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A new asymmetric synthesis of (2*S*,3*R*,4*R*,5*S*)-trihydroxypipecolic acid

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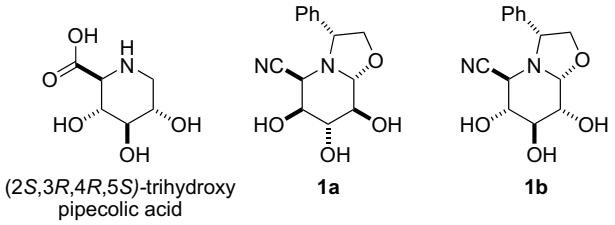
Abstract—A novel four step synthesis of enantiomerically pure (2*S*,3*R*,4*R*,5*S*)-trihydroxypipecolic acid, starting from readily available materials, that is, condensation products of (*R*)-(−)-phenylglycinol with a mesotrihydroxylated glutaraldehyde, is described. The scope and limitations of the reaction have also been investigated.

1. Introduction

Chemists have been inspired by the numerous bioactivities of the non-proteinogenic aminoacid pipecolic acid. Therefore, derivatives have been developed as well as many new enantioselective methods towards their synthesis.[1] Substituted pipecolic acids are key constituents of many synthetic and natural bioactive molecules and are useful building blocks for the preparation of peptides and peptide mimetics.[2] The replacement of simple amino acids by cyclic amino acids has been carried out in structure–activity relationship studies towards peptides with improved pharmacological profiles.[3] These factors have contributed to the growing interest in finding a convenient and efficient synthetic route to pipecolic acid and related amino acids. Following our research on the synthesis of carbohydrate mimetics,[4,5] we herein report a convenient method, which provides a very short enantioselective synthesis of (2*S*,3*R*,4*R*,5*S*)-trihydroxypipecolic acid (Fig. 1).

Since the use by Husson et al. of (*R*)- or (*S*)-phenylglycinol as a chiral inductor and nitrogen protective group,[6–9] a considerable interest has been devoted to these β-amino-alcohols.[10–12] In a preliminary report,[13] we disclosed the facile preparation of building blocks **1a** and **1b** (Fig. 1), obtained by the condensation of (*R*)-(−)-phenylglycinol with a mesotrihydroxylated glutaraldehyde.



(2*S*,3*R*,4*R*,5*S*)-trihydroxy pipecolic acid — **1a** — **1b**

Figure 1.

Compounds **1a** and **1b** appeared to be suitable starting materials for the development of a straightforward preparation of polyhydroxylated pipecolic acids, via a process involving only a few synthetic steps.

2. Results and discussion

Our first attempts were conducted on **2a**, obtained by the benzylation of major compound **1a** (Scheme 1). Treatment of **2a** with triethylsilane used as a reducing agent, in the presence of titanium(IV) chloride, gave two different products depending on the reaction temperature.

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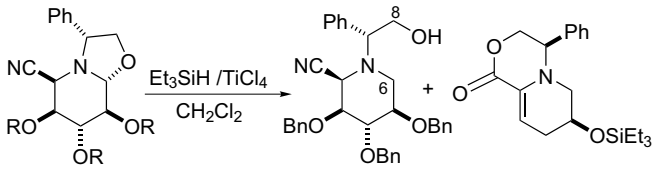
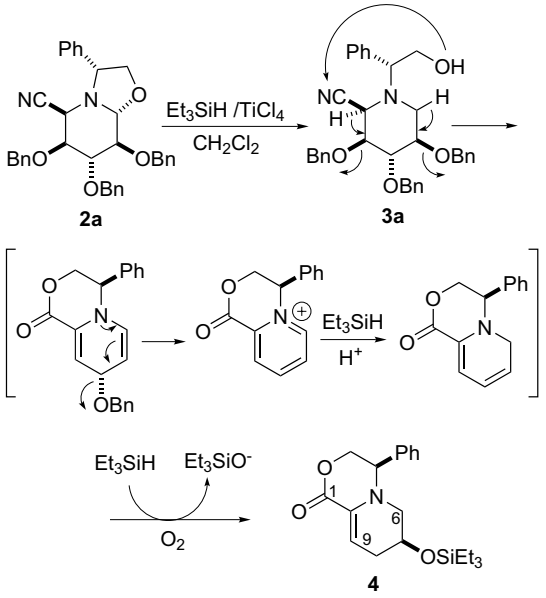


	3a		4
0 °C	-	48 hours	35%
-40 °C	20%	4 hours	-
-78 °C	68%	48 hours	-

Scheme 1.

