Synthesis of highly functionalized β-aminocyclopentanecarboxylate stereoisomers by reductive ring opening reaction of isoxazolines

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Full Research Paper

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Abstract

A rapid and simple procedure was devised for the synthesis of multifunctionalized cyclic β-amino esters and γ-amino alcohols via the 1,3-dipolar cycloaddition of nitrile oxides to β-aminocyclopentanecarboxylates. The opening of the isoxazoline reductive ring to the corresponding highly functionalized 2-aminocyclopentanecarboxylates occurred stereoselectively with good yields.

Introduction

Isoxazoline-fused amino acids are important bioactive derivatives in organic and medicinal chemistry (e.g., conformationally restricted aspartate and glutamate analogues) [1-6]. As a consequence of their ability to undergo reductive ring opening, isoxazolines are of interest as precursors for the synthesis of highly functionalized molecules such as β-hydroxyketones [7-10], amino alcohols or amino acids [11-17], etc. The multifunctionalized cyclic amino acids – e.g., the antibiotic Oryzoxymycin [18-21], the antiviral agents Tamiflu [22-33], Zanamivir and 2,3-didehydro-2-deoxy-N-acetylneuraminic acid (DANA) [34-38] – are bioactive derivatives of great significance for medicinal chemistry. A promising neuraminidase inhibitor, BCX-1812 (Peramivir), is currently under evaluation in clinical trials [39-45] (Figure 1). A series of Peramivir analogues has recently been investigated as potential antiviral agents [46,47].

Results and Discussion

We recently reported a regio- and stereoselective procedure for the formation of a series of isoxazoline-fused cispentacin and transpentacin regio- and stereoisomers (2-6) from bicyclic β-lactam ¹ [48,49] (Scheme 1). The syntheses consisted of a dipolar cycloaddition of nitrile oxide (generated with Boc₂O, Et₃N and DMAP) to the olefinic bond of cis-ethyl 2-aminocyclopent-3-ene carboxylate derived from ¹, during which the isoxazoline-fused amino ester regio- and stereoisomers (2 and
4) were formed, then separated and isolated. The cycloaddition of nitrile oxide to trans-ethyl 2-aminocyclopent-3-enecarboxylate under similar conditions proceeded selectively with the formation of 6. Epimerization of 2 and 4 afforded trans derivatives 3 and 5 [48,49].

Since isoxazoline-functionalized molecules are excellent precursors for the construction of different functional groups through reductive ring cleavage, our recent aim was to synthesize highly functionalized β-aminocyclopentanecarboxylate regio- and stereoisomers from the earlier prepared isoxazoline-fused cispentacin and transpentacin derivatives.

A number of methods are known for the reductive opening of the isoxazoline ring: Catalytic hydrogenation or reduction with Fe in the presence of NH$_4$Cl, NaBH$_4$, LiAlH$_4$, Raney Ni, BH$_3$·THF, or SmI$_2$/B(OH)$_3$/H$_2$O [7-17].

For the reduction, we selected model compound 2 from earlier prepared isoxazoline-fused cispentacin stereoisomers to execute the reduction under different conditions. The isoxazoline-fused derivative was treated with the above-mentioned reducing agents. Unfortunately, neither transformation nor isoxazoline opening with ester reduction was observed. When the reduction was carried out with NaBH$_4$ in EtOH, three products were obtained: The epimerized isoxazoline-fused amino carboxylate 7 and amino alcohols 8 and 9 which were separated by chromatography and isolated (Scheme 2).

Thus, this reaction did not lead to the formation of highly functionalized isoxazoline ring-opened β-amino ester either. When ammonium formate in EtOH in the presence of Pd/C was investigated for the reduction of 2, the ring opening resulted in carbonyl compound 10 in rather low yield through the corresponding hydroxyimine intermediate, followed by elimination and saturation (Scheme 3).

Combinations of NaBH$_4$ (as a mild and selective reducing agent) with cobalt, nickel, iridium or rhodium halide have previously been employed for cleavage of the isoxazoline ring system, which is otherwise inert to NaBH$_4$ without such metal halide additives [50]. Accordingly, we investigated the reduc-
fraction of isoxazoline-fused amino ester stereoisomers 2 [48,49] with NaBH₄ in the presence of NiCl₂ (Scheme 4), which was found to be a suitable reducing system.

