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Synthetic studies toward astins A, B and C. Efficient syntheses of *cis*-3,4-dihydroxyprolines and (−)-(3*S*,4*R*)-dichloroproline esters

Kelly K. Schumacher,[a] Jianjun Jiang [b] and Madeleine M. Joullié [a,*]

[a]*Department of Chemistry, University of Pennsylvania, Philadelphia, PA 19104-6323, USA*
[b]*Abbott Laboratories, Abbott Park, IL 60064, USA*

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Abstract

Efficient syntheses of the esters of *cis*-3,4-dihydroxyprolines and the first synthesis of the ester of the rare amino acid (−)-(3*S*,4*R*)-dichloroproline from *trans*-4-hydroxy-L-proline are presented. The synthetic route provides easy access to several substituted prolines and *cis*-hydroxylated proline esters. Various types of biological activities have been associated with these substituted prolines. The role of (−)-(3*S*,4*R*)-dichloroproline in astins A, B and C is under investigation.

1. Introduction

Three members of the astin family of cyclopentapeptides, astins A, B and C (**1–3**, Fig. 1), contain the unnatural amino acid (−)-*cis*-(3*S*,4*R*)-dichloro-L-proline. This rare amino acid appears in only two other natural products, cyclochlorotine[1] and islanditoxin,[2] both of which are structurally similar to the astins. The astins were isolated from the biologically active extracts of the root of *Aster tataricus* (Compositae).[3–7] Though all astins exhibit antitumor activity, the dichloroproline-containing astins are significantly more potent. Our synthetic route toward dichloroproline utilizes the precursor 3*R*,4*S*-dihydroxyproline. This approach also provides an efficient method for synthesizing a variety of important polyhydroxylated prolines and pyrrolidines. The various polyhydroxylated stereoisomers of proline[8–12] and the corresponding pyrrolidines (*cis*[13–15] and *trans*[16–21]) have been shown to have novel biological activity and have been synthesized by various methods. Several of these compounds including 1,4-dideoxy-1,4-imino-D-arabinitol[14] and 1,4-dideoxy-1,4-imino-D-lyxitol[14] are potent α-glucosidase and α-galactosidase inhibitors respectively. Biological activity against human immunodeficiency virus has also been reported.[10,17] Polyhydroxylated pyrrolidines and prolines also appear in a variety of natural

* Corresponding author. E-mail: mjoullie@sas.upenn.edu

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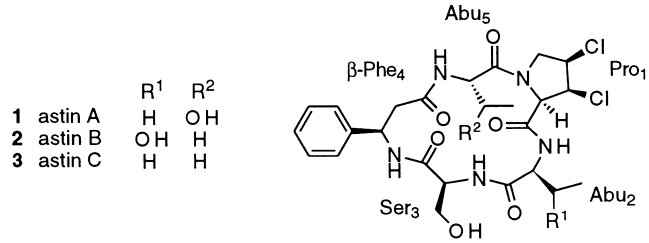
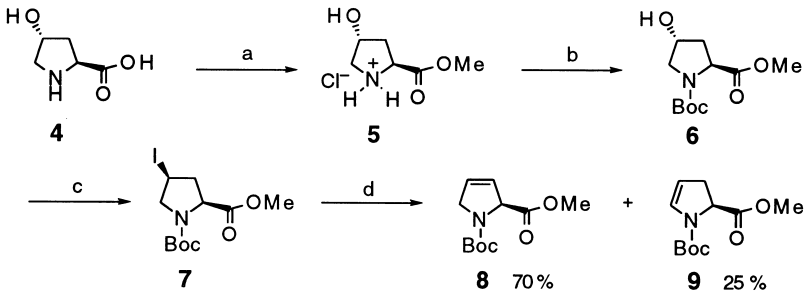


