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Synthesis of (*R*)-quinuclidine-2-carboxylic acid in enantiomerically pure form

Pablo Etayo, Ramón Badorrey, María D. Díaz-de-Villegas *, José A. Gálvez *

Departamento de Química Orgánica, Instituto de Ciencia de Materiales de Aragón, Instituto Universitario de Catálisis Homogénea, Universidad de Zaragoza-CSIC, E-50009 Zaragoza, Spain

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Abstract

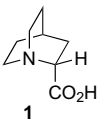
Enantiomerically pure (*R*)-quinuclidine-2-carboxylic acid has been prepared by following two related 7 step synthetic routes in 16% and 19% overall yield, respectively, from a 1,2,4-trisubstituted piperidine that is easily prepared from inexpensive D-mannitol.

Keywords: Azabicyclo[2.2.2]octane; Intramolecular cyclisations; Piperidines; Stereoselective synthesis

Quinuclidine-2-carboxylic acid is an interesting bicyclic amino acid with a close structural relationship to other bicyclic amino acids used as chiral ligands in enantioselective catalysis[1,2] or with biological activity.[3] In this context the potential use of this compound as an enantioselective catalyst or an intermediate in the synthesis of chiral drugs has recently been considered.[4]

In spite of this, synthetic methodologies described for the synthesis of quinuclidine-2-carboxylic acid are scarce. Since the first synthesis of the racemic compound, described by Prelog and Cerkovnikov,[5] only a few approaches to the synthesis of this compound have been reported in the literature.[2,6] Recently, Mi and Corey[4] obtained each enantiomer of this amino acid by chemical and enzymatic resolution of racemic intermediates from the synthetic pathway that they developed. We report herein full details on the synthesis of enantiomerically pure (*R*)-quinuclidine-2-carboxylic acid (**1**).

We reasoned that the 1-azabicyclo[2.2.2]octane skeleton could be obtained by intramolecular cyclisation of a 4-[2-(bromoethyl)]piperidine (Scheme 1). The appropriate substituent at C2 in the starting piperidine would provide the carboxylic acid moiety of quinuclidine-2-carboxylic acid.



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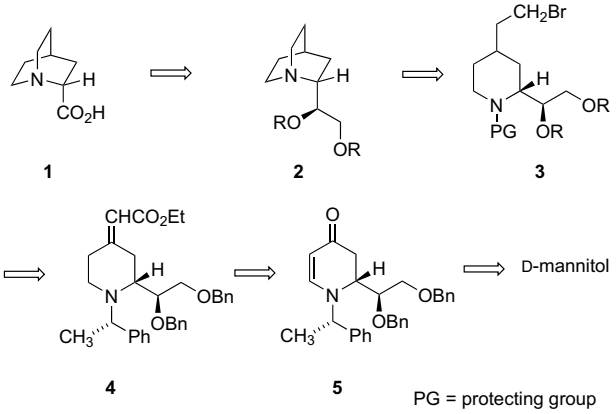

1 **2** **3** **4** **5**

Scheme 1. Retrosynthetic analysis for (*R*)-quinuclidine-2-carboxylic acid.

* Corresponding authors. Tel.: +34 976 762274; fax: +34 976 761202 (M.D.D.); tel.: +34 976 762273; fax: +34 976 761202 (J.A.G.).
E-mail addresses: loladiaz@unizar.es (M. D. Díaz-de-Villegas), jagl@unizar.es (J. A. Gálvez).

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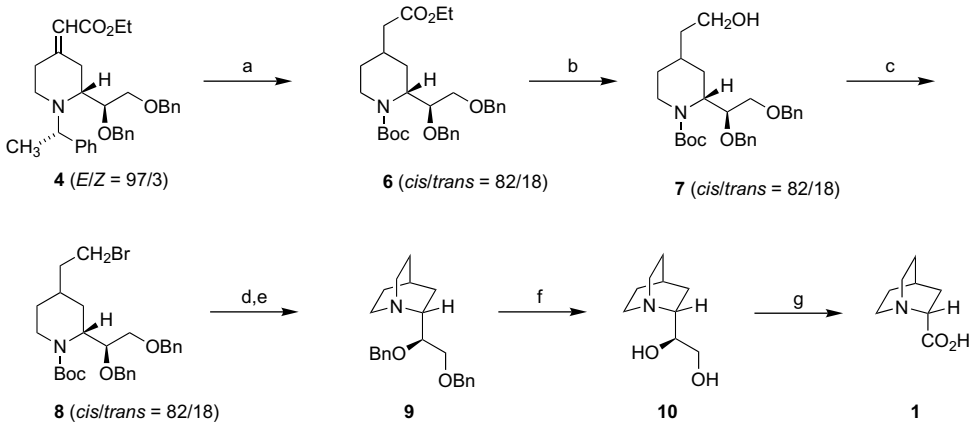


