On the diastereoselectivity of alkylations of bicyclic lactams

Jonathan H. Bailey, "Andrew T. J. Byfield," Philip J. Davis," Alison C. Foster," Michael Leech," Mark G. Moloney, *" Matthias Müller^b and C. Keith Prout^b

^a The Department of Chemistry, University of Oxford, Dyson Perrins Laboratory,

South Parks Road, Oxford, UK OX1 3QY. E-mail: mark.moloney@chem.ox.ac.uk ^b Chemical Crystallography Laboratory, University of Oxford, 9 Parks Rd, Oxford, UK OX1 3PD

Received (in Cambridge, UK) 17th January 2000, Accepted 19th April 2000 Published on the Web 30th May 2000

The diastereoselectivity in the alkylation of the enolates of bicyclic lactams 2 derived from pyroglutaminol 1a has been found to depend upon the nature of the hemiaminal ether protecting group. Although *exo*-alkylation has been widely reported for 2a,b,e, *endo*-alkylation is favoured for 2d. It is postulated that this is a result of the opening of the bicyclic structure of the enolate derived from 2d, and the consequent stereoelectronic facilitation of *endo*-facial attack.

Introduction

The demand for structurally modified amino acids for applications in synthetic, biological and materials chemistry has been met in part by the manipulation of naturally occurring and readily available amino acids.^{1,2} In this regard, aspartic and glutamic acids have proved to be important, and the alkylation of their ester enolates has been examined in some detail; recent results indicate that careful choice of protecting groups permits highly diastereoselective reactions.^{3,4} Pyroglutamic acid, essentially a protected form of glutamic acid, has found extensive application in this regard, and recent work has demonstrated the potential for manipulation of the ring periphery which makes use of lactam enolate chemistry.⁵ We have been interested in the chemistry of hemiaminal ethers † **2a** derived from



pyroglutaminol $1a^{6,7}$ since these can be readily prepared in enantiopure form, and the hydroxy and amide functionalities are simultaneously protected by a single benzylidene protecting

DOI: 10.1039/b000432o

group, making for great economy in molecular mass; this protecting group also provides a bicyclic template which might be expected to exert good diastereocontrol. Extensive investigations into the applications of the bicyclic system of 2a-e for synthesis have been reported in recent years by several groups.^{6,8-26} In particular, alkylations at C-7 via the lactam enolates of hemiaminal ethers 2a,b have received detailed attention;7,21,27-30 diastereoselection in these alkylations was found to depend on the nature of the electrophile. Thus, alkylations were found to predominantly occur in an exo-sense (especially for larger electrophiles) giving products of type 3a with ratios up to 19:1 (exo:endo), but more typically about 3-4:1. Notable exceptions, however, were methylation, chlorination and hydroxylation, for which endo-products 4a were obtained preferentially. This compares with predominant transalkylation reported for the separately protected pyrrolidinones 1b-e, although the levels of diastereoselection do critically depend on temperature of the reaction.³¹⁻³⁴ Recent work suggests that high levels of exo-alkylation for 2a may be possible using carefully optimised conditions and/or a kinetic protonation strategy.35 The preference for exo-alkylation in these systems has been most simply explained by assuming that the observed product ratio arises from competing reactions in which the exo-product is favoured on steric grounds, while the endo-product is kinetically favoured due to a stereoelectronic anti-directing effect from the nitrogen lone pair;^{10,30,35} the exact balance of these two effects crucially depends on the size of the electrophile. However, the importance of enolate solvation has also been proposed.36

These results might appear to be straightforward were it not for the well-known and extensive work of Meyers on a related O,N-acetal bicyclic lactam 5, in which the O and a methylene



are transposed relative to **2**.^{37,38} In this case, high levels of diastereoselection in the alkylation of the lactam enolate are routinely observed, and by careful choice of ring substituents R^1 and R^2 , exclusive *endo* (α)³⁸ or *exo* (β)^{39,40} alkylation is

J. Chem. Soc., Perkin Trans. 1, 2000, 1977–1982 1977



[†] This nomenclature conforms to IUPAC Recommendations 1995 (*Pure Appl. Chem.*, 1995, **67**, 1309–1375).

 Table 1
 Yields and diastereomeric ratios of products exo-7 and endo-8 from the alkylations of 2d

Electrophile	Yield (%)	Ratio 7 : 8	R _f		[<i>a</i>] _D		$\Delta \delta H_6$	
			7	8	7	8	7	8
a PhCH,Br	64	1.0:2.8	0.3	0.6	+39	+211	0.1	0.7
b pNO₂Č₅H₄CH₂Br	82	1.0:2.4	0.14	0.56	+30	+153	0.0	0.7
c <i>N</i> -BOC Indole-3-methyl bromide	77	1.0:2.5	0.47	0.61	+116	+68	0.0	0.7
d MeI	49	1.0:4.8	0.30	0.41	+160	+238	0.0	1.0
e TsCl	52	1.0:15.3	0.18	0.30	+142	+147	0.1	0.8

possible. Highly diastereoselective alkylations even in tricyclic systems have been reported.⁴¹ Some recent elegant work which has examined the reactions of simple γ -lactams 6^{42} and of the lactam systems 2 and 5 has ascribed the observed differences in diastereoselection to electronic and steric¹⁰ or torsional effects ⁴³ in the transition state of the alkylation reactions. These effects have been reported in related systems,⁴⁴ and the importance of the counter-cation has also been suggested.⁴⁵

We expected that greater levels of *exo*-diastereoselection of **2** would be favoured if the *endo*-face could be made more sterically encumbered. To this end, we synthesised the hemiaminal ether **2d** and examined the reactions of its enolate. We report here the surprising result that contra-steric alkylation of **2d** to favour the endo-product is observed for several electrophiles. This is the first report of an *endo*-alkylation of bicyclic lactams of type **2** suitable for various electrophiles, although a recent report of highly selective *endo*-hydroxylations of lactam **2a** has appeared.⁴⁶

Results and discussion

Treatment of pyroglutaminol **1a** with acetophenone dimethyl acetal^{47,48} in refluxing toluene with toluene-*p*-sulfonic acid and anhydrous zinc chloride gave the product **2d** as a single diastereoisomer in 75% yield after chromatographic purification. Although at this stage the C-2 configuration could not be assigned using NOE spectroscopy, later X-ray structural assignment of two derivatives indicated the (*R*)-stereo-chemistry, that is, with the C-2 phenyl substituent *exo*.