Fig. 1. Structures of astins A–C

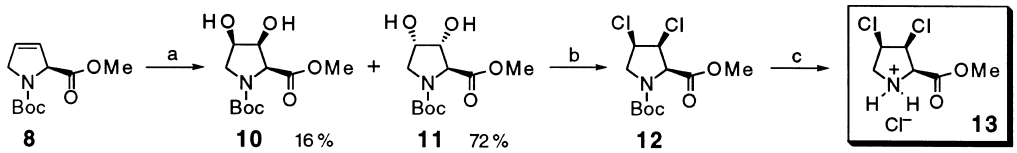
products.[8,11,12,15,18–22] Although there are no reports of the synthesis of a dichlorinated proline, the synthesis of a mono-chlorinated proline, *cis*-4-chloro-L-proline, has been reported by Andreatta et al.[23]

We have previously reported syntheses of α-aminobutyric acid and the tripeptide fragment common to most of the astins[24] as well as the total synthesis of astin G,[25] the 4-hydroxyproline and 3,4-dihydroxyproline analogs of astin G[26] and approaches toward the total synthesis of the 3,4-dehydroproline analog of astin G.[27] We now report the synthesis of (−)-*cis*-(3*S*,4*R*)-dichloro-L-proline and its useful precursor *cis*-3*R*,4*S*-dihydroxy-L-proline. This route is shown in Schemes 1 and 2.



[a] MeOH, $SOCl_2$, quant.; [b] Boc_2O, Et_3N, CH_2Cl_2, 92 %; [c] DEAD, Ph_3P, CH_3I, THF, 94 %; [d] DBU, toluene

Scheme 1.



[a] OsO_4, NMO, dioxane, H_2O; [b] CCl_4, Ph_3P, Δ, 68 %; [c] 3.0 M HCl in dioxane

Scheme 2.

Commercially available *trans*-4-hydroxy-L-proline **4** was converted to its methyl ester hydrochloride salt **5** with thionyl chloride and methanol. Compound **5** was subsequently protected as its *tert*-butoxycarbonyl derivative **6**. Inversion of stereochemistry at C-4 to afford the epimeric iodide **7** was effected with triphenylphosphine, diethyl azodicarboxylate and methyl iodide.[28] Elimination of HI using diazabicyclo-[5.4.0]undecene afforded the isomeric 3,4- and 4,5-dehydroprolines (**8** and **9**, respectively) in 70% and 25% yields.[28] The isomers were separated by column chromatography and were used immediately to avoid decomposition.

Osmium tetroxide oxidation of compound **8** to the diastereomeric diols **10** and **11** proceeded in 16% and 72% yields respectively. The diols were separable via flash column chromatography. AD-mix formulations did not provide satisfactory yields of the desired dihydroxyprolines. Treatment of *cis*-3*R*,4*S*-dihydroxy-L-proline **11** with triphenylphosphine and carbon tetrachloride afforded *cis*-3*S*,4*R*-dichloro-

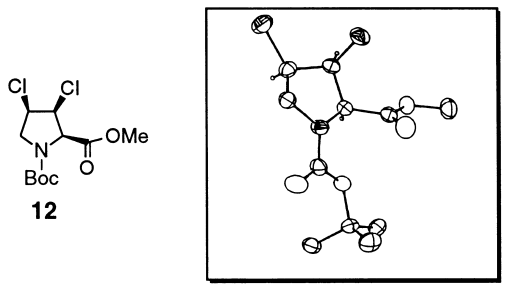


Fig. 2. Crystal structure of protected 3*S*,4*R*-dichloro-L-proline

L-proline in 68% yield. The *tert*-butoxycarbonyl protecting group was removed quantitatively using 3.0 M HCl in dioxane.

