Pergamon

Tetrahedron, Vol. 52, No. 3, pp. 1047-1068, 1996

0040-4020/96 $15.00 + 0.00

0040-4020(95)00938-8

Enantioselective Synthesis of (3*R*)- and (3*S*)-Piperazic Acids. The Comparative Unimportance of DMPU Mediated Retro-Hydrazination

Karl J. Hale,* Jiaqiang Cai, Vern Delisser, Soraya Manaviazar, S. Andrew Peak, Gurpreet S. Bhatia, Timothy C. Collins, and (in part) Neha Jogiya

The Christopher Ingold Laboratories, Department of Chemistry, University College London, 20 Gordon Street, London WC1H 0AJ, UK.

ABSTRACT: In response to a recent literature report by Decicco and Leathers (Ref. 13), the work of Hale, Delisser, and Manaviazar (1992) on the asymmetric synthesis of (3*R*)- and (3*S*)-piperazic acids has been reinvestigated, and the originally claimed product yields fully substantiated. The claims made in reference 13 about the proportions of cyclised product **6** and starting bromide **20** isolated from the low temperature electrophilic hydrazination-nucleophilic cyclisation of **20** with di-*t*-butylazodicarboxylate (DBAD) and DMPU as an additive are inaccurate. The retro-hydrazination reaction that they claim is problematic when DMPU is added to the hydrazinated reaction mixture has been demonstrated not to have a seriously detrimental effect on cyclisation product yield and to be unimportant. The other main assertion of reference 13, that the electrophilic hydrazination and nucleophilic cyclisation of **20** gives **6** in 91% isolated yield when *n*-Bu_4NI is employed as an additive (instead of DMPU) has also been shown to be in error. We have carefully repeated a scaled-down version of the *n*-Bu_4NI catalysed procedure (Ref. 13) and have found that **6** is generally isolated in yields of 50-56% after flash chromatography. We have concluded that *n*-Bu_4NI does not significantly increase the yields of cyclisation products **6** or **17** when it is employed as a cyclisation additive. Herein, we report details of our two preferred "crude" experimental procedures for preparing the enantiomers of piperazic acid in high optical purity, neither of which requires chromatographic purification of the reaction intermediates en route. Both these preferred "crude" methods for preparing **11** and **19** have been consistently reproduced many times in these laboratories over the past few years. In our view, they remain the most expedient and highest yielding methods currently available for obtaining **11** and **19** in high optical purity.

Introduction

Piperazic acid is an architecturally novel cyclic α-hydrazino acid that was first isolated in the late 1960's by Hassall and coworkers[1] during their chemical degradation studies on the monamycin family of antibiotics. Since that time, the enantiomeric forms of piperazic acid have been encountered in a large number of pharmacologically active molecules that include the azinothricin family of antitumour antibiotics (**1-3**),[2] verucopeptin,[3] the aurantimycins,[4] the C5a antagonist L-156,602,[5] the immunosuppressant IC101,[6] the oxytocin antagonist L-156,373,[7] and the matylastatin type-IV collagenase inhibitors.[8] In addition, the (*3S*)-enantiomer of piperazic acid resides within the bicyclic ring system of the synthetic ACE inhibitor cilazapril,™ a drug of considerable therapeutic importance for the treatment of hypertension and congestive heart failure.[9] (*3S*)-Piperazic acid is itself a fairly potent inhibitor of GABA-uptake in rat cerebral cortex slices,[10] and as such has clinical potential for the treatment of audiogenic seizures.

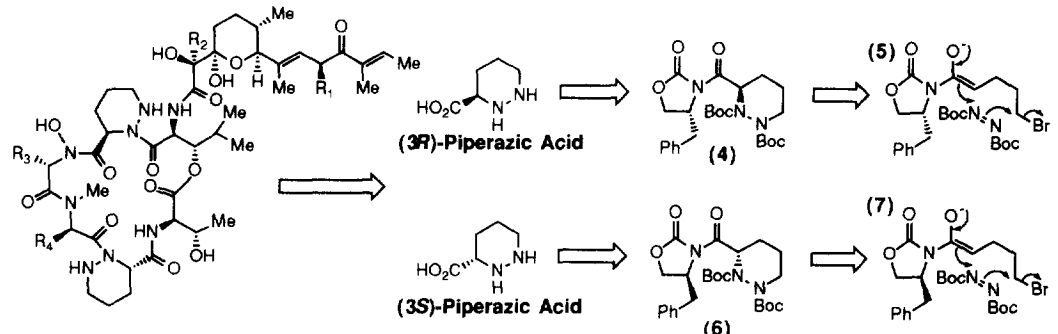
Our interest in piperazic acid stemmed from our total synthesis programme[11] on the azinothricin family of cyclodepsipeptide antibiotics (**1-3**). At the outset, we recognised that a good and reliable asymmetric synthesis of (3*R*)- and (3*S*)-piperazic acids would be a prerequisite if we were to make substantial progress on the total

synthesis of these three molecules. We were also conscious that this objective would probably necessitate us developing some new methodology for the construction of cyclic α-hydrazino acids in homochiral form. In this full paper, we report our solution to the problem of asymmetric piperazic acid synthesis,[12] and discuss our attempts at validating a number of inaccurate claims made by Decicco and Leathers in a recent publication[13] on our preliminary work.

Discussion

Our original retrosynthetic plan for obtaining (3*R*)- and (3*S*)-piperazic acids was founded on the Evans-Vederas electrophilic hydrazination[14,15] of chiral *N*-bromovaleryl carboximide enolates **5** and **7** with di-*t*-butylazodicarboxylate (DBAD). In both cases, it was felt that such an addition would not only allow the C(3)

Scheme 1

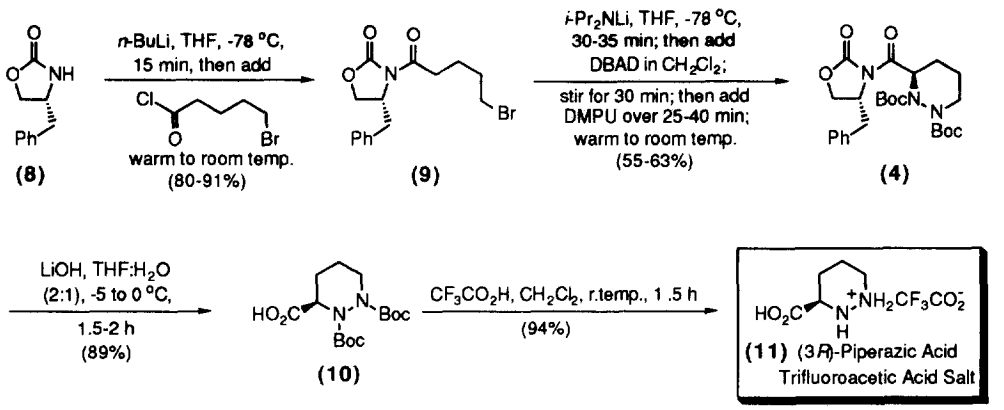


stereocentres in the target compounds to be introduced with high stereocontrol, but would also allow the regiospecific generation of an N^1-aza anion capable of undergoing nucleophilic cyclisation to give **4** or **6** respectively. Hydrolytic removal of the chiral auxiliary and *N*-deprotection would then furnish the target piperazic acids.

Our first route to **11**, which was originally disclosed in communication form,[12] is outlined in Scheme 2 and required only four steps. It began with a regioselective deprotonation of (4*R*)-phenylmethyl-2-oxazolidinone **8** with *n*-butyllithium in THF-hexanes at -78 °C for 15 min. The resulting amide anion was then *N*-acylated by dropwise addition of neat 5-bromovaleryl chloride over 15 min. Pure bromide **9** was obtained as white crystals in 80-91% yield after extractive work up and trituration of the crude reaction mixture with ice-cold hexanes and a small amount of ether. The structure of **9** was deduced from its 100 MHz ^{13}C NMR spectrum in $CDCl_3$, which contained *inter alia* two carbonyl resonances at δ 172.5 and 153.4 ppm, which were highly characteristic of the carbonyl groups in an *N*-acylated oxazolidinone. In addition, the IR spectrum of **9** contained two intense carbonyl absorptions at 1785 and 1700 cm^{-1}, which were also typical of an *N*-acylated oxazolidinone. Compound **9** also gave a satisfactory combustion microanalysis for a molecule with an empirical formula $C_{15}H_{18}NO_3Br$.

Treatment of **9** with lithium diisopropylamide in THF and hexanes at -78 °C for 35 min, followed by dropwise addition of di-*t*-butylazodicarboxylate (DBAD) in CH_2Cl_2 brought about a highly diastereoselective α-

Scheme 2



hydrazination, in accord with the earlier precedents of Evans and Vederas.[14,15] To our surprise, the resulting lithium coordinated N^1-aza anion did not readily engage in the expected nucleophilic displacement of the bromo substituent at -78 °C, with only poor yields of the cyclised product **4** ever being isolated after protic work-up. Usually, the major product formed under such conditions was the uncyclised bromovaleryl hydrazide **22**; it was typically isolated pure in 84% yield after flash chromatography (see: Scheme 7). Reasoning that cyclisation of **23** to the desired product **4** was being impeded by formation of a highly aggregated lithium aza anion at -78 °C, we decided to evaluate the effect of a number of additives that could potentially interact with the lithium ion, and thereby generate a more reactive form of the lithium aza enolate capable of more readily engaging in the desired nucleophilic cyclisation reaction at low temperature. One additive that was initially examined for this purpose was 1,3-dimethyl-3,4,5,6-tetrahydro-2[1H]-pyrimidinone (DMPU); when it (26 equiv)[16] was introduced slowly into the hydrazinated reaction mixture at -78 °C, the reaction mixture was found to thicken as the addition progressed, until eventually it became frozen after all of the DMPU had been added. In order to continue stirring, the reaction flask was removed from the cooling bath and allowed to warm to room temperature. As the reaction mixture began to warm, it started to melt, and by the time it had reached 4-5 °C, TLC analysis indicated that all the starting valeryl bromide **9** had been consumed and that a slower-moving major product **4**, and several slower-moving minor products, had formed. After extractive work up and separation of the crude reaction mixture by flash chromatography, the slow-moving major product **4** was isolated as a foam in 63% yield. Unfortunately, the 400 MHz ^{1}H NMR spectrum of **4** in $CDCl_3$ at 25 °C proved quite difficult to assign due to extensive broadening of the resonances, arising from restricted rotation of the Boc groups. However, when recorded at 125 °C in DMSO-d_6, the spectrum became quite highly resolved as the time-averaged spectrum was obtained. Importantly, it revealed that the desired cyclisation had been successful and that **4** had been isolated as essentially one diastereoisomer; the H(3) signal at δ 5.91 was particularly diagnostic in this regard since only one such resonance could be detected in this region. Further proof of the constitution of **4** came from its high resolution chemical ionisation mass spectrum which contained an $(M+H)^+$· ion at *m/e* 490.2559 (Calcd. for $C_{25}H_{36}N_3O_7$ $(M+H)^+$· *m/e* 490.2553). Significantly, the C, H, and N combustion microanalytical data for **4** indicated that it had an empirical formula of $C_{25}H_{35}N_3O_7$ and that bromine was no longer present. When considered alongside the combined spectral data, the latter result indicated that **4** had been obtained in pure condition. Delighted with this

successful result, our next objective was to repeat this procedure many times in order to confirm its reproducibility. We observed that the aforementioned procedure was completely reproducible, it typically furnishing **4** in yields of 55-63% after flash chromatography, as quoted in our original patent application.[12]

It must be emphasised that on the numerous occasions we have performed this cyclisation, only very small quantities (<5%) of starting valeryl bromide **9** have ever been detected in, and recovered from, the worked up reaction mixtures, which is a clear indication that competing retro-hydrazination[13] to regenerate the bromovaleryl enolate **5** and DBAD is not problematic under our reaction conditions (*vide infra*). Indeed, we contend that if any starting **9** is detected, its presence is most likely due to incomplete enolisation or hydrazination occurring (*vide infra*). The most significant minor by-product formed in this cyclisation reaction is the hydrazinated alkene **24** (see Scheme 7). It is always difficult to isolate in pure condition due to its co-elution with DBAD-related by-products during the flash chromatography. It arises from base-induced elimination of **23** which occurs as the reaction mixture is slowly warmed up (see Scheme 7). Typically, **24** never comprises more than 10% of the crude reaction mixture. Its identity has been verified by an independant chemical synthesis carried out in these laboratories for another project.

