Pergamon

Tetrahedron Letters, Vol. 38, No. 17, pp. 3059-3062, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)00544-3

Stereoselective Synthesis of all Stereoisomeric 2-Amino-3-Hydroxy-4-Phenylbutanolides

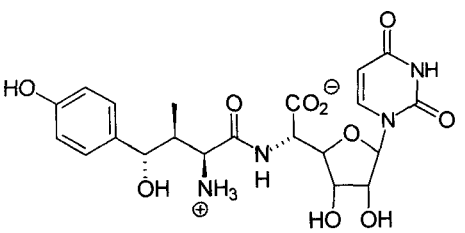
Susan Gair,[a] Richard F.W. Jackson,[a]* and Paul A. Brown[b]

[a] Department of Chemistry, Bedson Building, The University of Newcastle, Newcastle upon Tyne, NE1 7RU, UK

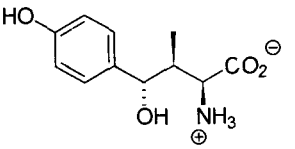
[b] Roche Products Limited, Research Centre, Welwyn Garden City, Hertfordshire, AL7 3AY, UK

Abstract: Diastereoselective methylation of the ketone **5a** leads to the anti-derivative **4a**; the other diastereoisomer **4b** may be obtained by a deprotonation/reprotonation sequence. Each of the methylated products may be reduced stereoselectively in either sense by appropriate choice of reagent, providing a route to all stereoisomers of the title 2-amino-3-hydroxy-4-phenylbutanolides **10a-d**.

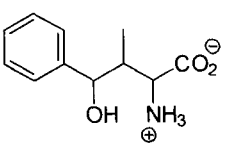
The synthesis of the N-terminal amino acid component **2** of the nucleoside peptide antibiotic Nikkomycin B **1** has attracted substantial interest, and there are now several methods for the stereoselective synthesis of this compound.[1] We have sought to develop a direct synthesis of this compound, which could be easily adapted to the preparation of analogues, and we now report a short, stereoselective route to all stereoisomers of the 2-amino-3-methyl-4-hydroxy-4-phenylbutanoic acid unit **3**, isolated as the corresponding N-protected lactones.



1

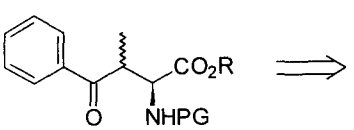


2

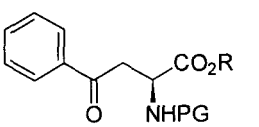


3

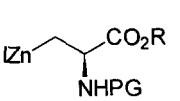
Our strategy is based on direct access to protected enantiomerically pure 4-phenyl-4-oxo-2-aminobutanoic acid **5**, available from palladium-catalysed coupling of a serine derived organozinc reagent **6** with benzoyl chloride according to our recently developed method.[2] We then intended to explore the stereoselective methylation of the ketone **5** to give the methylated analogues **4**, followed by their stereoselective reduction.[3]



4



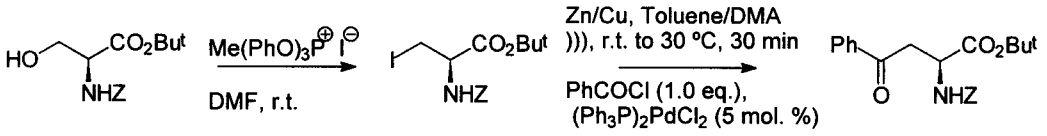
5



6

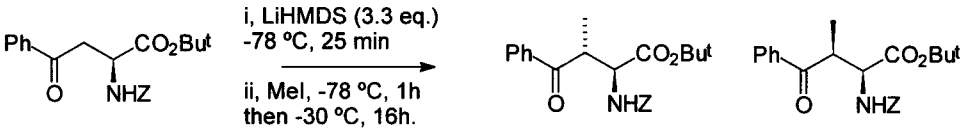
6a, R = Bu^t, PG = Z

Given our intention to generate the methylated derivatives **4** from ketone **5**, it was clear from literature precedent that the potentially labile amino acid α-proton could best be protected using a bulky ester group (we chose *tert*-butyl), as well as an N-protecting group that would allow removal of the acidic NH proton.[4] It also seemed most efficient to incorporate this protection at an early stage, so we decided to use the novel zinc reagent **6a**. The key starting material, iodide **7a**, was efficiently prepared in two steps from commercially available Z-protected L-serine, by conversion firstly into the *tert*-butyl ester **8a** using conditions developed by Martinez (67% - 86%),[5] followed by treatment with methyltriphenoxyphosphonium iodide in DMF (73% - 91%).[6] This latter reagent gave far superior yields of **7a** to those obtained over two steps *via* the tosylate (TsCl, Py) followed by *pseudo*-Finkelstein reaction (NaI, acetone, r.t.). Subsequent treatment of the iodide **7a** with zinc/copper couple in toluene/DMA (15:1) using our original conditions[2] gave the corresponding zinc reagent **6a**. Addition of benzoyl chloride and catalytic $(Ph_3P)_2PdCl_2$ then gave the desired ketone **5a** in yields ranging from 59% to 71% on a 3 mmol scale.



