COMMUNICATION

Convenient synthesis of enantiopure cyclic α-hydroxyalkyl α-amino esters

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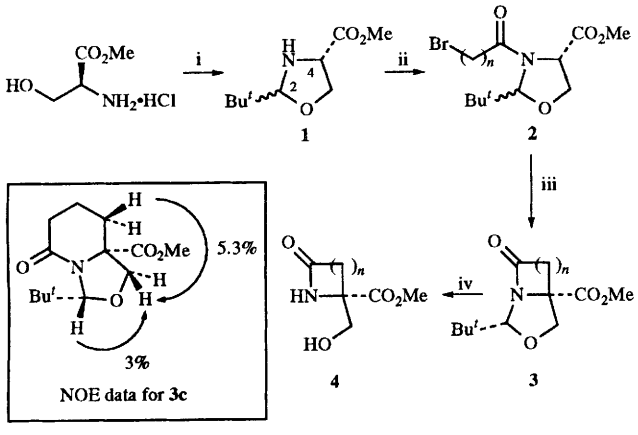
The preparation of cyclic α-hydroxyalkyl α-amino esters, the ring size of which varies varies from 4 to 7 members, in enantiopure form is readily achieved by intramolecular alkylative cyclisation of oxazolidine precursors.

Considerable attention has been given to the synthesis of α,α-disubstituted amino acids because of their ability to modify and control the conformation of peptides.[1–6] Cyclic α-substituted amino acids are of particular interest in this regard, and several methods for their synthesis have been reported.[7–9] We report here that α-hydroxyalkyl cyclic amino acids are readily available by intramolecular alkylation of an oxazolidine constructed in such a way that chiral integrity is maintained during the reaction, using the principles of Seebach's 'self regeneration of chirality'.[10]

The oxazolidine **1** was obtained from L-serine and trimethylacetaldehyde according to the Seebach protocol[1,11] without the need for purification and could be stored at 4 °C for several months without significant decomposition. This compound was readily acylated with several ω-bromo acid chlorides to give the products **2a–e**, in yields in the range 44–97% (Scheme 1 and Table 1).† Consistent with the observations of Seebach, only the *cis*-diastereoisomers of **2** were obtained. In the case of the butanoyl, pentanoyl and hexanoyl derivatives **2c–e** (Scheme 1, $n > 2$), careful exclusion of moisture was required in order to prevent hydrolysis of the ω-bromo function to the alcohol, with subsequent ring closure to generate the corresponding lactone and serine methyl ester. Cyclisation of compounds **2a–d**, by deprotonation at C-4 followed by intramolecular alkylation, under carefully optimised conditions (LDA, DMPU, THF, 0 °C)‡ gave derivatives **3a–d**. Attack by the electrophile on the *Re* face of the C-4 enolate of **2** led to retention of configurations, that is, alkylation *trans*- to the *tert*-butyl substituent, since this keeps the bulky *tert*-butyl group on the least hindered *exo*-face of the bicyclic system. The four- and five-membered ring products **3a,b** were obtained in poorest yield due, in the case of **3b**, to competing elimination to give the corresponding acrylate; the larger 6- and 7-membered ring compounds **3c,d** were obtained in good yield. The relative stereochemistry of **3c** was verified by NOE spectroscopy, and was consistent with the *syn*-relationship of the *tert*-butyl and methoxycarbonyl substituents (see Scheme 1). Larger rings than these, however, could not be obtained using this procedure. This type of construction of cyclic amino acids, by intramolecular alkylation, has not been widely employed previously.[12–14]

This reaction could also be performed on more hindered systems; thus, treatment of the oxazolidine **1** with chloro(phenyl)acetyl chloride gave the product **5a,b** in an 85% yield as a 1:1 mixture of diastereoisomers. These compounds could be readily separated, but the relative stereochemistry of the new chiral centre of the side chain was not assigned. When these compounds **5a,b** were treated with KOBu^t in THF at reflux, the corresponding [3.2.0]bicyclic products **6** and **7** were obtained in good overall yield (Table 2). The relative stereochemistry



Scheme 1 *Reagents:* i, Bu^{t}CHO, Et_3N; ii, $Br(CH_2)_nCOCl$, py; iii, LDA, DMPU, THF; iv, $HS(CH_2)_3SH$, HCl, CF_3CH_2OH or acetone, HCl

Table 1 Yields of the acylated oxazolidine **2**, the cyclic derivatives **3** and the deprotected compounds **4**

Compound	*n*	Yield **2** (%)	Yield **3** (%)	Yield **4** (%)
a	1	96	8 (25[a])	25[b]
b	2	44	19	83
c	3	93	62	75
d	4	93	57	73
e	5	97	0	—

[a] The yield is improved to 25% using KOBu^t–THF at room temperature for 40 h, although this product is contaminated with 7% of recovered starting material which could not be separated by column chromatography. [b] Isolated as the acetate ester.