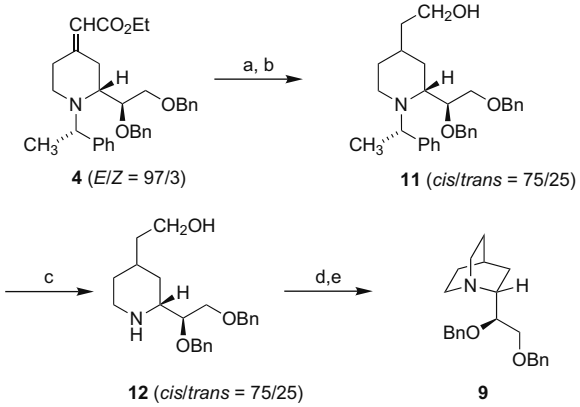
Scheme 2. Reagents and conditions refer to 1 mmol of substrate: (a) Pd/C cat, H_2, Boc_2O (3 mmol), EtOH, 1 atm, rt, 15 h (83%); (b) $LiBH_4$ (2 mmol), Et_2O, rt, 24 h, then satd aq NH_4Cl (89%); (c) CBr_4 (3 mmol) CH_2Cl_2, 0 °C, then PPh_3/PS (3 mmol), reflux, 8 h (65%); (d) 1.2:1 CH_2Cl_2/TFA, rt, 2 h, then satd aq $NaHCO_3$ to basic pH; (e) Et_3N (4 mmol), CH_3CN, reflux, 6 h, then NaOH to basic pH (87% two steps); (f) $Pd(OH)_2$/C cat, H_2, 100:1 EtOH/HCl_{concd}, 1 atm, rt, 19 h, then NaOH to basic pH; (g) $NaIO_4$ (4 mmol), $RuCl_3$ (0.1 mmol), 2:2:3 $CH_3CN/CCl_4/H_2O$, rt, 5 h, then Dowex 50WX8-200 (39%, two steps).

In turn, 4-[2-(bromoethyl)]piperidine derivative could be prepared from 4-ethoxycarbonylmethylidenepiperidine **4**, which is easily obtainable from inexpensive D-mannitol through intermediate enaminone **5**.[7] The nature of the azabicyclo[2.2.2]octane skeleton means that the absolute configuration of the final product only depends on the absolute configuration at C2 of the intermediate 2,4-dialkyl piperidines.

The synthesis of compound **1** began with a 97:3 *E*/*Z* mixture of 4-ethoxycarbonylmethylidenepiperidine **4**, which was obtained as previously described.[7c] Heterogeneous catalytic hydrogenation of compound **4** in the presence of di-*tert*-butyl pyrocarbonate and using Pd/C as the catalyst gave 83% isolated yield of compound **6**[8] as an 82:18 mixture of cis and trans diastereoisomers, as determined by ^1H NMR analysis of the crude reaction mixture. Reduction of compound **6** with $LiBH_4$ provided alcohol **7**[9] as an 82:18 mixture of cis and trans diastereoisomers in 89% yield.

