Pergamon

Tetrahedron: *Asymmetry* 12 (2001) 2941–2945

TETRAHEDRON: *ASYMMETRY*

Asymmetric synthesis of a homochiral differentially protected pseudo-*meso* bis-β-amino acid scaffold

Steven D. Bull, Stephen G. Davies* and Andrew D. Smith

The Dyson Perrins Laboratory, University of Oxford, South Parks Road, Oxford OX1 3QY, UK

Received 15 November 2001; accepted 27 November 2001

Abstract—A strategy for the asymmetric synthesis of a homochiral differentially protected pseudo-*meso* bis-β-amino acid scaffold utilising the conjugate addition of homochiral lithium amides and subsequent selective deprotection is demonstrated.

1. Introduction

There has been much recent interest in the β-amino acid structural motif, not only due to its potent pharmacological activity,[1] but also due to the propensity of pseudopeptide sequences containing this functionality to generate novel secondary and tertiary structures.[2] Similarly, advances in the understanding of the factors which promote peptide folding have led to the use of topological templates[3] that constrain the conformational freedom of attached peptides and help to nucleate structural interactions, enabling progress in the area of synthetic protein design.[4] The potential combination of these two concepts led us to prepare a range of C_2 symmetric (*R*,*R*)-bis-β-amino scaffolds as templates for probing the secondary structure of attached α- and β-pseudopeptidic fragments. For example, (*R*,*R*)-bis-β-amino ester **4** can be efficiently prepared in 95% d.e. and >99% e.e. using the double conjugate addition of homochiral lithium (*S*)-*N*-benzyl-*N*-α-methylbenzylamide **2** to bis-functionalised α,β-unsaturated acceptor **1** to furnish (3*R*,α*S*,3′*R*,α′*S*)-**3**, followed by hydrogenolytic debenzylation as described in Fig. 1.[5]

The potential utility of these bis-β-amino acid derivatives could be extended if a flexible approach could be developed that would allow for the unambiguous preparation of not only the (*R*,*R*)- or (*S*,*S*)-diastereoisomers, but also a suitably protected variant of the (*R*,*S*)-*meso* diastereoisomer.[6] A synthetic strategy for the construction of a protected *meso* diastereoisomer **5** is described in Fig. 2 and requires the preparation of α,β-unsaturated ester **6**, which in turn may be constructed via Horner–Wadsworth–Emmons methodology from aldehyde **7**, or via palladium-mediated Heck methodology from the halide **8**.

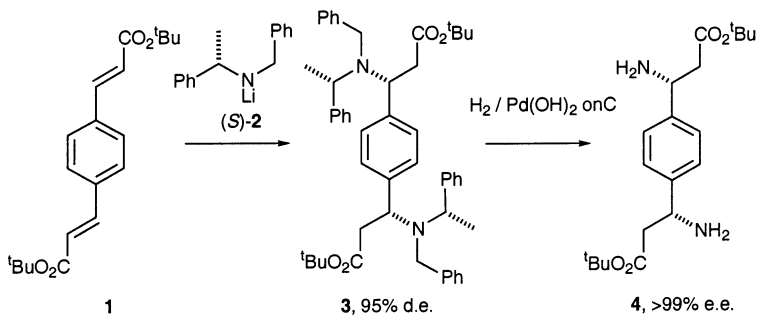


Figure 1.