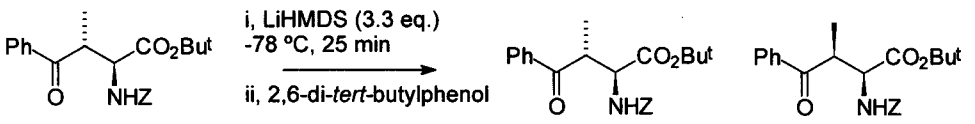
8a **7a** **5a**

With efficient access to the critical ketone **5a**, we then explored the stereoselective methylation reaction. Initial attempts to use LDA as the base gave poor results, but we eventually established that use of LiHMDS in THF (3.3 equiv.) under carefully controlled conditions, followed by treatment with iodomethane, gave good yields of the methylated compounds **4a** and **4b** (20:1, as determined by ^1H NMR). The major isomer could be isolated by flash chromatography (76%),[7] and its structure was confirmed by subsequent transformation into the lactones **10a** and **10b**.[8]



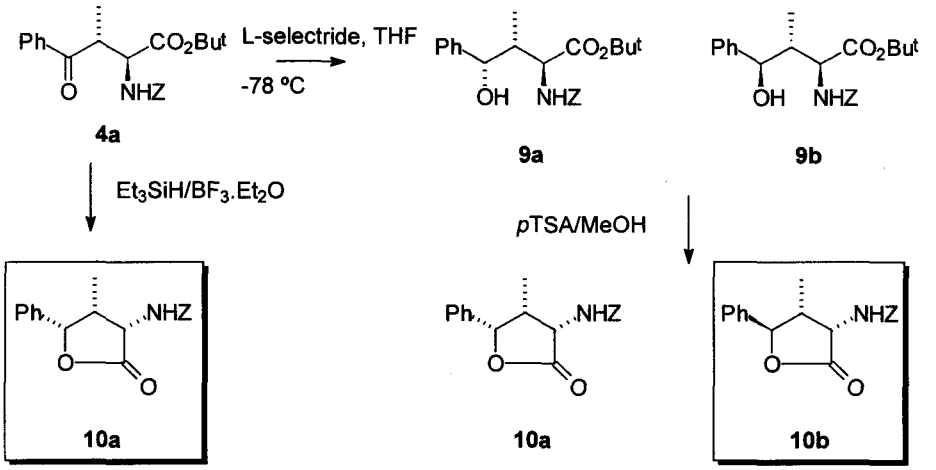
5a **4a** **4b**

Since the stereoselectivity of this process was not in the desired sense, we investigated the possibility of epimerisation at C-3 in ketone **4a** by a deprotonation-reprotonation sequence, on the basis that use of a sufficiently bulky proton source should give the desired ketone **4b**.[9] Treatment of the ketone **4a** with a substantial excess of LiHMDS (4 to 8 eq.) under similar conditions to those employed for its formation, followed by treatment with 2,6-di-*tert*-butylphenol gave, at best, a 1:1 mixture of the 2 diastereoisomeric ketones **4a** and **4b**. Unfortunately, substantial experimentation did not result in any improvement.[10]

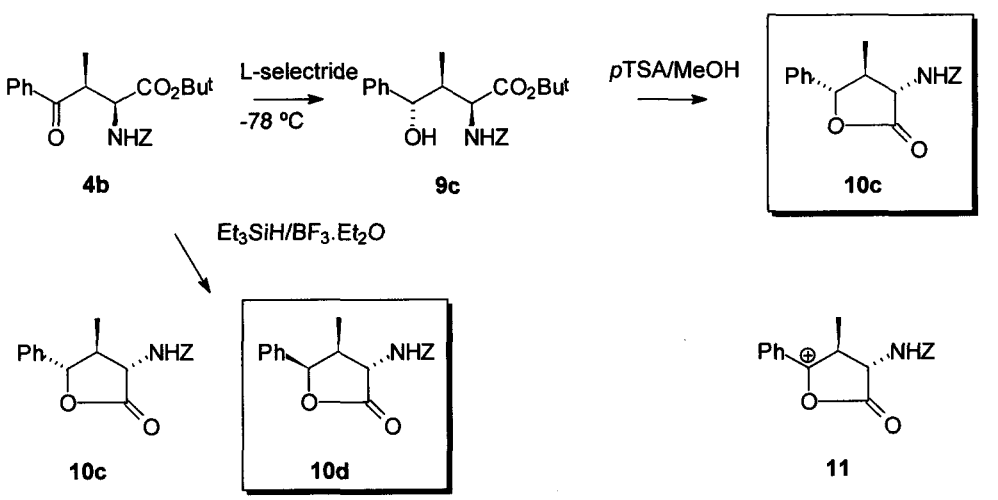


4a **4a** **4b**

Reduction of ketone **4a** with L-selectride® gave, initially, a mixture of the corresponding diastereoisomeric hydroxy esters **9a** and **9b**; treatment of these esters with *p*-toluenesulfonic acid gave the corresponding lactones **10a** and **10b** (ratio 1:4, 63% overall yield). Reduction with triethylsilane in boron trifluoride resulted in direct lactone formation. Analysis of the crude ^{1}H NMR indicated high selectivity (40:1) in favour of the isomer **10a**, which was subsequently isolated in satisfactory yield (69%).



