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# Synthesis of Thiazole, Imidazole and Oxazole Containing Amino Acids for Peptide Backbone Modification

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Abstract: Novel 5-ring heterocyclic building blocks are synthesized. These can be incorporated into analogs of peptide antibiotics such as microcin B17, which is a potent DNA-gyrase inhibitor that exhibits eight thiazole and oxazole moieties. In particular, the syntheses of imidazole and bisoxazole amino acids as novel peptidomimetics are reported, this includes a new procedure for the oxidative conversion of the intermediates oxazoline, imidazoline as well as oxazole–oxazoline into the corresponding heteroaromatic compounds. A mixture of 1,8-diazabicyclo-[5.4.0.]-undec-7-ene/carbon tetrachloride/acetonitrile and pyridine proved to be a very effective and mild agent. Copyright © 1999 European Peptide Society and John Wiley & Sons, Ltd.

Keywords: peptidomimetics; thiazole; imidazole; oxazole; oxazolyl–oxazole

## INTRODUCTION

The variety of natural products containing thiazole, oxazole and imidazole rings have encouraged numerous synthetic efforts. During the last decade a particularly broad spectrum of 5-ring heterocycles containing natural products, has been isolated from marine organisms [1–3]. Such 1,3-oxazole, thiazole and imidazole derivatives are the subjects of intensive research [4–16]. In particular, thiazole, oxazole and imidazole amino acids, which may also play a key role in biological activities of unusual peptides, are important intermediates for natural product synthesis and peptidomimetics. As part of our successful total synthesis of the 43-peptide gyrase inhibitor microcin B17 [17–21], we have developed efficient methods for the preparation of various thiazole and oxazole derived amino acids which are characteristic structural elements of this antibiotic. In this article, we report novel 5-ring heterocyclic building blocks that can be easily incorporated into new analogs of microcin B17 and related peptides. We discovered a novel procedure for the oxidative conversion of an imidazoline intermediate into the corresponding imidazoles using a mixture of 1,8-diazabicyclo[5.4.0.]-undec-7-ene, $CCl_4$, acetonitrile and pyridine [21].

## MATERIALS AND METHODS

Thin-layer chromatography: TLC-silica gel plates, glass sheets coated with silica gel (E. Merck, Darmstadt); solvent systems: A = $CHCl_3$/MeOH/$H_2O$ (80/30/5); B = $CHCl_3$/MeOH/$CH_3COOH$ (95/5/3); C = $CHCl_3$/MeOH/(9/1); D = EtOAc/*n*-hexane (1/1). Silica gel for flash chromatography was from J.T. Baker (Deventer, Holland).

Abbreviations: Boc, *tert*-butoxycarbonyl; Fmoc-Arg(Pbf)-, *N*-α-fluorenylmethoxycarbonyl - $N^G$ - (2,2,4,6,7 - pentamethyldihydrobenzofurane-5-sulfonyl)-2-amino-4-guanidino-butyl; Z, benzyloxycarbonyl; DME, dimethoxyethane; DMF, *N*,*N*-dimethylformamide; DBU, 1,8-diazabicyclo[5.4.0.]undec-7-ene; HMPT, tris-(diethylamino)-phosphinoxide.

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Mass Spectrometry: API III triple quadrupole mass spectrometer equipped with an electrospray ion source at atmospheric pressure (Sciex, Thornhill, Canada); electrospray ionization mass spectra (ESI-MS) were recorded in the positive mode.

NMR-Spectroscopy: Bruker AC 250 spectrometer (Bruker Physics, Karlsruhe, Germany); chemical shifts referenced to the solvent peaks [$\delta$ ($^1$H, [$D_4$]$CH_3OH$) = 3.31 and $\delta$ ($^{13}$C, [$D_4$]$CH_3OH$) = 49.15; $\delta$ ($^{13}$C, $CDCl_3$) = 77; ($^1$H, [$D_6$]DMSO) = 2.49 and $\delta$ ($^{13}$C[$D_6$]DMSO) = 39.5].