As a rule, the aqueous extractive conditions used to work up the cyclisation reaction (sat. aq. KH_2PO_4/Et_2O) *always* bring about partial hydrolysis of the cyclised product **4** (typically, between 5 and 10% of **10** is isolated). The extent to which this hydrolysis occurs depends quite markedly on the way in which the reaction mixture is initially quenched, and also on the time taken to perform the initial ether extraction. We have found that oxazolidinone hydrolysis can be minimised if the reaction mixture is poured into a large excess of Et_2O layered on top of a saturated aqueous solution of potassium dihydrogen phosphate in a separatory funnel. The two layers then need to be shaken quickly and the aqueous and DMPU (lower) layers quickly removed. The ethereal layer should then be quickly washed with water to remove residual DMPU and diisopropylamine. If chromatographic purification of the cyclised product is required for other purposes then it is essential to remove the deprotected acid **10** from the crude reaction mixture prior to attempting the chromatography. This is accomplished by washing the initial ethereal extract with saturated aqueous sodium bicarbonate; acidification of the bicarbonate extract to pH 2 with conc. HCl or solid $NaHSO_4$ and extraction with EtOAc then enables acid **10** to be recovered. If this base-wash procedure is omitted prior to attempting the chromatographic purification, then quite considerable difficulties will be encountered in separating **10** from the cyclised product, irrespective of the eluent used. [However, for the purpose of obtaining (3*R*)-piperazic acid in high optical purity and in the best possible overall yield, we strongly recommend that the aqueous sodium bicarbonate wash and the chromatographic purification steps both *be omitted* from the experimental procedure and that the crude reaction mixture be taken directly forward to **11** *without purification;* as described in our preferred "crude" experimental procedure *(vide infra)*].

In our original synthesis, the oxazolidinone auxiliary was detached from pure **4** by stirring it with a chilled (-5 °C) suspension of lithium hydroxide monohydrate (2.3 equiv) in aqueous THF for 1.5-2 h. The best work-up method involved diluting the reaction mixture with a small amount of water and extracting it with Et_2O. It was then possible to recover a reasonable quantity of the starting oxazolidinone auxiliary from the Et_2O extract, by drying over $MgSO_4$, filtering, and evaporating the solvent; a simple recrystallisation was usually sufficient to allow the auxiliary to be recovered in pure condition (typically in about 67% yield). The protected acid **10** was isolated in essentially pure condition in 89% yield from the combined aqueous layers by acidification to pH 2 with $NaHSO_4$ and multiple extraction with EtOAc. The same reaction conditions were also used to hydrolyse

crude **4** in the "crude" procedure we describe, and the resulting acid **10** also driven forward to the next step without purification *(vide infra)*. The 100 MHz ^{13}C NMR spectrum of pure **10** in $CDCl_3$ at 25 °C contained two carbonyl resonances at δ 171.6 and 170.6 which were clearly ascribable to the newly established carboxylic acid unit. In addition, the resonances associated with the phenylmethyl group of the chiral auxiliary were absent from this spectrum. The IR spectrum of **10** revealed three C=O absorptions at 1743, 1708 and 1667 cm^{-1}, which were assignable to the carbonyl groups of the carboxylic acid and the *t*-butyl urethane groups. There was also an extremely broad absorption centred at 3213 cm^{-1} which confirmed the presence of the carboxylic acid unit in **10**. Our structural assignment of **10** was further reinforced by satisfactory combustion microanalytical data which indicated it had an empirical formula of $C_{15}H_{26}N_2O_6$.

The BOC groups were detached from the nitrogen atoms of purified **10** by treatment with anhydrous trifluoroacetic acid in CH_2Cl_2 at 25 °C for 1.5 h.[17] This provided (3*R*)-piperazic acid trifluoroacetic acid salt **11** as a white crystalline solid in 94% yield after recrystallisation from ethyl acetate containing a minimal amount of absolute ethanol to ensure dissolution. The same procedure was applied with equal success on crude **10**. In this case, after removing the residual trifluoroacetic acid by coevaporation with toluene, the crude crystalline solid was ground up in Et_2O containing EtOAc, and then filtered, to furnish **11** in virtually pure condition; after recrystallisation as described above, **11** was obtained analytically pure typically in 68-71% overall yield from **9**. The 400 MHz ^1H NMR spectrum of pure **11** in D_2O (Fig.1) showed resonances for seven protons, as one would expect after hydrogen/deuterium exchange of the acidic hydrogens in **11** with the solvent. The lowest field signal appeared as a multiplet at δ 3.90; it was assignable to H(3) by virtue of its chemical shift, which indicated it was attached to the most electronegative carbon atom, which was C(3) due to it bearing a carboxylic acid and a hydrazine unit. There were also two multiplets further upfield at δ 3.28 and 3.14, each of which integrated to one proton; these were assignable to the C(6) hydrogen atoms, due to their low field positions which again suggested that they were connected to a carbon atom bearing an electronegative substituent (i.e. the hydrazino function). Finally, there was a one proton multiplet at δ 2.11 and a complex three proton multiplet centred at δ 1.86 which were assigned to the remaining four hydrogen atoms (i.e. the C(5)- and C(4)-hydrogens). Their complexity and upfield chemical shift positions were appropriate for methylene hydrogens flanked by two alkyl groups, but not far from electronegative groups. Further confirmation that the trifluoroacetic acid salt of piperazic acid had been prepared came from 400 MHz ^1H NMR comparison of **11** with an authentic sample of the racemate prepared according to an unpublished experimental procedure very kindly supplied to us by Dr Charles Caldwell of Merck, Sharpe & Dohme in Rahway (Dr Caldwell and his colleagues were the first workers to report a synthesis[17] of the racemic Piz TFA salt from racemic di-*t*-BOC Piz). Compound **11** also registered a satisfactory combustion microanalysis that fully corroborated an empirical formula of $C_7H_{11}N_2O_4F_3$.

At this point, we have to emphasise that we do not consider the 55-63% isolated yield of cyclisation product **4** to be an adequate reflection of the true success of our electrophilic hydrazination-nucleophilic cyclisation protocol, since recrystallised **11** is usually obtained in 68-71% overall yield from **9** via the preferred "crude" procedure we have described in the experimental section. This latter observation quite clearly suggests that the true yield of the cyclisation step is around 81%, since the next two steps proceed in 89 and 94% yields respectively. The quite significant reduction in yield that is observed when one attempts to isolate **4** in pure condition is attributable, (a) to the multiple flash chromatography that is required to remove minor reaction by-products from **4**, and (b) to the inevitable oxazolidinone hydrolysis that occurs when the cyclisation mixture is worked-up under aqueous conditions. Indeed, on some occasions, this hydrolysis reaction has actually been seen to consume as much as 10% of the cyclisation product **4**. Clearly, in our crude process for obtaining **11**, these

Fig.1 400 MHz ^{1}H NMR spectrum of (3*R*)-Piperazic Acid Trifluoroacetic Acid Salt **11** in D_2O (N.B. this sample was pre-exchanged with D_2O and stored *in vacuo* prior to the spectrum being recorded)

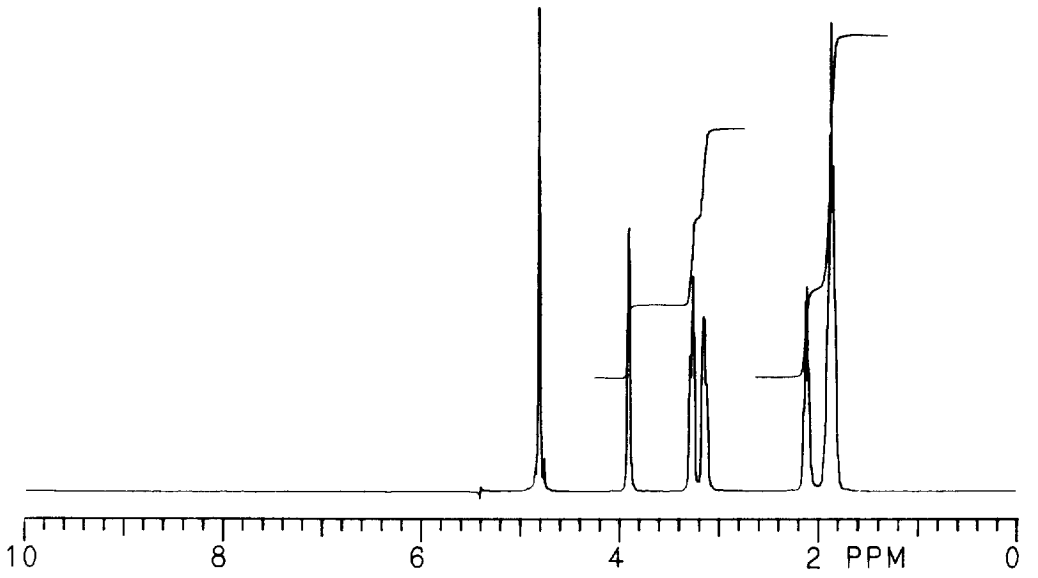
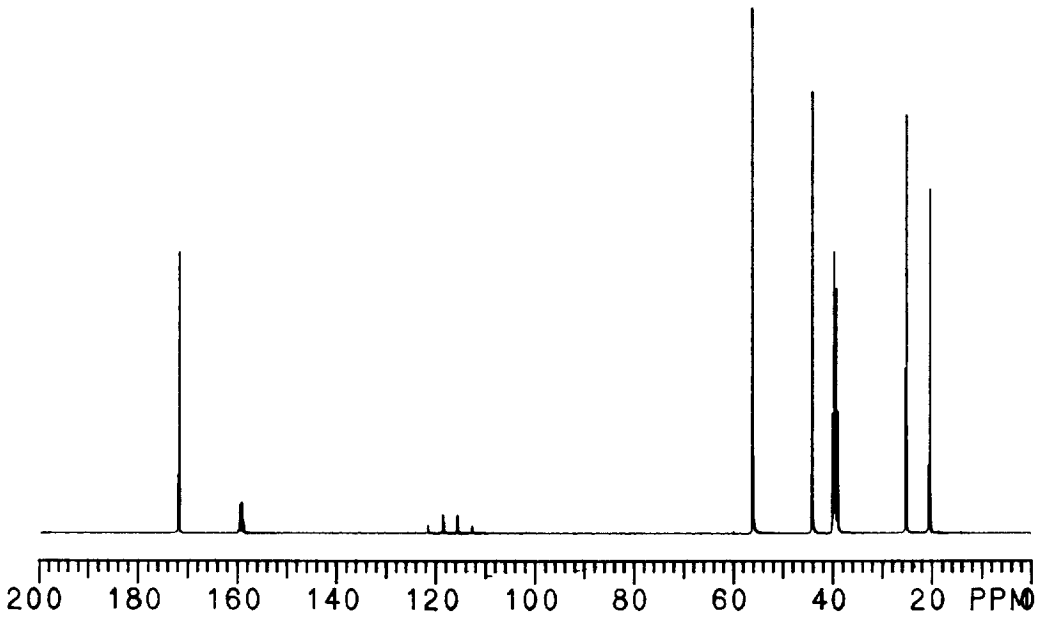


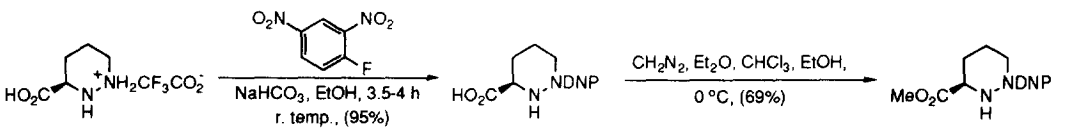
Fig. 2 100 MHz ^{13}C NMR spectrum of (3*R*)-Piperazic Acid Trifluoroacetic Acid Salt **11** in DMSO-d_6.



substantial material losses can be totally avoided, since the completely unnecessary and quite tedious chromatographic purification of **4** is now completely omitted.

