Synthesis of a chiral azodicarboxamide containing a bridging binaphthyl moiety: electrophilic amination reactions of achiral ester enolates

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A chiral azodicarboxamide 11 containing a bridging binaphthyl group has been prepared by an intermolecular cyclization reaction between the bis(*N*-methylamine) of 2,2′-dimethyl-1,1′-binaphthyl 6 and *N*,*N*′-bis(azidocarbonyl)hydrazine 9, followed by oxidation of the resulting hydrazodicarboxamide 10 with *N*-bromosuccinimide and pyridine. The crystal structure of azodicarboxamide 11 has been determined. Reaction of 11 with achiral oxazolidinone anions at −78 °C gives α-hydrazino acid derivatives with high stereoselectivity. The stereochemical outcome of the amination was determined by X-ray crystallography.

Introduction

Simple azodicarboxylate esters (*e.g.* diethyl azodicarboxylate)[1–3] have many uses in organic chemistry. They are reagents for Mitsunobu reactions,[4–6] electrophilic aminations,[7–14] and electrocyclic processes such as Diels–Alder[15] or ene reactions.[16] Previously we have reported the synthesis of simple chiral dialkyl (bornyl, isobornyl and menthyl) azodicarboxylates, which showed little or no stereoselectivity in amination reactions with achiral enolates of esters and *N*,*N*-dimethylamides.[17] This failure to influence amination stereochemistry was attributed to the conformational mobility and equal accessibility of both faces of the azo moiety to electrophilic attack. Therefore, cyclic azodicarboxylate esters wherein one face is shielded by a steroidal moiety were synthesized.[18] These proved to be unstable to protic conditions and, on formation, readily reduced back to the corresponding hydrazodicarboxylate esters with concomitant oxidation of bromide to bromine, possibly as a result of the rigid conformational constraints imposed by the steroidal bridge.

Recent studies by Ito and co-workers have found that *N*,*N*,*N*′,*N*′-tetraalkylated azodicarboxamides are more versatile reagents than the traditional diethyl azodicarboxylate for certain Mitsunobu reactions.[2,19–21] Hence, the present study investigates the preparation of a chiral macrocyclic azodicarboxamide, wherein one face of the azo moiety is bridged by a more flexible binaphthyl moiety, and examines its potential for the stereoselective amination of achiral enolates. The structures of both the binaphthyl azodicarboxamide and the protected α-hydrazino acid derived from electrophilic amination of 3-propionyl-1,3-oxazolidin-2-one enolate are determined by X-ray crystallography.

Results and discussion

The importance of optically active 1,1′-binaphthyl derivatives as chiral auxiliaries for asymmetric synthesis has encouraged development of methods to generate them without optical resolution of racemic compounds. One such procedure involves the asymmetric cross-coupling of 1-bromo-2-methylnaphthalene **1** with (2-methyl-1-naphthyl)magnesium bromide **2** in the presence of a chiral [(alkoxyalkyl)ferrocenyl]monophosphine–nickel catalyst.[22] Using this approach both (*R*)- and (*S*)-2,2′-dimethyl-1,1′-binaphthyl are readily synthesized in high enantiomeric excess, with the stereochemistry being determined by that of the ferrocenyl catalyst. This method was used to synthesize the (*R*) enantiomer **3**, which was further transformed to the dibromide **4** by *N*-bromosuccinimide (NBS) bromination (Scheme 1).[22] The enantiomeric purity of recrystallized **4** was confirmed by conversion to a cyclic ephedrine salt and comparison with literature data {$[\alpha]_D$ −180 (*c* 0.48, pyridine), lit.,[23] $[\alpha]_D$ −174 (*c* 0.6, pyridine)}. Since reaction of the dibromide with amines (such as ephedrine) results in formation of the corresponding cyclic ammonium salts[24] rather than bisaminated products needed for introduction of the dicarbonylazo moiety, dibromide **4** was first converted to diazide **5**. This readily forms the bis(*N*-methylated amine) **6** in high yield on reaction with bromodimethylborane, following a procedure developed by Dorow and Gingrich.[25]

Introduction of the dicarbonylhydrazine moiety of the hydrazodicarboxamide **10** in a cyclic manner was initially attempted following the procedure used by Tsunoda *et al.*, wherein *N*,*N*′-dimethylethylenediamine was condensed with diphenyl hydrazodicarboxylate **7** and oxidised to generate the cyclic azodicarboxamide 4,7-dimethyl-3,4,5,6,7,8-hexahydro-1,2,4,7-tetraazocine-3,8-dione.[20] However, this method is extremely slow and low-yielding with the chiral binaphthyl diamine **6**. To activate the hydrazodicarbonyl moiety towards nucleophilic attack, the more reactive bis(azidocarbonyl)hydrazine **9**[26] was synthesized from diphenyl hydrazodicarboxylate **7**, *via* *N*,*N*′-dicarbazoylhydrazine **8**. Attack of the binaphthyl diamine **6** on this highly reactive, explosive material, in the presence of triethylamine, affords the desired hydrazodicarboxamide **10** in 30% yield. This low yield is comparable to those obtained in similar cyclization reactions;[20,27] the majority of the isolated material appears to result from the hydrazinodicarbonyl moieties forming intermolecular bridges between binaphthyl groups, rather than cyclizing intramolecularly. Standard oxidation of **10** with NBS and pyridine gives the chiral binaphthyl azodicarboxamide **11**, the structure of which was determined by X-ray crystallographic analysis (Fig. 1).‡

Somewhat surprisingly, the three-dimensional structure of the azodicarboxamide **11** shows that this compound adopts a conformation which possesses a rotational axis of symmetry bisecting the N–N double bond of the azo moiety. The

