# Synthesis of α,α-Disubstituted β-Amino Esters and Peptide Derivatives

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**Abstract:** The synthesis of α,α-disubstituted β-amino esters and peptide derivatives from readily available 4-spiro-β-lactams **1** is described. The geminally disubstituted β-amino esters are obtained from the *N*-Boc spiro β-lactams **2** by treatment with potassium cyanide in methanol. Alternatively, the use of spiro β-lactams **2** as acylating agents of the amino group of *C*-protected amino acids, allowed its direct incorporation into a peptidic chain.

**Key words:** amino acids, lactams, peptides, ring opening, spiro compounds

β-Amino acids have attracted a great deal of interest during the last few years due to their presence in a wide number of natural products (e.g., the side chain of the anticancer agent, taxol). On the other hand, and perhaps even more interesting, recent results show that synthetic β-peptides (β-amino acids oligomers) present some interesting features. They form much more stable secondary structures than do their parents α-peptides,[1] and some of them exhibit biological activity acting as inhibitors of cholesterol and fat absorption[2] or as antibiotics.[3]

Among the available methods for the synthesis of β-amino acids (α- or β-monosubstituted), just a few are suitable for the preparation of α,α- and β,β-disubstituted ones.[4] Seebach et al.[5] have recently shown that α,α-disubstitution in β-peptides leads to the formation of very stable peptide secondary structures. In this context, especially remarkable folding properties were observed in β-peptides bearing a cyclic α,α-disubstitution pattern (Figure 1). These cyclic α,α-disubstituted β-peptides adopt unprecedented peptide secondary structures not only in the α-amino acid field, but also in realm of β-peptides.[6]

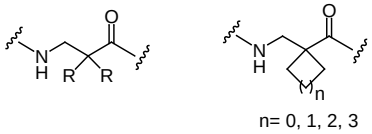
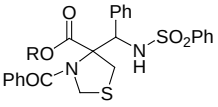



**Figure 1**

In this paper we describe the synthesis of cyclic α,α-disubstituted β-amino esters and peptide derivatives employing 4-spiro β-lactams **1** as starting materials (Scheme 1).[7] β-Lactams can be viewed as cyclic β-amino acids, in which both the amino and the acid moieties are simultaneously protected, and therefore they are usually employed as precursors of β-amino acids.[8] It is interesting to point out that a few synthetic methodologies to prepare spiro β-lactams have been described so far,[9] and only in one case they were employed as precursors of cyclic α,α-disubstituted β-amino acid derivatives (Figure 2).[10]




R= H, Me, Et

**Figure 2**

At this point, we thought that 4-spiro β-lactams **1**, could be useful intermediates for the preparation of β-amino acids with α,α-cyclic disubstitution. These α,α-disubstituted cyclic β-amino acids present some new interesting structural features: a) their unsymmetrical (tetrahydrofuran ring) α,α-disubstitution (almost all previously described cyclic α,α- or β,β-disubstituted β-amino acids bear a cycloalkane ring);[6,11] b) the presence of an oxygen atom in the tetrahydrofuran ring, since oxygen could act as a hydrogen bond acceptor increasing the conformational β-peptide possibilities and their hydrogen bond interactions with peptide receptors.

Although β-amino acids could be directly obtained from *N*-alkyl or *N*-aryl β-lactams by treatment with HCl (6 N) at 100 ºC, we previously transformed the β-lactams **1** to the *N*-Boc derivatives **2** (Scheme 1). The presence of an electron-withdrawing group, as the *tert*-butoxycarbonyl, on the β-lactam nitrogen allowed the cleavage of the amide bond under milder reaction conditions. Oxidative removal of the *N*-protecting *p*-methoxyphenyl group (PMP) with ceric ammonium nitrate (CAN)[12] and further treatment with di-*tert*-butyldicarbonate [$(Boc)_2O$] in the presence of a catalytic amount of DMAP[11] (Scheme 1) lead to the formation of *N*-Boc β-lactams **2**. These compounds were treated with a catalytic amount of potassium cyanide in methanol to give the α,α-disubstituted β-amino esters **3** in high yields (Table 1).[13]

The Boc protecting group on the β-amino ester **3a** could be easily removed by reaction with trifluoroacetic acid in dichloromethane at 0 ºC affording the free amine, that was directly coupled with a *N*-protected α-amino acid to give peptides **4** and **5** in good yields (Scheme 2).[14] Unfortu-

