Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron: Asymmetry
Tetrahedron: *Asymmetry* 15 (2004) 913–916

6-Methyl δ-lactol derived chiral glycine equivalents for the asymmetric synthesis of protected α-amino amides

Darren J. Dixon,[a,*] Richard A. J. Horan[a] and Nathaniel J. T. Monck[b]

[a]*Cambridge University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW, UK*
[b]*Vernalis Research Ltd, Oakdene Court, 613 Reading Road, Winnersh, Wokingham RG41 5UA, UK*

Received 23 December 2003; accepted 23 January 2004

Abstract—Two new δ-lactol derived chiral glycine equivalents have been prepared in one-pot processes in good yields from the known 6-methyltetrahydropyran-2-ol. Alkylation proceeds in moderate to good yields and moderate to good selectivities under experimentally simple conditions. The lactol chiral auxiliary is readily removed under mild acidic conditions to give *N*-Cbz protected alpha-amino amides in good yields.

1. Introduction

The chiral building block has enjoyed a prime position for the facile synthesis of a wide range of desirable multifunctional compounds in their enantio-enriched forms. Amine-containing building blocks have been designed primarily for the synthesis of α-amino acid derivatives. The work of Schöllkopf et al.,[1,2] Williams et al.,[3–5] Seebach et al.,[6–9] Myers and Gleason[10] and Davies et al.,[11] as well as many others,[12–21] employing chiral glycine equivalents,[22] are notable examples.

Our group has also been interested in the development of amine-containing building blocks, targeting not just α-amino acids, but any N-protected α-amino carbonyl compound. The reasoning for this was based on the idea of maximising the synthetic potential of the building block. If suitably protected amino carbonyl compounds (as well as amino acid derivatives) can be accessed rapidly from a building block, then their application towards the synthesis of amino acids, ketones, aldehydes and alcohols should be straightforward.

Placing these requirements on such a tool leads to a series of design implications and constraints that must be addressed. The building block should be available in both enantiomeric forms and readily synthesised on a multigram scale. Its chemistry should be general to a range of analogues. The stereocontrol in the asymmetric reaction should be acceptable and, where it is moderate, the diastereoisomers should be easily separable. Finally, conversion to the N-protected amino carbonyl compounds should be straightforward and efficient using readily prepared or commercially available organometallic reagents.

Herein we report our preliminary studies on the design, synthesis and alkylation of a new building block for the synthesis of N-protected α-amino carbonyl compounds.

2. Results and discussion

We chose to adopt the chiral enolate approach[22] owing to its conceptual simplicity and the availability of myriad alkyl halide electrophiles. Instead of placing chirality at the carboxylate end of the glycine derivative, such as the vast majority of literature examples, we decided to employ a simple carboxylic acid dimethyl amide. The enolates of dimethyl amides are readily prepared in the (*Z*)-form;[23] are highly reactive towards a range of electrophiles and yet are stable to relatively high reaction temperatures. Additionally, dimethyl amides are known to be precursors to aldehydes and ketones through nucleophilic attack of organometallic reagents.[24,25] Accordingly, the stereodirecting group had to be located on the N-terminus and be removable under nonracemising conditions (Fig. 1). We believed that a solution to the N-protecting/stereodirecting group

* Corresponding author. Tel.: +44-0-1223-763-965; fax: +44-0-1223-336-362; e-mail: djd26@cam.ac.uk

0957-4166/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetasy.2004.01.026

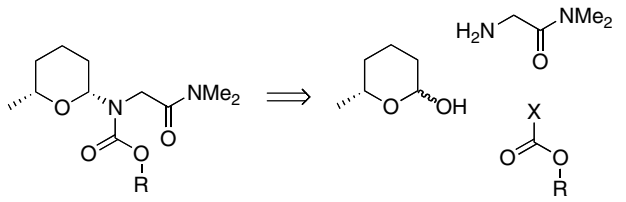
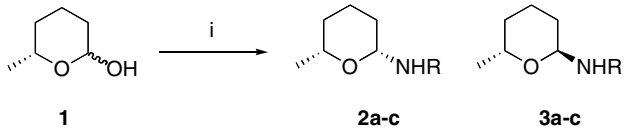


Figure 1. Building block disconnection.

problem was the enantiopure tetrahydropyranyl ring, which could be readily installed through a condensation reaction[26] and removed by mild acid hydrolysis. We have recently reported that the naked alkoxide anions of enantiopure tetrahydropyran-2-ols impart very high levels of stereo- control in oxy-Michael addition reactions.[27] It was hoped that this level of control could also be offered here in enolate alkylation reactions. In the main text the chiral tetrahydropyranyl group will be referred to as THP*.