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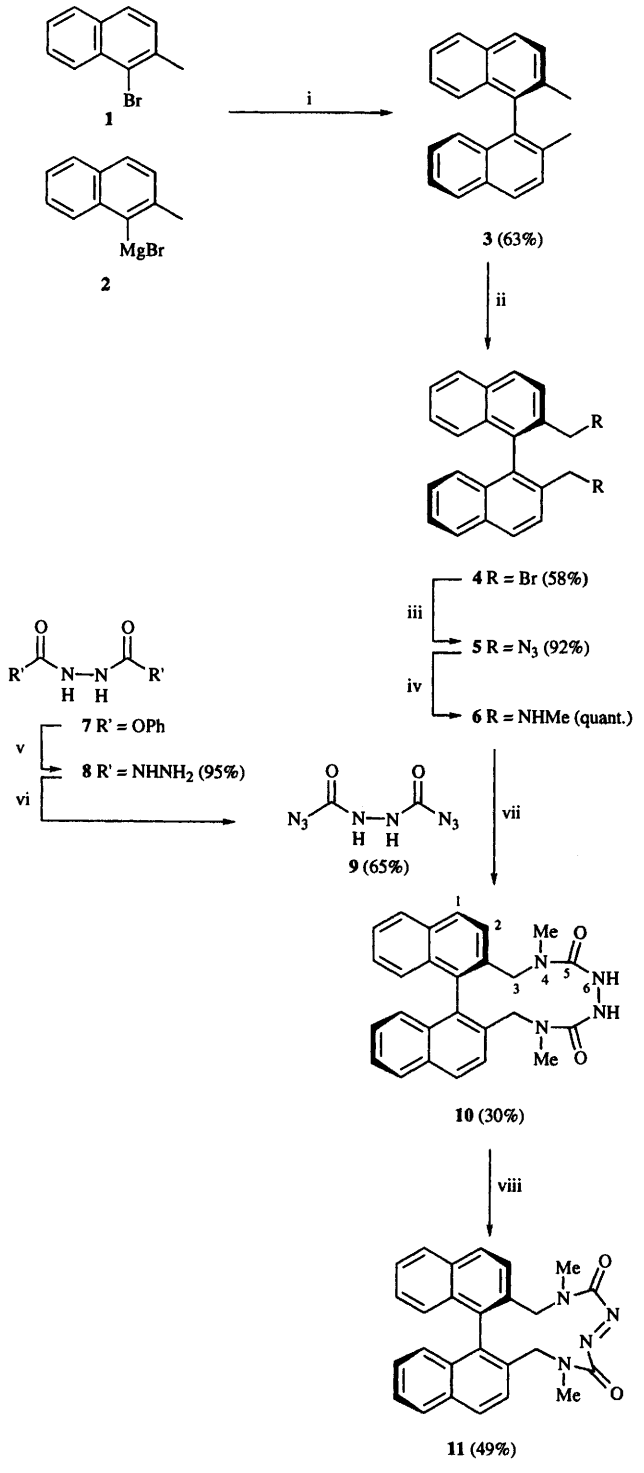
‡ See Experimental section for crystal data for compounds **11** and **14**. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC). See 'Instructions for Authors', *J. Chem. Soc., Perkin Trans. 1*, 1996, Issue 1. Any request to the CCDC for this material should quote the full literature citation and the reference number 207/54.



Scheme 1 *Reagents and conditions:* i, $NiBr_2$, [(*S*)-(*R*)-PPFOMe], MeMgBr; ii, NBS, $(PhCO)_2O_2$; iii, NaN_3 Bu_4NBr; iv, Me_2BBr; v, $NH_2NH_2{\cdot}H_2O$, MeOH; vi, AcOH, HCl, $NaNO_2$; vii, NEt_3; viii, NBS, pyridine

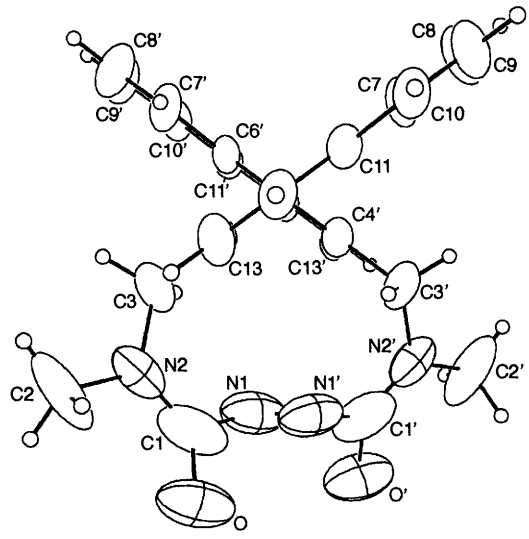
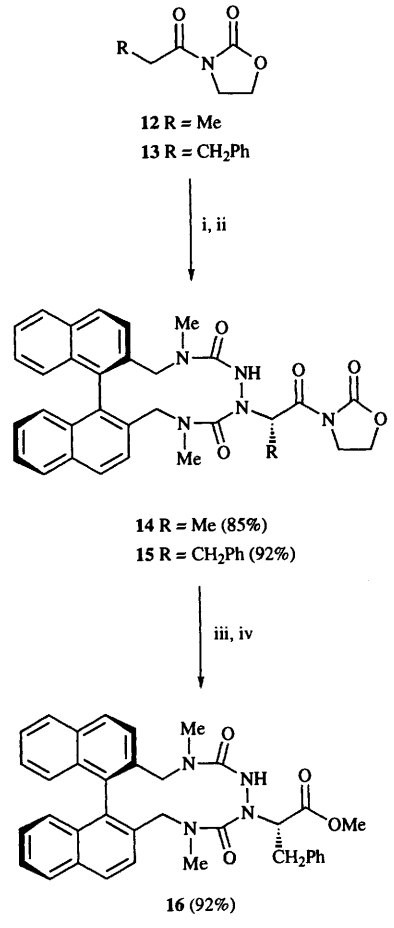


Fig. 1 Perspective view of the crystal conformation of azodicarboxamide **11** ($C_{26}H_{22}N_4O_2$). The torsion angle between the carbonyl and azo units (*i.e.* O–C–N–N) is 69.2 (12)°. Crystallographic numbering scheme is shown.



