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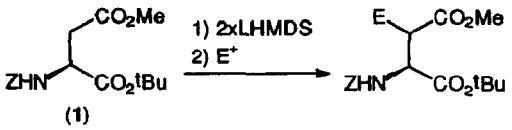
Asymmetric Synthesis of (2S,3S)-3-Carboxy-Proline

Ron Cotton[b], Andrew N.C. Johnstone[a], and Michael North[a]*

a) Department of Chemistry, University of Wales, Bangor, Gwynedd, U.K. LL57 2UW
b) Department of Chemistry Zeneca PLC, Mereside, Alderley Edge, Macclesfield, U.K. SK10 4TG

Abstract: *An asymmetric synthesis of (2S,3S)-3-carboxy-proline starting from (S)-aspartic acid is reported. The methodology also allows the preparation of 5-substituted derivatives.*

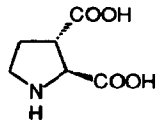
There is much current interest in the synthesis of unusual and unnatural amino acids, with many new synthetic routes being developed for the preparation of these compounds[1]. Over recent years, we have developed an asymmetric amino acid synthesis based upon the regiospecific deprotonation of aspartic acid derivatives[2], as shown in Scheme 1. We have previously shown, that the β-enolate of aspartic acid can be formed without any loss of stereochemical integrity at the α-centre, and that the enolate will react with both alkyl halides, and with aldehydes to give β-substituted aspartic acid derivatives[2].



(1)

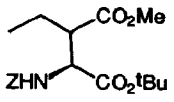
Scheme 1

In this manuscript, we show how this methodology can be used in the asymmetric synthesis of (2S,3S)-3-carboxy-proline (2) and its derivatives. 3-Carboxy-proline is an amino acid which combines the properties of two other amino acids in one structure. Thus the compound can be thought of either as a conformationally constrained aspartic acid derivative, or as a proline analogue with modified acidity due to the incorporation of the 3-carboxyl group. At the outset of our work, two previous syntheses of 3-carboxy-proline had been reported, one of the *cis*-isomer[3] and one of the *trans*-isomer[4], however both gave racemic material. After the work reported in this paper had been completed and the manuscript was being prepared, an asymmetric synthesis of both diastereomers of 3-carboxy-proline was reported[5]. This synthesis utilises the same retrosynthetic analysis as the synthesis we describe herein, but uses the aspartic acid β-enolate equivalent developed by Rapoport *et al.*[6], rather than the one we have previously developed[2].

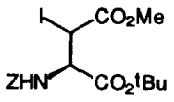


(2)

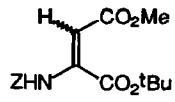
Our initial attempts to prepare compound (2) were based upon the reaction of the dienolate of aspartic acid derivative (1) with a 2-carbon *bis*-electrophile such as 1,2-dibromoethane or ethylene oxide. Unfortunately, whilst the dienolate of aspartate (1) reacted smoothly with ethyl bromide to give the β-ethyl aspartate derivative (3), attempted reaction with a wide range of *bis*-electrophiles was unsuccessful. Only with 1,2-diiodoethane as the *bis*-electrophile did any reaction occur, and in this case two products were isolated from the reaction, the β-iodoaspartate derivative (4) and the α,β-didehydroaspartate (5). Both (4) and (5) were obtained as a mixture of stereoisomers. No proline derivatives were ever isolated from these reactions.



(3)

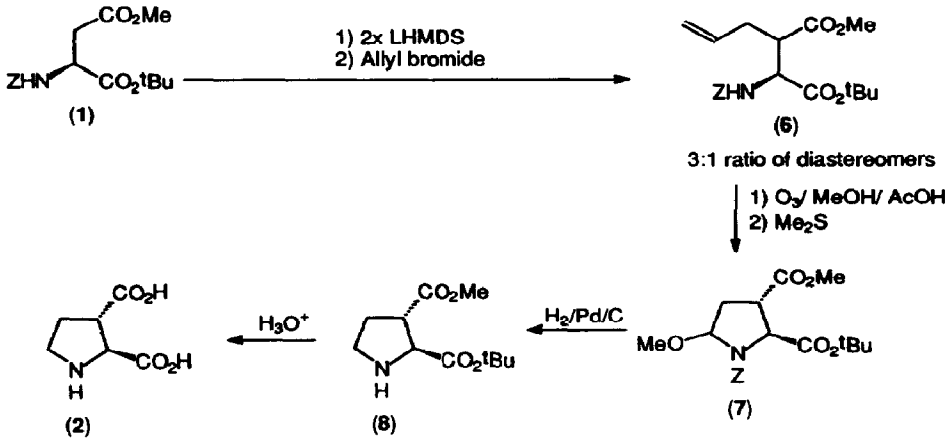


(4)



