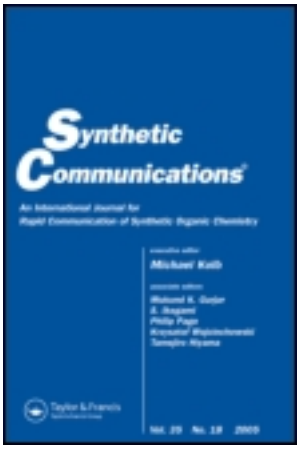

Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

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Version of record first published: 15 Feb 2011.

To cite this article: Andrew B. Hughes & Brad E. Sleebs (2008): Studies of 2-Substituted 1,3-Oxazolidin-5-ones and 1,3-Oxazinan-6-ones as Precursors for the Synthesis of N-Alkyl-β-Amino Acids, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 39:1, 48-60

To link to this article: http://dx.doi.org/10.1080/00397910802369612

Synthetic Communications®, 39: 48–60, 2009

ISSN: 0039-7911 print/1532-2432 online
DOI: 10.1080/00397910802369612

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Studies of 2-Substituted 1,3-Oxazolidin-5-ones and 1,3-Oxazinan-6-ones as Precursors for the Synthesis of *N*-Alkyl-β-Amino Acids

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Abstract: 1,3-Oxazolidin-5-ones and 1,3-oxazinan-6-ones have been shown to be useful precursors for the synthesis of *N*-methyl α- and β-amino acids, respectively. The methodology has now been expanded to allow for the synthesis of *N*-alkyl-β-amino acids.

Keywords: β-Amino acids, Arndt–Eistert homologation, 1,3-oxazolidin-5-ones, 1,3-oxazinan-6-ones

INTRODUCTION

N-Alkyl-β-amino acid and α-amino acid residues are of particular interest in peptidomimetics. α-Amino acid–derived peptides readily undergo proteolysis and possess poor membrane permeability. However, incorporation of *N*-alkyl-α- and β-amino acid residues, into a peptidomimetic may enhance its lipophilic character and confer proteolytic stability.[1] Hence, *N*-alkyl-β-amino residues have the capability to be useful entities in the area of peptidomimetics and therefore, potentially, the drug industry.

Received April 30, 2008.
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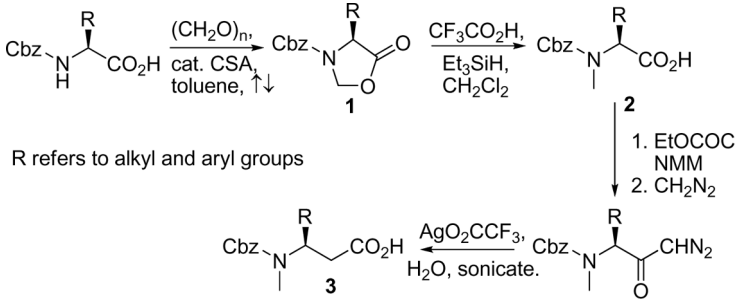
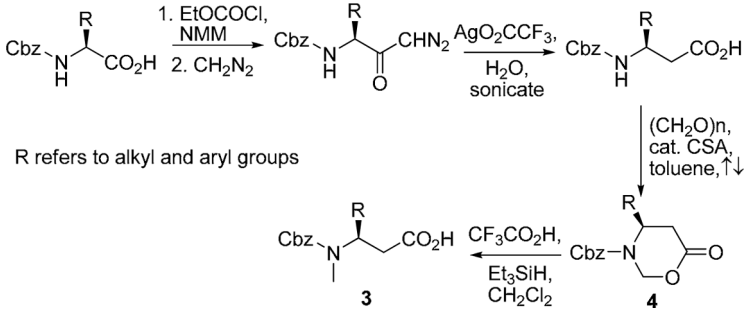


Scheme 1. Synthesis of *N*-methyl-α-amino acids **2** and *N*-methyl-β-amino acids **3** via 1,3-oxazolidin-5-ones **1**.

