Pergamon

Tetrahedron Letters 40 (1999) 1229–1232

TETRAHEDRON LETTERS

Convenient *in Situ* Synthesis of Nonracemic *N*-protected β-Amino Aldehydes from β-Amino Acids. Applications in Wittig Reactions and Heterocycle Synthesis

Simon B. Davies and M. Anthony McKervey *

School of Chemistry, The Queen's University, Belfast, BT9 5AG, N. Ireland

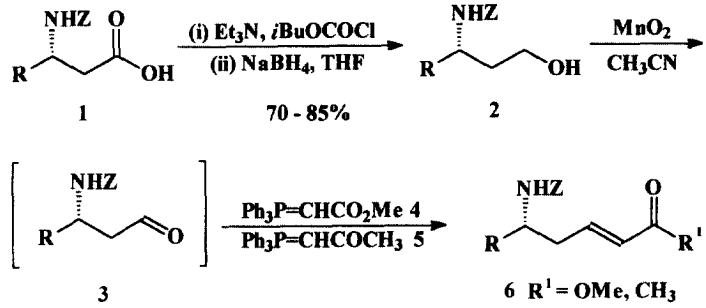
Received 5 November 1998; accepted 30 November 1998

Abstract: *N*-Z-γ-amino alcohols derived from nonracemic β-amino acids are smoothly oxidised by manganese dioxide in acetonitrile to afford aldehydes which can be trapped *in situ* in Wittig reactions with carbonyl-substituted phosphoranes. The application of this methodology to the synthesis of the alkaloids (*S*)-(+)-*N*-BOC-coniine, (*S*)-(-)-coniceine and a pipecoline precursor is described. © 1999 Published by Elsevier Science Ltd. All rights reserved.

Several recent publications have highlighted the advantages of generating reactive aldehydes *in situ* for use in Wittig reactions. Wei and Taylor[1] employed manganese dioxide to oxidise allylic, benzylic and propargylic alcohols to aldehydes in the presence of carbonyl-stabilised Wittig reagents. With similar objectives, Matsuda and co-workers[2] used the combination of barium permanganate and $Ph_3P{=}CHCO_2Et$ to transform allylic alcohols into dienyl esters. There are also examples of the use of Swern[3] and Dess Martin[4] oxidation in related one-pot procedures. The application of this approach to the preparation and *in situ* elaboration of β-amino aldehydes derived from β-amino acids has not been described. In fact, β-amino aldehydes have been little used as reaction intermediates in amino acid modification which may reflect in part the lack of general methods for their preparation,[5,6] unlike α-amino aldehydes whose use in synthesis is widespread and for which several reliable methods of synthesis are available. In both the α- and β-amino aldehyde series *N*-protection is essential if extensive self condensation is to be avoided. In view of the potential of β-amino aldehydes in synthesis and the recent publication of Davis et al.[7] describing the Horner-Wadsworth-Emmons reaction of enantiopure *N*-protected β-amino aldehydes derived from sulfinimines *via* asymmetric synthesis, we wish to report preliminary results on the *in situ* generation of *N*-protected β-amino aldehydes **3** from enantiopure amino alcohols and their reactions with carbonyl stabilised Wittig reagents. We also illustrate the use of the homologated derivatives in heterocycle synthesis.

The *N*-protected γ-amino alcohols **2** (Table 1) required as precursors were all prepared from the corresponding β-amino acids **1** by sodium borohydride reduction (Scheme 1) of the mixed anhydrides generated *in situ* by reaction with isobutyl chloroformate in tetrahydrofuran.[8] The β-amino acids, in turn, were obtained from their L-α-amino acid counterparts *via* diazoketones and the Arndt-Eistert synthesis, a well documented process known not to cause racemisation.[9] In all the transformations described here benzyloxycarbonyl (Z) was employed as the *N*-protecting group so as to allow for hydrogenolytic release of the free amino group for subsequent reactions (*vide infra*); alternative forms of *N*-protection, e.g. with BOC or ethoxycarbonyl, were equally applicable in the sequence in Scheme 1.

