A Facile Synthesis of 1,2,3,4-Tetrahydro-7-hydroxyisoquinoline-3-carboxylic Acid, a Conformationally Constrained Tyrosine Analogue

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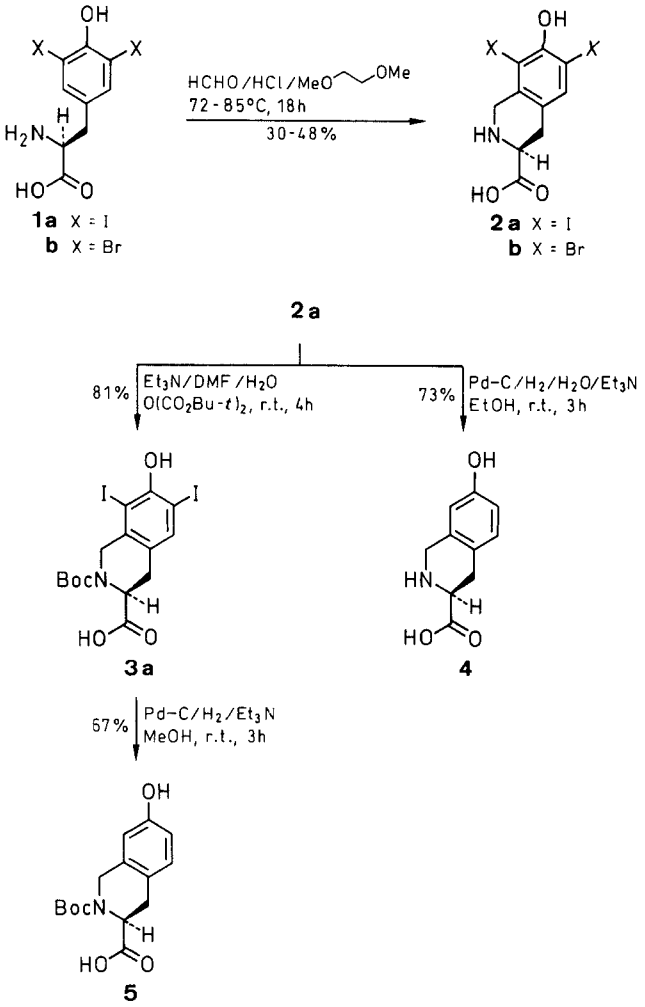
A rapid synthesis of 1,2,3,4-tetrahydro-7-hydroxyisoquinoline-3-carboxylic acid is given. Pictet–Spengler reaction on diiodo- or dibromo-substituted tyrosine (3-(3,5-dihalo-4-hydroxyphenyl)-2-aminopropanoic acid), followed by catalytic dehalogenation gives the desired compound in high optical purity.

The concept of conformational restriction of peptide hormones and neurotransmitters provides a useful approach to increase receptor potency and selectivity of these flexible molecules.[1,2] In this respect 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid can be considered as a phenylalanine analogue in which the sidechain orientation has been fixed by the methylene unit which bridges the 2′-position in the aromatic ring and the α-nitrogen.[3] It is generally prepared by a Pictet–Spengler reaction of phenylalanine with formaldehyde.[4] Similarly, a conformational restricted analogue of tryptophan[5] has been prepared by this method. The preparation of the corresponding tetrahydroisoquinoline derivative **4** starting from tyrosine by this method however does not succeed due to a polymerization reaction to a phenol–formaldehyde polymer.[6] When we stirred tyrosine with formaldehyde at pH 2 or pH 6 for 72 hours, the starting material gradually disapeared, but in the crude reaction product, no cyclized compound **4** was detected in the mass spectrum, in the NMR spectrum or on thin layer chromatography. On the other hand, when the phenolic hydroxy of tyrosine was protected as its benzyloxycarbonyl- or *o*-bromobenzyloxycarbonyl ester, reflux for 4 hours in 6N hydrochloric acid in the presence of formaldehyde gave only recovered starting material for more than 80%.

