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X=Y-ZH Compounds as Potential 1,3-Dipoles. Part 44.[1] Asymmetric 1,3-Dipolar Cycloaddition Reactions of Imines and Chiral Cyclic Dipolarophiles.

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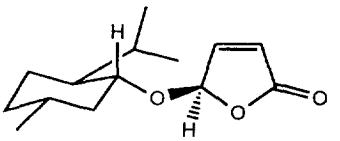
Abstract. Metallo - 1,3-dipoles generated in situ from both aryl and aliphatic imines of α-amino esters by the action of silver salts and tertiary amines undergo cycloaddition at room temperature to 5R-(1′R, 2′S, 5′R-menthyloxyl) - 2(5H)-furanone and to N-acetyl-5R-isopropoxy-2(5H)-pyrrolone giving homochiral cycloadducts in good yield in all cases. π-Interaction between the dipolarophile carbonyl group and the aryl group in the aryl imines is not required for good induction. The stronger the base the faster the cycloaddition with 2-t-butyl-1,1,3,3-tetramethylguanidine > DBU > NEt_3. X-Ray crystal structures of representative cycloadducts establish the absolute configuration of the pyrrolidine stereocentres.

There is a strong current interest in achieving asymmetric 1,3-dipolar cycloaddition reactions. There are three general approaches to this problem involving either (i) chiral 1,3-dipoles (ii) chiral dipolarophiles or (iii) chiral catalysts. Our own work involving metal ion catalysed regio- and stereo-specific cycloaddition of imines to electronegative olefins at ambient temperature offers an excellent opportunity to evaluate approaches to (ii) and (iii). These reactions are believed to involve metallo-azomethine ylides. We have recently reported full details of our work which employed chiral dipoles,[2] or menthyl acrylate as a chiral acyclic dipolarophile[1,3] and a preliminary report of our results with chiral Co(II) and Mn(II) catalysts has appeared.[4] This paper reports full details of our work on chiral cyclic dipolarophiles.

Feringa et al. have utilised homochiral 5-menthyloxy-2(5H)-furanones (1) in a range of 1,3-dipolar cycloaddition reactions[5] and Diels-Alder reactions[6] all of which occurred with good asymmetric induction. This encouraged us to evaluate (1) in our metallo-azomethine ylide cycloaddition reactions.

The choice of (1) with its enforced *s*-trans enone geometry was felt to provide an interesting contrast to menthyl acrylate which appears to undergo cycloaddition via the *s*-cis enone geometry (Figure 1).[1] A wide range of imines (2 a-l) were reacted with the dipolarophile (1) in acetonitrile at ambient temperature using silver acetate in combination with DBU or 2-t-butyl-1,1,3,3-tetramethylguanidine as a catalyst. Cycloadducts



(1)

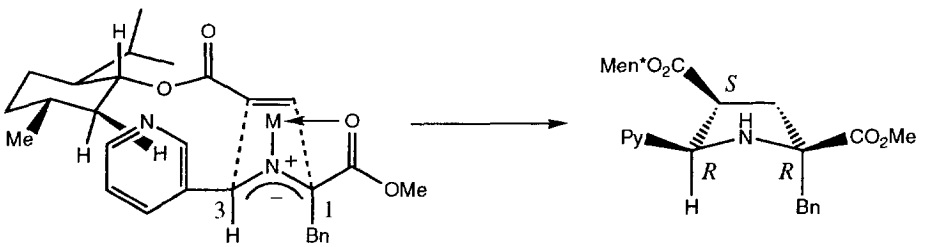
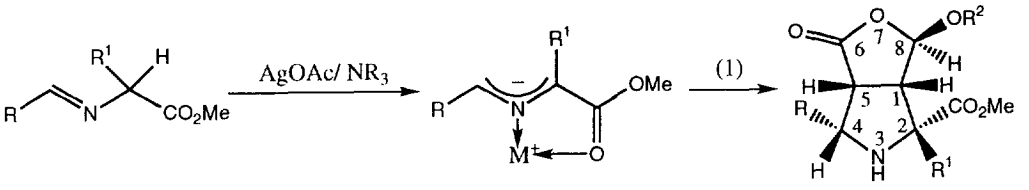


Figure 1 Schematic transition state for metalloazomethine ylide cycloaddition to menthyl acrylate.[1]

(4 a-l) were formed regio- and stereo-specifically and with d.e.'s greater than 95%, [^{1}H n.m.r. ($CDCl_3$) showed a single diastereomer] (Table 1). The choice of base followed experiments which showed the efficacy of amine bases to be 2-t-butyl-1,1,3,3-tetramethylguanidine > DBU > NEt_3. Increasing the base strength of the amine results in both shorter reaction times and increased yields of homochiral cycloadducts. For a more detailed comparison of the effect of variation of the base see our studies with menthyl acrylate.[1]



(2) (3) (4)

R^2 = 1*R*, 2*S*, 5*R*-Menthyl

Aryl imines (2 a-d), (2f and (2h) reacted at room temperature with dipolarophile (1) (AgOAc, 2-t-butyl-1,1,3,3-tetramethylguanidine, MeCN) to give the *syn-endo* adducts (4 a-d) (4f) and (4h) (70-91%) over 0.75-1.5 h. Aliphatic imines (2e) and (2g) are unstable to prolonged storage and were used immediately. The aliphatic imines (2 e,g,i-l) also gave the corresponding *syn-endo* cycloadducts (4 e,g,i-l), (71-91%) over 1.2-6 h. These latter examples are the first homochiral cycloadducts involving aliphatic aldimine precursors and in these cases the preferred solvent is toluene.[6] 2-t-Butyl-1,1,3,3-tetramethylguanidine was not evaluated as a base for the cycloadditions of imines (2i), (2k) and (2l) but its use would be expected to reduce the reaction time and increase the reaction yield. Thus for comparison when (2j) was reacted with (1) using DBU as base the reaction occurred over 5h and gave (4j) in 75% yield. The dipolarophile (1) judged on reaction times, is more reactive than menthyl acrylate[1] but less reactive than methyl acrylate.

Table 1 Homochiral cycloadducts from reaction of (2a-l) with (1).[a]

	Imine (2)		Reaction time (h)	Product	Yield (%)[b]
	R	R^1			
a.	3-pyridyl	$PhCH_2$	0.75	4a	89
b.	2-naphthyl	$CH_2CH\ Me_2$	1.0	4b	86
c.	2-naphthyl	H	1.0	4c	91
d.	2-naphthyl	Me	1.5	4d	83
e.	c-C_6H_{11}	Me	1.75	4e	91[c]
f.	2-naphthyl	$PhCH_2$	1.2	4f	83
g.	myrtenyl	$PhCH_2$	1.2	4g	86[c]
h.	2-IC_6H_4	Me	1.5	4h	70[d]
i.	$(CH_2)_2R^2$	H	5.0	4i	84[c,d]
j.	$(CH_2)_3R^2$	Me	4.0	4j	83[c]
k.	$(CH)_3R^2R^2$	3-indolylmethyl	5.5	4k	80[c,d]
l.	$(CH_2)_2R^2$	Me	6.0	4l	71[c,d]

R^2 = 2- (1,3-dioxolanyl)

a. All reactions carried out in dry MeCN using AgOAc (1.5mol) and 2-t-butyl-1,1,3,3-tetramethylguanidine (1.2mol) as the catalytic system unless otherwise specified.

b. Isolated yield of product with d.e. > 95% in all cases i.e. ^1H n.m.r. spectra showed a single diastereomer in each case.

c. Toluene as solvent.

d. DBU used as base.

Thus in all cases the cycloadducts (4a-l) are formed via endo-transition states involving the syn-dipoles (3). As expected the cycloaddition occurs in a facially specific manner on the face of the dipolarophile trans to the bulky O-menthyl group. The stereochemistry of the cycloadducts is based on n.O.e. and COSY data together with a single crystal X-ray structure of (4 h) (figure 2). An illustrative example of the n.O.e. data is provided by (4c): irradiation ($CDCl_3$) of 1-H (δ 3.02) effects a 12% enhancement of the signal for 5-H and a 10% enhancement of the signal for 2-H; irradiation of 8-H (δ5.01) resulted in only 3% enhancement of the signal for 1-H. The trans - relationship between 1-H and 8-H is strongly indicated by this latter low enhancement. Similar effects were observed for all the cycloadducts (4a-l) and the n.O.e. data for these compounds are collected in the experimental section.

The presence of a menthyl auxiliary of known absolute configuration allows the absolute configuration of the four chiral centres in the pyrrolidine ring of the cycloadducts to be assigned unequivocally based on the single crystal X-ray structure (figure 2) of (4h) which showed it to be the (1S, 2R, 4S, 5R) - adduct of 5R-(1′R, 2′S, 5′R-menthyloxy)-2(5H)-furanone. Thus (4h) is derived from a transition state involving addition of the E,E-dipole (neglecting M) via its α-re/β-si face to the lactone 3-si/4-re face (figure 3). The reaction occurs equally well when either aliphatic or aromatic aldimines are used showing that π-interactions between the lactone carbonyl group and the naphthyl moiety in the aldimine are not a prerequisite for good induction.