* Corresponding author. E-mail: steve.davies@chemistry.oxford.ac.uk

0957-4166/01/$ - see front matter
PII: S0957-4166(01)00544-4

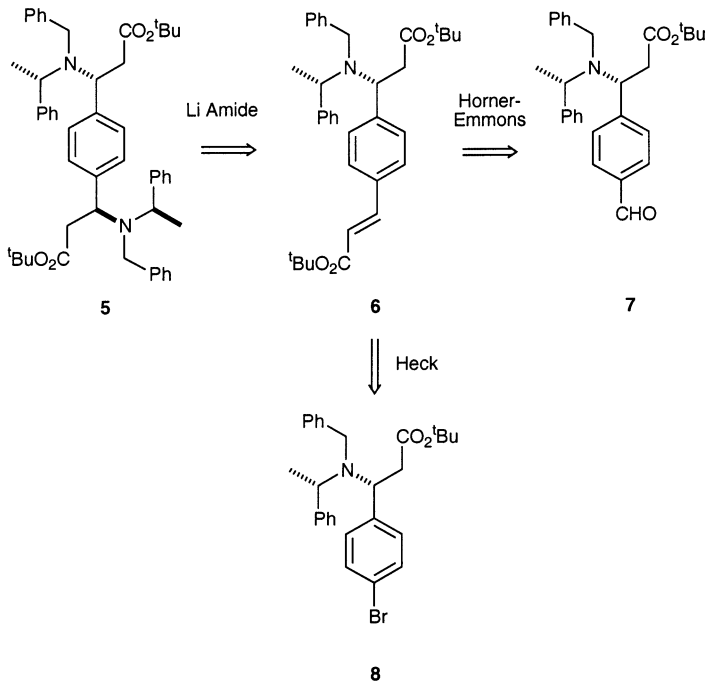


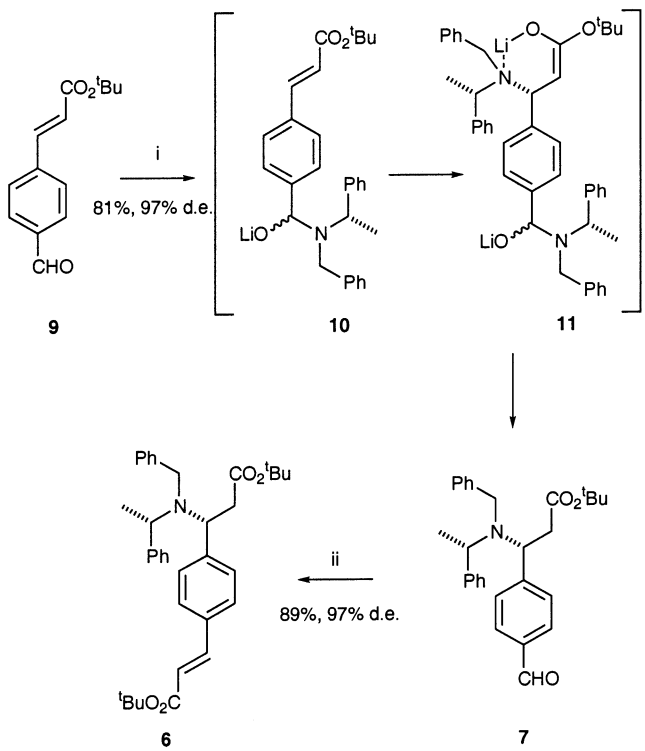
Figure 2.

While the generation of *meso* (*R*,*S*)-**5** itself is of interest, it is not of paramount importance since it would not be possible to elaborate selectively peptide chains onto either the (*R*)- or (*S*)-β-amino acid fragments. Rather it was envisaged that a pseudo-*meso* equivalent of **5**, which by virtue of differential protection would allow selective elaboration, would be the most appropriate target. We now report herein our preliminary results directed toward these aims.

2. Results and discussion

Synthetic investigations into the preparation of *meso*-diamine **5** were initially directed towards the preparation of chiral aldehyde **7**. Our strategy was to use the known propensity of lithium amides to form α-amino alkoxides upon addition to aldehydes,[7] thus acting as an in situ protecting group for the aldehyde, and enabling the α,β-unsaturated ester functionality to undergo an asymmetric conjugate addition reaction. Indeed, addition of an excess of lithium amide (*S*)-**2** to *tert*-butyl 3-(4-formylphenyl)prop-2-enoate[8] **9** proceeded to furnish the required β-amino aldehyde **7** in 97% d.e. and in 81% isolated yield, presumably through intermediate α-amino alkoxides **10** and **11**. Subsequent Horner–Emmons reaction of aldehyde **7** with the lithium anion of *tert*-butyl diethylphosphonoacetate gave α,β-unsaturated acceptor **6** in 97% crude d.e.,[9] and in 89% yield and 97% d.e. after chromatographic purification (Scheme 1).

