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Synthesis of novel isoxazoline-fused cispentacin stereoisomers

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ABSTRACT

New isoxazoline-fused cispentacins were prepared by the 1,3-dipolar cycloaddition of nitrile oxides to β-amino esters containing a cyclopentene skeleton. This synthetic procedure gave regio- and diastereoisomers of the cispentacins. The synthetic route was extended to the synthesis of these compounds in enantiomerically pure form.

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Isoxazolines, are versatile intermediates for the synthesis of a variety of bioactive compounds.[1,2] Substituted isoxazolines display, for example, anti-influenza activity[3] and antifungal properties.[4]

The 1,3-dipolar cycloaddition of nitrile oxides to alkenes is a widely used, efficient method for the synthesis of isoxazolines.[5] Nitrile oxides can be generated in situ by either (i) base-induced dehydrohalogenation of hydroximoyl chlorides[6] (Huisgen methodology), or (ii) dehydration of primary nitroalkane derivatives[7] (Mukaiyama methodology). Isoxazole carboxylic acids such as conformationally constrained aspartate and glutamate analogs were recently synthesized via the 1,3-dipolar cycloaddition of nitrile oxides to α-amino esters with a cyclopentene skeleton.[8] These derivatives proved to be inhibitors of excitatory amino acid transporters with neuroprotective activity.[8] Nitrile oxide cycloaddition to α-amino esters with a cyclopentene framework furnished isoxazoline-substituted diketopiperazines.[9] The 1,3-dipolar cycloaddition of nitrile oxides to γ-amino acids with a cyclopentene skeleton is the key step in the stereoselective synthesis of novel multisubstituted cyclopentene derivatives (BCX-1812, BCX-1827, etc.) which possess antiviral activity.[10] A novel approach to isoxazoline-carbocyclic nucleosides involves the regio- and stereoselective 1,3-dipolar cycloaddition of nitrile oxides to 2-azanorbornenes, followed by ring opening and a purine or pyrimidine base construction strategy.[11]

Alicyclic β-amino acids have received significant interest in recent years as a consequence of their pharmacological potential.[12] The naturally occurring β-amino acid cispentacin (1*R*,2*S*-2-aminocyclopentanecarboxylic acid), an antifungal antibiotic, is a very important member of this class of compounds. (1*R*,2*S*)-2-Amino-4-methylenecyclopentanecarboxylic acid (Icofungipen), is for example, a strong antifungal agent.[12b] Many cyclic, conformationally restricted β-amino acids have been used as building blocks for the synthesis of peptides.[13]

To our knowledge, cispentacin derivatives fused with a heterocyclic ring have not been prepared. Our present aim was to synthesize novel, isoxazoline-fused β-aminocyclopentanecarboxylate regio- and stereoisomers in racemic or enantiomerically pure form, starting from the corresponding N-protected ethyl 2-amino-3-cyclopentenecarboxylates **1a**–**b** as dipolarophiles. The nitrile oxide was generated using nitroethane in the presence of Boc_2O and 4-dimethylaminopyridine (DMAP). When amino ester **1a** (R = Boc) was submitted to the cycloaddition in THF at 20 °C for 15 h, two regioisomers **2a** and **3a** (in which the isoxazoline ring is trans relative to the ester and amino functions) were formed in good overall yield (67%) in a ratio of 10:1. A third isomer **4a**, in which the isoxazoline ring is cis arranged relative to the ester and amino moieties, was isolated from the reaction mixture, but only in low yield (6%) (Scheme 1). When the reaction was performed under similar conditions with the benzoyl-protected derivative **1b**, the overall yield increased (87%) and two trans-products, **2b** (Fig. 1) and **3b**, and a cis-derivative **4b** were isolated (Scheme 1). The ratio of **2b**:**3b** (5.7:1) was lower in comparison with that of **2a**:**3a**. The regio- and stereoisomers were separated and isolated by column

