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Enantioselective Synthesis of (*S*)-2-(Aminomethyl)butanedioic acid Using Chiral β-Alanine α-Enolate Equivalents

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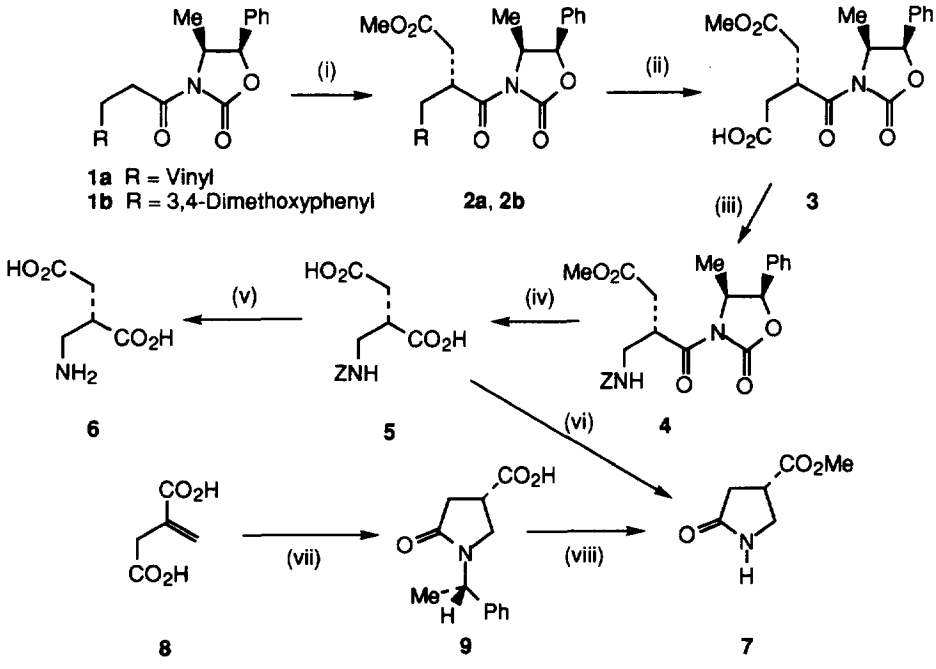
Abstract: (*S*)-2-(Aminomethyl)butanedioic acid (**6**) can been synthesised by stereoselective alkylation of the Na enolates of acyloxazolidinones **1a** and **1b** with methyl bromoacetate, then oxidation of the vinyl or dimethoxyphenyl substituent to a carboxyl group, followed by Curtius rearrangement and deprotection. The absolute configuration of **6** has been correlated with that of (*S*)-1-phenylethylamine by a combination of crystallographic and chemical means.

2-(Aminomethyl)butanedioic acid (**6**) is a homologue of aspartic acid and an isomer of glutamic acid, both of which are important neurotransmitters.[1] It has been shown that the neuroexcitatory effects upon the toad spinal cord follow the order D-Glu > (±)-**6** > D-Asp > L-Glu > L-Asp.[2] We now report the first asymmetric synthesis of **6**. Although there is considerable current interest in the stereoselective synthesis of β-amino acids,[3] there have been very few reports of enantioselective routes to α-substituted, β-unsubstituted β-alanine derivatives. The approaches that have been used include the use of a perhydropyrimidine derivative as a chiral β-alanine α-enolate equivalent,[4] the aminomethylation of a chiral enolate in an asymmetric Mannich reaction[5] and the Michael reactions of chiral α-methylene-β-alanine derivatives with carbon nucleophiles.[6] Here we describe a synthesis of (*S*)-**6** in which the 3-(pent-4-enoyl)- and 3-[3-(3,4-dimethoxyphenyl)propanoyl]- oxazolidinones **1a** and **1b** can be considered to act as new chiral β-alanine α-enolate equivalents.