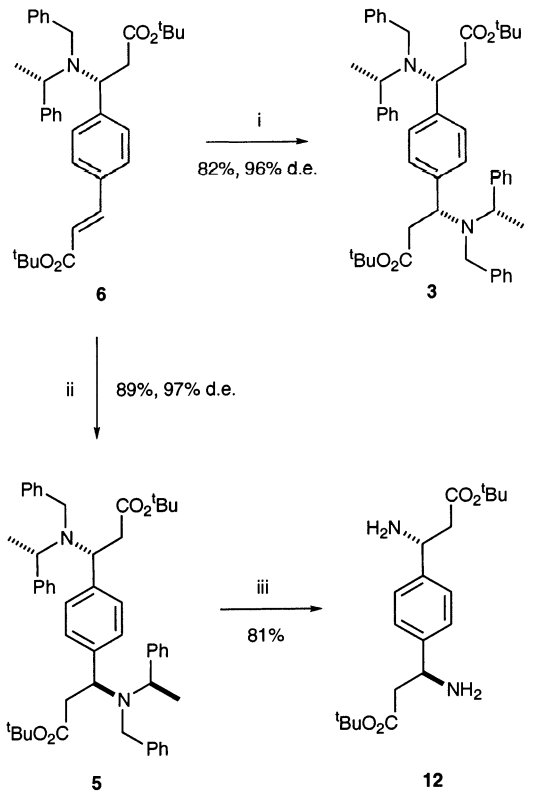
With the synthesis of α,β-unsaturated acceptor **6** in hand, the propensity of either enantiomer of lithium amide **2** toward conjugate addition was evaluated. Thus, addition of lithium amide (*S*)-**2** to α,β-unsaturated acceptor **6** proceeded in 96% crude d.e., furnishing the known C_2 symmetric bis-β-amino ester (3*R*,α*S*,3′*R*,α′*S*)-**3** in 82% yield and in 96% d.e. after purification, with identical spectroscopic properties to that previously reported.[5] Conjugate addition of



Scheme 1. *Reagents and conditions*: (i) (*S*)-**2** (3 equiv.), THF, −78°C then NH_4Cl (aq.); (ii) *tert*-butyl diethylphosphonoacetate (1.15 equiv.), *n*-BuLi (1.1 equiv.), THF, −78°C to rt.

lithium amide (*R*)-**2** to acceptor **6** proceeded in 97% crude d.e., furnishing *meso*-bis-β-amino ester (α*S*,3*R*,α′*R*,3′*S*)-**5** in 89% yield and in 97% d.e. The (α*S*,3*R*,α′*R*,3′*S*) stereochemistry of **5** was assigned by analogy with previous models developed to explain the stereoselectivity observed during addition of lithium amide (*R*)-**2** to α,β-unsaturated acceptors,[10] combined with the number of resonances observed in the ^{1}H and ^{13}C NMR spectra which were consistent with high symmetry, and lack of an observable specific rotation. Subsequent *N*-benzyl deprotection via hydrogenation, a process known to proceed without loss of stereochemical integrity,[5] furnished *meso*-diamine (3*R*,3′*S*)-**12** in 81% yield (Scheme 2).

With synthetic routes in hand for the preparation of either C_2 symmetric (*R*,*R*) or (*S*,*S*) diastereoisomers and (*R*,*S*)-*meso* diastereoisomers of bis-β-amino acid scaffolds, the second generation of β-amino acid templates were designed to allow for the selective functionalisation of either of the nitrogen or acid functionality through protecting group manipulation. This concept has previously been elegantly applied by Mutter et al. for protein de novo design, with Regioselectively Addressable Functionalised Templates (RAFTs) proposed for the preparation of complex protein architectures.[11] For this purpose, the ready availability of lithium *N*-allyl-*N*-α-methylbenzylamide and lithium *N*-benzyl-*N*-α-methylbenzylamide in either enantiomeric form, and the ability to deprotect the *N*-allyl protecting



