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Preliminary studies on a novel synthesis of β-amino acids: stereocontrolled transformation of D- and L-glyceraldehyde into 3-amino-2-(2′,2′-dimethyl-1′,3′-dioxolan-4′-yl)propanoic acids

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Abstract—A stereocontrolled synthesis of the methyl ester of (2*S*)-3-amino-2-((4′*S*)-2′,2′-dimethyl-1′,3′-dioxolan-4′-yl)propanoic acid from D-glyceraldehyde is described for the first time. This method involves the stereoselective Michael addition of the lithium salt of tris(phenylthio)methane to (*S*)-2,2-dimethyl-4-((*E*)-2-nitrovinyl)-1,3-dioxolane followed by hydrolysis of the resulting (4*S*)-2,2-dimethyl-4-((2′*S*)-3′-nitro-1′,1′,1′-tris(phenylthio)propan-2′-yl)-1,3-dioxolane to (2*S*)-methyl 2-((4′*S*)-2′,2′-dimethyl-1′,3′-dioxolan-4′-yl)-3-nitropropanoate, which was finally reduced to the target compound. A similarly stereocontrolled transformation of L-glyceraldehyde into (2*R*)-methyl 3-amino-2-((4′*R*)-2′,2′-dimethyl-1′,3′-dioxolan-4′-yl)propanoate is also described.

1. Introduction

The biological functions and pharmacological limitations of natural peptides have, in recent years, prompted intense work on the preparation of analogues resulting from the replacement of one or more α-amino acids by unnatural and rare amino acids. The resulting compounds have become increasingly important due to the significant biological activities that have been observed.[1,2] The best candidates for such replacements are β-amino acids, mainly because their oligomers do not exhibit the pharmacological limitations of natural peptides due to their resistance to enzymatic degradation and their tendency to be more rigid than α-peptides.[3] Accordingly, there has recently been a great deal of interest in the enantioselective synthesis of β-amino acids. However, while there are numerous routes to achiral β^2-amino acids, their EPC synthesis is currently the subject of many investigations.[4] Research efforts in this field are due to the importance of these compounds. In fact, it has been shown that when β^2-amino acids are included in peptides or in naturally occurring compounds, they lead to entities that, in some cases, show cytotoxic or antiviral activity.[2b,5] Moreover, these β-peptides can adopt novel and unique folding patterns.[3]

Nitroolefins are powerful Michael acceptors that have received considerable attention due to their special chemical properties.[6] These compounds are readily attacked by a wide range of nucleophiles to produce nitroalkanes bearing a stereogenic centre at the 2-position, a fact that makes them powerful tools for the construction of C–C bonds by addition of organometallics to the electron-deficient double bond. Following the addition reaction, the nitro group can be transformed into a diverse range of functionalities (amines, oximes, ketones, carboxylic acids, etc.) to provide a wide range of chemical compounds. This versatile chemical protocol has recently been applied to the enantioselective preparation of β^2-amino acids by the addition of organometallics to 3-nitropropenoates[7] and to 3,3-dialkoxy-1-nitroprop-1-enes[8] with asymmetric catalysis, followed by the reduction of the resulting 2-substituted 3-nitro derivatives and the subsequent generation of their respective carboxylic acid moieties. A variant of this strategy involves conjugate addition of organometallics to optically active nitroalkenes, such as 2,2-dimethyl-4-[(*E*)-2-nitrovinyl]-1,3-dioxolanes. These compounds are synthetic equivalents of nitroacrylates and have proven to be versatile precursors for the synthesis of enantiopure β-amino acids, in which the nitro group is again a precursor for

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the amino functionality and the dioxolanyl side chain provides the carboxylic acid moiety by glycol cleavage.[9]