At 0 °C, the exclusive formation of lactone **4** was observed, according to the postulated mechanism represented in Scheme 2. It is proposed that the process begins with reduction of the oxazolidine system in the presence of Et_3SiH, permitting the lactone cyclization. Subsequent benzyloxyl elimination gave the pyridinium intermediate, which was converted by the reducing agent into the corresponding 1,2 dihydropyridine. Formation of compound **4** was achieved, after oxidation of triethylsilane, by a nucleophilic attack of the consequent anion on the conjugated system.

The stereoselectivity of the reaction is not directly controlled by the steric interaction of the phenyl group, but by the conformation of the bicyclic ring system. This phenomenon had been previously observed in the Michael addition of an organocuprate on a related lactone.[14] The structure of compound **4** was ascertained by typical NMR signals at $\delta = 6.10$ ppm and at $\delta = 110.5$ ppm, observed in the ^1H and ^{13}C NMR spectra, respectively, attributed to the C-9 position. The equatorial position of the silyloxy substituent at C-7 is consistent with the constant ($J = 9$ Hz) between H-6ax and H-7ax.



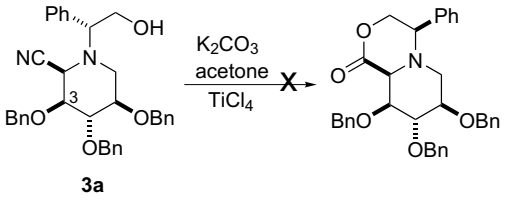
Scheme 2. Postulated mechanism.

In contrast, when the same reduction was performed at a lower temperature, the desired compound **3a** was obtained exclusively (Scheme 1). A careful analysis by ^1H and ^{13}C NMR allowed us to establish its structure and stereochemistry. The characteristic features of the ^{13}C NMR spectrum of **3a** included carbon resonances at 49.0 and 68.1 ppm corresponding to C-6 and C-8, respectively. The IR spectrum showed a signal at 3220 cm^{-1}, typical for a hydroxyl function.

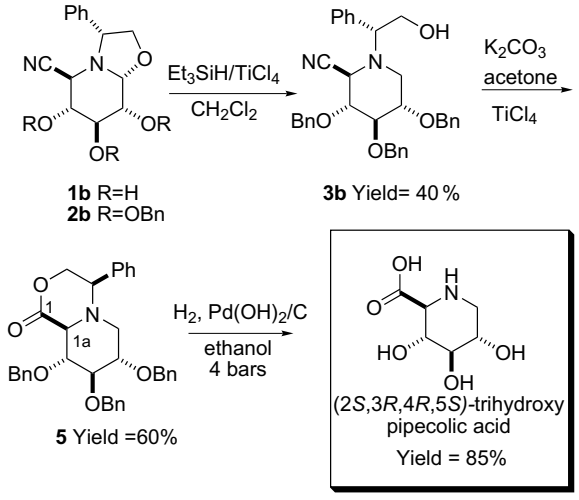
All our attempts towards hydrolysis of the nitrile of **3a**, into the corresponding carboxylic group, remained unsuccessful. For instance, treatment of **3a** with potassium carbonate in acetone did not allow us to obtain the desired lactone, most probably due to the presence of the adjacent benzyl group at the C-3 position, which hinders the β-face preventing the hydroxyl attack (Scheme 3).

Indeed, when the same reaction sequence was performed from compound **2b**, obtained by the benzylation of minor compound **1b**, compound **3b** was obtained and could be converted into the corresponding lactone **5** in 60% yield by the use of potassium carbonate in acetone (Scheme 4).