The lactam enolate was readily generated by treatment of 2d with LDA (1.3 equiv.), and guenched with several reactive electrophiles (Table 1). Yields were in general good; in all cases a readily separable mixture of diastereomers was obtained with preferential endo-alkylation. Chlorination led to dichloro compound 9a in addition to the expected 7e and 8e. For the exo-benzyl and exo-p-nitrobenzyl adducts 7a and 7b, the stereochemistry was unequivocally established by single crystal X-ray crystallographic analysis⁴⁹ (confirming the configurations in both cases as 2R and 7R respectively) and the stereochemistry of the endo-benzyl adduct 8a was determined by NOE spectroscopic analysis (Fig. 1); the presence of the $C-4(H_{exo}) \rightarrow C-5(H) \rightarrow C-6(H_{exo}) \rightarrow C-7(H_{exo})$ and $C-4(H_{endo}) \rightarrow C-7(H_{exo})$ $C-6(H_{endo}) \rightarrow PhCH_2$ enhancement sequences was crucial in this regard. Similar analysis was used to establish the relative stereochemistry of the compounds 7a,e and 8e (Fig. 1). The stereochemistry of the other products was assigned indirectly by comparison of ¹H NMR, $[a]_D$ and R_f values using a protocol established by Armstrong with the analogous bicyclic lactams 3a/4a, for which a consistent trend was observed³⁰ and subsequently found to be general;28,29 thus, the endo-diastereomers 8 consistently possessed higher $R_{\rm f}$ and optical rotation data, and a bigger difference in the chemical shift values for H-6_{ere} and $H-6_{endo}$, than for the *exo*-diastereomers 7.

Interestingly, alkylation of a monosubstituted enolate to afford a 7,7-disubstituted product resulted in diminished *endo*-stereoselection. Thus, deprotonation (LDA) of **8a** in THF at -78 °C, followed by treatment with MoOPD⁵⁰ (MoOPD = MoO₅-pyridine-DMPU) gave a 3:2 mixture of hydroxy deriv-



atives **9b,c** (relative stereochemistry not assigned). This compares with alkylation of either **3a** or **4a** ($R^2 = CH_2Ph$) with LDA/MeI, which both gave a 2.5:1 ratio of **10a:10b** (the stereochemistry of the former was established by NOE spectroscopic analysis, see Fig. 1), *i.e.* favouring *endo*-attack by the electrophile. However, alkylation with benzyl bromide of the enolate derived from **4a** ($R^2 = Me$) gave the same products **10a,b** in a ratio of 6:1. These observations are consistent with a preferred kinetic *endo*-attack for small electrophiles, which switches to a preferred *exo*-attack for larger electrophiles. A similar reduction in diastereoselectivity of reactions of C-7 monosubstituted lactams has been reported.²⁹

Meyers has recently proposed an explanation for the observed diastereoselectivity in the alkylations of lactam enolates⁴² in which the nitrogen lone pair exerts a strong anti-stereoelectronic directing effect in these systems, a phenomenon noted earlier by Eschenmoser in enamines.⁵¹ The deformation of amide groups in medium ring lactams and the stereochemical implications thereof have been investigated in some detail.52,53 For alkylations using methyl halides, Meyers 10 has indicated that both electronic and steric effects have significant roles in the observed diastereoselectivity of the alkylations of the enolates derived from bicyclic lactams 2 and 5, although Houk has recently suggested that only torsional and steric influences are significant.43 A more general explanation, originally proposed by Armstrong³⁰ and more recently confirmed by Madalengoitia³⁵ which is applicable for a range of electrophiles and consistent with existing published experimental data, suggests that two opposing factors are operating: endo-alkylation is favoured by virtue of the anti-stereoelectronic directing effect



of the nitrogen lone pair, but exo-alkylation by a sterically preferred entry of the electrophile to the more open (convex) face of the bicyclic system. The relative importance of these two factors appears to depend on the size of the incoming electrophile; noteworthy, however, is that the latter would appear to be relatively unimportant for lactams of type 5, but of considerable significance for lactams of type 2, for which progressively increasing levels of exo-diastereoselection are observed for bulky electrophiles; conversely, some highly endo-diastereoselective protonations have also been reported.30,35 In the case of alkylations of the enolate derived from 2d, the balance of these steric and electronic effects has been altered relative to 2a so as to favour endo-alkylation, although not exclusively. One possible reason for this is the fact that the C-2 (methyl) substituent of 2d impedes closure of the bicyclic lactam system, and thereby allows the stereoelectronic directing effect of the nitrogen to operate more effectively to the now more open *endo*-face. That this is possible is borne out by molecular modelling⁵⁴ of the enolates of lactams 2a and 2d: the degree of pyramidalisation of the nitrogen, as indicated by the distance of the nitrogen to the plane defined by its three carbon substituents,‡ is 11% lower for the enolate 2d than for 2a (0.47 and 0.42 Å respectively), the distance between H-4_{endo} and the C-2 substituent is increased by 15% for 2d over 2a (3.47 and 3.89 Å respectively), and so too is the C(8)-N-C(2) bond angle (116 vs. 120° respectively);§ the steric importance of H-4_{endo} in alkylations of 2a has been recognised.¹⁰ The differences in energies of the transition states for alkylation would also appear to be

reflected in the calculated and observed product stabilities: thus, for **4a** ($R^2 = Me$), **8a** and **8d**, the *endo*-isomer is more stable than the *exo*- (by 3.64, 14.1 and 0.33 kJ mol⁻¹ respectively) but for **3a** ($R^2 = PhCH_2$), the *exo*-isomer is more stable than the *endo*- (by 6.8 kJ mol⁻¹). This estimate of relative product stability is confirmed by equilibration experiments: the *endo*-diastereomers **8a** and **8d** could be converted to an *exo*: *endo* mixture (3:7 and 3:8 respectively) in refluxing methanol with NaOMe for 48 h, whereas equilibration of **4a** ($R^2 = PhCH_2$) gave the *exo*-diastereoisomer exclusively.

There could be several reasons, in addition to those previously identified, ^{10,35,43} for the intrinsically weaker *endo*-directing effect of lactams of type **2** compared to those of type **5**: a more shielded *endo*-face, coupled with better N-lone pair overlap with the adjacent C–O σ^* (anomeric effect) and higher intrinsic twist in the lactam, ^{52,55} could all diminish *endo*-facial bias in the corresponding enolate of the lactams **2**.

Conclusions

We have shown that by appropriate modification of the hemiaminal protecting group of bicyclic lactams derived from pyroglutaminol, *endo*-diastereoselective alkylations of the lactam enolate derived from 2 are feasible for several electrophiles. These alkylations would appear to be favoured by a stereoelectronic interaction involving the nitrogen lone pair in the enolate. This observation could be useful in the design of new lactam systems capable of displaying higher levels of diastereocontrol in their reactions.