Reaction of **7** with CBr_4 and polystyrene-supported PPh_3 afforded an 82:18 mixture of cis and trans diastereoisomers of the bromide **8**[10] in 65% yield. *N*-Boc deprotection by treatment of **8** with trifluoroacetic acid and subsequent triethylamine-promoted cyclisation gave diastereomerically pure bicyclic derivative **9**[11] in 87% yield. It is worth mentioning that both diastereoisomers of compound **8** led to the same diastereoisomer of compound **9**. Compound **9** was converted into (*R*)-quinuclidine-2-carboxylic acid by hydrogenolysis of *O*-benzyl ethers in the presence of HCl using $Pd(OH)_2$/C as the catalyst followed by oxidative cleavage of the diol moiety of crude **10**[12] by treatment with an excess of $NaIO_4$ in the presence of $RuCl_3$, a process that gave the desired compound **1**[13] as a white solid in 39% overall yield for the last two steps. The complete synthetic pathway shown in Scheme 2 leads to enantiomerically pure (*R*)-quinuclidine-2-carboxylic acid **1** in seven steps and gave an overall yield of 16%.

Alternatively, compound **4** was converted into bicyclic derivative **9** by the sequence shown in Scheme 3. Hydrogenation of **4** using Pt/C as the catalyst followed by the reduction of the obtained 75:25 cis/trans crude diastereomeric mixture of the saturated ester with $LiAlH_4$, as previously described,[14] gave compound **11**. Crude **11** was then submitted to N-debenzylation by hydrogenation using Pd/C as the catalyst to afforded amine **12** as a 75:25 mixture of cis and trans diastereoisomers. Subsequent reaction of crude **12** with CBr_4 and polystyrene-supported PPh_3 followed by triethylamine-promoted cyclisation gave diastereomerically pure bicyclic derivative **9**. The intermediates obtained did not require purification prior to use in the following step and the overall yield for the whole sequence was 51% (five steps). In this way, (*R*)-quinuclidine-2-carboxylic acid **1** was obtained from



Scheme 3. Reagents and conditions refer to 1 mmol of substrate: (a) Pt/C cat, H_2, EtOH, 1 atm, rt, 5 h; (b) $LiAlH_4$ (1.2 mmol), THF, rt, 1 h; then satd aq NH_4Cl; (c) Pd/C cat, H_2, 15:2 EtOH/H_2O, 1 atm, rt, 24 h; (d) CBr_4 (3 mmol) CH_2Cl_2, 0 °C, then PPh_3/PS (3 mmol), reflux, 8 h, then satd aq $NaHCO_3$ to basic pH; (e) Et_3N (4 mmol), CH_3CN, reflux, 6 h, then NaOH to basic pH (51%, five consecutive steps).

4-alkoxycarbonylmethylidenepiperidine **4** in seven steps with an overall yield of 19%.

In conclusion, enantiomerically pure (*R*)-quinuclidine-2-carboxylic acid **1** can be obtained from natural sources in a simple manner. The particular structure of the final product makes it possible to obtain (*R*)-quinuclidine-2-carboxylic acid from both diastereoisomers of chiral intermediates obtained in the proposed routes. This situation allows the transformation of these diastereomeric mixtures without complicated chromatographic isolation procedures. Given that the enantiomer of enaminone **5** has previously been obtained from commercially available L-mannonic γ-lactone,[15] (*S*)-quinuclidine-2-carboxylic acid could be obtained with equal efficiency.