Critical to the success of the building block is the chiral relay effect initiated by the condensation of the δ-lactol with an amine functionality. Preliminary studies to probe the condensation reaction were carried out using the known (*R*)-6-methyl δ-lactol **1**[28] and a range of glycine derivatives. In all cases the reactions were performed by simply mixing equimolar amounts of the glycine derivatives and the lactol neat at room temperature (Scheme 1, Table 1). Both the ethyl and *tert*-butyl ester of glycine condensed efficiently and with high stereoselectivity towards the 2,6-*cis*-THP* amine products (entries a and b, 24:1 and 28:1, *cis*:*trans*, respectively). A slightly lower diastereoselectivity was observed with glycine dimethyl amide but the reaction maintained its high efficiency (entry c, 7:1, *cis:trans*).

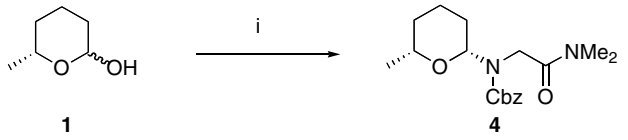


Scheme 1. Reagents and conditions: (i) RNH_2, neat, rt, 1–24 h.

Table 1. Condensation of δ-lactol with amines from Scheme 1

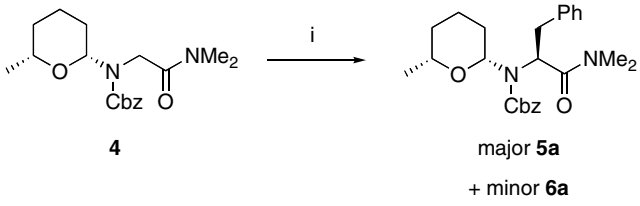
Entry	RNH_2	Ratio **2**:**3**
a	H-Gly-OEt	28:1
b	H-Gly-O^{t}Bu	24:1
c	H-Gly-NMe_2	7:1

These hemiaminal compounds were found to be unstable to chromatography on silica gel, reverting to starting materials under acidic conditions. However, using this key condensation reaction the desired building block **4** could be constructed in three steps and one pot by treating (*R*)-6-methyl δ-lactol with neat glycine dimethyl amide (1.2 equiv) at room temperature for 16 h, then reacting an ethereal solution of the crude product with CbzCl in the presence of aqueous Na_2CO_3 under biphasic conditions. Any excess CbzCl was scavenged using glycine and purification by chromatography on silica gel afforded the desired product **4** as a single diastereoisomer in 71% yield over the three steps (Scheme 2).



Scheme 2. Reagents and conditions: (i) (a) H-Gly-NMe_2, neat, rt, 3 h; (b) Cbz-Cl, Na_2CO_3, Et_2O/H_2O, 0 °C to rt, 3 h; (c) glycine, rt, 16 h, 71%.

With multigram quantities of **4** in hand, a preliminary screening of the lithium, sodium and potassium enolates and their reactions with benzyl bromide in various solvents was performed (Scheme 3, Table 2). The optimal selectivity was observed when the sodium enolate in THF, formed by treatment of **4** with NaHMDS (1.05 equiv), was reacted with benzyl bromide at −78 °C, then with slow warming to room temperature. In this case, the separable diastereoisomers **5a** and **6a** were formed in the ratio of 10:1 and with a combined yield of 86% (entry h).



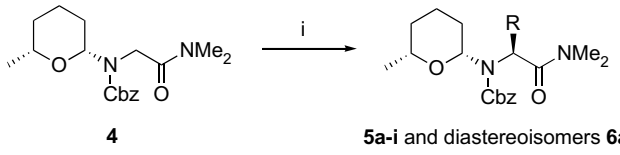
Scheme 3. Reagents and conditions: (i) (a) base, solvent, −78 °C, 30 min; (b) BnBr, −78 °C to rt.

