Synthesis of Enantiomerically Pure D- and L-Armentomycin and Its Difluoro Analogues from Aspartic Acid

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The synthesis of both enantiomers of 2-amino-4,4-dichlorobutanedioic acid (armentomycin) and their fluoro analogues from aspartic acid via 2-amino-4-oxobutanoic acid protected with hexafluoroacetone is described.

A series of halogeno α-amino acids possess interesting biological activities,1 because they frequently act as antagonists of naturally occurring α-amino acids. One of them, the antibiotically active L-armentomycin (6) (Figure 1) was isolated from Streptomyces armentosus var. armentosus in 1967.2 Three synthetic routes for the racemic3 or optically active4 6 have been reported so far including an electrochemical5 synthesis.

Figure 1

We now report on a new synthesis starting from aspartic acid using hexafluoroacetone (HFA) as protecting and activating reagent.5 The application of hexafluoroacetone in protecting the amino and carboxyl group of α-amino acids facilitates the synthesis of many natural and nonnatural α-amino acids in enantiomerically pure form from cheap chiral starting materials.

The protected 2-amino-4-oxobutanoic acid 4 (aspartic acid β-semialdehyde) is the key intermediate of the synthetic sequences reported here. It represents a very interesting intermediate for the syntheses of a variety of biologically active compounds. Several synthetic routes towards this aldehyde have been published, but most of them use expensive starting materials like allylglycine or homoserine. The protecting groups used often are not advantageous and cleavage in the presence of sensitive side chain functionalities is very difficult. Syntheses of optically pure compounds starting from readily available chiral compounds like aspartic acid or methionine have been reported.5

The reduction of aspartic acid derivatives to give the β-aldehyde can be achieved with NaBH₄ (via homoserine derives and subsequent oxidation), Bu₃SnH6 or Li(t-BuO)₂AlH.9 Better results can be achieved by Rosenmund reduction of the protected β-acid chloride.10

Aspartic acid reacts with HFA to form the 2,2-bis(trifluoromethyl)-1,3-oxazolidin-5-one 2.5 Hence, the carboxylic group and the α-amino group are protected simultaneously, while the carboxylic group in the side chain remains unaffected and can be converted regioselectively via the acid chloride 3.5 The latter is formed by reaction of 2 with thionyl chloride. Hydrogenation of 3 according to the Rosenmund protocol in the presence of palladium on barium sulfate catalyst leads to the β-semialdehyde 4. This conversion can be monitored by 19F NMR spectroscopy and is almost quantitative. The aldehyde 4 is obtained analytically pure after Kugelrohr distillation (Scheme 1).

Scheme 1

The transformation of 4 into the protected halogeno α-amino acids follows standard procedures. The hexafluoroacetone derivative of armentomycin 5 is formed upon chlorination of 4 with phosphorus pentachloride (Scheme 2).

Scheme 2

Fluorination of the aldehyde 4 is achieved with diethylamino sulfur trifluoride (DAST) under very mild conditions to yield the protected fluoro analogue 7 of armentomycin (Scheme 3). The free halogeno α-amino acids can be obtained easily from the corresponding 2,2-bis(trifluoromethyl)-1,3-oxazolidin-5-ones 5 or 7. Deprotection of the α-amino and the carboxylic group is achieved in one step by hydrolysis with water/propan-2-ol at room temperature. The reaction can be monitored by 19F NMR spectroscopy. Thus,
armentomycin (6) is obtained in 30% overall yield starting from aspartic acid. Physical and spectroscopical data are in accordance with the results published previously.\(^4\)

![Chemical Structure](image)

**Scheme 3**

In summary, protection of aspartic acid with hexafluoroacetone facilitates the synthesis of the \(\beta\)-semialdehyde of aspartic acid 4 in analytical purity. The conversion of 4 into halogeno amino acid derivatives 5,7 and their deprotection proceeds in good yields without racemization.

Solvents were purified and dried prior to use. Reagents were used as purchased. The catalyst (5% Pd/BaSO\(_4\)) is commercially available from Fluka.

Melting points (uncorrected) were determined on a Boetius heating table. Optical rotation indices were measured on a Polarotrac \(\rho\)-polarimeter (Schmidt & Haensch) in a 10 cm cell. For C, H, N analyses a CHNO-Rapid-Elemental-Analyser (Heraeus) was used. Mass spectra were recorded on a VG 12-250 (Masslab) electron ionization spectrometer (EI = 70 eV) or by GC/MS on a HPS890 MSD. IR spectra were obtained by using a Specord spectrometer (Carl Zeiss, Jena). \(^1\)H (199.975 or 300.075 MHz), \(^1^3\)C (50.289 or 75.462 MHz) and \(^3^1^P\) NMR (282.330 MHz) spectra were recorded on a Varian Gemini 200 or a Varian Gemini 300 spectrometer. TMS was used as a reference standard for \(^1\)H and \(^1^3\)C NMR spectra (internal) and CF\(_2\)CO\(_2\)H for \(^3^1^P\) NMR spectra (external). A GKR-50 heater (Büchi) was used for Kugelrohr distillations. All compounds gave correct microanalyses (± 0.3%).

