# An Improved Synthesis of (*3R*)-2-(*tert*-Butoxycarbonyl)-7-hydroxy-1,2,3,4tetrahydroisoquinoline-3-carboxylic Acid

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**Abstract:** An improved synthesis of (3R)-2-(*tert*-butoxycarbonyl)-7-hydroxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid is described wherein a modified Pictet–Spengler reaction was employed to provide 95% yield of the product with 7% racemization or less. The enantiomeric excess of the final product was improved to 99.4% via recrystallization. The overall yield of this four-step synthesis provides the title compound in 43% starting from D-tyrosine.

**Key words:** Pictet–Spengler, 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid, JDTic, synthesis

We recently reported the discovery of (3R)-7-hydroxy-N- $[(1S)-1-\{[(3R,4R)-4-(3-hydroxyphenyl)-3,4-dimethylpip$ eridin-1-yl]methyl}-2-methylpropyl]-1,2,3,4-tetrahydro-3-isoquinolinecarboxamide (JDTic, 1) as the first orally opioid active selective к receptor antagonist (Scheme 1).<sup>1-6</sup> The synthesis of JDTic is convergent and utilizes (3R)-2-(tert-butoxycarbonyl)-7-hydroxy-1,2,3,4tetrahydroisoquinoline-3-carboxylic acid (2) as one of the key starting materials. In preparing large quantities of **1** (>200 g) for biological testing we viewed the high cost of this key starting material 2 as an incentive to improve its preparation. The results of this investigation are described herein.

Compound 2 has been previously synthesized from Dtyrosine (3) using the Pictet–Spengler reaction when the *ortho*-hydrogen atoms were replaced by bromine or iodine to give 4a,b to prevent phenol-formaldehyde polymerization (Scheme 2).<sup>7</sup> Vershceuren et al. described the cyclization of both the diiodo and dibromo intermediates 4a,b to the corresponding tetrahydroisoquinolines 5a,b.<sup>7</sup> The synthesis of 5a using the diiodo intermediate 4a was described to be both higher yielding (55%) and less prone to racemization (<5%) than the sequence starting from dibromo intermediate 4b (30% yield). In our hands, however, the syntheses of **5a** from **4b** was quite cumbersome, forming tar-like intermediates that were very difficult to handle as the process was scaled up. The conversion of dibromo compounds 4b into 5b on the other hand produced easily manipulated solids. This feature prompted us to focus attention on improving this synthetic route to 2. Bromination of D-tyrosine (3) in acetic acid provided 3',5'dibromo-D-tyrosine hydrobromide (4b·HBr) suitable for use in the Pictet-Spengler reaction.<sup>8</sup> After some experimentation, it was found that the conversion of 4b HBr into 5b·HBr could be improved to 95% versus the 30% reported earlier by using hydrogen bromide/acetic acid and trifluoroacetic acid as the catalyst/solvent combination. Our initial trials of the cyclization of 4b·HBr to 5b·HBr at 80 °C for 18 hours showed significant racemization (~30%), but we found that this could be suppressed to 7% by conducting the reaction at 55 °C for 72 hours. Attempts to remove the 7% of S-isomer of 5b directly by recrystallization of diastereomeric mixtures of 5b·HBr with camphorsulfonic acids were not successful.9 However, we found that compound 6 could be purified to 99.4%ee by catalytic dehydrobromination of **5b**·HBr using palladium-on-carbon and hydrogen to give tetrahydroisoquinolin-3-carboxylic acid **6** followed by two recrystallizations from water. Protection of 6 with a tertbutoxycarbonyl group gave 2 in 43% overall yield from Dtyrosine.



### Scheme 1

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Scheme 2 Reaction conditions: (a) Br<sub>2</sub>, AcOH; (b) 33% HBr in AcOH, TFA, 55 °C; (c) 10% Pd/C, H<sub>2</sub>, EtOH; (d) Boc<sub>2</sub>O, Et<sub>3</sub>N, DMF.

In conclusion, we have made significant improvements to the reported synthesis of (3R)-2-(*tert*-butoxycarbonyl)-7hydroxy-1,2,3,4-tetrahydroisoquinoline (**2**) via modification of the Pictet–Spengler conditions together with crystallizations of the key intermediate (3*R*)-7-hydroxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (**6**). This provided the title compound in 43% overall yield and 99.4% ee starting from D-tyrosine.

NMR spectra were obtained on a Bruker spectrometer operating at 300 MHz for <sup>1</sup>H NMR and 75 MHz for <sup>13</sup>C NMR. Mass spectral data were obtained using a Finnegan LCQ electrospray mass spectrometer in positive ion mode at atmospheric pressure. Enantiomer ratios were obtained on a Dynamax HPLC system equipped with a Chiralcel OD column. Each HPLC sample was eluted with hexanes–*i*-PrOH–TFA (95:5:0.1) at 0.2 mL/min and the absorption was detected at 220 nm. Optical rotations were obtained on an Autopol III automatic polarimeter.

