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DEVELOPMENT OF AN ALANINE-DERIVED CHIRAL STABILIZED AZOMETHINE YLID BASED ON THE 5-(2′-NAPHTHYL)MORPHOLIN-2-ONE TEMPLATE

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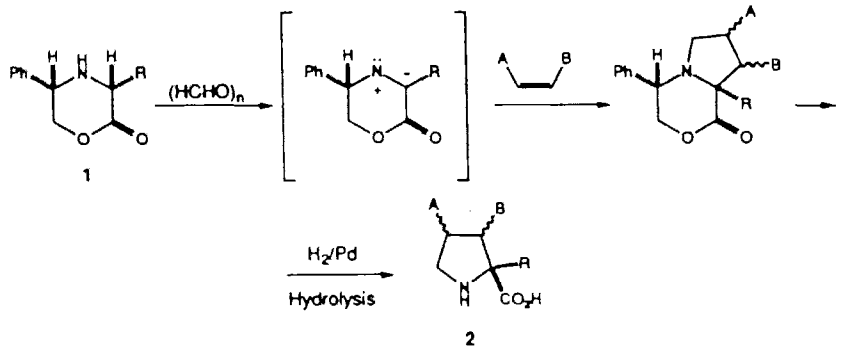
A route to enantiomerically pure α-methyl functionalized proline derivatives is presented, using a 1,3-dipolar cycloaddition strategy based upon a homochiral 5-(2′-naphthyl)morpholin-2-one template. A mild means of generating stabilized azomethine ylids using sonication and Lewis acid catalysis is developed, avoiding the use of excessive temperatures.

INTRODUCTION

In a series of papers we reported the results of our use of 5-phenylmorpholin-2-one (**1**, R = H)* [1] templates with the aim of relaying chiral information at C-3 of the precursor through the sequence of azomethine ylid generation and trapping, in order to produce homochiral proline derivatives **2** (Scheme 1) [2-8].

Scheme 1



The use of morpholin-2-ones, where R is other than hydrogen, leads to α-substituted proline derivatives **2**, where the absolute stereochemistry of the original α-amino acid center has carried through the ylid generation step. Synthesis of the 3-alkyl morpholin-2-ones (**1**) was accomplished by the method of Sunjic and co-workers [9] (Scheme 2) in which the stereochemistry of the starting α-amino acid is used to control the diastereoselectivity of the reduction of the 4,5-dehydro-mor-

*In this paper we use the trivial name morpholin-2-one to describe the 2,3,5,6-tetrahydro-4H-oxazin-2-one ring system.

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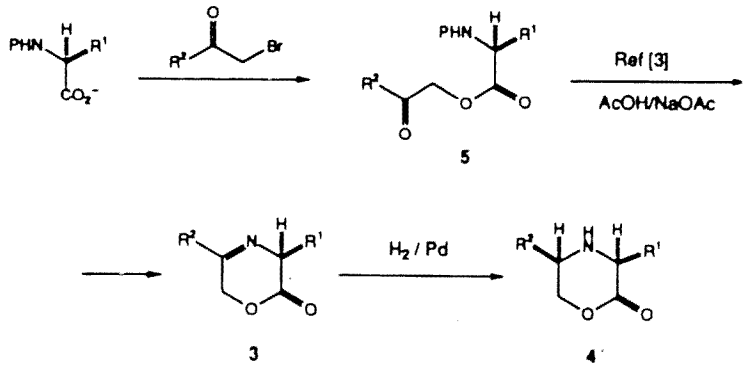
pholin-2-one (**3**) to give the desired morpholin-2-one template **4**. However, attempts to construct the morpholin-2-one template from 2′-bromoacetophenone failed when the starting α-amino acid was alanine, possibly due to the cyclic imine (**3**, R^1 = Me, R^2 = Ph) failing to precipitate from the aqueous buffer and undergoing subsequent hydrolytic decomposition.

Scheme 2



In principle, any α-bromomethyl ketone may be used for the synthesis of morpholin-2-ones [10]. However, if an aryl α-bromomethyl ketone is used, subsequent degradation of the morpholin-2-one template can be readily achieved by hydrogenolysis of the benzylic amine. We considered that use of 2′-bromo-2-acetonaphthone would not only fit this criterion but might allow the synthesis of hitherto unobtainable morpholin-2-ones due to increased hydrophobicity, and thus decreased water solubility of the intermediate 4,5-dehydromorpholin-2-ones (**3**, R^1 = Me, R^2 = naphthyl).

