Alternative Synthesis of the PDE5 Inhibitor RWJ387273 (R290629)

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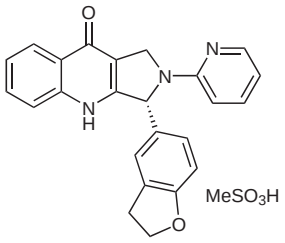
Abstract: An alternative synthesis of a PDE5 inhibitor is reported using a highly diastereoselective Pictet–Spengler reaction.

Key words: Pictet–Spengler reaction, β-tetrahydrocarboline oxidation, Buchwald–Hartwig coupling, PDE5 inhibitor

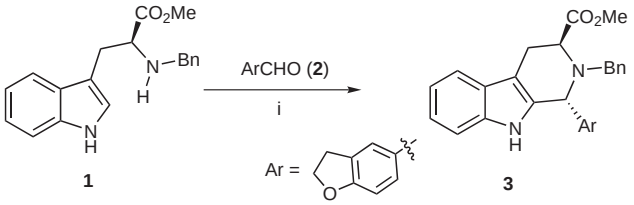
During the past few years, phosphodiesterase 5 (PDE5) inhibitors have been the focus of interest due to their ability to enhance penile erection.[1] Indeed, the first market introduction of a PDE5 inhibitor, Viagra® (sildenafil)[2] has been a worldwide commercial success. Recently, several other products, Levitra® (vardenafil)[3] and Cialis® (tadalafil),[4] have been developed. Eventually, new chemical entities, such as the pyrroloquinolones, have emerged as potent and selective inhibitors of PDE5. Medicinal chemists at Johnson & Johnson have identified **RWJ387273** as a potent and selective PDE5 inhibitor (Figure 1).[5] In order to provide sufficient quantities of this new compound for clinical trials, a novel synthesis has been devised.[6] In this report, we present an alternative synthesis of the API using a highly diastereoselective Pictet–Spengler reaction as the key step.



RWJ387273

Figure 1 Potential PDE5 inhibitor

In the original route developed by the discovery chemists, the β-tetrahydrocarboline **6** (Scheme 2) is obtained by a racemic Pictet–Spengler condensation between tryptamine and the aromatic aldehyde **2**. A chiral preparative liquid chromatography[5] or a resolution by diastereomeric salt formation[7] enabled the separation of the two enantiomers from the racemic mixture. Asymmetric Pictet–Spengler reactions have been reported using a chiral auxiliary linked to the nitrogen atom of the tryptamine.[8]



Scheme 1 *Reagents and conditions*: (i) 10 mol% PTSA, toluene, Dean–Stark, 22 h, 73%.

Based upon the work of Cox and Cook,[9] it was decided to use L-tryptophan derivatives as cheap sources of chiral materials. Moreover, it was anticipated that Pictet–Spengler cyclisation of **1** would give the desired *trans* product.

When the *N*-benzyl-L-tryptophan methyl ester (**1**) and a stoichiometric amount of the aromatic aldehyde **2** are refluxed in toluene in a Dean–Stark apparatus, in the presence of a catalytic amount of PTSA (10 mol%), a complete conversion to the β-tetrahydrocarboline **3** is achieved after 22 hours. We were delighted to observe the formation of the *trans* product **3** as a single diastereoisomer (as measured by NMR in the crude reaction mixture).[10,11,15] Crystallisation from *t*-BuOMe affords pure product **3** in a 73% yield (Scheme 1).