An alternative approach consisting of the addition of carboxyl-synthetic equivalents to electron-deficient nitroalkenes remains practically unexplored. To the best of our knowledge, only one example has been described and this involves an organocatalytic asymmetric addition of 2,4-pentadione to nitroolefins.[10] Following this addition, a long reaction sequence is required to generate the carboxyl function of the corresponding β-amino acids. Moreover, the preparation of β-amino acids involving the addition of a carboxyl-synthon equivalent to optically active nitroalkenes has not yet been described. We report here our preliminary results on a novel synthesis of sugar β-amino acids, illustrated by the diastereoselective transformation of D-glyceraldehyde into the corresponding β-amino acid ester **5a** via (*S*)-2,2-dimethyl-4-((*E*)-2-nitrovinyl)-1,3-dioxolane **2a**. L-Glyceraldehyde was similarly converted into β-amino acid ester **5b** via β-nitro acid ester **4b**. In our approach tris(phenylthio)methyl was used as a bulky carboxyl synthon.

Reaction of the lithium salt of tris(phenylthio)methane with nitroolefin **2a**[11] at −78 °C gave stereoisomer **3a**[12] as the only product (90% yield) (Scheme 1). The structure of **3a** was unambiguously established by X-ray diffraction (Fig. 1).[13] The stereoselectivity is due to the dioxolane subunit of the nitroolefin **2a**, which only allows attack by the bulky tris(phenylthio)methyl anion on the less hindered face of the double bond. Deprotection of the masked carboxyl group of **3a** by treatment with HgO and $BF_3{\cdot}OEt_2$ was followed by the reduction of the resulting β-nitro ester **4a** to the desired β-amino ester **5a** by catalytic hydrogenation with Pd–C. Freshly isolated **5a** was subjected to peptide coupling with benzyloxycarbonylglycine, TBTU and DIPEA to give the expected dipeptide **6a**. This compound was reacted with barium hydroxide and the resulting carboxylic acid was directly coupled with methoxycarbonylglycine in the presence of HATU and DIPEA to give tripeptide **7a**.

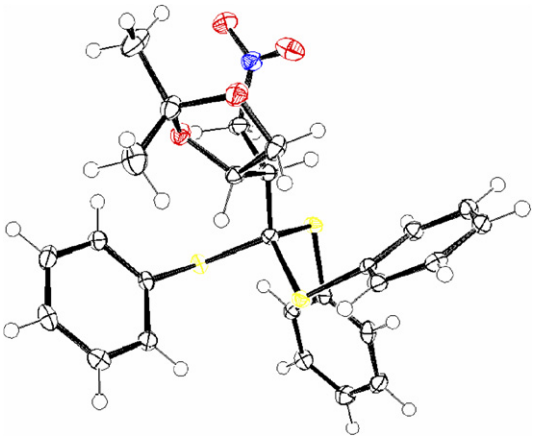


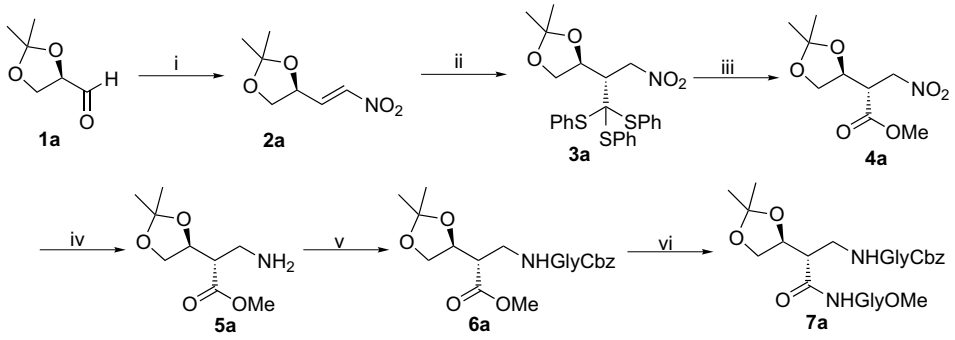
Figure 1. X-ray structure of compound **3a**.