Scheme 2 *Reagents and conditions:* i, LDA, −78 °C; ii, **11**, iii, LiOH, H_2O_2; iv, CH_2N_2

carbonyls are coplanar with the amide nitrogens and as a consequence are almost orthogonal to the azo group. This is in contrast to other azodicarboxamide and azodicarboxylate esters, whose X-ray crystallographic structures are known, in which the azo group tends to be coplanar with one of the attached carbonyls and the other carbonyl is orthogonal.[28–30]

In order to investigate the possibility of asymmetric induction by the chiral binaphthyl azodicarboxamide, achiral oxazolidinones **12** and **13** were aminated at −78 °C using the standard procedure,[7] to give products **14** and **15**, respectively (Scheme 2). In both cases, only one diastereomer could be detected using ^1H NMR spectrometry. The structure of the methyl analogue **14** was determined by X-ray crystallographic analysis (Fig. 2),‡ thereby showing that the new stereogenic centre has *S* stereochemistry. Comparison of the ^1H NMR spectra of the crude product and the recrystallized material confirms formation of a single diastereomer. The crystal structure of the methyl analogue **14** exhibits two crystallographically-independent (but chemically equivalent) molecules as a dichloromethane solvate.

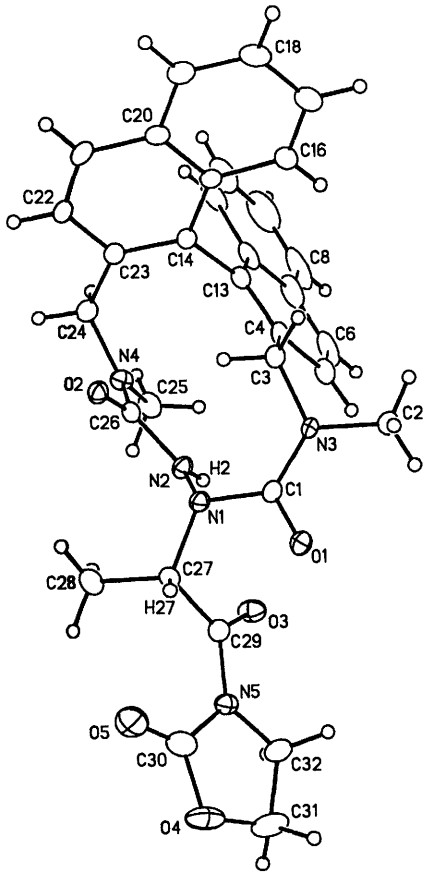


Fig. 2 Perspective view of the crystal conformation of one of the two crystallographically-independent molecules of hydrazodicarboxamide **14** ($C_{32}H_{31}N_5O_5$). Crystallographic numbering scheme is shown.

Although independent, the structures are equivalent within experimental error. Molecular models of the possible interactions between the azodicarboxamide **11** and the *Z*-enolate of the oxazolidinone **12** suggest that generation of the *S* isomer is preferred over the *R* due to unfavourable steric interactions in the latter. Additional chelation of the lithium ion with the carbonyl of the azodicarboxamide may further stabilize the *S* transition state. A representation of one possible transition state derived from the crystal coordinates for the azodicarboxamide **11** and the lithium-chelated *Z*-enolate of **12** is shown in Fig. 3.

Removal of the oxazolidinone auxiliary from compound **15** with lithium hydroperoxide,[17,31] followed by acidification and treatment with diazomethane generates the methyl ester **16**. Initial attempts to remove the binaphthyl moiety to produce the optically pure free α-hydrazino acid (or its methyl ester) have been unsuccessful thus far due to the harsh conditions necessary for cleavage of the amide bonds in such hydrazides. This characteristic, together with the number of steps (six) necessary for its preparation, makes **11** unlikely to be a practical aminating agent for achiral enolates, despite the very high stereoselectivity of the reaction. Nevertheless, the unique structural properties of this first chiral azodicarboxamide provide considerable potential for other types of reactions. This is especially true for Mitsunobu processes[4-6] that generate the reduced form **10**, which can be easily recovered and reoxidized to the parent reagent **11**. Current investigations on the use of **11** and other chiral azo derivatives in Mitsunobu reactions will be reported in the future.

Experimental

General procedures

All reactions were done under dry Ar. All solvents were purified and distilled according to Perrin *et al.*[32] Progress of reactions

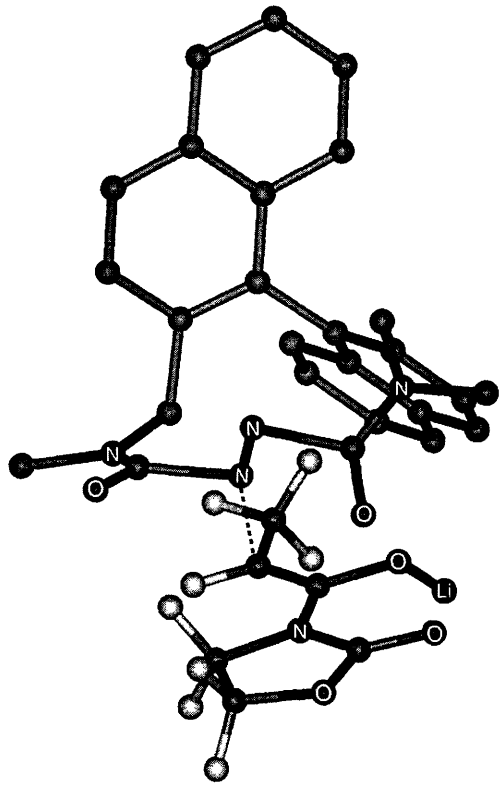


Fig. 3 Schematic representation of a possible transition state for the reaction between azodicarboxamide **11** (hydrogens not shown) and the enolate of oxazolidinone **12** to form the (*S*)-hydrazodicarboxamide **14**

