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Efficient synthesis of a new pipecolic acid analogue with a bicyclic structure

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Abstract—This report describes the synthesis of 2-azabicyclo[2.2.2]octane-1-carboxylic acid, a constrained pipecolic acid analogue. The route gives a very good total yield starting from cheap and readily available compounds and uses very easy reactions.
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1. Introduction

Pipecolic acid (pipecolinic acid, homoproline or 2-piperidinecarboxylic acid) is a non-proteinogenic amino acid usually found as a component of several metabolites in plants and fungi. This compound, which is a metabolite of lysine, has been found incorporated into complex biologically active molecules with interesting pharmacological activities, e.g., immunosupressors (rapamycin, FK506 and immunomycin) and the antitumor antibiotic sandramycin.[1] Nevertheless, pipecolic acid and related compounds most often occur free in biological systems, display interesting biological properties and have been used as precursors for synthetic peptides. Due to the great interest in these derivatives, a recent resolution has been reported[1] and the asymmetric synthesis of these systems has been reviewed[2] and recently updated.[3]

On the other hand, interest in peptide-based drugs has shown significant growth in recent years. Unmodified native peptides exhibit some properties that make them unfavourable for pharmacological purposes. The main limitations for their use as drugs are their low selectivity between different receptors, their ease of proteolysis by enzymes and the poor variety of delivery systems. Unnatural amino acids are currently playing a significant role in peptide research and in many cases have led to an improvement in the pharmacological profile of native peptides. When designing peptide analogues, the use of conformationally constrained amino acids is a major strategy.[4] The introduction of structural constraints on certain residues of a peptide chain can have a dramatic effect on the structure of the whole molecule. In an optimal rational design of a peptide, once its bioactive conformation has been clearly defined, the choice of the appropriate constraint should provide the desired three-dimensional topography.

In particular, the incorporation of quaternary α-amino acids into peptides is a strategy that is widely used to restrict and control peptide conformations. The stereoselective synthesis of these constrained amino acids has been reviewed.[5] In the case of quaternary pipecolic acid derivatives, several procedures have been reported and these include the diastereoselective alkylation and subsequent cyclization of chiral amino acid derivatives,[6] the ruthenium-catalyzed ring-closing olefin metathesis using α-alkyl-α-allylglycines as starting materials[7] or the asymmetric cyclization via memory of chirality.[8]

In recent years we have been involved in the synthesis of new constrained amino acids and, in particular, we have focused our attention on the synthesis of restricted prolines and phenylalanines. In the course of our research we have described the synthesis of 2,5-ethanoproline (7-azabicyclo[2.2.1]heptane-1-carboxylic acid).[9] This compound has been incorporated into a peptide of biological interest.[10] Furthermore, a structural study[11] and theoretical calculations on some derivatives have already been published.[12] Due to the interesting properties observed we decided to undertake a study into the behaviour of the homologue 2,5-ethanopipecolic acid (2-azabicyclo[2.2.2]octane-1-carboxylic acid) (Fig. 1). The only synthesis of this compound described to date corresponds to a patent[13] in which the experimental details are, to say the least, not particularly detailed. We would therefore like to report here a very easy and reproducible procedure to obtain this compound using cheap and readily available starting materials.

Keywords: Constrained amino acid; Quaternary amino acid; Proline analogue; 2,5-Ethanepipecolic acid; Chemoselective reduction.
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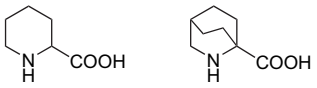


Figure 1. Structure of pipecolic acid and 2,5-ethanopipecolic acid.

2. Results

Taking into account the retrosynthetic analysis shown in Figure 2, the key steps of the procedure should be the chemoselective reduction of the lactam and the stereochemical control of the positions of the substituents in the cyclohexane ring in order to achieve the corresponding cyclization. Other possibilities from the disconnection approach do not seem to lead to appropriate starting materials.