In order to confirm the absolute configuration of the (3*R*)-piperazic acid trifluoroacetic acid salt **11** obtained by the above route, and also ascertain its enantiomeric purity, compound **11** was converted into known methyl (3*R*)-N^1-(2,4-dinitrophenyl)hexahydropyridazine carboxylate **13** (Scheme 3). The first step entailed treatment of **11** with excess 1-fluoro-2,4-dinitrobenzene and sodium bicarbonate in ethanol. After aqueous work up, the (3*R*)-N^1-2,4-dinitrophenyl derivative **12** was obtained as a bright yellow solid {m.p. 150.5-151.5 °C; Lit.[1] m.p. 151.5-152 °C; $[\alpha]_D$+341° (*c* 1, MeOH); Lit.[20a] $[\alpha]_D$ +324.6° (*c* 1, MeOH)}. The 400 MHz ^{1}H NMR spectrum of **12** in $CDCl_3$ contained three resonances between δ 8.37 and 6.97, each of which integrated to one proton; these were attributable to the 2,4-dinitrophenyl group. Acid **12** was then esterified with excess ethereal diazomethane to provide methyl (3*R*)-N^1-(2,4-dinitrophenyl)hexahydropyridazine-3-carboxylate **13** as a yellow crystalline solid {m.p. 96-97.5 °C, Lit.[1] 37-39 °C and 95-96 °C;[18] $[\alpha]_D$ +299° (*c* 1, $CHCl_3$), Lit.[18]$[\alpha]_D$

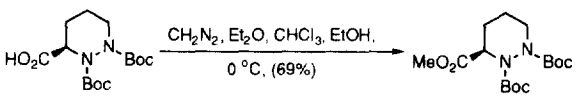
Scheme 3



(11) (12) (13)

-296° (*c* 1, $CHCl_3$) for the (3*S*)-enantiomer}. The 400 MHz ^{1}H NMR spectrum of **13** in C_6D_6 now contained a singlet at δ 3.18 which integrated to three protons and which was clearly assignable to the newly installed methyl ester group. The enantiomeric purity of **13** was found to be >96% according to HPLC analysis on a CHIRALCEL OD column; the same ee value was also found even if crude material was brought through the synthesis and no recrystallisations and chromatographic separations attempted. As a further check of enantiomeric purity, the crude acid **10** obtained from crude **4** was esterified with diazomethane to give **14** (Scheme 4). The latter was shown to have >96% ee by HPLC comparison with its racemate on a CHIRALCEL OD column.

Scheme 4

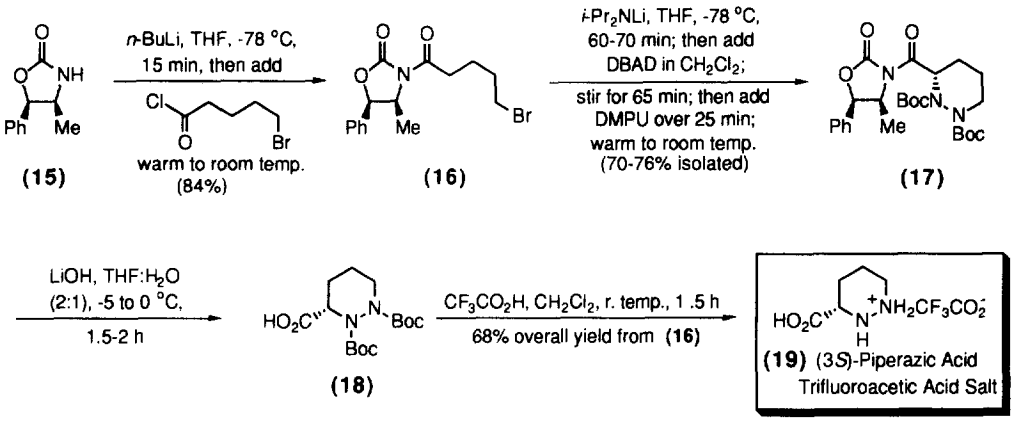


(10) (14)

During our efforts to develop an even better process for the preparation of optically pure piperazic acids, we evaluated the performance of Evans' alternative oxazolidinone **15**[19] in the above synthetic strategy (Scheme 5). Although it delivered (3*S*)-piperazic acid in slightly inferior ee (88-93%) than the oxazolidinone derived from L-phenylalaninol, we still found its use very attractive for a number of reasons. The foremost of these was its ease and convenience of preparation. Another reason was that it allowed the initial piperazic acid cyclisation product **17** to be crystallised (in virtually pure condition) in 52-60% yield directly from the crude reaction mixture. We felt that the latter feature would be a particularly welcome attribute for workers wishing to utilise this

intermediate for other synthetic purposes. We have also observed that **19**, obtained from auxiliary **15**, can be recrystallised to a state of complete optical purity (100% ee) from EtOAc and EtOH. In light of this, we now utilise the norephedrine auxiliaries routinely in these laboratories for the large scale preparation of **11** and **19**. In the experimental section we provide full experimental details of how to isolate the crystalline cyclisation product **17** in 70-76% yield from the crude cyclisation mixture, along with our preferred "crude" procedure for obtaining **19** from **16**.

Scheme 5

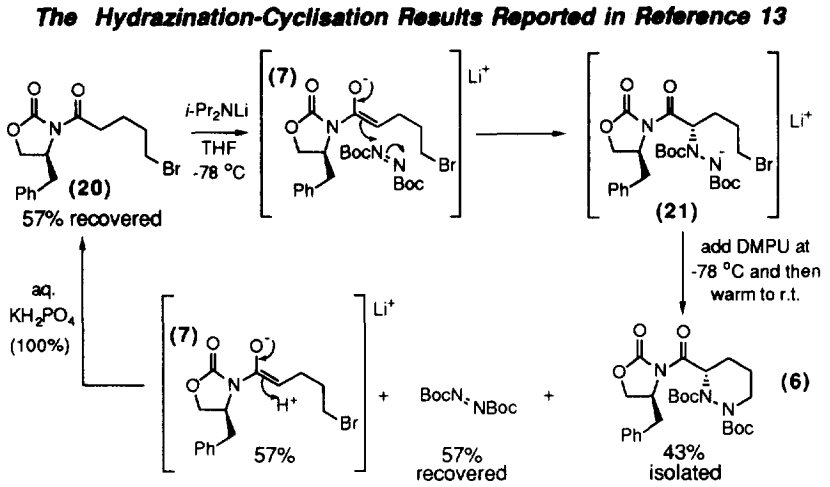


The Comparative Unimportance of Retro-Hydrazination in the Electrophilic Hydrazination and Nucleophilic Cyclisation of (20) with Di-t-Butylazodicarboxylate and DMPU as an Additive

In our previous publications on the asymmetric synthesis of (3*R*)- and (3*S*)-piperazic acids,[12] we reported that the electrophilic hydrazination and nucleophilic cyclisation of **20** affords **6** in yields of 55-63% when DMPU is employed as a cyclisation additive. Claiming to have followed our procedure, other workers[13] have subsequently reported that the cyclisation product **6** can only be isolated in 43% yield from this reaction, and that starting valeryl bromide **20** and DBAD are always the major components of their reaction mixtures (Scheme 6). Indeed, they claimed to have reisolated both starting compounds in correct mass balance (57% yield) after extractive workup and MPLC. They attributed their low yield of **6** and their recovery of starting materials to the occurrence of a significant and essentially irreversible retro-hydrazination reaction instigated by the addition of DMPU to anion **21**.[13] Their sole item of mechanistic evidence in support of this proposal was their HPLC observation that hydrazination was essentially complete (>95%) prior to their addition of DMPU.

In light of these claims, we felt obliged to carefully reinvestigate our procedure for the electrophilic hydrazination and nucleophilic cyclisation of **20** with DMPU as an additive. We found that our originally claimed product yields were indeed accurate. As we had observed previously, starting valeryl bromide **20** could only be detected in trace quantities in our crude reaction mixtures, and could never be reisolated in yields exceeding 5% by chromatography. In our view, if **20** is ever present in the crude reaction mixture, then it is probably there as a result of incomplete enolisation or incomplete hydrazination occurring, rather than the retro-hydrazination

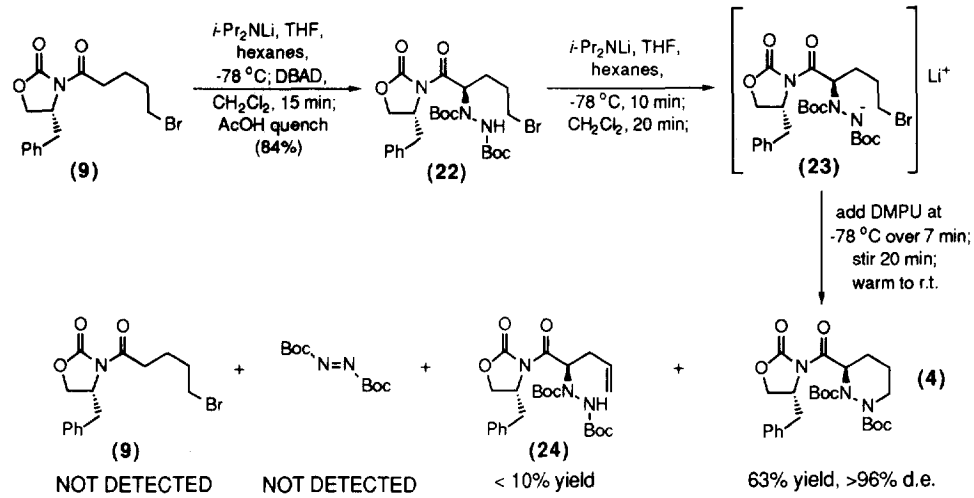
Scheme 6



reaction suggested by the authors of reference 13. Indeed, we are highly sceptical of the claims in this paper[13] that retro-hydrazination is a seriously detrimental and injurious side reaction of the DMPU process, primarily because of our extensive studies on the base-mediated cyclisation of **22** with DMPU present (Scheme 7). In particular, we would like to draw attention to the results we obtained after adding LDA (1.1 equiv) to highly pure **22** in THF and hexanes at -78 °C. After slow addition of CH_2Cl_2, followed by DMPU (16.4 equiv), warming of the reaction mixture to room temperature furnished the cyclisation product **4** in 63% yield after flash chromatography. Furthermore, after a very thorough and determined search of the reaction mixture, we were unable to detect valeryl bromide **9**, DBAD, or **22** amongst its components. A similar picture emerged when this experiment was conducted without CH_2Cl_2. In both these experiments, the only other noticeable component present in the crude reaction mixture (apart from **4** and hydrolysis products) was the elimination product **24**, and it was detected only as a very minor constituent. The fact that neither **9** nor DBAD were observed in the base-mediated cyclisation of **22** in the presence of DMPU refutes any suggestion that retro-hydrazination is a problematic and detrimental side reaction that competes disadvantageously with the DMPU-mediated nucleophilic cyclisation pathway. Naturally, we do not claim to have proven that retro-hydrazination is not occurring in cyclisation reactions mediated by DMPU. Rather, we have shown that if anion **23** does undergo retro-hydrazination to give DBAD and enolate **5**, then these would have to recombine almost instantaneously under our reaction conditions to recreate **23** in its entirity in > 96% d.e. Accordingly, we have concluded that DMPU-induced retro-hydrazination is a rather unimportant process that plays an insignificant role in the final outcome of the electrophilic hydrazination/nucleophilic cyclisation reactions of chiral *N*-bromovaleryl oxazolidinone enolates. It almost certainly would not lead to the significant quantities of **20** and DBAD claimed to have been reisolated by the authors of reference 13.

Scheme 7

Our Attempt at Deliberately Inducing the Retro-Hydrazination of Anion 23 With DMPU



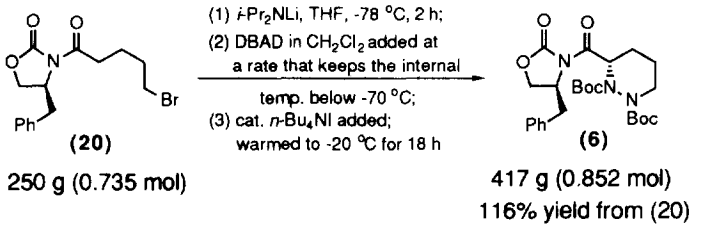
A Reappraisal of the n-Bu4NI Catalysed Procedure for Preparing Piperazic Acid Derivative 6 from Bromide 20

In this section, we reveal how the recent literature report[13] on the *n*-Bu_4NI catalysed conversion of **20** into **6** is quantitatively incorrect. We also report on how this work has been revised and augmented by us in what is essentially an extension of our own earlier work in this area.