### *N*-$\alpha$-Fluorenylmethoxycarbonyl-$N^G$-(2,2,4,6,7-pentamethyldihydrobenzofuran-5-sulfonyl)-arginine Amide (2)

Fmoc-Arg (Pbf)-OH (3.24 g, 5 mmol) (**1**), pyridine (0.25 ml) and $(Boc)_2O$ (1.5 g, 6.5 mmol) were dissolved in dioxane (15 ml), and then ammonium hydrogencarbonate (0.5 g, 6.3 mmol) was added and the mixture was stirred for 16 h [22]. The reaction mixture was diluted with water (30 ml) and stirred until crystallization was completed. The crude product was filtered off, washed with water and crystallized from EtOAc/*n*-hexane. Yield: 2.3 g (71%); ESI-MS: *m*/*z*: 648 $[M + H]^+$.

### *N*-$\alpha$-Fluorenylmethoxycarbonyl-$N^G$-(2,2,4,6,7-pentamethyldihydrobenzofuran-5-sulfonyl)-arginine Thioamide (3)

Lawesson's reagent (0.732 g, 1.8 mmol) and a solution of **2** (1.61 g, 2.5 mmol) in dimethoxyethane (50 mmol) was stirred at room temperature (r.t.) until the starting material was consumed (TLC monitoring in system C) [23]. Compound **3** was crystallized from EtOAc/*n*-hexane. Yield: 1.3 g (78%); ESI-MS: *m*/*z*: 664 $[M + H]^+$.

### 2-(*N*-$\alpha$-Fluorenylmethoxycarbonyl-$N^G$-(2,2,4,6,7-pentamethyldihydrobenzofuran-5-sulfonyl)-2-amino-4-guanidinobutyl)thiazole-4-carboxylic Acid (4)

3-Bromo-2-oxo-propionic acid (0.5 g, 3 mmol), thioamide **3**, (1.3 g, 2 mmol), and $CaCO_3$ (0.570 g, 5.57 mmol) were added to dry EtOH (60 ml) and stirred at r.t. under argon for 24 h [24]. The organic layer was concentrated *in vacuo*, and the residue was purified by crystallization from EtOAc/ether. Yield: 1.25 g (85.6%); $^{13}$C-NMR ([$D_6$]DMSO): 12.1, 15.07, 17.54 (Pbf, $CH_3$'s), 18.86 (Pbf, C-3), 25.6 (Arg $\gamma$-C), 25.8 (Pbf, $CH_3$'s on C-2), 28.1 (Arg $\beta$-C), 38.2 (Pbf C-4), 42.3 (Arg $\delta$-C), 47 (Fmoc-C-9), 53.1 (Arg $\alpha$-C), 65.5 (Fmoc-$CH_2$), 73 (Pbf C-2), 116.0–146.94 (C-aromatic), 131.5 ($C^5_{Thz}$), 146.9 ($C^4_{Thz}$), 156.03 (Fmoc-CO), 157.5 (Arg $\zeta$-C), 162.1 ($C^2_{Thz}$), 176.6 (Arg CO); ESI-MS: *m*/*z* 732 $[M + H]^+$.

### *N*-$\alpha$-*tert*-Butoxycarbonylglycine Amide (5)

Gly-$NH_2$·HCl (22.0 g, 0.2 mol), triethylamine (28.0 ml, 0.2 mol) and $(Boc)_2O$ (48.0 g, 0.22 mol) in THF/water (4:1) (300 ml) were stirred at r.t. until the starting material was consumed (TLC system A). Yield: 31.0 g (89%).

### *N*-$\alpha$-*tert*-Butoxycarbonyl-2-aminomethyl-iminoethylether (6)

The imino ether **6** was prepared from **5** according to the procedure described in Reference [25]. The triethyloxonium hexafluorophosphate (3 g, 10 mmol) was added in one portion to a stirred solution of **5** (1.75 g, 10 mmol) in chloroform (50 ml) at 0°C, and the mixture was stirred for 20 h; compound **6** was obtained as an oil and used without purification. Yield: 1.13 g (84.9%); IR (Nujol): $\nu = 1653$ cm$^{-1}$ (C=N); ESI-MS: *m*/*z*: 203 $[M + H]^+$.

