, sept, J=6.8, -*i*Pr-CH; 1.27, 3H, d, J=6.8 Hz, *i*Pr-Me; 1.18, 3H, d, J=6.8 Hz, *i*Pr-Me; n.O.e. expt: 3.80, ***7β-H***–*i*Pr-Me (10.3 %), –*i*Pr-CH (7.3 %), –8β-H (8.5 %); 3.60, ***2α-H***–9α-H (3 %), –3α-H (7.6 %), –Ph (10 %); 3.50, ***9β-H***–*i*Pr-CH (9.5 %), –9α-H (31 %), –8β-H (10.2 %); 3.25, ***8β-H***–7β-H (10.2 %), –9β-H (6.6 %); 3.10, ***9α-H***–8β-H (2.9 %), –9β-H (24 %), –2α-H (6.3 %), –Ph (2 %); 2.12, ***iPr-CH***–iPr-Me (15.2 %), –8β-H (3.7 %), –9β-H (7.5 %), –7β-H (5.6 %); δ_C (50 MHz, $CDCl_3$) 178.0, 176.2, 166.8, 136.9, 132.0, 129.1, 129.0,.127.8, 125.8, 72.5, 61.6, 54.2, 53.3, 44.1, 36.8, 25.5, 18.4, 18.1; m/z (DCI+, NH_3) 360, 343 (100 %, M+1), 299 (65%), 104 (8%); $[\alpha]_D^{20}$ +51.9 (c 0.78, $CHCl_3$).

N–phenyl 2(R),6(R),7(R),8(S) 6–isopropyl–2–phenyl–1–aza–4–oxa[4.3.0^{1,6}]bicyclononan–5–one–7,8–dicarboximide (**18**)

Colourless needles, (0.25 g, 7 %) m.p. 205-208 °C; R_f = 0.50, 2:1 ethyl acetate-hexane; (Found C, 71.37; H, 5.83; N, 6.78; $C_{24}H_{24}N_2O_4$ requires C, 71.29; H, 5.94; N, 6.9 %); ν_{max} ($CHCl_3$) 1 764 and 1 723 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.48-7.26, 10H, m, -Ph; 4.28, 1H, t, J=11.0 Hz, 3α/β–H; 4.21, 1H, dd, J=3.2, J'=11.5 Hz, 3α/β–H; 4.19, 1H, d, J=10.4 Hz, 7α–H; 3.96, 1H, dd, J=3.2, J'=10.5 Hz, 2α–H; 3.69, 1H, q, J=9.7 Hz, 8α–H; 3.38, 1H, dd, J=9.7, J'=13.7 Hz, 9α–H; 3.20, 1H, dd, J=9.6, J'=13.7 Hz, 9β–H; 3.00, 1H, sept, J=6.6, -*i*Pr-CH; 1.22, 3H, d, J=6.6 Hz, *i*Pr-Me; 1.06, 3H, d, J=6.6 Hz, *i*Pr-Me; n.O.e. expt: 4.00, ***2α-H***–9α-H (4 %), –8α-H (5 %), –3α-H (7 %), –Ph (11 %); 3.70, ***8α-H***–9α-H (5 %), –2α-H (3.3 %), –7α-H (9.5 %); 3.40, ***9α-H***–9β-H (25.6 %), –8α-H (7.5 %); 3.20, ***9β-H***–*i*Pr-Me (7.3 %), –9α-H (19.7 %); 3.00, ***iPr-CH***–*i*Pr-Me (7.7 %), –3β-H (3 %); δ_C (50 MHz, $CDCl_3$) 175.2, 173.8, 172.6, 137.6, 131.9, 129.3, 129.1,.128.7, 127.9, 126.4, 72.2, 61.4, 56.1, 55.2, 43.6, 35.2, 19.6, 18.1; m/z (DCI+, NH_3) 422, 405 (100 %, M+1), 361 (35%), 104 (8%); $[\alpha]_D^{20}$ –1.08 (c 1.0, $CHCl_3$).