was monitored by thin layer chromatography (TLC) on commercial silica gel plates (Merck 60F-254 or Merck RP-8F_{254}S) using either UV absorption, I_2 staining, ninhydrin (amino acids), bromocresol green (acids), or *p*-dimethylaminobenzaldehyde (hydrazine acids) spray for visualization. Flash chromatography employed Merck type 60 silica gel, 230–420 mesh. Normal phase medium pressure liquid chromatography (MPLC) was done using Merck type 60H silica gel. Melting points were determined either on a Thomas Hoover or Büchi apparatus using open ended capillary tubes and are uncorrected. Nuclear magnetic resonance spectra (NMR) were recorded on Bruker WP80, WH200, AM300, WM360 or AM400 instruments. The *J* values are given in Hz. Infrared spectra (IR) were determined with a Nicolet 7199 FT-IR spectrometer. Mass spectra (MS) were recorded with an ionizing voltage of 70 eV on a Kratos AEI MS50 instrument for electron impact (EI) ionization, on a MS12 for chemical ionization (CI), and on a MS-9 for fast atom bombardment (FAB). All literature compounds had ^{1}H NMR, IR and mass spectra consistent with assigned structures. Optical rotations were measured on Perkin-Elmer 241 or 141 polarimeters with a micro cell (100 mm, 0.9 ml) or a standard cell (100 mm, 8 ml), respectively. $[\alpha]_D$ Values are given in units of 10^{-1} deg cm^2 g^{-1}. Microanalyses were completed at the University of Alberta Microanalytical Laboratory.

(*R*)-2,2′-Dimethyl-1,1′-binaphthyl 3

Following the procedure of Hayashi *et al.*[22] the reaction of (2-methyl-1-naphthyl)magnesium bromide **2** (30 mmol) as a slurry prepared in diethyl ether (51 ml) and diluted with toluene (57 ml), with 1-bromo-2-methylnaphthalene **1** (6.18 ml, 40 mmol) in the presence of (*S*)-1-[(*R*)-2-(diphenylphosphino)-ferrocenyl]ethyl methyl ether (0.291 g, 0.68 mmol), anhydrous nickel bromide (0.075 g, 0.33 mmol) and methyl magnesium bromide (3.0 M in Et_2O; 0.291 ml, 0.89 mmol), in diethyl ether (9 ml) gave *binaphthyl* **3** (5.31 g, 63%) (Found: M$^+$, 282.141 42. $C_{22}H_{18}$ requires *M*, 282.140 84); δ_H(300 MHz; $CDCl_3$) 7.94 (2 H,

d, *J* 8.1), 7.92 (2 H, d, *J* 8.1), 7.56 (2 H, d, *J* 8.5), 7.44 (2 H, dd, *J* 8.1, 7.0), 7.25 (2 H, dd, *J* 8.1, 7.0), 7.13 (2 H, d, *J* 8.5) and 2.15 (6 H, s); *m/z* (EI) 282 (M^+, 100%), 267 ($M^+ - CH_3$, 29) and 252 ($M^+ - C_2H_6$, 19).

(*R*)-2,2′-Bis(bromomethyl)-1,1′-binaphthyl 4

Following the procedure of Hayashi *et al.*[22] the reaction of binaphthyl **3** (0.797 g, 2.82 mmol) with *N*-bromosuccinimide (1.03 g, 5.82 mmol) and benzoyl peroxide (0.013 g, 0.054 mmol) in carbon tetrachloride (16 ml), followed by recrystallization from toluene–hexane gave *dibromide* **4** (0.713 g, 57%), mp 171–174 °C (lit.,[22] 170–175 °C); $[\alpha]_D$ +148 (*c* 1.7, benzene) {lit.,[22] $[\alpha]_D$ +149 (*c* 1.0, benzene)}; δ_H(360 MHz; $CDCl_3$) 8.01 (2 H, d, *J* 8.5), 7.92 (2 H, d, *J* 8.1), 7.74 (2 H, d, *J* 8.5), 7.48 (2 H, ddd, *J* 8.1, 6.9, 1.2), 7.27 (2 H, ddd, *J* 8.4, 6.9, 1.2), 7.07 (2 H, d, *J* 8.4) and 4.25 (4 H, s).

(*R*)-2,2′-Bis(azidomethyl)-1,1′-binaphthyl 5

A solution of dibromide **4** (0.600 g, 1.36 mmol) in toluene (20 ml), under argon, was treated with sodium azide (0.355 g, 5.45 mmol) followed by tetrabutylammonium bromide (0.022 g, 0.068 mmol). The mixture was stirred at reflux for 24 h, then cooled to room temp. The solid residue was removed by filtration; the filtrate was washed with water (3 × 15 ml) and brine (15 ml), dried (Na_2SO_4) and concentrated under reduced pressure. Purification by flash chromatography [hexane–diethyl ether (100:0 to 90:10)] gave *diazide* **5** (0.456 g, 92%) as an oil (Found: M^+, 364.142 80. $C_{22}H_{16}N_6$ requires *M*, 364.143 65); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 2097 (N_3); δ_H(300 MHz; $CDCl_3$) 8.05 (2 H, d, *J* 8.5), 7.95 (2 H, d, *J* 8.2), 7.71 (2 H, d, *J* 8.5), 7.50 (2 H, ddd, *J* 8.2, 6.9, 1.2), 7.28 (2 H, ddd, *J* 8.5, 6.9, 1.3), 7.06 (2 H, d, *J* 8.5) and 4.08 (4 H, s); δ_C(75 MHz; $CDCl_3$) 133.95, 133.23, 132.66, 132.63, 129.12, 128.18, 127.00, 126.53, 126.08, 126.03 and 52.90; *m/z* (EI) 364 (M^+, 10%), 336 ($M^+ - N_2$, 2), 307 ($M^+ - H - 2N_2$, 15) and 294 ($M^+ - N_5$, 100).