In the experimental section of reference 13, it was stated that compound **6** (obtained from **20** via *n*-Bu_4NI catalysis) had given rise to an $(M+H)^{+\cdot}$ ion at *m/e* 507 in its mass spectrum. Since the theoretical *m/e* value for this ion is 490.2553, this raised further doubts about the validity of the cyclisation product yields quoted in this paper. Indeed, when we recalculated the percentage yield of **6** reported in the experimental procedure of reference

Scheme 8

The Results Reported in Reference 13 Using Catalytic n-Bu4NI as the Additive Instead of DMPU



13 (Scheme 8) using its correct relative molecular mass, we found that it was not 91% as claimed, but rather, an untenable 116% yield. In light of this error, we carefully repeated the *n*-Bu_4NI catalysed procedure described in reference 13, on reduced scale. We found that **6** was generally isolated in yields of 50-56% after flash chromatography, along with noticeable quantities of impure hydrazinated elimination product. The d.e. of **6** obtained in this way was >96%, which was in good agreement with the results reported in reference 13. Partial hydrolysis of the chiral auxiliary in **6** was also observed during the extractive workup. We verified our yields for the *n*-Bu_4NI-catalysed process by also subjecting bromide **16** to the same regimen. In this case, compound **17** was isolated in 53-55% yield after flash chromatography. Significantly, we noted that hydrazination and nucleophilic cyclisation of **20** proceeded in comparable yield (57% of purified **6**) (over a similar timeframe) when *n*-Bu_4NBr was employed as the additive instead of *n*-Bu_4NI (*n*-Bu_4NCl also worked in this capacity when it was applied on compound **16**). However, even more striking were our findings: (1) that the cyclisation of **20** to **6** could be executed in 56% isolated yield without additives, if hydrazination was performed in THF-CH_2Cl_2-hexanes at -78 °C for 20 min, and the reactants warmed to -20 °C for 18 h, and; (2) that the cyclisation of **16** produced **17** in 62-65% yield without additives, if hydrazination was performed in THF-CH_2Cl_2-hexanes at -78 °C for 30 min, and the reactants then warmed to room temperature for 2 h; indeed, the yield of the latter reaction was actually 68% if one includes the quantity of (3*S*)-di-*t*-BOC piperazic acid that was also recovered. However, the latter reaction, only furnished **19** in 74% ee (1st crop after one recrystallisation) when the crude cyclisation mixture was taken directly forward without isolation. Possibly, prolonged exposure of **17** to diisopropylamine at room temperature causes this loss in optical purity. As with the DMPU method, hydrazinated elimination products were also detected in these cyclisation reactions as minor by-products. In light of all these observations, we have concluded that tetra-*n*-butylammonium halides do not significantly increase the isolated yields of **6** or **17** when employed as additives. We have further concluded that it is the increase in reaction temperature from -78 °C to -20 °C in the *n*-Bu_4NI catalysed process that is probably more critical for facilitating the nucleophilic cyclisation step, as opposed to the *in situ* iodide displacement reaction promulgated in reference 13. One final point worth mentioning is that the optimised *n*-Bu_4NI catalysed cyclisation described in reference 13 takes considerably longer to reach completion than either of our DMPU-based processes. Furthermore, we have not been able to detect any distinct benefit in cyclisation product yield as a result of this considerably enhanced wait.

Conclusions

Quite clearly, our findings show that all of the criticisms levied against our work by Decicco and Leathers[13] lack firm foundation. The retro-hydrazination reaction that they claim is seriously detrimental to cyclisation product yield in the DMPU mediated process has been shown to be of little importance. We have also proven that the cyclisation product yield that they report for the *n*-Bu_4NI catalysed experimental procedure[13] is quantitatively incorrect, and should now be revised to 50-56% yield. Our results also cast considerable doubt on the importance of the iodide displacement mechanism suggested by Decicco and Leathers to facilitate the nucleophilic cyclisation step of this reaction.

In our view, the crude DMPU-assisted procedures remain the most effective methods[20] for the rapid medium-scale synthesis of homochiral piperazic acids (in our experience, cyclisations conducted with DMPU proceed in *ca.* 8-10% higher yield than those without). Both crude DMPU procedures can also be performed comfortably on 20-30 g scale without loss of yield or increased difficulty of product isolation. Although the norephedrine auxiliaries initially lead to **11** and **19** in slightly lower ee than their phenylalaninol counterparts, we still find their use attractive due to their cheaper cost and their more convenient preparation. The norephedrine

auxiliaries also allow the initial cyclisation product to be crystallised directly from the crude reaction mixtures in 52-60% yield and also in enhanced d.e. (>96%).

Experimental Section

Materials and Methods. DMPU (1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone) (Lancaster) was dried over *excess* 4A molecular sieves that had been activated by prolonged heating (1 h) with a Bunsen burner while under high vacuum (0.01 mm Hg). DMPU was stored and used under an atmosphere of dry N_2 and employed without further purification. CH_2Cl_2 and *i*-Pr_2NH were freshly distilled from CaH_2 under dry N_2. THF was freshly distilled from sodium metal under dry N_2. DBAD was dried for several hours *in vacuo* at 0.01 mm Hg prior to use. Analytical thin layer chromatography was performed on pre-coated glass-backed plates (Merck Kieselgel 60 F_{254}), and visualised by staining with either anisaldehyde/H_2SO_4/AcOH in EtOH and heating, or I_2, or $KMnO_4$ solution. Flash column chromatography was carried out on Sorbsil C60 40/60A (230-400 mesh) silica gel. Melting points were determined on a Reichert hot-stage apparatus and are uncorrected. Optical Rotations were measured on a Perkin Elmer 141 polarimeter. IR spectra were recorded on a Nicolet 205 FT IR spectrophotometer. ^1H and ^{13}C NMR spectra were recorded on a Varian AX-400 (400 MHz) spectrometer; the abbreviation (br) denotes broad ill-defined resonance. The chemical shifts in the 400 MHz ^1H NMR spectra that are recorded in $CDCl_3$ are reported in δ values relative to the residual $CHCl_3$ peak at δ 7.24 ppm. The chemical shifts in the 100 MHz ^{13}C NMR spectra recorded in $CDCl_3$ are reported in δ values relative to the residual $CHCl_3$ peak at δ 77.0 ppm. Mass spectra were measured by the ULIRS Mass Spectrometry Service Centre at the London School of Pharmacy on VG 70-70 or VG-ZAB mass spectrometers. Combustion microanalyses were performed by the Microanalytical Laboratory of University College London. High performance liquid chromatography (HPLC) was performed on a Gilson analytical chromatograph equipped with Gilson 303 and 305 pump systems, a Gilson 811b dynamic mixer, a Gilson 805s manometric module, and a Gilson 115 u.v. absorbance detector set at 254 nm. A CHIRALCEL OD™ (25 x 4.6 mm I.D.) column was employed for ee determination.

PART A: Our Recommended Experimental Procedures For Preparing (3R)- and (3S)-Piperazic Acids Along with Relevant Characterisation Data

(4*R*)-3-(5-Bromovaleryl)-4-phenylmethyl-2-oxazolidinone 9. To a stirred solution of *(4R)*-phenylmethyl-2-oxazolidinone **8** (5.6 g, 31.6 mmol) in dry THF (50 ml) under N_2 at -78 °C was added *n*-butyllithium (1.6 M solution in hexanes, 19.8 ml, 31.7 mmol) dropwise over 5 min. After the addition was complete the reactants were stirred at -78 °C for 15 min. 5-Bromovaleryl chloride (4.7 ml, 35.1 mmol) was then added dropwise over 3 min, and when the addition was complete, the reactants were maintained at -78 °C for 15 min. The cooling bath was then removed and the reaction mixture allowed to warm to room temperature, where it was stirred for a further 30 min. The reaction mixture was quenched with saturated aq. NH_4Cl solution at room temperature and extracted with CH_2Cl_2 (3 x 100 ml). The organic layer was washed with H_2O (200 ml), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The syrupy residue crystallised from cold hexanes when left overnight in the refrigerator (Yield of **9**: 9.78 g, 91%). An analytical sample (4*R*)-3-(5-bromovaleryl)-4-phenylmethyl-2-oxazolidinone **9** was obtained by recrystallisation from hexanes/Et_2O or hexanes/EtOAc; m.p. 66-67 °C; $[\alpha]_D$ -83° (*c* 1, MeOH); IR (KBr) 3065 (w), 3029 (m), 2954 (m), 2926 (m), 1785 (s), 1700 (s), 1499 (w), 1474 (w), 1455 (m), 1387 (s), 1379 (s), 1354 (s), 1299 (s), 1264 (s), 1239 (s), 1211 (s), 1145 (m), 1107 (s), 1050 (m), 1022 (m), 991 (m), 958 (m), 878 (w), 772 (m), 739 (s), 702 (s), 557 (m), 502 (m) cm^{-1}; 400

MHz ^{1}H NMR ($CDCl_3$) δ 7.35-7.18 (complex m, 5H), 4.67 (complex m, 1H), 4.18 (m, 2H), 3.44 (m, 2H), 3.28 (dd, *J* = 3.4, 13.4 Hz, 1H), 2.96 (complex m, 2H), 2.77 (dd, *J* = 9.5, 13.4 Hz, 1H), 2.00-1.79 (complex m, 4H); 100 MHz ^{13}C NMR ($CDCl_3$) δ 172.5, 153.4, 135.1, 129.3, 128.9, 127.3, 66.2, 55.0, 37.8, 34.5, 33.1, 31.9, 22.7; FAB LRMS Calcd. for $C_{15}H_{19}NO_3Br$ $(M+H)^{+\cdot}$:340, 342; Found: 340, 342; Anal. Calcd. for $C_{15}H_{18}NO_3Br$: C, 52.96; H, 5.33; N, 4.12; Br, 23.49. Found: C, 52.79; H, 5.43; N, 4.02; Br, 23.39.

(4*R*)-3-[(3*R*)-*N,N'*-bis-(*t*-butoxycarbonyl)hexahydropyridazine-3-carboxy]-4-phenylmethyl-2-oxazolidinone 4. To a stirred solution of *i*-Pr_2NH (2.36 ml, 16.7 mmol) in dry THF (19.8 ml) under N_2 at -78 °C was added *n*-butyllithium (2.5 M solution in hexanes, 6.81 mL, 17.0 mmol) dropwise over 4 min. The mixture was stirred at this temperature for 35 min, whereupon a precooled (-78 °C) solution of the (4*R*)-3-(5-bromovaleryl)-4-phenylmethyl-2-oxazolidinone **9** (5.49 g, 16.1 mmol) in dry THF (19.8 ml) was added in one portion via cannula. Stirring was continued at -78 °C for 35 min, whereupon a precooled[21] (-78 °C) solution of DBAD (4.45 g, 19.3 mmol) in dry CH_2Cl_2 (29.1 ml) was added in one portion via cannula. When the addition was complete the reactants were stirred at -78 °C for 30 min. DMPU (50 ml, 26 equiv.) was then added[16] dropwise over 40 min. By the end of the addition the reaction mixture had frozen. The cooling bath was removed, the reaction mixture warmed to room temperature, and stirring continued at this temperature for 5 min. The reaction mixture was then added to Et_2O (400 mL) layered on top of saturated aq. KH_2PO_4 (150 mL), and the two layers briefly but vigorously shaken. The aqueous fraction was further quickly extracted with Et_2O (2 x 150 ml), and the combined ether layers quickly washed with saturated aq. $NaHCO_3$ (1 x 150 ml), then with H_2O (250 mL), and then dried ($MgSO_4$) and filtered. The solvent was removed *in vacuo* to give a yellow oily residue that was purified by multiple SiO_2 flash chromatography, eluting with 1:1 Et_2O/hexanes; the cyclised piperazic acid derivative (4*R*)-3-[(3*R*)-*N,N'*-bis-(*t*-butoxycarbonyl)-hexahydropyridazine-3-carboxy]-4-phenylmethyl-2-oxazolidinone **4** (4.96 g, 63%) was obtained as a white foam (**4** stains with a characteristic golden/beige/white colour on TLC after treatment with anisaldehyde/H_2SO_4/AcOH/EtOH and heating); $[\alpha]_D$ -34 ° (*c* 1, MeOH); IR (neat film) 2979 (s), 2933 (m), 2868 (w), 1783 (s), 1698 (s), 1478 (s), 1455 (s), 1394 (s), 1367 (s), 1350 (s), 1327 (s), 1296 (s), 1253 (s), 1220 (s), 1167 (s), 1111 (s), 1087 (m), 1072 (m), 1049 (m), 1032 (m), 881 (m), 854 (m), 822 (w), 753 (s), 704 (m), 618 (w) cm^{-1}; 400 MHz ^{1}H NMR ($CDCl_3$) δ 7.34-7.15 (m), 6.03 (br s) and 5.74 (br d), 4.64 (br s), 4.25-3.86 (complex m), 3.38 (br m), 3.10-2.54 (br m), 2.64 (dd, *J* = 10.5, 13.3 Hz), 2.13 (very small br), 2.10-1.60 (br m), 1.47 (s), 1.45 (s), 1.42 (small s); LREI mass spectrum Calcd. for $C_{25}H_{36}N_3O_7$ $(M+H)^{+\cdot}$:490; Found: 490; Anal. Calcd for $C_{25}H_{35}N_3O_7$: C, 61.33; H, 7.21; N, 8.58. Found: C, 61.17; H, 7.36; N, 8.31; the faster-moving elimination product **24** is a foam that stains with a characteristic brown/black colour on TLC after treatment with anisaldehyde/H_2SO_4/AcOH/EtOH and heating. Compound **24** has the following data when pure: $[\alpha]_D$ -56.3 ° (*c* 1, MeOH); IR (KBr) 3400 (br w), 2981 (m), 2933 (w), 1781 (s), 1754-1698 (br s), 1649 (w), 1603 (w), 1480 (m), 1456 (m), 1394 (s), 1368 (s), 1325 (m), 1290 (m), 1241 (s), 1174 (s), 1159 (s), 1109 (m), 1052 (m), 1022 (m), 762 (m), 750 (m), 703 (m) cm^{-1}; 400 MHz ^{1}H NMR ($CDCl_3$) δ 7.34-7.18 (complex m), 6.75-6.30 (br), 5.91 (complex br m), 5.11 (m), 5.05 (d, *J* = 10.1 Hz), 4.56 (br), 4.16 (s), 4.15 (s), 3.30 (br), 2.90-2.40 (br m superimposed on 2 br), 1.46 (s), 1.45 (s); 100 MHz ^{13}C NMR spectrum ($CDCl_3$) (major peaks only) δ 152.6, 135.2, 133.8, 129.4, 129.0, 127.4, 117.8 (br), 66.5, 60.0 (very br), 55.6 (br), 37.6 (br), 28.2, 28.1; FAB HRMS Calcd. for $C_{25}H_{36}N_3O_7$ $(M+H)^{+\cdot}$ 490.2553; Found: 490.2550; Anal. Calcd. for $C_{25}H_{35}N_3O_7$: C, 61.33; H, 7.21; N, 8.58. Found:, C, 61.17; H, 7.36; N, 8.31.