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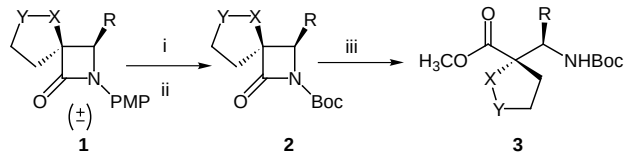



PMP= *p*-Methoxyphenyl

**Scheme 1** i) CAN, $H_2O/CH_3CN$, 0 °C, 30 min ii) $(Boc)_2O$, DMAP (cat.), $CH_3CN$, 0 ºC to r.t., 16 h. (40–83%) two steps iii) KCN (cat.), MeOH, r.t., 16 h

**Table 1** α,α-Disubstituted β-Amino Esters (**3**)

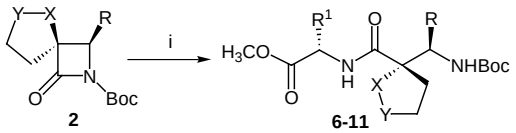
| | R | X | Y | Yield |
|---|---|---|---|---|
| **3a** | $C_6H_5$– | O | $CH_2$ | 93% |
| **3b** | $C_6H_5CH$=CH– | O | $CH_2$ | 95% |
| **3c** | $C_6H_5$– | $CH_2$ | O | 95% |

nately, the 1:1 diastereoisomeric mixtures obtained could not be separated by column chromatography.

The enhanced amide bond reactivity of the *N*-Boc β-lactams allowed its employment as acylating agent. Different nucleophiles can be used to promote the ring opening of the β-lactam. Thus, β-lactams can be directly coupled with the amino group of an α-aminoester[15] or with an alcohol[16] to form a peptidic bond or an ester respectively. The big influence of the steric hindrance at the 3- and 4-positions of the *N*-Boc β-lactams on its reactivity has also been reported. In these cases, a ring opening promoter additive like sodium azide[17] or potassium cyanide[12] is usually needed. In our case, we have observed the aforementioned influence of the steric hindrance of substituents at 3- and 4-positions in the ring opening of *N*-Boc β-lactams. In addition, the influence of the steric hindrance of the substituent at Cα of the α-amino ester employed as nucleophile in the ring opening, was also observed.

Due to the spiro substitution at the 4-position of our β-lactams **2**, we initially assumed that it would be necessary to use a ring-opening promoter for the coupling reaction with different α-amino esters (Scheme 3). This assumption was true for all cases except for the glycine methyl ester, which was coupled at r.t. in DMF without any ring opening promoter additive, to afford the dipeptide **6** in good yield. No coupling reaction was observed with other α-amino esters under these experimental conditions. The reactions were then carried out in DMF at 40 ºC in the presence of 1.5 equiv of potassium cyanide as a ring opening promoter, and 2 equiv of the amino ester, to give the peptides **6**–**11** (Table 2).[18] The 1:1 mixture of diastereoisomers obtained could be separated by column chromatography in the case of peptides **7** and **8**.[19]

One of the most popular procedures to establish the absolute configuration of a chiral secondary alcohol or a primary α-substituted amine is the NMR approach,[20] employing auxiliary reagents like α-metoxy-α-trifluoromethylphenyl acetic acid (MTPA) introduced by Mosher.[21]

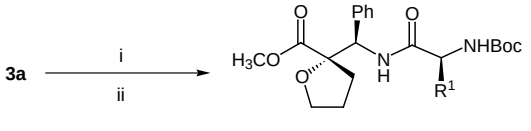



**Scheme 3** i) KCN (1.5 equiv), α-aminoester (2 equiv), DMF 40 ºC, 18 h. ii) Aqueous work up and chromatographic purification

**Table 2** Peptides **6**–**11**

| | X | Y | R | $R^1$ | Rto.[a] |
|---|---|---|---|---|---|
| **6** | O | $CH_2$ | $C_6H_5$– | H– | 82%[b] |
| **7a,b** | O | $CH_2$ | $C_6H_5$– | $CH_3$– | 66%[c] |
| **8a,b** | O | $CH_2$ | $C_6H_5$– | $(CH_3)_2CHCH_2$– | 56%[c] |
| **9** | O | $CH_2$ | $C_6H_5CH$=CH– | $CH_3$– | 64%[d] |
| **10** | $CH_2$ | O | $C_6H_5$– | $CH_3$– | 53%[d] |
| **11** | $CH_2$ | O | $C_6H_5$– | $(CH_3)_2CHCH_2$– | 49%[d] |

[a] Yield referred to the mixture of stereoisomers.
[b] Reaction carried out without KCN at r.t.
[c] Separable stereoisomers.
[d] Not separable stereoisomers.