We have recently demonstrated that the acyloxazolidinones **1a** and **1b** bearing Evans' chiral auxiliary[7] are able to undergo diastereoselective cyanomethylation by $BrCH_2CN$. Oxidation ($RuCl_3$-$NaIO_4$) of the vinyl and 3,4-dimethoxyphenyl substituents, to give carboxyl groups, can be performed with the chiral auxiliary in place.[8] In the present synthesis $BrCH_2CO_2Me$ is used as the electrophile.[9] The major alkylation product **2b** is crystalline and was found to be easier to purify than the **2a**, which remained oily. Oxidation of either **2a** or **2b** gave the same carboxylic acid **3** which, upon treatment with $(PhO)_2P(O)N_3/PhCH_2OH/Et_3N$, yielded the *N*-benzyloxycarbonyl-protected amino acid derivative **4** via a Curtius rearrangement of the acyl azide.[10] Cleavage of the chiral auxiliary and hydrolysis of the methyl ester group in **4** were performed in a single operation: it was observed that the ester hydrolysis was the slower of these two reactions. Catalytic hydrogenolysis and recrystallisation from H_2O-EtOH then afforded (*S*)-**6** as the monohydrate.



Scheme 1. *Reagents and conditions:* i, $NaN(SiMe_3)_2$, THF, -78 °C, 30 min, then MeO_2CCH_2Br, warm to -15 °C over 2h, then NH_4Cl (aq) (60% yield for **2a**, 53% for **2b**); ii, $RuCl_3$, $NaIO_4$, MeCN, CCl_4, H_2O, then *i*-PrOH (83% from **2a**, 75% from **2b**); iii, $(PhO)_2P(O)N_3$, Et_3N, $PhCH_2OH$, PhMe, 2 h, 20 °C then 2 h reflux (70%); iv, LiOH, H_2O_2, H_2O, THF, 0 °C, 4 h (65%); v, H_2, Pd-C, AcOH, 3 h, 20 °C (89%); vi, CH_2N_2, MeOH, 20 °C, then H_2, Pd-C, MeOH, 3 h, 20 °C, then Et_3N, MeOH, 1 d, 20 °C (41% from **5**); vii, (*S*)-1-phenylethylamine, 160 °C, 4 h then crystallisation from EtOAc (28%); viii, Na, NH_3 (l), *t*-BuOH, -33 °C, 1 h, then NH_4Cl then CH_2N_2, MeOH (5% from **9**).

In order to estimate the enantiomeric excess of the products **5** and **6** and to verify that their absolute configurations were in accord with the accepted model for alkylation of acyloxazolidinones,[7] the dicarboxylic acid **5** was esterified with diazomethane and then subjected to hydrogenolysis in methanol to give the dimethyl ester of **6**. Cyclisation to the lactam **7** was found to be rather slow, but did occur when the diester of **6** was treated with excess Et_3N in MeOH at 20 °C. The lactam **7** was purified by flash chromatography in EtOAc but was not recrystallised, so as to avoid disturbing the enantiomeric excess. The 600 MHz ^1H NMR spectrum of **7** (15 mg) in $CDCl_3$ (0.6 ml), in the presence of the chiral shift reagent tris[3-(trifluoromethylhydroxymethylene)-(+)-camphorato]europium (III) (20 mg), showed methyl ester signals at δ 3.97 and 3.92. These peaks, attributed respectively to the (*S*)- and (*R*)- enantiomers of the lactam **7**, were found to have integrals in the ratio > 97.5:2.5, corresponding to an enantiomeric excess for the lactam **7** of > 95%.

Heating itaconic acid (**8**) with (*S*)-1-phenylethylamine gives a 1:1 mixture of diastereoisomeric pyrrolidonecarboxylic acids, which have previously been separated by conversion into the methyl esters.[11,12] We found that one of the carboxylic acids had a relatively low solubility in ethyl acetate and could be isolated by recrystallisation from this solvent. An X-ray crystal structure (Fig. 1) confirmed that the less soluble acid **9** had the (*S*)- configuration at C-4. Reductive cleavage of the *N*-(α-methylbenzyl) group, followed by

esterification with diazomethane, then gave a sample of (*S*)-**7**, $[\alpha]^{35}_{D}$ -19 (*c* 0.56 in $CHCl_3$) {compare $[\alpha]^{30}_{D}$ -18 (*c* 1.1 in $CHCl_3$) for (*S*)-**7** prepared from **5**}.