Experimental

For general procedures, see our earlier report.²⁸ Zinc(II) chloride was washed with toluene, which was removed *in vacuo* and then dried under high vacuum to remove water prior to use. (+)-(2*S*)-2-(Hydroxymethyl)-5-oxopyrrolidine was prepared according to the literature method.⁵⁶ Acetophenone dimethyl acetal was prepared from acetophenone, trimethyl orthoformate and concentrated hydrochloric acid.⁴⁷ 3-(Bromomethyl)-1-(*tert*butyloxycarbonyl)indole was prepared from 1-*tert*-butoxycarbonyl-3-formyl indole ⁵⁷ using the literature method.⁵⁸

(+)-(2*R*,5*S*)-2-Methyl-2-phenyl-1-aza-3-oxabicyclo[3.3.0]octan-8-one 2d

To a vigorously stirred suspension of 1a (1.50 g, 13.0 mmol) in toluene (20 cm³) was added toluene-*p*-sulfonic acid (40 mg). After heating at reflux for 3 h using a Dean Stark trap to azeotropically remove water, the mixture was cooled to rt and acetophenone dimethyl acetal (13.0 g, 78.3 mmol) together with zinc(II) chloride (0.18 mg, 1.3 mmol) was added. After heating at reflux for 19 h the mixture was cooled to rt and partitioned with EtOAc (20 cm³) and saturated sodium bicarbonate solution (20 cm³). The organic layer was washed with water (20 cm³). The aqueous layer was extracted with EtOAc (20 cm³), and the combined organic extracts washed with brine (20 cm^3) , dried (MgSO₄), and solvent removed in vacuo to leave an orange liquid. Excess acetal was removed by Kugelrohr distillation (60 °C, 1 mmHg) to leave a dark orange gum, which was purified by flash column chromatography (50:50 EtOAc-petrol) to give the product **2d** as a yellow oil (2.1 g, 75%); R_{f} 0.32 (60:30 petrol-EtOAc); $[a]_{D}^{20}$ +244 (c, 1.0 in CHCl₃); v_{max} (film)/cm⁻¹ 1674 (s); δ_H(200 MHz, CDCl₃) 1.80-1.91 (m, 1H, C(6)H_{endo}), 1.99 (s, 3H, CH₃), 2.18-2.33 (m, 1H, C(6)H_{exo}), 2.56-2.92 (m, 2H, C(7)H₂), 3.60-3.70 (m, 1H, C(4)H), 4.05-4.17 (m, 2H, C(4)H and C(5)H), 7.30–7.56 (m, 5H, ArH); δ_{c} (50.3 MHz, CDCl₃) 25.01 (C(7)), 25.71 (CH₃), 36.26 (C(6)), 61.01 (C(5)), 70.00 (C(4)), 94.21 (C(2)), 125.06, 125.24, 128.12, 128.49 (ArCH), 143.45 (ArC), 173.48 (C=O); MS (CI⁺) m/z 218 (M + H⁺, 100%); HRMS 218.1181 (found), 218.1180 (calc. for C13H16NO2).

[‡] This parameter was defined and used by Meyers.10

[§] These values compare with 0.17 and 0.20, 4.52 and 4.28 Å, and 132 and 129° from the X-ray structures of the product lactams **7a,b** respectively. Meyers reports corresponding degrees of pyramidalisation of 0.5 Å for the enolate of **2e** and 0.1–0.3 Å for the lactam **2e** (determined from X-ray data), indicative that the enolate has a more pyramidalised nitrogen compared to the lactam; the values for the bicyclic system **5** are assumed to be similar.¹⁰

General method for deprotonations

To a solution of LDA (1.3 equiv., generated from diisopropylamine and *n*-butyllithium in dry THF) was added lactam **2d** (1.3–2.5 mmol) dropwise over 5 min and the solution left to stir for a further 15 min. The electrophile (0.9–1.1 equiv.) (see Table 1) was then added and the reaction left stirring at -78 °C until TLC analysis indicated completion. The reaction mixture was then warmed to rt and quenched with distilled water and partitioned with DCM (30 cm³). The aqueous layer was extracted with EtOAc and the combined organics washed with brine, then dried (MgSO₄). Solvent removal *in vacuo* and purification by flash column chromatography gave the products, as indicated below.

(+)-(2*R*,5*S*,7*S*)-2-Methyl-2-phenyl-7-(phenylmethyl)-1-aza-3-oxabicyclo[3.3.0]octan-8-one 8a and (+)-(2*R*,5*S*,7*R*)-2methyl-2-phenyl-7-(phenylmethyl)-1-aza-3-oxabicyclo[3.3.0]octan-8-one 7a. *exo*-Diastereomer 7a: white crystalline solid (0.12 g, 17%); mp 108–110 °C; *R*_f 0.3 (50:50 petrol–EtOAc); [*a*]_D²⁰ +39.0 (*c*, 1.0 in CHCl₃); found: C, 77.85; H, 6.85; N, 4.98. C₂₀H₂₁NO₂ requires C, 78.1; H, 6.9; N, 4.6%; *v*_{max} (film)/cm⁻¹ 1691 (s); $\delta_{\rm H}(200 \text{ MHz}, \text{CDCl}_3)$ 1.89–2.08 (2H, m, C(6)H₂), 1.97 (3H, s, CH₃), 2.92–2.99 (2H, m, PhCH₂), 3.08–3.15 (1H, m, C(7)H), 3.51–3.56 (1H, m, C(4)H_{endo}), 3.62–3.68 (m, 1H, C(5)H), 3.94–4.00 (1H, dd, *J* 7.5, 6.0 Hz, C(4)H_{exo}), 7.22–7.45 (10H, m, ArH); $\delta_{\rm C}(125.8 \text{ MHz}, \text{CDCl}_3)$ 25.66 (CH₃), 28.36 (CH₂Ph), 37.17 (C(6)), 49.44 (C(7)), 59.16 (C(5)), 70.19 (C(4)), 125.25, 126.83, 128.09, 128.44, 128.71, 129.42 (ArCH); *m*/*z* (CI⁺) 308 (M + H⁺, 100%), 188 (55).

endo-Diastereomer **8a**: yellow oil (0.34 g, 47%); $R_{\rm f}$ 0.6 (50:50 petrol–EtOAc); $[a]_{20}^{20}$ +210.8 (c, 1.0 in CHCl₃); $v_{\rm max}$ (film)/cm⁻¹ 1696 (s); $\delta_{\rm H}$ (500 MHz, CDCl₃) 1.50–1.57 (1H, m, C(6)H_{endo}), 1.98 (3H, s, CH₃), 2.22–2.27 (1H, m, C(6)H_{exo}), 2.76 (1H, dd, J 14.0 Hz, J' 10.0 Hz, PhCHH), 3.11–3.17 (1H, m, C(7)H), 3.32 (1H, dd, J 14.0 Hz, J' 4.0 Hz, PhCHH), 3.51 (1H, m, C(4)H_{endo}), 3.91–3.96 (1H, m, C(5)H), 4.03–4.06 (1H, m, C(4)H_{exo}), 7.22–7.40 (2H, m, ArH), 7.53–7.54 (8H, m, ArH); $\delta_{\rm C}$ (125.8 MHz, CDCl₃) 25.88 (CH₃), 32.11 (CH₂Ph), 36.55 (C(6)), 48.90 (C(7)), 58.39 (C(5)), 70.08 (C(4)), 125.29, 126.60, 128.17, 128.53, 128.74, 129.18 (ArCH); m/z (CI⁺) 308 (M + H⁺, 15%), 138 (30), 121 (95), 105 (100); HRMS 308.1651 (found), 308.1651 (calc. for C₂₀H₂₂NO₂).