Preparation of Michael adduct (19)

Colourless powder, (0.264 g, 39 %); m.p. 178–180 °C; R_f = 0.57, 2:1 ethyl acetate-hexane; (Found C, 63.0; H, 6.42; N, 3.8; $C_{19}H_{23}NO_6$ requires C, 63.2; H, 6.37; N, 3.9 %); ν_{max} ($CHCl_3$) 1 766, 1 738 and 1 733 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.45-7.27, 5H, m, -Ph; 4.79, 1H, dd, J=6.2, J'=12.0 Hz, 2–H; 4.68, 1H, s, =$CHCO_2Me$; 4.47, 1H, dd, J=6.2, J'=12.9 Hz, 3α–H; 4.35, 1H, t, J=12.4 Hz, 3β–H; 3.87, 1H, d, J=9.8 Hz, 6–H; 3.78, 3H, s, -CO_2Me; 3.56, 3H, s, -CO_2Me; 2.21, 1H, dsept., J=6.7, J'=9.8 Hz, -*i*Pr-CH; 1.32, 3H, d, J=6.6 Hz, *i*Pr-Me; 1.06, 3H, d, J=6.6 Hz, *i*Pr-Me; δ_C (50 MHz, $CDCl_3$) 167.1, 166.9, 164.8, 153.8, 135.2, 129.5, 128.9, 126.2, 92.0, 67.6, 67.4, 60.0, 52.9, 51.0, 32.5, 20.8, 18.9; m/z (DCI+, NH_3) 362 (100 %, M+1), 318, 261, 104 (48%). The product showed no optical activity at a range of wavelengths.

General procedure for the preparation compounds (20) – (22)

The cycloadduct (**16**) – (**18**) (1.0 mmol) was dissolved in methanol (125 ml), and Pearlman's Catalyst (palladium hydroxide, 300 mg) and trifluoroacetic acid (0.5 ml) added to the stirred solution. The resultant mixture was stirred under one atmosphere of hydrogen at room temperature for 18 h. Removal of the catalyst by filtration through a Celite© pad followed by evaporation of the solvent *in vacuo* furnished the crude free amino acid. Dry flash reverse-phase chromatography,[18] eluting with 1:1 methanol / water, yielded the pure amino acid:

2(R),3(S),4(R) 2–isopropyl–3,4–(N–phenyl dicarboximido)pyrrolidine–2–carboxylic acid (**20**)

Colourless filaments. (0.27 g, 72 %), 255-260 °C (dec.); R_f = 0.80, reverse-phase plates, 1:1 methanol / water; (Found C, 63.5; H, 5.91; N, 9.24; $C_{16}H_{18}N_2O_4$ requires C, 63.6; H, 5.96; N, 9.27 %); ν_{max} (KBr disc) 2 400-2 800, 1 780, 1 718 cm^{-1}; δ_H (200 MHz, D_4-MeOD) 7.5-7.3, 5H, m, -Ph; 3.91-3.77, 3H, m, 4β–H, 5α/β–H; 3.52, 1H, d, J=9.2 Hz, 3β–H; 2.3, 1H, m, -*i*Pr-CH; 1.3, 3H, d, J=6.3 Hz, *i*Pr-Me; 1.1, 3H, d, J=6.3 Hz, *i*Pr-Me; δ_C (50 MHz, D_6-DMSO) 176.6, 174.5, 170.1, 132.9, 128.7, 128.2, 127.1, 77.8, 51.4, 46.6, 45.9, 33.6, 18.5, 18.0; m/z (DCI+, NH_3) 317, 303 (100 %, M+1), 257 (70%), 215 (45%), 68 (38%); $[\alpha]_D^{20}$ –21.3 (c 0.78, 1 M HCl).