Acknowledgements

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8. A pure sample of compound *cis*-**6** was obtained by hydrogenolytic N-debenzylation of (2*R*,4*S*)-2-[(*S*)-1,2-dibenzyloxyethyl]-4-ethoxycarbonylmethyl-1-[(*S*)-1-phenylethyl]piperidine[14] in the presence of di-*tert*-butyl pyrocarbonate. Selected data for *cis*-**6**: Oil, $[\alpha]_D^{25}$ +47.1 (*c* 1.16, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 0.97–1.08 (m, 1H), 1.16 (t, $J = 7.1$ Hz, 3H), 1.36 (ddd, $J = 11.9$, 11.9, 11.9 Hz, 1H), 1.37 (s, 9H), 1.63–1.70 (m, 1H), 1.84–2.03 (m, 2H), 2.16 (d, $J = 6.8$ Hz, 2H), 2.87–2.96 (m, 1H), 3.54 (dd, $J = 10.4$, 6.6 Hz, 1H), 3.62 (dd, $J = 10.4$, 3.2 Hz, 1H), 3.67–3.71 (m, 1H), 3.70–3.76 (m, 1H), 4.04 (c, $J = 7.1$ Hz, 2H), 4.06–4.10 (m, 1H), 4.44 (d, $J = 12.0$ Hz, 1H), 4.49 (d, $J = 12.0$ Hz, 1H), 4.53 (d, $J = 11.8$ Hz, 1H), 4.72 (d, $J = 11.8$ Hz, 1H), 7.15–7.28 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.4, 28.1, 28.5, 28.6, 29.0, 38.1, 41.0, 54.1, 60.3, 71.6, 73.3, 73.5, 79.5, 80.3, 127.4, 127.6, 127.7, 127.7, 128.3, 128.4, 138.4, 138.9, 155.9, 172.4. IR (neat, cm^{-1}) 1733, 1690, 1246. HRMS (ESI+), *m*/*z* calcd for $[C_{30}H_{41}NO_6+Na]^+$: 534.2826. Found: 534.2812.
9. A pure sample of compound *cis*-**7** was obtained by reduction of pure *cis*-**6**. Selected data for *cis*-**7**: Oil, $[\alpha]_D^{25}$ +46.8 (*c* 0.89, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 0.95–1.03 (m, 1H), 1.25 (ddd, $J = 11.8$, 11.8, 11.4 Hz, 1H), 1.36 (s, 9H), 1.38–1.48 (m, 2H), 1.46–1.55 (m, 1H), 1.64 (ddd, $J = 11.4$, 6.8, 2.2 Hz, 1H), 1.66 (br s, 1H), 1.81–1.91 (m, 1H), 2.99 (ddd, $J = 14.0$, 10.6, 6.8 Hz, 1H), 3.54 (ddd, $J = 6.2$, 6.2, 1.6 Hz, 2H), 3.56 (dd, $J = 10.4$, 6.4 Hz, 1H), 3.63 (dd, $J = 10.4$, 3.1 Hz, 1H), 3.67–3.73 (m, 1H), 3.71–3.76 (m, 1H), 4.04 (ddd, $J = 11.8$, 6.8, 4.9 Hz, 1H), 4.46 (d, $J = 12.0$ Hz, 1H), 4.50 (d, $J = 12.0$ Hz, 1H), 454 (d, $J = 11.8$ Hz, 1H), 4.73 (d, $J = 11.8$ Hz, 1H), 7.16–7.29 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.5, 28.4, 29.0, 29.2, 38.2, 39.4, 54.2, 60.4, 71.5, 73.1, 73.4, 79.4, 80.1, 127.3, 127.5, 127.6, 127.6, 128.1, 128.3, 138.3, 138.8, 155.9. IR (neat, cm^{-1}) 3435, 1684, 1247. HRMS (ESI+), *m*/*z* calcd for $[C_{28}H_{39}NO_5+Na]^+$: 492.2720. Found: 492.2697.