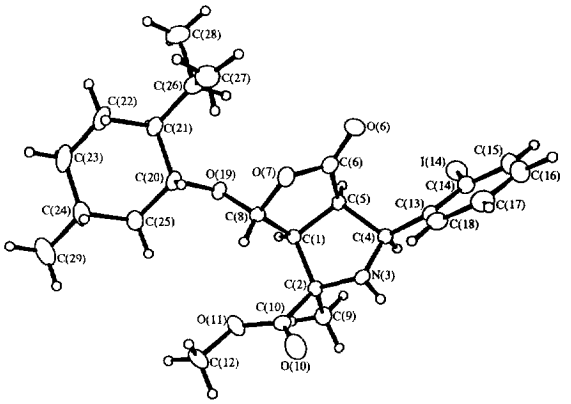


Figure 2. Molecular structure of compound **4h**.

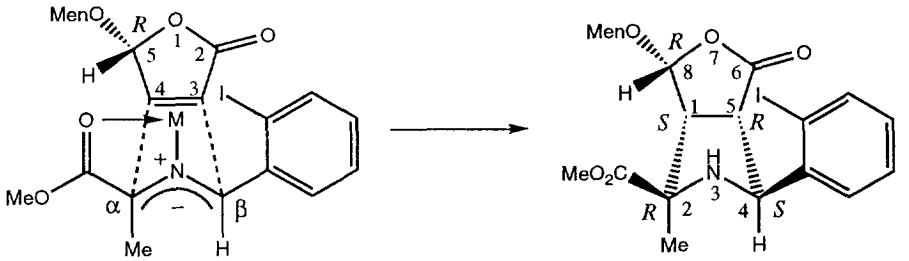
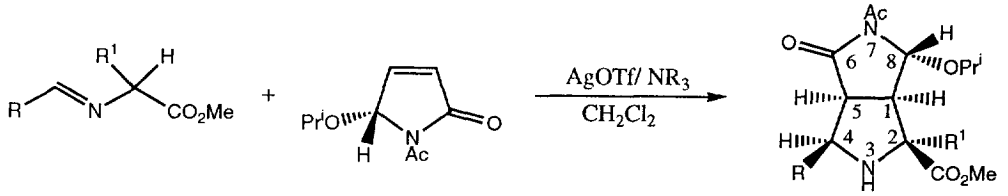


Figure 3. Schematic transition state for the cycloaddition of (1) and (3h).



(2) (5) (6)

A second series of cycloaddition reactions was carried out using the chiral 5R- lactam (5), developed by Heimstra and Speckamp,[7] as the dipolarophile. In this series of reactions we explored the use of a silver triflate/DBU catalyst combination in methylene chloride as solvent. The imines (2c-f) and (2m,n) all gave homochiral cycloadducts (6a-f) in 52-93% yield over 12-27h. The % d.e. in this series was determined by chiral h.p.l.c. on a Diacel AD column eluting with 15% isopropanol - 85% hexane. In all cases the cycloadducts were homochiral. The stereochemistry of the cycloadducts was established from n.O.e. data supplemented in the case of cycloadduct (6b) by a single crystal X-ray structure (figure 4). An illustrative example of the n.O.e. data is provided by (6b): irradiation ($CDCl_3$) of 4-H δ(4.84) effects a 12% enhancement of the signal for 5-H and a 4% enhancement of the signal for 2-Me whilst irradiation of 2-Me (δ1.62) effects

a 16% enhancement of the signal for 4-H and a 22% enhancement of the signal for 1-H. The trans-relationship between 1-H and 8-H is strongly indicated by the low enhancement (3%) of 1-H when 8-H (δ5.51) is irradiated and the absence of any enhancement of 8-H when 1-H (δ2.75) is irradiated.

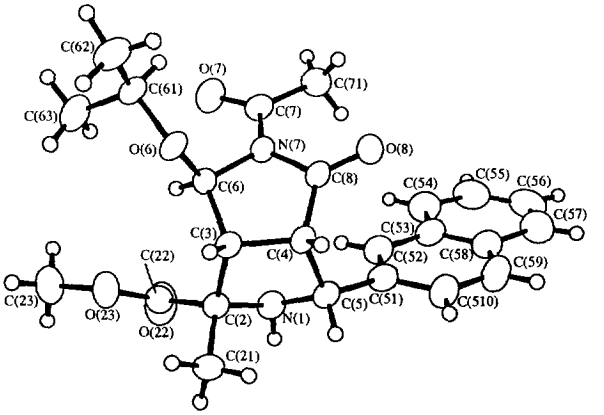


Figure 4. Molecular structure of compound **6b**.

Table 2. Homochiral cycloadducts from reaction of (2 c-f) and (2m,n) with (5)[a].

	Imine (2)		Reaction time (h)	Product	Yield (%)[b]
	R	R^1			
c.	2-naphthyl	H	12	6a	52
d.	2-naphthyl	Me	22	6b	93[c]
e.	c-C_6H_{11}	Me	24	6c	63[c]
f.	2-naphthyl	$PhCH_2$	24	6d	84
m.	2-naphthyl	3-indolylmethyl	27	6e	71
n.	2-naphthyl	CH_2OH	24	6f	56

a. All reactions carried out in dry CH_2Cl_2 using AgOTf (1mol) and DBU (1.5mol) as the catalytic system unless otherwise specified.

b. Isolated yield of product with d.e. 100% in all cases as established by chiral h.p.l.c. on a Diacel AD column.

c. Triethylamine used as base.

The single crystal X-ray structure of (6b) (figure 4) shows the cycloadducts (6a,b) and (6d-f) to be 1R, 2S, 4R, 5S, 8R-6-oxo-3,7-diazabicyclo[3.3.0]octanes. Note that (6c) is a 1R, 2S, 4S, 5S, 8R-6-oxo-3,7-diazabicyclo[3.3.0]octane due to a change in the Cahn-Ingold-Prelog preference at C-4. The established absolute stereochemistry indicates that the cycloadducts are derived from a transition state involving addition of the syn-or E,E-dipole (neglecting M) via its α-si/β-re face to the lactam 3-re/4-si face (figure 5), i.e. they are syn-endo cycloadducts. As expected the cycloaddition occurs on the face of the dipolarophile that is trans to the bulky isopropoxy substituent. The formation of (6c) demonstrates that aliphatic aldimines are viable

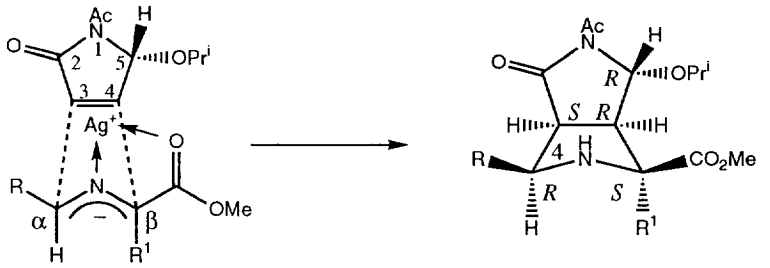


Figure 5. Schematic transition state for the cycloaddition of (2d) and (5) [note that for (6c) where R=c-C_6H_{11} the C-4 stereochemistry is S].

substrates and π-interactions between R and the lactam carbonyl moiety (figure 5) are not a prerequisite for chiral induction. The most rapid reaction was that of the glycine imine (2c) which reflects the pka's of the aldimines.[8] Reactions employing AgOTf/Et_3N as the catalytic system were much slower although they again gave homochiral cycloadducts. It is clear that substantial further rate enhancements should accrue by using 2-t-butyl-1,1,3,3-tetramethylguanidine as base.

Experimental. General experimental details were as previously described.[9] The aldimines were prepared by the general methods noted below. Most of the aryl aldimines were known compounds.[3] Optical rotations were determined on an Optical Activity Ltd., AA1000 polarimeter, and chiral h.p.l.c. was performed on a Chiralcel AD column (Daicel) eluting with 15% isopropanol in hexane and a flow rate of 1ml/min.

A. General Procedure for Aryl Aldimines. A mixture of the methyl ester of the appropriate amino acid as its hydrochloride salt, triethylamine (1eq) and anhydrous magnesium sulphate (excess) was stirred in dry dichloromethane for 1h before the addition of the aldehyde (1eq). The suspension was stirred at room temperature for a further 11h, filtered, the filtrate washed with brine (2x), dried (magnesium sulphate) and the solvent evaporated under vacuum. The residual gum was triturated with ether and the resulting solid crystallised from an appropriate solvent.