Thus we have further demonstrated the usefulness of the intermediates **2a** and **2b** in the synthesis of unusual amino acids of predictable absolute configuration.

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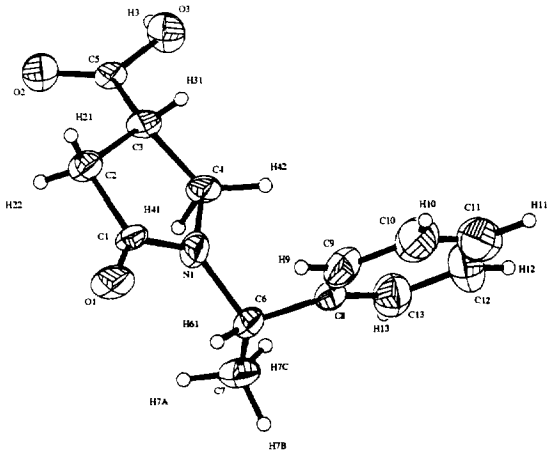

Fig. 1. X-Ray crystal structure of **9**. Crystallographic data:[13] orthorhombic, space group $P2_12_12_1$ with a = 6.584(1) Å, b = 8.258(1) Å, c = 22.310(2) Å, U = 1212.9(3) Å^3; Z = 4; D_c = 1.277 g cm^{-3}; T = 293(2) K; λ = 0.71069 Å; μ (Mo-K$_\alpha$) = 0.091 mm^{-1}; 567 independent reflections. Structure solved by direct methods. H atoms of the CO_2H, Me and Ph groups were placed in idealised positions using an atom-riding model. R_1 = 0.040, wR_2 = 0.088 for reflections with $I > 2\sigma(I)$.

OTHER SELECTED DATA

2a. Pale yellow oil, chromatographed on silica gel in CH_2Cl_2-Et_2O (49:1); ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.92 (d, 3 H, *J* 7 Hz), 2.18-2.33 (m, 1 H), 2.39-2.51 (m, 1 H), 2.53 (dd, 1 H, *J* 17, 5 Hz), 2.87 (dd, 1 H, *J* 17, 10 Hz), 3.64 (s, 3 H), 4.25-4.39 (m, 1 H), 4.76 (quintet, 1 H, *J* 7 Hz), 5.03-5.18 (m, 2 H), 5.65 (d, 1 H, *J* 7 Hz), 5.70-5.89 (m, 1 H), 7.30-7.47 (m, 5 H); *m/z* (EI) 331 (*M*$^+$, 44%), 178 (100), (found: 331.1419. $C_{18}H_{21}NO_5$ requires 331.1420).

2b. White crystals, chromatographed on silica gel in CH_2Cl_2-Et_2O (97:3), then recrystallised from Et_2O-petrol, m.p. 98-100°C, $[\alpha]^{31}_{D}$ = +59 (*c* 0.2, CH_2Cl_2); ν_{max} (KBr)/cm^{-1}: 1777, 1744, 1706; ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.90 (d, 3 H, *J* 7 Hz), 2.46 (dd, 1 H, *J* 17, 5 Hz), 2.62 (dd, 1 H, *J* 14, 9 Hz), 2.89 (dd, 1 H, *J* 17, 10 Hz), 3.00 (dd, 1 H, *J* 14, 6 Hz), 3.61 (s, 3 H), 3.86 (s, 3 H), 3.90 (s, 3 H), 4.45-4.60 (m, 1 H), 4.65 (quintet, 1 H, *J* 7 Hz), 5.42 (d, 1 H, *J* 7 Hz), 6.75-6.83 (m, 2 H), 6.90 (d, 1 H, *J* 2 Hz), 7.26-7.46 (m, 5 H); *m/z* (EI) 441 (*M*$^+$, 100%), (found: 441.1787. $C_{24}H_{27}NO_7$ requires 441.1788).