A very tedious preparation of **4** has been reported,[7] which requires the removal of an aromatic hydroxy group. We now report a simple, fast synthesis of **4**, starting from tyrosine derivatives in which the positions ortho to the phenolic OH are blocked by halogen atoms, **1a, b** X = I, Br. If one starts with 3′,5′-diiodo-L-tyrosine (**1a**) and uses refluxing conditions with formaldehyde and concentrated hydrochloric acid as described for phenylalanine,[4] iodine elimination, followed by polymerization occurs and no **2a** can be isolated. However, when a lower reaction temperature (75 °C) and longer reaction times (18 hours) were used, and 1,2-dimethoxyethane was added as cosolvent to increase solubility (this solvent has the additional advantage that after reaction, the unreacted starting material and the polymer which may be formed are washed away), **2a** (55%, HCl salt) was obtained. The reaction with 3′,5′-dibromo-L-tyrosine (**1b**) required a slightly higher reaction temperature (85 °C) (30%). Lower reaction temperatures have the additional advantage that racemization is limited. We have used derivatization with 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl isothiocyanate (GITC)[8] to monitor the chiral purity of the compounds. For phenylalanine the reflux conditions have been reported to result in extensive racemization.[9,10] We determined an ee of only 62% for this reaction (Table), whereas the lower reaction temperatures used for **1a** resulted in very limited racemization (< 5%). Compounds **2a** and **2b** can either be N^{α}-Boc-protected, as performed for **3a** (81%), followed by catalytic hydrogenolysis to give N^{α}-Boc-protected **5** (53%). Compounds **2a** and **2b** can immediately be dehalogenated to **4** (73%). No racemization occured during either of these steps.



This method gives rapid access to the conformationally constrained tyrosine analogue **4**, using starting materials that can be easily obtained. The incorporation of **5** into biologically active peptides has been performed and will be reported elsewhere.

Table. 1,2,3,4-Tetrahydroisoquinolines

Compound	Reaction Temp. (°C) (Time [h])	Yield (%)	ee (%)	$[\alpha]_D$	Molecular Formula[a]	mp (°C)	TLC (R_f)[b]			HLPC (k')[c]			^{1}H NMR (solvent, frequency) δ, J (Hz)	MS m/z (%)
							A	B	C	1	2	3		
L-Tic·HCl	100 (4)	74	62 (66[9])	−177.4 (c = 1, 1N NaOH)[10]	–	327 (dec)[9]	–	–	–	–	–	–	–	–
2a	72 (18.5)	48	97	−88.83 (c = 0.2, AcOH)	$C_{10}H_9I_2NO_3$ (445.0)	208–209	0.63	–	0.60	4.33	–	–	(D_2O/TFA, 250 MHz) 2.53 (dd, J = 17.0, 10.8, 1H, H-4), 2.69 (dd, J = 17.0, 5.3, 1H, H-4'), 3.54 (d, J = 16.5, 1H, H-1), 3.66 (dd, J = 10.8, 5.3, 1H, H-3), 3.79 (d, J = 16.5, 1H, H-1), 7.01 (s, 1H, H-5)	(CI) 446 (78, $M^+ + 1$), 400 (30), 320 (92), 272 (100), 194 (32)
2b	85 (18.5)	30 HCl salt	88	−81.03 (c = 0.2, AcOH)	$C_{10}H_9Br_2NO_3$ (350.9)	250	0.61	–	0.62	1.36	–	–	(D_2O/TFA, 250 MHz) 2.90 (dd, J = 17.2, 11.1, 1H, H-4), 3.09 (dd, J = 17.2, 5.2, 1H, H-4'), 3.96 (d, J = 16.4, 1H, H-1), 4.06 (dd, J = 5.2, 11.1, 1H, H-3), 4.23 (d, J = 16.4, 1H, H-1'), 7.16 (s, 1H, H-5)	(CI) 354 (47), 352 (100), 350 (60, $M^+ + 1$), 308 (14), 306 (29), 304 (20), 4 (28), 272 (32), 226 (15), 194 (6)
3a	25 (4)	87	97	+33.8 (c = 0.58, $CHCl_3$)	$C_{15}H_{17}I_2NO_5$ (545.1)	172–174[d]	–	0.64	–	–	–	7.75	(DMSO-d_6, 270 MHz) 1.39 + 1.45 (s, 9H, *cis* + *trans* Boc 54 : 46), 3.0 (m, 2H, H-4), 4.1–4.5 (m, 2H, H-1), 4.67 + 4.80 (t, J = 4.9, 1H, H-2 *cis* + *trans*), 7.62 (s, 1H, H-5), 9.45 (s, 1H, OH)	(FAB) 546 (4, $M^+ + 1$), 490 (34), 446 (100), 400 (55), 320 (66), 272 (75)
4 (from **2a**)	25 (3)	73	97	−169.09 (c = 1.0, AcOH)	$C_{10}H_{11}NO_3 \cdot H_2O$ (211.2)	294	0.51	–	0.60	–	2.08	–	(D_2O/TFA, 250 MHz) 2.85 (dd, J = 17.2, 10.2, 1H, H-4), 3.06 (dd, J = 17.2, 5.5, 1H, H-4'), 4.05 (dd, J = 5.5, 10.2, 1H, H-3), 4.09 (m, 2H, H-1,1'), 6.40 (d, J = 2.5, 1H, H-8), 6.54 (dd, J = 8.5, 2.5, 1H, H-6), 6.86 (d, J = 8.5, 1H, H-5)	(CI) 194 (100, $M^+ + 1$), 148 (7)
5 (from **3a**)	25 (3)	67	97	+8.2 (c = 0.16, MeOH)	$C_{15}H_{19}NO_5$ (293.3)	175[e]	–	0.66	–	–	–	4.5	(DMSO-d_6, 270 MHz) 1.37 + 1.44 (s, 9H, *cis* + *trans* Boc 54 : 46), 3.0 (m, 2H, H-4), 4.2–4.5 (m, 2H, H-1), 4.58 + 4.81 (t, J = 5.4, 1H, H-2, *cis* + *trans*), 6.5–6.6 (m, 2H, H-6, H-8), 6.96 (dd, J = 8.0, 4.7, 1H, H-5), 9.27 (s, 1H, OH)	(FAB.) 294 (21, $M^+ + 1$), 238 (51), 194 (100), 146 (91)