In order to obtain the key β-tetrahydrocarboline **5**, the ester function of compound **3** has to be removed (Scheme 2). Initially, it is converted into the cyano function in three steps: saponification of the methyl ester in alkaline media affords the corresponding carboxylic acid intermediate (not shown). Then, without purification, the amide derivative is formed by treatment with ammonium carbonate and EEDQ as coupling agent.[12] Finally, treatment of the primary amide with $POCl_3$[13] leads to its dehydration and to the formation of the cyano derivative **4** in 50% yield (over three steps and after crystallisation from *t*-BuOMe).[16] The cyano group is then substituted by a hydride in an ethanol–pyridine mixture by treatment with an excess of $NaBH_4$.[13,14,17] The (*R*)-β-tetrahydrocarboline **5** is isolated in 97% yield with an enantiomeric ratio (er) of 95.7:4.3 as measured by chiral HPLC. The benzyl group is removed by hydrogenolysis in the presence of catalytic amounts of palladium on charcoal. At room temperature, the debenzylated product **6** is isolated in 82% yield without loss of enantiomeric purity.[18] However, when the hydrogenolysis is performed at 50 °C, the er drops to 83.5:16.5 at complete conversion.

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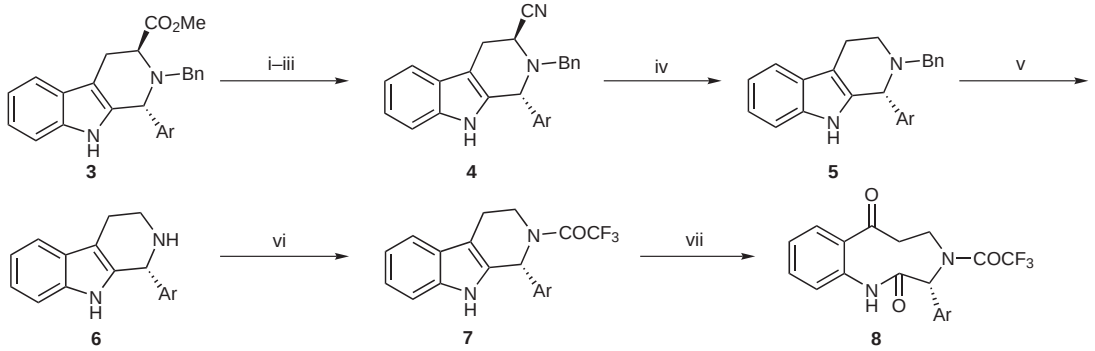
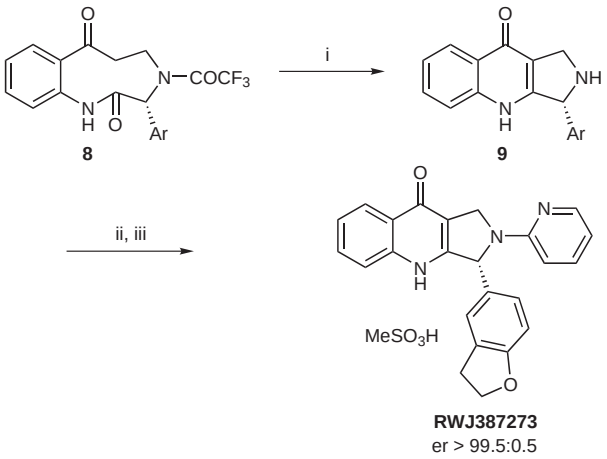


Scheme 2 *Reagents and conditions*: (i) NaOH 15% w/w, MeOH–THF 1:1, 28 h, r.t.; (ii) $(NH_4)_2CO_3$, EEDQ, CH_2Cl_2, 16 h, r.t.; (iii) $POCl_3$, DMF, 2 h, 0 °C, 50% from **3**; (iv) 2 × 5 equiv $NaBH_4$, pyridine–EtOH 1:2, 24 h, 70 °C, 97%; (v) H_2 (3 atm.), 5% w/w Pd/C 10%; cat. HCl, MeOH, r.t., 82%; (vi) 1.1 equiv $(CF_3CO)_2$, Et_3N, 1 h, 0 °C, >95%; (vii) acetone, oxone®, $NaHCO_3$, 0 °C then MCPBA, 60%.