2(R),3(S),4(R) 2–isopropyl–3,4–(N–methyl dicarboximido)pyrrolidine–2–carboxylic acid (**21**)

Colourless solid. (0.27 g, 77 %), 250-253 °C (dec.); R_f = 0.82, reverse-phase plates, 1:1 methanol-water; (Found C, 54.7; H, 6.83; N, 11.5 %; $C_{11}H_{16}N_2O_4$ requires C, 55.0; H, 6.67; N, 11.7 %); ν_{max} (KBr disc) 2 400-2 800, 1 780, 1 717, 1 629 cm^{-1}; δ_H (200 MHz, D_4-MeOD), 3.72-3.52, 3H, m, 4β–H, 5α/β–H; 3.45, 1H, d, J=8 Hz, 3β–H; 2.9, 3H, s, -NMe; 2.25, 1H, m, -*i*Pr-CH; 1.28, 3H, d, J=7.2 Hz, *i*Pr-Me; 1.1, 3H, d, J=7.2 Hz, *i*Pr-Me; δ_C (50 MHz, D_6-DMSO) 177.6, 175.6, 171.1, 76.7, 51.5, 46.7, 46.4, 33.4, 24.5, 18.1, 17.8; m/z (DCI+, NH_3) 241 (15 %, M+1), 195 (100%), 179 (18%), 83 (18%); $[\alpha]_D^{20}$ +15.3 (c 0.75, 1 M HCl).

2(R),3(R),4(S) 2–isopropyl–3,4–(N–phenyl dicarboximido)pyrrolidine–2–carboxylic acid (**22**)

Colourless solid. (0.040 g, 74 %), 255-260 °C (dec.); R_f= 0.50, reverse-phase plates, 1:1 methanol-water; (Found C, 63.5; H, 5.92; N, 9.3 %; $C_{16}H_{18}N_2O_4$ requires C, 63.6; H, 5.96; N, 9.3 %); ν_{max}(KBr disc) 2 400-2 800, 1 775, 1705 cm^{-1}; δ_H (200 MHz, D_4-MeOD) 7.5-7.2, 5H, m, -Ph; 3.77-3.71, 3H, m, 4α–H, 5α/β–H; 3.61, 1H, d, J=9.0 Hz, 3α–H; 2.3, 1H, m, -*i*Pr-CH; 1.3, 3H, d, J=6.3 Hz, *i*Pr-Me; 1.1, 3H, d, J=6.3 Hz, *i*Pr-Me; δ_C (50 MHz, D_6–DMSO) 177.3, 175.9, 172.1, 133.3, 127.7, 126.8, 125.1, 78.2, 54.4, 46.3, 45.3, 35.1, 18.8, 18.3; m/z (DCI+, NH_3) 303 (15 %, M+1), 257 (100%), 94 (26%), 44 (38%); $[\alpha]_D^{20}$ +19.6 (c = 0.75, 1 M HCl).

Preparation of adducts (23) – (26)

Freshly distilled benzaldehyde (10 equiv.) was added to a solution of *N*-methyl maleimide (7 equiv.) in sodium-dried benzene (300 ml). The flask was fitted with a condenser and a Soxhlet extractor containing activated 3Å sieves, and the mixture heated to reflux with stirring under nitrogen. Morpholinone (**1**) (3 mmol, 1 equiv.) dissolved in toluene (10 ml) was added dropwise *via* a cannula to by–pass the Soxhlet extractor. After 2h, the reaction mixture was allowed to cool to room temperature. Filtration followed by removal of solvent *in vacuo* yielded the crude mixture of products along with excess *N*-methyl maleimide as a pale yellow oil which partially crystallised on standing. Column chromatography using a gradient of 3:2 hexane-ethyl acetate to 1:1 ethyl acetate-hexane furnished the pure cycloadducts:

N–methyl 2(R),6(R),7(R),8(S),9(R) 2,9–diphenyl–1–aza–4–oxa[4.3.0^{1,6}]bicyclononan–5–one–7,8–dicarboximide (**23**)

