1,3-Dipolar Cycloadditions to Unsymmetrical Ketone-Derived Chiral Stabilized Azomethine Ylides: Strategies for the Synthesis of Highly Substituted Amino Acids

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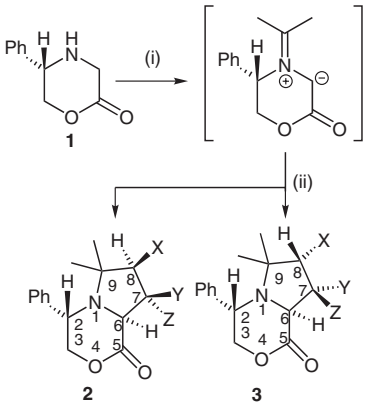
Dedicated to Professor Steven V. Ley FRS on the occasion of his 60th birthday

Abstract: We report herein, the first generation of unsymmetrical ketone-derived chiral stabilized azomethine ylides. Intramolecular and intermolecular cycloaddition strategies have been utilized to synthesize both an enantiomerically pure bicyclic proline derivative and an enantiomerically pure β-hydroxy-α-amino acid.

Key words: azomethine ylide, β-hydroxy-α-amino acid, proline, intramolecular, cycloaddition

A previous communication by this group has reported the cycloaddition of acetone-derived azomethine ylides with alkene dipolarophiles (Scheme 1).[1] These cycloadducts have been demonstrated to undergo degradation via catalytic hydrogenolysis to furnish highly substituted diastereomerically pure 5,5-dimethylprolines (Scheme 2). 5,5-Disubstitution of proline derivatives remains an important objective[2] due the profound effect of such residues upon *cis* peptide conformation[3] and stabilization of type 1 β-turn configuration.[4]

The intramolecular 1,3-dipolar cycloaddition of azomethine ylides is a useful method for the construction of biologically important heterocycles and has been the subject of a recent review.[5] Our group has reported several



Scheme 1 *Reagents and conditions*: (i) Δ, THF, $MgBr_2{\cdot}OEt_2$, acetone dimethyl ketal; (ii) dipolarophile

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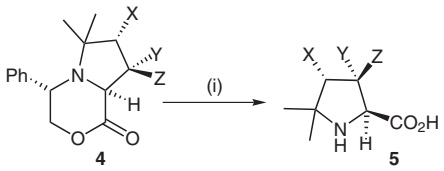
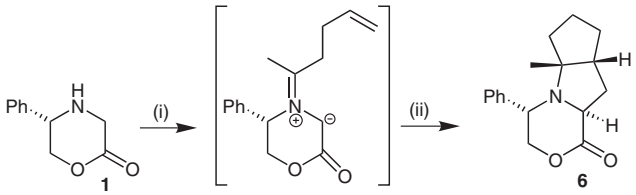


Scheme 2 *Reagents and conditions*: (i) aq MeOH Pearlman's catalyst, TFA, H_2 (5 atm)

stereoselective syntheses of bicyclic prolines via intramolecular cycloaddition of ylides derived from condensation of the (5*S*)-phenylmorpholine-2-one (**1**) template with aldehydes possessing a terminal double or triple bond.[6] Building on the success of this intramolecular strategy, a strategy towards 5-substituted bicyclic prolines utilizing a ketone equipped with an alkene tether was envisaged.

To this end, hept-6-en-2-one dimethyl ketal was synthesized by protection of the respective ketone and reacted with (5*S*)-phenylmorpholine-2-one (**1**) in the presence of magnesium bromide etherate in THF at reflux using a Soxhlet extractor loaded with 3Å molecular sieves to remove water. Gratifyingly this strategy resulted in the isolation of a single cycloadduct **6** in 20% overall purified yield with the *exo*- configuration at C-4 (Scheme 3). ^1H and ^{13}C NMR spectroscopic analyses were consistent with the predicted gross structure of the new cycloadduct and the configuration of the cycloadduct was confirmed by X-ray crystal structure determination (Figure 1).[7–10]

Following the success of the synthesis of a bicyclic proline derivative with a fused 5-membered ring, our attention turned to the synthesis of the six-membered bicyclic proline analogue. Unfortunately, the reaction of (5*S*)-phenylmorpholine-2-one (**1**) with oct-7-ene-2-one dimethyl



Scheme 3 *Reagents and conditions*: (i) and (ii) Δ, THF, $MgBr_2{\cdot}OEt_2$ (1 or 10 equiv), hept-2-ene-6-one dimethyl ketal

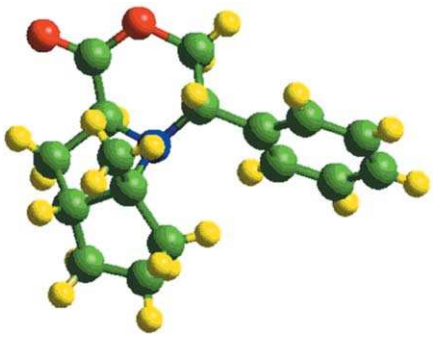
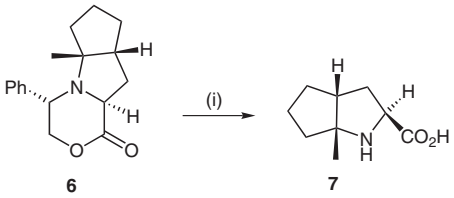


Figure 1 Crystal structure of cycloadduct **6**

acetal using the same conditions as above led only to decomposition of the starting materials; whereas use of a lower boiling point solvent (diethyl ether) resulted in recovery of the starting materials. The problem here appears to lie in the lack of stability of the ketal to the reaction conditions needed to promote ylide formation.

Hydrogenolysis of the cycloadduct **6** was achieved by stirring at room temperature in aqueous methanol using TFA and Pearlman's catalyst under five atmospheres of hydrogen for 48 hours. After work-up and removal of solvent, trituration of the resultant residue with diethyl ether afforded the bicyclic proline derivative **7** in quantitative yield (Scheme 4).



Scheme 4 *Reagents and conditions*: (i) aq MeOH TFA, Pearlman's catalyst, H_2 (5 atm)

We have observed that the presence of aromatic substituents on the azomethine ylide leads to stabilization of the ylide. Thus our attention turned to ylides derived from benzophenone in the hope that the two phenyl groups would stabilize the resultant ylide and widen the range of dipolarophiles that would react with these systems. However, reaction of benzophenone dimethyl acetal with (5*S*)-phenylmorpholine-2-one and *N*-methylmaleimide in refluxing THF in the presence of magnesium bromide etherate failed to yield any expected cycloadduct. Possibly the diphenyl-substituted ylide formed during this reaction is too sterically hindered to form or to allow the approach of the dipolarophile.

In order to reduce steric hindrance but still study the effect of adding an aryl substituent to stabilize the ylide, reaction between (5*S*)-phenylmorpholin-2-one (**1**) and acetophenone dimethyl acetal in the presence of dipolarophile was next investigated. Refluxing **1** and acetophenone dimethyl acetal in the presence of *N*-methylmaleimide and magnesium bromide etherate in THF yielded three out of the four possible cycloadducts. The stereochemistry of adduct **8a** was assigned by X-ray crystal structure determination as C-9-*syn*-C-7-*exo* and the proton at C-6 was established to be in the expected α-configuration (Figure 2).[11] The structures of the other cycloadducts were determined by ^{1}H NMR NOE experiments as *anti-exo* **8b** and *anti-endo* **8c**. No trace of the *syn-endo* adduct was detected on careful examination of the crude reaction mixture (Scheme 5).