Table 2. Screening of conditions for building block alkylation with benzyl bromide

Entry	Base	Solvent	Yield (%)[a]	Ratio **5a**:**6a**[b,c]
a	LiHMDS	PhMe	34	2.2:1
b	KHMDS	PhMe	42	3.1:1
c	NaHMDS	Dioxane	30	4.8:1
d	KHMDS	Dioxane	34	5.4:1
e	NaHMDS	Et_2O	38	3.6:1
f	KHMDS	Et_2O	57	3.5:1
g	LiHMDS	THF	86	4.3:1
h	NaHMDS	THF	86	10:1
i	KHMDS	THF	30	6.1:1
j	LiHMDS	DME	5	1.9:1
k	NaHMDS	DME	26	3.6:1
l	KHMDS	DME	38	4.8:1

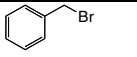
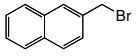
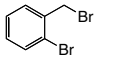
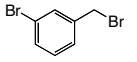
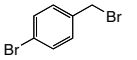
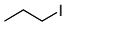
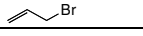
[a] Isolated yield **5a** and **6a** after column chromatography.
[b] From crude ^{1}H NMR.
[c] Stereochemistry of **6a** determined by chemical correlation and comparison of specific rotations.

Although the selectivity with benzyl bromide was not outstanding, the high chemical yield and the option to separate diastereoisomers encouraged us to screen further electrophiles to gauge the scope of the methodology. Accordingly, a range of aryl bromomethyl derivatives was reacted with the sodium enolate under the optimal conditions, and the results are given below (Scheme 4, Table 3, entries a–e).



Scheme 4. Reagents and conditions: (i) (a) NaHMDS, THF, −78 °C, 30 min; (b) RX, −78 °C to rt.

Table 3. Alkylation of **4**

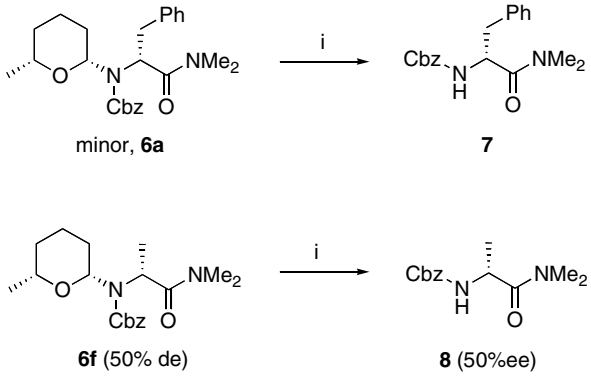
Entry	RX	Yield (%)[a]	Ratio **5**:**6**[b,c]
a		86	10:1
b		80	4.1:1
c		62	7.8:1
d		59	3.5:1
e		51	2.4:1
f		71	1:4.0
g		36	1:2.1
h		29	1:2.4
i		59	2.1:1

[a] Isolated yield **5** and **6** after column chromatography.
[b] From crude ^{1}H NMR.
[c] Stereochemistries were assigned by analogy with the benzyl bromide case and are supported by the relative positions of the ^{1}H NMR signals for the methine proton of the major and minor diastereoisomers.

Surprisingly, the diastereoselectivities for these alkylation reactions varied considerably throughout the series with the optimal case being for benzyl bromide. Notable is the series of *ortho*-, *meta*- and *para*-bromo benzyl bromide derivatives (Table 3, entries c–e) where the observed selectivities are 7.8:1, 3.5:1 and 2.4:1, respectively. While there is some steric effect on the favoured transition states, clearly the diastereoselectivity of the enolate alkylation is not solely dependent on steric factors.

More surprises were revealed when nonaryl electrophiles were reacted with the sodium enolate (entries f–i). With methyl, ethyl and *n*-propyl iodides, moderate diastereoselectivities were observed. However the stereofacial bias was reversed and products of attack at the *Re* face were found to dominate in the reaction mixtures. On the other hand, the reaction with allyl bromide gave the same facial selectivity as that observed with the aryl electrophiles.