3. Colourless oil, ν_{max} (film)/cm^{-1}: 1780, 1738, 1698; ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.90 (d, 3 H, *J* 7 Hz), 2.56-2.96 (m, 4 H), 3.68 (s, 3 H), 4.41-4.53 (m, 1 H), 4.79 (quintet, 1 H, *J* 7 Hz), 5.71 (d, 1 H, *J* 7.5 Hz), 7.27-7.47 (m, 5 H); *m/z* (EI) 349 (*M*$^+$, 48%), 107 (100), (found: 349.1155. $C_{17}H_{19}NO_7$ requires 349.1162).

4. Foam, chromatographed on silica gel in petrol-EtOAc, ν_{max} (KBr)/cm^{-1}: 3375, 1780, 1700; ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.88 (d, 3 H, *J* 7 Hz), 2.58 (dd, 1 H, *J* 16, 6 Hz), 2.89 (dd, 1 H, *J* 17, 9 Hz), 3.43-3.52 (m, 2 H), 3.64 (s, 3 H), 4.29-4.39 (m, 1 H), 4.65 (quintet, 1 H, *J* 7 Hz), 5.05-5.17 (m, 3 H), 5.60 (d, 1 H, *J* 7 Hz), 7.27-7.45 (m, 10 H); *m/z*: (EI) 454 (M^+, 64%), 91 (100), (found: 454.1746. $C_{24}H_{26}N_2O_7$ requires 454.1740).

5. White crystals (from EtOAc-petrol), m.p. 115°C, $[\alpha]^{31}_D$ = +9.0 (*c* 0.5, acetone) (Found: C, 55.5; H, 5.4; N, 4.9. $C_{13}H_{15}NO_6$ requires C, 55.5; H, 5.4; N, 5.0%); ^{1}H NMR (250 MHz, acetone-d_6): δ = 2.58 (dd, 1 H, *J* 17.5, 5 Hz), 2.72 (dd, 1 H, *J* 17.5, 7.5 Hz), 2.99-3.10 (m, 1 H), 3.36-3.62 (m, 2 H), 5.08 (s, 2 H), 6.39-6.52 (broad s), 7.23-7.44 (m, 5 H); *m/z* (EI) 281 (M^+, 14%), 91 (100), (found: 281.0889. $C_{13}H_{15}NO_6$ requires 281.0899).

6.H_2O. White crystals (from H_2O-EtOH), m.p. 161°C, $[\alpha]^{29}_D$ +7.3 (*c* 1.0, AcOH), $[\alpha]^{30}_D$ +1.6 (*c* 0.7, H_2O). (Found: C, 36.1; H, 6.6; N, 8.2. $C_5H_9NO_4.H_2O$ requires C, 36.4; H, 6.7; N, 8.5%); ^{1}H NMR (250 MHz, D_2O): δ = 2.57 (dd, 1 H, *J* 17.5, 7.5 Hz), 2.72 (dd, 1 H, *J* 17.5, 6 Hz), 2.88-2.99 (m, 1 H), 3.15 (dd, 1 H, *J* 13, 4.5 Hz), 3.22 (dd, 1 H, *J* 13, 9 Hz).

7. White crystals, chromatographed on silica gel in EtOAc, m.p. 78-80°C. ^{1}H NMR (250 MHz, $CDCl_3$) δ = 2.55 (dd, 1 H, *J* 17.5, 10 Hz), 2.67 (dd, 1 H, *J* 17.5, 7.5 Hz), 3.28-3.45 (m, 1 H), 3.62 ('d', 2 H, *J* 7.5 Hz), 3.74 (s, 3 H).

9. White crystals (from EtOAc), m.p. 199-202°C (lit.[12] for *ent*-**9**, 202-204°C), $[\alpha]^{30}_D$ -100 (*c* 1.1, MeOH) [lit.[12] for *ent*-**9**, +102 (MeOH)].

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