[a] Satisfactory elemental analysis for C, H, N within 0.4% of the theoretical values were obtained.
[b] Solvent systems: see experimental.
[c] HPLC: 1: 10% MeCN in 0.1% TFA/H_2O, 1.5 mL/min. 2: 0–20% MeCN in 0.1% TFA/H_2O in 20 min. 3: 20–50% MeCN in 0.1% TFA/H_2O in 20 min.
[d] The compound becomes brown around 165 °C, and decomposes above 174 °C.
[e] The compound starts foaming at 175 °C, the foam melts at 262–265 °C.

Melting points were determined in open capillary tubes with a Thomas-Hoover melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Bruker AM 270 or WM 250 MHz spectrometer with DMSO-d_6 or D_2O as solvent. Mass spectra were determined on a AEI MS 902 S mass spectrometer (FAB mode) or on a Hewlett Packard model No 5988A (chemical ionization with isobutane). Optical rotations were measured on a Perkin-Elmer polarimeter. TLC was performed using silica gel plates (Merck 60 or Analtech) with solvent systems: A: BuOH/AcOH/H_2O (4:1:1); B: EtOAc/MeOH (1:1); or C: MeCN/MeOH/H_2O (4:1:1). The TLC spots were detected with ninhydrin spray (0.2% in EtOH), giving a yellow colour. A Spectra-Physics SP800 HPLC was used to determine the homogeneity of all compounds (Table); chiral HPLC analysis was performed on a Spectra-Physics 8100 chromatograph, equipped with a Vydac 218TP54 (0.46 × 25 cm) column, and a linear gradient of MeCN/0.1% aq TFA (20% to 45% MeCN in 20 min) with a flow rate of 1.5 mL/min.[8] Elemental analysis was carried out by Desert Analytics Organic Microanalysis, Tucson, Arizona. 3',5'-Diiodo-L-tyrosine **1a** was obtained from Janssen Chimica (Beerse, Belgium), 3',5'-dibromo-L-tyrosine **1b** was obtained from Sigma Chemical Co. (St. Louis, USA).

