Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters
Tetrahedron Letters 45 (2004) 5167–5170

Synthesis of (±)-aporphine utilizing Pictet–Spengler and intramolecular phenol *ortho*-arylation reactions

Gregory D. Cuny*

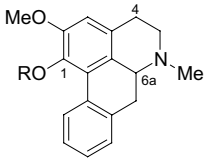
Laboratory for Drug Discovery in Neurodegeneration, Brigham & Women's Hospital and Harvard Medical School, 65 Landsdowne St., Cambridge, MA 02139, USA

Received 21 January 2004; accepted 9 April 2004

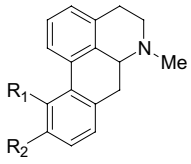
Dedicated to the memory of Dr. John T. Shaw: mentor, scholar and friend

Abstract—A synthesis of the alkaloid (±)-aporphine is reported. The initial key step of the synthesis involves a Pictet–Spengler cyclization of N-tosyl tyramine with 2-bromophenylacetaldehyde in trifluoroacetic acid. This step was followed by the second strategic transformation a palladium-mediated intramolecular phenol *ortho*-arylation reaction utilizing tricyclohexylphosphine as co-catalysts in the presence of cesium carbonate. Finally, de-oxygenation of the phenol, removal of the tosyl group and methylation gave the desired alkaloid.

Aporphines are a structurally diverse class of natural products.[1] Many members of this class of alkaloids also demonstrate interesting and assorted biological activities.[2] A common structural characteristic among many aporphine alkaloids is the presence of hydroxy or alkoxy groups at the 1- and 2-positions of the 5,6,6a,7-tetrahydro-4*H*-dibenzo[*de*,*g*]quinoline ring system. For example, (±)-lirinidine, **1**,[3] and nuciferine, **2**,[4] both contain this structural feature. Recently, syntheses of these two aporphine alkaloids were reported that took advantage of the oxygen functionality at the 1-position in the key synthetic transformation.[5] A palladium-mediated intramolecular phenol *ortho*-arylation was employed.[6,7] However, other members of this alkaloid class do not contain oxygen functionality at the 1- or 2-positions, for example, (±)-aporphine, **3**, and (±)-apocodeine, **4**. Herein is reported a synthesis of **3**[8] that utilizes a Pictet–Spengler cyclization for the construction of a crucial intermediate followed by an intramolecular phenol *ortho*-arylation reaction with subsequent removal of the oxygen functionality.



1 R = H
2 R = Me



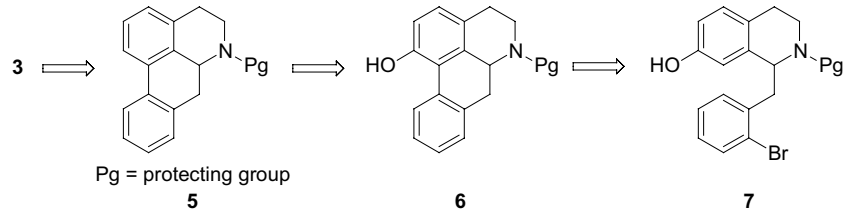
3 R_1 = H; R_2 = H
4 R_1 = OH; R_2 = OMe

A retrosynthetic analysis of **3** is shown is Scheme 1. Disconnection of the methyl amine of **3** gives a protected nor-aporphine **5**. This material was envisioned to arise from phenol **6** through a de-oxygenation reaction. The 1-hydroxyaporphine derivative **6** was anticipated to evolve from a benzyl tetrahydroisoquinoline derivative **7** employing an intramolecular phenol *ortho*-arylation reaction.