(+)-(2*R*,5*S*,7*S*)-2-Methyl-2-phenyl-7-(*p*-nitrophenylmethyl)-1-aza-3-oxabicyclo[3.3.0]octan-8-one 8b and (+)-(2*R*,5*S*,7*R*)-2methyl-2-phenyl-7-(*p*-nitrophenylmethyl)-1-aza-3-oxabicyclo-

[3.3.0]octan-8-one 7b. *exo*-Diastereomer **7b**: colourless solid (0.078 g, 24%), $R_{\rm f}$ 0.14 (2:1 petrol–EtOAc), mp 103–105 °C; found: C, 67.96; H, 5.61; N, 7.87. C₂₀H₂₀N₂O₄ requires C, 68.18; H, 5.68; N, 7.95%; $[a]_{\rm D}^{20}$ +30.3 (*c*, 1.0 in CHCl₃); $v_{\rm max}$ (CHCl₃)/cm⁻¹ 1694 (s), 1346 (s); $\delta_{\rm H}$ (200 MHz, CDCl₃) 1.96–2.07 (2H, m, C(6)H₂), 1.96 (3H, s, CH₃), 3.07–3.17 (3H, m, ArCH₂, C(7)H), 3.52–3.61 (2H, m, C(4)H and C(5)H), 3.98–4.03 (1H, m, C(4)H), 7.31–7.44 (7H, m, ArH), 8.02–8.08 (2H, m, ArH); $\delta_{\rm c}$ (50.3 MHz, CDCl₃) 25.42 (CH₃), 28.14 (CH₂Ph), 37.13 (C(6)), 48.85 (C(7)), 59.00 (C(5)), 70.13 (C(4)), 94.16 (C(2)), 123.90, 125.06, 128.30, 128.46, 130.22 (ArCH), 143.11, 146.40, 147.11 (ArC), 173.96 (C=O); *m/z* (EI⁺) 353.2 (M + H⁺, 50%), 323.2 (30), 233.1 (100).

endo-Diastereomer **8b**: colourless solid (0.19 g, 58%), $R_{\rm f}$ 0.56 (2:1 petrol–EtOAc); mp 93–95 °C; found: C, 67.9; H, 5.96; N, 7.31. C₂₀H₂₀N₂O₄ requires C, 68.17; H, 5.72; N, 7.95%; $[a]_{\rm D}^{20}$ +152.7 (c, 1.0 in CHCl₃); $v_{\rm max}$ (CHCl₃)/cm⁻¹ 1347, 1696 (s); $\delta_{\rm H}(200 \text{ MHz}, \text{CDCl}_3)$ 1.44–1.61 (1H, m, C(6)H_{endo}), 1.97 (3H, s, CH₃), 2.22–2.35 (1H, m, C(6)H_{exo}), 2.84–2.96 (1H, dd, J 14.0, 9.0 Hz, ArCH), 3.14–3.23 (1H, m, C(7)H_{exo}), 3.34–3.43 (1H, dd, J 14.0, 4.5 Hz, ArCH), 3.52–5.59 (1H, m, C(4)H_{endo}), 3.93–4.10 (2H, m, C(4)H_{exo} and C(5)H_{exo}), 7.28–7.54 (7H, m, ArH), 8.16– 8.21 (2H, d, J 8.5, ArH); $\delta_{\rm C}(50.3 \text{ MHz}, \text{CDCl}_3)$ 25.82 (CH₃), 32.34 (CH_2Ph), 36.30 (C(6)), 48.34 (C(7)), 58.30 (C(5)), 69.90 (C(4)), 94.39 (C(2)), 123.94, 125.10, 125.22, 128.56, 130.12, 143.02 (ArCH), 146.98, 147.53 (ArC), 173.00 (C=O); m/z (CI⁺) 353 (M + H⁺, 8%), 323 (50), 218 (100), 203 (40).

(+)-(2R,5S,7S)-7-{[1-(tert-Butyloxycarbonyl)-3-indolyl]methyl}-2-methyl-2-phenyl-1-aza-3-oxabicyclo[3.3.0]octan-8one 8c and (+)-(2R,5S,7R)-7-{[1-(tert-butyloxycarbonyl)-3indolyl]methyl}-2-methyl-2-phenyl-1-aza-3-oxabicyclo[3.3.0]octan-8-one 7c. exo-Diastereomer 7c: (20 mg, 22%); Rf 0.47 $(50:50 \text{ petrol-EtOAc}); [a]_{D}^{20} + 67.8 (c, 1.0 \text{ in CHCl}_3); v_{max} (film)/$ cm⁻¹ 1371 (s), 1453 (s), 1692 (s), 1731 (s); $\delta_{\rm H}$ (200 MHz, CDCl₃) 1.70 (9H, s, C(CH₃)₃), 1.98 (3H, s, CH₃), 1.90-2.20 (2H, m, C(6)H), 2.95-3.40 (3H, m, C(7)H and ArCH₂), 3.56-3.60 (1H, m, C(4)H), 3.80-4.16 (2H, m, C(4)H and C(5)H), 7.24-7.67 (9H, m, ArH), 8.10–8.14 (1H, m, ArH); $\delta_{\rm C}$ (50.3 MHz, CDCl₃) 25.75 (CH₃), 26.74 (ArCH₂), 28.14 (C(CH₃)₃), 28.97 (C(6)), 47.98 (C(7)), 59.26 (C(5)), 70.13 (C(4)), 83.80 (C(CH₃)₃), 94.57 (C(2)), 115.47 (Indole CH), 117.89 (Indole C), 119.37, 122.73, 123.76, 124.78 (Indole CH), 125.14, 127.87, 128.29 (PhCH), 130.64, 135.66 (Indole C), 143.38 (PhC), 149.97 (C=O(Boc)), 175.70 (lactam C=O); m/z (CI⁺) 447.0 (M + H⁺, 20%), 391.1 (30), 347 (90); HRMS 447.2284 (found), 447.2284 (calc. for $C_{27}H_{31}N_2O_4).$