(3*R*)-*N*,*N'*-bis-(*t*-butoxycarbonyl)hexahydropyridazine-3-carboxylic acid 10. To a stirred solution of (4*R*)-3-[(3*R*)-*N*,*N'*-bis-(*t*-butoxycarbonyl)hexahydropyridazine-3-carboxy)]-4-phenylmethyl-2-oxazolidinone **4** (2.0 g, 4.1 mmol) in THF (16.1 ml) at -5 °C was added a chilled (-5 °C) suspension of lithium hydroxide monohydrate (0.39 g, 9.29 mmol) in H_2O (8 ml) over 2-3 min via pipette. The reactants were vigorously stirred at between -5 and 0 °C for 1 h 40 min and then diluted with H_2O (20 mL). The mixture was extracted with Et_2O (3 x 50 ml), and the organic layer washed with saturated aq. $NaHCO_3$ (50 mL) to remove any residual **10** that was present. All the aqueous layers were then combined, acidified to pH 2 with solid $NaHSO_4$, and extracted with EtOAc (3 x 100 ml). The organic extract was then dried ($MgSO_4$), filtered, and concentrated *in vacuo*, to give pure (3*R*)-*N*,*N'*-bis-(*t*-butoxycarbonyl)hexahydropyridazine-3-carboxylic acid **10** (1.2 g, 89%) as white crystals; m.p. 115-118 °C; $[\alpha]_D$ +18 ° (*c* 1, MeOH); IR (KBr) 3213 (s), 3010 (m), 2986 (m), 1743 (s), 1708 (s), 1667 (s), 1455 (s), 1434 (s), 1384 (s), 1370 (s), 1163 (s), 1136 (s), 1090 (s), 915 (m), 880 (s), 854 (m), 843 (m), 826 (m), 753 (m), 738 (m) cm^{-1}; 400 MHz ^1H NMR ($CDCl_3$) δ 5.08-4.60 (br m), 4.03 (m), 3.89 (m), 3.32-2.92 (v br), 2.85 (br m), 2.30-1.36 (br m) superimposed on 1.48 (s) and 1.45 (s); 100 MHz ^{13}C NMR ($CDCl_3$) (major peaks only) δ 171.6, 170.6, 152.5, 83.6, 83.1, 56.3, 44.2, 42.1, 28.1, 28.0, 23.8, 23.3, 20.6, 20.2; FAB LRMS Calcd. for $C_{15}H_{27}N_2O_6$ $(M+H)^{+\cdot}$: 331; Found: 331; Anal. Calcd. for $C_{15}H_{26}N_2O_6$: C, 54.53; H, 7.93; N, 8.48. Found: C, 54.36; H, 7.85; N, 8.37.

Methyl (3*R*)-*N*,*N'*-bis-(*t*-butoxycarbonyl)hexahydropyridazine-3-carboxylate 14. A cooled (0 °C) solution of crude (3*R*)-*N*,*N'*-bis-(*t*-butoxycarbonyl)hexahydropyridazine carboxylic acid **10** (43.5 mg, 0.132 mmol) in $CHCl_3$ (1.4 ml) and EtOH (1 drop) was repeatedly treated with an ethereal solution of diazomethane until TLC analysis (4:1 $CHCl_3$:MeOH) indicated that starting acid **10** was no longer present. A stream of N_2 was then bubbled through the solution for 10 min to remove excess diazomethane, and the solvent removed *in vacuo*. The crude residue was purified by SiO_2 flash chromatography (7:1 hexanes:Et_2O) to afford methyl ester **14** (31.3 mg, 69%) as a colourless oil; IR (KBr) 2979 (m), 2934 (m), 1737 (s), 1703 (s), 1478 (m), 1456 (m), 1430 (m), 1408 (s), 1402 (s), 1367 (s), 1326 (m), 1298 (m), 1253 (s), 1168 (s), 1129 (m), 1086 (m), 1052 (w), 1034 (w), 1008 (w), 910 (w), 880 (w), 857 (w), 755 (w), 666 (w) cm^{-1}; 400 MHz ^1H NMR ($CDCl_3$) δ 4.97 (br), 4.77 (very br), 4.10 (br m), 3.95 (br), 3.70 (s), 2.90 (very br) superimposed on 2.79 (br m), 2.15-1.20 (complex br m) superimposed on 1.45 (s) and 1.44 (s); 100 MHz ^{13}C NMR ($CDCl_3$) (major peaks only) δ 170.5, 154.5, 81.7, 80.5, 80.3, 54.5, 52.0, 42.7, 28.3, 28.2, 24.9, 24.3, 20.0; FAB LRMS Calcd. for $C_{16}H_{28}N_2O_6Na$ $(M+Na)^{+\cdot}$: 367; Found: 367; HPLC comparison of **14** with its racemate using a CHIRALCEL OD column with 75:25 hexanes:isopropanol as eluant indicated that **14** was of 96% ee.

(3*R*)-Piperazic acid trifluoroacetic acid salt 11.[17] To a stirred solution of pure (3*R*)-*N*,*N'*-bis-(*t*-butoxycarbonyl)hexahydropyridazine-3-carboxylic acid **10** (0.85 g, 2.57 mmol) in dry CH_2Cl_2 (8.5 mL) under N_2 at room temperature was added CF_3CO_2H (8.5 mL, 110.0 mmol) in one portion. The mixture was stirred for 1.5 h, and the CF_3CO_2H and CH_2Cl_2 removed *in vacuo*. A crude white solid (742 mg) was obtained that contained traces of CF_3CO_2H. This crude sample of (3*R*)-Pip trifluoroacetic acid salt was coevaporated (x2) from PhMe and then recrystallised from EtOAc and EtOH to give analytically pure **11** (590 mg, 94%) as fluffy white crystals that were homogenous according to TLC analysis using 2:2:1 EtOAc;EtOH;H_2O as eluent; $[\alpha]_D$ -12.0 ° (*c* 1, MeOH); m.p. 147-149 °C; IR (KBr) 3293 (s), 3080 (s), 2981 (s), 1723 (s), 1666 (s), 1590 (s), 1517 (w), 1454 (m), 1442 (m), 1422 (s), 1233 (s), 1198 (s), 1183 (s), 1137 (s), 802 (s), 725 (m) cm^{-1}; 400 MHz ^1H NMR (D_2O, resonances are reported relative to HOD at δ 4.80) δ 3.90 (complex m, 1H), 3.28

(complex m, 1H), 3.14 (complex m, 1H), 2.11 (complex m, 1H), 1.86 (complex m, 3H); 100 MHz ^{13}C NMR (DMSO-d_6, resonances are reported relative to the DMSO septet at δ 39.5) δ 171.6, 159.0 (q, J = 32.1 Hz), 117.0 (q, J = 297.0 Hz), 56.0, 44.1, 25.1, 20.3; FAB LRMS Calcd. for $C_5H_{11}N_2O_2$ $(M+H)^{+\cdot}$: 131; Found: 131; Anal. Calcd. for $C_7H_{11}F_3N_2O_4$: C, 34.43; H, 4.54; N, 11.47. Found: C, 34.64; H, 4.48; N, 11.38.

(3*R*)-*N*^{1}-(2,4-dinitrophenyl)hexahydropyridazine-3-carboxylic acid 12. To a stirred suspension of (3*R*)-piperazic acid trifluoroacetic acid salt **11** (200 mg, 0.82 mmol) and $NaHCO_3$ (770 mg, 9.16 mmol) in EtOH (8.5 ml) was added 2,4-dinitrofluorobenzene (1.4 ml, 11.15 mmol) via syringe. The reaction mixture was stirred at room temperature for 3.5 h, poured into H_2O (20 ml), and multiply extracted with Et_2O (4 x 60 ml) to remove excess 2,4-dinitrofluorobenzene. The aqueous layer (containing the product) was then acidified with 10% aq. HCl and multiply extracted with EtOAc (3 x 100 ml). The combined EtOAc layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude residue, which was essentially pure according to TLC analysis, was purified by SiO_2 flash chromatography with 25:1 CH_2Cl_2:MeOH as eluent. This furnished **12** (230 mg, 95%) as a bright lemon crystalline solid; m.p. 150.5-151.5 °C (Lit.[1] m.p. 151.5-152 °C); $[\alpha]_D$ +341.0 ° (*c* 1, MeOH) {Lit.[20a] $[\alpha]_D$ +324.6 ° (*c* 1, MeOH)}; IR (KBr) 3680-2000 (br m), 1717 (s), 1608 (s), 1539 (s), 1518 (s), 1463 (s), 1440 (s), 1371 (s), 1337 (s), 1265 (s), 1236 (s), 1172 (s), 1134 (s), 1096 (w), 1068 (m), 921 (m), 908 (s), 865 (s), 831 (s), 819 (s), 742 (s), 695 (w), 583 (w), 506 (w), 428 (w) cm^{-1}; 400 MHz ^1H NMR ($CDCl_3$) δ 8.37 (d, J = 2.6 Hz, 1H), 8.18 (dd, J = 2.7, 9.3 Hz, 1H), 6.97 (d, J = 9.4 Hz, 1H), 5.50 (very br, 2H), 3.81 (m, 1H), 3.69 (dd, J = 3.4, 11.2 Hz, 1H), 3.10 (m, 1H), 2.19 (m, 1H), 1.99 (complex m, 2H), 1.60 (complex m, 1H); 100 MHz ^{13}C NMR ($CDCl_3$) δ 175.7, 147.4, 138.4, 127.4, 122.3, 115.0, 57.3, 47.6, 27.6, 22.8; FAB LRMS Calcd. for $C_{11}H_{13}N_4O_6$ $(M+H)^{+\cdot}$: 297. Found: 297; Anal. for $C_{11}H_{12}N_4O_6$, Calcd: C, 44.60; H, 4.08; N, 18.91. Found: C, 44.48; H, 3.96; N, 18.76.