(*R*)-2,2′-Bis(methylaminomethyl)-1,1′-binaphthyl 6

A solution of diazide **5** (1.95 g, 5.36 mmol) in 1,2-dichloroethane (90 ml), in a three-necked flask fitted with a condenser, was treated with bromodimethylborane (1.1 ml, 11.3 mmol). Immediate effervescence was observed, as nitrogen was released in an exothermic reaction, accompanied by a change in colour of the mixture from pale to dark yellow. The mixture was stirred at 60 °C for 1 h, then cooled to room temp. Ethanol (7.0 ml, 11.9 mmol) was added to quench the reaction. The mixture was stirred at room temp. for 20 min, then concentrated under reduced pressure. CH_2Cl_2 (50 ml) and sat. aq. Na_2CO_3 (50 ml) were added and the mixture was extracted with CH_2Cl_2 (3 × 75 ml). The organic phase was washed with sat. aq. Na_2CO_3 (2 × 75 ml), dried (Na_2SO_4) and concentrated under reduced pressure to give *bis*(N-*methylamine*) **6** (1.73 g, 95%) as a fluffy yellow solid, which was used without purification (Found: M^+, 340.194 98. $C_{24}H_{24}N_2$ requires *M*, 340.193 94); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3265 (NH); δ_H(360 MHz; $CDCl_3$) 7.98 (2 H, d, *J* 8.5), 7.92 (2 H, d, *J* 8.1), 7.75 (2 H, d, *J* 8.5), 7.44 (2 H, ddd, *J* 8.0, 6.9, 1.1), 7.22 (2 H, ddd, *J* 8.5, 6.9, 1.3), 7.01 (2 H, d, *J* 8.5), 3.45 (2 H, d, *J* 13.0), 3.33 (2 H, d, *J* 13.0) and 2.24 (6 H, s); δ_C(75 MHz; $CDCl_3$) 135.63, 134.56, 132.97, 132.94, 128.36, 128.10, 127.30, 126.49, 125.91, 125.87, 53.17 and 35.81; *m/z* (EI) 340 (M^+, 3%), 309 ($M^+ - NH_2CH_3$, 42) and 294 ($M^+ - C_2H_8N$, 100).

Diphenyl hydrazodicarboxylate (diphenyl bicarbamate) 7

Following the procedure of Kauer[33] the reaction of phenyl chloroformate (62.7 ml, 0.5 mol) with hydrazine monohydrate (12.1 ml, 0.25 mol), sodium carbonate (25.5 g, 0.25 mol), ethanol (125 ml) and water (125 ml) gave the known[2] *hydrazodicarboxylate* **7** (60.8 g, 89%) as a white powder (Found: C, 61.75; H, 4.27; N, 10.47%; M^+, 272.078 98. $C_{14}H_{12}N_2O_4$ requires C, 61.76; H, 4.44; N, 10.29%; *M*, 272.079 71); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3542, 3459 (NH), 1742 and 1721 (C=O); δ_H(360 MHz; $CDCl_3$) 7.27 (4 H, m), 7.13 (2 H, t, *J* 7.4) and 7.05 (4 H, d, *J* 7.7); *m/z* (EI) 272 (M^+, 6%), 178 (M^+ – PhOH, 7) and 94 (PhOH, 100).

***N*,*N*′-Dicarbazoylhydrazine 8**

A solution of hydrazodicarboxylate **7** (5.05 g, 18.6 mmol) in methanol (100 ml) was treated with hydrazine monohydrate (6.0 ml, 124 mmol). The mixture was stirred at room temp. overnight. The white precipitate formed was filtered and washed with methanol (10 ml) and diethyl ether (5 ml), then dried under reduced pressure to give known[26] *hydrazide* **8** (2.61 g, 95%) as a white solid (Found: M^+, 148.071 09. $C_2H_8N_6O_2$ requires *M*, 148.070 88); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3304, 3202, 3085, 2936 (NH), 1659 (C=O); *m/z* (EI) 148 (M^+, 2%), 117 ($M^+ - N_2H_3$, 48), 116 ($M^+ - N_2H_4$, 38), 101 ($M^+ - N_3H_5$, 2), 100 ($M^+ - N_2H_4O$, 1), 100 ($M^+ - N_3H_6$, 3) and 90 ($M^+ - N_2H_2CO$, 100).

***N*,*N*′-Bis(azidocarbonyl)hydrazine 9**

CAUTION: the product is explosive. A solution of hydrazide **8** (1.49 g, 10 mmol) in glacial acetic acid (24 ml), 5 M HCl (5 ml) and water (60 ml) was cooled in an ice–salt bath to −5 °C. This cooled solution was treated with a solution of sodium nitrite (1.44 g, 21 mmol) in water (10 ml) and stirred at −5 °C for 15 min. The mixture was allowed to warm to room temp. and diethyl ether (60 ml) was added. The mixture was extracted with diethyl ether (3 × 50 ml) and the organic phase was washed with water (3 × 50 ml) and brine (50 ml), dried (Na_2SO_4) and concentrated under reduced pressure to give the known[26] *diazide* **9** (1.11 g, 65%) as a white solid, which explodes readily on strong heating or violent concussion (Found: M^+, 170.030 40. $C_2H_2N_8O_2$ requires *M*, 170.030 08); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3232 (NH), 2156 (N_3), 1730 and 1688 (C=O); *m/z* (EI) 170 (M^+, 5%), 142 ($M^+ - N_2$, 1), 128 ($M^+ - N_3$, 6), 127 ($M^+ - N_3H$, 47) and 100 ($M^+ - N_3CO$, 4.5).

(*R*)-4,9-Dimethyl-3,4,5,6,7,8,9,10-octahydrodinaphtho[2,1-*f*:1′,2′-*h*][1,2,4,11]tetraazacyclododecine-5,8-dione 10