### *N*-$\alpha$-*tert*-Butoxycarbonyl-2-aminomethyl-imidazoline-4-carboxylic Acid Methyl Ester (7)

Imidazoline **7** was prepared according to the procedure described in Reference [26], starting from **6** (2 g, 10 mmol) and L-2,3-diaminopropionic acid methyl ester hydrochloride [27,28], (1.13 g, 7.3 mmol) in chloroform (30 ml). Crystallization from diethyl ether/*n*-hexane. Yield: 1.49 g (80%); $^1$H-NMR:([$D_4$]$CH_3OH$): $\delta = 1.45$ (s, 9H, Boc-$CH_3$), 3.31 (t, 2H, $CH^5_{Idz}$), 3.82 (s, 3H, $OCH_3$), 4.16 (d, 1H, $CH_2$), 4.84 (s, 1H, $CH^4_{Idz}$), 5.04 (s, 1H, NH).$^{13}$C-NMR: ([$D_4$]$CH_3OH$): $\delta = 28.53$ (Boc-$CH_3$), 37.94 ($CH_2$), 50 ($OOCH_3$), 53.6 ($C^4_{Idz}$), 59.2 ($C^5_{Idz}$), 81.68 (Boc-Cq), 155.1 (Boc-CO), 170.48 ($C^2_{Idz}$), 171.97 (COO); ESI-MS: *m*/*z*: 258 $[M + H]^+$.

### *N*-$\alpha$-*tert*-Butoxycarbonyl-2-aminomethyl-imidazole-4-carboxylic Acid Methyl Ester (8)

DBU (0.6 ml, 6 mmol) was added to **7** (0.5 g, 2 mmol) in a mixture of $CCl_4$ (10 ml), pyridine (15 ml) and acetonitrile (15 ml) [21]. After 3 h at r.t. the solvent was removed *in vacuo*, the residue dissolved in EtOAc, the solution extracted with 0.5 N HCl and the aqueous phase reextracted with EtOAc (2 ×). The EtOAc phase was washed with brine, dried, and the solvent evaporated. Crystallization from EtOAc/*n*-hexane. Yield: 0.425 g, (83%); $^1$H-NMR:

([$D_4$]$CH_3OH$): $\delta = 1.39$ (s, 9H, Boc-$CH_3$), 3.73 (s, 3H, $OCH_3$), 4.17 (d, 2H, $CH_2$), 8.02 (s, 1H, NH), 8.36 (s, 1H, $CH^5_{Idz}$). $^{13}$C-NMR: ([$D_4$]$CH_3OH$): $\delta =$ 29.2 (Boc-$CH_3$), 38.5 ($CH_2$), 50.4 ($OOCH_3$), 78.3 (Boc-Cq), 126.5 ($C^4_{Idz}$), 128 ($C^5_{Idz}$), 155.1 (Boc-CO), 170.2 ($C^2_{Idz}$), 173.1 (COO); ESI-MS: $m/z$: 256[M + H]$^+$.

### *N*-α-Benzyloxycarbonylglycine Amide (9)

Aqueous ammonia (20 ml) was added to Z-Gly-OH (8 g, 40 mmol) and NMM (4.5 ml, 40 mmol) in THF (50 ml) at −20°C. After 3 h at r.t. and subsequent evaporation, the residue was precipitated with 10% $NaHCO_3$, filtered, and the solid was washed with water, dried, and crystallized from EtOAc/*n*-hexane. Yield: 7.3 g (90%).

### *N*-α-Benzyloxycarbonyl-2-aminomethyl-iminoethylether (10)

The imino ether **10** was prepared from **9** (6.24 g 30 mmol) according to the procedure described in Reference [25], obtained as an oil and used without purification. Yield: 6.7 g (95%); ESI-MS: $m/z$: 237 [M + H]$^+$.