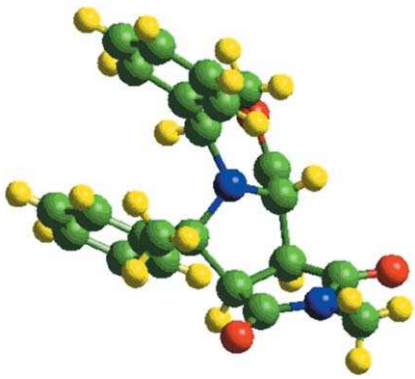
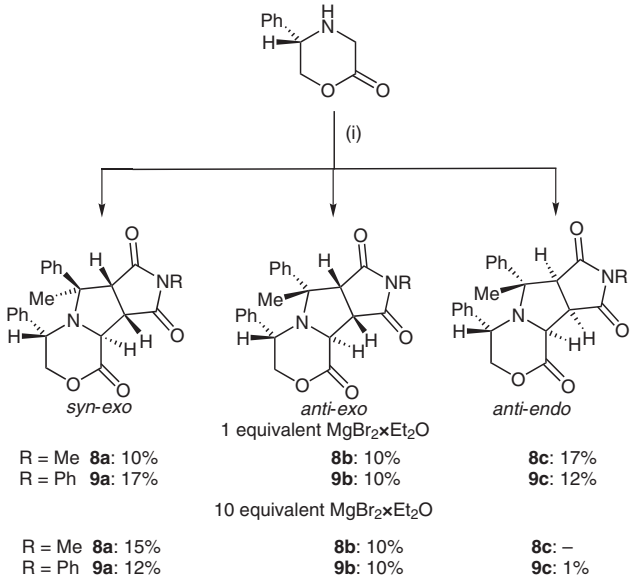


Figure 2 Crystal structure of cycloadduct **8a**



Scheme 5 *Reagents and conditions*: (i) Δ, THF, $MgBr_2{\cdot}OEt_2$, acetophenone dimethyl ketal; (ii) dipolarophile

Reaction of (5*S*)-phenylmorpholin-2-one (**1**) with acetophenone dimethyl acetal and *N*-phenylmaleimide in the presence of magnesium bromide etherate likewise yielded three adducts in the crude reaction mixture (Scheme 5). The configuration of the *anti-endo* cycloadduct **9c** was determined by X-ray crystal structure analysis (Figure 3)[11] and the two remaining adducts were assigned by ^{1}H NMR NOE experiments as the *syn-exo* **9a** and *anti-exo* **9b** cycloadducts. In both cycloadditions the *anti-endo* cycloadduct was the major product.

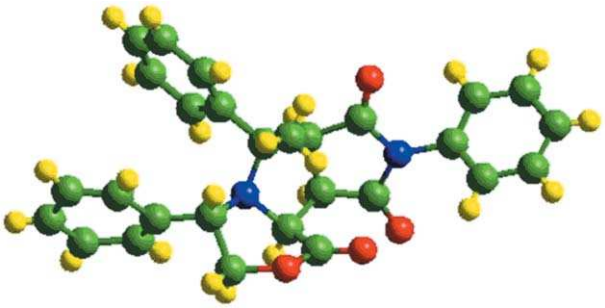
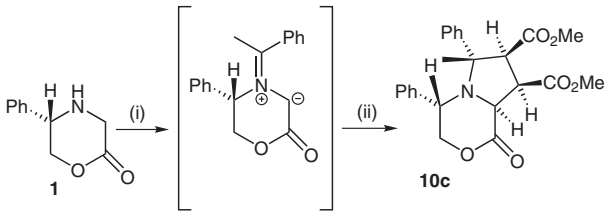


Figure 3 Crystal structure of cycloadduct **9c**

A study of the reaction of this ylide with non-maleimide dipolarophiles showed a greater stereoselectivity. Thus, reaction of (5*S*)-phenylmorpholin-2-one (**1**) with acetophenone dimethyl acetal and dimethyl maleate in the presence of magnesium bromide etherate in refluxing THF yielded only one cycloadduct, albeit in poor isolated yield (8%) (Scheme 6). Purification by flash column chromatography and X-ray crystal structure analysis of the cycloadduct revealed it to be the *anti-endo* cycloadduct **10c** (Figure 4).[11]



Scheme 6 *Reagents and conditions*: (i) Δ, THF, $MgBr_2 \cdot OEt_2$, acetophenone dimethyl ketal; (ii) dimethyl maleate

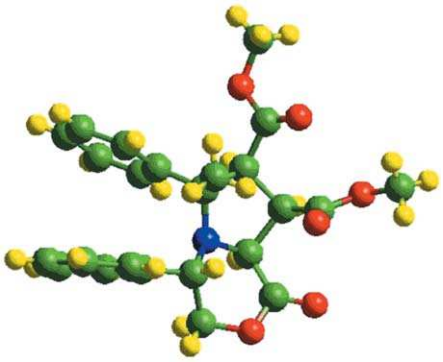
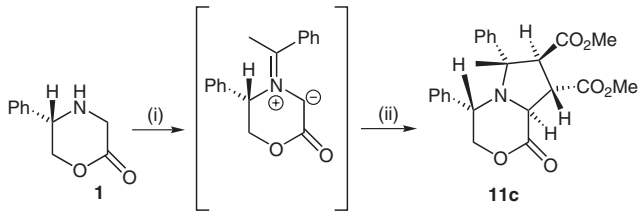


Figure 4 Crystal structure of cycloadduct **10c**

Likewise, reaction of (5*S*)-phenylmorpholin-2-one (**1**) with acetophenone dimethyl acetal and dimethyl fumarate under the same conditions yielded a single cycloadduct in 43% yield (Scheme 7). X-ray crystal structure determination (Figure 5) also revealed this to be the *anti-endo* cycloadduct **11c**.[11]

In order to investigate the reactivity of this ylide further, the cycloaddition of mono-activated alkene dipolarophiles was investigated. The reaction of (5*S*)-phenylmorpholin-2-one (**1**) with acetophenone dimethyl acetal and acrylonitrile in the presence of magnesium bromide etherate, yielded a single adduct in 20% isolated yield (Scheme 8), the configuration of which was determined to be *anti-endo*- **12c** by ^{1}H NMR NOE investigation. The cycloaddition was repeated using methyl acrylate as the dipolarophile, furnishing a single cycloadduct **13** in 38% yield upon purification by flash column chromatography (Scheme 9) and this was again assigned the *anti-endo* configuration **13c** by NOE analysis. Although these yields are modest, the reactions occur with very high diastereoselectivity. In addition, singly activated dipolarophiles are normally unreactive with stabilized ylides derived from the morpholinone template so this reactivity is noteworthy.