Such is the interest in *N*-methyl-amino acids that there is now a plethora of methods available for their synthesis.[2] Many of these methods can be applied to the synthesis of *N*-alkyl-amino acids. The most popular method is the use of a strong base in an *N*-alkylation reaction. However, potential exists when using a strong base for racemization of the chiral center.[3]

In previous studies, we have shown that 1,3-oxazolidin-5-ones **1** are useful substrates for the synthesis of *N*-methyl-α-amino acids **2** and *N*-methyl-β-amino acids **3** (Scheme 1).[4–9] In addition, we have also shown that the homologous 1,3-oxazinan-6-ones **4** are versatile precursors for gaining access to a range of *N*-methyl-β-amino acids **3** (Scheme 2).[7–9] Further, we provided one example of an *N*-alkyl-α-residue.[10] Herein we expand on this methodology to enable facile access to *N*-alkyl-β-amino acids.



Scheme 2. Synthesis of *N*-methyl-β-amino acids **3** via 1,3-oxazinan-6-ones **4**.

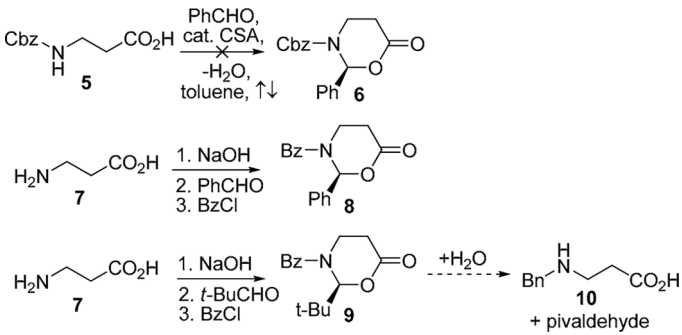
RESULTS AND DISCUSSION

In an extension of our previous work (Schemes 1 and 2)[7–9] it was envisaged that both 1,3-oxazolidin-5-ones and 1,3-oxazinan-6-ones could provide access to *N*-alkyl-β-amino acids by replacing formaldehyde with an aliphatic aldehyde. We first concentrated efforts on the synthesis of 2-substituted-1,3-oxazinan-6-ones to provide access to *N*-alkyl-β-amino acids.

The Cbz-*N*-β-amino acid **5** was subjected to condensation conditions used previously,[6] only varying paraformaldehyde to benzaldehyde (Scheme 3). However, under these conditions, no 2-substituted-1,3-oxazinan-6-one **6** was formed. An alternative route was therefore sought. Hiskey and Jung[11] demonstrated utilization of an amino acid Schiff's base to provide access to 2-oxazolidinones. Applying this methodology, initial condensation of benzaldehyde with a sodium salt of *β*-alanine **7** to form a Schiff's base and subsequent benzoylation allowed ring closure to provide the 2-substituted-1,3-oxazinan-6-one **8** in low yield (14%) (Scheme 3).

This methodology was then applied using pivaldehyde. Again a low yield (10%) of the 2-substituted-1,3-oxazinan-6-one **9** was obtained. It was found in ^{1}H NMR analysis of the 2-*t*-butyl-1,3-oxazinan-6-one **9**, that over time the ring underwent hydrolysis back to its parent aldehyde and the *N*-protected-β-alanine **10** (Scheme 3). Thus, the poor yields obtained could be attributed to the degradation of the 2-substituted-1,3-oxazinan-6-ones **6** and **9** once they had formed. Given these results, it was decided not to access *N*-alkyl-β-amino acids via this route.

1,3-Oxazolidin-5-ones **1** have already been used to great effect in the synthesis of *N*-methyl-α-amino acids **2**.[4–8] Ben-Ishai[12] originally demonstrated formaldehyde can be condensed with an amino acid



Scheme 3. Synthesis of 2-substituted-1,3-oxazinan-6-ones.

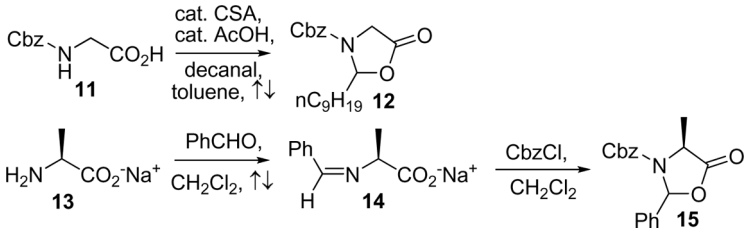
to form a 1,3-oxazolidin-5-one. Similarly, Freidinger et al.[13] produced 2-substituted oxazolidinones that could be subsequently reduced to *N*-alkyl residues. It was proposed to exploit this procedure to obtain the *N*-alkyl α-amino acids. The Arndt–Eistert homologation could then be applied to allow access to *N*-alkyl-β-amino acids.