### *N*-α-Benzyloxycarbonyl-2-aminomethyl-oxazoline-4-carboxylic Acid Methyl Ester (11)

Oxazoline **11** was prepared according to the procedure described in Refs. [29,30] starting from **10** (2.3 g 10 mmol) and H-Ser-OMe·HCl (1.55 g, 10 mmol) in chloroform (100 ml). Oxazoline **11** was obtained as an oil and used without purification. Yield: 2.86 g (98%).

### *N*-α-Benzyloxycarbonyl-2-aminomethyl-oxazole-4-carboxylic Acid Methyl Ester (12)

DBU (3 ml, 30 mmol) was added to **11** (2.8 g, 9.6 mmol) in $CCl_4$/acetonitrile/pyridine (2/3/3). After 3 h at r.t. the solvent was extracted with 0.5 N HCl and the aqueous phase was reextracted with EtOAc (2 ×). The EtOAc phase was washed with brine, dried, and the solvent evaporated. Chromatography on silica gel (EtOAc/*n*-hexane, 1/1) afforded oxazole **12**. Yield: 0.94 g (33%); ESI-MS: $m/z$: 291 [M + H]$^+$.

### *N*-α-Benzyloxycarbonyl-2-(2′-aminomethyloxazol-4-yl)Amide (13)

Aqueous ammonia (12 ml) was added in one portion to a stirred solution of **12** (2.1 g. 7 mmol) in MeOH (30 ml). The mixture was stirred at r.t. for 3 h, after which the MeOH was evaporated *in vacuo*. Crystallization was from methanol/diethyl ether. Yield: 1.88 g (98%); ESI-MS: $m/z$: 256 [M + H]$^+$.

### *N*-α-Benzyloxycarbonyl-2-(2′-aminomethyloxazol-4-yl)−iminoethylether (14)

The imino ether **14** was prepared from **13** as described for compound **10** (1.8 g, 6.88 mmol). The product was obtained as an oil and used without purification. Yield: 1.88 g (86%).

### *N*-α-Benzyloxycarbonyl-2-(2′-aminomethyloxazol-4-yl)-oxazoline-4-carboxylic Acid Methyl Ester (15)

The oxazolyl–oxazoline **15** was obtained from **14** (1.83 g, 5.7 mmol) and H-Ser·OMe·HCl (1.3 g, 8.4 mmol). After additional 24 h at r.t., work-up was carried out as described for compound **11**. Compound **15** was crystallized from EtOEt/*n*-hexane. Yield: 1.2 g (60%).$^1$H-NMR: ([$D_6$]DMSO): $\delta = 3.7$ (s, 3H, $OCH_3$), 4.37 (d, 2H, $CH_2$), 4.9 (2H, $CH_2$–NH), 5.06 (2H, $CH_2OCO$), 7.3 (5H, $C_6H_5$–H), 8.01 (br t 1H, NH), 8.6 (H, $C^5_{Oxa}$). $^{13}$C-NMR: ([$D_6$]DMSO): $\delta =$ 37.6 (NH–$CH_2$), 52.2 ($OCH_3$), 65.7 ($CH_2O$), 127.8 (Z, C-3,4), 128.3 ($C^5$Oxa), 129.3 ($C^{5'}$Oxa), 136.8 (Z, C-1), 142.9 ($C^4$Oxa), 145.4 ($C^{4'}$Oxa), 156.2 (OCO), 158.9 ($C^{2'}$Oxa), 162.5 ($C^2$Oxa), 171.1 (COOMe); ESI-MS: $m/z$: 360 [M + H]$^+$.