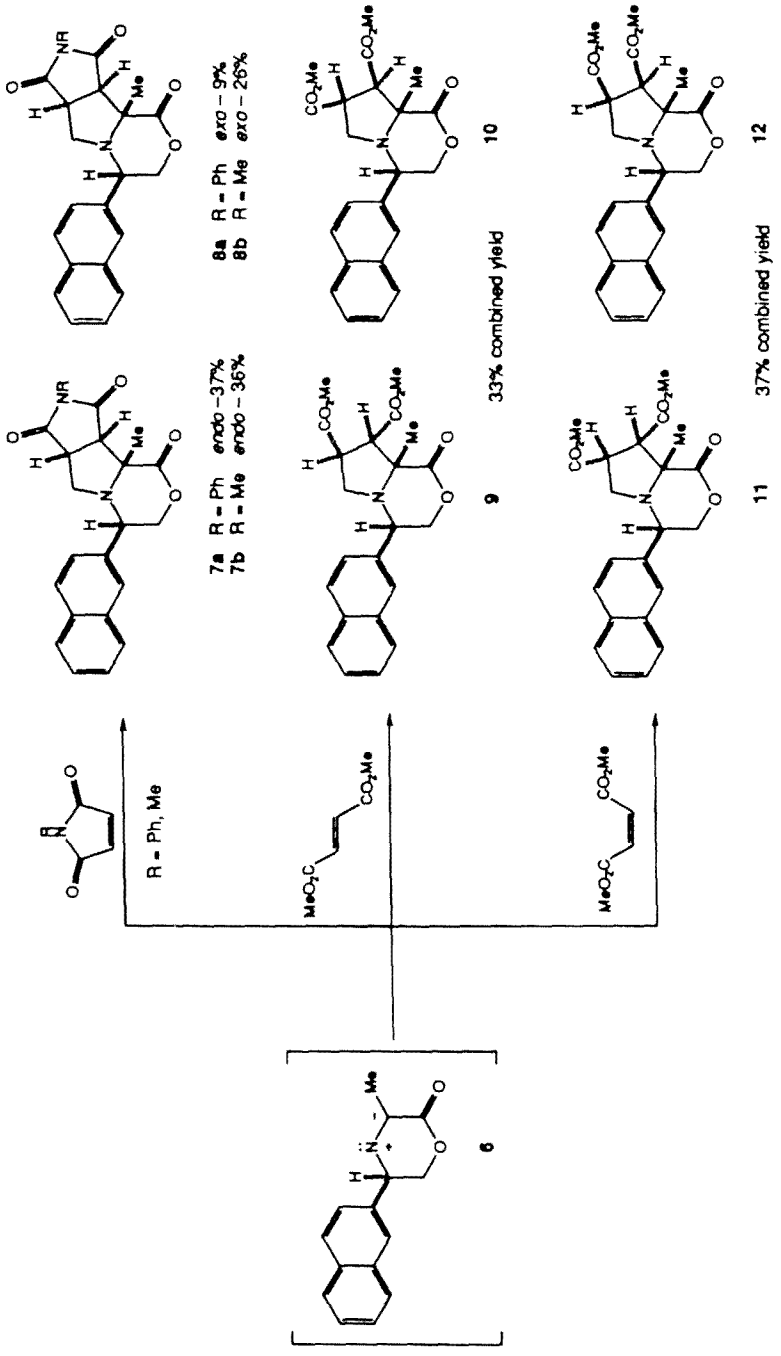
RESULTS AND DISCUSSION

Alanine was protected as its N-Boc derivative by standard procedures [11]. Reaction of the potassium salt of N-Boc-alanine with 2′-bromo-2-acetonaphthone gave the protected ester (**5**, R^1 = Me, R^2 = naphthyl, Scheme 2) in 72% yield, which could be purified by simple recrystallization. Deprotection of the N-Boc group was readily achieved in excellent yield (97%) by treatment of the ester **5** with hydrogen bromide in acetic acid. Neutralization and concomitant cyclization of the hydrogen bromide salt formed in the deprotection was accomplished in moderate yield (42%) by stirring the hydrobromide salt in aqueous buffer (70 mL 0.2 M sodium acetate, 30 mL 0.2 M acetic acid) for 6 h at room temperature. It is presumed that the modest yield obtained for this cyclization is due to competing hydrolysis of the imine **3**. Indeed, reaction times of longer than 6 h resulted in a marked decrease in the observed yield for this step. Reaction times of less than 6 h also gave rise to lower yields due to incomplete cyclization of the free amine. Stereospecific reduction of the 4,5-dehydromorpholin-2-one using 10% palladium on carbon gave the desired morpholin-2-one template **4**, (R^1 = Me, R^2 = naphthyl) in 53% yield. The use of alternative reduction catalysts and solvent systems did not increase the yield of this reduction and, even under the optimized conditions, reduction of the imine is sluggish, requiring 48 h at room temperature under ambient hydrogen pressure for completion. The five step overall yield of the desired chiral template **4** (R^1 = Me, R^2 = naphthyl) from alanine is 15%. All the intermediates involved in this synthesis are solids and can be purified by recrystallization, avoiding chromatography at any stage and resulting in a convenient synthetic route, amenable to preparations on a large scale.

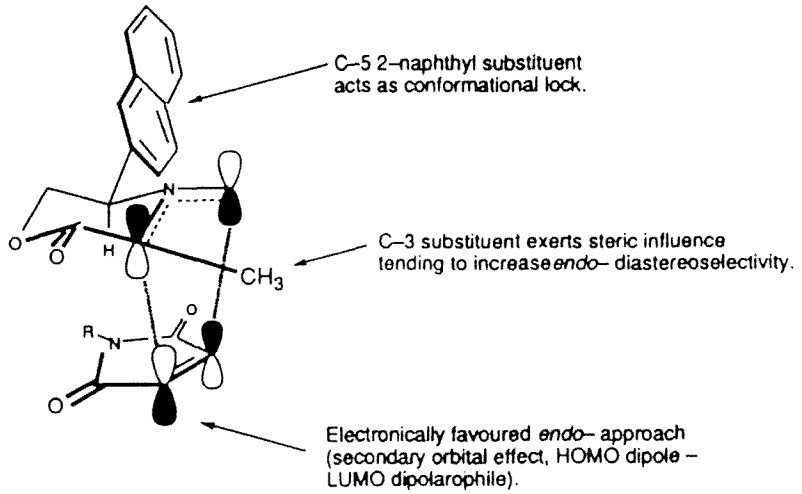
Subsequent reaction of **4** with paraformaldehyde in refluxing xylene, following a modified method based on that of Tsuge et al. [12], yielded the homochiral azomethine ylid **6** which could be trapped with a variety of dienophiles, with high stereocontrol. In all cases, only one configuration was observed at the regenerated C-3 stereogenic center of the morpholinone template in the cycloadduct. Yields of isolated cycloadducts were generally moderate to good (Scheme 3).