The stereochemistry at C-3 and C-4 of *cis*-3*S*,4*R*-dichloro-L-proline was established conclusively by the crystal structure of *N*-Boc-3*S*,4*R*-dichloroproline methyl ester **12** shown in Fig. 2. The crystal[29] shows the two chlorines in a gauche conformation. This solid state conformation closely mimics the solution state structure of dichloroproline in astins A, B and C established by NMR.[4–7]

In conclusion, the first synthesis of an ester of the unnatural amino acid (−)-*cis*-(3*S*,4*R*)-dichloro-L-proline has been completed. Incorporation of this amino acid into the astin macrocycle to complete the synthesis of astins A, B and C is in progress. Synthesis of various isomeric dihydroxyprolines has also been achieved. The biological activity of compound **12** is also under investigation.

2. Experimental

Solvents were dried according to published methods and distilled before use. HPLC grade methanol was used. All other reagents were commercial compounds of the highest purity available. Analytical thin-layer chromatography (TLC) was performed using Merck silica gel (60 F-254) plates (0.25 mm) precoated with a fluorescent indicator. Column chromatography was performed using Merck silica gel 60 particle size (0.040–0.063 mm). Melting points (mp) were determined with a Thomas–Hoover capillary melting point apparatus and are uncorrected. Proton (^{1}H) and carbon (^{13}C) magnetic resonance spectra (NMR) were recorded on a Bruker AM-500 [500 MHz (125 MHz for ^{13}C)] Fourier transform spectrometer, and chemical shifts were expressed in parts per million (δ) relative to tetramethylsilane (TMS, 0 ppm) or chloroform ($CHCl_3$, 7.24 ppm for ^{1}H and 77.00 ppm for C^{13}) as an internal reference. Infrared spectra (IR) were obtained on a Perkin–Elmer Model 1600 FT-IR spectrophotometer. Absorptions were recorded in wavenumbers (cm^{-1}). Optical rotations, $[\alpha]_D^{20}$, were recorded on a Perkin–Elmer Model 341 polarimeter at the sodium D line.

*2.1. 4-(*R*)-Hydroxypyrrolidine-1,2-(2*S*)-dicarboxylic acid 1-*tert*-butyl ester 2-methyl ester **6***

Freshly distilled thionyl chloride (5.86 mL, 0.080 mol) was added dropwise to a stirring solution of *trans*-4-hydroxy-L-proline **4** (10.53 g, 0.080 mol) and anhydrous methanol (100 mL) at 0°C. The solution was stirred at ambient temperature for 2 h and then heated at reflux for 8 h. The solvent was removed under reduced pressure. The crude oil was dissolved in methanol, followed by removal of the solvent under reduced pressure. This procedure was repeated three times to afford the *trans*-4-hydroxyproline methyl ester hydrochloride salt **5** (13.5 g, 93%). The crude product (13.5 g, 0.074 mol) was dissolved in methylene chloride (500 mL). Triethylamine (29.6 mL, 0.22 mol) and di-*tert*-butyl dicarbonate (18.7 g,

0.086 mol) were added to this solution. The reaction mixture was stirred at ambient temperature for 8 h. The solution was extracted with 1 N $KHSO_4$ (100 mL×3), sat. $NaHCO_3$ (100 mL), 10% citric acid (100 mL) and sat. NaCl (100 mL). The organic portion was dried over $MgSO_4$ and the solvent was removed in vacuo. Purification by column chromatography eluting with 1% MeOH/CH_2Cl_2 afforded **6** as a white solid (16.54 g, 91%). Mp 93°C; R_f 0.40 (5% EtOAc/petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.40–4.39 (m, 1H), 4.37 and 4.33 (t, J=7.93, 1H), 3.66 (s, 3H), 3.54 (dd, J=11.62, 4.14 Hz, 1H), 3.47 and 3.38 (d, J=11.47, 1H), 2.97 (br s, O*H*, 1H), 2.26–2.18 (m, 1H), 2.02–1.96 (m, 1H), 1.39 and 1.34 (s, 9H), rotamers; ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.6 and 173.4, 154.5 and 154.0, 80.3 and 80.2, 69.9 and 69.1, 57.9 and 57.5, 52.1 and 51.9, 39.0 and 38.3, 28.3 and 28.2, rotamers; IR (neat) 3440 (br), 2977, 1748, 1682, 1416, 1159 cm^{-1}; HRMS calcd for $C_{11}H_{20}NO_5$ (M+H): *m/z* 246.1341, found 246.1354; $[\alpha]_D^{20}$ −64.9 (c=0.98, $CHCl_3$); Anal. Calcd for $C_{11}H_{19}NO_5$: C, 53.85; H, 7.81; N, 5.71. Found: C, 53.94; H, 7.67; N, 5.60.