The synthesis we report begins with the complete hydrogenation of the commercially available methyl 4-hydroxybenzoate (**1**). It has been reported that the use of 5% rhodium on alumina[14] as a catalyst enables the complete reduction of aromatic rings to give the corresponding aliphatic cyclohexane. We found that hydrogen pressures between 20 and 25 bar were sufficient to produce complete reduction in quantitative yield. The stereochemistry of this reaction is not relevant because of the fact that in the next step the alcohol has to be converted into a carbonyl moiety. This transformation was successfully achieved using pyridinium chlorochromate (PCC) to give 4-carbomethoxycyclohexanone (**2**) in high yield (Scheme 1).

The most important strategies to obtain an amino acid moiety from a carbonyl compound are the Strecker synthesis and the Bucherer–Bergs reaction. The first approach uses ammonium hydroxide and potassium cyanide to obtain the corresponding aminonitrile compound, whereas the second employs ammonium carbonate and potassium cyanide to form the hydantoin ring. In both cases, final hydrolysis would allow the synthesis of the amino acid. In our case, two stereoisomeric products are possible, although it has been reported that in the case of 4-substituted cyclohexanones both reactions behave in a complementary manner (Fig. 3). In fact, Munday[15] found that the Bucherer–Bergs reaction of 4-*tert*-butylcyclohexanone predominantly gave one of the stereoisomeric hydantoins. Later, Edward and Jitrangsri[16] established the stereochemical course of both Strecker and Bucherer–Bergs reactions. These authors proved that the severe steric hindrance between the developing C=NH group and the 3,5-axial hydrogen atoms, in the key step of the mechanistic route, led to the compound in which the NH and the carboxylic acid groups are in a cis

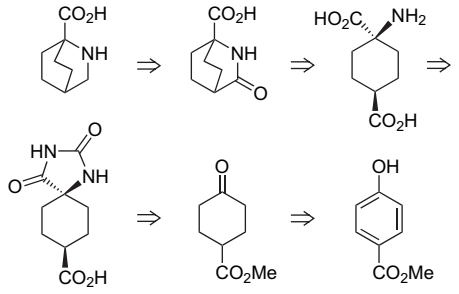
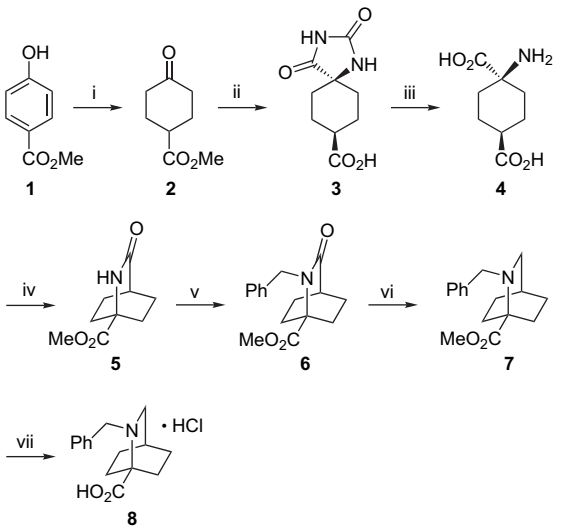


Figure 2. Retrosynthetic analysis for 2,5-ethanopipecolic acid.



Scheme 1. Reagents and conditions: (i) (a) H_2, Rh, Al_2O_3/MeOH, 20 bar; (b) PCC, NaOAc, Celite®/CH_2Cl_2; (ii) (a) 2 N KOH/MeOH; (b) $(NH_4)_2CO_3$, KCN/H_2O; (iii) 5 N NaOH, reflux; (iv) (a) $SOCl_2$/MeOH, reflux; (b) 210–220 °C; (v) NaH, NaI, BnBr/DMF; (vi) $RhH(CO)(PPh_3)_3$, Ph_2SiH_2/THF; (vii) 6 N HCl.