In the case of the maleimide dipolarophiles, mixtures of *endo*- (**7**a,b) and *exo*- (**8**a,b) adducts resulted, with the *endo*-isomer predominating (37.3% and 9.26°, respectively). This stereochemical control in favor of *endo*-form can be ra-

Scheme 3


R = Ph, Me
7a R = Ph endo – 37%
7b R = Me endo – 36%
8a R = Ph exo – 9%
8b R = Me exo – 26%
9
10
33% combined yield
11
12
37% combined yield
6

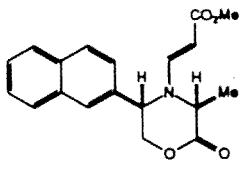
tionalized by envisaging an axial approach of the dipolarophile to the least hindered face of the ylid held in a chair conformation in which the 2-naphthyl group is equatorial.



The preference for *endo*-cycloadduct formation is similar to the selectivity previously noted for 5-phenylmorpholin-2-one [4]. Increasing the steric bulk of the C-5 substituent (Ph → Naphthyl) has little effect on the stereochemical outcome of the cycloaddition, and is consistent with our belief that the substituent at C-5 acts as a conformational lock rather than a steric blocking group. The influence of the C-3 methyl group upon *endo/exo* ratios is also minimal; whereas in the case of **1**, (R = i-Pr), *endo*-selectivity was enhanced [4.8:1 (N−Ph), and exclusively *endo*-isomer (N−Me)] [3].

The use of doubly activated alkenes was also investigated, with dimethyl fumarate and dimethyl maleate as dipolarophiles. In these cases, mixtures of diastereoisomers (**9**, **10** and **11**, **12**) resulted in 33 and 37% overcombined yields, respectively, but the cycloadducts obtained could not be separated under a variety of chromatographic conditions.

Attention was then turned to the use of alkynes as dipolarophiles, as cycloadditions would be free from the stereochemical complications arising from *endo*- or *exo*-attack. Generation of the azomethine ylid **6**, followed by reaction with methyl propiolate or dimethyl acetylenedicarboxylate (DMAD) furnished no cycloadducts, even after refluxing in xylene for 36 h. The starting morpholin-2-one template was recovered in 77% yield. This observation is in contrast to the 29% yield of cycloadduct obtained from the cycloaddition of DMAD with 5-phenylmorpholin-2-one and paraformaldehyde in refluxing toluene [4]. In the case of methyl propiolate, the only product obtained (**13**, 4% yield) was that resulting from Michael addition of the morpholin-2-one to the triple bond.

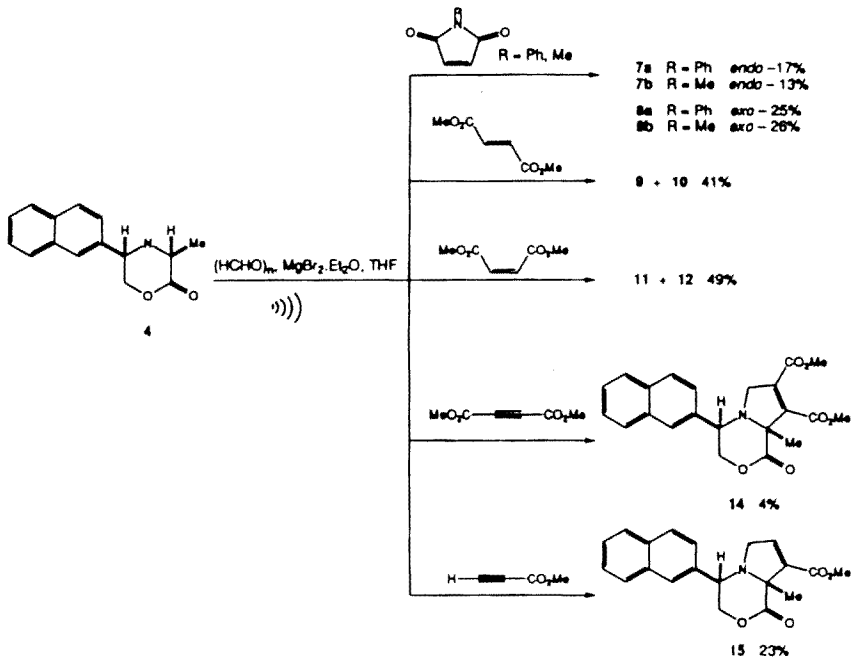


13

It had been previously observed that cycloadditions could be achieved at lower temperature, in refluxing tetrahydrofuran, in the presence of a Lewis acid catalyst [6], allowing the formation of the ylid **6** under milder conditions. In an attempt to move away from direct heating, sonication was investigated as a means of promoting the reaction [13]. In the presence of a Lewis acid, it was found that use of a conventional sonic bath led to moderate yields of cycloadducts **7a** (17%), **7b** (13%), **8a** (25%), **8b** (26%), **9** + **10** (41%), and **11** + **12** (49%) (Scheme 4). In the case of the maleimide dipolarophiles,

the previously observed inversion of stereocontrol on using Lewis acid catalysis (*exo*-attack predominating) was again present. Comparisons between Lewis acid catalysis in refluxing THF and using sonication gave very similar isolated yields of N-phenyl maleimide cycloadducts.