Scheme 7 *Reagents and conditions*: (i) Δ, THF, $MgBr_2 \cdot OEt_2$, acetophenone dimethyl ketal; (ii) dimethyl fumarate

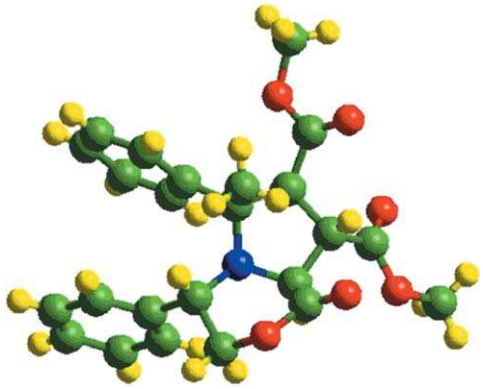
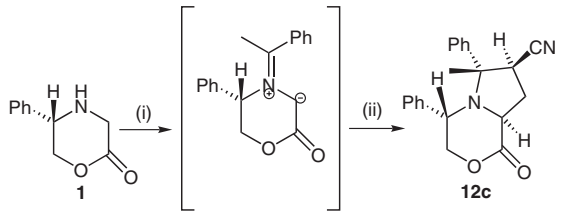
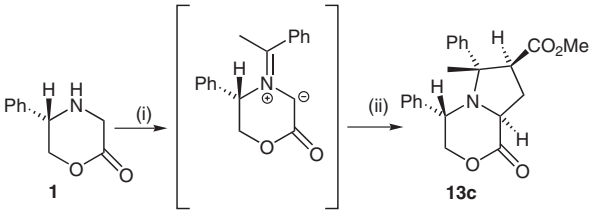


Figure 5 Crystal structure of cycloadduct **11c**



Scheme 8 (i) *Reagents and conditions*: (i) Δ, THF, $MgBr_2 \cdot OEt_2$, acetophenone dimethyl ketal; (ii) acrylonitrile, Δ

The favored formation of cycloadducts having the *anti-endo* configuration can be rationalized by invoking a cycloaddition pathway involving the *anti* ylide undergoing *endo* cycloaddition by a type 1 interaction. This result is in keeping with our previous studies with ylides derived from benzaldehyde.[12]



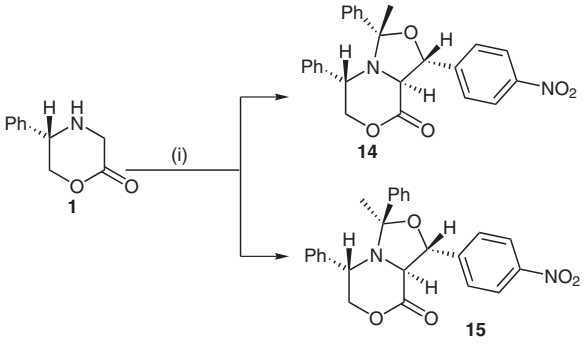
Scheme 9 (i) *Reagents and conditions*: (i) Δ, THF, $MgBr_2{\cdot}OEt_2$, acetophenone dimethyl ketal; (ii) methyl acrylate

In order to investigate the effect of switching the cycloaddition from type 1 to type 3, the cycloadditions were repeated using 10 equivalents of magnesium bromide etherate. In the case of the maleimide dipolarophiles a preference was shown for *exo* cycloaddition but no preference for reaction via the *syn* or *anti* ylide. In the case of dimethyl maleate or dimethyl fumarate dipolarophiles only the *anti-endo* configuration was observed (Schemes 6, 7). The hydrogenolysis of the major cycloadducts **8c**–**13c** to yield their corresponding 5-methyl-5-phenyl substituted prolines was attempted using the standard procedure [Pearlman's catalyst, H_2 (5 atm), MeOH–H_2O, TFA]. Unfortunately ^{1}H NMR analysis of the crude material resulting from the hydrogenolysis of the *N*-methylmaleimide cycloadduct **7c** showed a complex mixture of products and did not indicate the presence of the desired amino acid. It is proposed that additional hydrogenolysis of the second benzylamine is occurring. Repetition of the hydrogenolysis at atmospheric pressure showed two doublets δ = 1.55 and 1.47 on ^{1}H NMR analysis, which we assign to the C-5 methyl group suggesting the both benzylamine bonds had been cleaved and that an inseparable mixture of products was present.

Similarly, ^{1}H NMR analysis of the crude reaction mixtures from the hydrogenolysis of the cycloadducts formed by the cycloaddition of the other dipolarophiles revealed none of the desired amino acids. It is clear that the presence of a second benzylamine prevents the use of the acetophenone derived ylides for the synthesis of 5-methyl-5-phenyl substituted prolines.

To explore the reactivity of these acetophenone derived ylides further, it was decided to investigate the cycloaddition with aldehyde dipolarophiles. As previously demonstrated by our group with aldehyde derived cycloadducts, the products resulting from the trapping of ylides derived from (5*S*)-phenylmorpholin-2-one (**1**) with aldehydes furnish β-hydroxy-α-amino acids upon hydrogenolysis of the template.[13]

With this in mind, the reaction of (5*S*)-phenylmorpholin-2-one (**1**) with acetophenone dimethyl acetal in the presence of magnesium bromide etherate in refluxing 1,4-dioxane with *p*-nitrobenzaldehyde was attempted. After 2 hours, work-up and chromatographic purification furnished *anti-exo* **14** and *syn-exo* **15** cycloadducts in 42% and 18% yield respectively (Scheme 10). The configuration of the minor cycloadduct was confirmed by X-ray crystal structure determination (Figure 6).[11]



Scheme 10 *Reagents and conditions*: (i) Δ, THF, $MgBr_2{\cdot}OEt_2$, 1,1-dimethoxyethylbenzene, *p*-nitrobenzaldehyde

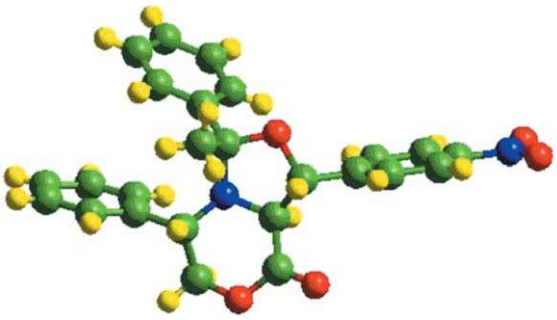
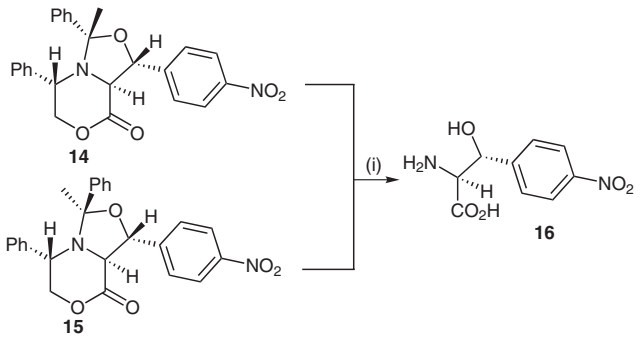


Figure 6 Crystal structure of cycloadduct **15**

Hydrogenolysis of both cycloadducts using standard procedures furnished the same product, (2*S*,3*R*)-2-amino-3-hydroxy-3-(4-aminophenyl)propanoic acid (**16**) (Scheme 11) showing the **14** and **15** to be epimeric at C-9 and indicating that stereochemical fidelity had been preserved at C-7. Thus both *syn*- and *anti*- ylides are involved in cycloaddition.