The structure of **3b** and **5** were unambiguously deduced from their spectra data. Indeed, in the ESI mass spectrum of compound **3b,** a pseudomolecular ion $[M+Na]^+ = 571$ was observed. The structure and stereochemistry of **3b** were further corroborated by a careful analysis of the ^1H and ^{13}C NMR spectra. The structure of lactone **5** was ascertained by typical NMR signals at $\delta = 3.33$ ppm and at $\delta = 64.0$ ppm, observed in the ^1H and ^{13}C NMR spectra,



Scheme 3.



Scheme 4.

respectively, attributed to the C-1a position (Scheme 4), deshielded by the adjacent carbonyl group.

Catalytic hydrogenolysis of **5** in ethanol, implying simultaneous recovery of the carboxylic function, debenzylation and removal of the chiral appendage, afforded the desired compound (Scheme 4). The absolute configuration of (2*S*,3*R*,4*R*,5*S*)-trihydroxypipecolic acid was determined by NMR analysis and by comparing the specific rotation with that in the literature.[15–17]

3. Conclusion

In conclusion, we have developed a convenient and expeditious method for the synthesis of enantiomerically pure polyhydroxylated pipecolic acid, starting from readily available materials. There is a general interest in the synthesis of chiral substrates with a substituted polyhydroxypiperidine core, since they are related to remarkable glycosidase inhibitors. Efforts in this direction are currently being pursued in our laboratory.

4. Experimental

4.1. (2*S*,3*R*,4*R*,5*S*)-Trihydroxypipecolic acid

Compound **5** (44 mg, 0.08 mmol) in ethanol solution (7 mL) was hydrogenated in the presence of palladium hydroxide on carbon (122 mg, 0.17 mmol). After four days of stirring at rt, the catalyst was removed by filtration over Celite and the solvent evaporated. Compound **1** was obtained after recrystallization in a mixture of H_2O/MeOH/acetone as white crystals (12 mg, 85%). $[\alpha]_D = +18$ (*c* 0.01, H_2O). ^1H NMR (D_2O): $\delta = 2.33$ (*t*, $J = 13$ Hz, 1H, 6ax-H), 2.86 (d, $J = 9$ Hz, 1H, 2ax-H), 3.01 (dd, $J = 5.5$, 13 Hz, 1H, 6eq-H), 3.23 (t, $J = 9$ Hz, 1H, 4ax-H), 3.30 (t, $J = 9$ Hz, 1H, 3ax-H), 3.39 (m, 1H, 5ax-H), 8.34 (s, 1H, COO*H*). ^{13}C NMR (D_2O): $\delta = 48.1$ (C-6), 64.3 (C-2), 70.8 (C-5), 73.4 (C-4), 77.7 (C-3), 171.0 (*C*OOH). This synthetic material was described previously in Ref. 9 ($[\alpha]_D$ literature = +18.3 1% w/w in H_2O).

4.2. Hexahydro-3-phenyl-6,7,8-trihydroxy-(3*R*)-[3α,5β,6β,7α,8β,8aβ]-5*H*-oxazolo[3,2-*a*]pyridine-5-carbonitrile 1a

The data were described previously in Ref. 13.

4.3. Hexahydro-3-phenyl-6,7,8-trihydroxy-(3*R*)-[3α,5β,6α,7β,8α,8aβ]-5*H*-oxazolo[3,2-*a*]pyridine-5-carbonitrile 1b

The data were described previously in Ref. 13.

4.4. Hexahydro-3-phenyl-6,7,8-tribenzyloxy-(3*R*)-[3α,5β,6β,7α,8β,8aβ]-5*H*-oxazolo[3,2-*a*]pyridine- 5-carbonitrile 2a

The data were described previously in Ref. 5.