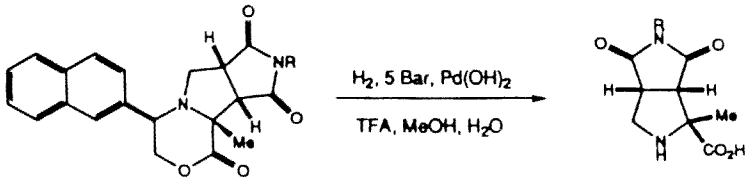
Scheme 4



Reaction of the azomethine ylid **6** with DMAD, under sonication and Lewis acid catalysis, resulted in a small yield (4%) of the expected cycloadduct **14**. Reaction with methyl propionate also furnished the desired cycloadduct **15** in moderate yield (23%). Under these sonication conditions, the yields of cycloadducts **9**, **10** and **11**, **12** derived from dimethyl fumarate and dimethyl maleate, respectively, also improved relative to thermal cycloaddition conditions used previously (33 → 42% for **9**, **10** and 37 → 49% for **11**, **12**). From a practical aspect, cycloadditions performed using sonication and Lewis acid catalysis suffer less from dienophile and cycloadduct degradation, resulting in cleaner reaction mixtures.

Removal of the morpholin-2-one chiral template (Scheme 5) from the *endo*-cycloadducts 7a,b obtained with the maleimide dipolarophiles was readily accomplished in good yield (77%) by hydrogenolysis, to give the dicarboximido prolines **16**a,b.

Scheme 5



7a R = Ph
7b R = Me

16a R = Ph
16b R = Me

Hydrogenolysis was carried out in methanol with trifluoroacetic acid and water, using Pearlman's catalyst ($Pd(OH)_2 \cdot H_2O$), at a hydrogen pressure of 5 bar. We have found previously [14] that hydrogenolyses at higher pressures gave better yields and cleaner material than those performed at atmospheric pressure.

EXPERIMENTAL

Infrared spectra were recorded on a Perkin-Elmer 297 spectrophotometer. Proton NMR spectra were recorded on Bruker WH300 (300 MHz) or AM500 (500 MHz) spectrometers. Carbon-13 NMR spectra were recorded on Bruker AM500 (127 MHz) spectrometer. Melting points were recorded on a Kofler hot-stage apparatus and are uncorrected. Mass spectra (*m/z*) were recorded on Masslab 20-250, V. G. Micromass 30F, ZAB IF or Trio-1 GCMS (DB-5 column) spectrometers, using desorption chemical ionization (NH_3 D.C.I.). Accurate mass measurements were recorded by the E.P.S.R.C. mass spectrometry service (University of Swansea). Microanalyses were carried out on a Carlo Erba 1106 elemental analyzer. Flash chromatography was carried out using Merck Kieselgel 60 (0.40-0.063 mm diameter) silica.

2-(2′-Naphthyl)-2-oxoethyl N-*tert*-Butoxycarbonyl Alanine Ester (5). N-*tert*-butoxycarbonylalanine (3.0 g, 16 mmol) was dissolved in 20 mL of methanol and added to a solution of potassium hydroxide (1.1 g, 20 mmol) in 25 mL of methanol. The reaction mixture was stirred at room temperature for ca. 20 min, after which time the methanol was removed *in vacuo* to leave a colorless solid. The residue was taken up in DMF (25 mL) and cooled to 0°C. Naphthyl α-bromomethyl ketone (4.0 g, 16 mmol) was dissolved in DMF (25 mL) and added dropwise to the cooled solution of N-*tert*-butoxycarbonylalanine potassium salt. The reaction mixture was stirred overnight, allowing it to come to room temperature. The DMF was removed *in vacuo*, and the residue taken up in ethyl acetate (200 mL). The organic layer was washed sequentially with water (150 mL), brine (150 mL), dried ($MgSO_4$), and solvent removed *in vacuo* to leave a yellow solid. Recrystallization from ethyl acetate/light petroleum gave the title compound as a colorless solid (4.1 g, 72%). M.p. = 140-141°C; found C 67.33, H 6.65, N 8.81; $C_{20}H_{23}NO_5$ requires C 67.22, H 6.49, N 3.92; δ_H (500 MHz, $CDCl_3$) 8.41 (1H, s), 7.96-7.88 (4H, m), 7.64-7.56 (2H, m), 5.66-5.63 (1H, d, J = 16.17 Hz), 5.43-5.40 (1H, d, J = 16.18 Hz), 5.12 (1H, bs), 4.53 (1H, bt), 1.58-1.56 (3H, d, J = 7.2 Hz), 1.47 (9H, s); δ_C (125.7 MHz, $CDCl_3$) 191.47, 172.98, 155.13, 135.89, 132.32, 131.32, 129.53, 129.48, 128.91, 128.86, 127.85, 127.07, 123.13, 79.88, 66.41, 49.24, 28.28, 18.68; $[\alpha]_D^{25}$ = −20.2 (c 1.15, $CDCl_3$).