The reduction carried out by adding NaBH₄ to a mixture of NiCl₂ and isoxazoline derivative 2 in EtOH/H₂O, followed by amino group protection with Boc₂O, selectively afforded only isoxazoline-opened product 12 as a single diastereomer in good yield. The reaction was exothermic and deposited a black granular precipitate, reflecting the presence of metal boride. The product was purified by column chromatography and the structure of 12 was certified by X-ray analysis (Figure 2).

The isoxazoline opening occurred with the formation of a new stereocenter at a one-carbon distance from C-3. In accordance with earlier results [39-47], the hydrogenation of the isoxazoline proceeded through hydrogen attack from the carbamate side (cis to –NHBoc) of the cyclopentane skeleton. This was confirmed by X-ray analysis of 12.

In order to increase the number of multifunctionalized amino ester stereoisomers, we next examined the reductions of isoxazoline-fused cispentacin and transpentacin stereoisomers (3–6) [49]. Reactions were carried out similarly with NaBH₄ in the presence of NiCl₂ in EtOH/H₂O and led selectively to the corresponding multifunctionalized amino esters 13–16 in good yields (Scheme 5) as single diastereoisomers.

**Conclusion**

The present work has furnished a facile and efficient stereoselective reduction of isoxazoline-fused cyclic β-amino esters to multifunctionalized 2-aminocyclopentanecarboxylates through the use of NaBH₄/NiCl₂ as reducing agent. As Peramivir related derivatives, highly functionalized cyclic amino esters may be regarded as promising bioactive compounds.
General procedure for the synthesis of 10
To a stirred solution of isoxazoline-fused β-aminocyclopentane-carboxylate 2 (1.6 mmol) in dry EtOH (15 mL), HCOONH$_4$ (3.2 mmol) and Pd/C (0.10 g) were added and the reaction mixture was stirred under reflux for 24 h. The mixture was filtered through a celite pad and the filtrate was evaporated in vacuo. The crude residue was diluted with EtOAc (30 mL), washed with H$_2$O (3 × 15 mL), dried over Na$_2$SO$_4$ and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (n-hexane/EtOAc), giving 10.

**General procedure for isoxazoline ring opening**
To a stirred solution of isoxazoline-fused β-aminocyclopentane-carboxylates 2–6 (0.96 mmol) in 8 mL of EtOH/THF (v:v = 3:1), NiCl$_2$ (1.92 mmol) and Boc$_2$O (1.92 mmol) were added. After stirring for 10 min, NaBH$_4$ (1.92 mmol) was added in portions. The reaction mixture was further stirred for 6 h at room temperature and the reaction was quenched by the addition of H$_2$O (5 mL). The reaction mixture was filtered through a celite pad and the filtrate was evaporated in vacuo. The crude residue was diluted with EtOAc (30 mL), washed with H$_2$O (3 × 15 mL), dried over Na$_2$SO$_4$ and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (n-hexane/EtOAc), giving the corresponding reduced product.

**Experimental**
The chemicals were purchased from Aldrich. The solvents were used as received from the supplier. Melting points were determined with a Kofler apparatus. NMR spectra were recorded on a Bruker DRX 400 MHz spectrometer in deuterated DMSO or CDCl$_3$. Chemical shifts are expressed in ppm (δ) from the signal of internal tetramethylsilane. Mass spectra were recorded on a Finnigan MAT 95S spectrometer. Elemental analyses were determined with a Kofler apparatus. NMR spectra were recorded on a Perkin-Elmer CHNS-2400 Ser II Elemental Analyzer. FTIR spectra were recorded on a Perkin-Elmer Spectrum 100 instrument. Cycloadducts 2–6 were synthesized according to previously published procedures [8].