\((S)-2,2\text{-Bis( trifluoromethyl)}\)-5-oxo-1,3-oxazolidin-4-yl ethanol (4): Compound 3 (29.9 g, 100 mmol) and 5% Pd/BaSO\(_4\) (13.0 g) were refluxed in toluene (300 mL) under a stream of H\(_2\). The reaction was usually complete after 2 h. The mixture was allowed to cool to rt. and the catalyst was filtered. The filtrate was evaporated under reduced pressure (bath temperature 30°C) and the residue distilled in vacuo in a Kugelrohr apparatus to give 4 as a colorless liquid (16.7 g, 63%); bp 45°C/0.1 mbar; \(\delta_{\text{H}}^2 = 42.5\) (c = 1.0, CHCl\(_3\)).

MS: \(m/z = 265\) [M\(^+\)], 166 [CF\(_3\)]\(_2\)CO\(^+\), 115 [M+CF\(_3\)]\(^+\), 69 [CF\(_3\)]\(^+\).

IR (film): ν = 3370 (NH), 1830 (CO)\(_{\text{amide I}}\), 1730 (CO)\(_{\text{amide II}}\) cm\(^{-1}\).

\(^1\)H NMR (CDCl\(_3\)/200 MHz): \(\delta = 2.84\) (dd, \(J = 19.0, 10.0\) Hz, 1H, CH\(_3\)), 3.20 (dd, \(J = 19.0, 2.5\) Hz, 1H, CH\(_3\)), 3.63 (d, \(J = 7.0\) Hz, 1H, NH), 4.41 (dd, \(J = 10.0, 7.0\) Hz, 2H, CH\(_3\)), 9.80 (s, 1H, CHO).

\(^1^3\)C NMR (CDCl\(_3\)/50 MHz): \(\delta = 47.5\) (CH\(_3\)), 49.7 (CH), 88.8 (q, \(J = 37, 37\) Hz, C(F\(_3\))\(_2\)), 120.5 (q, \(J = 284\) Hz, CF\(_3\)), 121.6 (q, \(J = 287\) Hz, CF\(_3\)), 170.9 (CO), 198.5 (CHO).

\(^3^1^P\) NMR (CDCl\(_3\)/300 MHz): \(\delta = -2.24\) (q, \(J = 9\) Hz, 3F, CF\(_3\)), -3.43 (q, \(J = 9\) Hz, 3F, CF\(_3\)).

\([/R/-2,2\text{-Bis( trifluoromethyl)}\]-5-oxo-1,3-oxazolidin-4-yl ethanol (ent-4): \(\delta_{\text{H}}^2 = 42.5\) (c = 1.0, CHCl\(_3\)).

\((S)-2,2\text{-Bis(trifluoromethyl)}\)-4-(2,2'-dichloroethyl)-1,3-oxazolidin-5-one (5): A solution of aldehyde 4 (2.7 g, 10 mmol) in CCl\(_4\) (5 mL) was added with stirring to PCI\(_2\) (2.3 g, 11 mmol) in CCl\(_4\) (50 mL) under a N\(_2\) atmosphere at 0°C (ice/water bath). The mixture was warmed up to rt. and the stirring continued for an additional 4 h. The mixture was then diluted with CH\(_2\)Cl\(_2\) (50 mL) and treated with ice/water (50 mL). The phases were separated and the aqueous layer was extracted with CH\(_2\)Cl\(_2\) (50 mL). The organic phases were combined, washed with sat. aq NaHCO\(_3\) (100 mL) and water (50 mL). After drying (MgSO\(_4\)), the solvent was removed under reduced pressure (bath temperature 25°C) and the residue purified by Kugelrohr distillation in vacuo to give a colorless liquid (2.15 g, 67%); bp 40°C/0.1 mbar; \(\delta_{\text{H}}^2 = 4.0\) (c = 1.0, CHCl\(_3\)).

MS: \(m/z = 222, 224, 226\) [M-CF\(_3\)-CO\(^-\)], 66 [CF\(_3\)]\(^+\).

IR (film): ν = 3375 (NH), 1830 (CO) cm\(^{-1}\).

\(^1\)H NMR (CDCl\(_3\)/200 MHz): \(\delta = 2.53\) (dd, \(J = 14.6, 8.9, 5.5\) Hz, 1H, CH\(_3\)), 2.78 (dd, \(J = 14.6, 6.8, 4.3\) Hz, 1H, CH\(_3\)), 3.34 (d, \(J = 7.3\) Hz, NH), 4.34 (dd, \(J = 8.9, 7.3, 4.3\) Hz, 1H, CH), 5.97 (dd, \(J = 6.8, 5.5\) Hz, 1H, CHCl\(_3\)).