Following the methodology of Freidinger et al.,[13] the 2-substituted oxazolidinone **12** was formed by refluxing the aldehyde, the *N*-carbamoyl-protected amino acid **11**, and a catalytic amount of camphorsulfonic acid in toluene, with azeotropic removal of water using a Dean–Stark trap. This resulted in a poor yield of the 2-alkyl-1,3-oxazolidin-5-one **12** (30%). However, addition of a catalytic amount of acetic acid to the reaction mixture resulted in the yield of the 2-alkyl-1,3-oxazolidin-5-one **12** increasing two-fold (70%) (Scheme 4).

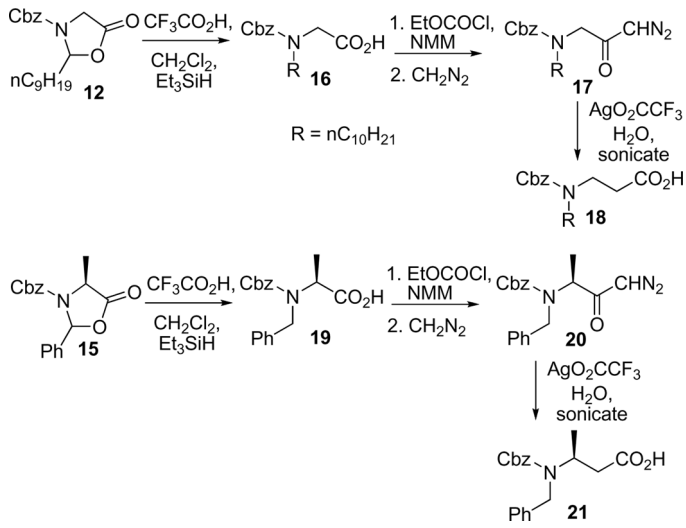
As a comparison, the approach described by Hiskey and Jung[11] was also attempted to gain access to 2-substituted-1,3-oxazolidin-5-ones. The procedure involved condensing the amino acid sodium salt **13** with benzaldehyde to form the Schiff's base **14**. Subsequent *N*-acylation of **14** afforded the 2-substituted oxazolidinone **15** in a mediocre yield (55%) (Scheme 4).

The *N*-carbamoyl 2-substituted oxazolidinones **12** and **15** were then subjected to reductive cleavage to afford the *N*-alkyl α-residues **16** and **19** in good yields (71 and 75%, respectively) (Scheme 5). The Arndt–Eistert homologation was then applied.[14] Activation of **16** and **19** to their mixed anhydrides and subsequent reaction with diazomethane produced the diazoketones **17** and **20** in 60 and 50% yields, respectively. Wolff rearrangement, using ultrasound in the presence of silver trifluoroacetate, produced the desired *N*-alkyl-β-residues **18** and **21** in good yields (66 and 83%, respectively) (Scheme 5).

In conclusion, a facile method was developed to access *N*-alkyl-β-residues. It was found that 2-substituted-1,3-oxazinan-6-ones could not be utilized in the synthesis of *N*-alkyl-β-residues, because of their instability. However, 1,3-oxazolidin-5-ones were successfully utilized as



Scheme 4. Synthesis of 2-substituted-1,3-oxazolidin-5-ones.



Scheme 5. Synthesis of *N*-alkyl-β-amino acids.

precursors to afford *N*-alkyl-β-amino acids in overall good yields. The effective nature of this pathway underpins the viability of such methodology being applied to other α-amino acids to produce various functionalized *N*-alkyl-β-amino acids.