### *N*-α-Benzyloxycarbonyl-2-(2′-aminomethyloxazol-4-yl)-oxazole-4-carboxylic Acid Methyl Ester (16)

The oxazolyl-oxazole **16** was prepared from **15** (0.7 g, 1.9 mmol) as described for compound **12**. Compound **16** was crystallized from EtOEt/*n*-hexane. Yield: 0.360 g (52%); $^1$H-NMR: ([$D_6$]DMSO): $\delta = 3.8$ (s, 3H, $OCH_3$), 4.05 (pt, 2H, $CH^{5'}$Oxa), 4.4 (d, 2H, $CH_2$), 4.76 (m, 1H, $CH^{4'}$Oxa), 5.06 (Z-$CH_2O$), 7.3 (s, 5H, $C_6H_5$–H), 8.07 (br t, 1H, NH), 8.95 (s, 1H, $CH^5$Oxa). $^{13}$C-NMR: ([$D_6$]DMSO):$\delta = 37.7$ (NH–$CH_2$), 51.9 ($OCH_3$), 65.7 ($CH_2O$), 67.6 ($C^{5'}$Oxa), 70.24 ($C^{4'}$Oxa), 127.7 (Z, C,3,4), 132.2 ($C^5$Oxa), 136.8 (Z, C1), 145.1 ($C^4$Oxa), 155.1 (OCO), 156.3 ($C^{2'}$Oxa), 160.8 ($C^2$Oxa), 163 (COOMe); ESI-MS: $m/z$: 358 [M + H]$^+$.

### *N*-α-Benzyloxycarbonyl-2-(2′-aminomethyloxazol-4-yl)-oxazole-4-carboxylic Acid (17)

The ester **16** (0.358 g, 1 mmol) was dissolved in dioxane (15 ml) and sodium hydroxide (0.12 g, in 5 ml of water) was added. The mixture was stirred at r.t. for 1 h. The solution was neutralized with 10%

 

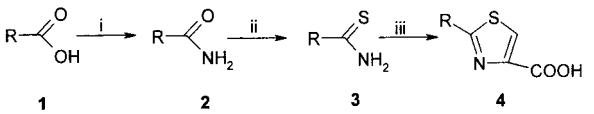

Figure 1 Synthesis of Fmoc-Arg(Pbf)-thiazole-4-carboxylic acid. R = Fmoc-Arg(Pbf)-; (i) $(Boc)_2O$, $NH_3HCO_3$; (ii) Lawesson's reagent; (iii) 3-bromo-2-oxo-propionic acid.

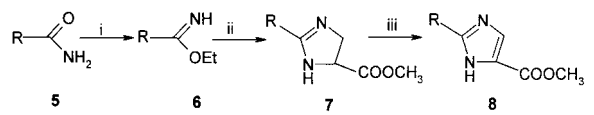

Figure 2 Synthesis of *N*-α-*tert*-butoxycarbonyl-2-aminomethyl-imidazole-4-carboxylic acid methyl ester. R = Boc-NH–$CH_2$–; (i) $ET_3OPF_6$; (ii) L-2,3-diaminopropionic acid-OMe·HCl; (iii) DBU, $CCl_4$, $CH_3CN$,Py.

aqueous solution $KHSO_4$ to pH 6. Removal of the dioxane *in vacuo* was followed by acidification to pH 3 and the aqueous solution was extracted *in vacuo*. Crystallization from EtOAc/*n*-hexane. Yield: 0.3 g (90%); $^1$H-NMR ([$D_6$]DMSO): $\delta = 4.44$ (d, 2H, $CH_2$), 5.06 (Z-$CH_2O$), 7.3 (s, 5H, Z aromatic), 8.04 (br t 1H, NH), 8.8 (s, 1H, $CH^{5'}$Oxa), 8.83 (s, 1H, $CH^{5}$Oxa); $^{13}$C-NMR ([$D_6$]DMSO): $\delta$ 37.8 (NH–$CH_2$), 65.9 ($CH_2O$), 127.9 (Z, C-3,4), 128.9 ($C^5$Oxa), 134.4 ($C^{5'}$Oxa), 136.9 (Z, C-1), 140.8 ($C^4$Oxa), 145 ($C^{4'}$Oxa), 155.1 (OCO), 156.5 ($C^{2'}$Oxa), 161.9 ($C^2$Oxa), 163.1 (COOH); ESI-MS: $m/z$: 343[M + H]$^+$ (Figure 4).