\(^1^3\)C NMR (CDCl\(_3\)/75 MHz): \(\delta = 46.3\) (CH\(_3\)), 52.0 (CH), 88.5 (q, \(J = 34, 34\) Hz, C(F\(_3\))\(_2\)), 120.0 (q, \(J = 285\) Hz, CF\(_3\)), 120.9 (q, \(J = 288\) Hz, CF\(_3\)), 169.9 (CO).

\(^1^F\) NMR (CDCl\(_3\)/300 MHz): \(\delta = 2.47\) (q, \(J = 8.5\) Hz, 3F, CF\(_3\)), -3.46 (q, \(J = 8.5\) Hz, 3F, CF\(_3\)).

\((R)-2,2\text{-Bis( trifluoromethyl)}\)-4-(2,2'-dichloroethyl)-1,3-oxazolidin-5-one (ent-5): \(\delta_{\text{H}}^2 = 4.0\) (c = 1.0, CHCl\(_3\)).

**S-(2,2-Amino-4,4-dichlorobutanoic Acid (6):**

A solution of 5 (3.2 g, 1 mmol) in a mixture of propan-2-ol (20 mL) and water (5 mL) was stirred for 7 d. The solvent was removed under reduced pressure, the residue dissolved in water and lyophilized. The operation was repeated until HFA-hydrate could not be detected any more by \(^1^F\) NMR spectroscopy. Recrystallization from MeOH/H\(_2\)O afforded colorless crystals of 6 (1.48 g, 86%); mp 155°C (dec); \(\delta_{\text{H}}^2 = 6.9\) (c = 0.75, H\(_2\)O), [\(\text{lit.}^2\) mp 153°C (dec); \(\delta_{\text{H}}^2 = 6.7\) (c = 0.74, H\(_2\)O)].

MS: \(m/z = 172\) [M\(^+\)], 126, 128 [M-CO\(_2\)H\(^+\)].

IR (KBr): ν = 3400, 3000, 1620, 1500, 1420 cm\(^{-1}\).

\(^1\)H NMR (D\(_2\)O/300 MHz): \(\delta = 2.78\) (dd, \(J = 15.0, 6.8, 6.8\) Hz, 1H, CH\(_3\)), 2.97 (dd, \(J = 15.0, 6.0, 6.0\) Hz, 1H, CH\(_3\)), 4.10 = 4.14 (m, 1H, CH\(_3\)), 6.24-6.28 (m, 1H, CHCl\(_3\)).
$^{13}$C NMR (D$_2$O/75 MHz): $\delta = 43.6$ (CH$_3$), 51.7 (CH), 69.8 (CHCl$_3$), 172.4 (CO).

(R)-2-Amino-4,4-dichlorobutanoic Acid (ent-6): $[\alpha]_{D}^{23} + 6.9$ (c = 0.75, H$_2$O).

(S)-2-Amino-4,4-difluorobutanoic Acid (8):
A solution of 7 (2.87 g, 10 mmol) in a mixture of propan-2-ol (20 mL) and water (5 mL) was stirred for 7 days. The solvent was removed under reduced pressure, the residue dissolved in water and lyophilized. This operation was repeated until HFA-hydrate could not be detected any more by $^{19}$F NMR spectroscopy. Recrystallization from MeOH/H$_2$O gave white crystals of 7 (1.24 g, 89%); mp 225°C (dec); $[\alpha]_{D}^{23} - 4.0$ (c = 1.0, H$_2$O).


IR (KBr): ν = 3400, 3000, 1610, 1520, 1420, 1400 cm$^{-1}$.

$^3$H NMR (D$_2$O/300 MHz): $\delta = 2.40–2.80$ (m, 2 H, CH$_3$), 4.06 (dd, J = 8.0, 4.7 Hz, 1 H, CH), 6.27 (dd, J = 55, 55, 3.8 Hz, 1 H, CHF$_3$).

$^{13}$C NMR (D$_2$O/75 MHz): $\delta = 34.5$ (dd, J = 22, 22 Hz, CH$_3$), 49.4 (dd, J = 5, 5 Hz, CH), 115.9 (dd, J = 238, 238 Hz, CHF$_2$), 172.9 (CO).

$^{19}$F NMR (D$_2$O/300 MHz): $\delta = -37.8$ (ddd, J = 286, 55, 20 Hz, 1 F, CHF$_3$), $-39.8$ (ddd, J = 286, 55, 20 Hz, 1 F, CHF$_2$).

(R)-2-Amino-4,4-difluorobutanoic Acid (ent-8): $[\alpha]_{D}^{23} + 4.0$ (c = 1.0, H$_2$O).

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