The oxidation of the β-tetrahydrocarboline **6** into **9** has already been described using potassium superoxide.[7] However, we have recently reported on the hazardous behaviour of this oxidation especially on large scale.[6] The oxidation of trifluoroacetamide **7**[19] by dimethyldioxirane, generated in situ, followed by addition of MCPBA leads to compound **8** in 60% yield in a safe and scalable manner.[20]

Treatment of the nine-membered heterocycle **8** with two equivalents of KOH in ethanol affords the N-deprotected pyrroloquinolone **9** in 90% yield (Scheme 3).[21] At that stage, compound **9** could be enantioselectively enriched to >99.5:0.5 either by chiral preparative HPLC or by enantioselective crystallisation of the HCl salt.[22] Finally the desired PDE5 inhibitor **RWJ387273** is obtained in 90% yield by the coupling of the secondary amine **9** with 2-bromopyridine under palladium catalysis in THF at 60 °C.[23] The temperature range for the coupling is relatively small: (1) in refluxing THF or in higher boiling solvent such as 1,4-dioxane, epimerisation of the stereogenic centre is observed; (2) below ca. 45 °C, the conversion is slow due to the poor solubility of the starting material. Crystallisation of the methanesulfonate salt of **RWJ387273** from methanol leads to final API in >99.5:0.5 er[24] and 80.5% yield.

In conclusion, we have developed a scalable, safe and highly enantioselective synthesis of **RWJ387273** based upon a diastereoselective Pictet–Spengler reaction starting from a cheap amino acid derivative. The synthesis consists of a 12-step sequence and delivers the final product with an enantiomeric ratio of >99.5:0.5.



Scheme 3 *Reagents and conditions*: (i) 2 equiv KOH, EtOH, 16 h, r.t., 90%; (ii) 2-bromopyridine, *t*-BuONa, $Pd(dba)_2$, BINAP, THF, 60 °C, 9 h, 90%; (iii) $MeSO_3H$, MeOH, 20 °C, 20 h, 80.5%.

References and Notes

(1) Corbin, J. D.; Francis, S. H. *J. Biol. Chem.* **1999**, *274*, 13729.

(2) For Viagra®(sildenafil), see: Brook, G. *Drugs Today* **2000**, *26*, 125.

(3) For Levitra®(vardenafil), see: Sorbera, L. A.; Martin, L.; Rabasseda, X.; Castaner, J. *Drugs Future* **2001**, *26*, 141.

(4) (a) For Cialis®(tadalafil), see: Sorbera, L. A.; Martin, L.; Leeson, P. A.; Castaner, J. *Drugs Future* **2001**, *26*, 15. (b) For discovery of tadalafil, see: Daugan, A.; Grondin, P.; Ruault, C.; Gouville, A.-C. L. M.; Coste, H.; Kirilovsky, J.; Hyafil, F.; Labaudinière, R. *J. Med. Chem.* **2003**, *46*, 4525. (c) Daugan, A.; Grondin, P.; Ruault, C.; Gouville, A.-C. L. M.; Coste, H.; Kirilovsky, J.; Linget, J.-M.; Hyafil, F.; Labaudiniere, R. *J. Med. Chem.* **2003**, *46*, 4533.