4.5. Hexahydro-3-phenyl-6,7,8-tribenzyloxy-(3*R*)-[3α,5β,6α,7β,8α,8aβ]-5*H*-oxazolo[3,2-*a*]pyridine-5-carbonitrile 2b

Sodium hydride (865 mg, 36.2 mmol) was added under argon to a solution of compound **1b** (1 g, 3.62 mmol) in dry DMF (40 mL). The reaction mixture was stirred for 1 h at rt and cooled to 0 °C. A solution of freshly distilled benzyl bromide (9.5 mL, 79.64 mmol) was then added dropwise. Stirring was continued for 22 h at rt. After the addition of methanol (17 mL), the mixture was stirred continuously for a further hour. The reaction mixture was then quenched by adding a saturated aqueous sodium hydrogeno-carbonate solution (30 mL). The mixture was extracted with CH_2Cl_2 (4 × 120 mL), the combined organic layers were dried with Na_2SO_4 and the solvent was evaporated under reduced pressure. Flash chromatography of the resulting yellow oil on silica gel (cyclohexane/AcOEt, 9:1) yielded **2b** (1.5 g, 75%) as an oil. $R_f = 0.48$ (cyclohexane/AcOEt, 8:2). $[\alpha]_D = -35$ (*c* 0.2, $CHCl_3$). IR (KBr): $\nu = 2229\ cm^{-1}$. ^1H NMR ($CDCl_3$): $\delta = 3.74$ (t, $J = 2.5$ Hz, 1H, 6-H), 3.82 (dd, $J = 7.5$, 8.5 Hz, 1H, 2-H), 3.86 (t, $J = 2.5$ Hz, 1H, 7-H), 3.93 (t, $J = 2.5$ Hz, 1H, 8-H), 4.01 (d, $J = 2.5$ Hz, 1H, 5-H), 4.06 (dd, $J = 7.5$, 8.5 Hz, 1H, 3-H), 4.31 (t, $J = 7.5$ Hz, 1H, 2-H), 4.3–4.6 (2d AB, $J = 12.5$ Hz, 4H, O–CH_2-Ph), 4.72 (d, $J = 2.5$ Hz, 1H, 8a-H), 4.7–4.9 (2d AB, $J = 12.5$ Hz, 2H, O–CH_2-Ph), 7.2–7.4 (m, 20H, arom.). ^{13}C NMR ($CDCl_3$): $\delta = 49.3$ (C-5), 63.4 (C-3), 72.3 (O–CH_2-Ph), 72.4 (O–CH_2-Ph), 73.3 (C-8), 73.6 (C-2), 73.7 (O–CH_2-Ph), 74.6 (C-6), 76.5 (C-7), 89.1 (C-8a), 114.7 (CN), 127–129 (CH arom.), 136.0–139.0 (Cq arom.). MS (ESI): $m/z = 569$ $[M+Na]^+$.

4.6. 3,4,5-Tribenzyloxy-1-(2-hydroxy-1-phenyl-ethyl)-(1*R*)-[1α,2β,3β,4α,5β]piperidine-2-carbonitrile 3a

To 35 mL of dry CH_2Cl_2 was added compound **2a** (240 mg, 0.44 mmol). The solution was cooled at −78 °C under argon. Triethylsilane (0.36 mL, 2.2 mmol) followed by 1 M titanium(IV) chloride (0.66 mL, 0.66 mmol) was added. The reaction mixture was stirred for 3 h and then quenched by the addition of water. The mixture was extracted with CH_2Cl_2 (4 × 20 mL). The combined organic layers were dried over Na_2SO_4 and filtered. The solvent was evaporated under reduced pressure. Flash chromatography of the resulting crude on silica gel (cyclohexane/AcOEt, 8:2) yielded **3a** (163 mg, 68%) as an oil. $R_f = 0.2$ (cyclohexane/ether, 6:4). $[\alpha]_D = -36$ (*c* 0.4, $CHCl_3$). IR (KBr): $\nu = 2920\ cm^{-1}$. ^1H NMR ($CDCl_3$): $\delta = 2.58$ (t, $J = 11$ Hz, 1H, 6-H), 3.39 (dd, $J = 5$, 11 Hz, 1H, 6-H), 3.43 (dd, $J = 5$, 9 Hz, 1H, 3-H), 3.5–3.7 (m, 3H, 2-H, 5-H, C*H*-Ph), 3.72 (t, $J = 9$ Hz, 1H, 4-H), 3.7–3.8 (m, 2H, CH_2OH), 4.4–4.9 (6H, O–CH_2-Ph), 7.2–7.4 (m, 20H, arom.). ^{13}C NMR ($CDCl_3$): $\delta = 49.0$ (C-6), 55.2 (C-2), 64.1 (*C*H-Ph), 68.1 (CH_2OH), 73.4 (2 × O–CH_2-Ph), 76.0 (O–CH_2-Ph), 77.5 (C-5), 78.2 (C-3), 83.4 (C-4), 115.0 (CN), 127–129 (CH arom.), 137–139 (Cq arom.). MS (ESI): $m/z = 571$ $[M+Na]^+$.