**General procedure for the synthesis of compounds 8 and 9**
To a solution of isoxazoline-fused β-aminocyclopentane-carboxylate 2 (0.96 mmol) in dry EtOH (15 mL) NaBH$_4$ (2.88 mmol) was added and the reaction mixture was stirred under reflux for 16 h. The reaction was quenched by the addition of H$_2$O (10 mL) and then, the mixture was concentrated under reduced pressure. The reaction mixture was further stirred for 6 h at room temperature and the reaction was quenched by the addition of H$_2$O (5 mL). The reaction mixture was filtered through a celite pad and the filtrate was evaporated in vacuo. The crude residue was diluted with EtOAc (3 × 15 mL), dried over Na$_2$SO$_4$ and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (n-hexane/EtOAc) giving 8 and 9.

tert-Butyl (3aR*,4R*,5R*,6aR*)-[5-(hydroxymethyl)-3-methyl-4,5,6,6a-tetrahydro-3aH-cyclopenta[d]isoxazol-4-yl]carbamate (8): Light-yellow oil; yield 48% (124 mg); R$_f$ 0.35 (n-hexane/EtOAc); IR (KBr) v/cm$^{-1}$: 3344, 3265, 2979, 1678, 1563, 1184; $^1$H NMR (400 MHz, CDCl$_3$) δ 1.45 (s, 3H, CH$_3$), 1.56 (s, 9H, CH$_3$), 1.65–1.72 (m, 2H, CH$_2$), 2.19–2.25 (m, 1H, H-5), 2.75–2.81 (m, 1H, H-3a), 3.19–3.25 (m, 1H, H-6a), 3.59–3.71 (m, 1H, H-4), 3.63–3.72 (m, 2H, CH$_2$), 5.42 (br s, 1H, N-H), OH group not observed – exchanged; $^{13}$C NMR (100 MHz, CDCl$_3$) δ 16.0, 28.6, 30.2, 32.5, 43.0, 44.4, 59.2, 63.9, 78.0, 155.2, 155.6; MS (ESI) m/z: 293 [M + Na]$^+$; Anal. calcd for C$_{13}$H$_{22}$N$_2$O$_4$: C, 57.76; H, 8.20; N, 10.36; found: C, 57.60; H, 8.07; N, 10.23.

tert-Butyl (35*,3aR*,4R*,5R*,6aR*)-[5-(hydroxymethyl)-3-methylhexahydro-2H-cyclopenta[d]isoxazol-4-yl]carbamate (9): Colorless oil; yield 12% (31 mg); R$_f$ 0.29 (n-hexane/ EtOAc); IR (KBr) v/cm$^{-1}$: 3460, 3331, 2978, 1683, 1531, 1174; $^1$H NMR (400 MHz, CDCl$_3$) δ 0.98–1.05 (m, 3H, CH$_3$), 1.36 (s, 9H, CH$_3$), 1.55–1.75 (m, 2H, CH$_2$), 2.22–2.27 (m, 1H, H-5), 2.38–2.47 (m, 1H, H-3a), 2.78–2.86 (m, 1H, H-3), 3.17–3.24 (m, 1H, H-6a), 3.59–3.69 (m, 1H, H-4), 3.36–3.68 (m, 2H, CH$_2$), 5.32 (br s, 1H, N-H), 6.12 (br s, 1H, N-H), OH group not observed – exchanged; $^{13}$C NMR (100 MHz, CDCl$_3$) δ 15.0,
Ethyl (1R*,2S*,3S*)-3-acetyl-2-(tert-butoxycarbonyl-amino)cyclopentanecarboxylate (10): White solid; yield 32% (153 mg); mp 109–110 °C; Rf 0.62 (n-hexane/EtOAc); IR (KBr) v/cm⁻¹: 3354, 2978, 1716, 1684, 1531, 1171; ¹H NMR (400 MHz, CDCl₃) δ 1.29 (t, J = 7.54 Hz, 3H, CH₃), 1.41 (s, 9H, CH₃), 1.59–1.71 (m, 2H, CH₂), 1.74–1.95 (m, 2H, CH₂), 2.05 (s, 3H, CH₃), 2.83–2.97 (m, 1H, H-1), 3.01–3.15 (m, 1H, H-3), 4.18–4.29 (m, 2H, OCH₂), 4.31–4.44 (m, 1H, H-2), 5.76 (br s, 1H, N-H); ¹³C NMR (100 MHz, CDCl₃) δ 13.98, 20.05, 25.76, 29.31, 31.21, 43.97, 46.01, 52.70, 80.21, 155.67, 176.01, 206.52; MS (ESI) m/z: 322 [M + Na⁺]; Anal. calcd for C₁₃H₂₃NO₃: C, 60.18; H, 8.42; N, 6.48; found: C, 60.05; H, 8.35; N, 4.54.