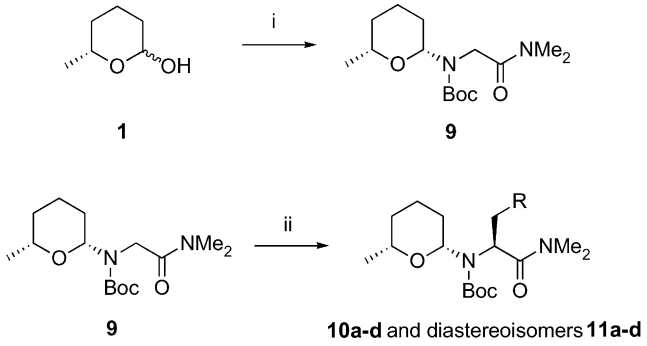
The absolute stereochemistry of the benzylated and methylated products was determined by THP* removal and comparison of the specific rotation {**7** $[\alpha]_D^{25} = -35.0$ (*c* 0.26, $CHCl_3$); **8** (50% ee) $[\alpha]_D^{25} = -6.4$ (*c* 0.405, $CHCl_3$)} with material prepared from commercial sources {ent-**7** $[\alpha]_D^{25} = +35.4$ (*c* 1.326, $CHCl_3$); ent-**8** $[\alpha]_D^{25} = +17.8$ (*c* 1.164, $CHCl_3$)} (Scheme 5).



Scheme 5. Reagents and conditions: (i) TFA/H_2O (9:1), rt, 24 h; **7** quant; **8** 83%.

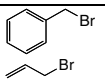
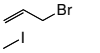
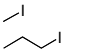
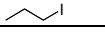
The variation in selectivity with the arylmethyl bromides and the reversal in facial selectivity with nonaryl alkyl halides suggested that the *N*-Cbz group was playing an active role in determining the stereochemical outcome of the reactions. In order to probe this possibility further the *N*-Boc derivative **9** was prepared in an analogous manner to **4** above and alkylated with a range of electrophiles using the sodium enolate (Scheme 6, Table 4).

As can be seen from the results in Table 4, alkylation follows a similar pattern to the *N*-Cbz building block but with increased selectivity for alkylation of the *Re* face. Assuming the (*Z*)-enolate reacts via a seven ring chelate to the ring oxygen, the metal cation, with its associated coordinated solvent molecules, appears to block the approach to the *Si* face of the enolate with



Scheme 6. Reagents and conditions: (i) (a) H-Gly-NMe_2, neat, rt, 16 h; (b) Boc_2O, DCM, 0 °C to rt, 24 h, 57% (two steps); (ii) (a) NaHMDS, THF, −78 °C, 30 min; (b) RX, −78 °C to rt.

Table 4. Alkylation of **9**

Entry	RX	Yield (%)[a]	Ratio **10**:**11**[b,c]
a		42	3.2:1
b		64	1:1.3
c		43	1:35[d]
d		22	1:7.4

[a] Isolated yield **10** and **11** after column chromatography.
[b] From crude ^{1}H NMR.
[c] Stereochemistries were assigned by analogy with the previous cases and are supported by the relative positions of the ^{1}H NMR signals for the methine proton of the major and minor diastereoisomers.
[d] Stereochemistry determined by X-ray crystallography.

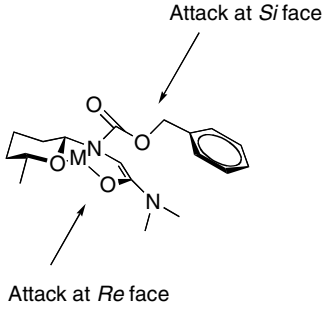


Figure 2.

saturated alkyl halides. However, with unsaturated derivatives, pre-coordination of the unsaturated system appears to assist delivery to the *Si* face. This could be through secondary π-cation interactions[29] between the electrophile and the cation in the transition state. In the Boc building block, the increased steric bulk of the *tert*-butyl group will disrupt any π-cation interactions while blocking the *Si* face to a greater extent and hence increasing the selectivity for alkylation at the *Re* face. As the amount of π-cation stabilisation will depend on the nature and substituents of the π system, some validity is given to this model by the variations noted above (Fig. 2).

3. Conclusion

In conclusion, a new chiral building block for the synthesis of α-amino carbonyl compounds has been developed. Facially selective enolate alkylation reactions are used to create a new stereogenic centre. Although the selectivities are not yet optimal, in most cases the diastereomeric products can be separated. Further optimisation of the system and its application to natural product synthesis, as well as an enhanced understanding of the curious reversal of selectivity in the alkylation with aryl or nonaryl electrophiles, will be reported in due course.