Scheme 2. *Reagents and conditions*: (i) (*S*)-**2** (3 equiv.), THF, −78°C; (ii) (*R*)-**2** (3 equiv.), THF, −78°C; (iii) $Pd(OH)_2$, MeOH, AcOH, H_2 (5 atm).

group using Wilkinson's catalyst in the presence of *N*-benzyl nitrogen protecting groups[12] seemed ideally suited for differentiation of the nitrogen protecting groups. The relative acid and base lability of *tert*-butyl and *iso*-propyl esters was selected for differentiation of the acid functionality,[13] and so the synthesis of a model pseudo-*meso* diamine **13**, in which the nitrogen or ester functionalities could be selectively deprotected was investigated (Fig. 3).

Having demonstrated that aldehyde **7** is a viable precursor to *meso* (*R*,*S*)-**5**, the ability of bromide **15** to act as a precursor for the synthesis of pseudo-*meso* **13** via a Heck coupling approach was evaluated. Thus, conjugate addition of lithium (*R*)-*N*-benzyl-*N*-α-methylbenzylamide **2** to (*E*)-*iso*-propyl 3-(4-bromophenyl)prop-2-enoate **14** gave β-amino ester (3*S*,α*R*)-**15** in 95% crude d.e., and in 89% yield and in 95% d.e. after purification. Palladium mediated Heck reaction of bromide (3*S*,α*R*)-**15** with *tert*-butyl acrylate gave α,β-unsaturated ester (3*S*,α*R*)-**16** in 89% yield and in 95% d.e after purification. Conjugate addition of lithium (*S*)-*N*-allyl-*N*-α-methylbenzylamide **17** furnished the required pseudo-*meso* scaffold **13** in 95% crude d.e., and in 79% yield and in 95% d.e. after purification (Scheme 3).

As a model system for selective peptide scaffold formation, deallylation of template **13** by treatment with Wilkinson's catalyst gave diamine **18** in 79% yield, leaving the benzylic *N*-protecting groups intact and thereby enabling differentiation between the *N*-substituents. To simulate the formation of a peptide bond, the secondary amine functionality of **18** was protected as its *Z*-carbamate to afford amide **19** in 70% yield. Treatment of amide **19** with formic acid under reflux[14] gave acid **20** in 75% yield, in which differential deprotection of both the ester and *N*-protecting fragments of the pseudo-*meso* diamino template **13** has been achieved (Scheme 4).[15]

In conclusion, the synthesis and selective deprotection of a pseudo-*meso* bis-β-amino acid template using a matrix of protecting groups for the potential attachment of α- and β-pseudopeptidic fragments for secondary structural investigations has been achieved. Further investigations within this area are currently underway.