## RESULTS AND DISCUSSION

2-Fmoc-[Arg(Pbf)]-thiazole-4-carboxylic acid (**4**) was synthesized according to Figure 1. The amide **2** was obtained following Pozdnev's method [22] from Fmoc-Arg(Pbf)-OH (**1**) and converted into thioamide **3** by Lawesson's reagent [23]. Cyclocondensation of **3** with 3-bromo-oxo-propionic acid [24] leads to **4** in 82% yield. For the synthesis of Boc-protected 2-aminomethyl-imidazole-4-carboxylic acid methyl ester (Figure 2), treatment of the amide **5** with triethyloxonium hexafluorophosphate gave the imino ether **6** [25]. The intermediate imidazoline **7** was obtained in high yield (80%) by cyclization of the imino ether **6** with L-2,3-diaminopropionic acid methyl ester·HCl [27,28] according to Reference [26]. Oxidation of **7** gave the imidazole **8** (83%) using a mixture of DBU/$CCl_4$/acetonitrile/pyridine [21].

The synthesis of Boc-2-(2-aminomethyloxazole-4-yl)-oxazole-4-carboxylic acid methyl ester was accomplished *via* a novel route (Figure 3). The amide **9** was converted into the imino ether **10** as described for compound **6**. We were able to obtain the intermediate oxazoline **11** by cyclization of the imino ether with a serine ester in chloroform [29,30]. Oxidation of **11** was performed with the reagent DBU/$CCl_4$/acetonitrile/pyridine.

The amide **13** was converted into the imino ether **14** as described for compound **10**. Formation of the oxazolyloxazoline **15** occurred in 60% yields as described for compound **11**. For oxidation of the compound **15** to compound **16**, we preferred the procedure described for compound **12** and the ester **16** was converted to **17** using base hydrolysis.

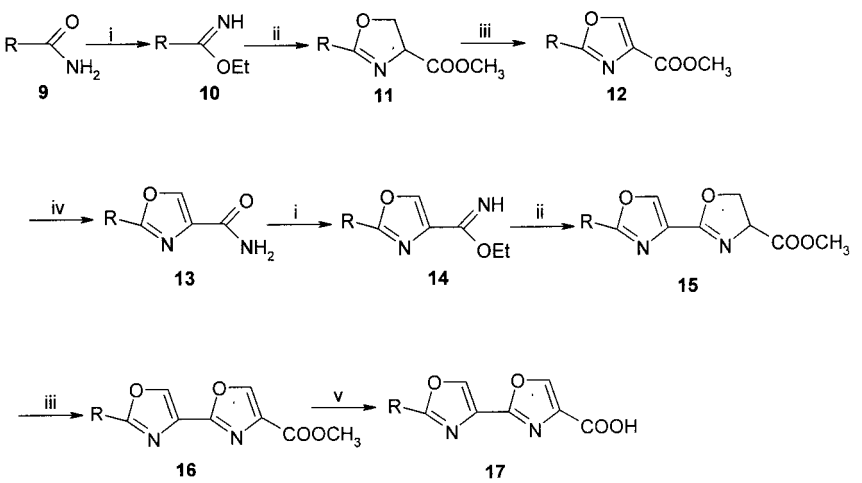

Figure 3 Synthesis of *N*-α-benzyloxycarbonyl-2-(2′aminomethyloxaol-4-yl)-oxazole-4-carboxylic acid. R = Z-NH–$CH_2$; (i) $Et_3OPF_6$; (ii) Ser-OMe·HCl; (iii) DBU, $CCl_4$, $CH_3CN$, Py; (iv) MeOH/$NH_4OH$; (v) NaOH/dioxan.