EXPERIMENTAL

General

All melting points are uncorrected and were recorded on a Reichert Thermopan microscope hot-stage apparatus. Infrared spectra were recorded on a Brüker Vector 22 Fourier-transform spectrometer or a Perkin-Elmer 1720-X FT-IR spectrometer using a diffuse reflectance accessory with KBr background. Optical rotations were recorded on a Perkin-Elmer 141 polarimeter. NMR were performed in (D)-chloroform at 300 K unless otherwise stated on a Brüker Avance DRX-300 spectrometer. Electrospray mass spectrometry (ESMS) was performed on a Fission VG Bio-Q electrospray mass spectrometer, in the Department of Chemistry, La Trobe University. Low- and high-resolution mass spectra (LSIMS) were also measured at the University of Tasmania by Noel Davies and coworkers on a Kratos Concept mass spectrometer at 70 eV, all using water/methanol/acetic acid (0:99:1 or 50:50:1) mixtures as the

mobile phase. Microanalyses were performed by E. Mocellin and coworkers from Chemical and Microanalytical Services in Belmont, Victoria. Flash chromatography was carried out using silica-gel 60, particle size 0.040–0.063 μm (230–400 mesh ASTM), supplied by Merck Chemicals. Ethyl acetate and hexane used for chromatography were distilled prior to use. All solvents were purified by distillation. Thin-layer chromatography (TLC) was performed on Merck kieselgel 60 F_{254} plates and visualized with a UV lamp or by staining. Permanganate stain consists of potassium permanganate (1% v/w), potassium carbonate (20% v/w), and sodium hydroxide (1% v/w) in water. Ammonium molybdate stain consists of 7% ammonium molybdate and 10% sulfuric acid in ethanol. Molybdenum polyphosphoric acid stain consists of 10% molybdenum polyphosphoric acid in ethanol. For dry solvents, procedures from Perrin and Armarego[15] were followed. All other reagents and solvents were purified or dried as described by Perrin and Armarego.[15] All synthetic yields reported are unoptimized.

2-Substituted-1,3-oxazinan-6-ones

N-Benzoyl-2-phenyl-6-oxo-1,3-oxazinane **8**

β-Alanine **7** (0.03 mol) was dissolved in a 1 N sodium hydroxide solution (0.03 mol), and the solution was evaporated to dryness under reduced pressure. The residue was suspended in methylene chloride (40 mL), and benzaldehyde (0.036 mol) was added. The solution was refluxed for 6 h, removing water azeotropically using a Dean–Stark trap under an inert atmosphere. The solution was allowed to cool, and benzoyl chloride (0.03 mol) was added at 0 °C. The solution was allowed to warm to room temperature, and it was stirred for 20 h. The mixture was diluted with dichloromethane (30 mL), and the organic layer was washed successively with water (50 mL), saturated sodium hydrogen carbonate (50 mL), 10% citric acid solution (50 mL), and brine (50 mL). The organic layer was dried ($MgSO_4$) and concentrated in vacuo. Column chromatography was performed eluting with 5–15% ethyl acetate–hexane to afford the oxazinanone **8** as a solid (14% yield). Found: C, 72.49; H, 5.32; N, 4.87. $C_{17}H_{15}NO_3$ requires C, 72.58; H, 5.37; N, 4.98%. Mp 99–103 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55–7.42 (10H, m, ArCH), 7.11 (1H, bs, H-2), 4.30 (1H, bs, H-4A), 3.46–3.38 (1H, m, H-4B), 2.88–2.72 (1H, m, H-5A), 2.51–2.41 (1H, m, H-6A). ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.14, 167.54 (CO), 136.17, 133.19 (Aryl C), 130.84, 129.38, 129.04, 128.59, 125.2 (aryl CH), 86.11 (C-2), 36.36 (C-4) 29.32 (C-5).