(*S*)-1,2,3,4-Tetrahydro-7-hydroxy-6,8-diiodoisoquinoline-3-carboxylic Acid (2a):

A suspension of 3',5'-diiodo-L-tyrosine · $2H_2O$ (**1a**, 18.1 g, 40 mmol)' in conc. HCl (180 mL), 1,2-dimethoxyethane (12 mL) and formaldehyde (13.2 mL, 37 wt% in H_2O, 160 mmol) was stirred vigorously and slowly heated to 72°C over 0.5 h. After 0.5 h conc. HCl (80 mL), 1,2-dimethoxyethane (6 mL) and formaldehyde solution (6.6 mL) were added and stirring was continued for 18 h at 72–75°C. The suspension was then cooled in an ice bath and filtered. The filter cake was washed thoroughly several times with 1,2-dimethoxyethane (20 mL) and dried under vacuum. The resulting white powder is pure **2a** HCl salt: 10.6 g (55%). A sample is recrystallized from MeOH/H_2O. The free amino acid can be obtained by dissolving the HCl salt in EtOH/H_2O (1:2) and adjusting the pH to 6 with NH_4OH. After cooling overnight in a refrigerator, the precipitate was filtered.

Yield: 8.6 g (48%). See Table for properties.

(*S*)-6,8-Dibromo-1,2,3,4-tetrahydro-7-hydroxy-isoquinoline-3-carboxylic Acid (2b):

Using the procedure described above, and starting from 3',5'-dibromo-L-tyrosine **1b** (10 mmole) and at a reaction temperature of 85°C, 1.15 g of the HCl salt **2b** was obtained (30%). See Table for properties.

(*S*)-2-*tert*-Butoxycarbonyl-1,2,3,4-tetrahydro-7-hydroxy-6,8-diiodoisoquinoline-3-carboxylic Acid (3a):

Compound **2a** (1.44 g, 3 mmol) and Et_3N (835 µL, 6 mmol) were dissolved in DMF/H_2O (4/1, 10 mL) (pH 8). Di-*tert*-butyl dicarbonate (0.98 g, 4.5 mmol) was added and the mixture was stirred for 4 h at r.t. The solvent was removed completely under high vacuum and the residue was dissolved in H_2O. At 0°C the aqueous layer was acidified with 10% $KHSO_4$ in the presence of EtOAc (pH 2–3). The aqueous layer was extracted with EtOAc (3 × 25 mL) and the combined organic phases were dried ($MgSO_4$) and evaporated. The residue was redissolved in a minimum amount of EtOAc and this solution was added dropwise to petroleum ether (40–60°C). Yield: 1.32 g (81%).

(*S*)-2-*tert*-Butoxycarbonyl-1,2,3,4-tetrahydro-7-hydroxyisoquinoline-3-carboxylic Acid (5):

To a solution of **3a** (1.63 g, 3 mmol) in dry MeOH (60 mL) containing Et_3N (835 µL, 6 mmol) was added 186 mg 10% Pd–C catalyst. The mixture was shaken for 3 h under H_2 pressure (50 psi) in a Parr apparatus. The catalyst was filtered off, the filtrate was evaporated and treated as described for **3a**. Further crystallization from EtOAc/cyclohexane or from MeOH/H_2O gave pure **5**: 0.58 g (67%). See Table for properties.

(*S*)-1,2,3,4-Tetrahydro-7-hydroxyisoquinoline-3-carboxylic Acid (4):

A solution of 1,2,3,4-tetrahydro-7-hydroxy-6,8-diiodoisoquinoline-3-carboxylic acid (**2a**; 4.45 g) in EtOH (150 mL) and H_2O (50 mL) containing 4% Et_3N (8 mL) was hydrogenated at 40 psi in the presence of 10% Pd–C (0.62 g) for 3 h. The catalyst was filtered off. The solution slightly colored, and thus, some crystals of $Na_2S_4O_6$ are added. The solution was evaporated until crystals start to appear and the pH is adjusted to 6. After cooling overnight in the refrigerator, the crystals are filtered, washed with cold H_2O and dried to give 1.42 g of **4** (73%). See Table for properties.

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