B. General Procedure for Aliphatic Aldimines. A mixture of the methyl ester of the appropriate amino acid as its hydrochloride salt (1.2eq.), in dichloromethane was shaken with concentrated aqueous ammonia solution. The dichloromethane was separated, dried with magnesium sulphate and filtered. Fresh anhydrous magnesium sulphate was added to the amino ester free base in dry dichloromethane followed by the appropriate aldehyde (1.0eq.). The mixture was stirred at room temperature until imine formation was complete, then filtered and the filtrate evaporated under reduced pressure. The residual gum was triturated with an appropriate solvent, crystallised, or in some cases used immediately in the cycloaddition

Methyl *N*-(2-naphthylidene)leucinate (2b). Leucine methyl ester hydrochloride (1.00g, 5.5mmol), triethylamine (0.60g, 5.9mmol) and 2-naphthaldehyde (0.72g, 4.6mmol) reacted over 12h to give the product (1.29g, 85%), which crystallised from ether-petroleum ether as colourless rods. m.p. 80-83 °C (Found: C, 76.0; H, 7.5; N, 4.85. $C_{18}H_{21}NO_2$ requires C, 76.3; H, 7.5; N, 4.95%); m/z(%) 283(M^+,3), 224(100) and 181(41); δ8.41(s, 1H, HC=N), 8.10 - 7.40 (m, 7H, naphthyl-H), 4.18(m, 1H, HCN), 3.78(s, 3H, OMe), 1.90(t, 2H, J 6.7Hz,$\underline{CH_2}CH$), 1.60 (m, 1H, $\underline{CH}Me_2$) and 0.93 and 0.91(2 x d, 2 x 3H, J 6.6Hz, 2 x Me).

Methyl *N*-(myrtenylidene)phenylalaninate (2g). Phenylalanine methyl ester hydrochloride (6.77g, 31.4mmol), triethylamine (3.44g, 34.1mmol) and myrtenal (3.93g, 26.2mmol) reacted over 12h using Method A to give the product as a viscous yellow gum (6.52g, 80%) [Found (H.R.M.S.): 311.1881. $C_{20}H_{25}NO_2$ requires 311.1885]; m/z(%) 311(M^+,37), 252(33), 220(100) and 91(83); δ8.02(s, 1H, HC=N), 7.31 - 7.06 (m, 5H, phenyl-H), 5.84(s, 1H, HC=), 3.92(dd, 1H, J4.3 and 9.6Hz, HCN). 3.74(s, 3H, OMe), 3.26(dd, 1H, J4.2 and 13.3Hz, CHPh), 3.03(dd, 1H, J9.6 and 13.3Hz, CHPh), 2.57(m, 1H, myrt-H), 2.48-2.35(m, 2H, myrt-H), 2.12-2.11(m, 1H, myrt-H), 1.35(s, 3H, Me), 1.10 - 1.03(m, 2H, myrt-H) and 0.73(s, 3H, Me).

Methyl *N*-(o-iodobenzylidene)alaninate (2h). Alanine methyl ester hydrochloride (4.97g, 35.8mmol), triethylamine (3.92g, 38.8mmol) and *o*-iodobenzaldehyde (6.97g, 29.8mmol) reacted over 11h to give the product as a yellow oil (7.66g, 81%), b.p. 186-188 °C/l atm. (Found (H.R.M.R.): 316.9906. $C_{11}H_{12}NO_2I$ requires 316.9913); m/z(%) 317(M^+,1), 302(24), 258(100), 231(16) and 130(84); δ8.51(s, 1H, HC=N), 8.05 - 7.00(m, 4H, phenyl-H), 4.20(q, 1H, J6.7Hz, HCN), 3.80(s, 3H, OMe) and 1.61(d, 3H, J6.7Hz, Me).

Methyl *N*-(1,3-dioxolan-2-yl)ethylideneglycinate (2i). Glycine methyl ester (0.94g, 10.6mmol) and 4,4-ethylenedioxybutanal (1.14g, 8.8mmol) reacted over 2h to give the product (1.45g, 82%), as a pale yellow oil [Found (H.R.M.S.): 201.2291. $C_9H_{15}NO_4$ requires 201.2242]; m/z(%) 201(M^+,4) and 142(100); δ7.78(t, 1H, J8.9Hz, HC=N), 4.83(t, 1H, J4.9Hz, OCHO), 4.62(s, 2H, CH_2N), 3.89(m, 4H, CH_2O), 3.69(s, 3H, OMe) and 1.78(m, 4H, 2 x CH_2); υ_{max}(film) 1746 and 1140cm^{-1}.

Methyl *N*-(1,3-dioxolan-2-yl)propylidenealaninate (2j). Alanine methyl ester (2.10g, 20.0mmol) and 5,5-ethylenedioxypentanal (2.40g, 16.6mmol) reacted over 3.5h to give the product (2.82g, 74%), as a pale yellow oil [Found (H.R.M.S.): 229.2482. $C_{11}H_{19}NO_4$ requires: 229.2484]; m/z(%) 229(M^+,1), 214(12), 170(100) and 155(72); δ7.75(t, 1H, J9.1Hz, HC=N), 4.80(t, 1H, J4.6Hz, OCHO), 4.15(q, 1H, HCN), 3.92(m, 4H, CH_2O), 3.69(s, 3H, OMe), 1.75 - 1.61(m, 6H, 3 x CH_2) and 1.57(d, 3H, J6.7Hz, Me); υ_{max}(film): 1726 and 1141cm^{-1}.

Methyl *N*-(1,3-dioxolan-2-yl)propylidenetryptophanate (2k). Tryptophan methyl ester (1.56g, 7.16mmol) and 5,5-ethylenedioxypentanal (0.86g, 5.96mmol) reacted over 3h to give the product, (1.68g, 82%), as a pale yellow oil [Found (H.R.M.S.): 344.3456. $C_{19}H_{24}N_2O_4$ requires 344.3458]; m/z(%) 344(M^+,1), 285(59) and 226(100); δ8.20(s, 1H, ArH), 7.71(t, 1H, J9.1Hz, HC=N), 7.60-7.28(m, 4H, ArH), 4.80(t, 1H, J4.9Hz, OCHO), 3.85(m, 4H, CH_2O), 3.68(s, 3H, OMe), 3.50(dd, 1H, J4.7 and 14.1Hz, CH_2C=C), 3.12(dd, 1H, J8.9 and 13.7Hz, CH_2C=C) and 1.78-1.68(m, 6H, 3xCH_2); υ_{max}(film) 3095, 2957, 1740 and 1146cm.$^{-1}$

Methyl *N*-(1,3-dioxolan-2-yl)ethylidenealaninate (2l). Alanine methyl ester (1.3g, 10.0mmol) and 4,4-ethylenedioxybutanal (1.08g, 8.3mmol) reacted over 2.5h to give the product (1.42g, 79%) as a pale yellow oil [Found (H.R.M.S.): 215.2512. $C_{10}H_{17}NO_4$ requires 215.2503]; m/z(%) 215(M^+,4), 200(24), 156(100) and 141(42); δ7.81(t, 1H, J9.5Hz, HC=N), 4.80(t, 1H, J4.8Hz, OCHO), 4.20(q, 1H, HCN), 3.85(m, 4H, CH_2O), 3.67(s, 3H, OMe), 1.75(m, 4H, 2xCH_2) and 1.61(d, 3H, J6.7Hz, Me); υ_{max}(film) 1726 and 1141cm.$^{-1}$

Cycloadditions of Chiral Dipolarophiles

General Procedure for 5R-(1′R, 2′S, 5′R-menthyloxy)-2(5H)-furanone. A mixture of the methyl ester of the appropriate imine (1.0eq), 2-t-butyl-1,1,3,3-tetramethylguanidine. (1.2eq), silver acetate (1.5eq) and 5R-(1′R, 2′S, 5′R-menthyloxy)-2(5H)-furanone (1.2eq) were stirred at room temperature in dry acetonitrile or dry toluene for the time shown in Table 1. The mixture was then filtered, the filtrate evaporated and the residue partitioned between dichloromethane and brine. The organic layer was separated and washed with sodium carbonate solution, dried (magnesium sulphate) and the solvent evaporated under vacuum. The residue was purified by column chromatography. When toluene was used as solvent the reaction mixture was filtered and then washed with brine directly. Yields are collected in Table 1.

General Procedure for N-acetyl-5R-isopropoxy-2(5H)-pyrrolone. The appropriate imine (1eq) and silver triflate (1eq) were added to dry methylene chloride and the mixture stirred at room temperature for 5 min. The chiral dipolarophile (5) (1.1eq) and DBU (1.5eq) were then added and stirring continued at room temperature for the time shown in Table 2. The reaction mixture was then washed with water, dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography. Yields are collected in Table 2.