4.7. 3,4,5-Tribenzyloxy-1-(2-hydroxy-1-phenyl-ethyl)-(1*R*)-[1α,2β,3α,4β,5α]piperidine-2-carbonitrile 3b

Identical procedure as for **3a** starting from **2a**. $R_f = 0.36$ (cyclohexane/AcOEt, 7:3). Mp: 114 °C. $[\alpha]_D = -5$ (*c* 0.2, $CHCl_3$). IR (KBr): $\nu = 2918\ cm^{-1}$. ^1H NMR ($CDCl_3$): $\delta = 1.82$ (dd, $J = 10$, 11.5 Hz, 1H, 6-H), 2.50 (br, 1H, OH), 3.10 (dd, $J = 4.5$, 11.5 Hz, 1H, 6-H), 3.22 (d, $J = 9$ Hz, 1H, 2-H), 3.32 (t, $J = 8.5$ Hz, 1H, 4-H), 3.6–3.7 (m, 1H, 5-H), 3.8–3.9 (m, 2H, 3-H and CH_2OH), 3.98 (dd, $J = 10$, 11 Hz, 1H, C*H*-Ph), 4.45 (m, 1H, CH_2OH), 4.6–4.9 (6H, O–CH_2-Ph), 7.2–7.4 (m, 20H, arom.). ^{13}C NMR ($CDCl_3$): $\delta = 47.0$ (C-6), 56.0 (C-2), 60.6 (*C*H-Ph), 66.0 (CH_2OH), 73.4 (O–*C*H_2-Ph), 75.4 (O–*C*H_2-Ph), 76.0 (O–*C*H_2-Ph), 77.9 (C-5), 79.8 (C-3), 84.0 (C-4), 117.7 (CN), 128–129 (CH arom.), 132–138 (Cq arom.). MS (ESI): $m/z = 571$ $[M+Na]^+$.

4.8. 4-Phenyl-7-(triethyl-silanyloxy)-3,4,7,8-tetrahydro-(4*S*)-[4β,7β]-6*H*-pyrido[2,1-*c*][1,4]oxazin-1-one 4