2-(2′-Naphthyl)-2-oxoethyl Alanine Ester Hydrobromide Salt. 2-Naphthyl-2-oxoethylester of N-*tert*-butoxycarbonyl alanine **5** (1.0 g, 2.8 mmol) was suspended in diethyl ether (10 mL). Hydrobromic acid (33% w/w solution in glacial acetic acid, 5 mL) was added to the suspension and the reaction mixture stirred for 30 min at room temperature. Once carbon dioxide evolution had stopped, the hydrobromide salt was filtered off and washed with ether (2 × 50 mL) until no more hydrobromic acid was present, leaving the title compound as a colorless solid (921 mg, 97%) δ_H (300 MHz, $CDCl_3$) 8.6 (1H, s), 7.92-7.79 (4H, m), 7.72-7.57 (2H, m), 5.82-5.91 (1H, d, J = 16.4 Hz), 5.69-5.78 (1H, d, J = 16.3 Hz), 4.39-4.28 (1H, q, J = 7.5 Hz), 1.7-1.76 (3H, t, J = 7.4 Hz); $[\alpha]_D^{25}$ = +10.0 (c 1.04, MeOH).

(3*S*) 3-Methyl-5-(2′-naphthyl)-4,5-dehydromorpholin-2-one (3). 2-Naphthyl-2-oxoethyl alanine ester hydrobromide salt (3.0 g, 10 mmol) was dissolved in aqueous buffer (70 mL, 0.2 M sodium acetate, 30 mL, 0.2 M acetic acid) and the solution was stirred at room temperature for 6 h. The resulting precipitate was filtered off and dried by suction, giving a colorless solid (1.0 g, 42%). Recrystallization from ethyl acetate/light petroleum gave an analytically pure sample as colorless rods; M.p. = 129-132°C; found C 75.5, H 5.3, N 6.1; $C_{15}H_{13}NO_2$ requires C 75.3, H 5.4, N 5.9%; ν_{max} (KBr)/cm^{-1} 1747, 1620; δ_H (500 MHz, $CDCl_3$) 8.13-7.27 (7H, m), 5.64 (1H, dd, J = 15.9, J' = 1.1 Hz), 5.38 (1H, dd, J = 15.9, J' = 2.8 Hz), 4.38 (1H, ddq, J = 7.2, J' = 1.8, J'' = 1.1 Hz), 1.77 (3H, d, J = 7.2 Hz); *m/z* (DCI, NH_3) 241 (100%, M+1), 240 (100), 239 195,154; $[\alpha]_D^{25}$ = −188.9 (c 1.00, $CDCl_3$).

(3*S*,5*R*) 3-Methyl-5-(2′-naphthyl)-morpholin-2-one (4). The crude imine **3** (1.0 g, 4.2 mmol) was dissolved in ethyl acetate (30 mL). Palladium (10%) on carbon (30% by weight, 300 mg) was added and the flask fitted with a three-way tap connected to a hydrogen balloon. The reaction vessel was purged with hydrogen and the reaction mixture then stirred at room temperature for 48 h under an atmosphere of hydrogen. The catalyst was filtered through a pad of Celite® and the solvent removed *in vacuo* to leave a yellow solid. Recrystallization from ethanol/light petroleum gave the title compound as a colorless solid (522 mg, 53%). M.p. = 105-106°C; found C 74.7, H 6.3, N 5.7; $C_{15}H_{15}NO_2$ requires C 74.7, H 6.2, N 5.8%; ν_{max} (KBr)/cm^{-1} 3307, 1740, 1211; δ_H (200 MHz, $CDCl_3$) 8.0-7.5 (7H, m), 4.4 (3H, m), 3.95 (1H, q, J = 5.8 Hz), 1.8 (1H, bs), 1.55 (3H, d, J = 5.8 Hz); m/z (DCI, NH_3) 242 (100%, M+1), 154 (30); $[\alpha]_D^{25}$ = −85.0 (c 1.00, $CDCl_3$).

General Procedure for Thermal Cycloadditions

(3*S*,5*R*) 3-Methyl-5-(2′-naphthyl)morpholin-2-one (4) (100 mg, 0.41 mmol), paraformaldehyde (15 mg, 0.49 mmol) and the appropriate dienophile (0.49 mmol) were added to a flask equipped with a Soxhlet extractor under an argon atmosphere.

The Soxhlet extractor was charged with freshly activated 4 Å molecular sieves, and xylene (20 mL) was added. The reaction mixture was refluxed for ca. 16 h. The reaction mixture was allowed to cool to room temperature and the xylene was removed *in vacuo*, to leave a dark brown residue. Column chromatography (ethyl acetate/light petroleum, gradient elution) gave the title compounds as colorless solids.