On the other hand, nitroolefin **2b** was easily obtained from L-glyceraldehyde[14] in a similar way to the preparation of analogue **2a**. As expected, reaction of **2b** with the lithium salt of tris(phenylthio)methane under the same conditions as for **2a**, gave compound **3b** (90% yield) as the only stereoisomer. When compound **3b** was subjected to the above protocol, β-amino ester **5b** (enantiomer of **5a**) was formed via β-nitro ester **4b** (Scheme 2). Incorporation of this novel β-amino acid **5b** into tripeptide **7b** via dipeptide **6b** was carried out using the same approach as for the preparation of tripeptide **7a**.

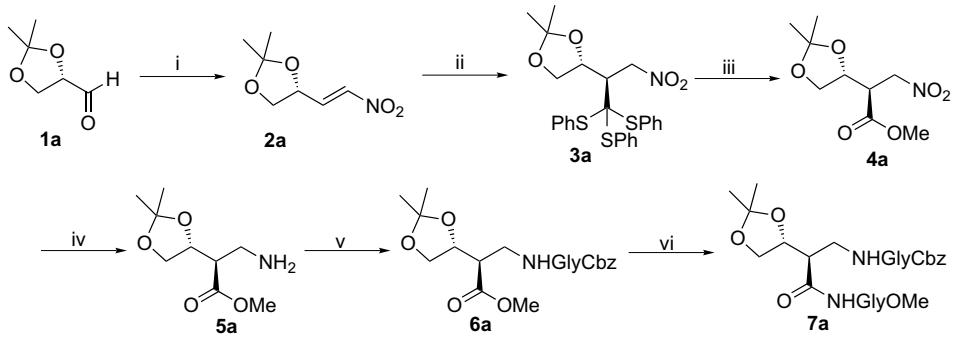
2. Conclusion

In conclusion, we have reported here the preliminary results on a novel synthesis of β-amino acids, which may prove to be simpler and more efficient than previous approaches. The route involves the Michael addition of lithium tris(phenylthio)methane (a carboxyl synthetic equivalent) to nitroolefins, followed by removal of the carboxyl masking group and reduction of the nitro group to the amino group. The remarkable stereoselectivity achieved in the preparation of the novel amino acids **5a** and **5b** suggests that this approach will be of particular interest for the stereoselective preparation of β-amino acids derived from nitroethylenes bearing a chiral substituent at the 2-position.

Work is currently in progress to extend this route to the plethora of tetroses, pentoses and hexoses in order to pre-



Scheme 1. Reagents and conditions: (i) (a) CH_3NO_2, $KF{\cdot}2H_2O$, *i*PrOH, rt, 14 h, 90% yield; (b) MsCl, Et_3N, CH_2Cl_2, −20 °C, 15 min, 94% yield. (ii) $(PhS)_3CH$, *n*-BuLi, THF, −78 °C, 15 min, 90% yield. (iii) HgO, $BF_3{\cdot}OEt_2$, MeOH/THF/H_2O, rt, 48 h, 66% yield. (iv) H_2, Pd–C, AcOEt, rt, 4 h, 68% yield. (v) CbzGlyOH, TBTU, DIPEA, CH_2Cl_2, rt, 12 h, 62% yield. (vi) (a) $Ba(OH)_2{\cdot}8H_2O$, THF/H_2O, rt, 30 min, 90% yield; (b) MeOGlyH·HCl, HATU, DIPEA, CH_2Cl_2, rt, 12 h, 69% yield.