N-Benzoyl-2-*tert*-butyl-6-oxo-1,3-oxazinane **9**

β-Alanine **7** (0.03 mol) was dissolved in a 1 N sodium hydroxide solution (0.03 mol), and the solution was evaporated to dryness under reduced pressure. The residue was suspended in methylene chloride (40 mL), and pivaldehyde (0.036 mol) was added. The solution was refluxed for 6 h, removing water azeotropically using a Dean–Stark trap under an inert atmosphere. The solution was allowed to cool, and benzoyl chloride (0.03 mol) was added at 0 °C. The solution was allowed to warm to room temperature and stirred for 20 h. The mixture was diluted with dichloromethane (30 mL), and the organic phase was washed successively with water (50 mL), saturated sodium hydrogen carbonate (50 mL), 10% citric acid solution (50 mL), and brine (50 mL). The organic layer was dried ($MgSO_4$) and concentrated in vacuo. Column chromatography was performed eluting with 5–15% ethyl acetate–hexane to afford the oxazinanone **9** as an oil (10% yield) (this compound degraded over time to *N*-benzoyl-β-alanine **10** and pivaldehyde). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38–7.34 (5H, m, ArH), 6.24 (1H, bs, H-2), 4.01 (1H, bs, H-4A), 3.62–3.52 (1H, m, H-4B), 2.48 (2H, bs, H-5), 1.01 [9H, s, $C(CH_3)_3$]. ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.46, 167.10 (CO), 134.20 (aryl C), 130.28, 128.47, 126.52 (aryl CH), 89.91 (C-2), 39.49 (C-4), 38.49 [$\mathbf{C}(CH_3)_3$], 30.43 [C-5], 25.72 ($C(\mathbf{C}H_3)_3$].

2-Alkyl-1,3-Oxazolidin-5-ones

3-Benzyloxycarbonyl-2-nonyl-1,3-oxazolidin-5-one **12**

Camphorsulfonic acid (1.0 mmol), acetic acid (1.0 mmol), and decanal (0.015 mol) were added to the glycine benzylcarbamate **11** (0.01 mol) in toluene (80 mL). The solution was refluxed with azeotropic removal of water using a Dean–Stark trap for 20 h. The solution was concentrated under reduced pressure, and the residue was dissolved in ethyl acetate (70 mL). The organic layer was washed with saturated sodium bicarbonate (70 mL); the organic layer was dried ($MgSO_4$) and concentrated in vacuo. The residue was purified using column chromatography eluting with 5% ethyl acetate–hexane to furnish the oxazolidinone **12** as an oil (70% yield), ν_{max}(NaCl)/cm^{-1}3034, 2926, 2855 (CH), 1807, 1714 (CO), 1416, 1360, 1253, 1080, 766, 698. ^{1}H NMR (300 MHz, $CDCl_3$) (rotamers) δ 7.34 (5H, s, ArH), 5.80–5.77 (1H, m, H-2), 5.18 and 5.13 (2H, q, J_{AB} 12.2 Hz, $ArCH_2O$), 4.21–4.16 (1H, m, H-4), 3.92–3.87 (1H, m, H-2), 1.88–1.71 (2H, m, $CHC\mathbf{H}_2$), 1.23 (14H, bs, $(CH_2)_7$), 0.86 (3H, t, *J* 6.3 Hz, $CH_2C\mathbf{H}_3$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.26, 152.62 (CO),

135.4 (Aryl C), 128.49, 128.36, 128.20, 128.06, 127.89 (Aryl CH), 90.44 (C-2), 67.69 ($ArCH_2$), 44.67 (C-4), 34.81, 31.67, 29.25, 29.22, 29.07, 28.88, 22.69, 22.49 (CH_2), 13.93 ($CH_2\mathbf{C}H_3$).

(4*S*)-Benzyl 4-Methyl-5-oxo-2-phenyl-1,3-oxazolidine-3-carboxylate **15**

L-Alanine (0.03 mol) was dissolved in a 1 N sodium hydroxide solution (0.03 mol), and the solution was evaporated to dryness under reduced pressure. The residue was suspended in methylene chloride (40 mL), and benzaldehyde (0.036 mol) was added. The solution was refluxed for 6 h, removing water azeotropically using a Dean–Stark trap under an inert atmosphere. The solution was allowed to cool, and benzyl chloroformate (0.03 mol) was added at 0 °C. The solution was allowed to warm to room temperature, and it was stirred for 20 h. The mixture was diluted with dichloromethane (30 mL) and washed successively with water (50 mL), saturated sodium hydrogen carbonate (50 mL), 10% citric acid solution (50 mL), and brine (50 mL). The organic layer was dried ($MgSO_4$) and concentrated in vacuo. Column chromatography was performed on the residue, eluting with 15% ethyl acetate–hexane to afford the oxazolidinone **15** as an oil (55% yield), which was identical in all respects with previously reported material.[16]