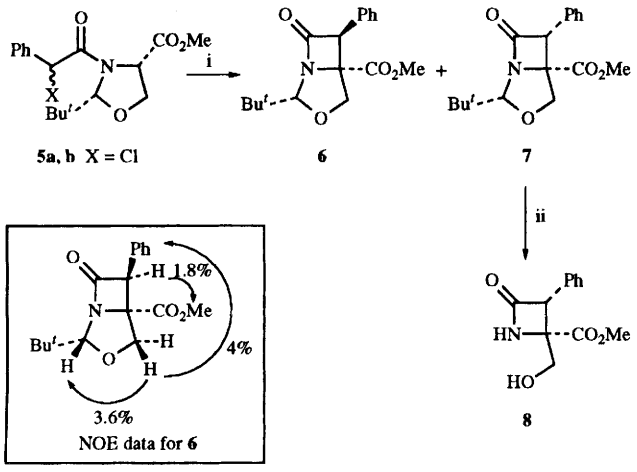
Table 2 Yields of the lactams **6** and **7** from **5a,b**

Oxazolidine	Conditions	Yield **6** (%)	Yield **7** (%)
5a	KOBu^t–THF, reflux, 3 h	42	25
5b	KOBu^t–THF, reflux, 3 h	56	8
5b	KHMDS–THF, 0 °C	46	11

† All new compounds gave satisfactory spectroscopic and analytical data.

‡ LDA = lithium diisopropylamide, DMPU = 1,3-dimethyl-3,4,5,6-tetrahydropyrimidin-2(1*H*)-one, THF = tetrahydrofuran, MTPA = methoxy(trifluoromethyl)phenylacetic acid KHMDS = potassium hexamethyldisilazanide.

of **6** was determined by NOE spectroscopy (Scheme 2). This represents a convenient strategy for the preparation of highly functionalised β-lactams.



Scheme 2 *Reagents:* i, base (see Table 2); ii, $HS(CH_2)_3SH$, HCl, CF_3CH_2OH

Subsequent deprotection using 6 mol dm^{-3} hydrochloric acid–acetone for **3a**, and propanedithiol in acidic trifluoroethanol[15] for **3b–d**, gave the free lactam alcohols **4b–d** in good yield; these adducts were found to be stable to retro-aldol type decomposition. For the deprotection of **3a**, the crude product **4a** resisted all attempts at purification, being particularly sensitive to lactam ring opening. It was, therefore, converted into the corresponding acetate, before purification by column chromatography. The optical integrity of the products **4c,d** was confirmed by conversion into the MTPA derivatives,[16] and NMR analysis indicated that **4c** had an ee of >98%, while **4d** had an ee of >96%. Deprotection of the lactam **7** under the propanedithiol–acidic trifluoroethanol conditions gave the alcohol **8** in 41% yield.

The ease with which the required starting materials can be obtained, and subsequently cyclised, provides a convenient method for the construction of α-hydroxyalkyl amino acids, which can be readily deprotected or, alternatively, should prove to be useful synthetic intermediates for further manipulation. Work to demonstrate further the potential of these compounds is currently underway.

Experimental

The following are sample procedures.

Methyl (2*R*,4*S*)-3-(4′-bromobutanoyl)-2-*tert*-butyloxazolidine-4-carboxylate 2c

To a stirred solution of methyl 2-*tert*-butyloxazolidine-4-carboxylate (0.75 g, 4.0 mmol) and pyridine (0.36 g, 4.6 mmol) in CH_2Cl_2 (10 cm^3), under N_2 at 0 °C, was added dropwise a solution of 4-bromobutanoyl chloride (0.82 g, 4.4 mmol) in CH_2Cl_2 (5 cm^3). The mixture was stirred at 0 °C for 15 min and then at room temperature for 5 h. The reaction mixture was filtered through a silica plug under N_2, the silica then being washed with EtOAc–light petroleum (7:3; 250 cm^3). The combined filtrates were evaporated under reduced pressure with purification of the residue by column chromatography (EtOAc–CH_2Cl_2, 1:9) to give the title compound **2c** as a viscous oil (1.25 g, 93%).