Colourless needles, (0.136 g, 13 %) m.p. 188-191 °C; R_f = 0.54, 2:1 ethyl acetate/hexane; (Found C, 70.0; H, 5.23; N, 7.1; $C_{22}H_{20}N_2O_4$ requires C, 70.2; H, 5.32; N, 7.4 %); ν_{max} ($CHCl_3$) 1 753 and 1 708 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.27-6.89, 10H, m, -Ph; 4.78, 1H, s, 6β–H; 4.38, 1H, dd, J=5.9, J'=12.5 Hz, 3β–H; 4.27, 1H, t, J=11.6 Hz, 3α–H; 4.22, 1H, d, J=9.1 Hz, 9α–H; 4.07, 1H, d, J=8.1 Hz, 7α–H; 3.78, 1H, dd, J=5.9, J'=11.5 Hz, 2α–H; 3.52, 1H, t, J=8.5 Hz, 8α–H; 2.96, 3H, s, –NMe; n.O.e. expt: 4.80, ***6β-H***–7α-H (3.8 %), –3α-H (5.1 %); 4.38, ***3β-H***–2α-H (6.6 %), –3α-H (4.7 %); 4.27, ***3α-H***–3β-H (10.8 %), –6β-H (8.7 %); 4.21, ***9α-H***–8α-H (16.4 %), –2α-H(15.6 %); 4.08, ***7α-H***–8α-H (8.6 %), –6α-H (4.5 %); 3.78, ***2α-H***–9α-H (9.9 %), –3β-H (6.7 %); 3.53, ***8α-H***–7α-H (10.2 %), –9α-H (10.9 %); δ_C (50 MHz, $CDCl_3$) 177.4, 174.4, 170.1, 138.3, 134.4, 128.6, 128.5,.128.4, 128.0, 126.8, 72.9, 70.8, 61.1, 61.0, 49.0, 45.8, 25.1; m/z (DCI+, NH_3) 394, 377 (100 %, M+1), 104 (15%); $[\alpha]_D^{20}$ +88.5 (c 0.60, $CHCl_3$).

N–methyl 2(R),6(R),7(S),8(R),9(R) 2,9–diphenyl–1–aza–4–oxa[4.3.0^{1,6}]bicyclononan–5–one–7,8–dicarboximide (**24**)

Colourless rods, (0.405 g, 38 %) m.p. 183-186 °C; R_f = 0.46, 2:1 ethyl acetate/hexane; (Found C, 70.2; H, 5.30; N, 7.4; $C_{22}H_{20}N_2O_4$ requires C, 70.2; H, 5.32; N, 7.4 %); ν_{max} ($CHCl_3$) 1 779, 1 754 and 1 698 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.25-7.09, 10H, m, -Ph; 4.60, 1H, d, J=8.1 Hz, 9α–H; 4.28, 1H, d, J=4.8 Hz, 6β–H; 4.25, 2H, m, 3α/β–H; 3.81, 1H, t, J=8.7 Hz, 8β–H; 3.73, 1H, dd, J=6.8, J'=8.7 Hz, 2α–H; 3.37, 1H, dd, J=4.8, J'=9.1 Hz, 7β–H; 3.05, 3H, s, –NMe; n.O.e. expt: 4.65, ***9α-H***–8β-H (14.1 %), –3α/β-H (4.2 %); 4.28, ***3α/β-H***–2α-H (7.4 %), –9α-H (7.3 %); 3.85, ***8β-H***–7β-H (11.3 %), –6β-H (7.3 %), –9α-H (13.2 %); 3.75, ***2α-H***–3α/β-H (17.4 %); 3.40, ***7β-H***–8β-H (10.1 %), –6β-H (4 %); δ_C (50 MHz, $CDCl_3$) 176.8, 175.2, 166.9, 139.2, 136.5, 128.9, 128.6,.127.9, 127.4, 127.0, 72.3, 70.3, 61.5, 60.7, 52.7, 47.8, 25.4; m/z (DCI+, NH_3) 394, 377 (100 %, M+1), 104 (25%); $[\alpha]_D^{20}$ +38.9 (c 1.10, $CHCl_3$).