endo-Diastereomer **8c**: (0.050 g, 55%); $R_f 0.61$ (50:50 petrol-EtOAc); $[a]_{D}^{20} + 116.6$ (*c*, 1.0 in CHCl₃); ν_{max} (film)/cm⁻¹ 1371 (s), 1452 (s), 1693 (s), 1730 (s); δ_H (200 MHz, CDCl₃) 1.50–1.70 (1H, m, C6(H)_{endo}), 1.80 (9H, s, C(CH₃)₃), 2.00 (3H, s, CH₃), 2.25–2.40 (1H, m, C6(H)_{exo}), 2.75–2.90 (1H, m, ArCH), 3.20–3.45 (3H, m, ArCH and C-7(H)), 3.50–3.52 (1H, m, C-4(H)), 3.80–4.20 (2H, m, C-4(H) and C-5(H)), 7.25–7.60 (8H, m, ArH), 8.13–8.17 (1H, m, ArH); δ_C (50.3 MHz, CDCl₃) 25.60 (C(7)), 25.92 (CH₃), 28.14 (C(CH₃)₃), 32.00 (C(6)), 47.32 (C(7)), 58.39 (C(5)), 70.07 (C(4)), 83.61 (*C*(CH₃)₃), 94.26 (C(2)), 115.50 (Indole CH), 118.11 (Indole C), 119.16, 122.74, 123.57, 124.70 (Indole CH), 125.31, 128.05, 128.56 (PhCH), 130.84, 135.73 (Indole C), 143.41 (PhC), 149.97 (C=O), 173.94 (lactam C=O); *m*/*z* (CI⁺) 447 (M + H⁺, 20%), 347 (100), 190 (60), 145 (90); HRMS 447.2284 (found), 447.2284 (calc. for C₂₇H₃₁N₂O₄).

(+)-(2*R*,5*S*,7*S*)-2,7-Dimethyl-2-phenyl-1-aza-3-oxabicyclo-[3.3.0]octan-8-one 8d and (+)-(2*R*,5*S*,7*R*)-2,7-dimethyl-2phenyl-1-aza-3-oxabicyclo[3.3.0]octan-8-one 7d. *exo*-Diastereomer 7d: yellow oil (10 mg, 3%); $R_{\rm f}$ 0.3 (50:50 40–60 petrol– EtOAc); $[a]_{\rm D}^{20}$ +160 (*c*, 0.5 in CHCl₃); $\delta_{\rm H}$ (200 MHz, CDCl₃) 1.34 (3H, d, *J* 7.4 Hz, CH₃), 1.84–2.18 (2H, m, C(6)H₂), 1.97 (3H, s, CH₃), 2.79–2.88 (1H, m, C(7)H), 3.55–3.70 (1H, m, C(4)H), 4.06–4.17 (2H, m, C(4)H and C(5)H), 7.29–7.53 (m, 5H, ArH); *m*/*z* (CI⁺) 232 (M + H⁺, 20%), 121 (90), 105 (100); HRMS 232.1338 (found), 232.1338 (calc. for C₁₄H₁₈NO₂).

endo-Diastereomer **8d**: yellow solid (0.15 g, 46%); mp 50– 55 °C; $R_{\rm f}$ 0.41 (50:50 petrol–EtOAc); $[a]_{\rm D}^{20}$ +238 (c, 1.0 in CHCl₃); found: C, 72.87; H, 7.63; N, 5.66. C₁₄H₁₇NO₂ requires C, 72.7; H, 7.4; N, 6.1%; $v_{\rm max}$ (film)/cm⁻¹ 1695 (s); $\delta_{\rm H}$ (200 MHz, CDCl₃) 1.26 (3H, d, *J* 7.0 Hz, *CH*₃), 1.48 (1H, dd, *J'* 12.0 Hz, *J* 3.0 Hz, C(6)H_{endo}), 1.97 (3H, s, CH₃), 2.40–2.52 (1H, m, C(6)H_{exo}), 2.83–2.93 (1H, m, C(7)H), 3.63 (2H, t, *J* 7.0 Hz, C(4)H_{endo}), 3.95–4.31 (2H, m, C(4)H_{exo} and C(5)H), 7.29–7.40 (4H, m, ArH), 7.51–7.55 (1H, m, ArH); $\delta_{\rm C}$ (50.3 MHz, CDCl₃) 16.0 (CH₃), 26.0 (CH₃), 35.0 (C(6)), 42.5 (C(7)), 59.0 (C(5)), 70.0 (C(4)), 94.0 (C(2)), 125.0, 128.0, 128.5 (ArCH), 143.0 (ArC), 175.0 (C=O).

(+)-(2*S*,5*S*,7*S*)-7-Chloro-2-methyl-2-phenyl-1-aza-3-oxabicyclo[3.3.0]octan-8-one 8e, (+)-(2*S*,5*S*,7*R*)-7-chloro-2-methyl-2-phenyl-1-aza-3-oxabicyclo[3.3.0]octan-8-one 7e, and (+)-(2*R*, 5*S*)-7,7-dichloro-2-methyl-2-phenyl-1-aza-3-oxabicyclo[3.3.0]octan-8-one 9a. *exo*-Diastereomer 7e: colourless solid (21 mg, 9%); *R*_f 0.18 (4:1 petrol–EtOAc); mp 135–140 °C; $[a]_D^{20}$ +142.6 (*c*, 1.0 CHCl₃); ν_{max} (CHCl₃)/cm⁻¹ 1710; δ_H (200 MHz, CDCl₃) 1.98 (1H, s, CH₃), 2.31–2.38 (1H, m, C(6)H_{endo}), 2.44–2.47 (1H, m, C(6)H_{exo}), 3.66–3.74 (1H, m, C(4)H_{endo}), 4.10–4.18 (1H, dd, J 8.1 Hz, C(4)H_{exo}), 4.39 (1H, m, C(5)H), 4.56–4.58 (1H, d, J 5.9 Hz, C(7)H), 7.28–7.54 (5H, m, ArH); $\delta_{\rm C}(50.3$ MHz, CDCl₃) 25.65 (CH₃), 29.60 (C(6)), 36.55 (C(7)), 59.1 (C(5)), 68.98 (C(4)), 125.13, 128.46, 128.75 (ArCH); *m*/*z* (CI⁺) 252 (M + H⁺, 100%), 202.0 (55), 131.9 (95).

endo-Diastereomer **8e**: colourless solid (0.10 g, 43%); R_f 0.30 (4:1 petrol–EtOAc), mp 85–88 °C; found: C, 62.67; H, 5.86; N, 5.44. C₁₃H₁₄NO₂ requires C, 62.03; H, 5.57; N, 5.57%); $[a]_{20}^{20}$ +147.4 (c, 1.0 in CHCl₃); v_{max} (CHCl₃)/cm⁻¹1699; δ_H (200 MHz, CDCl₃) 2.01 (3H, s, CH₃), 1.95–2.16 (1H, m, C(6)H_{endo}), 2.86–2.99 (1H, m, C(6)H_{exo}), 3.69–3.77 (1H, dd, *J* 7.7, 7.5 Hz, C(4)H_{endo}), 3.90–3.98 (1H, m, C(5)H), 4.12–4.19 (1H, dd, *J* 7.9, 6.3 Hz, C(4)H_{exo}), 4.71–4.80 (1H, dd, *J* 11.2, 7.65 Hz, C(7)H), 7.30–7.54 (5H, m, ArH); δ_C (50.3 MHz, CDCl₃) 25.56 (CH₃), 37.22 (C(5)), 56.85 (C(7)), 58.24 (C(5)), 69.89 (C(4)), 95.24 (C(2)), 125.14 (ArH), 128.46 (ArH), 128.64 (ArH), 142.54, 167.72 (C=O); m/z (CI⁺) 252.1 (M + H⁺, 60%), 131.9 (100).