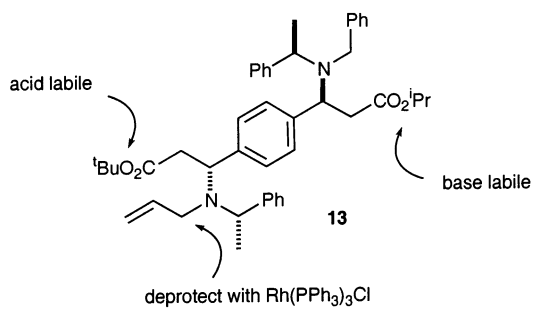
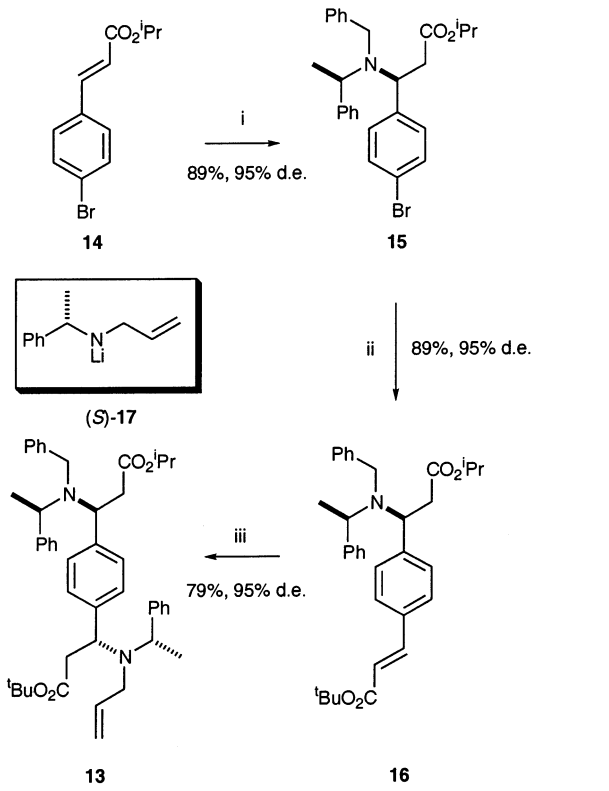
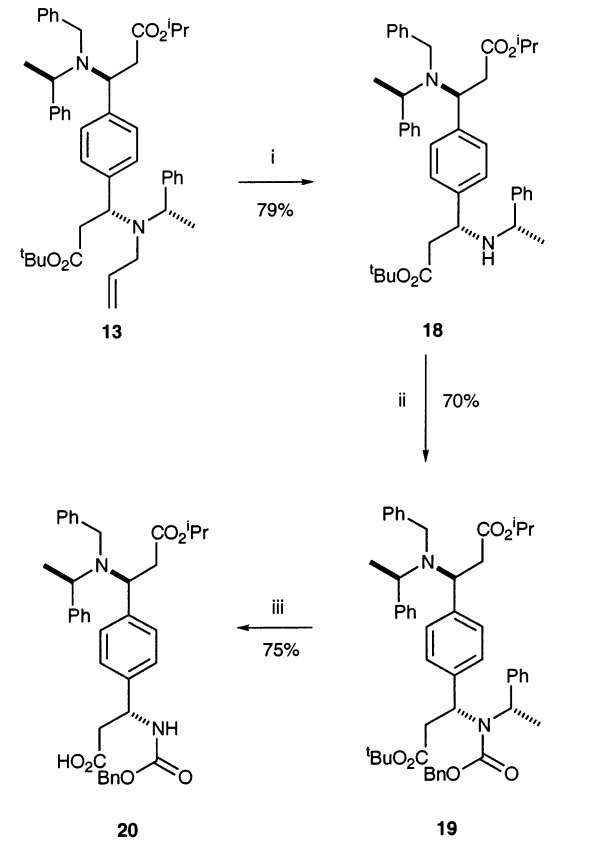


Figure 3.



Scheme 3. *Reagents and conditions*: (i) (*R*)-**2** (1.6 equiv.), THF, −78°C; (ii) NEt_3, *tert*-butyl acrylate, $Pd(OAc)_2$, tri-*o*-tolylphosphine; (iii) (*S*)-**17** (3 equiv.), THF, −78°C.



Scheme 4. *Reagents and conditions*: (i) $Rh(PPh_3)_3Cl$, MeCN:H_2O (8.5:1.5), Δ; (ii) Cbz_2O, vacuum, rt; (iii) HCO_2H, 60°C.

Acknowledgements

The authors wish to acknowledge the support of the EPSRC and Rhône Poulenc Rorer for a CASE Award (A.D.S.) and New College, Oxford for a Junior Research Fellowship (A.D.S.).

