Pergamon

Tetrahedron Letters 41 (2000) 5963–5966

TETRAHEDRON LETTERS

syn-Selective boron mediated aldol condensations for the asymmetric synthesis of β-hydroxy-α-amino acids

S. Caddick,[a,*] N. J. Parr[a] and M. C. Pritchard[b]

[a]*Centre for Biomolecular Design and Drug Development, School of Chemistry, Physics and Environmental Sciences, University of Sussex, Falmer, Brighton BN1 9QJ, UK*
[b]*Parke-Davis NRC, Forvie Site, Robinsons Way, Cambridge CB2 2QB, UK*

Received 23 March 2000; accepted 4 May 2000

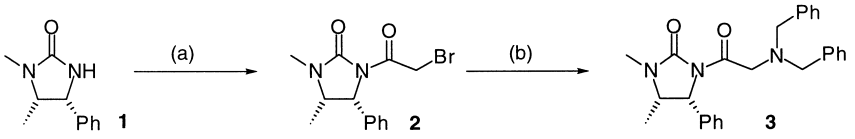
Abstract

Imidazolidinone-bound glycine enolate derivatives have been shown to undergo aldol condensation with aromatic and aliphatic aldehydes in good yields and with excellent stereocontrol (62–84%, 93–95% d.e.). Removal of the pendant imidazolidinone auxiliary and hydrogenolysis affords the β-hydroxy-α-amino acid derivatives.

Keywords: aldol; β-hydroxy-α-amino acids; glycine enolates; boron; imidazolidinone; asymmetric synthesis.

α-Amino-β-hydroxyacid derivatives have been shown to act effectively in enzymatic inhibition[1] and are important precursors to many β-lactam antibiotics.[2] Reports in the literature for the formation of these compounds have focused primarily on racemic syntheses,[3] with only a few reports addressing the enantioselective preparation of the *anti*- and *syn*-aldol diastereomers.[4] Herein we wish to report boron-mediated aldol condensations of a dibenzylated glycine enolate derivative for the enantioselective preparation of *syn* β-hydroxy-α-amino acids.[5]

The protected glycine template (**3**) was prepared from the commercially available imidazolidinone (**1**) via acylation to the α-bromo-amide (**2**), followed by nucleophilic displacement with dibenzylamine (Scheme 1).

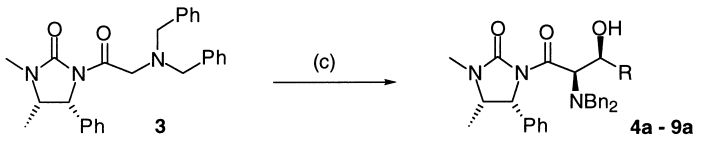


Scheme 1. Reagents and conditions: (a) $BrCOCH_2Br$, 2,6-lutidine, –30°C, CH_2Cl_2, 99%; (b) $(PhCH_2)_2NH$, THF, 74%

* Corresponding author.

0040-4039/00/$ - see front matter
PII: S0040-4039(00)00734-6

The 9-BBN vinyloxyborane of (**3**) reacts in a highly diastereoselective fashion with aromatic and aliphatic aldehydes to produce the *syn*-aldol derivatives (**4a**–**9a**) (Scheme 2). Selected results obtained for the aldol condensation with the chiral glycine derivative (**3**) and a range of aldehydes is provided in Table 1.



Scheme 2. Reagents and conditions: (c) 9-BBNOTf, Et_3N, CH_2Cl_2, 0°C, 1 h, then RCHO, 2 h, pH7 (phosphate buffer), MeOH, H_2O_2 (aq), 0°C, 1h.