To 15 mL of dry CH_2Cl_2 was added compound **3a** (100 mg, 0.183 mmol). At 0 °C under argon, triethylsilane (0.15 mL, 0.93 mmol) followed by 1 M titanium(IV) chloride (0.975 mL, 0.27 mmol) was added. The solution was stirred at 0 °C under argon for 2 days. The reaction was then quenched by adding 30 mL of water. The mixture was extracted with CH_2Cl_2 (30 mL × 5) and the combined organic layers were dried over Na_2SO_4, filtered and the solvent was evaporated under reduced pressure. Flash chromatography of the resulting brownish oil on silica gel (cyclohexane/ether 9:1) yielded **4** (23 mg, 35%) as a yellow oil. $R_f = 0.35$ (cyclohexane/ether, 7:3). IR (KBr): $\nu = 1705\ cm^{-1}$. ^1H NMR ($CDCl_3$): $\delta = 0.60$ (q, $J = 9$ Hz, 6H, Si–CH_2–CH_3), 0.92 (t, $J = 9$ Hz, 9H, Si–CH_2–CH_3), 2.21 (dt, $J = 5$, 19 Hz, 1H, 8-H), 2.55 (dtd, $J = 2$, 2.5, 19 Hz, 1H, 8-H), 2.73 (dt, $J = 2$, 11 Hz, 1H, 6-H), 2.88 (ddd, $J = 2$, 9, 11 Hz, 1H, 6-H), 4.11 (dddd, $J = 2$, 4, 5, 9 Hz, 1H, 7-H), 4.16 (dd, $J = 3.5$, 6 Hz, 1H, 4-H), 4.36 (dd, $J = 6$, 11 Hz, 1H, 3-H), 4.49 (dd, $J = 3.5$, 11 Hz, 1H, 3-H), 6.10 (t, $J = 4.5$ Hz, 1H, 9-H), 7.2–7.4 (m, 5H, arom.). ^{13}C NMR ($CDCl_3$): $\delta = 4.7$ (Si–*C*H_2–CH_3), 6.6 (Si–CH_2–*C*H_3), 33.0 (C-8), 52.9 (C-6), 59.4 (C-4), 64.1 (C-7), 71.5 (C-3), 110.5 (C-9), 127–129 (CH arom.), 136.6 (Cq arom.), 161.5 (CO). MS (ESI): $m/z = 360$ $[M+H]^+$.

4.9. Hexahydro-4-phenyl-7,8,9-tribenzyloxy-4*S*-[1aβ,4β,9α,8β,7α]-pyrido[2,1-*c*][1,4]oxazin-1-one 5

To a solution of **3b** (66 mg, 0.12 mmol), in dry acetone cooled at −20 °C, was added under argon potassium carbonate (50 mg, 0.36 mmol) followed by 1 M titanium(IV) chloride (0.18 mL, 0.18 mmol). The solution was warmed to 40 °C under argon and stirring was continued for 1 day. The reaction was quenched by adding 15 mL of water. The mixture was extracted with CH_2Cl_2 (20 mL × 3) and the combined organic layers were dried over Na_2SO_4, filtered and the solvent was evaporated under reduced pressure. Flash chromatography of the resulting brownish oil on silica gel (cyclohexane/AcOEt, 90:10 to 80:20) yielded **5** (39 mg, 60%) as white crystals. Mp: 143 °C $R_f = 0.56$ (cyclohexane/AcOEt, 7:3). $[\alpha]_D = -29$ (*c* 0.02, $CHCl_3$). IR (KBr): $\nu = 1737\ cm^{-1}$. ^1H NMR ($CDCl_3$): $\delta = 2.09$ (t, $J = 11$ Hz, 1H, 6-H), 3.00 (dd, $J = 4.5$, 11 Hz, 1H, 6-H), 3.33 (d, $J = 9$ Hz, 1H, 1a-H), 3.54 (m, 1H, 7-H), 3.60 (t, $J = 9$ Hz, 1H, 8-H), 3.73 (t, $J = 6$ Hz, 1H, 4-H), 3.92 (t, $J = 9$ Hz, 1H, 9-H), 4.25 (dd, $J = 6$, 11.5 Hz, 1H, 3-H), 4.43 (dd, $J = 6$, 11.5 Hz, 1H, 3-H), 4.5–4.6 (2d AB, $J = 11.5$ Hz, 2H, O–CH_2-Ph), 4.8–5.2 (4H, O–CH_2-Ph), 7.2–7.5 (m, 20H, arom.). ^{13}C NMR ($CDCl_3$): $\delta = 53.9$ (C-6), 63.5 (C-4), 64.0 (C-1a), 71.2 (C-3), 72.8 (O–CH_2-Ph), 75.6 (O–CH_2-Ph), 75.8 (O–CH_2-Ph), 77.7 (C-7), 79.4 (C-9), 87.1 (C-8), 127–129 (CH arom.), 138–139 (Cq arom.) 168.3 (CO). MS (ESI): $m/z = 572$ $[M+Na]^+$.

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