*2.2. 4-(*S*)-Iodopyrrolidine-1,2-(2*S*)-dicarboxylic acid 1-*tert*-butyl ester 2-methyl ester **7***

To a flame-dried round-bottomed flask equipped with a magnetic stir bar and an addition funnel under N_2 was added *N*-Boc-*trans*-4-hydroxy-L-proline methyl ester **6** (19.29 g, 0.079 mol), triphenylphosphine (24.78 g, 0.094 mol) and anhydrous THF (275 mL). The solution was cooled to 0°C. Diethyl azodicarboxylate (DEAD, 14.9 mL, 0.094 mmol) in anhydrous THF (15 mL) was added dropwise, followed by the addition of methyl iodide (5.88 mL, 0.094 mmol). Upon addition of MeI, the solution turned from dark brown to bright yellow. The reaction mixture was allowed to warm to ambient temperature and stirred for 10 h. The solvent was removed under reduced pressure and the crude oil was purified by column chromatography, eluting with 5% EtOAc/petroleum ether to afford **7** as a white solid (26.22 g, 93.8%). Mp 64°C; R_f 0.54 (20% EtOAc/petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.28 and 4.20 (t, J=7.50, 1H), 4.10–4.00 (m, 2H), 3.72 (s, 3H), 3.63 (dd, J=10.16, 8.21 Hz, 1H), 2.85–2.82 (m, 1H), 2.35–2.26 (m, 1H), 1.43 and 1.38 (s, 9H), rotamers; ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.1 and 171.8, 153.2 and 152.6, 80.7, 59.1 and 58.6, 57.0 and 56.6, 52.4 and 52.2, 42.8 and 41.9, 28.3 and 28.2, 12.7 and 11.9, rotamers; IR (neat) 2976, 2361, 1750, 1702, 1393, 1157 cm^{-1}; HRMS calcd for $C_{11}H_{19}NO_4I$ (M+H): *m/z* 356.0359, found 356.0350; $[\alpha]_D^{20}$ −20.9 (c=0.82, $CHCl_3$).

*2.3. 2,5-Dihydropyrrole-1,2-(2*S*)-dicarboxylic acid 1-*tert*-butyl ester 2-methyl ester **8***

To compound **7** (1.12 g, 3.15 mmol) in toluene (30 mL) at ambient temperature was added 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 0.52 mL, 3.46 mmol) while stirring. After the addition, the solution was heated at 80–90°C for 8 h. The reaction mixture was allowed to stand to complete precipitation of DBU hydroiodide. The filtrate was concentrated under reduced pressure and purified by column chromatography, eluting with 5% EtOAc/petroleum ether to afford two isomeric dehydroprolines **8** (0.503 g, 70%) and **9** (0.181 g, 25%) as colorless oils. R_f 0.41 (20% EtOAc/petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.00–5.99 and 5.98–5.93 (m, 1H), 5.76–5.74 and 5.72–5.70 (m, 1H), 5.05–5.04 and 4.98–4.95 (m, 1H), 4.31–4.15 (m, 2H), 3.74 and 3.73 (s, 3H), 1.48 and 1.43 (s, 9H), rotamers; ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.1 and 170.8, 153.8 and 153.3, 129.4 and 129.2, 124.7 and 124.6, 80.2 and 80.1, 66.5 and 66.2, 53.5 and 53.2, 52.2 and 52.1, 28.4 and 28.2, rotamers; IR (neat) 3505, 2976, 2931, 2868, 1758, 1705, 1398, 1174, 1127 cm^{-1}; HRMS calcd for $C_{11}H_{18}NO_4$ (M+H): *m/z* 228.1236, found 228.1247; $[\alpha]_D^{20}$ −131.0 (c=1.22, $CHCl_3$).