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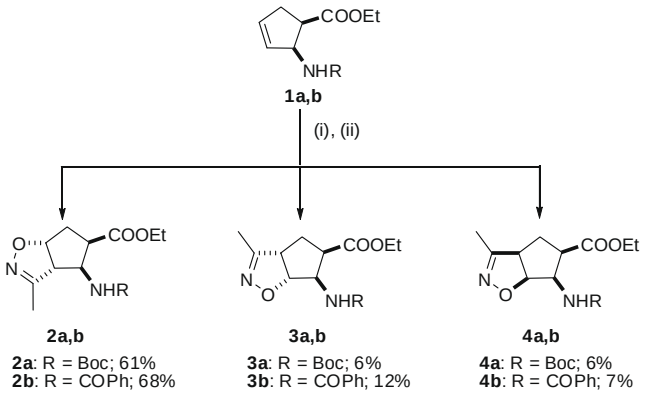
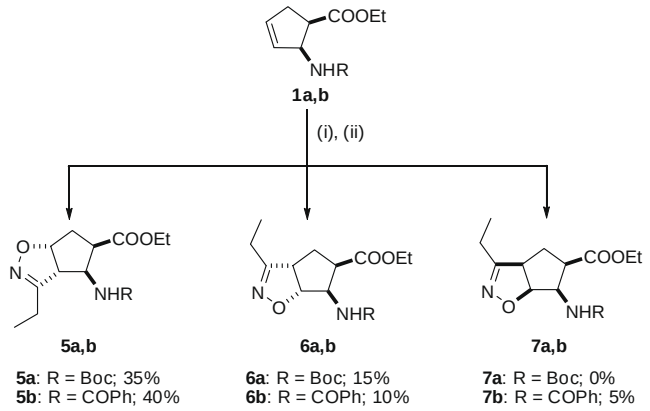


Scheme 1. Synthesis of isoxazoline-fused ethyl 2-aminocyclopentanecarboxylates: (i) nitroethane, Boc_2O, DMAP, THF, 20 °C, 15 h; (ii) column chromatography.



Scheme 2. Synthesis of isoxazoline-fused ethyl β-aminocyclopentanecarboxylates: (i) 1-nitropropane, Boc_2O, DMAP, THF, 20 °C, 15 h; (ii) column chromatography.

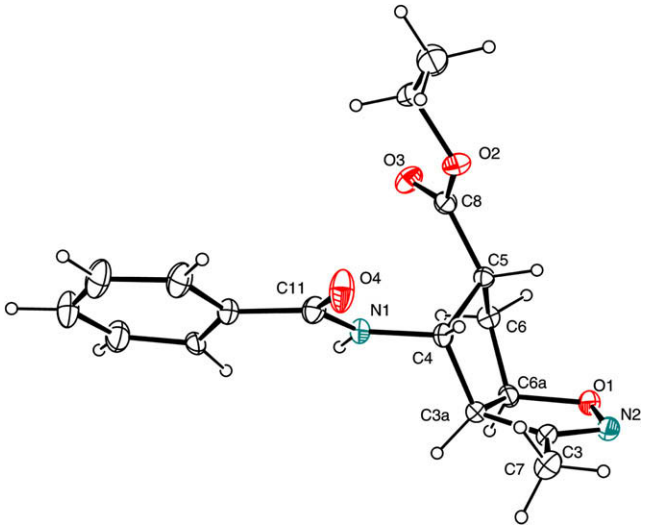


Figure 1. ORTEP diagram of compound **2b**.

chromatography on silica gel, and their structures were elucidated by X-ray and 2D NMR analysis.