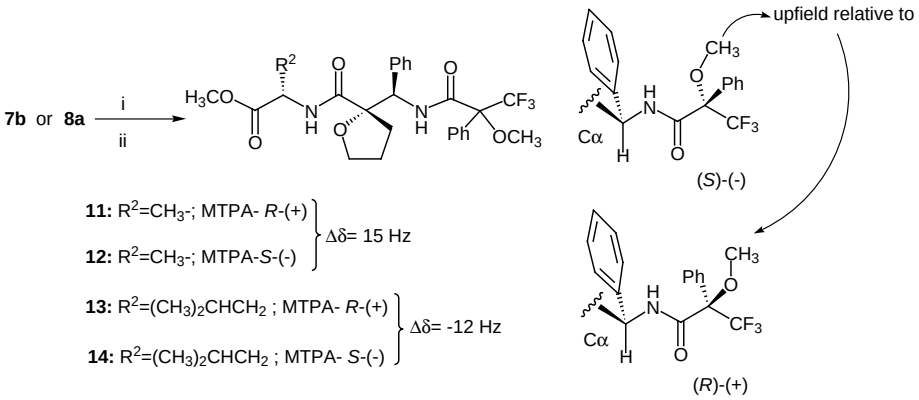



**4:** $R^1$=$CH_3$- 81%

**5:** $R^1$=Bn- 76%

**Scheme 2** i) TFA, $CH_2Cl_2$ 0 ºC to r.t., 2 h ii) HOBT, DCC, BocN-$HCH(R^1)CO_2H$, THF, 0 ºC to r.t., 16 h

Therefore, we removed the Boc protecting group of diastereoisomers **7b** and **8a**. Reaction of the amines with both enantiomers of Mosher's acid chloride (MTPACl) (Scheme 4) gave the diastereoisomeric amides **11**-**14**. The difference in the $^1$H NMR chemical shifts values ($\Delta\delta = \delta_{(S)MTPA} - \delta_{(R)MTPA}$) of the methoxy group of the diastereoisomeric MTPA amides, were employed to determine the absolute configuration of compounds **7b** and **8a** (Figure 3). The influence of the phenyl ring anisotropy on the Cα of the MTPA amide in the chemical shift value of methoxy group, allowed us to establish the absolute configuration of this chiral centre. We assume that the difference in chemical shift observed in the methoxy group of compounds **11**,**12** and **13**,**14**, is due to the anisotropic shielding produced by the Cα aromatic ring depending upon the absolute stereochemistry of this chiral centre as can be seen in the model proposed by Mosher et al. (Scheme 4).[20a] This result, in conjunction with previous




**Scheme 4** i) TFA, $CH_2Cl_2$, 0 ºC to r.t., 2 h ii) (+or –) MTPA acid chloride (1.2 equiv), $NEt_3$, $CH_2Cl_2$, r.t., 16 h

NOE experiments on the starting spiro β-lactam that revealed the *cis* relative stereochemistry of the 3- and 4-substituents, allowed us to establish the absolute stereochemistry of the peptide derivatives (Figure 2).

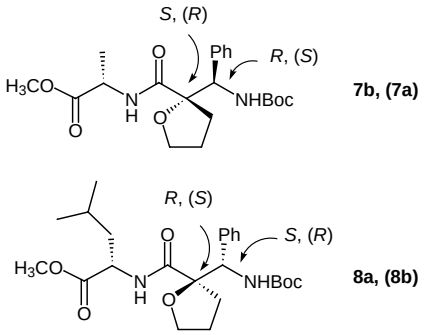



**Figure 3** Assignment of the stereochemistry of the peptides **7b** and **8a**. Peptides **7a** and **8b** are in parentheses

In conclusion, we have shown the synthetic utility of the readily available 4-spiro β-lactams in the synthesis of new α,α-cyclic disubstituted β-amino esters and peptide derivatives. These compounds have been shown as useful precursors for the construction of β-peptides with new folding patterns.