N–methyl 2(R),6(R),7(R),8(S),9(S) 2,9–diphenyl–1–aza–4–oxa[4.3.0^{1,6}]bicyclononan–5–one–7,8–dicarboximide (**25**)

Colourless needles, (0.100 g, 9 %), m.p. 216–220 °C; R_f = 0.60, 2:1 ethyl acetate/hexane; (Found C, 70.3; H, 5.52; N, 7.5 %; $C_{22}H_{20}N_2O_4$ requires C, 70.2; H, 5.32; N, 7.4 %); ν_{max} ($CHCl_3$) 1 772, 1 749 and 1 705 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.41–7.04, 10H, m, -Ph; 4.43, 1H, d, J=2.1 Hz, 9β–H; 4.34, 1H, dd, J=3.2, J'=8.4 Hz, 7α–H; 4.33, 1H, d, J=3.3 Hz, 6β–H; 4.22, 2H, m, 3α/β–H; 3.74, 1H, dd, J=5.7, J'=9.7 Hz, 2α–H; 3.57, 1H, dd, J=2.1, J'=8.4 Hz, 8α–H; 3.12, 3H, s, –NMe; n.O.e. expt: 4.43, ***9β-H***–8α-H (4.9 %), –2α-H(2.4 %), 2β-Ph, 9α-Ph (3.5 %, 13.5 %); 3.74, ***2α-H***–9β-H (2.2 %), –3α/β-H (6.1 %), 2β-Ph, 9α-Ph (10 %, 4.6 %); 3.57, ***8α-H***–6β-H (8.4 %), –9β-H (3.7 %), 9α-Ph (6.2 %); δ_C (50 MHz, $CDCl_3$) 177.2, 177.1, 170.6, 137.7, 136.2, 134.2, 129.3, 128.9, 128.8, 128.5, 128.3, 127.2, 71.3, 67.6, 61.8, 56.8, 52.4, 45.3, 25.5; m/z (DCI+, NH_3) 394, 377 (100 %, M+1), 104 (30%); $[\alpha]_D^{20}$ –101.0 (c 0.6, $CHCl_3$).

N–methyl 2(R),6(R),7(S),8(R),9(S) 2,9–diphenyl–1–aza–4–oxa[4.3.0^{1,6}]bicyclononan–5–one–7,8–dicarboximide (**26**)

Colourless powder, (0.117 g, 11 %), m.p. 232-235 °C; R_f = 0.31, 2:1 ethyl acetate/hexane; (Found C, 70.19; H, 5.25; N, 7.36; $C_{22}H_{20}N_2O_4$ requires C, 70.2; H, 5.32; N, 7.4 %); ν_{max} ($CHCl_3$) 1 775, 1 738 and 1 699 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.48–7.04, 10H, m, -Ph; 4.92, 1H, dd, J=4.5, J'=11.2 Hz, 3α–H; 4.75, 1H, d, J=11.2 Hz, 3β–H; 4.05, 1H, d, J=4.4 Hz, 2α–H; 3.68, 1H, d, J=9.2 Hz, 6β–H; 3.66, 1H, dd, J=5.3, J'=7.5 Hz, 8β–H; 3.36, 1H, d, J=5.4 Hz, 9β–H; 3.25, 1H, dd, J=7.3, J'=9.5 Hz, 7β–H; 2.93, 3H, s, –NMe;

n.O.e. expt: 4.95, ***3α-H***–2α-H (9.2 %), –2β-H (20.0 %); 4.75, ***2β-H***–2α-H (3.0 %), –3β-H (29.1 %), –Ph (3.6%); 4.05, ***2α-H***–2β-H (3.5 %), –3β-H (5.8 %), –Ph (11.2 %); 3.30, ***9β-H***–8β-H (18.3 %), –Ph (5.3 %); 3.25, ***7β-H***–6β/8β-H (19.5 %); δ_C (50 MHz, $CDCl_3$) 182.5, 175.6, 162.0, 149.7, 134.6, 131.7, 129.3, 129.1, 128.9, 128.7, 65.6, 59.1, 54.2, 48.0, 45.3, 29.7, 24.9; m/z (DCI+, NH_3) 394, 377 (100 %, M+1), 104 (15%); $[\alpha]_D^{20}$ –20.4 (c 0.25, $CHCl_3$).