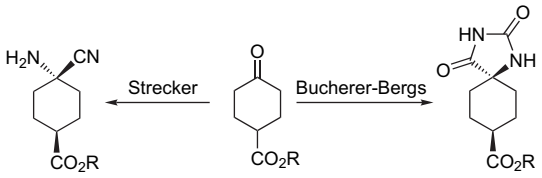


Figure 3. Relative stereochemistry of the products obtained by Strecker synthesis and Bucherer–Bergs reaction.

disposition. However, in the Strecker reaction this hindrance is not a factor and, as a result, this pathway furnished the thermodynamically most stable product, which has a trans disposition.

Bearing in mind that our objective was to obtain the cis configuration between the amino and carboxylic acid groups prior to the subsequent cyclization, the Bucherer–Bergs reaction was used. In order to improve the final results, the synthesis of the hydantoin was performed after saponification of the methyl ester in order to increase the solubility of the corresponding salt in the aqueous reaction medium. This is a very important feature and markedly increases the final yield. In this way, the reaction was achieved in the presence of potassium cyanide and ammonium carbonate using water as the solvent. Thus, the spirohydantoinic compound **3** was obtained directly in good yield and with high purity by precipitation in an acidic medium (Scheme 1). Moreover, the new carboxylic acid moiety was a key element in the next step.

The hydantoinic systems are normally very much insoluble and the opening of these rings requires very harsh conditions like high temperatures and concentrated acidic or basic solutions. In the present case, the carboxylic acid group makes basic hydrolysis easy and complete opening of the heterocyclic system was achieved by heating a solution of the hydantoin at 120 °C in 5 N NaOH. Precise adjustment of

the pH led to the aminodicarboxylic compound (**4**) in excellent yield and with very high purity.

Recently, Chung and Ho[17] described direct lactam formation from a cis/trans mixture of 4-aminocyclohexane carboxylic acid by heating a slurry of the substrate in Dowtherm® A at 250–256 °C. On the other hand, several years ago, Werner and Ricca[18] found that the cyclization could be achieved by working at lower temperatures when the carboxylic acid was previously transformed into an ester. We therefore decided to esterify the carboxylic acids in **4** using thionyl chloride and methanol. The resulting oily product was then heated for 10 min at 210–220 °C to furnish lactam **5** with an overall yield of 71%.

The next step in our synthesis involved the chemoselective reduction of lactam **5**. Most of the methods described for the reduction of lactams, e.g., the use of $LiAlH_4$, $NaBH_4$–$AlCl_3$, DIBAL-H, $AlClH_2$ and $AlCl_2H$,[19] are not compatible with the presence of ester groups. Some authors have described the selective transformation of secondary lactams with 9-borabicyclo[3.3.1]nonane (9-BBN) or borane–methyl sulfide complex.[20] Unfortunately, in the present case these methodologies were unsuccessful. Other strategies require a tertiary lactam to produce the chemoselective reduction in the presence of an ester. In particular, it has been reported that $LiEt_3BH/Et_3SiH$–$Et_2O\cdot BF_3$ can be used to achieve a highly chemoselective lactam reduction with *N*-Boc protection in the presence of groups such as double bonds, esters, nitriles or carbamates.[21] However, all attempts to reduce our bicyclic system using this method resulted in very complex mixtures and the yield was 28% in the best case. Fortunately, much better results were obtained by following the method described by Ito and co-workers for the reduction of tertiary amides with diphenylsilane and rhodium catalysts.[22] In order to use this methodology, prior *N*-benzyl protection of compound **5** using benzyl bromide in the presence of NaH was necessary. The reduction of the corresponding *N*-benzyl lactam (**6**) was easily achieved and enabled the synthesis of compound **7** in excellent yield. Finally, this isoquinuclidine was easily hydrolyzed in 6 N hydrochloric acid to give the desired *N*-benzyl amino acid **8**, which is suitably protected for incorporation into a peptide chain.