Methyl 1S, 2R, 4S, 5R, 8R-2-benzyl-4-(3′-pyridyl)-3-aza-6-oxo-7-oxa-8-(1′R, 2′S, 5′R-menthyloxy)-bicyclo[3.3.0]octane-2-carboxylate (4a). Work up followed by column chromatography eluting with 7:2 v/v ether-petroleum ether gave the **product** as colourless needles, m.p. 76-78 °C. (Found: C, 70.95; H, 7.85; N, 5.4. $C_{30}H_{38}N_2O_5$ requires C, 71.1; H, 7.55; N, 5.55%); $[\alpha]_D$ + 86.1 °(c. 1.1, $CHCl_3$); m/z(%) 505(M-1,8), 447(100) and 204(20); δ 8.67 - 7.01(m, 9H, pyridyl-H, phenyl-H), 5.48(d, 1H, J2.9Hz, 8-H), 4.84(d, 1H, J8.9Hz, 4-H), 3.77(s, 3H, OMe), 3.60(t, 1H, J9.0Hz, 5-H), 3.50(m, 1H, menthyl-OCH), 3.36(dd, 1H, J4.7 and 13.5Hz, CHPh), 3.13(dd, 1H, J9.2 and 13.4Hz, CHPh), 3.04(dd, 1H, J8.8 and 2.8Hz, 1-H), 2.06(m, 2H, menthyl-H), 1.64 and 1.19(2 x m, 2 x 3H, menthyl-H), 0.96(d, 3H, J7.0Hz, Me), 0.85(m, 1H, menthyl-H) and 0.80 and 0.72(2 x d, 2 x 3H, J6.9Hz, $CH\underline{Me}_2$).

Proton irradiated	**Enhancement (%)**			
	1-H	5-H	4-H	8-H
1-H	-	10		2
5-H	9	-	9	
4-H		12	-	
8-H	2			-

Methyl 1S, 2R, 4S, 5R, 8R-2-isobutyl-4-(2′-naphthyl)-3-aza-6-oxo-7-oxa-8-(1′R, 2′S, 5′R-menthyloxy)-bicyclo [3.3.0]octane-2-carboxylate (4b). Work up and column chromatography eluting with 3:1 v/v ether-petroleum ether gave the **product** as colourless needles, m.p. 139-140 °C. (Found: C, 73.5; H, 8.25; N, 2.55. $C_{32}H_{43}NO_5$ requires C, 73.5; H, 8.25; N, 2.55. $C_{32}H_{43}NO_5$ requires C, 73.65; H, 8.25; N, 2.55%); $[\alpha]_D$ + 158.2 ° (c. 0.9, $CHCl_3$); m/z(%) 521(M^+,8), 462(49), 249(100) and 152(28); δ 8.00 - 7.41(m, 7H, naphthyl-H), 5.45(d, 1H, J2.6Hz, 8-H), 4.78(d,.1H, J8.4Hz, 4-H), 3.82(s, 3H, OMe), 3.72(t, 1H, J8.5Hz, 5-H), 3.61(m, 1H, menthyl-OCH), 2.84(dd, 1H, J8.5 and 2.8Hz, 1-H), 2.06(m, 2H, menthyl-H), 1.91(t, 2H, J9.5Hz, $\underline{CH}_2CH$), 1.73(m, 1H, $\underline{CH}Me_2$), 1.60 and 1.19(2 x m, 2 x 3H, menthyl-H), 0.99(d, 3H, J6.7Hz, menthyl-H), 0.90(2 x

d, 2 x 3H, J5.1Hz, 2 x Me), 0.81(m, 1H, menthyl-H) and 0.71 and 0.62(2 x d, 2 x 3H, J7.0Hz, CH$\underline{Me}_2$).

Methyl 1S, 2R, 4S, 5R, 8R-4-(2′-naphthyl)-3-aza-6-oxo-7-oxa-8-(1′R, 2′S, 5′R-menthyloxy)-bicyclo[3.3.0]octane-2-carboxylate (4c). Work up and column chromatography eluting with 3:1 v/v ether-petroleum ether gave the **product** as colourless plates, m.p. 193-195 °C (Found: C, 72.25; H, 7.8; N, 2.9. $C_{28}H_{35}NO_5$ requires C, 72.25; H, 7.6; N, 3.0%); $[\alpha]_D$ + 36.8 ° (c. 3.2, $CHCl_3$); m/z(%) 465(M^+,2) 326(13), 227(100), 194(41) and 167(54); δ7.81 - 7.42(m, 7H, naphthyl-H), 5.52(d, 1H, J2.7Hz, 8-H), 4.60(d, 1H, J9.7Hz, 4-H), 4.00(d, 1H, J6.8Hz, 2-H), 3.80(s, 3H, OMe), 3.42(m, 2H, OCH, 5-H), 3.11(m, 1H, 1-H), 2.02, 1.64 and 1.19(3 x m, 3 x 3H, menthyl-H), 0.96(d, 3H, J7.0Hz, Me) and 0.81 and 0.72(2 x d, 2 x 3H, J6.9Hz, CH$\underline{Me}_2$).

Methyl 1S, 2R, 4S, 5R, 8R-2-methyl-4-(2′-naphthyl)-3-aza-6-oxo-7-oxa-8-(1′R, 2′S, 5′R-menthyloxy)-bicyclo[3.3.0]octane-2-carboxylate (4d). Work up followed by column chromatography eluting with 3:1 v/v ether-petroleum ether gave the **product** as colourless plates, m.p. 205-206 °C (Found: C, 72.3; H, 7.6; N, 2.8. $C_{29}H_{37}NO_5$ requires C, 72.6; H, 7.8; N, 2.8%); $[\alpha]_D$ + 172.7 ° (c. 2.6, $CHCl_3$); m/z(%) 479(M^+,4), 226(100) and 166(65); δ 8.01 - 7.41(m, 7H, naphthyl-H), 5.51(d,1H, J.2.0Hz, 8-H), 4.52(d, 1H, J9.0Hz, 4-H), 3.87(s, 3H, OMe), 3.54(t, 1H, J9.0Hz, 5-H), 3.47(m, 1H, menthyl-OCH), 2.93(dd, 1H, J2.0 and 9.0Hz, 1-H), 2.16(s, 3H, 2-Me), 2.02(m, 2H, menthyl-H), 1.64 and 1.19(2 x m, 2 x 3H, menthyl-H), 0.96(d, 3H, J7.0Hz, Me), 0.85(m, 1H, menthyl-H) and 0.81 and 0.72(2 x d, 2 x 3H, J.6.9Hz, CH$\underline{Me}_2$).

Menthyl 1S, 2R, 4S, 5R, 8R-2-methyl-4-cyclohexyl-3-aza-6-oxo-7-oxa-8-(1′R, 2′S, 5′R-menthyloxy)-bicyclo[3.3.0]octane-2-carboxylate (4e). Work up followed by column chromatography eluting with 3:1 v/v ether-petroleum ether gave the **product** as colourless plates, m.p. 108-109 °C. (Found: C, 69.0; H, 9.25; N, 3.25. $C_{25}H_{41}NO_5$ requires C, 68.9; H, 9.5; N, 3.2%); $[\alpha]_D$ + 127.7 °(c.2.1, $CHCl_3$); m/z(%) 435(M^+,4), 377(93), 280(11) and 170(100); δ 5.21(d, 1H, J 2.6Hz, 8-H), 3.78(s, 3H, OMe), 3.45(, 1H, menthyl-OCH), 3.28(t, 1H, J 6.8Hz, 4-H), 3.04(dd, 1H, J 5.8 and 6.7Hz, 5-H), 2.80(dd, 1H, J 5.8 and 2.7Hz, 1-H), 2.02(m, 2H, menthyl-H), 1.90 - 1.81(m, 1H, cyclohexyl-H), 1.80(s, 3H, Me), 1.64(m, 3H, menthyl-H), 1.19(m, 4H, cyclohexyl-H), 0.96(d, 3H, J 7.0Hz, menthyl-H), 0.91 - 0.87(m, 4H, cyclohexyl-H), 0.85(m, 2H, menthyl-H), 0.80(m, 4H, menthyl-H and cyclohexyl-H) and 0.72 and 0.62(2 x d, 2 x 3H, J 6.9Hz, CH$\underline{Me}_2$).

Proton	**Enhancement (%)**				
irradiated	Me	1-H	5-H	4-H	8-H
1-H	4		12		3
5-H		8		10	
4-H	7		14		
8-H		2			

Menthyl 1S, 2R, 4S, 5R, 8R-2-benzyl-4-(2′-naphthyl)-3-aza-6-oxo-7-oxa-8-(1′R, 2′S, 5′R-menthyloxy)-bicyclo[3.3.0]octane-2-carboxylate (4f). Work up followed by column chromatography eluting with 3:1 v/v ether-petroleum ether gave the product as pale yellow needles, m.p. 209-211 °C. (Found: C, 75.5; H, 7.3; N, 2.55. $C_{35}H_{41}NO_5$ requires C, 75.65; H, 7.45; N, 2.5%); $[\alpha]_D$ + 174.4 °(c. 2.3, $CHCl_3$); m/z(%) 555(M^+,1), 251(46), 157(12) and 80(40); δ 8.01 - 7.01(m, 12H, naphthyl-H, phenyl-H), 5.50(d, 1H, J3.0Hz, 8-H), 4.95(d,

1H, J 9.0Hz, 4-H), 3.89(s, 3H, OMe), 3.6(t, 1H, J 9.0Hz, 5-H), 3.46(m, 1H, menthyl-OCH), 3.36(dd, 1H, J 4.7 and 13.5Hz, CHPh), 3.13(dd, 1H, J 9.2 and 13.4Hz, CHPh), 3.11(dd, 1H, J 3.0 and 9Hz, 1-H), 2.02(m, 2H, menthyl-H), 1.64 and 1.19(2 x m, 2 x 3H, menthyl-H), 0.96(d, 3H, J 7.0Hz, Me), 0.85(m, 1H, menthyl-H) and 0.80 and 0.72(2 x d, 2 x 3H, J 6.9Hz, $CH\underline{Me}_2$).