(5) (a) Jiang, W.; Alford, V.; Qiu, Y.; Bhattacharjee, S.; John, Y. M.; Haynes-Johnson, D.; Kraft, P. J.; Lundeen, S. G.; Sui, Z. *Bioorg. Med. Chem.* **2004**, *12*, 1505. (b) Lanter, J.; Sui, Z.; Macielag, M. J.; Fiordeliso, J.; Jiang, W.; Qiu, Y.; Bhattacharjee, S.; Kraft, P.; John, T. M.; Haynes-Johnson, D.; Craig, E.; Clancy, J. *J. Med. Chem.* **2004**, *47*, 656. (c) Jiang, W.; Sui, Z. WO 2004000842, **2003**. (d) Qiu, Y.; Bhattacharjee, S.; Kraft, P.; John, T. M.; Craig, E.; Haynes-Johnson, D.; Guan, J.; Jiang, W.; Macielag, M.; Sui, Z.; Clancy, J.; Lundeen, S. *Eur. J. Pharmacol.* **2003**, *472*, 73. (e) Jiang, W.; Sui, Z. WO 2003042213, **2003**. (f) Jiang, W.; Sui, Z.; Macielag, M.; Walsh, S. P.; Fiordeliso, J. J.; Lanter, J. C.; Guan, J.; Qiu, Y.; Kraft, P.; Bhattacharjee, S.; Craig, E.; Haynes-Johnson, D.; John, T. M.; Clancy, J. *J. Med. Chem.* **2003**, *46*, 441. (g) Jiang, W.; Sui, Z.; Chen, X. *Org. Lett.* **2003**, *5*, 43. (h) Jiang, W.; Sui, Z.; Chen, X. *Tetrahedron Lett.* **2002**, *43*, 8941. (i) Sui, Z.; Guan, J.; Macielag, M.; Jiang, W.; Zhang, S.; Qiu, Y.; Kraft, P.; Bhattacharjee, S.; John, T. M.; Hyanes-Johnson, D.; Clancy, J. *J. Med. Chem.* **2002**, *456*, 4094. (j) Sui, Z.; Macielag, M.; Guan, J.; Jiang, W.; Lanter, J. C. WO 2001087882, **2001**. (k) Jiang, W.; Guan, J.; Macielag, J. M.; Zhang, S.; Qiu, Y.; Kraft, P.; Bhattacharjee, S.; John, T. M.; Haynes-Johnson, D.; Lundeen, S.; Sui, Z. *J. Med. Chem.* **2005**, *48*, 2126.