N-Alkyl-α-amino Acids

N-Benzyloxycarbonyl-*N*-decyl-acetic Acid **16**

Triethylsilane (10 mmol) was added to the oxazolidinone **12** (5 mmol) dissolved in dichloromethane (5 mL) and trifluoroacetic acid (5 mL). The solution was allowed to stand for 3 days. The mixture was evaporated under reduced pressure; the residue was dissolved in toluene (10 mL) and reduced in vacuo (2×). The resulting oil was purified using column chromatography, eluting with 20% ethyl acetate–hexane, to afford the acid **16** as a clear colorless oil (71% yield). Found: M + H, 350.2332. $C_{20}H_{31}NO_4$ requires M + H, 350.2331. $\nu_{max}(NaCl)/cm^{-1}$ 3300 (OH), 3034, 2925, 2854 (CH), 1714, 1696, 1681 (CO), 1429, 1367, 1226, 1107, 696. ^1H NMR (300 MHz, $CDCl_3$) δ 7.90 (1H, s, COOH), 7.33–7.29 (5H, m, ArH), 5.15–5.12 (2H, m, $ArCH_2$), 4.03–3.98 (2H, m, NCH_2CO), 3.35–3.29 (2H, m, NCH_2), 1.51–1.23 [16H, m, $(CH_2)_8$], 0.87 (3H, t, *J* 6.6 Hz, $CH_2C\mathbf{H}_3$). ^{13}C NMR (75 MHz, $CDCl_3$) (rotamers) δ 174.80, 174.42, 156.83, 155.91 (CO), 136.31 (aryl C), 128.40, 127.96, 127.88, 127.70 (aryl CH), 67.61, 67.40 ($ArCH_2$), 48.79, 48.29 ($N\mathbf{C}H_2CO$),

31.81 (NCH_2), 29.46, 29.22, 28.17, 27.97, 26.60 (CH_2), 22.60 ($\mathbf{C}H_2CH_3$), 14.04 ($CH_2\mathbf{C}H_3$).

(2*S*)-*N*-(Benzyloxycarbonyl)-2-aminobenzyl-propanoic Acid **19**

Triethylsilane (10 mmol) was added to the oxazolidinone **15** (5 mmol) dissolved in dichloromethane (5 mL) and trifluroacetic acid (5 mL). The solution was allowed to stand for 3 days. The mixture was evaporated under reduced pressure, the residue was dissolved in toluene (10 mL), and the solution was concentrated in vacuo (2×). The resulting oil was purified using column chromatography eluting with 20% ethyl acetate–hexane to furnish the acid **19** as a clear colorless oil (75% yield). (Found: M + H, 314.1396. $C_{18}H_{20}NO_4$ requires M + H, 314.1392. $[\alpha]_D^{20}$-29.2 (*c*, 0.68 in CH_2Cl_2). ν_{max}(NaCl)/cm^{-1} 3089, 2946 (CH), 1703 (CO), 1454, 1238, 1015, 735, 698. ^{1}H NMR (300 MHz, $CDCl_3$) (rotamers) δ 9.39 (1H, bs, COOH), 7.30 (10H, s, ArH), 5.18 (2H, s, $ArCH_2$), 4.73–4.24 (3H, m, NCH, NCH_2), 1.41–1.39 (3H, d, *J* 7.0 Hz, $CHC\mathbf{H}_3$). ^{13}C NMR (75 MHz, $CDCl_3$) (rotamers) δ 177.26, 156.45 (CO), 137.95, 136.08 (aryl C), 128.49, 128.40, 127.98, 127.78, 127.26, 127.06 (aryl CH), 67.71 ($ArCH_2$), 55.45, 54.99 (NCH), 51.03, 50.05 (NCH_2), 15.76, 15.10 ($CH\mathbf{C}H_3$).