Scheme 2. Reagents and conditions: (i) (a) CH_3NO_2, $KF{\cdot}2H_2O$, *i*PrOH, rt, 14 h, 87% yield; (b) MsCl, Et_3N, CH_2Cl_2, −20 °C, 15 min, 93% yield. (ii) $(PhS)_3CH$, *n*-BuLi, THF, −78 °C, 15 min, 82% yield. (iii) HgO, $BF_3{\cdot}OEt_2$, MeOH/THF/H_2O, rt, 48 h, 69% yield. (iv) H_2, Pd–C, AcOEt, rt, 4 h, 83% yield. (v) CbzGlyOH, TBTU, DIPEA, CH_2Cl_2, rt, 12 h, 70% yield. (vi) (a) $Ba(OH)_2{\cdot}8H_2O$, THF/H_2O, rt, 30 min, 98% yield; (b) MeOGlyH·HCl, HATU, DIPEA, CH_2Cl_2, rt, 12 h, 64% yield.

pare a wide range of novel sugar β-amino acids, including polyhydroxylated cyclopentane and cyclohexane β-amino acids, which could be of great interest for incorporation into peptides. Our future plans also include the application of this novel approach to β-amino acids to a wide range of nitroolefins in order to explore its general applicability.

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12. All new compounds gave satisfactory spectroscopic and analytical data. Selected physical and spectroscopic data are as follows. Compound **3a**: $[\alpha]_D^{27} = -44.5$ (*c* 1.05, $CHCl_3$). ^1H NMR ($CDCl_3$) δ 1.19, 1.29 (2 × s, 6H, 2 × CH_3), 3.31 (ddd, $J_{2',3'} = 8.0$ Hz, $J_{2',4} = 5.8$ Hz, $J_{2',3'} = 2.0$ Hz, 1H, H-2′), 3.47 (dd, $J_{5,5} = 8.5$ Hz, $J_{5,4} = 6.8$ Hz, 1H, H-5), 4.12 (dd, $J_{5,5} =$ 8.5 Hz, $J_{5,4} = 6.3$ Hz, 1H, H-5), 4.65 (dd, $J_{3',3'} =$ 15.0 Hz, $J_{3',2'} = 9.0$ Hz, 1H, H-3′), 4.68–4.76 (m, 1H, H-4), 4.87 (dd, $J_{3',3'} = 15.0$ Hz, $J_{3',2'} = 2.0$ Hz, 1H, H-3′), 7.30–7.47 (m, 9H, 9 × Ar–H); 7.64–7.70 (m, 6H, 6 × Ar–H). ^{13}C NMR ($CDCl_3$) δ 24.65, 25.05, 48.74, 70.69, 73.40, 73.75, 77.00, 108.76, 128.65, 129.70, 130.16, 135.97. MS (CI) *m*/*z* (%) 514 (MH^+, 2); 498 (1); 456 (1); 438 (2); 404 (88); 111 (100). Compound **4a**: $[\alpha]_D^{26} = -23.2$ (*c* 1.23, $CHCl_3$). ^1H NMR ($CDCl_3$) δ 1.33, 1.42 (2 × s, 6H, 2 × CH_3), 3.22 (dt, $J_{2,3} = 8.0$ Hz, $J_{2,3} = 3.9$ Hz, $J_{2,4'} = 3.9$ Hz, 1H, H-2), 3.77 (s, 3H, OCH_3); 3.91 (dd, $J_{5',5'} = 8.7$ Hz, $J_{5',4'} = 5.2$ Hz, 1H, H-5′); 4.21 (dd, $J_{5',5'} = 8.7$ Hz, $J_{5',4'} = 6.0$ Hz, 1H, H-5′); 4.29–4.37 (m, 1H, H-4′); 4.75 (dd, $J_{3,3} = 15.0$ Hz, $J_{3,2} = 3.9$ Hz, 1H, H-3); 4.87 (dd, $J_{3,3} = 15.0$ Hz, $J_{3,2} = 8.0$ Hz, 1H, H-3). ^{13}C NMR ($CDCl_3$) δ 24.55, 26.11, 46.90, 52.35, 68.04, 72.23, 72.80, 109.62, 169.75. MS (CI) *m*/*z* (%) = 234 (MH^+, 42), 218 (23), 175 (100), 129 (9). Compound **6a**: $[\alpha]_D^{27} = -14.7$ (*c* 1.20, $CHCl_3$). ^1H NMR ($CDCl_3$) δ 1.33, 1.41 (2 × s, 6H, 2 × CH_3), 2.65–2.75 (m, 1H, H-2), 3.60–3.69 (m, 2H, H-3 + H-3), 3.71 (s, 3H, OCH_3), 3.77 (dd, $J_{5',5'} = 8.5$ Hz, $J_{5',4'} = 6.0$ Hz, 1H, H-5′), 3.85 (2 × d, $J_{H,H} = 5.8$ Hz, $J_{H,H} = 5.8$ Hz, 2H, CH_2Gly), 4.12 (dd, $J_{5',5'} = 8.5$ Hz, $J_{5',4'} = 6.3$ Hz, 1H, H-5′), 4.29–4.37 (m, 1H, H-4′), 5.13 (s, 2H, CH_2Ph), 5.34 (br s, 1H, NH), 6.58 (br s, 1H, NH), 7.32–7.38 (m, 5H, 5 × Ar–H). ^{13}C NMR ($CDCl_3$) δ 24.92, 26.30, 38.07, 44.27, 48.56, 51.98, 66.87, 67.80, 74.51, 109.41, 127.86, 127.88, 128.02, 128.33, 135.96, 156.46, 169.14, 171.95. MS (CI) *m*/*z* (%) = 395 (MH^+,