Dichlorinated product **9a**: colourless solid (24 mg, 10%); mp 125–129 °C; $R_{\rm f}$ 0.43 (petrol–EtOAc); $[a]_{\rm D}^{20}$ +184.4 (*c*, 0.5 in CHCl₃); $\nu_{\rm max}$ (CHCl₃)/cm⁻¹ 1732; $\delta_{\rm H}$ (200 MHz, CDCl₃) 1.99 (3H, s, CH₃), 2.42–2.64 (1H, m, C(6)H), 3.15–3.24 (1H, dd, *J* 13.54, 5.21 Hz, C(6)H), 3.74–3.79 (1H, m, C(5)H), 4.10–4.17 (2H, m, C(4)H₂), 7.26–7.49 (5H, m, ArH); $\delta_{\rm C}$ (50.3 MHz, CDCl₃) 25.65 (CH₃), 36.51 (C(7)), 59.01 (CH₂Ph), 60.11 (C(6)), 69.01 (C(5)), 125.13, 126.17, 128.34, 128.74; *mlz* (CI⁺) 288.2 ((M + 2H)⁺, 10%), 218.1 (100), 121.7 (35).

(+)-(2*R*,5*S*,7*S*)-7-Hydroxy-2-methyl-2-phenyl-7-(phenylmethyl)-1-aza-3-oxabicyclo[3.3.0]octan-8-one 9b and (+)-(2*R*,5*S*,7*R*)-7-hydroxy-2-methyl-2-phenyl-7-(phenylmethyl)-1-

aza-3-oxabicyclo[3.3.0]octan-8-one 9c. To a stirred solution of diisopropylamine (0.07 cm³, 0.51 mmol) in dry THF (5 cm³), was added *n*-butyllithium (1.7 M, 0.28 cm³, 0.51 mmol) and the solution left stirring at -78 °C for 15 min. Lactam 8a (120 mg, 0.39 mmol) was added dropwise as a solution in THF (10 cm³). After stirring for a further 15 min the solution of preformed enolate was transferred via cannula to a suspension of MoOPD (226 mg, 0.59 mmol) in THF (5 cm³) at -78 °C and left stirring at this temperature for 4 h until TLC analysis indicated completion. The reaction was allowed to warm to rt and diethyl ether (10 cm³) was added. The reaction mixture was partitioned with 2 M hydrochloric acid (10 cm³). The organic layer was washed with saturated sodium bicarbonate solution (10 cm³) and the aqueous layer extracted with diethyl ether (10 cm³). The combined organic layers were washed with brine (10 cm³) and dried (MgSO₄). Solvent removal in vacuo and purification by flash column chromatography (EtOAc) gave both diastereomers of the product 9b and 9c.

Diastereomer 1: (40 mg, 32%); $[a]_{20}^{0}$ +207 (*c*, 1.0 in CHCl₃); found: C, 74.56; H, 6.26; N, 4.18. C₂₀H₂₁NO₃ requires C, 74.28; H, 6.55; N, 4.33%; v_{max} (film)/cm⁻¹ 1687 (s), 3373 (br); $\delta_{\rm H}$ (500 MHz, CDCl₃) 1.94–1.98 (1H, m, C(6)H_{endo}), 1.99 (3H, s, CH₃), 2.53 (1H, dd, *J* 12.7 Hz, *J*′ 6.3 Hz, C(6)H_{exo}), 3.03 (1H, d, *J* 13.3 Hz, PhCH*H*), 3.09 (1H, d, *J* 13.3 Hz, PhCH*H*), 3.16 (1H, m, C(5)H), 3.57 (1H, m, C(4)H), 3.65 (1H, m, OH), 4.01 (1H, dd, *J* 8.1 Hz, *J*′ 6.4 Hz, C(4)H), 7.14–7.42 (10H, m, ArH); $\delta_{\rm C}$ (125.8 MHz, CDCl₃) 25.21 (CH₃), 37.98 (C(6)), 44.55 (CH₂Ph), 55.68 (C(5)), 70.36 (C(4)), 82.48 (C(7)), 94.23 (C(2)), 124.97, 127.03, 127.99, 128.19, 128.27, 129.99 (ArCH), 134.83 (ArC), 142.35 (ArC), 173.79 (C=O); *m*/*z* (CI⁺) 324 (M + H⁺, 100%).

Diastereomer 2: yellow oil (26 mg, 21%); $[a]_{20}^{D}$ +64.1 (*c*, 1.0 in CHCl₃); found: C, 74.41; H, 6.35; N, 3.89. C₂₀H₂₁NO₃ requires C, 74.28; H, 6.55; N, 4.33%; ν_{max} (film)/cm⁻¹ 1681 (s), 3365 (br); $\delta_{\rm H}$ (500 MHz, CDCl₃) 1.86–1.94 (1H, m, C(6)H_{endo}), 1.90 (3H, s, CH₃), 2.08–2.12 (1H, m, C(6)H_{exo}), 2.94 (1H, s, OH), 3.07 (1H, d, *J* 13.6 Hz, PhC*H*H), 3.16 (1H, t, *J* 8.2 Hz, C(4)H), 3.23 (1H, d, *J* 13.6 Hz, PhC*H*H), 3.99–4.02 (1H, m, C(4)H), 4.09–4.14 (1H, m, C(5)H), 7.22–7.51 (10H, m, ArH); $\delta_{\rm C}$ (125.8 MHz,

CDCl₃) 25.67 (CH₃), 35.34 (C(6)), 43.62 (CH₂Ph), 57.10 (C(5)), 69.82 (C(4)), 83.73 (C(7)), 93.84 (C(2)), 124.95, 127.06, 128.01, 128.34, 128.46 (ArCH), 130.37 (ArC), 135.80 (ArCH), 142.73 (ArC), 172.43 (C=O); *m*/*z* 324 (M + H⁺, 30%), 308 (100), 118 (90).

Epimerisations

To a stirred solution of lactams **8a,d** (62 mg, 0.20 mmol) in THF was added sodium methoxide (12 mg, 0.22 mmol) in MeOH and the reaction refluxed at 65 °C for 48 h. After this time TLC analysis indicated partial epimerisation had taken place. Water (10 cm³) and EtOAc (10 cm³) were added. The aqueous layer was extracted with EtOAc (3×10 cm³) and the combined organic layers washed with water (10 cm³) and brine (10 cm³), dried (MgSO₄) and solvent removed *in vacuo* to leave a yellow gum. By 500 MHz ¹H NMR the isolated product was found to be a mixture of the diastereomers in the ratio 8:3 and 7:3 in favour of the *endo*-compounds **8a,d** respectively.