Scheme 11 *Reagents and conditions*: (i) MeOH, HCl, Δ, 1 h, then Pearlman's catalyst, TFA, H_2 (1 atm)

In conclusion we have reported the first instance of generation and trapping of unsymmetrical ketone-derived chiral stabilized azomethine yildes. In investigating the reactivity of these ylides we have demonstrated an intriguing *exo*-stereoselective intramolecular dipolar cycloaddition. Hydrogenolysis of the template yields the diastereomerically pure bicyclic proline derivative **7**. The reactivity of acetophenone derived ylides with alkene di-

polarophiles with different catalyst loading has been demonstrated. Finally a ketone derived ylide precursor has been identified which favors reaction with an electron-deficient aldehyde dipolarophile. This has been illustrated with the synthesis of the enantiomerically pure β-hydroxy-α-amino acid **16**.

Reagents were obtained from Aldrich, Fluka (Poole Dorset) and used as supplied. All aldehydes were distilled under reduced pressure before use. CH_2Cl_2 and MeCN were dried by distillation over CaH_2. THF and Et_2O were dried by distillation over sodium benzophenyl ketyl under dry N_2. Petroleum ether (PE) used refers to the fraction with boiling range 30–40 °C. TLC analysis was carried out using Merck aluminum-backed plates coated with 0.2 mm silica and were visualized either by fluorescence quenching or development using 2% aq $KMnO_4$. Flash column chromatography was carried out using Merck 60 silica gel. IR spectra were recorded on a Perkin-Elmer Paragon 1000 FT-IR spectrometer and recorded as KBr discs or as a thin film between NaCl plates. NMR spectra were recorded using a Bruker DPX250 or a Bruker AMX400 instrument. Peak positions are recorded in ppm. Deuterated solvents were purchased from Goss Scientific and were >99% pure Specific rotation measurements were recorded on a Perkin-Elmer 341 polarimeter, using the sodium D line. Melting points were recorded using a Kofler heated stage microscope and are uncorrected. Mass spectrometric data were recorded using a VG Fisons Autospec, under conditions of chemical ionization using ammonia as the ionizing source peaks are quoted in the form of *m*/*z* (relative intensity).

(2*R*,6*R*,8*S*,12*S*)-2-Methyl-12-phenyl-1-aza-10-oxa[6.4.0^{1,8}.0^{2,6}]tricyclododecan-9-one (6)

(5*S*)-5-Phenylmorpholin-2-one (**1**; 200 mg, 1.13 mmol, 1 equiv) and magnesium bromide etherate (290 mg, 1.13 mmol, 1 equiv) were refluxed under N_2 in anhyd THF for 1 h. The flask was fitted with a Soxhlet extractor containing activated 3 Å molecular sieves and with a condenser. Hept-6-en-2-one dimethyl ketal (535 mg, 3.39 mmol, 3 equiv), was added to the reaction mixture, which was then refluxed for a further 2 h. The solution was then allowed to cool down to r.t. and was filtered through a short pad of silica which was washed with Et_2O. The solvent was removed in vacuo to furnish the crude cycloadduct, which was purified by flash chromatography on silica using PE–Et_2O (5:1) to give colorless needles (61 mg, 20%); mp 103–105 °C; $[\alpha]_D^{25}$ –44.4 (*c* = 0.5, $CHCl_3$); R_f 0.35 (PE–Et_2O, 5:1).

IR (KBr): 1747 cm^{-1} (C=O).

^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.37–7.21 (5 H, m, Ph-H), 4.24–4.13 (3 H, m, 12β-H, 11β-H, 8α-H), 3.99 (1 H, dd, *J* = 9.9, 12.7 Hz, 11α-H), 2.60–2.51 (1 H, m, 7α-H), 2.19–2.15 (1 H, m, 6α-H), 1.86–1.73 (2 H, m, 7β-H, 5α-H), 1.66–1.23 (1 H, m, 4β-H), 1.53–1.44 (1 H, m, 5β-H), 1.39–1.29 (1 H, m, 4α-H), 1.24–1.15 (1 H, m, 3β-H), 1.06 (3 H, s, CH_3), 1.00–0.93 (1 H, m, 3α-H).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 175.0 (C=O), 141.1 (C_{arom}), 129.0 (CH_{arom}), 128.3 (CH_{arom}), 127.3 (CH_{arom}), 74.0 (C), 71.4 (CH_2), 59.0 (CH or CH_3), 56.6 (CH or CH_3), 50.3 (CH or CH_3), 39.4 (CH_2), 33.7 (CH_2), 30.8 (CH_2), 21.6 (CH).

MS (CI): *m*/*z* (%) = 272 (100), 104 (62).

HRMS (CI): *m*/*z* calcd for (MH^+) $C_{17}H_{22}NO_2$: 272.1650; found: 272.1649.

Anal. Calcd for $C_{17}H_{21}NO_2$: C, 75.25; H, 7.80; N, 5.16. Found: C, 75.09; H, 7.83; N, 5.09.

(1*R*,3*S*,5*R*)-2-Aza-1-methyl[3.3.0.^{1,5}]bicyclooctane-3-carboxylic Acid (7)

The cycloadduct **6** (40 mg, 0.14 mmol, 1 equiv) was dissolved in MeOH (2 mL) and H_2O (0.1 mL) in a Fisher Porter bottle. TFA (11 μL, 0.12 mmol, 1 equiv) and Pearlman's Catalyst [$Pd(OH)_2$, 40 mg] were added to the stirring suspension, which was then degassed and subjected to hydrogen at 5 atm for 24 h. The solution was then passed through a pad of Celite® to remove the catalyst and the solvent was removed in vacuo. Trituration of the crude mixture with Et_2O led to precipitation of the amino acid, which was then recrystallized from EtOH–PE and dried in vacuo to give a colorless powder (23 mg, ~100%); mp 157–160 °C; $[\alpha]_D^{25}$ –13.2 (*c* = 0.25, MeOH).

^{1}H NMR (250 MHz, CD_3OD): δ = 4.45 (1 H, dd, *J* = 7.6, 9.1 Hz, 2α-H), 2.42–2.15 (2 H, m), 2.14–1.90 (5 H, m), 1.88–1.58 (2 H, m), 1.55 (3 H, s, CH_3).

^{13}C NMR (62.5 MHz, CD_3OD): δ = 174.3 (C=O), 76.1 (C), 63.4 (CH), 51.0 (CH or CH_3), 40.1 (CH_2), 36.7 (CH_2), 33.6 (CH_2), 26.1 (CH_2), 25.8 (CH_3 or CH).

MS (CI): *m*/*z* (%) = 170 (100), 124 (51).

HRMS (CI): *m*/*z* calcd for (MH^+) $C_9H_{15}NO_2$: 170.1181; found: 170.1180.