Ethyl (1R*,2S*,3S*,4R*)-2-(tert-butoxycarbonyl)-3-((S*)-1-(tert-butoxycarbonyl)ethyl)-4-hydroxycyclopentanecarboxylate (12): White solid; yield 80% (320 mg); mp 120–121 °C; Rf 0.46 (n-hexane/EtOAc 1:1); IR (KBr) v/cm⁻¹: 3426, 3378, 3333, 2979, 1688, 1718, 1703, 1522, 1176; ¹H NMR (400 MHz, CDCl₃) δ 1.21–1.30 (m, 6H, CH₃), 1.40–1.46 (m, 18H, CH₂), 1.84–1.97 (m, 2H, CH₂, H-4), 2.03–2.20 (m, 2H, CH₂, H-1), 2.54 (q, J = 9.10 Hz, 1H, H-2), 3.73–3.82 (m, 1H, H-3), 3.87–4.04 (m, 2H, N-H, OCH₂), 4.09–4.22 (m, 2H, OCH₂), 4.83 (br s, 1H, N-H), OH group not observed – exchanged; ¹³C NMR (100 MHz, CDCl₃) δ 14.1, 20.0, 27.5, 28.7, 28.8, 45.6, 46.1, 46.8, 60.9, 62.5, 78.1, 80.1, 80.3, 154.0, 156.4, 174.6; MS (ESI) m/z: 418 [M + 2H⁺]; Anal. calcd for C₂₀H₃₆NO₇: C, 57.67; H, 8.71; N, 6.73; found: C, 57.41; H, 8.37; N, 6.59.

Ethyl (1S*,2R*,3R*,4S*)-2-(tert-butoxycarbonyl)-4-((R*)-1-(tert-butoxycarbonyl)ethyl)-3-hydroxycyclopentanecarboxylate (15): White solid; yield 85% (340 mg); mp 141–142 °C; Rf 0.32 (n-hexane/EtOAc 1:1); IR (KBr) v/cm⁻¹: 3485, 3368, 3353, 2975, 1733, 1681, 1667, 1533, 1167; ¹H NMR (400 MHz, CDCl₃) δ 1.17–1.31 (m, 6H, CH₃), 1.79–1.85 (m, 2H, CH₂, H-1), 2.03–2.20 (m, 2H, CH₂, H-4), 2.31–2.54 (m, 2H, CH₂, H-3), 2.90–3.21 (m, 1H, H-3), 3.68–4.01 (m, 2H, H-4, H-2), 4.08–4.19 (m, 3H, OCH₂, H-3), 5.75 (br s, 1H, N-H), 4.83 (br s, 1H, N-H), OH group not observed – exchanged; ¹³C NMR (100 MHz, CDCl₃) δ 14.6, 21.6, 28.7, 28.8, 47.2, 49.0, 59.9, 61.2, 61.6, 69.4, 74.7, 80.0, 85.9, 117.5, 156.1, 158.8, 171.3; MS (ESI) m/z: 418 [M + 2H⁺]; Anal. calcd for C₂₀H₃₆NO₇: C, 57.67; H, 8.71; N, 6.73; found: C, 57.43; H, 8.40; N, 6.95.

**X-ray crystallographic study of 12:** Crystallographic data were collected at 123 K with a Nonius-Kappa CCD area detector diffractometer, using graphite-monochromatized Mo Kα radiation (λ = 0.71073 Å) as reported earlier [51].

**Crystal data for 12:** C₂₀H₃₆NO₇, Mᵣ = 416.51, triclinic, space group P-1 (no. 2), a = 9.3765(2), b = 13.7078(4), c = 18.7792(4) Å, α = 96.609(2), β = 95.261(1), γ = 100.965(1), V = 104
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