The reduction of the diastereoisomeric ketone **4b** was then explored. Reduction with L-selectride® gave, after cyclisation of the intermediate hydroxy ester **9c**, a single lactone (66%) which was identified as **10c**, with no trace of the isomeric lactone **10d**. This result is entirely consistent with the report in the literature on the reduction of a closely related compound,[11] and demonstrates the potential of our approach in the synthesis of the amino acid **2**. Reduction using triethylsilane in boron trifluoride gave a mixture of the two lactones **10c** and **10d** (ratio 1:6, 70%).



The stereochemical outcome of each of these ketone reduction processes appears to be controlled by the adjacent methyl group, with a smaller influence from the remote α-centre. In the case of reduction of both **4a** and **4b** with L-selectride®, the Felkin-Anh model allows the results to be nicely rationalised, leading in each case to a 3,4 *anti*-relationship between the substituents. In the case of reduction with triethylsilane/ boron trifluoride, delivery of hydride to an intermediate carbocation (for example, **11** derived from **4b**) from the face not shielded by the adjacent methyl group results in a 3,4 *syn*-relationship between the substituents. It is also clear why the reduction of **4a** with triethylsilane in boron trifluoride is more selective than the corresponding reduction of **4b**, since the effects from both stereocentres reinforce each other.

Acknowledgements: We thank the EPSRC and Roche Products, Welwyn for support under the CASE scheme (SG). RFWJ also thanks the Nuffield Foundation for a One Year Science Research Fellowship.

References and Notes

1. Kapeller, H; Jary, W.G.; Hayden. W.; Griengl, H.; *Tetrahedron:Asymmetry* **1997**, *8*, 245, and references cited therein.
2. Jackson, R.F.W.; Wishart, N.; Wood, A.; James, K.; Wythes, M.J. *J. Org. Chem.* **1992**, *57*, 3397.
3. For previous work on the stereoselective reduction of 4-oxo amino acids, see: Jackson, R.F.W.; Rettie, A.B.; Wood, A.; Wythes, M.J. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1719, and references therein.
4. See, for example: Seebach, D.; Estermann, H. *Tetrahedron Lett.* **1987**, *28*, 3103; Baldwin, J.E.; Moloney, M.G.; North, M. *Tetrahedron* **1989**, *45*, 6309; Wolf, J.-P.; Rapoport, H. *J.Org. Chem.* **1989**, *54*, 3164; Dunn, P.J.; Häner, R.; Rapoport, H. *J.Org. Chem.* **1994**, *59*, 5017; Fernandez-Megía, E.; Paz, M.M.; Sardina, F.J. *J. Org. Chem.* **1994**, *59*, 7643.
5. Chevallet, P.; Garrouste, P.; Malawska, B.; Martinez, J. *Tetrahedron Lett.* **1993**, *34*, 7409.
6. Verheyden, J.P.H.; Moffatt, J.G. *J. Org. Chem.* **1970**, *35*, 2319.
7. While the protecting groups in **5a** had been chosen to prevent racemisation during the methylation reaction, the enantiomeric purity of the methylated product **4a** was confirmed as follows. Deprotection of the *tert*-butyl ester (*p*-TSA, toluene, 75 °C, 22 h) , and subsequent separate reaction of the carboxylic acid with each of (R)- and (S)-α-methylbenzylamine (HOBt, DCC, CH_2Cl_2, 0 °C then r.t., 6 h) gave the corresponding amides. ^1H NMR analysis of these amides indicated that each of the products was diastereoisomerically pure and hence, within the limits of detection, that **4a** was enantiomerically pure.
8. The Boc protected analogues of all four lactones **10a-d** (with a 4-methoxyphenyl group in place of phenyl at C-4) have been prepared, and the proton NMR spectra (specifically the chemical shift of the methyl doublet) of our compounds **10a-d** matched the reported values very closely: Barluenga, J.; Viado, A.L.; Aguilar, E.; Fustero, S.; Olano, B. *J. Org. Chem.* **1993**, *58*, 5972.
9. For the use of 2,6-di-*tert*-butylphenol as a bulky proton source see, for example: Davies, S.G.; Ichihara, O.; Walters, I.A.S. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1141.
10. A highly diastereoselective synthesis of the desired stereoisomer, in racemic form, has been developed by Professor H. Heaney, Loughborough. We thank Professor Heaney for informing us of his results.
11. Reduction of the corresponding methyl ester leads to the same stereochemical outcome; however, since *in situ* cyclisation of the hydroxy ester occurs in this case, partial reduction of the lactone to the lactol cannot be avoided, somewhat complicating the isolation procedure: Palomo, C.; Aizpurua, J.M.; García, J.M.; Iturbura, M.; Odriozola, J.M. *J. Org. Chem.* **1994**, *59*, 5184.

(*Received in UK* 7 *October* 1996; *revised* 17 *March* 1997; *accepted* 21 *March* 1997)