Methyl (3*R*)-*N*^{1}-(2,4-dinitrophenyl)hexahydropyridazine-3-carboxylate 13. A 0 °C solution of **12** (100 mg, 0.338 mmol) in $CHCl_3$ (3.5 ml) and EtOH (2 drops) was repeatedly treated with ethereal diazomethane until TLC (4:1 $CHCl_3$:MeOH) indicated that no starting material remained. A stream of N_2 was then bubbled through the solution for 10 min to remove excess diazomethane, and the solvent removed *in vacuo*. The crude residue was purified by SiO_2 flash chromatography with 2:1 hexanes:EtOAc to afford methyl ester **13** (72.1 mg, 69% yield) as a yellow crystalline solid; m.p. 96-97.5 °C (Lit.[1] m.p. 37-39 °C); $[\alpha]_D$ +299.0 ° (*c* 1, $CHCl_3$) {Lit.[18] $[\alpha]_D$ -296 ° (*c* 1, $CHCl_3$) for (3*S*)-enantiomer}, $[\alpha]_D$ +358.0 ° (*c* 0.64, MeOH); IR (KBr) 3233 (m), 3080 (m), 2952 (m), 1743 (s), 1609 (s), 1583 (s), 1542 (s), 1502 (s), 1463 (m), 1435 (m), 1370 (s), 1332 (s), 1320 (s), 1301 (s), 1271 (s), 1258 (s), 1232 (s), 1219 (s), 1171 (m), 1132 (s), 1058 (m), 1029 (m), 922 (m), 884 (m), 859 (m), 830 (m), 811 (m), 751 (m) cm^{-1}; 400 MHz ^1H NMR (C_6D_6, resonances are reported relative to residual C_6H_6 peak at δ 7.15) δ 8.12 (d, J = 2.7 Hz, 1H), 7.68 (dd, J = 2.6, 9.3 Hz, 1H), 5.82 (d, J = 9.3 Hz, 1H), 3.40 (ddd, J = 3.4, 11.3, 11.3 Hz, 1H), 3.18 (s, 3H), 3.12 (d, J = 11.5 Hz, 1H), 2.61 (m, 1H), 1.82 (complex m, 1H), 1.46 (complex m, 1H), 1.13-0.84 (complex m, 3H); 100 MHz ^{13}C NMR ($CDCl_3$) δ 171.4, 147.5, 138.2, 127.3, 122.4, 115.0, 57.4, 52.2, 47.7, 27.7, 22.7; FAB LRMS Calcd. for $C_{12}H_{15}N_4O_6$ $(M+H)^{+\cdot}$: 311; Found: 311; Anal. Calcd. for $C_{12}H_{14}N_4O_6$: C, 46.45; H, 4.55; N, 18.06. Found: C, 46.40; H, 4.61; N, 17.86. HPLC analysis of **13** using a CHIRALCEL OD column with 75:25 hexanes:isopropanol as eluent indicated that it was of >96% ee after comparison with racemic material.

PREFERRED "CRUDE" PROCEDURE FOR CONVERTING BROMIDE 9 INTO (3*R*)-PIPERAZIC ACID TRIFLUOROACETIC ACID SALT 11.

To a stirred solution of *i*-Pr_2NH (3.98 mL, 28.2 mmol) in dry THF (20 ml) under N_2 at -78 °C was added *n*-butyllithium (1.6 M in hexanes, 16.2 mL, 25.9 mmol) over 1 min. The mixture was stirred at that temperature for 80 min, whereupon a solution of bromide **9** (8.0 g, 23.5 mmol) in dry THF (20 ml) was added dropwise over 10 min via syringe. Stirring was continued at -78 °C for 70 min, whereupon a solution of di-*tert*-butylazodicarboxylate (6.49 g, 28.2 mmol) in dry CH_2Cl_2 (20 mL) was added dropwise over 8 min. When the addition was complete the reactants were stirred at -78 °C for 65 min. DMPU (47 mL, 16.5 equiv) was then added dropwise over 25 min, and the mixture stirred at -78 °C for a further 25 min. The cooling bath was then removed and the reaction mixture allowed to warm to room temperature, whereupon it was stirred for a further 5 min. The reaction mixture was then poured into Et_2O (1 L) layered on top of a saturated solution of aqueous KH_2PO_4 (150 mL) in a separatory funnel, and the two layers mixed briefly by vigorous shaking. The ethereal layer was then removed and rapidly washed with H_2O (2 x 200 mL). The combined aqueous layers were then acidified to pH 2 with solid $NaHSO_4$ and extracted with Et_2O (200 mL); the ethereal layer was washed with H_2O (100 mL) and combined with the original ether extract. The combined ethereal layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue containing mainly **4** was dissolved in THF (80 mL) and cooled to between -5 °C and 0 °C. A chilled (0 °C) solution of lithium hydroxide monohydrate (2.3 g, 54.8 mmol) in H_2O (48 mL) was added in portions over 5 min via Pasteur pipette. The resulting mixture was stirred for 2.5 h at that temperature, and then diluted with Et_2O (200 mL) and H_2O (50 mL) and the mixture shaken. The aqueous layer was removed and further extracted with Et_2O (100 mL). The combined ethereal layers (which contained significant quantities of acid **10**) were then washed with sat. aq. $NaHCO_3$ solution (50 mL) and the aqueous layer removed. The aqueous layers were then combined and acidified to pH 2 with solid $NaHSO_4$, and rapidly extracted with EtOAc (4 x 150 mL). The combined EtOAc extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The resulting waxy residue was dissolved in dry CH_2Cl_2 (40 mL) under N_2 and CF_3CO_2H (40 mL, 519.0 mmol) added over 30 sec. The mixture was stirred at room temperature for 20 min and concentrated *in vacuo*. This led to an oily residue that was coevaporated with PhMe (150 mL) to remove residual traces of CF_3CO_2H; the (3*R*)-Piz TFA salt **11** was obtained as an off-white crystalline cake. Crude **11** was then suspended in Et_2O containing a small amount of EtOAc and the solid extensively ground up for 20-30 min with a spatula. The resulting solid was filtered off, and washed with Et_2O and EtOAc. TLC of this material with EtOAc:MeOH:H_2O (2:2:1) as eluent indicated that **11** had been obtained in virtually pure condition (it appears as a bright yellow spot after staining with anisaldehyde/H_2SO_4/AcOH/EtOH stain and heating); 200 MHz ^1H NMR spectroscopy in D_2O confirmed this observation; conversion of **11** to **13** at this stage, and subsequent CHIRALCEL OD HPLC analysis indicated this material was of >96% ee. Recrystallisation of **11** from EtOAc and a minimal amount of EtOH to ensure dissolution furnished analytically pure **11** (3.90 g, 68% overall yield from **9**) as fluffy white crystals over several crops (sometimes, the addition of a small amount of Et_2O and cooling to 0 °C facilitated the full recovery of **11**).

(4*S*,5*R*)-3-(5-Bromovaleryl)-4-methyl-5-phenyl-2-oxazolidinone 16. To a stirred solution of *(4S,5R)*-4-methyl-5-phenyl-2-oxazolidinone (28.0 g, 158.0 mmol) in dry THF (250 ml) under N_2 at -78 °C was added *n*-butyllithium (1.6 M solution in hexanes, 99.0 ml, 158.4 mmol) dropwise over 10 minutes. After the addition was complete the reactants were stirred at -78 °C for 15 min. 5-Bromovaleryl chloride (23.5 ml, 175.5 mmol) was then added dropwise over 10 min., and the reactants maintained at -78 °C for 30 min. The cooling

bath was then removed and the reaction mixture allowed to warm to room temperature. After 30 min saturated aq. NH_4Cl solution was added and the mixture extracted with CH_2Cl_2 (3 x 300 ml). The organic layer was washed with H_2O (200 ml), dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The syrupy residue crystallised from cold hexanes when left overnight in the refrigerator (Yield of **16**: 45.2 g, 84%). An analytically pure sample of **16** was obtained by recrystallisation from hexanes/Et_2O or hexanes/EtOAc; m.p. 70.5-72 °C; $[\alpha]_D$ -9.6 ° (*c* 2, MeOH); IR (KBr) 2965 (m), 2945 (m), 2879 (m), 1789 (s), 1765 (s), 1709 (s), 1703 (s), 1463 (m), 1455 (m), 1439 (w), 1408 (m), 1383 (s), 1375 (s), 1352 (s), 1289 (s), 1240 (s), 1219 (s), 1207 (s), 1197 (s), 1150 (m), 1121 (m), 1068 (m), 1045 (m), 1031 (m), 989 (m), 960 (m), 914 (w), 889 (w), 771 (s), 730 (s), 701 (s), 652 (w), 630 (w) cm^{-1}; 400 MHz ^1H NMR ($CDCl_3$) δ 7.43-7.24 (m, 5H), 5.65 (d, *J* = 7.5 Hz, 1H), 4.74 (m, 1H), 3.42 (m, 2H), 2.96 (m, 2H), 1.93 (complex m, 2H), 1.82 (complex m, 2H), 0.88 (d, *J* = 6.6 Hz, 3H); 100 MHz ^{13}C NMR ($CDCl_3$) δ 172.4, 153.0, 133.2, 128.8, 128.7, 125.6, 79.0, 54.8, 34.7, 33.1, 32.0, 22.8, 14.6; FAB HRMS Calcd. for $C_{15}H_{18}NO_3BrNa$ $(M+Na)^{+\cdot}$: 362.0369; Found: 362.0374; Anal. Calcd. for $C_{15}H_{18}NO_3Br$: C, 52.96; H, 5.33; N, 4.12; Br, 23.49. Found: C, 52.87; H, 5.40; N, 3.93; Br, 23.36.

(4*S*,5*R*)-3-[(3*S*)-*N*,*N'*-bis-(*t*-butoxycarbonyl)hexahydropyridazine-3-carboxy]-4-methyl-5-phenyl-2-oxazolidinone 17. To a stirred solution of *i*-Pr_2NH (3.98 ml, 28.2 mmol) in dry THF (20 ml) under N_2 at -78 °C was added *n*-butyllithium (1.6 M solution in hexanes, 16.2 ml, 25.9 mmol) over 1 min. The mixture was stirred at that temperature for 80 min, whereupon a solution of **16** (8.0 g, 23.5 mmol) in THF (20 ml) was added dropwise over 10 min. Stirring was continued at -78 °C for 70 min, whereupon a solution of DBAD (6.49 g, 28.2 mmol) in dry CH_2Cl_2 (20 ml) was added dropwise over 8 min. When the addition was complete the reactants were stirred at -78 °C for 65 min. DMPU (47 ml, 16.5 eq) was then added dropwise over 25 min. By the end of the addition the reaction mixture became a thick slurry; this was stirred at -78 °C for a further 25 min. The cooling bath was then removed and the reaction mixture allowed to warm to room temperature, whereupon it was stirred for 5 min. The reaction mixture was then poured into Et_2O (1 L) layered on top of a saturated solution of aq. KH_2PO_4 (150 ml) in a separatory funnel, and the two layers mixed briefly through vigorous shaking. The aqueous fraction was separated and the organic layer washed with saturated aq. $NaHCO_3$ (1 x 100 ml), then with brine, dried ($MgSO_4$), and filtered under suction. The solvent was removed *in vacuo* to give a yellow oily residue that was triturated with hexanes/Et_2O (1:1); the cyclised piperazic acid derivative **17** crystallised in virtually pure form and was filtered off (Yield of **17**: 6.0 g, 52%).The mother liquors were concentrated *in vacuo* and the residue subjected to SiO_2 flash chromatography with hexanes/EtOAc (gradient elution: 6:1, 5:1, and finally 4:1) to afford a further batch of pure crystalline product (2.01 g) after trituration with 1:1 hexanes/Et_2O (combined yield: 69.6%). Further chromatography of these mother liquors with 15:1 CH_2Cl_2/Et_2O afforded a further 77 mg of **17**; the combined isolated yield of **17** was 8.09 g (70%) {other runs have afforded 8.62 g (75%) of **17**}; m.p. 146.5-148.5 °C; $[\alpha]_D$ -19 ° (*c* 2, MeOH); IR (neat film) 2980 (m), 2935 (m), 1787 (s), 1697 (br s), 1478 (m), 1458 (s), 1393 (s), 1367 (s), 1346 (s), 1295 (s), 1253 (s), 1219 (m), 1197 (s), 1161 (s), 1122 (s), 1091 (m), 1068 (m), 1031 (m), 882 (w), 854 (w), 767 (m), 756 (m), 701 (m); 400 MHz ^1H NMR ($CDCl_3$) δ 7.43-7.24 (complex m), 6.12 (br), 5.80 (br), 5.64 (m), 5.30 (small and very br), 4.75 (m superimposed on br), 4.30-3.96 (br superimposed on br), 3.92 (m), 3.15 (small and very br), 3.10-2.78 (br superimposed on br), 2.23-1.60 (br superimposed on br), 1.47 (s), 1.45 (s), 1.41 (s), 1.39 (s), 0.93 (small d, *J* = 6.5 Hz), 0.88 (large d, *J* = 6.5 Hz), 0.85 (medium d, *J* = 6.7 Hz); 100 MHz ^{13}C NMR ($CDCl_3$, major peaks only) δ 169.6, 169.2, 154.6, 152.2, 152.0, 133.7, 133.2, 128.7, 128.6, 128.5, 126.0,

125.5, 81.4, 81.2, 80.4, 80.1, 79.1, 78.9, 54.9, 54.6, 54.2, 52.7, 44.8, 42.4, 28.2, 28.1, 24.8, 19.8, 19.2, 14.5; FAB HRMS Calcd. for $C_{25}H_{35}N_3O_7Na$ $(M+Na)^{+\cdot}$: 512.2373; Found: 512.2386; Anal. Calcd for $C_{25}H_{35}N_3O_7$: C, 61.33; H, 7.21; N, 8.58. Found: C, 61.26; H, 7.25; N, 8.50.