(2*R*,6*S*,7*S*,8*R*) N-Phenyl-6-methyl-2-(2′-naphthyl)-1-aza-4-oxa[4.3.0]bicyclononan-5-one-7,8-dicarboximide (7a). *Endo*-cycloadduct: (37%); M.p. = 98-102°C; found C 73.2, H 5.3, N 6.5; $C_{26}H_{22}N_2O_4$ requires C 73.2, H 5.2, N 6.6%; ν_{max} (KBr)/cm^{-1} 1752, 1714, 1176; δ_H (500 MHz, $CDCl_3$) 7.87-7.26 (12H, m), 4.30 (1H, t, J = 10.8 Hz), 4.25 (1H, dd, J = 11.4, J′ = 3.5 Hz), 4.13 (1H, dd, J = 10.3, J′ = 3.5 Hz), 3.72 (1H, d, J = 8.2 Hz), 3.63 (1H, dd, J = 14.0, J′ = 9.5 Hz), 3.47 (1H, ddd, J = 9.4, J′ = 8.3, J″ = 2.3 Hz), 3.42 (1H, dd, J = 14.0, J′ = 2.4 Hz), 1.77 (3H, s); *m/z* (DCI, NH_3) 444 (M + NH_4^+, 7%), 427 (25), 155 (100), 154 (100); $[\alpha]_D^{25}$ = −133.7 (c 0.73, $CHCl_3$).

(2*R*,6*S*,7*R*,8*S*) N-Phenyl-6-methyl-2-(2′-naphthyl)-1-aza-4-oxa[4.3.0]bicyclononan-5-one-7,8-dicarboximide (8a). *Exo*-cycloadduct: (9%); M.p. = 223-225°C; found C 73.3, H 5.1, N 6.6; $C_{26}H_{22}N_2O_4$ requires C 73.2, H 5.2, N 6.6%; ν_{max} (KBr)/cm^{-1} 1738, 1713, 1181; δ_H (500 MHz, $CDCl_3$) 7.89-7.27 (12H, m), 4.65 (1H, dd, J = 12.2, J′ = 6.0 Hz), 4.56 (1H, t, J = 12.0 Hz), 4.34 (1H, d, J = 9.0 Hz), 4.26 (1H, dd, J = 11.3, J′ = 6.0 Hz), 3.74 (1H, dd, J = 11.0, J′ = 2.7 Hz), 3.51 (1H, ddd, J = 8.9, J′ = 8.1, J″ = 2.7 Hz), 3.19 (1H, dd, J = 11.0, J′ = 8.0 Hz), 1.75 (3H, s); δ_C (50 MHz, $CDCl_3$) 176.6, 173.9, 171.8, 134.8, 133.4, 131.9, 129.3, 129.0, 128.8, 127.9, 127.8, 126.7, 126.5, 126.3, 126.1, 124.2, 70.5, 67.8, 61.6, 56.9, 51.9, 44.4, 23.6; *m/z* (DCI, NH_3) 427 (M + H^+, 30%), 326 (50), 155 (100), 154 (100); $[\alpha]_D^{25}$ = +92.4 (c 0.66, $CHCl_3$).

(2*R*,6*S*,7*S*,8*R*) N-Methyl 6-Methyl-2-(2′-naphthyl)-1-aza-4-oxa[4.3.0]bicyclononan-5-one-7,8-dicarboximide (7b). *Endo*-cycloadduct (36%); M.p. = 223-226°C; found 365.150 $[C_{21}H_{20}N_2O_4]$+H requires 365.1502; δ_H (500 MHz, $CDCl_3$) 7.86-7.81 (3H, m), 7.63 (1H, s), 7.54-6.52 (2H, m), 7.35-7.33 (1H, dd, J = 8.48 and 1.75 Hz), 4.30-4.26 (1H, t, J = 11.2 Hz), 4.23-4.20 (1H, dd, J = 11.3, J′ = 3.4 Hz), 3.74-3.47 (1H, dd, J = 10.34, J′ = 3.36 Hz), 3.55-3.47 (2H, m), 3.33-3.27 (2H, m), 3.09 (3H, s), 1.72 (3H, s); δ_C (125.7 MHz, $CDCl_3$) 178.3, 175.8, 168.6, 133.6, 133.4, 133.2, 129.2, 127.9, 127.8, 127.6, 126.7, 124.7, 72.9, 69.8, 60.8, 56.2, 53.2, 43.7, 27.1, 25.7; $[\alpha]_D^{25}$ = −10.8 (c 1.12, $CDCl_3$).

(2*R*,6*S*,7*R*,8*S*) N-Methyl 6-Methyl-2-(2′-naphthyl)-1-aza-4-oxa[4.3.0]bicyclononan-5-one-7,8-dicarboximide (8b). *Exo*-cycloadduct (26%); M.p. = 168-171°C; found 365.150 $[C_{21}H_{20}N_2O_4]$+H requires 365.1502; ν_{max} (KBr)/cm^{-1} 3487, 3434, 2956, 1740, 1690, 1507, 830, 751; δ_H (500 MHz, $CDCl_3$) 7.86-7.78 (4H, m), 7.54-7.49 (2H, m), 7.44-7.42 (1H, dd, J = 8.5, J′ = 1.6 Hz), 4.58-4.51 (2H, m), 4.19-4.16 (2H, m), 3.61-3.58 (1H, dd, J = 11.1, J′ = 3.1 Hz), 3.37-3.32 (1H, dt, J = 11.6, J′ = 8.6, J″ = 3.0 Hz), 3.33-3.07 (1H, m), 3.06 (3H, s), 1.65 (3H, s); δ_C (125.7 MHz, $CDCl_3$) 177.6, 175.0, 171.9, 134.6, 133.2, 128.9, 127.8, 127.7, 126.6, 126.4, 126.2, 124.3, 70.5, 67.3, 61.8, 56.4, 52.0, 44.2, 25.1, 23.6; $[\alpha]_D^{25}$ = +78.0 (c 1.01, $CDCl_3$).