A solution of bis(*N*-methylamine) **6** (1.60 g, 4.7 mmol) in 1,2-dichloroethane (200 ml) was treated with triethylamine (1.45 ml, 10.4 mmol) and stirred at room temp. for 15 min. Diazide **9** (0.80 g, 4.7 mmol) was added to the solution. The mixture was stirred for a further 15 min at room temp. and then at reflux for 20 h. The mixture was cooled to room temp., water (100 ml) was added, and the mixture was extracted with CH_2Cl_2 (3 × 150 ml). The organic phase was washed with sat. aq. Na_2CO_3 (2 × 50 ml), water (3 × 100 ml) and brine (100 ml), dried (Na_2SO_4) and concentrated under reduced pressure. Purification by flash chromatography [$CHCl_3$–MeOH (100:0 to 90:10)] gave *hydrazodicarboxamide* **10** (0.597 g, 30%) as a glassy oil (Found: M^+, 424.189 92. $C_{26}H_{24}N_4O_2$ requires *M*, 424.189 94); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3267 (NH) and 1652 (C=O); δ_H(360 MHz; $CDCl_3$) 8.02 (2 H, d, *J* 8.4), 7.94 (2 H, d, *J* 8.1), 7.66 (2 H, d, *J* 8.4), 7.48 (2 H, ddd, *J* 8.1, 7.0, 1.1), 7.29 (2 H, ddd, *J* 8.3, 7.0, 1.1), 7.03 (2 H, d, *J* 8.4), 5.92 (2 H, s), 4.27 (2 H, d, *J* 17.0), 3.93 (2 H, d, *J* 17.0) and 2.98 (6 H, s); δ_C(75 MHz; $CDCl_3$) 157.37, 135.44, 132.90, 132.82, 132.43, 129.08, 128.42, 127.18, 126.22, 125.40, 124.84, 52.74 and 39.11; *m/z* (EI) 424 (M^+, 20%), 309 ($M^+ - C_3H_5N_3O_2$, 33) and 294 ($M^+ - C_4H_8N_3O_2$, 100).

(*R*)-4,9-Dimethyl-4,5,9,10-tetrahydro-3*H*,8*H*-naphtho[2,1-*f*:1′,2′-*h*][1,2,4,11]tetraazacyclododecine-5,8-dione 11

A solution of hydrazodicarboxamide **10** (0.470 g, 0.111 mmol) in CH_2Cl_2 (3 ml) was treated with pyridine (0.009 ml, 0.111 mmol) and stirred at room temp. for 5 min. NBS (0.0207 g, 0.117 mmol) was added and the clear solution immediately turned orange. The mixture was stirred at room temp. overnight. Water (5 ml) was added, and the mixture was extracted with CH_2Cl_2 (3 × 10 ml). The organic phase was washed with

water (3 × 10 ml) and brine (10 ml), dried (Na_2SO_4) and concentrated under reduced pressure. Purification by flash chromatography [hexane–EtOAc (1:1)] gave *azodicarboxamide* **11** (0.023 g, 49%) as a yellow solid, mp 214–218 °C (from CH_2Cl_2) (Found: M^+, 422.174 22. $C_{26}H_{22}N_4O_2$ requires *M*, 422.174 29); $[\alpha]_D$ +217 (*c* 0.28, $CHCl_3$); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 1714 (C=O); δ_H(360 MHz, $CDCl_3$) 8.00 (2 H, d, *J* 8.7), 7.93 (2 H, d, *J* 8.2), 7.62 (2 H, d, *J* 8.7), 7.50 (2 H, ddd, *J* 8.2, 7.1, 1.2), 7.32 (2 H, ddd, *J* 8.5, 7.1, 1.2), 7.05 (2 H, d, *J* 8.5), 4.15 (2 H, d, *J* 17.4), 3.86 (2 H, d, *J* 17.4) and 3.50 (6 H, s); δ_C(100 MHz, $CDCl_3$) 163.10, 133.61, 132.72, 132.16, 129.39, 128.47, 127.39, 126.49, 125.70, 123.72, 50.34 and 39.52; *m/z* (EI) 422 (M^+), 365 ($M^+ - C_2H_3NO$, 27%) and 294 ($C_{22}H_{16}N^+$, 100).

(*R*)-4,9-Dimethyl-6-[(1*S*)-1-methyl-2-oxo-2-(2-oxo-1,3-oxazolidin-3-yl)ethyl-3,4,5,6,7,8,9,10-octahydrodinaphtho-[2,1-*f*:1′,2′-*h*][1,2,4,11]tetraazacyclododecine-5,8-dione 14

Following the procedure of Trimble and Vederas,[7] a solution of 0.85 mol l^{-1} lithium diisopropylamide in THF (1.0 ml) [2.5 mol l^{-1} BuLi in hexane (5 ml) and diisopropylamine (1.8 ml) in THF (8 ml)] at −78 °C was added dropwise to a stirred solution of 3-propionyl-1,3-oxazolidin-2-one **12** (0.085 g, 0.594 mmol) in THF (9 ml) at −78 °C. The mixture was stirred at −78 °C for 20 min, then a cooled solution of azodicarboxamide **11** (0.049 g, 0.116 mmol) in THF (4 ml) and CH_2Cl_2 (1.5 ml) was added over 2 min. After being stirred for 5 min the reaction was quenched at −78 °C with a solution of acetic acid (0.04 ml) in THF (1 ml) and warmed to room temp. The solution was extracted with CH_2Cl_2 (3 × 10 ml). The organic phase was washed with water (3 × 10 ml) and brine (10 ml), dried (Na_2SO_4) and concentrated under reduced pressure. Purification by flash chromatography (ethyl acetate) gave *oxazolidinone* **14** (0.056 g, 85%) as a solid, mp 219–221 °C (from CH_2Cl_2–Et_2O) (Found: M^+, 565.232 40. $C_{32}H_{31}N_5O_5$ requires *M*, 565.232 54); $[\alpha]_D$ +265 (*c* 0.38, CH_2Cl_2); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3410 (NH), 1783 (C=O), 1678 (C=O) and 1648 (C=O); δ_H(360 MHz; $CDCl_3$) 8.02 (1 H, d, *J* 8.5), 7.93 (2 H, d, *J* 8.4), 7.89 (1 H, d, *J* 8.1), 7.75 (1 H, d, *J* 8.6), 7.62 (1 H, d, *J* 8.5), 7.47 (1 H, ddd, *J* 8.1, 6.8, 1.2), 7.40 (1 H, ddd, *J* 8.0, 6.7, 1.1), 7.32 (1 H, ddd, *J* 8.4, 6.9, 1.3), 7.21 (1 H, m), 7.19 (1 H, d, *J* 8.5), 6.99 (1 H, d, *J* 8.0), 6.55 (1 H, s), 5.59 (1 H, q, *J* 7.2), 4.82 (1 H, d, *J* 15.0), 4.55 (1 H, d, *J* 18.9), 4.42 (2 H, m), 4.10 (1 H, ddd, *J* 10.6, 9.4, 6.8), 3.89 (1 H, ddd, *J* 10.7, 9.1, 7.2), 3.77 (1 H, d, *J* 15.0), 3.54 (1 H, d, *J* 18.9), 3.08 (3 H, s), 1.39 (3 H, s) and 1.31 (3 H, d, *J* 7.2); δ_C(75 MHz; $CDCl_3$) 177.11, 161.63, 155.84, 152.51, 137.11, 136.80, 133.63, 133.00, 132.69, 132.21, 131.67, 130.82, 128.51, 128.45, 128.40, 128.26, 128.16, 127.08, 126.61, 125.72, 125.48, 125.06, 124.54, 122.81, 62.25, 57.38, 56.78, 52.37, 42.05, 39.98, 34.93 and 13.40; *m/z* (EI) 565 (M^+, 16%), 478 ($M^+ - C_3H_5NO_2$, 35), 393 ($M^+ - C_6H_{10}N_3O_3$, 56) and 294 ($C_{22}H_{16}N^+$, 100).