In all cases, the *trans*-isoxazoline derivatives **2a,b** were formed as major products, with the oxygen atom of the isoxazoline unit furthest from the carbamate or amide group. This regioselectivity is probably best explained by electronic factors, the negatively charged oxygen of the dipolar agent prefers to attack the carbon atom of amino ester **1a,b** most distant from the carbamate or amide group because of the electron-withdrawing effect of the nitrogen atom at position 4 of the cyclopentane skeleton. Similar regioselectivities were observed in the reactions of nitrile oxides with γ-amino carboxylates with a cyclopentene skeleton.[10]

Experiments were next performed with a primary nitroalkane homolog. The cycloadditions of 1-nitropropane to **1a,b** were performed under similar conditions as previously described for nitroethane. As expected the main products formed in the cycloaddition of Boc-protected derivative **1a** were the *trans*-isoxazoline derivatives **5a** and **6a** in 50% overall yield, the major product being regioisomer **5a** (Scheme 2). The cis-isomer was not detected in the reaction mixture. It is noteworthy that the ratio of the two trans-isomers (**5a** and **6a**) in this case was only 2.3:1, that is, much lower than that was found for nitroethane.

With the benzoyl-protected β-amino ester **1b** under the same conditions, the cis-stereoisomer **7b** (5%) was isolated together with the main trans-derivatives **5b** in 40% yield (Fig. 2) and **6b** in 10% yield (Fig. 3).

The synthetic route was next applied to synthesize enantiomerically pure isoxazoline-fused β-aminocyclopentane carboxylates (Scheme 3). The enantiomerically pure Boc-protected amino ester (−)-**1a**[14] was transformed (without affecting the stereocenters) in reactions with both nitrile oxide species (derived from nitropropane or nitroethane) into the corresponding isoxazoline-fused β-aminocyclopentanecarboxylate enantiomers (Scheme 3).

In summary, novel, regio-, and stereoisomers of isoxazoline-fused cispentacin derivatives have been synthesized via 1,3-dipolar cycloadditions of nitrile oxides to ethyl 2-amino-3-cyclopentenecarboxylates. This synthetic pathway was also applied for the preparation of these new compounds in enantiomerically enriched form. Although, the cycloaddition was not completely selective, it permitted preparation of three different regio- and diastereoisomers of isoxazoline-fused cispentacin derivatives.

The ee values of **2a**–**6a** were determined by gas chromatography using a chiral column: Chromopack Chiralsil-Dex CB column (25 m) [190 °C; 140 kPa]; retention times (min), (+)-**2a**: 20.48 (antipode: 20.16); (−)–**3a**: 32.97 (antipode: 30.88); (+)–**4a**: 24.69 (antipode: 25.88); (+)–**6a**: 42.11 (antipode: 40.16); Chromopack L-Val column (25 m) [190 °C; 140 kPa]; retention times (min), (+)–**5a**: 9.43 (antipode: 8.95).

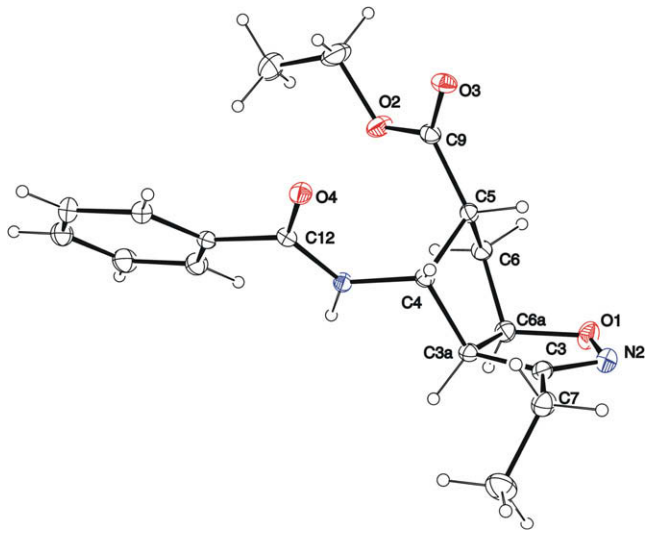


Figure 2. ORTEP diagram of compound **5b**.