Dimethyl(2*R*,6*S*,7*S*,*R*,8*R*,*S*)6-Methyl-2-(2′-naphthyl)-1-aza-4-oxa[4.3.0]bicyclononan-5-one-7,8-dicarboxylate(9, 10). A mixture (1:1.4) of diastereoisomers was obtained (33%); found C 66.33, H 5.62, N 3.27; $C_{22}H_{23}NO_6$ requires C 66.50; H 5.79; N 3.53; δ_H (500 MHz, $CDCl_3$) 7.89-7.84 (3.4H, m), 7.56-7.49 (2.6H, m), 4.43-4.29 (2.1H, m), 4.09-4.07 (0.5H, dd, J = 11.1, J = 3.7 Hz), 3.82 (1.5H, s), 3.78 (1.1H, s), 3.73 (1.1H, s), 3.68-3.67 (0.4H, d, J = 4.6 Hz), 3.65 (1.5H, s), 3.62-3.56 (0,6H, m), 3.47-3.43 (0.5H, dd, J = 11.2, J′ = 5.7 Hz), 3.44-3.40 (0.5H, dd, J = 7.7, J′ = 2.5 Hz), 3.22-3.10 (0.4H, m), 3.14-2.72 (0.4H, dd, J = 11.2, J′ = 7.7 Hz), 2.75-2.71 (0.6H, t, J = 10.0 Hz), 1.71 (1.1H, s), 1.60 (3H, s); δ_C (125.7 MHz, $CDCl_3$) 174.2, 172.8, 172.7, 172.3, 172.1, 171.2, 134.9, 134.4, 133.5, 133.3, 128.8, 127.8, 127.8, 127.2, 126.9, 126.5, 126.4, 126.3, 124.5, 124.7, 72.5, 71.5, 69.9, 66.9, 64.1, 61.5, 58.2, 55.0, 54.4, 53.1, 52.6, 52.4, 55.2, 46.0, 44.7, 30.5, 26.1.

Dimethyl (2*R*,6*S*,7*R*,*S*,8*R*,*S*) 6-Methyl-2-(2′-naphthyl)-1-aza-4-oxa[4.3.0]bicyclononan-5-one-7,8-dicarboxylate (11, 12). A mixture of diastereoisomers (1:1.3) was obtained (37%); M.p. = 53-55°C; found C 66.66, H 5.48, N 3.35; $C_{22}H_{23}NO_6$ requires C 66.50, H 5.79, N 3.53; ν_{max} (KBr)/cm^{-1} 3055, 2952, 2899, 2849, 1736, 1437, 1368; δ_H (500 MHz, $CDCl_3$) 7.89-7.84 (3.6H, m), 7.54-7.49 (2.7H, m), 4.56-4.28 (2.1H, m), 4.16-4.07 (1.4H, m), 3.78 (1.5H, s), 3.74 (1.3H, s), 3.65 (1.5H, s), 3.65 (1.3H, s), 3.50-3.43 (0.7H, m), 3.29-3.14 (1.7H, m), 2.96-2.55 (0.6H, m), 1.72 (1.5H, s), 1.68 (1.3H, s).

Methyl (3*S*,5*R*) 2-{N-[3-Methyl-5-(2′-naphthyl)morpholin-2-onyl]}-Z-propenoate (13). Attempts to generate the azomethine ylid **6** with paraformaldehyde and subsequently trap the ylid with methyl propiolate in refluxing xylene (thermal conditions) gave no expected cycloadduct, instead, a small amount of material resulting from Michael addition to the methyl propiolate was obtained (4%); δ_H (500 MHz, $CDCl_3$) 7.91-7.90 (1H, d, J = 8.5 Hz), 7.88-7.84 (2H, m), 7.76 (1H, s), 7.57-7.54 (2H, m), 7.43-7.40 (1H, d, J = 1H, 13.5 Hz), 7.35-7.33 (1H, dd, J = 8.5, J′ = 1.9 Hz), 4.88-4.85 (1H, dd, J = 9.8,

J' = 4.9 Hz), 4.65-4.62 (1H, d, J = 13.5 Hz), 4.59-4.55 (1H, dd, J = 12.5, J' = 4.9 Hz), 4.52-4.47 (1H, dd, J = 12.55, J' = 9.8 Hz), 4.46-4.41 (1H, q, J = 7.3 Hz), 3.56 (3H, s), 1.77-1.75 (3H, d, J = 7.3 Hz); δ_C (125.7 MHz, $CDCl_3$) 169.0, 168.7, 148.5, 133.4, 133.3, 132.3, 129.7, 127.9, 127.8, 126.9, 126.6, 123.6, 90.0, 69.1, 59.3, 56.9, 50.8, 19.4.

General Procedure for Cycloadditions under Sonication with Magnesium Bromide Etherate Catalysis

(3*S*,5*R*) 3-Methyl-5-(2'-naphthyl)morpholin-2-one 4 (100 mg, 0.41 mmol) was added to a flask containing freshly activated 4 Å molecular sieves under an argon atmosphere. Paraformaldehyde (15 mg, 0.49 mmol) and the appropriate dienophile (0.49 mmol) were added, followed by THF (15 mL). The reaction mixture was placed in a sonication bath, freshly prepared magnesium bromide etherate [6] (0.5 mL) added, and the reaction mixture sonicated for 12 h. After this time the reaction mixture was filtered, diluted with water (60 mL), and the aqueous solution extracted with dichloromethane (50 mL). The organic layer was washed with brine (50 mL), dried ($MgSO_4$), and removed *in vacuo* to leave the crude residue. Column chromatography (ethyl acetate/light petroleum, gradient elution) gave the cycloadducts as colorless or pale yellow solids [(**7**) = 17%, (**8a**) 25%, (**7b**) 13%, (**8b**) 26%, (**9** and **10**) 49%, (**11** and **12**) 41%, all with spectroscopic data identical to materials obtained under thermal conditions].