Methyl 1S, 2R, 4S, 5R, 8R-2-benzyl-4-myrtenyl-3-aza-6-oxo-7-oxa-8-(1′R,2′S,5′R-menthyloxy)-bicyclo[3.3.0]octane-2-carboxylate (4g). Work up followed by column chromatogaphy eluting with 7:2 v/v ether-petroleum ether gave the product as colourless plates, m.p. 54-56 °C. (Found: C, 73.95; H, 8.55; N, 2.35. $C_{34}H_{47}NO_5$ requires C, 74.15; H, 8.75; N, 2.55%); $[\alpha]_D$ + 68.1 ° (c. 1.5, $CHCl_3$); m/z(%) 550(M + 1,4), 458(40), 310(23) and 246(100); δ 7.39 - 6.95(m, 5H, phenyl-H), 5.52(m, 1H, HC=C), 5.35(d, 1H, J 3.0Hz, 8-H), 3.95(d, 1H, J 6.5Hz, 4-H), 3.77(s, 3H, OMe), 3.62(m, 1H, menthyl-OCH), 3.54(t, 1H, J 6.4Hz, 5-H), 3.36(dd, 1H, J 4.6 and 13.3Hz, CHPh), 3.13(dd, 1H, J 8.9 and 13.4Hz, CHPh), 2.92(dd, 1H, J 3.0 and 7.0Hz, 1-H), 2.37 - 2.35(m, 1H, myrt-H), 2.25 - 2.22 and 2.07 - 2.04(2 x m, 2 x 2H, myrt-H), 2.02(m, 2H, menthyl-H), 1.64(m, 3H, menthyl-H), 1.26(s, 3H, myrt-Me), 1.19(m, 4H, menthyl-H), 1.10(s, 3H, myrt-Me), 0.96(d, 3H, J 7.0Hz, Me), 0.85(m, 1H, menthyl-H) and 0.81 and 0.72(2 x d, 2 x 3H, J 6.9Hz, $CH\underline{Me}_2$).

Methyl 1S, 2R, 4S, 5R, 8R-2-methyl-4-(2′-iodophenyl)-3-aza-6-oxo-7-oxa-8-(1′R, 2′S, 5′R-menthyloxy)-bicyclo[3.3.0]octane-2-carboxylate (4h). Work up followed by column chromatography eluting with 3:1 v/v ether-petroleum ether gave the product as colourless prisms, m.p. 205 - 206 °C. (Found: C, 53.95; H, 5.95; N, 2.35. $C_{25}H_{34}NO_5I$ requires C, 54.0; H, 6.2; N, 2.5%); $[\alpha]_D$ + 126.7 ° (c. 2.1, $CHCl_3$); m/z(%) 555(M^+,4), 496(100) and 317(65); δ 7.82 - 7.00(m, 4H, phenyl-H), 5.40(d, 1H, J 3.0Hz, 8-H), 4.86(d, 1H, J 8.0Hz, 4-H), 3.83(s, 3H, OMe), 3.78(t, 1H, J 9.0Hz, 5-H), 3.45(m, 1H, menthyl-OCH), 2.92(dd, 1H, J 3.0 and 9.0Hz, 1-H), 2.16(s, 3H, Me), 2.02(m, 2H, menthyl-H), 1.58(d, 3H, J 6.2Hz, Me), 1.19(m, 3H, menthyl-H), 0.96 and 0.80(2 x m, 2 x 2H, menthyl-H) and 0.72 and 0.62(2 x d, 2 x 3H, J 6.9Hz, $CH\underline{Me}_2$).

Methyl 1S, 2R, 4S, 5R, 8R-4-[2′-(1′,3′-dioxylanyl)ethyl]-3-aza-6-oxo-7-oxa-8-(1′R, 2′S, 5′R-menthyloxy)-bicyclo[3.3.0]octane-2-carboxylate (4i). Work up followed by column chromatography eluting with 5:1 v/v ether-petroleum ether gave the **product** as colourless needles, m.p. 161-163 °C. (Found: C, 62.65; H, 8.55; N, 3.1. $C_{23}H_{37}NO_7$ requires C, 62.85; H. 8.5; N, 3.2%); $[\alpha]_D$ + 77.4 ° (c. 1.2, $CHCl_3$); m/z(%) 439(M^+,1), 381(46), 121(12) and 74(100); δ 5.30(d, 1H, J 3.0Hz, 8-H), 4.95(t, 1H, J 5.0Hz, OCHO), 4.61(m, 1H, 4-H), 4.01(d, 1H, J 7.1Hz, NH), 3.89(s, 3H, OMe), 3.84(m, 4H, CH_2O), 3.63(t, 1H, J 9.0Hz, 5-H), 3.46(m, 1H, menthyl-OCH), 3.11(dd, 1H, J 3.0 and 9.0Hz, 1-H), 2.02(m, 2H, menthyl-H), 1.78(m, 4H, 2 x CH_2), 1.64 and 1.19(2 x m, 2 x 3H, menthyl-H), 0.96(d, 3H, J 7.0Hz, Me), 0.85(m, 1H, menthyl-H) and 0.80 and 0.72(2 x d, 2 x 3H, J 6.9Hz, $CH\underline{Me}_2$); υ_{max} (nujol) 1762 and 1734cm^{-1}

Methyl 1S, 2R, 4S, 5R, 8R-2-methyl-4-[2′-(1′3′-dioxolanyl)propyl]-3-aza-6-oxo-7-oxa-8-(1′R, 2′S, 5′R-menthyloxy)-bicyclo[3.3.0]octane-2-carboxylate (4j). Work up followed by column chromatography eluting with 5:1 v/v ether-petroleum ether gave the **product**, as a colourless liquid. (Found: C, 64.2; H, 8.95; N, 2.95. $C_{25}H_{41}NO_7$ requires C, 64.35; H, 8.65; N, 3.0%); $[\alpha]_D$ + 55.1 ° (c. 1.0, $CHCl_3$); m/z (%) 466 (M-1, 1), 451(46) and 392(100); δ 5.24(d, 1H, J 3.0Hz, 8-H), 4.95(t, 1H, J 5.0Hz, OCHO), 3.89(m, 5H, CH_2O and 4-H), 3.84(s, 3H, OMe), 3.63(t, 1H, J 9.0Hz, 5-H), 3.46(m, 1H, menthyl-OCH), 3.11(dd, 1H, J 3.0 and 9.0Hz, 1-H), 2.02(m, 2H, menthyl-H), 1.78(m, 6H, 3 x CH_2), 1.64(m, 3H, menthyl-H), 1.41(s, 3H, Me), 1.19(m, 3H,

menthyl-H), 0.96(d, 3H, J 7.0Hz, Me), 0.85(m, 1H, menthyl-H) and 0.80 and 0.72(2 x d, 2 x 3H, J 6.9Hz, CH<u>Me</u>$_2$); ν_{max} (nujol): 1774 and 1738cm.$^{-1}$

Methyl 1S, 2R, 4S, 5R, 8R-2-(3′-indolylmethyl)-4-[2′-(1′,3′-dioxolanyl)propyl]-3-aza-6-oxo-7-oxa-8-(1′R, 2′S,5′R-menthyloxy)-bicyclo[3.3.0]octane-2-carboxylate (4k). Work up followed by column chromatography eluting with 6:1 v/v ether-petroleum ether gave the **product**, as colourless needles, m.p. 155-157 °C. (Found: C, 68.75; H, 8.1; N, 4.6. $C_{34}H_{48}N_2O_7$ requires C, 68.65; H, 8.1; N, 4.7%); $[\alpha]_D$ + 127.2 °(c.1.9, $CHCl_3$); m/z(%) 594(M^+,4), 537(40), 466(50) and 59(100); δ 8.20(s, 1H, ind-H), 7.60 - 7.28(m, 4H, phenyl-H), 5.30(d, 1H, J 3.0Hz, 8-H), 4.95(t, 1H, J 5.0Hz, OCHO), 4.61(m, 1H, 4-H), 4.01(d, 1H, J 2.6Hz, NH), 3.89(s, 3H, OMe), 3.84(m, 4H, CH_2O), 3.63(t, 1H, J 9.0Hz, 5-H), 3.50(dd, 1H, J 4.7 and 14.1Hz, CH_2C=C), 3.46(m, 1H, menthyl-OCH), 3.12(dd, 1H, J 8.9 and 13.7Hz, CH_2C=C), 3.09(dd, 1H, J 3.0 and 9.0Hz, 1-H), 2.02(m, 2H, menthyl-H), 1.78(m, 6H, 3 x CH_2), 1.64 and 1.19(2 x m, 2 x 3H, menthyl-H), 0.96(d, 3H, J 7.0Hz, Me), 0.85(m, 1H, menthyl-H) and 0.80 and 0.72(2 x d, 2 x 3H, J 6.9Hz, CH<u>Me</u>$_2$); ν_{max} (nujol) 3468, 1771 and 1457cm.$^{-1}$