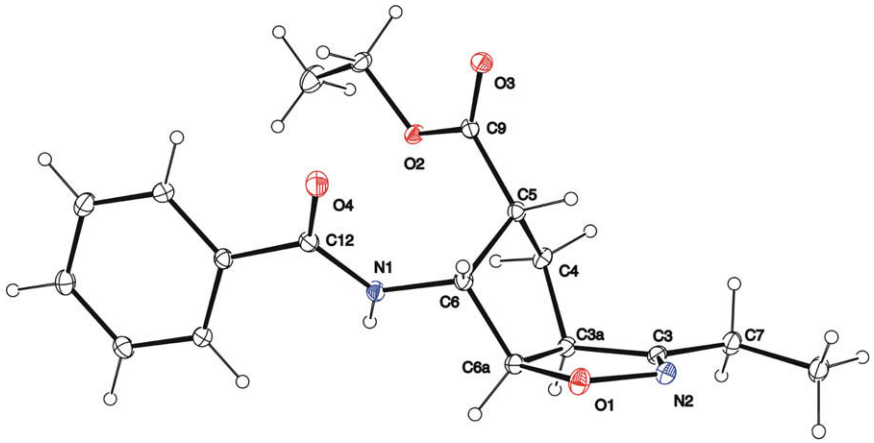
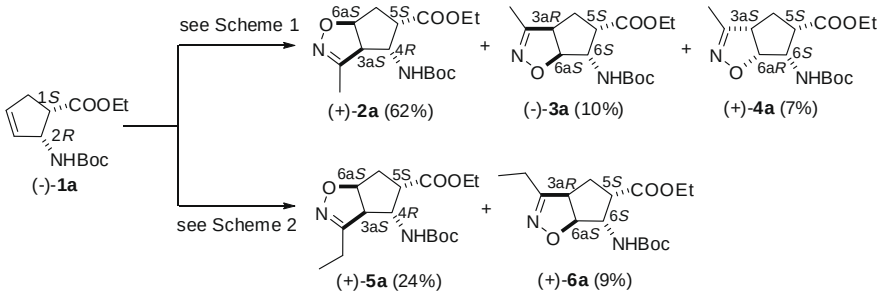


Figure 3. ORTEP diagram of compound **6b**.



Scheme 3. Synthesis of the isoxazoline-fused ethyl β-aminocyclopentanecarboxylate enantiomers (+)-**2a**, (−)-**3a**, (+)-**4a**, (+)-**5a,** and (+)-**6a**.

General procedure for the synthesis of isoxazoline-fused β-aminocyclopentanecarboxylates

To a solution of amino ester **1a–b** (3 mmol) in THF (20 mL), nitroalkane (3.2 mmol), DMAP (0.6 mmol, 20 mol %), and Boc_2O (9 mmol, 3 equiv) were added and the mixture was stirred at 20 °C for 15 h. The reaction mixture was then diluted with water (50 mL) and extracted with EtOAc (3 × 15 mL). The combined organic layer was washed with 5% HCl (15 mL) and brine (2 × 20 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The crude residue was purified by column chromatography on silica gel (hexane–EtOAc).

Characterization of enantiomeric products.

Ethyl (3a*S*,4*R*,5*S*,6a*S*)-4-(*tert*-butoxycarbonylamino)-3-methyl-4,5,6,6a-tetrahydro-3a*H*-cyclopenta[d]isoxazole-5-carboxylate [(+)-2a]

Yield: 62%; white solid; R_f = 0.65 (hexane-EtOAc); mp 80–82 °C; $[\alpha]_D^{25}$ +10.9 (*c* 0.34, EtOH), ee > 99%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.29 (t, 3H, CH_3, *J* = 7.15 Hz), 1.44 (s, 9H, CH_3), 2.08 (s, 3H, CH_3), 2.23–2.39 (m, 2H, CH_2), 2.90–2.99 (m, 1H, H-5), 3.63–3.67 (m, 1H, H-3a), 4.13–4.22 (m, 3H, OCH_2 and H-4), 5.06–5.11 (m, 1H, H-6a), 5.22 (br s, 1H, N–H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.6, 14.8, 29.0, 37.6, 45.5, 57.2, 61.9, 64.5, 80.4, 84.2, 152.0, 155.3, 155.8. MS: (ES, pos) *m/z* = 313 (M+1). Anal. Calcd for $C_{15}H_{24}N_2O_5$: C, 57.68; H, 7.77; N, 8.97. Found: C, 57.22; H, 7.45; N, 8.50.