(*R*)-6-[(1*S*)-1-Benzyl-2-oxo-2-(2-oxo-1,3-oxazolidin-3-yl)ethyl]-4,9-dimethyl-3,4,5,6,7,8,9,10-octahydrodinaphtho[2,1-*f*:1′,2′-*h*]-[1,2,4,11]tetraazacyclododecine-5,8-dione 15

The above procedure with a solution of 0.85 mol l^{-1} LDA (0.62 ml, 0.527 mmol) and 3-(3′-phenylpropionyl)-1,3-oxazolidin-2-one **13** (0.105 g, 0.479 mmol) in THF (9 ml) and azodicarboxamide **11** (0.039 g, 0.092 mmol) in THF (2 ml) and CH_2Cl_2 (3 ml) gave *oxazolidinone* **15** (0.054 g, 92%) as a glassy solid (Found: M^+, 641.264 25. $C_{38}H_{35}N_5O_5$ requires *M*, 641.263 79); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3405 (NH), 1784 (C=O), 1678 (C=O) and 1650 (C=O); δ_H(300 MHz; $CDCl_3$) 8.01 (1 H, d, *J* 8.6), 7.95 (1 H, d, *J* 8.5), 7.94 (1 H, d, *J* 8.1), 7.90 (1 H, d, *J* 8.1), 7.72 (1 H, d, *J* 8.6), 7.63 (1 H, d, *J* 8.5), 7.47 (1 H, ddd, *J* 8.0, 6.7, 1.0), 7.43 (1 H, ddd, *J* 8.0, 6.8, 1.0), 7.30 (1 H, ddd, *J* 8.3, 6.7, 1.0), 7.23 (1 H, ddd, *J* 8.3, 6.8, 1.2), 7.21–7.11 (4 H, m), 7.09–7.07 (2 H, m), 6.99 (1 H, d, *J* 8.4), 6.68 (1 H, s), 5.93 (1 H, br), 4.83 (1 H, d, *J* 15.0), 4.57 (1 H, d, *J* 18.7), 4.09 (1 H, m), 3.90–3.55 (3 H, m), 3.79 (1 H, d, *J* 15.0), 3.56 (1 H, d, *J* 18.6), 3.34 (1 H, dd, *J* 12.9, 5.5), 3.08 (3 H, s), 2.76 (1 H, t, *J* 12.6) and 1.44 (3 H, s); δ_C(75 MHz; $CDCl_3$) 176.72, 161.53, 155.83, 151.56, 137.04, 136.67, 135.42, 133.60, 133.01, 132.72, 132.22, 131.70, 130.84, 129.62, 128.50, 128.42, 128.29, 128.13, 127.97, 127.10, 126.83, 126.66, 125.75, 125.53, 125.07, 124.57, 122.89, 61.55, 60.00, 57.44, 52.35, 41.97, 40.09, 35.53 and 34.96; *m/z* (EI) 641 (M^+, 6%), 554 ($M^+ - C_3H_5NO_2$, 20), 393 ($M^+ - C_{12}H_{14}N_3O_3$, 23), 294 ($C_{22}H_{16}N^+$, 49) and 279 ($C_{22}H_{15}^+$, 100).

(*R*)-6-[(1*S*)-1-Methoxycarbonyl-2-phenylethyl]-4,9-dimethyl-3,4,5,6,7,8,9,10-octahydrodinaphtho[2,1-*f*:1′,2′-*h*][1,2,4,11]-tetraazacyclododecine-5,8-dione 16