PREFERRED "CRUDE" PROCEDURE FOR CONVERTING BROMIDE 16 INTO (3*S*)-PIPERAZIC ACID TRIFLUOROACETIC ACID SALT 19.

To a stirred solution of *i*-Pr_2NH (3.98 ml, 28.2 mmol) in dry THF (20 ml) under N_2 at -78 °C was added *n*-butyllithium (1.6 M in hexanes, 16.2 ml, 25.9 mmol) over 1 min. The mixture was stirred at that temperature for 80 min, whereupon a solution of bromide **16** (8.0 g, 23.5 mmol) in dry THF (20 ml) was added dropwise over 10 min via syringe. Stirring was continued at -78 °C for 70 min, whereupon a solution of DBAD (6.49 g, 28.2 mmol) in dry CH_2Cl_2 (20 ml) was added dropwise over 8 min. When the addition was complete the reactants were stirred at -78 °C for 65 min. DMPU (47 ml, 16.5 eq) was then added dropwise over 25 min, and the mixture stirred at -78 °C for a further 25 min. The cooling bath was then removed and the reaction mixture allowed to warm to room temperature, whereupon it was stirred for a further 5 min. The reaction mixture was then poured into Et_2O (1 L) layered on top of a saturated solution of aqueous KH_2PO_4 (150 ml) in a separatory funnel, and the two layers very briefly mixed by vigorous shaking. The ethereal layer was then removed and rapidly washed with H_2O (2 x 200 mL). The combined aqueous layers were then acidified to pH 2 with solid $NaHSO_4$ and extracted with Et_2O (200 mL); this ethereal layer was washed with H_2O (100 mL) and combined with the first ether extract. The combined ethereal layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was dissolved in THF (80 mL) and cooled to between -5 °C and 0 °C. A chilled (0 °C) solution of lithium hydroxide monohydrate (2.3 g, 54.8 mmol) in H_2O (48 mL) was added in portions over 8 min via Pasteur pipette. The resulting mixture was stirred for 2 h 40 min at that temperature, and then diluted with Et_2O (200 mL) and H_2O (50 mL) and the mixture shaken. The aqueous layer was removed and further extracted with Et_2O (100 mL). The combined ether layers were then washed with sat. aq. $NaHCO_3$ solution (50 mL) and the aqueous layer removed. The combined aqueous layers were then acidified to pH 2 with solid $NaHSO_4$, and rapidly extracted with EtOAc (4 x 150 mL). The combined EtOAc layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The resulting di-*t*-BOC-protected (3*S*)-piperazic acid derivative was dissolved in dry CH_2Cl_2 (40 mL) under N_2 and CF_3CO_2H acid (40 mL, 519.0 mmol) added via syringe over 30 sec. The mixture was stirred at room temperature for 1 h and concentrated *in vacuo*. The oily residue was then coevaporated with PhMe (150 mL) to remove residual traces of CF_3CO_2H; the (3*S*)-Piperazic Acid TFA salt **19** was obtained as an off-white crystalline solid. Crude **19** was then suspended in Et_2O containing a small amount of EtOAc and the solid extensively ground up for 20-30 min with a spatula. The solid was filtered off, and then washed with Et_2O and EtOAc. TLC of this material with EtOAc:MeOH:H_2O (2:2:1) as eluent indicated that **19** had been obtained in virtually pure condition (it appears as a single bright yellow spot after staining with anisaldehyde/H_2SO_4/AcOH/EtOH stain and heating); 200 MHz ^1H NMR spectroscopy confirmed this observation; conversion to the N^1-2,4-DNP methyl ester at this stage and HPLC analysis on a CHIRALCEL OD column indicated that **19** had 90% ee. Recrystallisation of this product (**19**) from EtOAc containing a minimal amount of EtOH furnished analytically pure **19** (3.74 g, 65% yield from **16**) as fluffy white crystals; this material also had 90% ee. Further recrystallisation of **19** using increased volumes of EtOH allowed material with higher optical purity to be obtained but in lower overall yield (*ca.* 56% from **16**).

PART B: Our Experimental Work on Retro-Hydrazination

(4*R*)-3-[(2*R*)-*N*,*N'*-bis-(*t*-butoxycarbonyl)hydrazino-(5-bromovaleryl)]-4-phenylmethyl-2-oxazolidinone 22. To a stirred solution of *i*-Pr_2NH (1.68 ml, 11.9 mmol) in dry THF (10 mL) at -78 °C under N_2 was added *n*-butyllithium (1.6 M solution in hexanes, 6.7 ml, 10.7 mmol) over 1 min. The mixture was stirred at -78 °C for 40 min, whereupon a solution of bromide **9** (3.4 g, 9.99 mmol) in dry THF (10 mL) was added dropwise over 4 min. The resulting solution was stirred at -78 °C for 40 min prior to adding a solution of DBAD (2.77 g, 12.0 mmol) in CH_2Cl_2 (10 mL) dropwise over 3 min. The mixture was then stirred at -78 °C for 15 min, and glacial acetic acid (0.56 mL) added dropwise over 1 min. After stirring at that temperature for a further 2 min, the mixture was diluted with EtOAc (50 mL) and organic phase washed with H_2O (4 x 50 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude residue was purified by SiO_2 flash chromatography with CH_2Cl_2:EtOAc (initially 100:1 then 50:1) as eluent to give **22** (4.8 g, 84%) as a white foam; $[\alpha]_D$ -58.6 ° (*c* 2, MeOH); IR (KBr) 3402 (br w), 2971 (w), 2931 (w), 1782 (s), 1716 (s), 1696 (s), 1483 (w), 1450 (w), 1397 (s), 1364 (s), 1350 (m), 1238 (m), 1164 (m), 1111 (w), 1052 (w), 766 (w), 706 (w) cm^{-1}; 400 MHz ^1H NMR ($CDCl_3$) at 25 °C δ 7.36-7.17 (complex m), 6.72 (br) superimposed on 6.65 (br), 6.45 (br), 5.72 (br), 4.56 (br), 4.22 (m), 3.42 (m) superimposed on 3.36 (br), 3.23 (br), 2.80 (br) superimposed on 2.68 (br), 2.42-1.70 (complex br m), 1.49 (small s), 1.46 (large s), 1.45 (large s); 400 MHz ^1H NMR at 100 °C (DMSO-d_6, resonances reported relative to residual DMSO quintet at δ 2.49 ppm) indicated that **22** was essentially a single diastereoisomer with resonances at δ 8.15 (br 1H), 7.35-7.22 (m, 5H), 5.65 (m, 1H), 4.65 (m, 1H), 4.35 (m, 1H), 4.16 (dd, *J* = 8.7, 3.5 Hz, 1H), 3.48 (m, 2H), 3.14 (m, 1H), 2.89 (m, 1H), 2.10-1.75 (m, 4H), 1.44 (s) and 1.41 (s) (the 2 singlets combined integrated to 18H); 100 MHz ^{13}C NMR ($CDCl_3$, major peaks only) δ 174.0, 154.8, 152.6, 134.9, 134.7, 129.4, 129.0, 127.4, 82.2, 82.0, 81.5, 80.7, 66.5, 60.5, 59.7, 55.5, 37.2, 34.0, 32.5, 29.6, 29.1, 28.2, 28.0, 27.7; FAB HRMS Calcd. for $C_{25}H_{37}N_3O_7Br$ $(M+H)^{+\cdot}$: 570.1815; Found: 570.1811; FAB LRMS *m/e* 570 and 572.

The Conversion of Bromovaleryl Hydrazide 22 into (3*R*)-Piperazic Acid Derivative 4 Using LDA and DMPU. To a stirred solution of *i*-Pr_2NH (0.47 mL, 3.33 mmol) in dry THF (4.7 mL) at -78 °C under N_2 was added *n*-butyllithium (2.5 M in hexanes, 1.22 mL, 3.05 mmol, 1.1 eq) and the mixture stirred at that temperature for 1 h. The resulting solution of LDA was then added over 2 min (via syringe) to a solution of **22** (1.58 g, 2.77 mmol, 1.0 eq) in dry THF (4.7 mL) under N_2 at -78 °C. After 10 min, CH_2Cl_2 (7.0 ml) was added dropwise over 4 min and stirring continued for a further 20 min at -78 °C. DMPU (5.5 mL, 45.51 mmol) was then added dropwise over 7 min and stirring continued for 20 min prior to removing the cooling bath and allowing the reaction mixture to warm to room temperature for 20 min. After extractive work-up as described previously for **4**, SiO_2 flash chromatography of the crude reaction mixture with hexanes/EtOAc (gradient elution: 5:1 then 4:1 then 3:1) afforded essentially pure **4** (860 mg, 63%) as a dry foam. Conversion of this material to **13** (without recrystallisation *en route*) and analysis by HPLC on a CHIRALCEL OD column indicated **13** had >96% ee. We also found that if the crude cyclisation mixture (containing mainly **4**) was carried forward to **11**, the overall yield of pure **11** was 500 mg (74%); conversion of crude **4** into **13** without any recrystallisations *en route* also gave **13** with >96% ee.

Part C: Revision and Augmentation of the n-Bu4NI Cyclisation Procedure Reported in Reference 13

Preparation of 6 from 20 Using *n*-Bu$_4$NI as an Additive. LDA was prepared by adding *n*-butyllithium (2.5 M in hexanes, 2.15 mL, 5.38 mmol) over 1 min to *i*-Pr$_2$NH (0.76 mL, 5.39 mmol) in dry THF (1.75 mL) at 0 °C under N_2, and stirring the reactants for 20 min. The LDA solution was then cooled to -78 °C over 10 min, and a solution of bromide **20** (1.7 g, 5.0 mmol) in dry THF (4.25 mL) added dropwise over 8 min. Stirring was continued at -78 °C for 2 h, whereupon a solution of DBAD (1.38 g, 5.99 mmol) in dry CH_2Cl_2 (2.50 mL) was added dropwise over 5 min (ensuring the internal temperature did not rise above -70 °C). After 20 min, *n*-Bu$_4$NI (0.27 g, 0.73 mmol) was added in one portion against a counter-flow of N_2. After a further 5 min at -78 °C, the reaction flask was very quickly transferred to a thermostat-controlled cooling bath at -20 °C. Stirring was continued at -20 °C for a further 18 h. The reaction mixture was then poured into Et_2O (200 mL) layered on top of saturated aq. KH_2PO_4 (150 mL). The two layers were shaken quickly and the aqueous layer removed, and further extracted with Et_2O (100 mL). The combined ethereal layers were then washed quickly with sat. aq. $NaHCO_3$ (50 mL) followed by H_2O (100 mL), and then dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by multiple flash chromatography on SiO_2 with hexanes:Et_2O (2:1 to 1:1) to afford pure **6** (1.36 g, 56%) as a foam {another run on this scale gave 1.27 g (52%) of **6**}. Compound **6** obtained via this method[13] had >96% de.