100), 379 (35), 319 (87), 261 (13), 91 (62). Compound **7a**: $[\alpha]_D^{27} = -15.8$ (*c* 2.30, $CHCl_3$). ^1H NMR ($CDCl_3$) δ 1.34, 1.47 ($2 \times$ s, 6H, $2 \times CH_3$), 2.68–2.79 (m, 1H, H-2), 3.18–3.20 (m, 1H, H-3), 3.67–3.74 (m, 1H, H-3), 3.71 (s, 3H, OCH_3), 3.77 (s, 2H, CH_2Gly), 3.85–4.07 (m, 3H, H-5′ + CH_2Gly), 4.13–4.35 (m, 2H, H-4′ + H-5′), 5.09 (s, 2H, CH_2Ph), 5.79 (br s, 1H, NH), 7.13 (br s, 2H, $2 \times$ NH), 7.31–7.39 (m, 5H, $5 \times$ Ar–H). ^{13}C NMR ($CDCl_3$) δ 25.21, 26.72, 39.42, 41.07, 44.61, 49.52, 52.44, 67.13, 67.65, 74.87, 109.41, 128.00, 128.20, 128.47, 136.02, 147.38, 167.10, 169.52, 169.78. MS (CI) *m*/*z* (%) 452 (MH^+, 21), 436 (15), 376 (100), 328 (18), 268 (66), 91 (97).

13. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as Supplementary Publication No. CCDC 624162 (**3a**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: (+44)1223 336 033; e-mail: deposit@ccdc.cam.ac.uk]. Crystallographic data for **3a**. $C_{26}H_{27}NO_4S_3$, $M = 513.67$, $T = 100(2)$ K. Orthorhombic, space group *P*212*121* with $a = 10.5316(19)$, $b = 12.851(2)$, $c = 17.959(3)$ Å, $\alpha = 90°$, $\beta = 90°$, $\gamma = 90°$, $V = 2430.6(8)$ Å^3, D_c ($Z = 4$) = 1.404 Mg/m^3. $F(000) = 1080$, absorbtion coefficient = 0.339 mm^{-1}. Data were obtained on an Smart-CCD-1000 BRUKER diffractometer (graphite crystal monochromator, $\lambda = 0.71073$ Å) using the $\omega = 2\theta$ scan method; absorption corrections were applied. Refinement, with anisotropic displacement parameters applied to each of the nonhydrogen atoms, was by full-matrix least squares on F^2 (SHELXL-93) using all data; $wR^2 = [(\sum w(F_o^2 - F_c^2)^2 / \sum w(F_o^2)^2]^{1/2}$.
14. L-Glyceraldehyde was obtained as stated in: Hubschwerlen, C. *Synthesis* **1986**, 962.