#### 3',5'-Dibromo-D-tyrosine Hydrobromide (4b·HBr)

 $Br_2$  (173.0 g, 1.08 mol) in AcOH (30 mL) was added dropwise, at r.t., to a heterogeneous soln of D-tyrosine (**3**, 100.0 g, 0.55 mol) in AcOH (300 mL). The mixture was stirred for 4 h, and then concentrated on a rotary evaporator. The residue was further dried under high vacuum to give **4b**·HBr (227.1 g, 98%) as an off-white solid.

<sup>1</sup>H NMR (CD<sub>3</sub>OD):  $\delta$  = 7.45 (s, 2 H), 4.27 (t, *J* = 6.6 Hz, 1 H), 3.21 (dd, *J* = 5.7, 14.2 Hz, 1 H), 3.11 (dd, *J* = 6.6, 14.2 Hz, 1 H).

### (3*R*)-6,8-Dibromo-7-hydroxy-1,2,3,4-tetrahydroisoquinoline-3carboxylic Acid Hydrobromide (5b·HBr)

Compound **4b**·HBr (10.0 g, 23.1 mmol) was finely ground with a mortar and pestle and suspended in TFA (30 mL). 33% HBr in AcOH (4.4 mL) was added dropwise to the suspension. The vigorous gaseous evolution was allowed to pass through aq NaOH soln before vented in the hood. Upon the complete addition of HBr, paraformaldehyde (1.44 g) was added. The mixture was stirred at 55 °C for 72 h, cooled to r.t., and stored in the refrigerator overnight. The solids were collected by filtration and washed (EtOAc) to give **5b**·HBr (9.7 g, 95%) as an off-white solid; 86% ee.

<sup>1</sup>H NMR (CD<sub>3</sub>OD):  $\delta$  = 7.53 (s, 1 H), 4.47 (d, *J* = 16.5 Hz, 1 H), 4.38 (dd, *J* = 5.1, 10.8 Hz, 1 H), 4.25 (d, *J* = 16.5 Hz, 1 H), 3.41 (dd, *J* = 8.1, 16.8 Hz, 1 H), 3.18 (dd, *J* = 11.1, 16.8 Hz, 1 H).

**Determination of the Ratio of Enantiomers; Typical Procedure** The ratio of enantiomers was determined in the following way: Et<sub>3</sub>N (0.4 mL) and Boc<sub>2</sub>O (164 mg) were added sequentially to a soln of **5b**·HBr (43 mg) in DMF–H<sub>2</sub>O (1 mL/0.5 mL) at r.t. The mixture was stirred for 1 h and diluted with EtOAc. The organic phase was washed with 20% aq NaHSO<sub>4</sub> (1 ×), H<sub>2</sub>O (2 ×), and brine (1 ×), dried (Na<sub>2</sub>SO<sub>4</sub>), and concentrated. The residue was passed through silica gel (pipette column) (hexanes–EtOAc, 1:1). Fractions were collected and concentrated. The residue was diluted with hexanes–*i*-PrOH (95:5) to yield a soln (1–2 mg/mL) for HPLC: *t*<sub>R</sub> = 76.4 (*R*-isomer), 81.8 min (*S*-isomer).

# (3*R*)-7-Hydroxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylic Acid (6)

EtOH (50 mL), H<sub>2</sub>O (50 mL), Et<sub>3</sub>N (12.4 mL, 89.2 mmol), and 10% Pd/C (0.97 g) were added sequentially to a soln of **5b**·HBr (9.7 g, 0.0224 mol) in MeOH (50 mL) at r.t. The resulting mixture was placed on a Parr hydrogenator at 3.1 bar for 3 h. The mixture was filtered and the Pd cake was washed with H<sub>2</sub>O. The pH of the filtrate was adjusted to 6 by 1 M HCl to give a white precipitate. After storage at 5 °C overnight, the solids were collected by filtration and washed with cold H<sub>2</sub>O (2 ×) to yield **6** (3.0 g, 69%) as a white crystalline powder; 97.8% ee. The enantiomeric ratio of **6** was measured as described for the typical procedure for **5b**. HPLC:  $t_{\rm R}$  = 86.5 (*S*-isomer), 90.1 min (*R*-isomer). Compound **6** (3.0 g) was further recrystallized (H<sub>2</sub>O, 90 mL) to yield **6** (2.3 g, 77%) as a crystalline solid; 99.4% ee.

 $[\alpha]_{D}^{25}$  +157.5 (*c* 0.78, AcOH) {Lit.<sup>7</sup>  $[\alpha]_{D}$  -169.09 (*c* 1.0, AcOH)}.