A solution of oxazolidinone **15** (0.025 g, 0.039 mmol) in THF (0.6 ml) and H_2O (0.2 ml) was cooled to 0 °C. Hydrogen peroxide (30% aqueous; 0.022 ml, 0.195 mmol) was added followed by lithium hydroxide monohydrate (0.0033 g, 0.078 mmol). The mixture was stirred in an ice bath for 1 h. Excess peroxide was quenched at 0 °C with a 10% excess of 1.5 M sodium sulfite (0.143 ml, 0.215 mmol). The solution was buffered to pH 10 with aq. $NaHCO_3$. The THF was evaporated under reduced pressure and the resulting solution was extracted with CH_2Cl_2 (3 × 1 ml). The organic phase was washed with H_2O (3 × 1 ml) and brine (1 ml), dried (Na_2SO_4) and concentrated under reduced pressure to give a glassy oil. A solution of this oil in Et_2O (2 ml), THF (0.8 ml) and CH_2Cl_2 (0.5 ml) was acidified with 10% formic acid (0.020 ml). A solution of diazomethane in diethyl ether was added until evolution of N_2 had ceased and a persistent pale yellow colour remained. The resulting solution was concentrated under reduced pressure. Purification by flash chromatography (ethyl acetate) gave *ester* **16** (0.021 g, 92%) (Found: M^+, 586.257 56. $C_{36}H_{34}N_4O_4$ requires *M*, 586.258 00); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3404 (NH), 1729 (C=O), 1678 (C=O) and 1651 (C=O); δ_H(300 MHz; $CDCl_3$) 8.02 (1 H, d, *J* 8.6), 7.94 (2 H, d, *J* 8.4), 7.89 (1 H, d, *J* 8.1), 7.73 (1 H, d, *J* 8.6), 7.62 (1 H, d, *J* 8.3), 7.47 (1 H, dd, *J* 8.1, 6.9), 7.41 (1 H, dd, *J* 8.1, 6.9), 7.31 (1 H, dd, *J* 8.2, 7.0), 7.25–7.15 (5 H, m), 7.07 (2 H, d, *J* 7.7), 6.99 (1 H, d, *J* 8.5), 6.47 (1 H, s), 4.78 (1 H, d, *J* 15.2), 4.73 (1 H, dd, *J* 10.0, 5.5), 4.57 (1 H, d, *J* 18.6), 3.78 (1 H, d, *J* 15.1), 3.57 (1 H, d, *J* 18.9), 3.48 (3 H, s), 3.33 (1 H, dd, *J* 13.5, 5.3), 3.08 (3 H, s), 2.74 (1 H, dd, *J* 13.5, 10.5) and 1.40 (3 H, s); δ_C(75 MHz; $CDCl_3$) 174.74, 161.22, 155.81, 137.27, 136.90, 136.76, 133.58, 133.05, 132.74, 132.29, 131.80, 131.00, 130.30, 129.10, 128.53, 128.42, 128.32, 128.23, 128.18, 127.98, 127.26, 127.11, 126.71, 126.45, 125.78, 125.59, 125.07, 124.64, 122.87, 63.50, 57.12, 52.53, 51.51, 40.28, 35.37 and 35.10; *m/z* (EI) 586 (M^+, 1%), 294 ($C_{22}H_{16}N^+$, 3) and 279 ($C_{22}H_{15}^+$, 4).

Crystal data for azodicarboxamide 11

Data were acquired on a Siemens P4/RA diffractometer with a rotating anode generator (18 kW). All intensity measurements were performed using graphite monochromated Mo-Kα radiation ($\lambda = 0.710\ 73$ Å). Azodicarboxamide **11** ($C_{26}H_{22}N_4O_2$) was obtained as colourless tetragonal crystals, $P4_32_12$ (No. 96), $a = 11.490$ (2), $c = 16.782$ (3) Å, $V = 2215.6$ (5) Å^3, $Z = 4$, $T = 295$ K, $D_C = 1.267$ g cm^{-3}, $\mu = 0.082$ mm^{-1}. A total of 2886 reflections were collected (1953 unique, $R_{int} = 0.036$). Due to the low value of the linear absorption coefficient (μ) no absorption correction was applied to the data. The data were corrected for Lorentz and polarization effects. The structure was solved by direct methods[34] and refined by full-matrix least-squares methods on F^2.[35] In the final refinement cycle 1952 reflections with $F_o^2 > -3\sigma(F_o^2)$ were used, with 145 parameters varied; the model converged with unweighted and weighted agreement factors $R_1 = 0.0751$ [based on 687 reflections with $F_o^2 > 2\sigma(F_o^2)$][36a] and $wR_2 = 0.1447$,[36b] with a goodness of fit indicator (*S*) of 1.036.[36c] Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre (see footnote ‡ for details).

Crystal data for hydrazodicarboxamide 14

Data were acquired on a Siemens P4/RA diffractometer with a

rotating anode generator (18 kW). All intensity measurements were performed using graphite monochromated Cu-Kα radiation ($\lambda = 1.541\ 78$ Å). Hydrazodicarboxamide **14** {$C_{65}H_{64}Cl_2N_{10}O_{10}$ [$2(C_{32}H_{31}N_5O_5)\cdot CH_2Cl_2$]} was obtained as colourless monoclinic crystals, $P2_1$ (No. 4), $a = 10.3883$ (9), $b = 15.1512$ (9), $c = 18.7469$ (12) Å, $\beta = 93.020$ (9)°. $V = 2946.6$ (4) Å^3, $Z = 2$, $T = 213$ K, $D_C = 1.371$ g cm^{-3}, $\mu = 1.570$ mm^{-1}. A total of 8732 reflections were collected (7882 unique, $R_{int} = 0.028$). An absorption correction was applied to the data using the method of Gaussian integration (employing the exact crystal dimensions and face indices). The data were corrected for Lorentz and polarization effects. The structure was solved by a combined direct methods–fragment search approach [37] and refined by full-matrix least-squares methods on F^2.[35] In the final refinement cycle all 7882 unique reflections were used [all of these having $F_o^2 > -3\sigma(F_o^2)$], with 784 parameters varied; the model converged with unweighted and weighted agreement factors $R_1 = 0.0491$ [based on 6472 reflections with $F_o^2 > 2\sigma(F_o^2)$][36a] and $wR_2 = 0.1183$,[36b] with a goodness of fit indicator (S) of 1.022.[36c] Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre (see footnote ‡ for details).

Acknowledgements

We thank J. Drew Sutherland for technical assistance and Dr Nancy Fregeau Gallagher for assistance with molecular modelling. These investigations were supported by the Natural Sciences and Engineering Research Council of Canada, and the Alberta Heritage Foundation for Medical Research (postdoctoral fellowship J. M. H.).

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36 (*a*) $R_1 = \Sigma||F_o| - |F_c||/\Sigma|F_o|$; (*b*) $wR_2 = [\Sigma w(F_o^2 - F_c^2)^2/\Sigma w(F_o^4)]^{\frac{1}{2}}$; (*c*) $S = [\Sigma w(F_o^2 - F_c^2)^2/(n-p)]^{\frac{1}{2}}$ (n = number of data; p = number of parameters varied; $w = [\sigma^2(F_o^2) + (a_1P)^2 + a_2P]^{-1}$ where $P = [\max(F_o^2, 0) + 2F_c^2]/3$) and the factors a_1 and a_2 are adjusted for the structure by the refinement program (for **11**, $a_1 = 0.0254$ and $a_2 = 0.5943$; for **14**, $a_1 = 0.0496$ and $a_2 = 1.8477$).
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Paper 6/04394A
Received 24th *June* 1996
Accepted 9th *August* 1996