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(7) Typical experimental procedure for **1**: To a solution of the imine (2 mmol) and dry $Et_3N$ (0.41 mL, 3 mmol) in dry refluxing toluene (15 mL) was added dropwise a solution of the corresponding 2- or 3-tetrahydrofuroyl chloride (0.269 g, 2 mmol) in toluene (5 mL). The reaction mixture was refluxed overnight, cooled to r.t., and diluted with $CH_2Cl_2$ (30 mL). The resultant solution was washed with 5% $NaHCO_3$(20 mL) and brine (20 mL). The organic layer was dried ($Na_2SO_4$) and concentrated in vacuo. Flash chromatography over silica gel (EtOAc–hexanes) of the crude reactions afforded the final spiro β-lactams **1**.
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(13) Typical experimental procedure for **3**: To a stirred solution of the *N*-Boc β-lactam **2** (1 mmol) in MeOH (10 mL) was added a catalytic amount of potassium cyanide (10–15% mol). After the consumption of the starting material (monitored by TLC), the methanol was removed in vacuo, 10 mL of $NaHCO_3$ (5%) and 10 mL of EtOAc were then added. The aqueous solution was extracted with EtOAc (2 × 15 mL). The mixed organic layers were washed with brine (2 × 25 mL) and dried over anhydrous $Na_2SO_4$ and concentrated in vacuo. The crude oil was submitted to a short silica gel column chromatography (1:1, EtOAc–hexanes) to afford **3a**–**c**. Data for **3a**: IR (KBr): 3465, 1736, 1686, 1095 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$): δ 1.36 (s, 9 H), 1.64 (m, 1 H), 1.86 (m, 2 H), 2.08 (m, 1 H), 3.74 (s, 3 H), 3.86 (m, 2 H), 5.04 (d, *J* = 10.0 Hz, 1 H), 5.79 (broad d, *J* = 10.0 Hz, 1 H), 7.29 (m, 5 H). $^{13}C$ NMR (75 MHz, $CDCl_3$): δ 174.2, 154.6, 137.8, 128.2, 127.8, 127.4, 88.2, 79.1, 69.5, 58.6, 52.2, 33.2, 27.9, 24.7. HRMS calcd for $C_{14}H_{16}NO_4$ 262.1077 ($M^+ - C_4H_9$), found 262.1079.
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(18) Typical experimental procedure for **7-13**: To a solution of the *N*-Boc β-lactam **2** (1 mmol) in dry DMF (10 mL) at 40 ºC was added 2 mmol of the corresponding amino ester and (77 mg, 1.5 equiv) of KCN. After stirring the solution during 16 h, brine (10 mL) was added. The solution was extracted with EtOAc (2 × 15 mL) and the mixed organic layers were washed with 5% $NaHCO_3$ (15 mL), 1 N HCl (15 mL) and brine (25 mL). The organic layer was dried over anhydrous $Na_2SO_4$ and concentrated in vacuo. Flash chromatography over silica gel (EtOAc-hexanes) of the crude reactions afforded the final dipeptides **6-11**. Data for **8a**: $[\alpha]_D^{20} = -30.8$ (c = 0.76, $CHCl_3$); IR (KBr): 3323, 1731, 1697, 1646 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$): δ 0.89 (d, *J* = 6.2 Hz, 6 H), 1.38 (s, 9 H), 1.50 (m, 3 H)1.82 (m, 1 H), 2.24 (m, 1 H), 3.58 (s, 3 H), 3.98 (m, 2 H), 4.45 (m, 1 H), 4.76 (d, *J* = 9.2 Hz, 1 H), 6.56 (broad d, *J* = 9 Hz, 1 H), 6.87 (broad d, *J* = 9.2 Hz, 1 H), 7.27 (m, 5 H). $^{13}C$ NMR (75 MHz, $CDCl_3$): δ 173.7, 171.7, 155.2, 138.6, 127.6, 127.5, 127.1, 87.6, 79.1, 69.6, 59.4, 52.0, 49.9, 41.3, 34.6, 28.1, 25.4, 24.7, 22.6, 21.5. HRMS calcd for $C_{14}H_{16}NO_4$ 448.2573 ($M^+$), found 448.2576.
(19) Compound letter were assigned according to their $R_f$ values in column chromatography (silica gel Merck 230-400 mesh, 1:1, hexane-EtOAc as eluent). $R_f$ **7a**<**7b**; $R_f$ **8a**<**8b**.
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