3. Conclusion

In summary, we have developed a new, competitive and reproducible method for the synthesis of 2-azabicyclo-[2.2.2]octane-1-carboxylic acid, an analogue of pipecolic acid. The procedure gives a good overall yield starting from methyl 4-hydroxybenzoate. The conformational tendencies of the new amino acid are currently being studied and the results will be published in due course.

4. Experimental

4.1. General

Thin layer chromatography was performed on Merck 60 F_{240} precoated silica gel polyester plates and products were visualized under UV light (254 nm), iodine vapor, anisaldehyde or phosphomolybdic acid reaction, as appropriate. Column chromatography was performed using silica gel (Kieselgel 60). Solvents were dried, when necessary, by standard methods. Melting points were determined on a Gallenkamp apparatus and were not corrected. IR spectra were registered on a Mattson Genesis FTIR spectrophotometer; ν_{max} is given for the main absorption bands. ^1H and ^{13}C NMR spectra were recorded on a Bruker AV-400 instrument at room temperature in $CDCl_3$, D_2O or DMSO-d_6, using the residual solvent signal as the internal standard; chemical shifts (δ) are expressed in parts per million and coupling constants (J) in hertz. Elemental analyses were carried out on a Perkin–Elmer 200 C,H,N,S analyzer.

4.2. 4-Carbomethoxycyclohexanone (2)

A mixture of methyl *p*-hydroxybenzoate (**1**) (15.0 g, 99 mmol) and 5% rhodium on alumina (1.5 g) in MeOH (60 mL) was shaken under hydrogen (20 bar) for 3 days. The catalyst was removed by filtration through Celite® and then rinsed with MeOH. The combined filtrates were evaporated to dryness under reduced pressure to give a colourless oil (15.0 g, 95 mmol), which was used without further purification in the next step. To a mixture of dry CH_2Cl_2 (100 mL), oven-dried Celite® (6.0 g) and NaOAc (1.9 g, 23 mmol), under Ar, was added pyridinium chlorochromate (25.0 g, 116 mmol). CH_2Cl_2 (60 mL) was added to the reaction mixture and then a solution of the oily compound obtained in the previous step (12.8 g, 77 mmol) in CH_2Cl_2 (60 mL) was added by syringe under Ar. The mixture was stirred for 3.5 h and Et_2O (200 mL) was added with vigorous stirring. The reaction mixture was filtered under vacuum through silica gel and the silica gel was washed with Et_2O. The combined filtrates were concentrated to yield **2** (10.30 g, 66 mmol) as a colourless oil. Yield 82%. IR (neat, cm^{-1}): 1731, 1711. ^1H NMR (400 MHz, $CDCl_3$): δ=1.95–2.08 (m, 2H), 2.15–2.23 (m, 2H), 2.29–2.39 (m, 2H), 2.42–2.50 (m, 2H), 2.75 (tt, J=3.9, 9.7 Hz, 1H), 3.71 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=28.48, 39.69, 40.56, 51.54, 174.57, 210.0.

4.3. 4-Spirohydantoincyclohexanecarboxylic acid (3)

A 2 N solution of KOH in MeOH (50 mL) was added to 4-carbomethoxycyclohexanone (**2**) (10.30 g, 66 mmol) and the mixture was stirred at room temperature until the starting material had been consumed. The solvent was evaporated to give a pale yellow solid, which was used without further purification. To a solution of this solid in water (60 mL) was added $(NH_4)_2CO_3$ (25.34 g, 264 mmol) followed by KCN (6.5 g, 100 mmol). The reaction mixture was stirred for 16 h at room temperature, followed by 24 h at 50–60 °C. The mixture was allowed to cool and concentrated HCl was added dropwise. The precipitated spirohydantoin was filtered off under vacuum, washed with water and acetone and dried (8.30 g, 39.2 mmol). Yield 59%. Mp 309–311 °C. IR (Nujol, cm^{-1}): 3450–2300, 1772, 1731, 1685. ^1H NMR (400 MHz, DMSO-d_6): δ=1.52–1.72 (m, 6H), 1.82–1.92 (m, 2H), 2.20–2.30 (m, 1H), 8.43 (br s, 1H), 10.59 (br s, 1H), 12.15 (br s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ=23.41, 32.40, 40.58, 61.55, 156.28, 175.84, 178.39. Anal. Calcd for $C_9H_{12}N_2O_4$: C, 50.94; H, 5.70; N, 13.20; found: C, 51.12; H, 5.86; N, 13.37.