(6) (a) Willemsens, B.; Vervest, I.; Ormerod, D.; Aelterman, W.; Fannes, C.; Mertens, N.; Markó, I. E.; Lemaire, S. *Org. Process Res. Dev.* **2006**, *10*, 1275. (b) Li, X.; Lemaire, S.; Markó, I.; Willemsens, B. WO 2006093719, **2006**.
(7) Li, X.; Branum, S.; Russel, R. K.; Jiang, W.; Sui, Z. *Org. Process Res. Dev.* **2005**, *9*, 640.
(8) Jiang, W.; Sui, Z.; Chen, X. *Tetrahedron Lett.* **2002**, *43*, 8941.
(9) Cox, E. D.; Cook, J. M. *Chem. Rev.* **1995**, *95*, 1797.
(10) To confirm the stereochemistry of compound **3**, the two diastereoisomers *trans*-**3** and *cis*-**3** were prepared in a two-step sequence. Treatment of unprotected L-tryptophan methyl ester with aldehyde **2** leads to the quantitative formation of the corresponding carbolines in a 45:55 *cis*:*trans* ratio. An NMR study allowed the identification of both diastereoisomers without ambiguity. After separation by chromatography, each isomer was benzylated leading to pure compounds *cis*-**3** and *trans*-**3** used as references to assess the *trans* stereochemistry of compound **3** obtained from tryptophan derivative **1**.
(11) For the attribution of the *cis*:*trans* ratio, see: (a) Ungemach, F.; Soerens, D.; Weber, R.; DiPierro, M.; Campos, O.; Mokry, P.; Cook, J. M.; Silverton, J. V. *J. Am. Chem. Soc.* **1980**, *102*, 6976. (b) Bailey, P. D.; Hollinshead, S. P.; McLay, N. R. *Tetrahedron Lett.* **1987**, 5177.
(12) (a) Josse, O.; Labar, D.; Marchand-Brynaert, J. *Synthesis* **1999**, 404. (b) For the mechanism: Belleau, B.; Martel, R.; Lacasse, G.; Menard, M.; Weinberg, N. L.; Perron, Y. G. *J. Am. Chem. Soc.* **1968**, 823. (c) Belleau, B.; Malek, G. *J. Am. Chem. Soc.* **1968**, 1651.
(13) Peng, S.; Guo, M.; Winterfeldt, E. *Liebigs Ann. Chem.* **1993**, 137.
(14) Peng, S.; Zhang, L.; Cai, M.; Winterfeldt, E. *Liebigs Ann. Chem.* **1993**, 141.
(15) **Procedure for Compound 3 (65 mmol scale).**
In a round-bottomed flask charged with toluene (6 L/mol), *N*-benzyl-L-tryptophan methyl ester (1 equiv) and the aromatic aldehyde **2** (1.05 equiv) were added at r.t. Finally, PTSA (0.1 equiv) was added and the reaction mixture was refluxed in a Dean–Stark apparatus for 22 h. After cooling to r.t., sat. aq $NaHCO_3$ (0.2 L/mol) was added. After 15 min of stirring and then separation of the two phases, the organic solvent was evaporated under vacuum. The obtained crude product was purified by crystallisation from *t*-BuOMe (3 L/mol) to afford compound **3** in 73% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.51–7.07 (m, 12 H), 6.72 (d, 1 H, *J* = 8 Hz), 5.39 (s, 1 H), 4.53 (t, 2 H, *J* = 9 Hz), 3.94 (m, 1 H), 3.80 (m, 2 H), 3.61 (s, 3 H), 3.19 (m, 2 H), 3.13 (t, 2 Hz, *J* = 9 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.7, 160.0, 139.7, 136.5, 135.6, 134.0, 128.9, 128.5, 128.3, 127.7, 127.1, 127.0, 125.3, 121.5, 119.3, 118.2, 110.8, 108.9, 71.4, 60.4, 56.1, 54.2, 51.3, 29.6, 24.5. IR: 3388, 1732, 1601, 1488, 1451 cm^{-1}. MS (EI, 70eV): *m/z* = 438.3, 379.4, 347.1, 184.2.
(16) **Procedure for Compound 4 (46 mmol scale).**
Compound **3** (1 equiv) was dissolved in MeOH–THF (6 L/mol; 1:1) at r.t. Then, aq NaOH (3 L/mol, 15% w/w) was added in one portion. After 28 h of stirring at r.t., the organic mixture was acidified to pH 6–7 and extracted by CH_2Cl_2 (5 L/mol). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.20 (br s, 1 H), 7.60 (s, 1 H), 7.43 (d, 1 H, *J* = 8 Hz), 7.21–6.94 (m, 10 H), 6.58 (d, 1 H, *J* = 14 Hz), 5.22 (s, 1 H), 4.40 (t, 2 H, *J* = 9 Hz), 3.88 (m, 1 H), 3.85 (AB, 1 H, *J* = 14 Hz), 3.74 (AB, 1 H, *J* = 14 Hz), 3.13 (d, 2 H, *J* = 5 Hz), 3.00 (t, 2 H, *J* = 9 Hz). Then, at r.t., $(NH_4)_2CO_3$ (3 equiv) and EEDQ (1.1 equiv) were added to the CH_2Cl_2 phase. After a 16 h stirring period, the organic phase was filtered over dicalite. Then the organic layer was washed with H_2O (3 L/mol) and the organic solvent was evaporated under reduced pressure. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.72–7.64 (m, 2 H), 7.40–7.15 (m, 8 H), 6.90–6.64 (m, 4 H), 5.60 (br s, 1 H), 4.90 (s, 1 H), 4.52 (t, 2 H, *J* = 9 Hz), 3.90 (m, 1 H), 3.88 (AB, 1 H, *J* = 4 Hz), 3.66 (AB, 1 H, *J* = 4 Hz), 3.15 (m, 2 H), 3.07 (t, 2 H, *J* = 9 Hz). The obtained primary amide (1 equiv) was dissolved in dry DMF (10 L/mol) at 0 °C. After addition of pyridine (0.7 L/mol), $POCl_3$ (1.2 equiv) was added dropwise to the reaction mixture. After a 2 h stirring period at 0 °C, the reaction mixture was quenched with a $CuSO_4$ aq solution and extracted with CH_2Cl_2. After evaporation of the organic solvent, the obtained solid was purified by crystallization from *t*-BuOMe to afford compound **4** in 50% yield. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.62–7.58 (m, 1 H), 7.47–7.16 (m, 11 H), 6.84 (d, 1 H, *J* = 11 Hz), 4.96 (s, 1 H), 4.76 (t, 2 H, *J* = 11 Hz), 4.19 (AB, 1 H, *J* = 18 Hz), 3.60 (AB, 1 H, *J* = 18 Hz), 3.46–3.20 (m, 2 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 160.4, 137.4, 136.4, 134.3, 131.4, 129.0, 128.6, 128.5, 128.1, 127.7, 126.6, 125.3, 121.9, 119.5, 118.1, 117.2, 110.9, 109.3, 104.8, 71.4, 61.9, 55.4, 48.4, 29.4,25.5. IR: 3388, 2848, 2219, 1612, 1489, 1467, 1453, 1302, 1234 cm^{-1}. MS (EI, 70 eV): *m/z* = 404.4, 260.1, 233.1, 169.1, 91.5.
(17) **Procedure for Compound 5 (1.23 mmol scale).**
Compound **4** (1 equiv) was dissolved in EtOH–pyridine (5 L/mol, 2:1) at r.t. Then, $NaBH_4$ (5 equiv) was added and the reaction mixture was heated to 70 °C for 12 h. A second portion of $NaBH_4$ (5 equiv) was added and the reaction mixture was stirred for additional 12 h at 70 °C. After completion, aq NH_4Cl (5 L/mol) and CH_2Cl_2 (5 L/mol) were added. The organic layers were separated and the organic solvent was evaporated under reduced pressure to afford compound **5** in 97% yield; er 95.7:4.3. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.56–7.03 (m, 11 H), 6.81 (d, 1 H, *J* = 8 Hz), 4.64 (t, 3 H, *J* = 9 Hz), 3.92 (AB, 1 H, *J* = 14 Hz), 3.42 (AB, 1 H, *J* = 14 Hz), 3.35–3.19 (m, 3 H), 3.00–2.61 (m, 3 H). MS (EI, 70 eV): *m/z* = 380.1, 355.1, 261.2, 260.1, 184.1, 91.0, 73.1. IR: 3406, 1614, 1488, 1307, 1241, 981 cm^{-1}.
(18) **Procedure for Compound 6 (2.95 mmol scale).**
See ref. 5f and 6b: ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.63–7.52 (m, 2 H), 7.25–7.02 (m, 5 Hz), 6.73 (d, 1 H, *J* = 8 Hz), 5.08 (s, 1 H), 4.55 (t, 2 H, *J* = 8 Hz), 3.35 (m, 1 H), 3.12 (t, 2 H, *J* = 8 Hz), 3.08 (m, 1 H), 2.85 (m, 2 H), 1.80 (s, 1 H).
(19) **Procedure for Compound 7 (69 mmol scale).**
Compound **6** (1 equiv) was partially dissolved in CH_2Cl_2 (5 L/mol) at r.t. After cooling at 0 °C, Et_3N (1.5 equiv) was added followed by the dropwise addition over 10 min of $(CF_3CO)O$ (1.2 equiv) in CH_2Cl_2 (1 L/mol). After a 0.5 h stirring period, the reaction mixture was quenched with sat. $NaHCO_3$. The organic layer was evaporated under reduced pressure to afford compound **7** in >95% yield.^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.90 (br s, 1 H), 7.54 (d, 1 H, *J* = 7 Hz), 7.32–7.02 (m, 5 H), 6.82 (s, 1 H), 6.69 (d, 1 H, *J* = 8 Hz), 4.55 (t, 2 H, *J* = 9 Hz), 4.08 (m, 1 H), 3.55 (m, 1 H), 3.13 (t, 2 H, *J* = 9 Hz), 2.98 (m, 2 H). ^{13}C NMR (150 MHz, $CDCl_3$): δ = 160.5, 136.3, 130.4, 130.3, 128.9, 127.8, 126.2, 125.6, 122.5, 119.9, 118.2, 111.2, 109.4, 109.2, 71.5, 53.6, 45.9, 29.4, 22.2. ^{19}F NMR (300 MHz, $CDCl_3$): δ = –68.64.
(20) **Procedure for Compound 8 (44 mmol scale).**
Confer ref. 6a, mixture of tautomers: ^{1}H NMR (600 MHz, DMSO-d_6): δ = 10.94 (s, 1 H, 90%), 10.68 (s, 1 H, 10%), 7.62 (m, 1 H), 7.43 (m, 2 H), 7.30 (m, 1 H), 7.06 (s, 1 H), 6.89 (d, 1 H, *J* = 8 Hz), 6.73 (m, 1 H), 6.13 (s, 1 H, 90%), 6.02 (s, 1 H, 10%), 4.51 (t, 2 H, *J* = 9 Hz), 4.42 (m, 1 H), 3.55 (m, 1 H), 3.16 (m, 2 H), 3.02 (m, 1 H), 2.93 (m, 1 H). ^{13}C NMR (150 MHz, DMSO-d_6): δ = 202.2, 168.4, 159.5, 137.9, 136.4, 132.5, 128.0, 127.6, 127.0, 126.7, 126.3, 125.4, 123.9, 108.6, 71.2, 61.8, 44.0, 43.3, 39.8, 39.6, 39.3, 3.09, 29.1.