N-Alkyl-diazoketones

N-Benzyloxycarbonyl-3-aminodecyl-1-diazo-propan-2-one **17**

The *N*-alkyl residue **16** (1 mmol) was dissolved in anhydrous THF (5 ml/mmol), and the solution was cooled to −15 °C. To the solution, ethyl chloroformate (1.05 mmol) and *N*-methylmorpholine (1.05 mmol) were added successively, and the mixture was stirred for 15 min before an anhydrous dichloromethane solution of diazomethane (5 mmol) (CAUTION!) was added slowly to the mixture. The yellow solution was allowed to warm to room temperature, and it was stirred for 1 h. Excess diazomethane was destroyed by addition of acetic acid. The mixture was concentrated under reduced pressure, and the residue was dissolved in ethyl acetate (30 mL). The organic phase was washed successively with saturated sodium bicarbonate (25 mL), 10% citric acid solution (25 mL), and brine (25 mL). The organic layer was dried ($MgSO_4$) and concentrated in vacuo. The residue was of sufficient purity to be used in the following reaction. If required for analysis, compounds

were purified using column chromatography, eluting with 5–10% ethyl acetate–hexane to afford the diazoketone **17** as a clear yellow oil (60% yield). Found: M + H, 374.2444. $C_{21}H_{32}N_3O_3$ requires M + H, 374.2441. ν_{max}(NaCl)/cm^{-1} 3089, 2925, 2854 (CH), 2107 (CHN_2) 1701, 1654, (CO), 1497, 1466, 1362, 1226, 1107, 770, 697. ^{1}H NMR (300 MHz, $CDCl_3$) (rotamers) δ 7.23–7.20 (5H, m, ArH), 5.33–5.22 (1H, m, CHN_2), 5.04–5.01 (2H, m, $ArCH_2$), 3.87–3.82 (2H, m, NCH_2CO), 3.22–3.18 (2H, m, NCH_2), 1.42–1.17 [16H, m, $(CH_2)_8$], 0.79 (3H, t, *J* 6.2 Hz, $CH_2C\mathbf{H}_3$). ^{13}C NMR (75 MHz, $CDCl_3$) (rotamers) δ 191.03, 190.83, 156.00, 155.19 (CO), 136.06 (aryl C), 128.39, 127.99, 127.81, 127.57, 127.41, 127.34 (aryl CH), 66.97, 66.87 ($ArCH_2$), 54.30, 54.01 (CHN_2), 48.51, 47.96 ($N\mathbf{C}H_2CO$), 31.43 (NCH_2), 29.08, 28.84, 27.82, 27.45, 26.24 (CH_2), 22.27 ($\mathbf{C}H_2CH_3$), 13.65 ($CH_2\mathbf{C}H_3$).

(3*S*)-*N*-Benzyloxycarbonyl-3-aminobenzyl-1-diazo-butan-2-one **20**

The *N*-alkyl residue **19** (1 mmol) was dissolved in anhydrous THF (5 ml/mmol) and the solution was cooled to − 15 °C. To the solution, ethyl chloroformate (1.05 mmol) and *N*-methylmorpholine (1.05 mmol) were added successively, and the mixture was stirred for 15 min before an anhydrous dichloromethane solution of diazomethane (5 mmol) (CAUTION!) was added slowly to the mixture. The yellow solution was allowed to warm to room temperature, and it was stirred for 1 h. Excess diazomethane was destroyed by addition of acetic acid. The mixture was concentrated under reduced pressure, and the residue was dissolved in ethyl acetate (30 mL). The organic phase was washed successively with saturated sodium bicarbonate (25 mL), 10% citric acid solution (25 mL), and brine (25 mL). The organic layer was dried ($MgSO_4$) and concentrated in vacuo. The residue was of sufficient purity to be used in the following reaction. If required for analysis, compounds were purified using column chromatography, eluting with 5–10% ethyl acetate–hexane to afford the diazoketone **20** as a clear yellow oil (50% yield). Found: M + H, 338.1508. $C_{19}H_{20}N_3O_3$ requires M + H, 338.3805). $[\alpha]_D^{20}$ − 106.1 (*c*, 2.6 in CH_2Cl_2). ν_{max}(NaCl)/cm^{-1} 3065, 2943 (CH), 2106 (CHN_2), 1697, 1645 (CO), 1496, 1454, 1358, 1244, 770, 699. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 (10H, s, ArH), 5.39–5.15 (3H, m, CHN_2, $ArCH_2$), 4.90–4.30 (3H, m, NCH, NCH_2), 1.27 (3H, d, *J* 4.3 Hz, $CHC\mathbf{H}_3$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.70, 155.91 (CO), 137.94, 135.95 (aryl C), 128.20, 128.12, 127.78, 127.72, 127.06 (aryl CH), 67.39 ($ArCH_2$), 58.97 (CHN_2), 52.82 (NCH), 49.40 (NCH_2), 14.08 ($CH\mathbf{C}H_3$).