Acknowledgements

We thank Vernalis for a studentship (to RAJH), the National Mass Spectrometry Service at Swansea for HRMS and Prof. Steven V. Ley for continued and valued support.

References and notes

1. Schöllkopf, U.; Groth, U.; Deng, C. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 798–799.
2. Pettig, D.; Schöllkopf, U. *Synthesis* **1988**, 173–175.
3. Williams, R. M.; Sinclair, P. J.; Zhai, D.; Chen, D. *J. Am. Chem. Soc.* **1988**, *110*, 1547–1557.
4. Williams, R. M.; Im, M.-N. *Tetrahedron Lett.* **1988**, *29*, 6075–6078.
5. Williams, R. M.; Im, M.-N. *J. Am. Chem. Soc.* **1991**, *113*, 9276–9286.
6. Seebach, D.; Juaristi, E.; Miller, D. D.; Schickli, C.; Weber, T. *Helv. Chim. Acta* **1987**, *70*, 237–261.
7. Fitzi, R.; Seebach, D. *Tetrahedron* **1988**, *44*, 5277–5292.
8. Seebach, D.; Gees, T.; Schuler, F. *Liebigs Ann. Chem.* **1993**, 785–799.
9. Studer, A.; Seebach, D. *Liebigs Ann. Chem.* **1995**, 217–222.
10. Myers, A. G.; Gleason, J. L. *Org. Syn.* **1999**, *76*, 57–76.
11. Bull, S. D.; Davies, S. G.; Epstein, S. W.; Leech, M. A.; Ouzman, J. V. A. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2321–2330.
12. Review: Duthaler, R. O. *Tetrahedron* **1994**, *50*, 1539–1650.
13. Review: Hegedus, L. *Acc. Chem. Res.* **1995**, *28*, 299–305.
14. Review: Bloch, R. *Chem. Rev.* **1998**, *98*, 1407–1438.
15. Review: Calmes, M.; Daunis, J. *Amino Acids* **1999**, *16*, 215–250, and references cited therein.
16. Liu, W.-Q.; Roques, B. P.; Garbay-Jaureguiberry, C. *Tetrahedron: Asymmetry* **1995**, *6*, 647–650.
17. Josien, H.; Martin, A.; Chassaing, G. *Tetrahedron Lett.* **1991**, *32*, 6547–6550.
18. Chinchilla, R.; Falvello, L. R.; Galindo, N.; Nájera, C. *J. Org. Chem.* **2000**, *65*, 3034–3041.
19. Tanaka, K.; Ahn, M.; Watanabe, Y.; Fuji, K. *Tetrahedron: Asymmetry* **1996**, *7*, 1771–1782.
20. Iwanowicz, E. J.; Blomgren, P.; Cheng, P. T. W.; Smith, K.; Lau, W. F.; Pan, Y. Y.; Gu, H. H.; Malley, M. F.; Gougoutas, J. Z. *Synlett* **1998**, 664–666.
21. Dixon, D. J.; Harding, C. I.; Ley, S. V.; Tilbrook, D. M. G. *Chem. Commun.* **2003**, 468–469.
22. For a discussion of the different approaches to the synthesis of α-amino acids see: Williams, R. M. *Synthesis of Optically Active α-Amino Acids*; Pergamon: Oxford, 1989.
23. Evans, D. A.; Takacs, J. M. *Tetrahedron Lett.* **1980**, *21*, 4233–4236.
24. Brown, H. C.; Tsukamoto, A. *J. Am. Chem. Soc.* **1964**, *86*, 1089–1095.
25. Nájera, C.; Abellán, T.; Sansano, J. M. *Eur. J. Org. Chem.* **2000**, 2809–2820.
26. Noe, C. R.; Knollmüller, M.; Steinbauer, G.; Jangg, E.; Völlenkle, H. *Chem. Ber.* **1988**, *121*, 1231–1239.
27. Adderley, N. J.; Buchanan, D. J.; Dixon, D. J.; Lainé, D. I. *Angew. Chem., Int. Ed.* **2003**, *42*, 4241–4244.
28. Dixon, D. J.; Ley, S. V.; Tate, E. W. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2385–2394.
29. Ma, J. C.; Dougherty, D. A. *Chem. Rev.* **1997**, *97*, 1303–1324.