(2*R*,5*S*,7*R*)-2-Phenyl-7-(phenylmethyl)-7-methyl-1-aza-3oxabicyclo[3.3.0]octan-8-one 10a and (2*R*,5*S*,7*S*)-2-phenyl-7-(phenylmethyl)-7-methyl-1-aza-3-oxabicyclo[3.3.0]octan-8-one

10b. To *endo* benzyl compound **4a** ($R = PhCH_2$) (100 mg, 0.31 mmol) in dry THF (3 cm³) at -78 °C was added dropwise LiHMDS (1 M soln. in THF (0.38 cm³, 0.38 mmol)). After stirring for 15 minutes, MeI (0.070 cm³, 1.1 mmol) was added and the reaction warmed to room temperature and stirred at this temperature for 2 hours. The reaction was quenched with water (10 cm³) and extracted with DCM (3×30 cm³). The combined organic extracts were dried (MgSO₄), and the solvent removed *in vacuo* giving the product as a mixture of 2 diastereomers which were separated by chromatography (1:1 ethyl acetate-petrol).

Compound **10a**: (52 mg, 50%); $[a]_D^{20}$ +34.5 (*c*, 1.0 in CHCl₃); v_{max} (CHCl₃)/cm⁻¹ 1697; δ_{H} (500 MHz, CDCl₃) 1.34 (3H, s, Me), 1.69 (1H, dd, *J* 6.6 Hz, *J'* 13.2 Hz, C(6)H_{endo}), 2.45 (1H, dd, *J* 6.6, 13.5 Hz, C(6)H_{exo}), 2.72 (1H, d, *J* 13.5 Hz, CH₂Ph), 3.01 (1H, d, *J* 13.5 Hz, CH₂Ph), 3.27–3.33 (1H, m, C(5)), 3.37 (1H, dd, *J* 8.0, 8.0 Hz, C(4)H_{endo}), 4.06 (1H, dd, *J* 12.0, 6.0 Hz, C(4)H_{exo}), 7.15–7.35 (10H, m, ArH); δ_{C} (125 MHz, CDCl₃) 25.40, 37.21, 45.31, 50.99, 55.24, 72.62, 86.69, 126.12, 126.76, 128.17, 128.23, 128.46, 130.01, 137.13, 138.36, 179.73; *m/z* (CI⁺) 308 (M + H⁺, 100%); HRMS 307.1562 (found), 307.1572 (calc. for C₂₀H₂₁NO₂).

Compound **10b**: (20 mg, 18%); $[a]_D^{20} + 213.8$ (*c*, 1.0 in CHCl₃); v_{max} (CHCl₃)/cm⁻¹ 1697; δ_{H} (200 MHz, CDCl₃) 1.38 (3H, s, Me), 1.98–2.00 (2H, m, C(6)H₂), 2.67–2.72 (2H, m, C(4)H_{endo} and CHPh), 3.16 (1H, d, *J* 13.5 Hz, CHPh), 3.97–4.04 (2H, m, C(5)-H and C(4)-H_{exo}), 6.22 (1H, s, C(2)H), 7.21–7.45 (10H, m, ArH); δ_C (125 MHz, CDCl₃) 25.89, 35.12, 43.47, 50.49, 55.20, 71.74, 86.63, 125.95, 126.72, 128.34, 128.39, 128.49, 130.33, 137.93, 138.86, 181.03; *m*/*z* (CI⁺) 308 (M + H⁺, 100%).

Acknowledgements

We gratefully acknowledge the use of the EPSRC Chemical Database Service at Daresbury,⁵⁹ the EPSRC National Mass Spectrometric Service Centre at Swansea, and Zeneca for a Strategic Research Award to M. G. M.

References

- 1 G. M. Coppola and H. F. Schuster, *Asymmetric Synthesis*. *Construction of Chiral Molecules using Amino Acids*, John Wiley, New York, 1987.
- 2 R. M. Williams, Synthesis of Optically Active a-Amino Acids, Pergamon, Oxford, 1989.
- 3 S. Hanessian and R. Margarita, Tetrahedron Lett., 1998, 39, 5887.
- 4 S. Hanessian, R. Margarita, A. Hall and X. Luo, *Tetrahedron Lett.*, 1998, **39**, 5883.
- 5 C. Najera and M. Yus, Tetrahedron: Asymmetry, 1999, 10, 2245.

- 6 J. K. Thottathil, C. Przybyla, M. Malley and J. Z. Gougoutas, Tetrahedron Lett., 1986, 27, 1533.
- 7 J. K. Thottathil, J. M. Moniot, R. H. Mueller, M. K. Y. Wong and T. P. Kissick, J. Org. Chem., 1986, 51, 3140.
- 8 R. Zhang and J. S. Madalengoitia, J. Org. Chem., 1999, 64, 330.
- 9 R. Zhang, A. Mamai and J. S. Madalengoitia, J. Org. Chem., 1999, **64**, 547.
- 10 A. I. Meyers, M. A. Seefeld, B. A. Lefker, J. F. Blake and P. G. Williard, J. Am. Chem. Soc., 1998, 120, 7429.
- 11 J. Dyer, S. Keeling and M. G. Moloney, Chem. Commun., 1998, 461. 12 C. Herdeis, A. Aschenbrenner, A. Kirfel and F. Schwabenlander,
- Tetrahedron: Asymmetry, 1997, 8, 2421. 13 N. Langlois, O. Calvez and M.-O. Radom, Tetrahedron Lett., 1997, 38, 8037.
- 14 T. Nagasaka and T. Imai, Chem. Pharm. Bull., 1997, 45, 36.
- 15 P. W. H. Chan, I. F. Cottrell and M. G. Moloney, Tetrahedron Lett., 1997, 38, 5891.
- 16 J. H. Bailey, D. T. Cherry, K. M. Crapnell, M. G. Moloney, S. B. Shim, M. Bamford and R. B. Lamont, Tetrahedron, 1997, 53, 11731.
- 17 T. Nagasaka and T. Imai, Heterocycles, 1995, 41, 1927.
- 18 C. Herdeis, H. P. Hubmann and H. Lotter, Tetrahedron: Asymmetry, 1994. 5. 119.
- 19 D. Griffart-Brunet and N. Langlois, Tetrahedron Lett., 1994, 35, 119
- 20 D. Griffart-Brunet and N. Langlois, Tetrahedron Lett., 1994, 35, 2889.
- 21 J. E. Baldwin, M. G. Moloney and S. B. Shim, Tetrahedron Lett., 1991, 32, 1379.
- 22 Y. Hamada, O. Hara, A. Kawai, Y. Kohno and T. Shioiri, Tetrahedron, 1991, 47, 8635.
- 23 S. Hanessian and V. Ratovelomanana, Synlett, 1991, 222.
- 24 S. Hanessian and V. Ratovelomanana, Synlett, 1990, 501.
- 25 N. E. Allen, D. B. Boyd, J. B. Campbell, J. B. Deeter, T. K. Elzey, B. J. Foster, L. D. Hatfield, J. N. Hobbs, W. J. Hornback, D. C. Hunden, N. D. Jones, M. D. Kinnick, J. M. Morin, J. E. Munroe, J. K. Swartzendruber and D. G. Vogt, Tetrahedron, 1989, 30, 1905.
- 26 Y. Hamada, A. Kawai, Y. Kohno, O. Hara and T. Shioiri, J. Am. Chem. Soc., 1989, 111, 1524.
- 27 R. Zhang, F. Brownewell and J. S. Madalengoitia, J. Am. Chem. Soc., 1998, 120, 3894.
- 28 M. J. Beard, J. H. Bailey, D. T. Cherry, M. G. Moloney, S. B. Shim, K. Statham, M. Bamford and R. B. Lamont, Tetrahedron, 1996, 52, 3719.
- 29 T. Nagasaka and T. Imai, Chem. Pharm. Bull., 1995, 43, 1081.
- 30 R. W. Armstrong and J. A. DeMattei, Tetrahedron Lett., 1991, 32, 5749.
- 31 L. J. Brena-Valle, R. C. Sanchez and R. Cruz-Almanza, Tetrahedron: Asymmetry, 1996, 7, 1019.
- 32 K. C. Woo and K. Jones, Tetrahedron Lett., 1991, 32, 6949.
- 33 Z. Q. Gu, X. F. Lin and D. P. Hesson, Bioorg. Med. Chem. Lett., 1995, 5, 1973.
- 34 Y. S. Hon, Y. C. Chang and M. L. Gong, *Heterocycles*, 1990, **31**, 191. 35 R. Zhang, F. Brownewell and J. S. Madalengoitia, *Tetrahedron Lett.*,
- 1999, 40, 2707. 36 K. A. Durkin and D. Liotta, J. Am. Chem. Soc., 1990, 112, 8162.