PII: S0040-4039(98)02573-8



1 2 3 6 R^1 = OMe, CH_3

Scheme 1

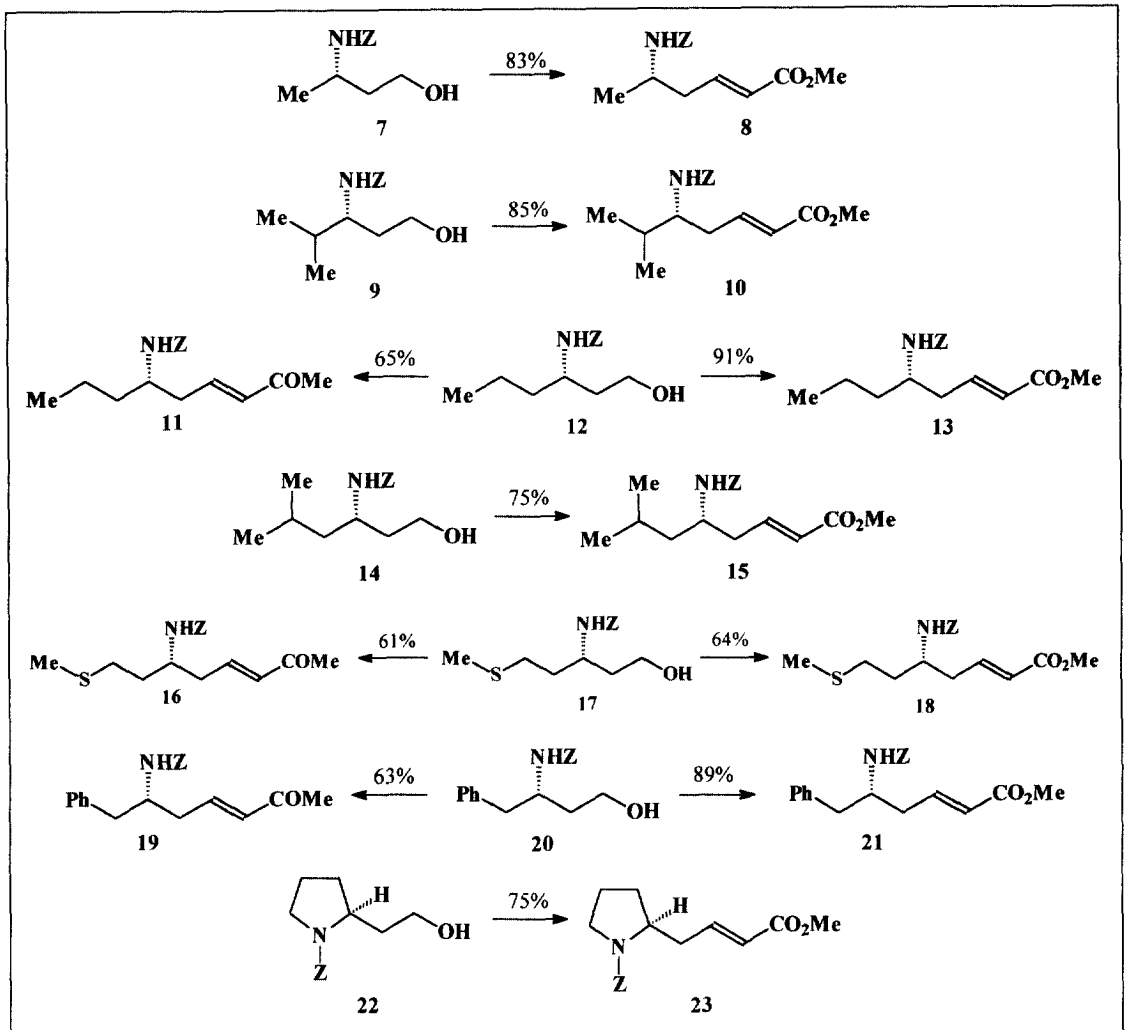
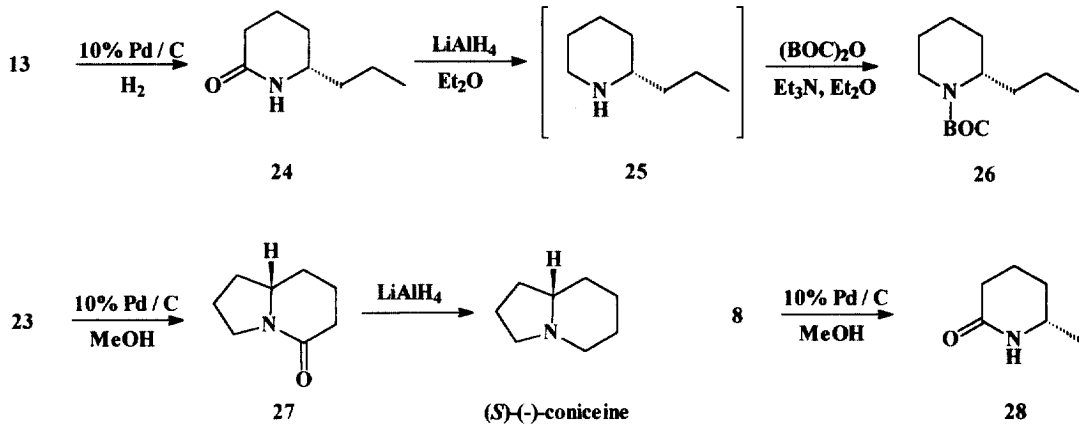