Ethyl (3a*R*,5*S*,6*S*,6a*S*)-6-(*tert*-butoxycarbonylamino)-3-methyl-4,5,6,6a-tetrahydro-3a*H*-cyclopenta[d]isoxazole-5-carboxylate [(-)-3a]

Yield: 10%; white solid; R_f = 0.45 (hexane–EtOAc); mp 104–106 °C; $[\alpha]_D^{25}$ −7.5 (*c* 0.41, EtOH), ee > 99%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.27 (t, 3H, CH_3, *J* = 7.15 Hz), 1.44 (s, 9H, CH_3), 1.95 (s, 3H, CH_3), 1.99–2.03 (m, 1H, CH_2), 2.25–2.33 (m, 1H, CH_2), 2.94–2.98 (m, 1H, H-5), 3.63–3.67 (m, 1H, H-3a), 4.12–4.20 (m, 2H, OCH_2), 4.28–4.30 (m, 1H, H-6), 4.89 (br s, 1H, N–H). 4.90–4.94 (m, 1H, H-6a). ^{13}C NMR (100 MHz, DMSO): δ = 12.0, 14.8, 29.0, 29.9, 46.3, 54.3, 60.5, 60.8, 79.0, 89.4, 155.0, 158.1, 171.7. MS: (ES, +) *m/z* = 647 (2M+Na). Anal. Calcd for $C_{15}H_{24}N_2O_5$: C, 57.68; H, 7.77; N, 8.97. Found: C, 57.24; H, 7.43; N, 8.52.

Ethyl (3a*S*,5*S*,6*S*,6a*R*)-6-(*tert*-butoxycarbonylamino)-3-methyl-4,5,6,6a-tetrahydro-3a*H*-cyclopenta[*d*]isoxazole-5-carboxylate [(+)-4a]

Yield: 7%; white solid; R_f = 0.40 (hexane–EtOAc); mp 82–85 °C; $[\alpha]_D^{25}$ +430 (*c* 0.07, EtOH), ee > 99%. ^{1}H NMR (400 MHz, DMSO): δ = 1.18 (t, 3H, CH_3, *J* = 7.15 Hz), 1.41 (s, 9H, CH_3), 1.89–1.98 (m, 1H, CH_2), 2.00 (s, 3H, CH_3), 2.19–2.24 (m, 1H, CH_2), 2.97–3.05 (m, 1H, H-5), 3.56–3.62 (m, 1H, H-3a), 3.92–4.05 (m, 2H, OCH_2), 4.10–4.15 (m, 1H, H-6), 4.78–4.83 (m, 1H, H-6a), 6.03 (br s, 1H, N–H). ^{13}C NMR (100 MHz, DMSO): δ = 11.9, 14.7, 28.6, 29.0, 44.5, 54.2, 57.6, 60.9, 83.8, 155.6, 158.1, 172.1. MS (ES, +) *m/z* = 647 (2M+Na). Anal. Calcd for $C_{15}H_{24}N_2O_5$: C, 57.68; H, 7.77; N, 8.97. Found: C, 57.20; H, 7.46; N, 8.54.