4.4. *cis*-1-Aminocyclohexane-1,4-dicarboxylic acid (4)

A solution of spirohydantoin **3** (3.5 g, 16.50 mmol) in 5 N NaOH (25 mL) was heated at 120 °C for 48 h. The mixture was allowed to cool and the pH of the solution was adjusted to 8.5–9 with 4 N HCl. The resulting precipitate was filtered off. The mother liquor was then adjusted to pH 2.5 with 4 N HCl to give a white solid (2.46 g, 13.14 mmol), which was filtered off, washed with water and dried. Yield 80%. Mp 253–256 °C. IR (Nujol, cm^{-1}): 3529, 3437, 3300–2400, 1687. ^1H NMR (400 MHz, $CDCl_3$): δ=1.78–1.93 (m, 6H), 2.05–2.16 (m, 2H), 2.55–2.60 (m, 1H), 10.17 (br s, 1H), 14.47 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=23.73, 30.15, 36.89, 58.81, 176.29, 179.16. Anal. Calcd for $C_8H_{13}NO_4$: C, 51.33; H, 7.00; N, 7.48; found: C, 51.50; H, 7.13; N, 7.61.

4.5. Methyl 3-oxo-2-azabicyclo[2.2.2]octane-1-carboxylate (5)

$SOCl_2$ (2.8 g, 23.53 mmol) was added dropwise at 0 °C to a stirred suspension of **4** (2 g, 10.69 mmol) in anhydrous MeOH (40 mL) under Ar. The reaction mixture was heated at 80 °C for 4 h with vigorous stirring and $SOCl_2$ (1.4 g, 11.77 mmol) was added carefully. The reaction was maintained at 80 °C for a further 4 h. The mixture was allowed to cool and the solvent was evaporated. The solid residue was fractionated between AcOEt and 5% $NaHCO_3$ solution. The aqueous solution was extracted with AcOEt, and the combined organic phases were dried, filtered and the solvent removed to give a pale oil residue, which was used in the next step without further purification. This oil was placed in a Schlenk tube and heated in a sand bath to 215–220 °C for 10 min under vacuum. On cooling a crystalline solid appeared and this was recrystallized from CH_2Cl_2 to yield **5** (1.38 g, 7.53 mmol) as a white solid. Yield 71%. Mp 129–132 °C. IR (Nujol, cm^{-1}): 3173, 1724, 1673. ^1H NMR (400 MHz, $CDCl_3$): δ=1.73–1.90 (m, 6H), 2.00–2.10 (m, 2H), 2.60 (m, 1H), 3.81 (s, 3H), 6.65 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=23.45, 31.15, 37.70, 52.91, 58.76, 172.37, 175.80, Anal. Calcd for $C_9H_{13}NO_3$: C, 59.00; H, 7.15; N, 7.65; found: C, 58.86; H, 7.22; N, 7.76.