Table 1*

* Yields based on product isolated by chromatography; products represented as their favoured *trans* isomer.

The results summarised in Table 1 were obtained by addition of manganese dioxide (25 equiv.) to a solution of the *N*-protected γ-amino alcohol (1 equiv.) and the phosphorane **4** or **5** (1.2 equiv.) in dry acetonitrile. The reaction mixture was stirred under reflux for 16 hr after which manganese dioxide was removed by filtration through celite. The product α, β-unsaturated ester or ketone **6** was isolated by flash chromatography over silica gel. The results show that in all cases aldehyde formation from alcohols **7**, **9**, **12**, **14**, **17**, **20** and **22** derived from L-alanine, L-valine, L-norvaline, L-leucine, L-methionine, L-phenylalanine and L-proline, respectively, and subsequent Wittig reaction occurs in good to excellent yield, to afford the desired α, β-unsaturated ester or ketone. The product in each case was a separable mixture of *cis* and *trans* isomers with the latter predominating by a factor of approximately 9 : 1.[10] Interestingly from a practical point of view, the manganese dioxide could be recycled. Thus the sample of manganese dioxide recovered by filtration from the oxidation of amino alcohol **7** was oven-dried at 110°C for 24 hours and reused in a repeat experiment to convert **7** to **8** in 79% yield.



Scheme 2

Use of these adducts in the synthesis of enantiopure *N*-heterocycles is illustrated by further transformations of the norvaline derived ester **13**, Scheme 2. Exposure to hydrogen over palladium on carbon brought about hydrogenation of the double bond and hydrogenolysis of the Z group to form a product which spontaneously cyclised to lactam **24** in 87% yield. Subsequent reduction of **24** with lithium aluminium hydride afforded (*S*)-(+)-coniine **25** which, because of its volatility, was isolated as its BOC derivative **26** (74% yield), $[\alpha]_D^{20}$ +33.0° (c, 1.3 in $CHCl_3$).[11] Similarly, the proline derived ester **23** was transformed (Scheme 2) by hydrogen / palladium into the known bicyclic lactam **27** $[\alpha]_D$ - 2.7° (c, 1.1 in CH_2Cl_2), (84 % yield), whose conversion into (*S*)-(-)-coniceine *via* $LiAlH_4$ reduction has already been described.[12] A final example involved transformation of the alanine derived ester **8** into the known lactam **28** which proceeded in 89% yield, $[\alpha]_D^{20}$ +26.0° (c, 2.0 in H_2O).[13] A similar sequence, previously described by McIntosh and Acquaah[14] employed the preformed aldehyde produced by DIBAL reduction of *N*-*t*-BOC-L-β-homoalanine methyl ester.