Ethyl (3a*S*,4*R*,5*S*,6a*S*)-4-(*tert*-butoxycarbonylamino)-3-ethyl-4,5,6,6a-tetrahydro-3a*H*-cyclopenta[*d*]isoxazole-5-carboxylate [(+)-5a]

Yield: 24%; white solid; $R_f = 0.53$ (hexane-EtOAc); mp 105–107 °C; $[\alpha]_D^{25}$ +2 (*c* 0.325, EtOH), ee > 99%. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.23$ (t, 3H, CH_3, $J = 8.20$ Hz), 1.29 (t, 3H, CH_3, $J = 7.10$ Hz), 1.44 (s, 9H, CH_3), 2.26–2.41 (m, 3H, CH_2), 2.50–2.56 (m, 1H, CH_2), 2.92–2.98 (m, 1H, H-5), 3.67–3.71 (m, 1H, H-3a), 4.14–4.23 (m, 3H, OCH_2 and H-4), 5.05–5.11 (m, 1H, H-6a), 5.19 (br s, 1H, N–H). ^{13}C NMR (100 MHz, DMSO): $\delta = 11.5$, 14.8, 20.5, 28.9, 35.8, 46.9, 56.9, 60.8, 62.3, 78.9, 84.3, 155.5, 159.2, 171.6. MS (ES, +) $m/z = 675$ (2M+Na). Anal. Calcd for $C_{16}H_{26}N_2O_5$: C, 58.88; H, 8.03; N, 8.58. Found: C, 58.48; H, 7.87; N, 8.20.

Ethyl (3a*R*,5*S*,6*S*,6a*S*)-6-(*tert*-butoxycarbonylamino)-3-ethyl-4,5,6,6a-tetrahydro-3a*H*-cyclopenta[*d*]isoxazole-5-carboxylate [(+)-6a]

Yield: 9%; white solid; $R_f = 0.35$ (hexane-EtOAc); mp 78–81 °C; $[\alpha]_D^{25}$ +77 (*c* 0.295, EtOH), ee > 99%. ^{1}H NMR (400 MHz, DMSO): $\delta = 1.18$ (t, 3H, $J = 7.10$ Hz), 1.23 (t, 3H, $J = 7.15$ Hz), 1.44 (s, 9H, CH_3), 1.90–1.99 (m, 1H, CH_2), 2.18–2.41 (m, 3H, CH_2), 2.64–2.77 (m, 1H, H-3a), 3.60–3.72 (m, 1H, H-5), 3.97–4.08 (m, 2H, OCH_2), 4.21–4.31 (m, 1H, H-6), 6.59–4.70 (m, 1H, H-6a), 7.08–7.17 (br s, 1H, N–H). ^{13}C NMR (100 MHz, DMSO): $\delta = 11.4$, 14.8, 20.0, 29.0, 30.1, 46.4, 53.1, 60.5, 60.8, 79.0, 89.4, 155.6, 162.2, 171.7. MS: (ES, +) $m/z = 675$ (2M+Na). Anal. Calcd for $C_{16}H_{26}N_2O_5$: C, 58.88; H, 8.03; N, 8.58. Found: C, 58.51; H, 7.84; N, 8.12.

X-ray crystallographic studies

Crystallographic data for **2b**, **5b**, and **6b** were collected at 173 K with a Nonius-Kappa CCD area detector diffractometer, using graphite-monochromatized MoK radiation ($\lambda = 0.71073$ Å). The structures were solved by direct methods by use of the SIR-97 program, and full-matrix, least-squares refinements on F^2 were performed by use of the SHELXL-97 program. The CH hydrogen atoms were included at fixed distances with fixed displacement parameters from their host atoms. The NH hydrogen atoms were refined isotropically with fixed displacement parameters. The deposition numbers CCDC 707421 (**2b**), 707422 (**5b**), and 707423 (**6b**) contain the supplementary crystallographic data for this Letter.[15]

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15. The details of the crystallographic data for **2b**, **5b**, and **6b** in CIF format can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Center, 12 Union Road, Cambridge CB2 1EZ, UK; Fax: (internat.) +44-1223-336-033; E-mail: deposit@ccdc.cam.ac.uk].