- 37 A. I. Meyers and G. P. Brengel, Chem. Commun., 1997, 1.
- 38 D. Romo and A. I. Meyers, Tetrahedron, 1991, 47, 9503.
- 39 G. P. Roth, S. F. Leonard and L. Tong, J. Org. Chem., 1996, 61, 5710.
- 40 A. I. Meyers, M. A. Seefeld and B. A. Lefker, J. Org. Chem., 1996, 61, 5712.
- 41 J. A. Ragan and M. C. Claffey, Heterocycles, 1995, 41, 57.
- 42 A. I. Meyers, M. A. Seefeld, B. A. Lefker and J. F. Blake, J. Am. Chem. Soc., 1997, 119, 4565.
- 43 K. Ando, N. S. Green, Y. Li and K. N. Houk, J. Am. Chem. Soc., 1999, 121, 5334.
- 44 S. Nagumo, M. Mizukami, N. Akutsu, A. Nishida and N. Kawahara, *Tetrahedron Lett.*, 1999, **40**, 3209.
- 45 L. Micouin, V. Jullian, J.-C. Quirion and H.-P. Husson, Tetrahedron: Asymmetry, 1996, 7, 2839.
- 46 O. Hara, J. Takizawa, T. Yamatake, K. Makino and Y. Hamada, Tetrahedron Lett., 1999, 40, 7787.
- 47 M. T. Bogert and P. P. Herrera, J. Am. Chem. Soc., 1923, 45, 238.
- 48 G. A. Olah, S. C. Narang, D. Meidar and G. F. Salem, Synthesis, 1981, 282.
- 49 Atomic coordinates have been deposited with the Cambridge Crystallographic Data Centre (CCDC number 207/433). The coordinates can be obtained, on request, from Cambridge Crystallographic Data Centre, 12 Union Rd, Cambridge, UK CB2 1EZ. Crystallographic data were collected on an Enraf-Nonius CAD-4 diffractometer, and the structures were solved and refined with full matrix least squares analysis using DENZO.60
 - Crystal data and data collection parameters for compound 7a: $C_{20}H_{21}NO_2$, M = 307.39, monoclinic, a = 10.114(2), b = 8.171(3), $C_{20}^{-1} P_{11}^{-1} (C_{22}, \mu = 50, 109)$, increasing, u = 100000000, $A, \beta = 100.77(2)^{\circ}$, V = 831.3(3) A^{3} . Space group $P2_{1}$, Z = 2, $D_{x} = 1.23$ g cm⁻³, $\mu = 5.891$ cm⁻¹. The compound was crystallised from EtOAc-petrol.
 - Crystal data and data collection parameters for compound 7b: $C_{20}H_{20}O_4N_2$, M = 352.39, orthorhombic, a = 8.547(1), b = 9.880(1), C_{20} T_{20} O_4 V_5 , M = 505, or the function for the function D_5 U = 10.963 (1), δ , V = 1685.76 Å³. Space group $P_{21}2_{12}$, Z = 4, $D_x = 1.39$ g cm⁻³, cell parameters from 17034 reflections, $\theta = 2.04-26.65^\circ$, $\mu = 0.09$ mm⁻¹, T = 100 K. The compound was crystallised from DCM, Et₂O. A PDB file of compound **7b** is available as supplementary data. For direct electronic access see http://www.rsc. org/suppdata/p1/b0/b000432o/.
- 50 J. C. Anderson and S. C. Smith, Synlett, 1990, 107.
- 51 K. L. Brown, L. Damm, J. D. Dunitz, A. Eschenmoser, R. Hobi and C. Kratky, Helv. Chim. Acta, 1978, 61, 3108.
- 52 F. K. Winkler and J. D. Dunitz, J. Mol. Biol., 1971, 59, 169.
- 53 J. D. Dunitz and F. K. Winkler, Acta Crystallogr., Sect. B, 1975, 31, 251.
- 54 Structures optimised with Spartan[®] (3-21G or PM3 semi-empirical basis set in the gas phase) or Chem 3D Pro 3.5 (PM3 basis set).
- 55 A. J. Kirby, I. V. Komarov, P. D. Wothers and N. Feeder, Angew. Chem., Int. Ed., 1998, 37, 785.
- 56 R. B. Silverman and M. A. Levy, J. Org. Chem., 1980, 45, 815.
- 57 Y. Wolman, Synthesis, 1975, 732.
- 58 U. Schoellkopf, R. Lonsky and P. Lehr, Liebigs Ann. Chem., 1985, 413
- 59 D. A. Fletcher, R. F. McMeeking and D. Parkin, J. Chem. Inf. Comput. Sci., 1996, 36, 746.
- 60 Z. Otwinowski and W. Minor, Methods Enzymol., 1997, 276, 307.

View Article Online