Acknowledgements

S. B. D. acknowledges the receipt of a postgraduate award from the Northern Ireland Department of Education.

References

1. Wei, X.; Taylor R. J. K., *Tetrahedron Lett.*, **1998**, *39*, 3815-3818.
2. Shuto, S.; Niizuma, S.; Matsuda, A., *J. Org. Chem.*, **1998**, *63*, 4489-4493.
3. Ireland, R. E.; Norbeck, D. W., *J. Org. Chem.*, **1985**, *50*, 2198-2200. For an example of a Swern oxidation with subsequent *in situ* Grignard reaction see Hegde, S. G.; Myles D. C., *Tetrahedron*, **1997**, *32*, 11179-11190.
4. Barrett, A. G. M.; Hamprecht, D.; Ohkubo, M., *J. Org. Chem.*, **1997**, *62*, 9376-9378.
5. (a). Chesney, A.; Markó, I. E., *Synth. Commun.*, **1990**, *20*, 3167-3180. (b). Chesney, A.; Markó, I. E., *SynLett.*, **1992**, 275-278. (c). Davies, S. G.; McCarthy, T. D., *SynLett.*, **1995**, 700-702. (d). Toujas, J. L.; Jost, E.; Vaultier, M., *Bull. Soc. Chim. Fr.*, **1997**, *134*, 713-717.
6. Darkins, P.; McCarthy, N.; McKervey, M. A.; Ye, T., *J. Chem. Soc., Chem. Commun.*, **1993**, 1222-1223.
7. Davis, F. A.; Szewczyk, J. M., *Tetrahedron Lett.*, **1998**, *39*, 5951-5954.
8. Rodriguez, M.; Llinares, M.; Doulut, S.; Heitz, A.; Martinez, J., *Tetrahedron Lett.*, **1991**, *32*, 923-926.
9. (a) Podlech, J.; Seebach, D., *Liebigs Ann.*, **1995**, *7*, 1217-1228. (b) Doyle, M. P.; McKervey, M. A.; Ye, T, "Modern Catalytic Methods for Organic Synthesis with Diazo Compounds", John Wiley & Sons, New York, **1997**, pg. 487-533. (c) Juaristi, E., "Enantioselective Synthesis of β-Amino acids", Wiley-VCH, John Wiley & Sons, New York **1997**.
10. Geometric ratio determined by ^{1}H NMR.
11. Lit., $[\alpha]_D^{20}$ + 33.5° (c, 0.43 in $CHCl_3$), Enders, D.; Tiebes, J., *Liebigs Ann. Chem.*, **1993**, 173-177.
12. Lit., $[\alpha]_D^{20}$ - 2.4° (c, 0.75 in CH_2Cl_2), Hua, D. H.; Bharathi, S. N.; Panangadan, J. A. K.; Tsujimoto, A., *J. Org. Chem.*, **1991**, *56*, 6998-7007.
13. Lit., $[\alpha]_D^{20}$ + 27.0° (c, 2.03 in H_2O), Cervinka, O.; Fábryová, A.; Novák, V., *Coll. Czech. Chem. Commun.*, **1965**, *30*, 1742-1743.
14. McIntosh, J. M.; Acquaah, S. O., *Can. J. Chem.*, **1988**, *66*, 1752-1756.