Methyl 1S, 2R, 4S, 5R, 8R-2-methyl-4-[2′-(1′,3′-dioxolanyl)ethyl]-3-aza-6-oxo-7-oxa-8-(1′R, 2′S,5′R-menthyloxy)-bicyclo[3.3.0]octane-2-carboxylate (4l). Work up followed by column chromatography eluting with 6:1 v/v ether-petroleum ether gave the **product** as a colourless liquid. (Found: C, 63.8; H, 8.6; N, 2.95. $C_{24}H_{39}NO_7$ requires C, 63.55; H, 8.7; N, 3.1%); $\alpha]_D$ + 78.2 °(c. 1.7, $CHCl_3$); m/z(%) 454(M + 1, 5), 439(36), and 380(100); δ 5.27(d, 1H, J 3.0Hz, 8-H), 4.82(t, 1H, J 5.0Hz, OCHO), 3.92(m, 5H, CH_2O and 4-H), 3.80(s, 3H, OMe), 3.43(t, 1H, J 9.0Hz, 5-H), 3.46(m, 1H, menthyl-OCH), 2.81(dd, 1H, J 3.0 and 9.0Hz, 1-H), 2.02(m, 2H, menthyl-H), 1.78(m, 4H, 2 x CH_2), 1.61(m, 3H, menthyl-H), 1.51(s, 3H, Me), 1.19(m, 3H, menthyl-H), 0.91(d, 3H, J 7.0Hz, Me), 0.85(m, 1H, menthyl-H) and 0.80 and 0.68(2 x 3H, J 6.9Hz, CH<u>Me</u>$_2$); ν_{max} (film) 1774, 1739 and 2954cm^{-1}.

Methyl 1R, 2S, 4R, 5S, 8R-4-(2′-naphthyl)-6-oxo-3,7-diaza-7-acetyl-8-isopropyloxy-bicyclo[3.3.0]octane-2-carboxylate (6a). Flash chromatography, eluting with 7:3 v/v ether-petroleum ether, followed by crystallisation from ether-petroleum ether afforded the **product** as colourless prisms, m.p. 89-93 °C. (Found: C, 67.3; H, 6.45; N, 6.85. $C_{23}H_{26}N_2O_5$ requires C, 67.3; H, 6.4; N, 6.8%); $[\alpha]_D$ + 100.8 ° (c.0.52, $CHCl_3$); m/z(%) 410(M^+,8), 351(15), 167(100), 127(13), and 43(83); δ 7.82-7.45(m, 7H, ArH), 5.50(s, 1H, OCHN), 4.55(d, 1H, J 7.4Hz, 4-H), 4.10(d, 1H, J 9.3Hz, 2-H), 4.04(m, 1H, J 7.4Hz, C<u>H</u>Me$_2$), 3.88(s, 3H, OMe), 3.56(t, 1H, J 8.8Hz, 5-H), 3.06(t, 1H, J 9.3Hz, 1-H), 2.18(s, 3H, COMe), and 1.24 and 1.15(2xd, 3H, J 6.5Hz, CH<u>Me</u>$_2$).

Methyl 1R, 2S, 4R, 5S, 8R-2-methyl-4-(2′-naphthyl)-6-oxo-3,7-diaza-7-acetyl-8-isopropyloxy-bicyclo[3.3.0]octane-2-carboxylate (6b). Flash chromatography, eluting with 1:1 v/v ether-petroleum ether followed by crystallisation from ether-petroleum ether afforded the **product** as colourless prisms, m.p. 147-150 °C. (Found: C, 68.1; H, 6.6; N, 6.6. $C_{24}H_{28}N_2O_5$ requires C, 67.9; H, 6.65; N, 6.6%); $[\alpha]_D$ + 95.3 ° (c.0.76, $CHCl_3$); m/z(%) 424(M+,5), 365(40), 241(100), 59(5), and 43(72); δ 7.82-7.45(m, 7H, ArH), 5.51(s, 1H, OCHN), 4.84(d, 1H, J 7.4Hz, 4-H), 3.98 (m, 1H, J 6.5Hz, C<u>H</u>Me$_2$), 3.86(s, 3H, OMe), 3.68(t, 1H, J 8.3Hz, 5-H), 2.75(d, 1H, J 8.3Hz, 1-H), 2.14(s, 3H, COMe), 1.62(s, 3H, Me), and 1.24 and 1.15(2xd, 6H, J 6.5Hz, CH<u>Me</u>$_2$).

Methyl 1R, 2S, 4R, 5S, 8R-2-methyl-4-cyclohexyl-6-oxo-3,7-diaza-7-acetyl-8-isopropyloxy-bicyclo[3.3.0]octane-2-carboxylate (6c). Flash chromatography, eluting with 1:1 v/v ether-petroleum ether afforded the **product** as a colourless oil. (Found: C, 63.05; H, 8.3; N, 7.6. $C_{20}H_{32}N_2O_5$ requires C, 63.15; H, 8.45; N, 7.35%); $[\alpha]_D$ + 14.0 ° (c.0.20, $CHCl_3$); m/z(%) 380(M^+,1), 321(64), 297(28), 195(100), 59(5) and 43(65); δ 5.40(s, 1H, OCHN), 3.91(m, 1H, J 7.4Hz, C<u>H</u>Me_2), 3.76(s, 3H, OMe), 3.42(t, 1H, J 7.4Hz, 5-H), 2.95(dd, 1H, J 4.6 and 10.2Hz, 4-H), 2.50(d, 1H, J 8.3Hz, 1-H), 2.44(s, 3H, COMe), 1.95(m, 2H, cyclohexyl-H), 1.72(m, 4H, cyclohexyl-H), 1.48(s, 3H, Me), 1.25(m, 1H, cyclohexyl-H), 1.22 and 1.12(2xd, 6H, J 7.4Hz, CH<u>Me</u>$_2$) and 1.00(m, 4H, cyclohexyl-H).

Methyl 1R, 2S, 4R, 5S, 8R-2-benzyl-4-(2′-naphthyl)-6-oxo-3,7-diaza-7-acetyl-8-isopropyloxy-bicyclo[3.3.0]octane-2-carboxylate (6d). Flash chromatography eluting with 4:6 v/v ether-petroleum ether followed by crystallisation from ether-petroleum ether afforded the **product** as colourless plates, m.p. 51-54 °C. (Found: C, 71.7; H, 6.6; N, 5.45. $C_{30}H_{32}N_2O_5$ requires C, 72.0; H, 6.45; N, 5.6%); $[\alpha]_D$ + 55.6 ° (c.0.18, $CHCl_3$); m/z(%) 501(M + 1,7), 441(10), 409(100), 252(100), 127(9), and 43(85); δ 7.84-7.10(m, 12H, ArH), 5.55(s, 1H, OCHN), 4.95(d, 1H, J 7.4Hz, 4-H), 4.04(m, 1H, J 7.4Hz, C<u>H</u>Me_2), 3.76(s, 3H, OMe), 3.66(t, 1H, J 8.3Hz, 5-H), 3.40 and 3.11(2xd, 1H, J 13.9Hz, $ArCH_2$), 2.92(d, 1H, J 8.3Hz, 1-H), 2.06(s, 3H, COMe), and 1.28 and 1.15(2xd, 6H, J 5.6Hz, CH<u>Me</u>$_2$).

Methyl 1R, 2S, 4R, 5S, 8R-2-(3′-indolylmethyl)-4-(2′-naphthyl)-6-oxo-3,7-diaza-7-acetyl-8-isopropyloxy-bicyclo[3.3.0]octane-2-carboxylate (6e). Flash chromatography, eluting with 6:4 v/v ether-petroleum ether followed by crystallisation from petroleum ether afforded the **product** as colourless rods m.p. 226 °C. (Found: C, 71.0; H, 6.25; N, 7.6. $C_{32}H_{33}N_3O_5$ requires C, 71.25; H, 6.15; N, 7.8%); $[\alpha]_D$ - 16.8 ° (c.0.38, $CHCl_3$); m/z(%) 539(M^+,2), 480(4), 130(100), 127(4), and 43(13); δ 7.84-6.96(m, 12H, ArH), 5.56(s, 1H, OCHN), 5.0(d, 1H, J 8.3Hz, 4-H), 4.05(m, 1H, J 6.5Hz, C<u>H</u>Me_2), 3.67(t, 1H, J 7.4Hz, 5-H), 3.65(s, 3H, OMe), 3.60 and 3.28(2xd, 1H, J 13.9Hz, CH_2 ind), 2.96(d, 1H, J 8.3Hz, 1-H), 2.10(s, 3H, COMe) and 1.30 and 1.16(2xd, 6H, J 7.4Hz, CH<u>Me</u>$_2$).