Cycloadducts 8,9; General Procedure

Acetophenone dimethyl acetal (0.37 mL, 2.26 mmol, 2 equiv) was added via syringe to a suspension of (5*S*)-5-phenylmorpholin-2-one (**1**; 200 mg, 1.13 mmol, 1 equiv), the requisite dipolarophile (3.39 mmol, 3 equiv) and magnesium bromide etherate (290 mg, 1.13 mmol, 1 equiv) in THF (15 mL). The reaction mixture was refluxed under N_2 between 3 and 6 h, monitoring for disappearance of starting material by TLC. The solution was then allowed to cool to r.t. and filtered through a short pad of silica which was washed with Et_2O. Removal of the solvent in vacuo yielded the crude product. Flash chromatography using gradient elution, typically PE–Et_2O (2:1) to pure Et_2O, furnished the pure cycoladducts.

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

Colorless crystals (10%); mp 205–210 °C; $[\alpha]_D^{25}$ +57.1 (*c* = 0.35, $CHCl_3$); R_f 0.45 (Et_2O–PE, 1:1).

IR (KBr): 1777 (C=O), 1755 (C=O), 1703 cm^{-1} (C=O).

^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.47–7.18 (10 H, m, Ph-H), 4.71 (1 H, d, *J* = 1.7 Hz, 6α-H), 4.41 (1 H, dd, *J* = 1.7, 9.2 Hz, 7β-H), 4.05 (2 H, m, 3β-H, 3α-H), 3.86 (1 H, d, *J* = 9.2 Hz, 8-βH), 3.71 (1 H, dd, *J* = 7.7, 9.4 Hz, 2β-H), 3.94 (3 H, s, NCH_3), 1.26 (3 H, s, CH_3); NOE: H-2β → Ph-H (19.2%), H-7β → H-8β (11.1%), H-8β → H-7β (9.6%) → Ph-H (19.2%).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 178.5 (C=O), 176.0 (C=O), 172.2 (C=O), 142.2 (C), 139.9 (C), 129.3 (C_{arom}), 128.7 (C_{arom}), 127.4 (C_{arom}), 127.3 (C_{arom}), 71.3 (C-3), 70.5 (C-9), 62.2 (C-6), 56.8 (C-8), 56.7 (C-2), 46.5 (C-7), 25.4 (CH_3), 25.1 (CH_3).

MS (CI): *m*/*z* (%) = 391 (100), 104 (25).

HRMS (CI): *m*/*z* calcd for (MH^+) $C_{23}H_{22}N_2O_4$: 391.1658; found: 391.1676.

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

Oil (10%); mp 205–210 °C; $[\alpha]_D^{25}$ –73.0 (*c* = 1.00, $CHCl_3$); R_f 0.25 (Et_2O–PE, 1:1).

IR (KBr): 1779 (C=O), 1752 (C=O), 1702 cm^{-1} (C=O).

^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.14–6.81 (10 H, m, Ph-H), 4.80 (1 H, s, 6α-H), 4.33 (1 H, dd, *J* = 6.5z, 11.7 Hz, 3β-H), 4.19 (1 H, t, *J* = 11.7 Hz, 3α-H), 4.04 (1 H, d, *J* = 8.2 Hz, 7β-H), 3.64 (1 H, dd,

J = 6.5, 11.7 Hz, 2β-H), 3.20 (1 H, d, J = 8.2 Hz, 8-βH), 2.78 (3 H, s, NCH_3), 1.70 (3 H, s, CH_3); NOE: H-2β → CH_3β (6.8%), H-6α → H-3α (8.3%) → H-7β (7.9%), H-7β → H-6α (5.2%) → H-8β (11.0%) → CH_3 (6.8%), H-8β → H-7β (15.0%) → CH_3 (4.9%).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 178.2 (C=O), 175.1 (C=O), 173.1 (C=O), 140.1 (C), 139.3 (C), 128.9 (C_{arom}), 128.3 (C_{arom}), 128.0 (C_{arom}), 127.8 (C_{arom}), 127.5 (C_{arom}), 72.3 (C-9), 71.0 (C-3), 60.9 (C-6), 57.6 (C-22 or C-8), 55.9 (C-8 or C-2), 45.5 (C-7), 25.5 (CH_3), 23.3 (CH_3).

MS (CI): m/z (%) = 391 (100), 104 (73).

HRMS (CI): m/z calcd for (MH^+) $C_{23}H_{22}N_2O_4$: 391.1658; found: 391.1649.

N-Methyl (2S,6S,7R,8S,9S)-9-Methyl-2,9-diphenyl-1-aza-4-oxa[4.3.0^{1,6}]bicyclononan-5-one-7,8-dicarboximide (8c)
Colorless crystals (17%); mp 227–229 °C; $[\alpha]_D^{25}$ –12.5 (c = 0.3, $CHCl_3$); R_f 0.12 (Et_2O–PE, 1:1).

IR (KBr): 1753 (br, C=O), 1697 cm^{-1} (C=O).

^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.31–7.00 (10 H, m, Ph-H), 4.62 (1 H, d, J = 8.4 Hz, 6α-H), 4.29–3.99 (3 H, m, 3α-H, 3β-H, 2β-H), 3.75 (1 H, t, J = 8.4 Hz, 7α-H), 3.53 (1 H, d, J = 8.4 Hz, 8α-H), 3.00 (3 H, s, NCH_3), 1.43 (3 H, s, CH_3); NOE: H-3α → H-3β (24.3%) → H-6α (9.3%), H-6α → H-3α (6.2%) → H-7α (14.6%), H-7α → H-6α (11.9%) → H-8α (14.5%), H-8α → H-7α (11.3%) → Ph-H (13.4%).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 175.8 (C=O), 175.0 (C=O), 170.4 (C=O), 145.4 (C), 139.4 (C), 129.0 (C_{arom}), 128.6 (C_{arom}), 128.4 (C_{arom}), 127.6 (C_{arom}), 127.4 (C_{arom}), 126.7 (C_{arom}), 72.0 (C-3), 71.0 (C-9), 60.1 (C-6), 57.9 (C-8), 56.3 (C-2), 46.6 (C-7), 25.6 (CH_3), 19.6 (CH_3).

MS (CI): m/z (%) = 391 (100), 104 (94).

HRMS (CI): m/z calcd for (MH^+) $C_{23}H_{22}N_2O_4$: 391.1658; found: 391.1646.

N-Phenyl (2S,6S,7S,8R,9R)-9-Methyl-2,9-diphenyl-1-aza-4-oxa[4.3.0^{1,6}]bicyclononan-5-one-7,8-dicarboximide (9a)
Colorless crystals (7%); mp 221–225 °C; $[\alpha]_D^{25}$ –13.4 (c = 0.55, $CHCl_3$); R_f 0.64 (PE–Et_2O, 1:1).

IR (KBr): 1779 (C=O), 1756 (C=O), 1714 cm^{-1} (C=O).

^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.45–7.14 (15 H, m, Ph-H), 4.75 (1 H, d, J = 1.5 Hz, 6α-H), 4.48 (1 H, dd, J = 1.5, 9.25 Hz, 7β-H), 4.06–3.96 (3 H, m, 3α-H, 3β-H, 8-βH), 3.67 (1 H, dd, J = 7.6 Hz, J' = 9.7 Hz, 2β-H), 1.31 (3 H, s, CH_3).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 177.5 (C=O), 175.1 (C=O), 171.9 (C=O), 142.2 (C), 139.9 (C), 132.1 (C), 129.8 (CH_{arom}), 129.3 (CH_{arom}), 128.8 (CH_{arom}), 127.4 (CH_{arom}), 126.7 (CH_{arom}), 71.3 (C-3 and C-9), 62.6 (C-6), 56.8 (C-8), 56.6 (C-2), 46.7 (C-7), 25.7 (CH_3).