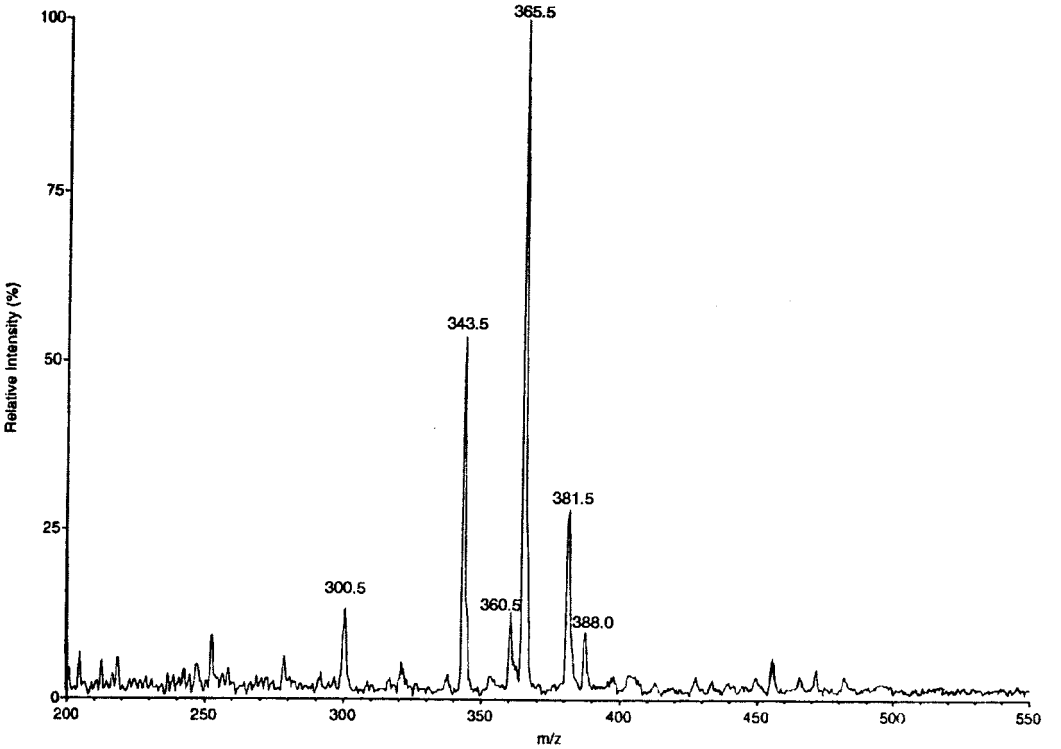


Figure 4 ESI-mass spectrum of *N*-α-benzyloxycarbonyl-2-(2′aminomethyl-oxazol-4-yl)-oxazole-4-carboxylic acid. Mass spectrum of Z-Oxa-Oxa-OH: 343.4 $[M + H]^+$, 360.5 $[M + NH_4]^+$, 365.5 $[M + Na]^+$, 381.5 $[M + K]^+$.

The oxazole **12** was converted into the amide **13** with methanol/aqueous ammonia.

## CONCLUSIONS

In this study, we extended the scope of our various synthetic routes aiming for a larger variety of 5-ring heterocyclic building blocks that could be useful in natural product and peptide chemistry, and also in combinatorial syntheses of compound collections [31] for lead structure search.

Three novel 5-ring amino acid derivatives were made accessible. Firstly, a new thiazole containing dipeptide mimetic derived from L-arginine was synthesized, constituting a trifunctional scaffold which can be selectively addressed to its amino, guanidino or carboxy functions. The yields obtained in all three steps of the synthesis of **4** from commercially available Fmoc-Arg(Pbf)-OH were satisfying. The ESI-MS and $^{13}$C-NMR analysis proved the identity of the final product **4**.

Secondly, the dipeptide mimetic 2-aminomethyl-imidazole-4-carboxylic acid was synthesized. This is of obvious interest for a variety of applications in peptidomimetics. During our experiments, we developed a novel and useful procedure for the oxidative conversion of intermediate imidazoline into the corresponding imidazole with a mixture of DBU, $CCl_4$, acetonitrile and pyridine. This reagent proved to be superior to the commonly used reagent, $CuBr_2$/DBU/tris-(dimethylamino)-phosphinoxide (HMPT). It should be noted that our chosen reagent yielded the desired product with a higher degree of purity and a faster condensation than the copper(II) bromide reagent.

Thirdly, a ten step synthesis was worked out starting with glycine, to eventually yield the new oxazolyl–oxazole tripeptide mimetic with two fused 5-ring heterocycles. This building block may be used for the synthesis of microcin B17 analogs [18–21] replacing the structurally related building blocks in this 43-peptide gyrase inhibitor.

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