10. A pure sample of compound *cis*-**8** was obtained by bromination of pure *cis*-**7**. Selected data for *cis*-**8**: Oil, $[\alpha]_D^{25}$ +38.4 (*c* 0.64, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ 0.98–1.06 (m, 1H), 1.33 (ddd, $J = 12.3$, 12.3, 12.3 Hz, 1H), 1.43 (s, 9H), 1.57–1.67 (m, 1H), 1.65–1.71 (m, 1H), 1.73–1.86 (m, 2H), 1.89–1.99 (m, 1H), 2.97 (ddd, $J = 14.0$, 10.6, 6.7 Hz, 1H), 3.36 (ddd, $J = 7.1$, 7.1, 1.3 Hz, 2H), 3.62 (dd, $J = 10.5$, 6.6 Hz, 1H), 3.69 (dd, $J = 10.5$, 3.3 Hz, 1H), 3.76 (ddd, $J = 6.6$, 4.3, 3.3 Hz, 1H), 3.77–3.83 (m, 1H), 4.08–4.15 (m, 1H), 4.52 (d, $J = 12.0$ Hz, 1H), 4.56 (d, $J = 12.0$ Hz, 1H), 4.60 (d, $J = 11.8$ Hz, 1H), 4.80 (d, $J = 11.8$ Hz, 1H), 7.24–7.38 (m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.4, 28.4, 28.7, 29.7, 30.9, 38.2, 39.5, 54.2, 71.5, 73.2, 73.5, 79.5, 80.1, 127.4, 127.5, 127.6, 127.7, 128.2, 128.3, 138.3, 138.8, 155.9. IR (neat, cm^{-1}) 1689, 1246. HRMS (ESI+), *m*/*z* calcd for $[C_{28}H_{38}BrNO_4+Na]^+$: 554.1876. Found: 554.1854.
11. Selected data for **9**: Oil, $[\alpha]_D^{25}$ +30.1 (*c* 1.10, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ 1.33 (dd, $J = 12.0$, 8.5 Hz, 1H), 1.46 (ddd, $J = 7.6$, 7.6, 1.8 Hz, 2H), 1.51–1.57 (m, 2H), 1.57–1.65 (m, 1H), 1.78–1.84 (m, 1H), 2.80 (ddd, $J = 14.1$, 7.1, 7.1 Hz, 1H), 3.00 (dd, $J = 8.0$, 5.9 Hz, 2H), 3.02–3.09 (m, 1H), 3.07 (ddd, $J = 8.5$, 8.5, 8.1 Hz, 1H), 3.52 (ddd, $J = 8.1$, 5.0, 3.4 Hz, 1H), 3.64 (dd, $J = 10.5$, 5.0 Hz, 1H) 3.72 (dd, $J = 10.5$, 3.4 Hz, 1H), 4.51 (d, $J = 12.0$ Hz, 1H) 4.56 (d, $J = 12.0$ Hz, 1H), 4.68 (d, $J = 12.1$ Hz, 1H) 4.79 (d, $J = 12.1$ Hz, 1H) 7.22–7.41 (m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.7, 25.6, 26.6, 29.6, 42.7, 49.9, 57.4, 71.3, 72.6, 73.4, 79.3, 127.2, 127.5, 127.6, 127.8, 128.1, 128.3, 138.3, 139.1. IR (neat, cm^{-1}) 1602, 1551, 1203, 1092, 1021. HRMS (ESI+), *m*/*z* calcd for $[C_{23}H_{29}NO_2+H]^+$: 352.2271. Found: 352.2255.
12. NMR data for crude **10**: ^1H NMR (400 MHz, $CDCl_3$) δ 1.05 (dd, $J = 12.4$, 8.3 Hz, 1H), 1.37–1,52 (m, 2H), 1.47–1,58 (m, 2H), 1.65–1.77 (m, 1H), 1.78–1.85 (m, 1H), 2.68 (ddd, $J = 13.5$, 10.5, 3.2 Hz, 1H), 2.79 (ddd, $J = 8.6$, 8.6, 8.3 Hz, 1H), 2.87–2.97 (m, 1H), 2.88 (dd, $J = 7.2$, 7.2 Hz, 2H), 3.35 (br s, 2H), 3.45–3.52 (m, 2H), 3.75–3.82 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.3, 25.7, 26.6, 29.4, 41.5, 49.5, 56.6, 62.7, 72.1.
13. Selected data for **1**: Mp 269–274 °C (lit.[2] 268–271 °C). $[\alpha]_D^{25}$ +119.8 (*c* 1.00, H_2O) [lit.[2] $[\alpha]_D^{23}$ +120.6 (*c* 1, H_2O)]. ^1H NMR (500 MHz, D_2O) δ 1.80–1.94 (m, 4H), 1.92–1.99 (m, 1H), 2.17–2.23 (m, 1H), 2.20–2.29 (m, 1H), 3.22–3.33 (m, 2H), 3.35–3.49 (m, 2H), 3.93 (ddd, $J = 11.0$, 9.0, 2.0 Hz, 1H); ^{13}C NMR (125 MHz, D_2O) δ 20.5, 21.9, 22.4, 27.4, 44.1, 47.6, 59.6, 173.8. IR (KBr, cm^{-1}) 3700–2400, 1616. HRMS (ESI+), *m*/*z* calcd for $[C_8H_{13}NO_2+H]^+$: 156.1019. Found: 156.1024. Anal. Calcd for $C_8H_{13}NO_2$:C, 61.91; H, 8.44; N, 9.03. Found: C, 61.99; H, 8.68; N, 8.88.
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