MS (CI): m/z (%) = 453 (100).

HRMS (CI): m/z calcd for (MH^+) $C_{28}H_{25}N_2O_4$: 453.1814; found: 453.1800.

N-Phenyl (2S,6S,7S,8R,9S)-9-Methyl-2,9-diphenyl-1-aza-4-oxa[4.3.0^{1,6}]bicyclononan-5-one-7,8-dicarboximide (9b)
Colorless crystals (10%); mp 90–105 °C; $[\alpha]_D^{25}$ –116.1 (c = 0.25, $CHCl_3$); R_f 0.35 (PE–Et_2O, 1:1).

IR (KBr): 1779 (C=O), 1752 (C=O), 1714 cm^{-1} (C=O).

^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.31–6.88 (15 H, m, Ph-H), 4.94 (1 H, s, 6α-H), 4.35 (1 H, dd, J = 6.7, 12.8 Hz, 3β-H), 4.27–4.19 (2 H, m, 7β-H, 3α-H), 4.02 (1 H, dd, J = 6.7, 11.5 Hz, 2β-H), 3.35 (1 H, d, J = 8.5 Hz, 8β-H), 1.77 (3 H, s, CH_3); NOE: H-2β → H-3β (7.1%) → Ph-H (14.0%) → CH_3β (6.5%), H-3β → H-3α (8.3%) → H-2β (8.3%) → H-3α (30.2%), H-8β → H-7β (15.9%) → CH_3β (5.4%).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 177.8 (C=O), 174.2 (C=O), 173.1 (C=O), 140.6 (C), 139.3 (C), 132.0 (C), 129.5 (CH_{arom}), 129.1 (CH_{arom}), 128.9 (CH_{arom}), 128.2 (CH_{arom}), 127.4 (CH_{arom}), 126.2 (CH_{arom}), 72.6 (C-9), 71.1 (C-3), 61.2 (C-6), 57.4 (C-8 or C-2), 55.9 (C-2 or C-8), 45.9 (C-7), 24.0 (CH_3).

MS (CI): m/z (%) = 453 (100).

HRMS (CI): m/z calcd for (MH^+) $C_{28}H_{25}N_2O_4$: 453.1814; found: 453.1824.

N-Phenyl (2S,6S,7R,8R,9S)-9-Methyl-2,9-diphenyl-1-aza-4-oxa[4.3.0^{1,6}]bicyclononan-5-one-7,8-dicarboximide (9c)
Colorless crystals (12%); mp 254–260 °C; $[\alpha]_D^{25}$ +23.4 (c = 0.25, $CHCl_3$); R_f 0.19 (PE–Et_2O, 1:1).

IR (KBr): 1779 (C=O), 1752 (C=O), 1713 cm^{-1} (C=O).

^{13}C NMR (250 MHz, $CDCl_3$): δ = 7.43–7.00 (15 H, m, Ph-H), 4.75 (1 H, d, J = 8.4 Hz, 6α-H), 4.31 (1 H, dd, J = 3.7, 9.6 Hz, 3β-H), 4.24–4.13 (2 H, m, 2β-H, 3α-H), 3.93 (1 H, dd, J = 8.4, 10.0 Hz, 7α-H), 3.70 (1 H, d, J = 10.0 Hz, 8α-H), 1.18 (3 H, s, CH_3).

^{13}C NMNR (63 MHz, $CDCl_3$): δ = 174.8 (C=O), 174.2 (C=O), 171.0 (C=O), 145.4 (C), 139.3 (C), 132.3 (C), 129.6 (CH_{arom}), 129.2 (CH_{arom}), 129.0 (CH_{arom}), 128.6 (CH_{arom}), 128.4 (CH_{arom}), 127.6 (CH_{arom}), 127.5 (CH_{arom}), 126.9 (CH_{arom}), 126.8 (CH_{arom}), 71.9 (C-3), 71.2 (C-9), 60.4 (C-6), 58.2 (C-8), 56.2 (C-2), 46.3 (C-7), 19.0 (CH_3).

MS (CI): m/z (%) = 453 (100), 104 (35).

HRMS (CI): m/z calcd for (MH^+) $C_{28}H_{25}N_2O_4$: 453.1814; found: 453.1812.

Dimethyl (2S,6S,7R,8S,9S)-9-Methyl-2,9-diphenyl-1-aza-4-oxa[4.3.0^{1,6}]bicyclononan-5-one-7,8-dicarboxylate (10c)
Colorless needles (8%); mp 210–212 °C; $[\alpha]_D^{25}$ –88.8 (c = 0.20, $CHCl_3$); R_f 0.20 (Et_2O–PE, 1:2).

IR (KBr): 1734 cm^{-1} (br, C=O).

^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.47–7.06 (10 H, m, Ph-H), 4.76 (2 H, m, 6α-H, 2β-H), 4.30 (1 H, t, J = 11.6 Hz, 3α-H), 4.14 (1 H, dd, J = 3.7, 11.6 Hz, 3β-H), 3.75 (3 H, s, CO_2CH_3), 3.63 (3 H, s, CO_2CH_3), 3.19 (1 H, dd, J = 6.0, 9.4 Hz, 7α-H), 2.96 (1 H, d, J = 6.0 Hz, 8α-H), 1.35 (3 H, s, CH_3).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 173.3 (C=O), 170.8 (C=O), 169.7 (C=O), 148.1 (C_{arom}), 140.0 (C_{arom}), 129.0 (CH_{arom}), 128.7 (CH_{arom}), 128.3 (CH_{arom}), 128.1 (CH_{arom}), 127.4 (CH_{arom}), 126.0 (CH_{arom}), 71.6 (C-3), 71.4 (C-9), 61.7 (C-6), 58.3 (C-2), 56.8 (C-8), 52.6 (CO_2CH_3), 52.3 (CO_2CH_3), 47.2 (C-7), 20.9 (CH_3).

MS (CI): m/z (%) = 424 (100), 104 (35).

HRMS (CI): m/z calcd for (MH^+) $C_{24}H_{26}NO_6$: 424.1760; found: 424.1747.

Dimethyl (2S,6S,7S,8S,9S)-9-Methyl-2,9-diphenyl-1-aza-4-oxa[4.3.0^{1,6}]bicyclononan-5-one-7,8-dicarboxylate (11c)
Colorless crystals (43%); mp 128–140 °C; $[\alpha]_D^{25}$ –17.0 (c = 1.00, $CHCl_3$); R_f 0.25 (Et_2O–PE, 1:1).

IR (KBr): 1767–1719 cm^{-1} (br, C=O).