References

1. For examples of biologically active β-amino acids, see: (a) Grieco, P. A.; Hon, Y. S.; Perez-Madrano, A. *J. Am. Chem. Soc.* **1988**, *110*, 1630; (b) Morikawa, K.; Morikawa, S.; Nakano, A.; Oseko, F. *Int. J. Immunopharmacol.* **1989**, *11*, 905; (c) Jarstand, C.; Blomgren, H. *J. Clin. Lab. Immunol.* **1982**, *7*, 115.
2. (a) Appella, D. H.; Christianson, L. A.; Klein, D. A.; Powell, D. R.; Huang, X.; Barchi, J. J.; Gellman, S. H. *Nature* **1997**, *387*, 381; (b) Seebach, D.; Matthews, J. L. *J. Chem. Soc., Chem. Commun.* **1997**, 2015; (c) Gellman, S. H. *Acc. Chem. Res.* **1998**, *31*, 173; (d) Seebach, D.; Abele, S.; Gademann, K.; Guichard, G.; Hintermann, T.; Jaun, B.; Matthews, J. L.; Schreiber, J. V.; Oberer, L.; Hommel, U.; Widmer, H. *Helv. Chim. Acta* **1998**, *81*, 932.
3. (a) Mutter, M.; Altmann, E.; Altmann, K.-H.; Hersperger, R.; Koziej, P.; Nebel, K.; Tuchscherer, G.; Vuilleumier, S. *Helv. Chim. Acta* **1988**, *71*, 835; (b) Tuchscherer, G.; Mutter, M. *Pure Appl. Chem.* **1996**, *68*, 2153.
4. (a) Tuchscherer, G.; Dömer, B.; Sila, U.; Kamber, B.; Mutter, M. *Tetrahedron* **1993**, *49*, 3559; (b) Grell, D.; Richardson, J. S.; Mutter, M. *J. Pept. Sci.* **2001**, *7*, 146; (c) Mutter, M.; Tuchscherer, G. *Chimia* **2000**, *54*, 552; (d) Tuchscherer, G.; Grell, D.; Mathieu, M.; Mutter, M. *J. Pept. Res.* **1999**, *54*, 185.
5. Bull, S. D.; Davies, S. G.; Smith, A. D. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2931.
6. For other approaches to both C_2 symmetric, *meso*- and differentially protected diamino diacid derivatives, see: (a) Williams, R. M.; Liu, J. *J. Org. Chem.* **1998**, *63*, 2130; (b) Tanaka, K.; Sawanishi, H. *Tetrahedron: Asymmetry* **2000**, *11*, 3837; (c) Hernandez, N.; Martin, V. S. *J. Org. Chem.* **2001**, *66*, 4934.
7. (a) Comins, D. L. *Synlett* **1992**, 615; (b) Bremand, N.; Mangeney, P.; Normant, J. F. *Tetrahedron Lett.* **2001**, *42*, 1883.
8. Niiya, K.; Thompson, R. D.; Silvia, S. K.; Olsson, R. A. *J. Med. Chem.* **1992**, *35*, 4562.
9. As determined by ^1H NMR spectroscopic analysis of the crude reaction mixture.
10. Costello, J. F.; Davies, S. G.; Ichihara, O. *Tetrahedron: Asymmetry* **1994**, *5*, 3919.
11. (a) Dumy, P.; Eggleston, I. M.; Cervigni, S.; Sila, U.; Sun, X.; Mutter, M. *Tetrahedron Lett.* **1995**, *36*, 1255; (b) Scheibler, L.; Dumy, P.; Stamou, D.; Duschl, C.; Vogel, H.; Mutter, M. *Tetrahedron* **1998**, *39*, 3725; (c) Tuchscherer, G.; Scheibler, L.; Dumy, P.; Mutter, M. *Biopolymers* **1998**, *47*, 63.

12. Fenwick, D. R.; Davies, S. G.; Ichihara, O. *Tetrahedron: Asymmetry* **1997**, *8*, 3387.
13. Greene, T. W.; Wuts, P. G. M. *Protecting Groups In Organic Synthesis*, 3rd ed.; Wiley, 1999.
14. (a) Joullie, M. M.; Wang, P. C.; Semple, J. E. *J. Am. Chem. Soc.* **1980**, *102*, 887; (b) Chen, S. Y.; Joullie, M. M. *J. Org. Chem.* **1984**, *49*, 1769; (c) Semple, J. E.; Wang, P. C.; Lysenko, Z.; Joullie, M. M. *J. Am. Chem. Soc.* **1980**, *102*, 7505.
15. All new compounds were fully characterised.