Table 1
Aldol products derived from (**3**)

Aldehyde	Product	Yield (%)	*2'R3'S:2'S3'R:*Others a : b : c	Diastereomeric Excess (%)
Benzaldehyde	**4a**	**84**	**1 :0: 0**	**>95**
4-Methoxybenzaldehyde	**5a, b**	**66**	**32: 1: 0**	**94**
4-Fluorobenzaldehyde	**6a**	**62**	**1: 0: 0**	**>95**
4-Nitrobenzaldehyde	**7a**	**72**	**1: 0: 0**	**>95**
Butyraldehyde	**8a**	**69**	**1: 0: 0**	**>95**
2-Furaldehyde	**9a, b**	**65**	**94:6: 0**	**88**

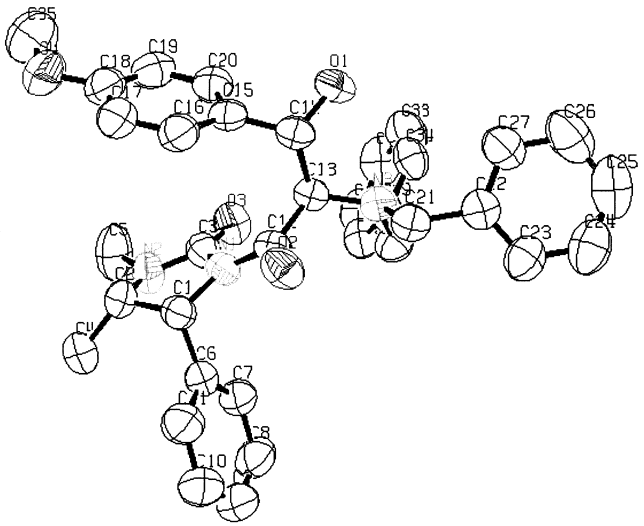


Figure 1. Molecular structure of **5a**, 2′(*R*), 3′(*S*)

Absolute stereochemical assignments are made on the analogous ^{1}H NMR chemical shifts and coupling constants[6] of H2′ and H3′ to the 4″-methoxy derivatives (**5a**) and (**5b**) both having been confirmed by X-ray crystal data (Figs. 1 and 2).

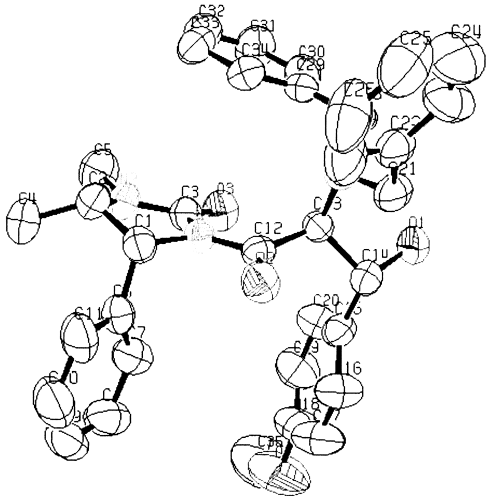


Figure 2. Molecular structure of **5b**, 2′(*S*), 3′(*R*)

Assuming (*Z*)-boron enolate generation under the reaction conditions, the stereoselectivity observed for the 9-BBN enolates can be explained by invoking a chair-like transition state. The chiral auxiliary adopts a conformation in which the dipole–dipole repulsion between the two oxygen atoms of the enolate is minimized, thus hindering approach of the aldehyde from the α-face (Fig. 3).[7]

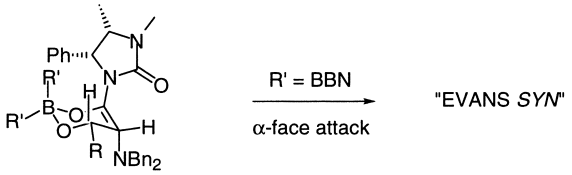
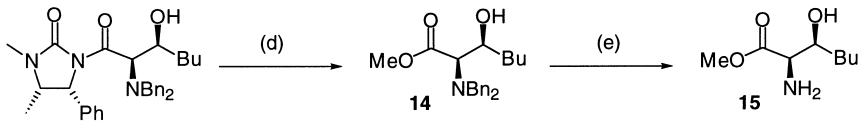


Figure 3.