^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.18–6.88 (10 H, m, Ph-H), 4.74 (1 H, d, J = 5.0 Hz, 6α-H), 4.44 (1 H, dd, J = 5.0, 10.6 Hz, 7-βH), 4.31–4.20 (2 H, m, 3α-, 3β-H), 3.93 (1 H, dd, J = 5.4, 11.7 Hz, 2β-H), 3.81 (3 H, s, CO_2CH_3), 3.61 (1 H, d, J = 10.6 Hz, 8α-H), 3.53 (3 H, s, CO_2CH_3), 1.43 (3 H, s, CH_3).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 174.1 (C=O), 173.4 (C=O), 170.7 (C=O), 141.0 (C_{arom}), 139.2 (C_{arom}), 129.1 (CH_{arom}), 128.9

(CH_{arom}), 128.3 (CH_{arom}), 127.9C_{arom}), 127.8 (C_{arom}), 127.7 (C_{arom}), 127.6 (C_{arom}), 127.4 (C_{arom}), 70.7 (C-3), 69.6 (C-9), 60.0 (C-8), 59.8 (C-6), 56.9 (C-2), 53.2 (CO_2CH_3), 52.4 (CO_2CH_3), 45.3 (C-7), 14.1 (CH_3).

MS (CI): *m*/*z* (%) = 424 (100).

HRMS (CI): *m*/*z* calcd for (MH^+) $C_{24}H_{26}NO_6$: 424.1760; found: 424.1747.

(2*S*,6*S*,8*S*,9*S*)-9-Methyl-2,9-diphenyl-1-aza-4-oxa[4.3.0^{1,6}]bicyclononan-5-one-8-nitrile (12c)

Colorless crystals (20%); mp 170–175 °C; $[\alpha]_D^{25}$ +15.0 (*c* = 0.35, $CHCl_3$); R_f 0.22 (PE–Et_2O, 1:1).

IR (KBr): 2245 (C≡N), 1752 cm^{-1} (C=O).

^1H NMR (250 MHz, $CDCl_3$): δ = 7.38–6.82 (10 H, m, Ph-H), 4.38 (1 H, dd, *J* = 5.5, 9.0 Hz, 6α-H), 4.27 (1 H, t, *J* = 11.9 Hz 3α-H), 4.16 (1 H, dd, *J* = 5.0, 11.9 Hz, 3β-H), 3.88 (1 H, dd, *J* = 5.0, 11.9 Hz, 2β-H), 3.17 (1 H, dd, *J* = 9.0, 11.0 Hz, 8α-H), 2.85 (1 H, m, 7β-H), 2.62 (1 H, m, 7α-H), 1.57 (3 H, s, CH_3). NOE: H-2β → H-3β (5.0%), H-3α → H-3β (17.3%), H-3β → H-3α (15.6%) → H-8β (8.3%), H-6α → H-7α (1.0%), H-7α → H-6α (1.4%) → H-7β (16.1%) → H-8α (1.4%), H-7β → H-7α (62.3%) → CH_3β (2.4%), H-8α → (1.7%), Ph-H (6.9%).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 174.2 (C=O), 139.9 (C_{arom}), 138.9 (C_{arom}), 129.4 (CH_{arom}), 128.6 (CH_{arom}), 128.4 (CH_{arom}), 128.1 (CH_{arom}), 127.8 (CH_{arom}), 127.6 (CH_{arom}), 125.7 (CH_{arom}), 119.0 (CN), 70.7 (C-3), 68.8 (C-9), 57.6 (C-2), 56.9 (C-6), 43.4 (C-8), 28.7 (C-7), 14.7 (CH_3).

MS (CI): *m*/*z* (%) = 333 (100), 104 (35).

HRMS (CI): *m*/*z* calcd for (MH^+) $C_{21}H_{21}N_2O_2$: 333.1603; found: 333.1615.

Methyl (2*S*,6*S*,8*S*,9*S*)-9-Methyl-2,9-diphenyl-1-aza-4-oxa[4.3.0^{1,6}]bicyclononan-5-one-8-carboxylate (13c)

Yellow foam (38%); mp 45–50 °C; $[\alpha]_D^{25}$ –21.8 (*c* = 0.90, $CHCl_3$); R_f 0.29 (PE–Et_2O, 1:1).

IR (KBr): 1748 cm^{-1} (br C=O).

^1H NMR (250 MHz, $CDCl_3$): δ = 7.25–6.84 (10 H, m, Ph-H), 4.37 (1 H, dd, *J* = 5.1, 9.4 Hz, 6α-H), 4.22–3.97 (3 H, m, 2β-H, 3α-H, 3β-H), 3.45 (3 H, s, CO_2CH_3), 3.17 (1 H, m, 8α-H,), 2.96 (1 H, m, 7β-H), 2.41 (1 H, m, 7α-H), 1.34 (3 H, s, CH_3).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 174.9 (C=O), 172.3 (C=O), 143.0 (C_{arom}), 139.8 (C_{arom}), 128.4 (CH_{arom}), 127.8 (CH_{arom}), 127.7 (CH_{arom}), 127.6 (CH_{arom}), 127.5 (CH_{arom}), 127.0 (CH_{arom}), 70.9 (C-3), 68.9 (C-9), 57.5 (C-6), 57.2 (C-2), 56.2 (C-8), 52.0 (CO_2CH_3), 27.6 (C-7), 14.8 (CH_3).

MS (CI): *m*/*z* (%) = 366 (100), 104 (56).

HRMS (CI): *m*/*z* calcd for (MH^+) $C_{22}H_{24}NO_4$: 366.1705; found: 366.1699.

Cycloadducts 14 and 15

Acetophenone dimethyl acetal (0.37 mL, 2.26 mmol, 2 equiv), (5*S*)-5-phenylmorpholin-2-one (**1**; 200 mg, 1.13 mmol, 1 equiv) and magnesium bromide etherate (290 mg, 1.13 mmol, 1 equiv) were refluxed under nitrogen in 1,4-dioxane for 4 h. *p*-Nitrobenzaldehyde (176 mg, 1.13 mmol, 1 equiv) was added to the reaction mixture, which was then refluxed for a further 2 h. The solution was then allowed to cool to r.t. and filtered through a short pad of silica and the silica was washed with Et_2O. The solvent was removed in vacuo and the two cycloadducts were separated by flash chromatography on silica using gradient elution (PE–Et_2O, 4:1 to 2:1).

(2*S*,6*S*,7*R*,9*R*)-9-Methyl-2,9-diphenyl-7-(4-nitrophenyl)-1-aza-4,8-dioxa[4.3.0^{1,6}]bicyclononan-5-one (14)

Colorless needles (207 mg, 42%); mp 149–151 °C; $[\alpha]_D^{25}$ –29.1 (*c* = 0.65, $CHCl_3$); R_f 0.62 (PE–Et_2O, 1:1).

IR (KBr): 1755 (C=O), 1522 (NO_2), 1348 cm^{-1} (NO_2).

^1H NMR (250 MHz, $CDCl_3$): δ = 8.33 (2 H, m, Ar-H), 7.86 (2 H, m, Ar-H), 7.41–7.24 (5 H, m, Ph-H), 6.15 (1 H, d, *J* = 4.8 Hz, 6α-H), 4.32 (1 H, d, *J* = 4.8 Hz, 7β-H), 4.19–4.08 (2 H, m, 3α-, 3β-H), 3.95 (1 H, dd, *J* = 5.1, 10.25 Hz, 2β-H), 1.60 (3 H, s, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.7 (C=O), 148.8 (C_{arom}), 147.8 (C_{arom}), 139.8 (C_{arom}), 138.0 (C_{arom}), 128.9 (CH_{arom}), 128.6 (CH_{arom}), 128.5 (CH_{arom}), 127.5 (CH_{arom}), 127.0 (CH_{arom}), 126.5 (CH_{arom}), 124.0 (CH_{arom}), 101.0 (C-9), 79.1 (C-6), 71.4 (C-3), 65.4 (C-7), 57.1 (C-2), 28.9 CH_3).