Preparation of cycloadduct (27)

Freshly distilled benzaldehyde (10 equiv.) was added to a solution of dimethyl maleate (7 equiv.) in sodium-dried benzene.(300 ml). The flask was fitted with a condenser and a Soxhlet extractor containing activated 3Å sieves, and the mixture heated with stirring to reflux under nitrogen. Morpholinone (**1**) (3 mmol, 1 equiv.) dissolved in benzene (10 ml) was added dropwise *via* a cannula to by–pass the Soxhlet extractor. After 2h, the reaction mixture was allowed to cool to room temperature. Filtration followed by removal of solvent *in vacuo* yielded the crude mixture as a pale yellow oil. Column chromatography using a gradient of 3:2 hexane-ethyl acetate to 1:1 ethyl acetate-hexane furnished pure **27** as the only indentifiable, monomeric material.

2(R),6(R),7(S),8(R),9(R) dimethyl 2,9–diphenyl–1–aza–4–oxa[4.3.0^{1,6}]bicyclononan–5–one–7,8–dicarboxylate (**27**)

Colourless rods, (0.097 g, 8 %) m.p. 207-210 °C; R_f = 0.48, 2:1 ethyl acetate/hexane; (Found C, 67.8; H, 5.55; N, 3.3; $C_{23}H_{23}NO_6$ requires C, 67.5; H, 5.62; N, 3.4 %); ν_{max} ($CHCl_3$) 1 733 and 1 723 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.27-6.96, 10H, m, -Ph; 4.72, 1H, d, J=6.3 Hz, 6β–H; 4.46, 1H, dd, J=9.7, J'=11.6 Hz, 2α–H; 4.45, 1H, d, J=10.5 Hz, 9α–H; 4.40, 2H, m, 3α/β–H; 3.90, 1H, t, J=6.8 Hz, 7β–H; 3.77, 3H, s, –CO_2Me; 3.57, 3H, s, –CO_2Me; 3.32, 1H, dd, J=7.3/10.5 Hz, 8β–H; δ_C (50 MHz, $CDCl_3$) 139.2, 136.5, 128.9, 128.6,.127.9, 127.4, 127.0, 72.3, 70.3, 61.5, 60.7, 52.7, 47.8, 25.4; m/z (DCI+, NH_3) 427, 410 (100 %, M+1), 104 (45 %); $[\alpha]_D^{20}$ –57.1 (c 0.60, $CHCl_3$).

Acknowledgement We gratefully acknowledge support for this work from the S.E.R.C. (A.S.A), and valuable assistance from Mrs Elizabeth McGuinness in carrying out NMR analyses.

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20. *Crystal data* for (**24**): $C_{22}H_{20}N_2O_4$, monoclinic, $P2_1$, a =12.7314, b = 5.6935, c = 13.2744 Å, α = 90.033, β = 99.381, γ = 90.033 °, V = 949.3 Å^3, Z = 2, D_c = 1,2679 g cm^{-3}, F(000) = 384, μ(Cu–K_α) = 6.4805 cm^{-1}. 2139 Independent reflections with $I > \sigma(I)$ were used in the analysis. Final R = 3.87, final Hamiltonian weighted R = 3.50. Data for crystallographic analysis were measured ($2\theta_{max}$ = 150°) on an Enraf–Nonius CAD 4 diffractometer using Cu–K_α radiation and ω–2θ scans. Structures were solved by direct methods and refined by least squares using the CRYSTAL package. Atomic co–ordinates, bond lengths and angles, and thermal parameters have been deposited at he Cambridge Crystallographic Data Centre.