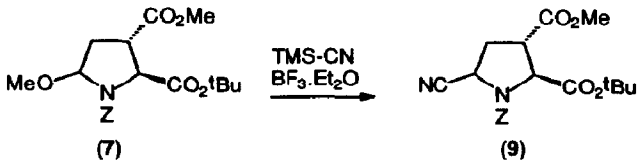
(5)

Although reaction of the dienolate of compound (1) with 2-carbon *bis*-electrophiles was unsuccessful, we have previously shown that this dianion will react with allyl bromide, to give the β-allyl aspartate in high yield[2]. It was envisaged that the allyl derivative could function as a masked 2-carbon unit. Indeed, reaction of aspartate (1) with two equivalents of lithium hexamethyldisilazide followed by allyl bromide as previously described[2], gave the β-allyl derivative (6) as a 3:1 ratio of stereoisomers at the new chiral centre (Scheme 2). At this stage, the stereochemistry of the newly created chiral centre of the major diastereomer of compound (6) was not clear, however the diastereomers could be separated by flash chromatography. Ozonolysis of the major diastereomer of allyl derivative (6) in methanol containing acetic acid followed by the addition of dimethyl sulphide gave proline derivative (7) as the major product (as a 2:1 mixture of stereoisomers at the newly created chiral centre[7]). Hydrogenation of methoxy derivative (7) resulted in simultaneous hydrogenolysis of the benzyloxycarbonyl protecting group, loss of methanol, and hydrogenation of the resulting imine to give the 3-carboxy-proline derivative (8). Deprotection of compound (8) was accomplished by treatment with 6N HCl at 60°C, giving (2S,3S)-3-carboxy-proline (2), the nmr and optical rotation data of which were in full agreement with those previously reported for (2S,3S)-3-carboxy-proline[5], and were significantly different to those reported for (2S,3R)-3-carboxy-proline[5].



Scheme 2

A key feature of our synthesis of (2S,3S)-3-carboxy-proline is the intermediate methoxy derivative (**7**). This compound should allow the synthesis of a wide range of 5-substituted-3-carboxy-proline derivatives, as it is well established that the methoxy group in such compounds can be displaced by electrophiles in the presence of Lewis acids[8]. As an example of this, treatment of compound (**7**) with TMS-CN and $BF_3.OEt_2$ gave the 5-cyano-derivative (**9**) as a mixture of stereoisomers at the 5-position as shown in Scheme 3. Another feature of this synthesis is the use of orthogonal protecting groups for the two carboxyl groups. This will allow the further manipulation of compound (**8**), and facilitate its use in peptide synthesis. Further studies along these lines are currently in progress and will be reported in due course.



Scheme 3

Acknowledgements

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7. Compound (7): colourless oil; δ_H ($CDCl_3$) 1.23 and 1.37 (9H, s, $OC(CH_3)_3$), 1.9-2.1 (1H, m, ring-CH_2), 2.3-2.6 (1H, m, ring-CH_2) 3.22 and 3.39 (3H, s, OCH_3) 3.4-3.7 (1H, m, $CHCO_2Me$) 3.66 and 3.68 (3H, s, CO_2CH_3) 4.45 (1H, d *J* 8.6Hz, NCH), 5.07 (2H, ABq *J* 12.4Hz, $PhCH_2$) 5.18 and 5.30 (1H, d *J* 4.9 and 5.2Hz, NCHOMe), 7.2-7.4 (5H, m, Ph) peak assignments were confirmed by a ^1H-^1H COSY spectrum); δ_C ($CDCl_3$) 27.76 and 27.90 ($OC(\underline{C}H_3)_3$) 32.96 and 33.78 (ring-CH_2) 43.84 and 44.85 (OCH_3) 52.15 (OCH_3) 55.92 and 56.67 ($CHCO_2$) 61.43 and 61.67 ($NCHCO_2$) 67.55 and 67.65 ($PhCH_2$) 82.18 and 82.32 ($OCMe_3$) 88.47 and 89.08 (NCHOMe), 128.03, 128.10, 128.19, 128.52 and 128.56 (ArCH), 135.90 and 136.22 (ArC), 154.39 and 154.83 (NCO_2) 168.59, 170.28 and 170.48 (CO_2) ; m/z (CI) 411.2131 ($M+NH_4^+$), $C_{20}H_{27}NO_7.NH_4$ requires 411.2131.

8. See for examples: Katoh, T.; Nagata, Y.; Kobayashi, Y.; Arai, K.; Minami, J.; Terashima, S.; *Tetrahedron*, **1994**, 21, 6221; Corey, E.J.; Yuen, P.-W.; Hannon, F.J.; Wierda, D.A.; *J. Org. Chem.*, **1990**, 55, 784; Langlois, N.; Rojas, A.; *Tetrahedron*, **1993**, 49, 77.

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