Anal. Calcd for $C_{25}H_{22}N_2O_5$: C, 69.76; H, 5.15; N, 6.50. Found: C, 69.47; H, 5.11; N,6.31.

MS (CI): *m*/*z* (%) = 431 (32), 280 (100).

HRMS (CI): *m*/*z* calcd for (MH^+) $C_{21}H_{21}N_2O_2$: 431.1606; found: 431.1616.

(2*S*,6*S*,7*R*,9*S*)-9-Methyl-2,9-diphenyl-7-(4-nitrophenyl)-1-aza-4,8-dioxa[4.3.0^{1,6}]bicyclononan-5-one (15)

Colorless needles (89 mg, 18%); mp 144–146 °C; $[\alpha]_D^{25}$ –100.3 (*c* = 0.35, $CHCl_3$); R_f 0.40 (PE–Et_2O, 1:1).

IR (KBr): 1748 (C=O), 1522 (NO_2), 1348 cm^{-1} (NO_2).

^1H NMR (250 MHz, $CDCl_3$): δ = 8.12 (2 H, m, Ar-H), 7.54 (2 H, m, Ar-H), 7.42–7.07 (5 H, m, Ph-H), 5.48 (1 H, d, *J* = 7.6 Hz, 6α-H), 4.36–4.15 (4 H, m, 2β-H, 3α-H, 3β-H, 7β-H), 1.54 (3 H, s, CH_3).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 170.2 (C=O), 148.3 (C_{arom}), 147.2 (C_{arom}), 143.1 (C_{arom}), 137.4 (C_{arom}), 128.9 (CH_{arom}), 128.6 (CH_{arom}), 128.5 (CH_{arom}), 128.3 (CH_{arom}), 128.2 (CH_{arom}), 127.7 (CH_{arom}), 126.8 (CH_{arom}), 124.1 (CH_{arom}), 100.4 (C-9), 78.6 (C-6), 72.6 (C-3), 66.1 (C-7), 57.5 (C-2), 23.0 CH_3).

MS (CI): *m*/*z* (%) = 431(15), 280 (100).

MS (CI): *m*/*z* calcd for (MH^+) $C_{21}H_{21}N_2O_2$: 431.1606; found: 431.1626.

(2*S*,3*R*)-2-Amino-3-hydroxy-3-(4-aminophenyl)propanoic Acid (16)

To a solution of the cycloadduct **14** or **15** (90 mg, 0.2 mmol, 1 equiv) in MeOH (4 mL) was added 1 M HCl (1 mL) and the mixture was refluxed for 1 h. The mixture was transferred into a Fisher Porter bottle. TFA (16 μL, 0.2 mmol, 1 equiv) and Pearlman's catalyst (90 mg) were added to the solution, which was then degassed and subjected to H_2 at 1 atm. for 24 h with stirring. The solution was then passed through a pad of Celite® to remove the catalyst and the solvent was removed in vacuo. The crude mixture was purified on an acidic ion-exchange column to yield the title compound in each case as a pale yellow powder (60 and 68%, respectively); $[\alpha]_D^{25}$ –12.1 (*c* = 0.55, H_2O) {Lit.[13b] $[\alpha]_D^{24}$ –7.5 (*c* = 1.0, H_2O)}.

IR (KBr): 3420 (NH), 1653 cm^{-1} (C=O).

^1H NMR (250 MHz, D_2O): δ = 7.15 (2 H, d, *J* = 8.37 Hz), 6.78 (2 H, d, *J* = 8.37 Hz), 5.05 (1 H, d, *J* = 4.75 Hz), 3.72 (1 H, d, *J* = 4.75 Hz).

^{13}C NMR: (62.5 MHz, D_2O): δ = 172.4 (C=O), 130.8, 127.4, 117.3, 71.5, 61.2.

MS (CI): *m*/*z* (%) = 197 (20), 179 (100).

HRMS (CI): *m*/*z* calcd for (MH^+) $C_9H_{13}N_2O_3$: 197.0926; found: 197.0920.

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(7) X-ray Crystal Data: **6** $C_{17}H_{21}NO_2$, M = 271.35, orthorhombic, space group P212121, *Z* = 4, *a* = 6.715 (10), *b* = 13.502 (8), *c* = 16.73 (2), *V* = 1517 Å^3, d = 1.188 Mg/m^3, 1545 independent reflections were collected with MoKα radiation on the MAR research Image Plate system. Data analysis was carried out with the XDS program[8] the structure was solved by direct methods using Shelx86[9] and refined on F2 using Shelx[10] to *R*1 0.0686, *wR*2 0.1937. **8a** $C_{23}H_{22}N_2O_4$, M = 390.43, orthorhombic, space group P212121–, *Z* = 4, *a* = 9.510 (12), *b* = 9.934 (14), *c* = 21.23 (2), *V* = 2006 Å^3, d = 1.293 Mg/m^3, 3554 independent reflections were collected. The structure was solved by direct methods and refined on F2 to *R*1 0.0834, *wR*2 0.2490. **9c** $C_{28}H_{24}N_2O_4$, M = 452.49, monoclinic, space group P21–, Z = 2, *a* = 10.857 (12), *b* = 8.120 (10), *c* = 28.75 (3), *β* = 96.895 (i1)°, *V* = 2516 Å^3, d = 1.194 Mg/m^3, 4541 independent reflections were collected. The structure was solved by direct methods and refined on F2 to *R*1 0.1749, *wR*2 0.4199. **10c** $C_{24}H_{25}NO_6$, M = 423.45.31, orthorhombic, space group P212121, *Z* = 4, *a* = 11.389 (15), *b* = 13.320 (14), *c* = 15.080 (17), *V* = 2272 Å^3, d = 1.238 Mg/m^3, 2480 independent reflections were collected. The structure was solved by direct methods and refined on F2 to *R*1 0.0488, *wR*2 0.1277. **11c** $C_{24}H_{25}NO_6$, M = 423.45.31, orthorhombic, space group P212121, *Z* = 4, *a* = 6.212 (10), *b* = 16.72 (2), *c* = 20.33 (3), *V* = 2111 Å^3, d = 1.332 Mg/m^3, 6680 independent reflections were collected. The structure was solved by direct methods and refined on F2 to *R*1 0.1078, *wR*2 0.2857. **15** $C_{25}H_{22}N_2O_5$, M = 430.45, orthorhombic, space group P212121, *Z* = 4, *a* = 7.481 (10), *b* = 13.464 (17), *c* = 21.72 (3), *V* = 2188 Å^3, d = 1.307 Mg/m^3, 6487 independent reflections were collected. The structure was solved by direct methods and refined on F2 to *R*1 0.0996, *wR*2 0.2057. Atomic co-ordinates, bond lengths and angles and thermal parameters have been deposited with the Cambridge Crystallographic Service.
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