Methyl 1R, 2S, 4R, 5S, 8R-2-hydroxymethyl-4-(2′-naphthyl)-6-oxo-3,7-diaza-7-acetyl-8-isopropyloxy-bicyclo[3.3.0]octane-2-carboxylate (6f). Flash chromatography, eluting with 8:2 v/v ether-petroleum ether, followed by crystallisation from ether-petroleum ether afforded the **product** as colourless needles, m.p. 126-127 °C. (Found: C, 65.3; H, 6.6; N, 6.2. $C_{24}H_{28}N_2O_6$ requires C, 65.45; H, 6.4; N, 6.35%); $[\alpha]_D$ + 81.9 ° (c.0.21, $CHCl_3$); m/z(%) 440(M^+,6), 409(95), 381(21), 252(100), 59(5), and 43(59); δ 7.82-7.46(m, 7H, ArH), 5.55(s, 1H, OCHN), 4.66(d, 1H, J 6.5Hz, 4-H), 3.96(m, 1H, J 6.5Hz, C<u>H</u>Me_2), 3.94 and 3.61(2xd, 2x1H, J 10.2Hz, OCH_2), 3.86(s, 3H, OMe), 3.77(t, 1H, J 7.4Hz, 5-H), 2.65(d, 1H, J 7.4Hz, 1-H), 2.24(s, 3H, COMe) and 1.23 and 1.11(2xd, 6H, J 6.5Hz, CH<u>Me</u>$_2$).

*Single crystal X-ray diffraction analysis of **4h** and **6b*** - All crystallographic measurements for both complexes were carried out on a Stoe STADI4 diffractometer. In both cases data were collected in the range $4.0° < 2\theta < 130.0°$ using ω-θ scans. An empirical absorption correction using azimuthal ψ-scans was applied to **4h** (minimum and maximum transmission factors 0.4169 and 0.5356 respectively) but not to **6b**.

Both structures were solved by direct methods using SHELXS-86[10] and were refined by full-matrix least-squares (based on F^2) using SHELXL-93.[11] The weighting scheme used in both refinements was $w = [\sigma^2(F_o^2) + (xP)^2 + yP]^{-1}$ where $P = (F_o^2 + 2F_c^2)/3$. In both cases all non-hydrogen atoms were refined anisotropically whilst hydrogen atoms were constrained to predicted positions with the exception of the amino hydrogen atoms which were located on Fourier difference syntheses. Refinement of **4h** included an isotropic extinction parameter, x, so that $F_c' = kF_c [1 + 0.001 * x * F_c^2 * \lambda^3]^{-¼}$ where k is the overall scale factor. The absolute configuration of **4h** was initially based on the known configuration of the (-)-menthyl starting material and later confirmed by refinement of a 'Flack' enantiopole parameter[12] to -0.018(11). The residuals wR_2 and R_1, given below, are defined as $wR_2 = (\Sigma[w(F_o - F_c^2)^2] / \Sigma[wF_o^4])^{½}$ and $R_1 = \Sigma \, | |F_o| - |F_c| | / \Sigma \, |F_o|$.

*Crystal data for **4h*** - $C_{25}H_{34}INO_5$, 0.68 x 0.46 x 0.19 mm, M = 555.43, monoclinic, space group $P2_1$, a = 9.9479(10), b = 12.1987(13), c = 10.3961(10) Å, β = 97.057(9)°, U = 1252.0(2) Å^3, Z = 2, D_c = 1.473 Mg m^{-3}, μ = 1.313 mm^{-1}, $F(000)$ = 568, T = 140K.
Data collection - Graphite monochromated Mo-K_α radiation, λ = 0.71069 Å, scan speeds 1.5 - 8.0° min^{-1}, ω scan widths 1.05° + α-doublet splitting, $3.0 < 2\theta < 50.0°$, 4656 Data collected 4428 of which were unique, R_{int} = 0.0155, R_{sig} = 0.0133. There were 4284 reflections with $F_o > 4.0\,\sigma(F_o)$.
Structure refinement - Number of parameters = 298, isotropic extinction parameter, x = 0.0060(6), goodness of fit, s = 1.056; weighting parameters x, y = 0.0335, 0.3074; wR_2 = 0.0496, R_1 = 0.0186.

*Crystal data for **6b*** - $C_{24}H_{28}N_2O_5$, 0.35 x 0.30 x 0.18 mm, M = 424.48, triclinic, space group P-1, a = 8.1496(10), b = 9.7635(12), c = 14.562(2) Å, α = 107.755(8), β = 99.127(8) γ = 92.166(9)°, U = 1084.9(2) Å^3, Z = 2, D_c = 1.299 Mg m^{-3}, μ = 0.745 mm^{-1}, $F(000)$ = 452, T = 293K.
Data collection - As for *(4h)* but with graphite monochromated Cu-K_α radiation, λ = 1.54184 Å, $4.0 < 2\theta < 130.0°$, 4866 Data collected, 3588 unique, R_{int} = 0.0517, R_{sig} = 0.0220, 2931 reflections with $F_o > 4.0\,\sigma(F_o)$.
Structure refinement - Number of parameters = 289, goodness of fit, s = 1.056; weighting parameters x, y = 0.094, 1.2609; wR_2 = 0.01833, R_1 = 0.0631.

Non-hydrogen atomic co-ordinates for **4h** and **6b** are listed in Tables 3 and 4 respectively whilst selected bond lengths and angles for **4h** and **6b** are listed in Tables 5 and 6 respectively.

Supplementary data-sets for both structures, which include hydrogen co-ordinates, all thermal parameters and complete sets of bond lengths and angles, have been deposited at the Cambridge Crystallographic Data Centre and are available on request.

Table 3. Non-hydrogen atom co-ordinates (x 10^4) and equivalent isotropic thermal parameters ($Å^2$ x 10^3) for **4h** with estimated standard deviations (e.s.d.s) in parentheses.

Atom	x	y	z	U_{eq}*
I(14)	7735.48(13)	8998.20(11)	9300.86(12)	31.13(7)
C(1)	4602(2)	9328(2)	5014(2)	15.8(4)
C(2)	5220(2)	8313(2)	4405(2)	18.0(4)
N(3)	5326(2)	7520(2)	5461(2)	18.9(4)
C(4)	5826(2)	8106(2)	6650(2)	18.2(4)
C(5)	4979(2)	9188(2)	6491(2)	16.8(5)
O(7)	2596.2(13)	9039(2)	6037.8(13)	22.8(3)
C(6)	3633(2)	9061(3)	7022(2)	21.4(4)
O(6)	3432(2)	8984(2)	8129.6(13)	31.2(3)
C(8)	3043(2)	9388(2)	4833(2)	18.0(4)
C(9)	6600(2)	8619(2)	3955(2)	24.6(5)
C(10)	4352(2)	7824(2)	3230(2)	21.6(5)
O(10)	4035(2)	6881(2)	3112(2)	41.3(5)
O(11)	4010(2)	8591.3(14)	2332(2)	27.8(4)
C(12)	3193(3)	8237(2)	1153(2)	33.7(6)
C(13)	5686(2)	7423(2)	7849(2)	18.8(4)
C(14)	6432(2)	7637(2)	9049(2)	23.5(5)
C(15)	6339(3)	6975(2)	10122(3)	32.8(6)
C(16)	5472(3)	6082(2)	10010(3)	37.5(7)
C(17)	4706(3)	5860(2)	8839(3)	32.4(6)
C(18)	4809(3)	6525(2)	7770(3)	24.9(5)
O(19)	2623.1(14)	10459.5(12)	4586(2)	18.2(3)
C(20)	1216(2)	10558(2)	4009(2)	19.3(5)
C(21)	507(2)	11465(2)	4683(2)	21.7(5)
C(22)	-937(3)	11597(3)	3950(3)	30.7(7)
C(23)	-920(3)	11847(2)	2533(3)	33.9(6)
C(24)	-207(3)	10951(2)	1857(2)	28.4(5)
C(25)	1218(2)	10776(2)	2571(2)	25.1(5)
C(26)	533(3)	11290(2)	6143(3)	27.5(7)
C(27)	72(3)	12326(3)	6822(3)	39.0(7)
C(28)	-294(3)	10306(3)	6517(3)	38.2(6)
C(29)	-146(3)	11207(3)	428(3)	41.0(7)

*U_{eq} = $^1/_3$ x the trace of the orthogonalised U_{ij} matrix.

Table 4. Non-hydrogen atom co-ordinates (x 10^4) and equivalent isotropic thermal parameters ($Å^2$ x 10^3) for **6b** with e.s.d.s in parentheses.