Electrophilic Hydrazination-Nucleophilic Cyclisation Of 20 To Give 6 With *n*-Bu$_4$NBr As An Additive. To a cooled (-78 °C), stirred, solution of *i*-Pr$_2$NH (0.84 mL, 5.95 mmol) in dry THF (1.75 mL) under N_2 was added *n*-butyllithium (2.5 M solution in hexanes, 2.14 mL, 5.35 mmol) in one portion. The mixture was briefly warmed to 0 °C for 2 min and then recooled to -78 °C for 20 min. To this LDA solution was added dropwise over 4 min a solution of bromide **20** (1.7 g, 5.00 mmol) in dry THF (4.25 mL). After 40 min, a solution of DBAD (1.38 g, 5.99 mmol) in dry CH_2Cl_2 (2.5 mL) was added dropwise over 3 min. Stirring was continued at -78 °C for 20 min prior to a solution of *n*-Bu$_4$NBr (242 mg, 0.75 mmol) in dry CH_2Cl_2 (1 mL) being added over 1 min {N.B. The *n*-Bu$_4$NBr was azeotropically predried by multiple coevaporation from dry C_6H_6 and stored under high vacuum for 3 h prior to use}. The mixture was stirred at -78 °C for 5 min, and then transferred to a cooling bath at -20 °C; stirring was continued at this temperature for a further 18 h. After this time, the reaction mixture was poured into EtOAc (50 mL) and saturated aq. KH_2PO_4 (14 ml). The two layers were briefly shaken, separated, and the organic layer washed successively with sat. aq. $NaHCO_3$ (20 mL), brine (2 x 20 mL), and H_2O (2 x 20 mL). It was then dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by SiO_2 flash chromatography using hexanes/EtOAc (5:1 to 4:1 to 3:1) as eluent to give **6** (1.39 g, 57%) as a foam; d.e. not determined.

Electrophilic Hydrazination-Nucleophilic Cyclisation Of 20 To Give 6 Without Any Additives. To a cooled (-78 °C), stirred, solution of *i*-Pr$_2$NH (0.84 mL, 5.95 mmol) in dry THF (1.75 mL) under N_2 was added *n*-butyllithium (2.5 M solution in hexanes, 2.14 mL, 5.35 mmol) in one portion. The mixture was briefly warmed to 0 °C for 2 min and then recooled to -78 °C for 20 min. To this LDA solution was added a solution of bromide **20** (1.7 g, 5.00 mmol) in dry THF (4.25 mL) dropwise over 4 min. After 40 min, a solution of DBAD (1.38 g, 5.99 mmol) in dry CH_2Cl_2 (2.5 mL) was added dropwise over 3 min. Stirring was

continued at -78 °C for 20 min and the reaction mixture then transferred to a cooling bath at -20 °C; stirring was continued at this temperature for a further 18 h. After this time, the reaction mixture was processed as described for the last experiment to give **6** (1.38 g, 56%) as a foam; d.e. not determined.

Electrophilic Hydrazination-Nucleophilic Cyclisation Of 16 To Give 17 Without Any Additives. To a stirred solution of *i*-Pr_2NH (0.74 mL, 5.24 mmol) in dry THF (8.5 mL) at -78 °C under N_2 was added *n*-butyllithium (2.5 M in hexanes, 2.14 mL, 5.35 mmol) over 1 min. After 50 min at -78 °C, a solution of bromide **16** (1.7 g, 5.00 mmol) in dry THF (8.5 mL) was added dropwise over 3 min, and the mixture stirred for a further 50 min. DBAD (1.38 g, 5.99 mmol) dissolved in dry CH_2Cl_2 (12.8 mL) was then added dropwise over 3 min. After a further 15 min stirring at -78 °C, the cooling bath was removed and the reaction mixture warmed to room temperature. After a further 2 h, the reaction mixture was worked up by Et_2O extraction in the usual way. Trituration of the crude reaction mixture residue with Et_2O-hexanes furnished crystalline **17** (1.52 g, 62%) in two crops; very little **17** remained in the mother liquors according to TLC analysis. Acidification (pH 2) of the aqueous extracts with solid $NaHSO_4$ and multiple extraction with EtOAc, allowed a small quantity (95 mg) of (3*S*)-*N*,*N*'-bis-(*t*-butoxycarbonyl)-hexahydropyridazine-3-carboxylic acid to be isolated, which increased the total yield of the cyclisation to 68%. {Another run on this scale, with trituration, and subsequent chromatographic purification of the mother liquors on SiO_2 remaining after the crystallisation, furnished 1.59 g of **17** (65%)}. We have also performed this cyclisation on the same scale and carried the crude product forward to **19**. Compound **19** was obtained as two crops in 60% overall yield from **16** after recrystallisation; the first crop had an ee of 74%.

Acknowledgements: It is a pleasure to thank the EPSRC for financial support of this programme through project grants GR/G43102 and GR/J92590 and studentships awarded to VMD, TCC (CASE, Pfizer), and NJ. Rohm & Haas (Philadelphia) and Pfizer (Sandwich) are also thanked for their continued financial support of our work, along with the University of London Central Research Fund. We are grateful to Dr Sally Redshaw of Roche Products for supplying us with an authentic sample of (3*S*)-piperazic acid, and to Dr Charles G. Caldwell and Dr Philippe L. Durette of Merck, Sharpe & Dohme (Rahway, NJ) for supplying us with experimental details of their synthesis of (3*RS*)-piperazic acid developed for the total synthesis of L-156,602.[17] We acknowledge very valuable mechanistic discussions with Kevin Dack of Pfizer (Sandwich).

References and Notes

1. Bevan, K.; Davies, J.S.; Hassall, C.H.; Morton, R.B.; Phillips, D.A.S., *J. Chem. Soc. (C)*, **1971**, 514; Hassall, C.H.; Ogihara, Y.; Thomas, W.A., *J. Chem. Soc. (C)*, **1971**, 522.
2. **Azinothricin**: Maehr, H.; Liu, C.-M.; Palleroni, N.J.; Smallheer, J.; Todaro, L.; Williams, T.H.; Blount, J.F., *J. Antibiotics*, **1986**, *39*, 17; **A83586C**: Smitka, T.A.; Deeter, J.B.; Hunt, A.H.; Mertz, F.P.; Ellis, R.M.; Boeck, L.D.; Yao, R.C., *J. Antibiotics*, **1988**, *41*, 726; **Citropeptin**: Nakagawa, M.; Hayakawa, Y.; Furihata, K.; Seto, H., *J. Antibiotics*, **1990**, *43*, 477; Hayakawa, Y.; Nakagawa, M.; Toda, Y.; Seto, H., *Agric. Biol. Chem.*, **1990**, *54*, 1007.
3. Suguwara, K.; Toda, S.; Moriyama, T.; Konishi, M.; Oki, T., *J. Antibiotics*, **1993**, *46*, 928.
4. Grafe, U.; Schlegel, R.; Ritzau, M.; Ihn, W.; Dornberger, K.; Stengel, C.; Fleck, W.F.; Gutsche, W.; Hartle, A., *J. Antibiotics*, **1995**, *48*, 119.
5. Hensens, O.D.; Borris, R.P.; Koupal, L.R.; Caldwell, C.G.; Currie, S.A.; Haidri, A.A.; Homnick, C.F.;

Honeycutt, S.S.; Lindenmayer, S.M.; Schwartz, C.D.; Weissberger, B.A.; Woodruff, H.B.; Zink, D.L.; Zitano, L.; Fieldhouse, J.M.; Rollins, T.; Springer, M.S.; Springer, J.P., *J. Antibiotics*, **1991**, *44*, 249.

6. Ueno, M.; Amemiya, M.; Someno, T.; Masuda, T.; Iinuma, H.; Naganawa, H.; Hamada, M.; Ishizuka, M.; Takeuchi, T., *J. Antibiotics*, **1993**, *46*, 1658.
7. Pettibone, D.J.; Clineschmidt, B.V.; Anderson, P.S.; Freidinger, R.M.; Lundell, G.F.; Koupal, L.R.; Schwartz, C.D.; Williamson, J.M.; Goetz, M.A.; Hensens, O.D.; Liesch, J.M.; Springer, J.P., *Endocrinology*, **1989**, *125*, 217.
8. Ogita, T.; Sato, A.; Enokita, R.; Suzuki, K.; Ishii, M.; Negishi, T.; Okazaki, T.; Tamaki, K.; Tanzawa, K., *J. Antibiotics*, **1992**, *45*, 1723; Tamaki, T.; Ogita, T.; Tanzawa, K.; Sugimura, Y., *Tetrahedron Lett.*, **1993**, *34*, 683; Tamaki, K.; Kurihara, S.; Sugimura, Y. *Tetrahedron Lett.*, **1993**, *34*, 8477.
9. Attwood, M.R.; Francis, R.J.; Hassall, C.H.; Krohn, A.; Lawton, G.; Natoff, I.L.; Nixon, J.S.; Redshaw, S.; Thomas, W.A., *FEBS Lett.*, **1984**, *165*, 201; Attwood, M.R.; Hassall, C.H.; Krohn, A.; Lawton, G.; Redshaw, S., *J. Chem. Soc. Perkin Trans. 1*, **1986**, 1011.
10. Johnston, G.A.R.; Stephanson, A.L.; Twitchin, B., *J. Pharm. Pharmacol.*, **1977**, *29*, 240.
11. Hale, K.J.; Bhatia, G.S.; Peak, S.A.; Manaviazar, S., *Tetrahedron Lett.*, **1993**, *34*, 5343; Hale, K.J.; Delisser, V.M.; Yeh, L.-K.; Peak, S.A.; Manaviazar, S.; Bhatia, G.S., *Tetrahedron Lett.*, **1994**, *35*, 7685; Hale, K.J.; Cai, J.; Manaviazar, S.; Peak, S.A., *Tetrahedron Lett.*, **1995**, *36*, 6965.
12. Hale, K.J.; Delisser, V.M.; Manaviazar, S., *Tetrahedron Lett.*, **1992**, *33*, 7613; Hale, K.J., *Patent Application No. PCT/GB93/02327*; (this patent application has recently been relinquished by UCL so that any commercial organisation is now free to use our method without having to pay a royalty).
13. Decicco, C.P.; Leathers, T., *SYNLETT*, **1995**, 615; *210th ACS Meeting*, Chicago, **1995**, Abstract 205.
14. Evans, D.A.; Britton, T.C.; Dorow, R.L.; Dellaria, J.F., *J. Am. Chem. Soc.*, **1986**, *108*, 6395; Evans, D.A.; Britton, T.C.; Dorow, R.L.; Dellaria, J.F., *Tetrahedron*, **1988**, *44*, 5525.
15. Trimble, L.A.; Vederas, J.C., *J. Am. Chem. Soc.*, **1986**, *108*, 6397.
16. It is not essential to use 26 eq. of DMPU in this experiment; 16.5 eq of DMPU gives identical results.
17. Durette, P.L.; Baker, F.; Barker, P.L.; Boger, J.; Bondy, S.S.; Hammond, M.L.; Lanza, T.J.; Pessolano, A.A.; Caldwell, C.G., *Tetrahedron Lett.*, **1990**, *31*, 1237; *198th ACS Meeting*, Miami Beach, **1989**, Abstracts 118 and 119.
18. Nakamura, Y.; Ito, A.; Shin, C., *Bull. Chem. Soc. Jpn*, **1994**, *67*, 2151; Nakamura, Y.; Shin, C., *Chem. Lett.*, **1991**, 1953.
19. Evans, D.A.; Ennis, M.O.; Mathre, D.J., *J. Am. Chem. Soc.*, **1982**, *104*, 1737.
20. For alternative synthetic strategies to piperazic acid derivatives see: (a) Hassall, C.H.; Johnson, W.H.; Theobald, C.J., *J. Chem. Soc. Perkin Trans.1*, **1979**, 1451; (b) Adams, C.E.; Aguilar, D.; Hertel, S.; Knight, W.H.; Paterson, J., *Synth. Comm.*, **1988**, *18*, 2225; (c) Hughes, P.; Clardy, J., *J. Org. Chem.*, **1989**, *54*, 3260; (d) Aspinall, I.H.; Cowley, P.M.; Mitchell, G.; Stoodley, R.J., *J. Chem. Soc. Chem. Commun.*, **1993**, 1179; (e) Schmidt, U.; Riedl, B., *Synthesis*, **1993**, 809; (f) Rutjes, F.P.J.T.; Teerhuis, N.M.; Hiemstra, H.; Speckamp, W.N., *Tetrahedron*, **1993**, *49*, 8605; (g) Ciufolini, M.A.; Xi, N., *J. Chem. Soc. Chem. Commun.*, **1994**, 1867; (h) see also Ref.18.
21. It was later found more convenient to add the DBAD solution dropwise via syringe without precooling. The latter sometimes caused partial crystallisation of the DBAD. When this occurred during cannulation, more CH_2Cl_2 was added to the remaining residue, and the -78 °C solution cannulated into the reaction mixture.

(*Received in UK* 28 *September* 1995; *revised* 24 *October* 1995; *accepted* 26 *October* 1995)