<sup>1</sup>H NMR (DMSO- $d_6$ ):  $\delta = 9.44$  (br s, 2 H), 6.96 (d, J = 8.3 Hz, 1 H), 6.66 (dd, J = 2.3, 8.3 Hz, 1 H), 6.59 (d, J = 2.3 Hz, 1 H), 3.52 (dd, J = 4.9, 10.6 Hz, 1 H), 3.03 (dd, J = 4.5, 16.6 Hz, 1 H), 2.87 (dd, J = 10.6, 16.6 Hz, 1 H).

### (3*R*)-2-(*tert*-Butoxycarbonyl)-7-hydroxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylic Acid (2)

Et<sub>3</sub>N (6.6 mL, 47.6 mmol) and Boc<sub>2</sub>O (3.9 g, 0.018 mol) were added sequentially to a soln of **6** (2.3 g, 0.012 mol) in DMF–H<sub>2</sub>O (4:1, 50 mL) at r.t. After stirring for 4 h, the mixture was concentrated to a residue that was dissolved in EtOAc (150 mL). The organic phase was washed with 20% NaHSO<sub>4</sub> (1 ×), H<sub>2</sub>O (2 ×), and brine (1 ×), dried (Na<sub>2</sub>SO<sub>4</sub>), and concentrated. The residue was treated with hexanes (200 mL) whereupon white precipitates formed. These solids were collected by filtration and washed (hexanes) to give **2** (3.1 g, 87%) as a white solid; 99.4% ee. The enantiomeric ratio for **2** was determined as described for the typical procedure for **5b**. HPLC:  $t_{\rm R} = 86.5$  (*S*-isomer), 90.1 min (*R*-isomer).  $[\alpha]_D^{25}$  -15.0 (c 0.16, MeOH) {Lit.<sup>7</sup> S-isomer  $[\alpha]_D$  +8.2 (c 0.16, MeOH)}.

<sup>1</sup>H NMR (CD<sub>3</sub>OD):  $\delta$  = 6.98 (t, *J* = 5.1 Hz, 1 H), 6.65–6.57 (m, 2 H), 4.96–4.70 (m, 1 H), 4.56–4.43 (m, 2 H), 3.15–3.07 (m, 2 H), 1.53 (s, 4 H), 1.47 (s, 5 H).

 $^{13}\text{C}$  NMR (CD<sub>3</sub>OD):  $\delta$  = 175.8, 175.3, 164.1, 157.8, 157.7, 157.3, 136.3, 135.6, 130.8, 130.3, 124.9, 124.4, 115.6, 114.1, 113.9, 82.4, 82.3, 56.4, 54.8, 46.4, 45.7, 32.2, 31.9, 29.2, 29.0, 28.3.

MS (APCI):  $m/z = 294.3 [M + H]^+$ .

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## References

(1) Thomas, J. B.; Atkinson, R. N.; Rothman, R. B.; Fix, S. E.; Mascarella, S. W.; Vinson, N. A.; Xu, H.; Dersch, C. M.; Lu, Y.; Cantrell, B. E.; Zimmerman, D. M.; Carroll, F. I. J. Med. Chem. 2001, 44, 2687.

- (2) Beardsley, P. M.; Howard, J. L.; Shelton, K. L.; Carroll, F. I. *Psychopharmacology (Berlin)* **2005**, *183*, 118.
- (3) Carroll, F. I.; Harris, L. S.; Aceto, M. D. Eur. J. Pharmacol. 2005, 524, 89.
- (4) Thomas, J. B.; Fix, S. E.; Rothman, R. B.; Mascarella, S. W.; Dersch, C. M.; Cantrell, B. E.; Zimmerman, D. M.; Carroll, F. I. J. Med. Chem. 2004, 47, 1070.
- (5) Carroll, F. I.; Thomas, J. B.; Dykstra, L. A.; Granger, A. L.; Allen, R. M.; Howard, J. L.; Pollard, G. T.; Aceto, M. D.; Harris, L. S. *Eur. J. Pharmacol.* **2004**, *501*, 111.
- (6) Thomas, J. B.; Atkinson, R. N.; Vinson, N. A.; Catanzaro, J. L.; Perretta, C. L.; Fix, S. E.; Mascarella, S. W.; Rothman, R. B.; Xu, H.; Dersch, C. M.; Cantrell, B. E.; Zimmerman, D. M.; Carroll, F. I. *J. Med. Chem.* **2003**, *46*, 3127.
- (7) Verschueren, K.; Toth, G.; Tourwe, D.; Lebl, M.; Van Binst, G.; Hruby, V. *Synthesis* **1992**, 458.
- (8) Vert, M. Eur. Polym. J. 1972, 8, 513.
- (9) Shiraiwa, T.; Furukawa, T.; Tsuchida, T.; Sakata, S.; Sunami, M.; Kurokawa, H. Bull. Chem. Soc. Jpn. 1991, 64, 3729.