Removal of the imidazolidinone auxiliary,[8] exemplified in the formation of (**14**), followed by hydrogenation using Pearlmanns catalyst[9] afforded the corresponding β-hydroxy-α-amino acid derivative (**15**) in high yield, with no observed epimerization (Scheme 3).[10]



Scheme 3. Reagents and conditions: (d) NaOMe, MeOH, 77%; (e) $Pd(OH)_2/C$, H_2, MeOH, 96%

In conclusion, the imidazolidinone derivative (**3**) offers a new and practical chiral glycine enolate equivalent. The simplicity of the experimental procedures, the excellent levels of optical purity obtained and the uniformity of the chemical yields make this an attractive procedure for the preparation of β-hydroxy-α-amino acid derivatives.

Acknowledgements

We thank the EPSRC and Parke-Davis for financial support. We also thank GlaxoWellcome, AstraZeneca, and SmithKline Beecham for additional support. We gratefully acknowledge the contributions of the EPSRC mass spectrometry service, Swansea (UK), Dr. P. B. Hitchcock, Dr. A. Abdul-Sada and Dr. A. G. Avent (Sussex).

References

1. Nakasuka, T.; Miwa, T.; Mukaiyama, T. *Chem. Lett*. **1981**, 279. Nakasuka, T.; Miwa, T.; Mukaiyama, T. *Chem. Lett*. **1982**, 145.
2. Sykes, R. B. *Nature* **1981**, *19*, 49. Cimarusti, C. M.; Sykes, R. B. *Chem. In Brit*. **1983**, 302; Miller, M. J. *Acc. Chem. Res*. **1986**, *19*, 49.
3. Shanzer, A.; Somekh, L.; Butina, B. *J. Org. Chem*. **1979**, *44*, 3967. Guanti, G.; Banfi, L.; Narisano, E.; Scolastico, C. *Tetrahedron Lett*. **1984**, *25*, 4693. Gunati, G.; Banfi, L.; Narisano, E. *Tetrahedron Lett*. **1985**, *26*, 3517. Guanti, G.; Banfi, L.; Narisano, E.; Scolastico, C. *Tetrahedron* **1988**, *44*, 3671. Grandel, R.; Kazmaier, U.; Nuber, B. *Liebigs Ann*. **1996**, 1143. Kazmaier, U.; Grandel, R. *J. Org. Chem*. **1998**, 409. Kazmaier, U.; Grandel, R. *J. Org. Chem*. **1998**, 1833.
4. Evans, D. A.; Weber, A. E. *J. Am. Chem. Soc*. **1986**, *108*, 6757. Bold, G.; Duthaler, R. O.; Riediker, M. *Angew. Chem., Int. Ed. Engl*. **1989**, *28*, 497. Alker, D.; Hamblett, G.; Harwood, L. M.; Robertson, S.; Watkin, D. J.; Williams, D. J. *Tetrahedron* **1998**, *54*, 6089. Righi, G.; Rumboldt, G.; Bonini, C. *Tetrahedron* **1995**, *51*, 13401. Iwanowicz, E. J.; Blomgren, P.; Cheng, P. T. W.; Smith, K.; Lau, W. F.; Pan, Y. Y.; Gu, H. H.; Malloy, M. F.; Gougoutas, J. Z. *Synlett*. **1998**, 664. Grandel, R.; Kazmaier, U. *Eur. J. Org. Chem*. **1998**, 409.
5. For recent related α-amino-acid syntheses, see: Guillena, G.; Najera, C. *Tetrahedron: Asymmetry* **1998**, *9*, 3935. Cardillo, G.; Gentilucci, L.; Tolomelli, A.; Tomasini, C. *Tetrahedron Lett*. **1997**, *38*, 6953. Myers, A. G.; Gleason, J. L. *Org. Synth*. **1999**, *76*, 57.
6. Heathcock, C. H.; Pirrung, M. C.; Sohn, J. E. *J. Org. Chem*. **1979**, *44*, 4294.
7. Drewes, S. E.; Malissar, D. G. S.; Roos, G. H. P. *Chem. Ber*. **1993**, *126*, 2663, and references cited therein.
8. Kubo, A.; Kubota, H.; Takahashi, M.; Nunami, K. *J. Org. Chem*. **1997**, *62*, 5830.
9. Laib, T.; Chastanet, J.; Zhu, J. *J. Org. Chem*. **1998**, *63*, 1709.
10. All compounds gave spectroscopic data and microanalyses or high resolution mass spectra consistent with their structures.