Atom	x	y	z	U_{eq}*
N(1)	4301(3)	3004(3)	3467(2)	36.5(6)
C(2)	4920(3)	2146(3)	2594(2)	31.6(6)
C(21)	6798(4)	2472(3)	2633(2)	39.7(7)
C(22)	3973(4)	2446(3)	1700(2)	37.2(7)
O(22)	3067(3)	3380(3)	1714(2)	61.9(7)
O(23)	4325(3)	1526(2)	878.7(15)	44.8(5)
C(23)	3540(5)	1706(4)	-36(2)	56.5(9)
C(3)	4571(3)	594(3)	2618(2)	28.1(6)
C(4)	4663(3)	753(3)	3713(2)	29.5(6)
C(5)	4929(3)	2422(3)	4256(2)	34.2(6)
C(51)	4104(4)	2924(3)	5145(2)	40.0(7)
C(52)	2524(4)	3309(3)	5095(2)	44.2(7)
C(53)	1739(4)	3679(3)	5963(2)	43.3(7)
C(54)	107(5)	4074(4)	5915(3)	56.8(9)
C(55)	-564(6)	4458(4)	6755(3)	68.7(11)
C(56)	356(6)	4414(4)	7655(3)	69.2(12)
C(57)	1909(6)	4007(4)	7705(3)	64.1(11)
C(58)	2698(4)	3628(3)	6836(2)	47.3(8)
C(59)	4324(5)	3248(4)	6889(2)	53.9(9)
C(510)	5020(5)	2914(3)	6062(2)	46.9(8)
C(6)	2828(3)	-172(3)	2098(2)	29.3(6)
O(6)	3117(2)	-1580(2)	1556.9(13)	34.2(5)
C(61)	1776(4)	-2468(3)	809(2)	37.6(7)
C(62)	2412(4)	-3951(3)	498(3)	51.4(9)
C(63)	1382(5)	-1872(4)	-33(2)	54.4(9)
N(7)	1928(3)	-176(2)	2895(2)	30.7(5)
C(7)	165(3)	-277(3)	2742(2)	34.4(6)
O(7)	-603(2)	-398(3)	1937(2)	48.6(6)
C(71)	-656(4)	-198(4)	3601(2)	43.6(7)
C(8)	2997(3)	116(3)	3794(2)	29.4(6)
O(8)	2642(2)	-114(2)	4511.7(14)	38.3(5)

*U_{eq} = $^1/_3$ x the trace of the orthogonalised U_{ij} matrix.

Table 5. Selected bond lengths (Å) and angles (°) for **4h** with e.s.d.'s in parentheses

I(14)-C(14)	2.103(2)	C(1)-C(8)	1.540(3)
C(1)-C(5)	1.545(3)	C(1)-C(2)	1.552(3)
C(2)-N(3)	1.457(3)	C(2)-C(10)	1.528(3)
C(2)-C(9)	1.549(3)	N(3)-C(4)	1.462(3)
N(3)-H(3)	0.74(3)	C(4)-C(13)	1.521(3)
C(4)-C(5)	1.564(3)	C(5)-C(6)	1.518(3)
O(7)-C(6)	1.361(2)	O(7)-C(8)	1.444(3)
C(6)-O(6)	1.196(2)	C(8)-O(19)	1.387(3)
C(10)-O(10)	1.196(3)	C(10)-O(11)	1.336(3)
O(11)-C(12)	1.451(3)	O(19)-C(20)	1.458(2)
C(20)-C(25)	1.519(3)	C(20)-C(21)	1.528(3)
C(21)-C(26)	1.530(4)	C(21)-C(22)	1.549(4)
C(22)-C(23)	1.507(4)	C(23)-C(24)	1.522(4)
C(24)-C(29)	1.526(4)	C(24)-C(25)	1.532(3)
C(26)-C(28)	1.532(4)	C(26)-C(27)	1.545(4)
C(8)-C(1)-C(5)	104.1(2)	C(8)-C(1)-C(2)	115.6(2)
C(5)-C(1)-C(2)	104.9(2)	N(3)-C(2)-C(10)	108.9(2)
N(3)-C(2)-C(9)	113.8(2)	C(10)-C(2)-C(9)	106.7(2)
N(3)-C(2)-C(1)	102.6(2)	C(10)-C(2)-C(1)	115.1(2)
C(9)-C(2)-C(1)	110.0(2)	C(2)-N(3)-C(4)	107.3(2)
H(3)-N(3)-C(2)	112(2)	H(3)-N(3)-C(4)	108(2)
N(3)-C(4)-C(13)	111.6(2)	N(3)-C(4)-C(5)	101.6(2)
C(13)-C(4)-C(5)	116.5(2)	C(6)-C(5)-C(1)	104.8(2)
C(6)-C(5)-C(4)	111.3(2)	C(1)-C(5)-C(4)	105.0(2)
C(6)-O(7)-C(8)	111.1(2)	O(6)-C(6)-O(7)	121.4(2)
O(6)-C(6)-C(5)	128.1(2)	O(7)-C(6)-C(5)	110.5(2)
O(19)-C(8)-O(7)	108.7(2)	O(19)-C(8)-C(1)	110.1(2)
O(7)-C(8)-C(1)	107.0(2)	O(10)-C(10)-O(11)	124.2(2)
O(10)-C(10)-C(2)	125.0(2)	O(11)-C(10)-C(2)	110.8(2)
C(10)-O(11)-C(12)	116.7(2)	C(8)-O(19)-C(20)	114.0(2)
O(19)-C(20)-C(25)	107.6(2)	O(19)-C(20)-C(21)	110.2(2)
C(25)-C(20)-C(21)	112.4(2)	C(20)-C(21)-C(26)	113.6(2)
C(20)-C(21)-C(22)	107.6(2)	C(26)-C(21)-C(22)	113.8(2)
C(23)-C(22)-C(21)	112.4(2)	C(22)-C(23)-C(24)	111.6(2)
C(23)-C(24)-C(29)	112.2(2)	C(23)-C(24)-C(25)	109.4(2)
C(29)-C(24)-C(25)	110.8(2)	C(20)-C(25)-C(24)	112.8(2)
C(21)-C(26)-C(28)	114.7(2)	C(21)-C(26)-C(27)	111.6(2)
C(28)-C(26)-C(27)	109.0(2)		

Table 6. Selected bond lengths (Å) and angles (°) for **6b** with e.s.d.'s in parentheses

N(1)-C(5)	1.461(4)	N(1)-C(2)	1.469(3)
N(1)-H(1)	0.85(4)	C(2)-C(22)	1.519(4)
C(2)-C(21)	1.540(4)	C(2)-C(3)	1.543(4)
C(22)-O(22)	1.192(4)	C(22)-O(23)	1.339(4)
O(23)-C(23)	1.448(4)	C(3)-C(4)	1.543(4)
C(3)-C(6)	1.544(3)	C(4)-C(8)	1.509(4)
C(4)-C(5)	1.569(4)	C(5)-C(51)	1.511(4)
C(6)-O(6)	1.411(3)	C(6)-N(7)	1.470(3)
O(6)-C(61)	1.452(3)	C(61)-C(63)	1.506(4)
C(61)-C(62)	1.517(4)	N(7)-C(8)	1.395(3)
N(7)-C(7)	1.413(3)	C(7)-O(7)	1.207(3)
C(7)-C(71)	1.494(4)	C(8)-O(8)	1.208(3)
C(5)-N(1)-C(2)	106.6(2)	C(5)-N(1)-H(1)	110(2)
C(2)-N(1)-H(1)	112(2)	N(1)-C(2)-C(22)	108.8(2)
N(1)-C(2)-C(21)	114.0(2)	C(22)-C(2)-C(21)	108.0(2)
N(1)-C(2)-C(3)	101.8(2)	C(22)-C(2)-C(3)	114.4(2)
C(21)-C(2)-C(3)	109.8(2)	O(22)-C(22)-O(23)	124.0(3)
O(22)-C(22)-C(2)	125.6(3)	O(23)-C(22)-C(2)	110.3(2)
C(22)-O(23)-C(23)	116.6(2)	C(2)-C(3)-C(4)	104.9(2)
C(2)-C(3)-C(6)	116.2(2)	C(4)-C(3)-C(6)	105.9(2)
C(8)-C(4)-C(3)	105.9(2)	C(8)-C(4)-C(5)	111.5(2)
C(3)-C(4)-C(5)	105.0(2)	N(1)-C(5)-C(51)	114.3(2)
N(1)-C(5)-C(4)	101.9(2)	C(51)-C(5)-C(4)	114.7(2)
O(6)-C(6)-N(7)	111.8(2)	O(6)-C(6)-C(3)	105.3(2)
N(7)-C(6)-C(3)	104.9(2)	C(6)-O(6)-C(61)	118.7(2)
O(6)-C(61)-C(63)	111.4(2)	O(6)-C(61)-C(62)	104.4(2)
C(63)-C(61)-C(62)	112.3(3)	C(8)-N(7)-C(7)	126.3(2)
C(8)-N(7)-C(6)	112.4(2)	C(7)-N(7)-C(6)	120.8(2)
O(7)-C(7)-N(7)	119.2(3)	O(7)-C(7)-C(71)	123.1(3)
N(7)-C(7)-C(71)	117.7(2)	O(8)-C(8)-N(7)	125.4(2)
O(8)-C(8)-C(4)	126.1(2)	N(7)-C(8)-C(4)	108.5(2)

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