N-Alkyl-β-amino Acids

N-Benzyloxycarbonyl-3-aminodecyl-propanoic Acid **18**

The diazoketone **17** (1 mmol) was dissolved in a solution of dioxane/water (9:1, v/v, 15 mL). On addition of silver trifluoroacetate (0.01 mmol), the mixture was sonicated in an ultrasound bath for 30 min or until no presence of the diazoketone remained as indicated by TLC (ethyl acetate–hexane). The mixture was concentrated in vacuo. The resulting residue was purified using column chromatography eluting with 20% ethyl acetate–hexane to afford the acid **18** as a clear colorless oil (66% yield). Found: C, 69.37; H, 9.17; N, 3.76. $C_{21}H_{33}NO_4$ requires C, 69.39; H, 9.15; N, 3.85% ν_{max}(NaCl)/cm^{-1} 3034, 2926, 2855 (CH), 1736, 1706, (CO), 1408, 1424, 1283, 1137, 1101, 770, 697. ^{1}H NMR (300 MHz, $CDCl_3$) (rotamers) δ 9.60 (1H, bs, COOH), 7.31 (5H, s, ArH), 5.12 (2H, s, $ArCH_2$), 3.55–3.51 (2H, m, NCH_2), 3.27–3.30 (2H, m, CH_2CO), 2.66–2.62 (2H, m, NCH_2), 1.50–1.23 [16H, m, $(CH_2)_8$], 0.87 (3H, t, *J* 6.5 Hz, $CH_2C\mathbf{H}_3$). ^{13}C NMR (75 MHz, $CDCl_3$) (rotamers) δ 176.58, 156.14 (CO), 136.44 (aryl C), 128.29, 127.80, 127.63, 126.84 (aryl CH), 67.07 ($ArCH_2$), 48.00, 47.81 ($N\mathbf{C}H_2$), 43.46, 42.65 (CH_2CO), 33.52, 32.92 ($N\mathbf{C}H_2CH_2$), 31.72, 29.37, 29.13, 28.49, 28.00, 26.56 (CH_2), 22.51 ($\mathbf{C}H_2CH_3$), 13.94 ($CH_2\mathbf{C}H_3$).

(3*S*)-*N*-Benzyloxycarbonyl-3-aminobenzyl-butanoic Acid **21**

The diazoketone **20** (1 mmol) was dissolved in a solution of dioxane/water (9:1, v/v, 15 mL). On addition of silver trifluoroacetate (0.01 mmol), the mixture was sonicated in an ultrasound bath for 30 min or until no presence of the diazoketone remained as indicated by TLC (ethyl acetate–hexane). The mixture was concentrated in vacuo. The resulting residue was purified using column chromatography eluting with 20% ethyl acetate–hexane, to afford the acid **21** as a clear colorless oil (83% yield). Found: M + H, 328.1547. $C_{19}H_{22}NO_4$ requires M + H, 328.1549). $[\alpha]_D^{20}$ + 23.6 (*c*, 1.2 in CH_2Cl_2). ν_{max}(NaCl)/cm^{-1} 3065, 2977 (CH), 1713, 1681 (CO), 1454, 1338, 1215, 1170, 735, 698. ^{1}H NMR (300 MHz, $CDCl_3$) (323 K) δ 10.46 (1H, bs, CO_2H), 7.31–7.27 (10H, m, ArH), 5.21 (2H, s, $ArCH_2$), 4.64–4.32 (3H, m, NCH_2, NCH), 2.76–2.54 (2H, m, CH_2CO), 1.23 (3H, bs, $CHC\mathbf{H}_3$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.62, 156.82 (CO), 138.07, 136.09 (aryl C), 128.50, 128.44, 128.07, 127.92, 127.32 (aryl CH), 67.82 ($ArCH_2$), 50.80 (NCH), 49.68 (NCH_2), 39.45 (CH_2CO), 18.71 ($CH\mathbf{C}H_3$).

ACKNOWLEDGMENT

The authors thank La Trobe University for a post graduate scholarship provided to B.E.S.

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