4.6. Methyl 3-oxo-*N*-benzyl-2-azabicyclo[2.2.2]octane-1-carboxylate (6)

NaH (72 mg, 2.99 mmol) was added to a solution of the bicyclic lactam (500 mg, 2.73 mmol) in anhydrous DMF at 0 °C under Ar. After 10 min, benzyl bromide (510 mg, 2.99 mmol) was added and the reaction mixture was stirred at room temperature. After 4 h, saturated NH_4Cl (10 mL) was added and the mixture was extracted several times with AcOEt. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered and evaporated to give a residue, which was chromatographed (eluent: hexane/AcOEt 7/3) to furnish **6** (599 mg, 2.16 mmol) as a white solid. Yield 80%. Mp 88–89 °C. IR (KBr, cm^{-1}): 2943, 1738, 1653. ^1H NMR (400 MHz, $CDCl_3$): δ=1.64–1.77 (m, 4H), 1.82–1.98 (m, 4H), 2.69 (m, 1H), 3.46 (s, 3H), 4.71 (s, 2H), 7.04–7.27 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=23.59, 31.23, 38.16, 44.91, 52.28, 63.57, 127.29, 127.79, 128.30, 137.87, 170.51, 175.98. Anal. Calcd for $C_{16}H_{19}NO_3$: C, 73.31; H, 7.01; N, 5.12; found: C, 73.20; H, 7.22; N, 5.24.

4.7. Methyl *N*-benzyl-2-azabicyclo[2.2.2]octane-1-carboxylate (7)

To a mixture of lactam **6** (507 mg, 1.86 mmol) and $RhH(CO)(PPh_3)_3$ (17 mg, 0.019 mmol) in anhydrous THF was added Ph_2SiH_2 (857 mg, 4.65 mmol) under Ar. The mixture was stirred for 12 h at room temperature. The solvent was removed under vacuum and the oily residue was partitioned between Et_2O and 1 N HCl. The organic phase was extracted several times with 1 N HCl and the combined aqueous phases were neutralized with solid NaOH until pH 9–10. The resulting suspension was extracted with AcOEt and the organic layers were combined, dried over anhydrous $MgSO_4$, filtered and the solvent removed to give **7** (462 mg, 1.79 mmol) as a white solid. Yield 96%. Mp 61–62 °C. IR (KBr, cm^{-1}): 1724. ^1H NMR (400 MHz, $CDCl_3$): δ=1.57–1.78 (m, 5H), 1.79–1.88 (m, 2H), 2.24–2.35 (m, 2H), 2.75 (m, 2H), 3.59 (s, 2H), 3.71 (s, 3H), 7.22–7.42 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=24.56, 26.17, 28.03, 51.96, 55.28, 59.05, 60.22, 126.77, 128.17, 128.85, 139.69, 176.11. Anal. Calcd for $C_{16}H_{21}NO_2$: C, 74.10; H, 8.16; N, 5.40; found: C, 74.24; H, 8.01; N, 5.56.

4.8. *N*-Benzyl-2-azabicyclo[2.2.2]octane-1-carboxylic acid hydrochloride (8)

Isoquinuclidine **7** (462 mg, 1.79 mmol) was suspended in 6 N HCl (30 mL) and heated under reflux for 12 h. The mixture was allowed to cool and then evaporated to dryness. The residue was partitioned between Et_2O and H_2O. The organic layer was discarded and final lyophilization furnished pure **8** (494 mg, 1.75 mmol) as a white solid. Yield 98%. Mp 265–266 °C. IR (KBr, cm^{-1}): 3600–2200, 3400, 1732. ^1H NMR (400 MHz, D_2O): δ=1.72–1.84 (m, 2H), 1.91–2.00 (m, 2H), 2.09–2.26 (m, 4H), 2.34–2.44 (m, 2H), 3.17–3.24 (m, 1H), 3.37–3.44 (m, 1H), 4.12–4.22 (m, 1H), 4.48–4.58 (m, 1H), 7.47–7.62 (m, 5H). ^{13}C NMR (100 MHz, D_2O): δ=20.22, 21.61, 21.82, 23.41, 28.96, 54.42, 58.49, 65.07, 129.22, 129.29, 130.10, 130.93, 173.76. Anal. Calcd for $C_{15}H_{20}ClNO_2$: C, 63.94; H, 7.15; N, 4.97; found: C, 64.13; H, 6.98; N, 5.10.

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