2.4. 2,3-Dihydropyrrole-1,2-(2S)-dicarboxylic acid 1-tert-butyl ester 2-methyl ester **9**

R_f 0.47 (20% EtOAc/petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.63 and 6.50 (s, 1H), 4.93 and 4.88 (d, 1H, J=24.0), 4.65–4.56 (m, 1H), 3.74 (s, 3H), 3.09–2.99 (m, 1H), 2.68–2.60 (m, 1H), 1.47 and 1.42 (s, 9H), rotamers; ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.5 and 172.3, 151.5 and 151.4, 130.1, 105.1, 80.9, 58.5 and 57.9, 52.2, 35.5 and 34.4, 28.3, rotamers; HRMS calcd for $C_{11}H_{18}NO_4$ (M+H): *m/z* 228.1236, found 228.1231; $[\alpha]_D^{20}$ −97.98 (c=0.89, $CHCl_3$).

2.5. 3,4-(3S,4R)-Dihydroxypyrrolidine-1,2-(2S)-dicarboxylic acid 1-tert-butyl ester 2-methyl ester **10**

Freshly purified **8** (0.0907 g, 0.40 mmol) was dissolved in 1,4-dioxane (2.7 mL) and H_2O (0.7 mL). The resulting solution was stirred at ambient temperature while *N*-methyl morpholine *N*-oxide (0.0594 g, 0.44 mmol) and osmium tetroxide (catalytic amount) were added. The solution was stirred at ambient temperature for 30 h. The oxidation was quenched with 10% $Na_2S_2O_3$ (3 mL). The mixture was extracted with EtOAc (15 mL×3). The organic layer was washed with 1 N HCl (5 mL), sat. $NaHCO_3$ (5 mL), and H_2O (5 mL), dried over $MgSO_4$ and concentrated under reduced pressure. Purification of the diastereomeric diols using 2% methanol/methylene chloride afforded **10** (0.0165 g, 16%) and **11** (0.0745 g, 72%) as a white solid and colorless oil respectively: mp 70°C; R_f 0.41 (5% MeOH/CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.44–4.35 (m, 2H), 4.14 (s, 1H), 3.76 (s, 3H), 3.65 (dd, J=12.22, 2.44 Hz, 1H), 3.61–3.57 (m, 1H), 3.34 (br s, O*H*, 1H), 1.89 (br s, O*H*, 1H), 1.37 (s, 9H), rotamers; ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.1 and 172.9, 154.2 and 153.7, 80.8, 72.5 and 71.72, 71.65 and 70.8, 61.9 and 61.3, 52.7 and 52.5, 52.2 and 51.5, 28.3 and 28.2, rotamers; IR (neat) 3422 (br), 2975, 2360, 1740, 1701, 1406, 1164 cm^{-1}; HRMS calcd for $C_{11}H_{19}NO_6$ (M+NH_4): *m/z* 279.1556, found 279.1552; $[\alpha]_D^{20}$ −4.7 (c=0.51, $CHCl_3$); Anal. Calcd for $C_{11}H_{19}NO_6$: C, 50.55; H, 7.33; N, 5.36; found: C, 50.81; H, 7.13; N, 5.23.