(21) **Procedure for Compound 9 (12 mmol scale).**
Compound **8** (1 equiv) was dissolved in EtOH (10 L/mol) at r.t. Then, KOH (2 equiv) dissolved in H_2O was added to the reaction mixture. After a 16 h stirring period at r.t., sat. NH_4Cl was added and the reaction mixture was extracted with EtOAc. The evaporation of the organic layer under reduced pressure afforded compound **9** in 90% yield. ^{1}H NMR (400 MHz, DMSO): δ = 11.58 (s, 1 H), 8.13 (d, 1 H, *J* = 7.81 Hz), 7.61–7.53 (m, 2 H), 7.29 (ddd, 1 H, *J* = 8.12, 5.85, 2.14 Hz), 7.17 (s, 1 H), 7.07 (dd, 1 H, *J* = 8.31, 1.76 Hz), 6.73 (d, 1 H, *J* = 8.31 Hz), 5.38 (br s, 1 H), 4.50 (t, 2 H, *J* = 9.06 Hz), 4.18 (dd, 1 H, *J* = 12.97, 2.90 Hz), 4.02 (dd, 1 H, *J* = 12.97, 1.38 Hz), 3.60 (br s, 1 H), 3.13 (t, 2 H, *J* = 8.69 Hz). ^{13}C NMR (100 MHz, DMSO): δ = 173.5, 159.3, 153.9, 140.7, 134.5, 131.0, 127.6, 127.4, 125.2, 124.7, 124.3, 122.7, 118.4, 118.0, 108.6, 71.0, 66.3, 48.9, 29.0.