Dimethyl (2*R*,6*S*) 6-Methyl-2-(2'-naphthyl)-1-aza-4-oxa[4.3.0]bicyclononan-7-en-5-one-7,8-dicarboxylate (14). (7.8 mg, 4%), found 396.1447, [$C_{21}H_{21}NO_6$] + H requires 396.1448, δ_H (500 MHz, $CDCl_3$) 7.90-7.86 (4H, m), 7.54-7.552 (3H, m), 4.41-4.37 (1H, t, J = 11.2 Hz), 4.33-4.30 (1H, m), 4.18-4.16 (1H, dd, J = 10.7, J' = 3.2 Hz), 4.08-4.05 (1H, d, J = 16.8 Hz), 3.92 (3H, s), 3.72 (3H, s), 3.70-3.67 (1H, d, J = 16.7 Hz), 1.955 (3H, s); δ_C (125.7 MHz, $CDCl_3$) 169.6, 164.8, 162.4, 143.9, 134.3, 133.66, 133.4, 132.0, 128.9, 127.9, 127.8, 127.2, 126.6, 126.5, 124.9, 75.4, 71.6, 63.8, 59.0, 52.6, 52.3, 29.3; *m/z* (DCI, NH_3) 396 (100%, MH^+), 198 (50), 154 (55).

Methyl (2*R*,6*S*) 6-Methyl-2-(2'-naphthyl)-1-aza-4-oxa[4.3.0]bicyclononan-7-en-5-one-7-carboxylate (15). (32 mg, 23%), found 338.1392 [$C_{20}H_{19}NO_4$] + H requires 338.1393; δ_H (500 MHz, $CDCl_3$) 7.93-7.86 (4H, m), 7.57-7.50 (3H, m), 6.82-6.81 (1H, t, J = 2.1 Hz), 4.53-4.48 (1H, t, J = 11.7 Hz), 4.34-4.32 (1H, dd, J = 11.9, J' = 4.0 Hz), 4.46-4.11 (1H, m), 4.06-4.02 (1H, dd, J = 17.5, J' = 2.2 Hz), 3.85 (3H, s), 3.48-3.44 (1H, dd, J = 17.5, J' = 2.2 Hz), 2.4 (3H, s); δ_C (125.7 MHz, $CDCl_3$) 171.4, 163.6, 139.2, 135.2, 135.0, 133.4, 133.3, 128.8, 127.8, 127.7, 126.4, 126.3, 124.8, 70.4, 66.0, 60.5, 51.8, 28.7; *m/z* (DCI, NH_3) 338 (100%, MH^+), 154 (40).

General Procedure for Degradation of Morpholin-2-one Template. The cycloadduct **7a** or **7b** (0.2 mmol), trifluoroacetic acid (35 mg, 0.3 mmol, 23 mL), water (500 mg, 28.7 mmol, 500 mL), methanol (10 mL), and Pearlman's catalyst (74 mg) were all loaded into a Fischer-Porter bottle. The Fischer-Porter bottle was pressurized to 5 Bar with hydrogen (hazard) and the reaction mixture stirred vigorously at room temperature for 2 days. The catalyst was removed by filtration through a pad of Celite® and the methanol removed *in vacuo* to leave a yellow oil. Trituration with ether (2 mL) caused precipitation of the carboxylic acid as a colorless solid. Collection and washing by centrifugation followed by drying under a stream of nitrogen gave the amino acid as a free flowing colorless powder.

(2*R*,3*S*,4*R*) 2-(Methyl)-3,4-(N-methyl dicarboximido)pyrrolidine-2-carboxylic Acid (16a). (31 mg, 73%); δ_H (500 MHz, D_2O) 4.03-4.01 (1H, d, J = 8.5 Hz), 3.79-3.76 (1H, t, J = 8.0 Hz), 3.74-3.71 (1H, dd, J = 12.7, J' = 1.5 Hz), 3.65-3.61 (1H, dd, J = 12.8, J' = 9.3 Hz), 2.94 (3H, s), 1.6 (3H, s); $[\alpha]_D^{25}$ = +2.5 (c 1.02, 2 M HCl).

(2*R*,3*S*,4*R*) 2-(Methyl)-3,4-(N-phenyl dicarboximido)pyrrolidine-2-carboxylic Acid (16b). (25 mg, 73%); M.p. = 219-223°C; ν_{max} (KBr)/cm^{-1} 3100-2800, 1782, 1711; δ_H (200 MHz, CD_3OD) 7.8-7.2 (5H, m), 3.80-3.71 (3H, m), 3.61 (1H, d, J = 8.0 Hz), 1.30 (3H, s); *m/z* (DCI, NH_3) 229 ($M^+ - CO_2H$, 40%), 122 (80), 94 (60), 61 (100); $[\alpha]_D^{25}$ = −24.8 (c 0.75, 1 M HCl).

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