2.6. 3,4-(3R,4S)-Dihydroxypyrrolidine-1,2-(2S)-dicarboxylic acid 1-tert-butyl ester 2-methyl ester **11**

R_f 0.37 (10% MeOH/CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.24–4.22 (m, 1H), 4.18 and 4.10 (d, J=5.11, 2H), 3.81 (br s, O*H*, 1H), 3.73 (s, 3H), 3.62 (dd, J=11.64, 5.12 Hz, 1H), 3.48 and 3.40 (dd, J=7.55, 3.93 Hz, 1H), 1.44 (br s, O*H*, 1H), 1.35 (s, 9H), rotamers; ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.3 and 171.9, 154.6 and 154.0, 80.8 and 80.7, 75.7 and 74.8, 70.5 and 69.8, 64.6 and 64.4, 52.5 and 52.3, 51.0 and 50.7, 28.3 and 28.2, rotamers; IR (neat) 3401 (br), 2977, 2356, 1748, 1681, 1416, 1171 cm^{-1}; HRMS calcd for $C_{11}H_{19}NO_6$ (M+H): *m/z* 262.1290, found 262.1285; $[\alpha]_D^{20}$ −9.4 (c=0.99, $CHCl_3$).

2.7. 3,4-(3S,4R)-Dichloropyrrolidine-1,2-(2S)-dicarboxylic acid 1-tert-butyl ester 2-methyl ester **12**

To a stirred solution of **11** (0.533 g, 2.04 mmol) in carbon tetrachloride (50 mL) was added triphenylphosphine (2.14 g, 8.17 mmol) at ambient temperature. The mixture was then heated at 80–90°C for 12 h. The solution was concentrated under reduced pressure and was purified by column chromatography, eluting with 5% EtOAc/petroleum ether to afford **12** (0.45 g, 74.5%) as colorless crystals. R_f 0.45 (20% EtOAc/petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.72 (m, 1H), 4.67 (m, 1H), 4.35 (m, 1H), 4.03 (m, 1H), 3.78 (s, 3H), 3.63 (t, J=10.15, 1H), 1.46 and 1.39 (s, 9H), rotamers; ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.6 and 166.9, 153.7 and 152.9, 81.4, 63.8 and 63.4, 61.8 and 61.2, 55.4 and 55.2, 52.5 and 52.3, 51.1 and 50.6, 28.3 and 28.1, rotamers; IR ($CHCl_3$) 2980 (s), 2360 (w), 1761 (vs), 1704 (vs), 1395 (vs), 1256 (s), 1212 (s), 1159 (vs) cm^{-1}; HRMS calcd for $C_{11}H_{18}NO_4Cl_2$ (M+H): *m/z* 298.0613, found

298.0604; $[\alpha]_D^{20}$ −22.3 (c=0.71, $CDCl_3$); Anal. Calcd for $C_{11}H_{17}NO_4Cl_2$: C, 44.30; H, 5.71; N, 4.70; found: C, 44.72; H, 5.72; N, 4.62.

*2.8. 3,4-(3*S*,4*R*)-Dichloropyrrolidine-1,2-(2*S*)-dicarboxylic acid 2-methyl ester hydrochloride **13***

At ambient temperature, 3.0 M HCl in dioxane (1.0 mL, 3.0 mmol) was added to **12** (0.155 g, 0.52 mmol). The resulting solution was stirred for 2 h, then concentrated under reduced pressure to afford **13** (0.101 g, 99%) as a colorless oil. R_f 0.26 (20% MeOH/CH_2Cl_2); ^{1}H NMR (500 MHz, MeOH-d_4) δ 4.62–4.45 (m, 1H), 4.42–4.30 (m, 2H), 3.35 (m, 3H), 3.26–3.04 (m, 1H), 2.90–2.70 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.9, 65.2, 62.8, 55.9, 54.4, 49.8; IR ($CHCl_3$) 3400 (w), 3030 (w), 2990 (s), 2900 (m), 1760 (vs), 1440 (m), 1370 (m), 1250 (s), 1060 (w) cm^{-1}; HRMS calcd for $C_6H_{10}NO_2Cl_2$ (M+H): *m/z* 198.0088, found 198.0086; $[\alpha]_D^{20}$ +8.5 (c=0.38, MeOH).

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