Methyl (3*R*,8a*S*)-9-*tert*-butyl-5-oxohexahydrooxazolo[3,4-*a*]-pyridine-8a-carboxylate 3c

To a solution of diisopropylamine (100 mm^3, 72 mg, 0.71 mmol) and DMPU (0.5 cm^3) in THF (6 cm^3) at 0 °C, under N_2, was added BuLi (2.5 mol dm^{-3}; 0.25 cm^3, 0.63 mmol). The mixture was stirred at 0 °C for 30 min after which a solution of the oxazolidine **2c** (200 mg, 0.59 mmol) in THF (4 cm^3) was added dropwise to it. After 5 h at 0 °C the reaction mixture was partitioned between diethyl ether (40 cm^3) and aq. NH_4Cl (40 cm^3) and the diethyl ether layer was separated, washed with brine (30 cm^3), dried ($MgSO_4$) and evaporated under reduced pressure. Purification of the residue by column chromatography (EtOAc–light petroleum, 3:7) gave the title compound **3c** (94 mg, 62%) as a colourless crystalline solid.

(2*S*)-2-Hydroxymethyl-6-oxopiperidine-2-carboxylate 4c

To a solution of **3c** (115 mg, 0.45 mmol) in acidic trifluoroethanol [1.5% (w/v) HCl; 3 cm^3] was added propane-1,3-dithiol (50 mm^3, 54 mg, 0.50 mmol). The mixture was stirred at room temperature for 20 h and then evaporated under reduced pressure at room temperature. Purification of the residue by column chromatography (EtOAC increasing polarity to EtOAc–MeOH, 9:1) gave the title compound **4c** (63 mg, 75%) as colourless crystals.

References

1 D. Seebach, J. D. Aebi, M. Gander-Coquoz and R. Naef, *Helv. Chim. Acta*, 1987, **70**, 1194.
2 R. M. Williams, *Synthesis of Optically Active α-Amino Acids*, Pergamon, Oxford, 1989, pp. 62–84; R. O. Duthaler, *Tetrahedron*, 1994, **50**, 1539.
3 M. Tabcheh, A. E. Achqar, L. Pappalardo, M.-L. Roumestant and P. Viallefont, *Tetrahedron*, 1991, **47**, 4611.
4 D. Obrecht, U. Bohdal, R. Ruffieux and K. Muller, *Helv. Chim. Acta*, 1994, **77**, 1423.
5 D. H. Hua, N. Lagneau, H. Wang and J. Chen, *Tetrahedron: Asymmetry*, 1995, **6**, 349.
6 F. Alonso and S. G. Davies, *Tetrahedron: Asymmetry*, 1995, **6**, 353.
7 D. Seebach and R. Naef, *Helv. Chim. Acta*, 1981, **64**, 2704.
8 U. Groth, W. Halfbrodt and U. Schöllkopf, *Liebigs Ann. Chem.*, 1992, 351.
9 D. Obrecht, C. Spiegler, P. Schonholzer, K. Muller and H. Heimgartner, *Helv. Chim. Acta*, 1992, **75**, 1666.
10 A. Jeanguenat and D. Seebach, *J. Chem. Soc., Perkin Trans. 1*, 1992, 2291 and references therein.
11 D. Seebach and J. D. Aebi, *Tetrahedron Lett.*, 1984, **25**, 2545.
12 P. Gmeiner, P. L. Feldman, M. Y. Chu-Moyer and H. Rapoport, *J. Org. Chem.*, 1990, **55**, 3068.
13 U. Schöllkopf, R. Hinrichs and R. Lonsky, *Angew. Chem., Int. Ed. Engl.*, 1987, **26**, 143.
14 A. Denicola, C. Einhorn, J. Einhorn and J. L. Luche, *J. Chem. Soc., Chem. Commun.*, 1994, 879.
15 E. J. Corey and G. A. Reichard, *J. Am. Chem. Soc.*, 1992, **114**, 10 677.
16 J. A. Dale and H. S. Mosher, *J. Am. Chem. Soc.*, 1969, **95**, 512.

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