(22) **Enantioselective Enrichment of Compound 9 (33.35 mol scale).**
Compound **9** (1 equiv) was dissolved in H_2O (2 L/mol) at r.t. Then, aq HCl 34.5% w/w (0.09 L/mol) was dropwise added to the heterogeneous mixture. Afterwards, the reaction mixture was heated at 60 °C and 2-PrOH (0.54 L/mol) was added dropwise. After 30 min, the reaction mixture was cooled down to r.t. and stirred overnight. The reaction mixture was filtered and dried under reduced pressure. The obtained HCl salt was dissolved in EtOH (4 L/mol) at r.t. and aq NH_3 50.5% w/w (0.1 L/mol) was added dropwise. After addition of H_2O (2 L/mol) and seeding with compound **9**, the reaction mixture was stirred for 16 h at r.t. The desired compound **9** was obtained by filtration with an er >99.5:0.5 in 59% yield.

(23) **Procedure for RWJ387273 (2.5 mol scale).**
In degassed THF (10 L/mol) under inert atmosphere, $Pd_2(dba)_3$ (0.04 equiv) was added followed by the addition of (±)-BINAP (0.09 equiv) at r.t. After stirring for 30 min, 2-bromopyridine (1.2 equiv) was added over 10 min. Finally, pyrroloquinolone **1** (1 equiv) and *t*-BuONa (2.5 equiv) were added and the mixture was allowed to warm up to 60 °C and kept at that temperature for 5 h. After cooling to r.t., dicalite (20 g/mol) was added and the mixture was filtered. The cake was washed with THF (2 L/mol). Then, H_2O (8 L/mol) was added to the organic mixture, followed by aq HCl 34.5% w/w (0.275 L/mol). After stirring for 30 min at r.t., EtOAc (4.3 L/mol) was added and the mixture was stirred for another 15 min. The two layers were separated and the organic layer was discarded. Then, EtOAc (5.4 L/mol) was added to the aqueous layer, followed by the addition of aq NH_3 50% w/w (0.26 L/mol). After stirring for 30 min, the aqueous layer was removed and the organic phase was evaporated to dryness. The desired pyrroloquinolone **2** (yield = 135%) was obtained with a quality of 66.1%, corresponding to an active yield of 89.2%. The ee of the *R*-enantiomer was 99%. The product contained 2530 ppm of residual Pd.
The obtained pyrroloquinolone was dissolved in MeOH (80 L/mol) at r.t. After heating to 60 °C, the mixture was stirred for 1 h at this temperature. Then, Norit A Supra (35 g/mol) and dicalite (3.5 g/mol) were added. The mixture was stirred for another 20 min and thereafter filtered. The cake was washed with MeOH (1.7 L/mol). The solvent was reduced to 10%, at 50 °C. Subsequently, MsOH (1.02 equiv), dissolved in MeOH (0.3 L/mol) was added over 10 min to the mixture. Finally, the solution was cooled down to 20 °C and stirred for 20 h. The mixture was filtered and the cake was washed with MeOH (0.5 L/mol). After drying for 45 h, **R290629** were obtained (yield 80.5%) with a HPLC quality of 100% and >99.5:0.5 er. The amount of residual Pd was below 10 ppm.
Free base: ^{1}H NMR (400 MHz, CD_3OD): δ = 8.30 (d, 1 H, *J* = 9.3 Hz), 8.02 (m, 1 H), 7.35 (m, 4 H), 7.10 (m, 3 H), 6.55 (m, 2 H), 4.85 (d, 1 H, *J* = 22.0 Hz), 4.54 (d, 1 H, *J* = 22.0 Hz), 4.40 (t, 2 H, *J* = 9.5 Hz), 2.92 (t, 2 H, *J* = 9.5 Hz).

(24) **Analytical Method.**
The progress of the reaction and the purity of the products were measured by HPLC, employing (Method A: LCC01/209/01/01) a 10 cm Hypersil BDS column (4.0 mm I.D., 3 μm spherical material, UV wavelength of 254 nm) at r.t. The elution gradient was 5% MeCN/95% NH_4OAc (0.5% in H_2O) ramping to 95% MeCN/5% NH_4OAc (0.5% in H_2O) over 16 min, at a flow rate of 1.2 mL/min, then kept 95% MeCN/5% NH_4OAc (0.5% in H_2O) for 3 min. Optical purities were measured by Capillary Electrophoresis employing (Method B: CEO 01/211/01/01) a 57 cm uncoated fused silica column (75 μm I.D., 375 μm O.D., UV wavelength of 200 nm) at 20 °C. The mobile phase consisted of a 50 mM phosphate buffer, at pH 3.0; the chiral selector of 10 mM DM-β-CD. Each run lasted 30 min.