The initial task was the construction of the requisite benzyl tetrahydroisoquinoline derivative **7**. In the syntheses of **1** and **2** similar compounds (Pg = CO_2Me) were prepared utilizing a Bischler–Napieralski cyclization followed by reduction of the resulting imine and conversion of the amine to a methyl carbamate.[5] However, with Bischler–Napieralski substrate **8** that lacks an alkoxy group para to the site of cyclization, the reaction

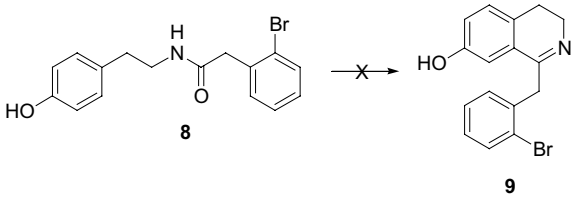
Keywords: Pictet–Spengler; Palladium; *ortho*-Arylation; Phenol; Aporphine.
* Tel.: +1-617-768-8640; fax: +1-617-768-8606; e-mail: gcuny@rics.bwh.harvard.edu

0040-4039/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2004.04.194



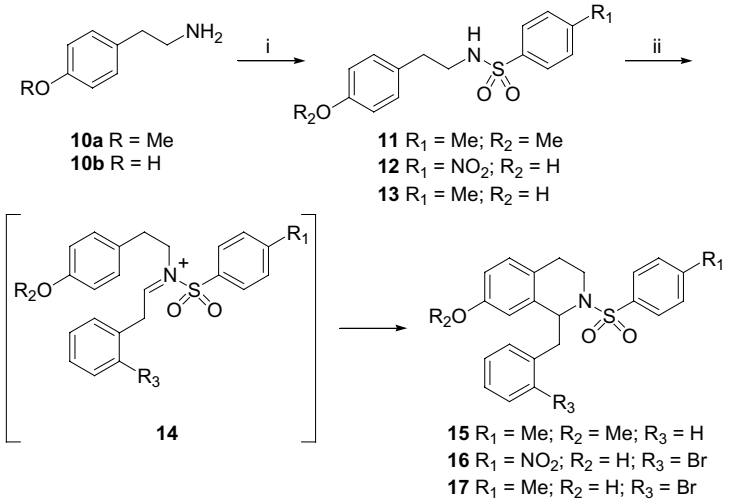
Scheme 1.

failed ($POCl_3$, CH_3CN, 65 °C) to give imine **9**. Therefore, an alternative route was pursued.

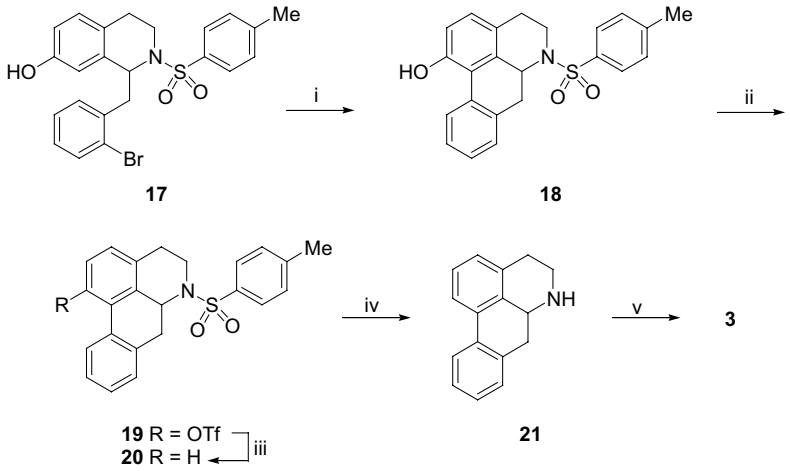


Barn et al. has recently shown that tetrahydroisoquinolines that lack electron-donating groups on the aryl ring could be prepared utilizing a Pictet–Spengler reaction between phenethylamine sulfonamides and aliphatic aldehydes in warm trifluoroacetic acid (TFA).[9] In pursuit of testing this strategy 4-methoxyphenethylamine, **10a**, was readily converted to sulfonamide **11** in DMF and in the presence of *i*-Pr_2EtN in excellent yield (Scheme 2). The sulfonamide was allowed to react with phenylacetaldehyde in TFA at 70 °C for 5 h to give the tetrahydroisoquinoline derivative **15** in 69% yield, presumably through an intermediate such as **14**. Having demonstrated the effectiveness of this strategy for the synthesis of benzyl tetrahydroisoquinolines it was next applied towards the synthesis of (±)-aporphine. Tyramine, **10b**, was first converted to sulfonamides **12** and **13**. These materials were allowed to react with 2-bromophenylacetaldehyde (generated at room temperature from 2-bromophenethyl alcohol with PCC in dichloromethane for 1.5 h)[10] to give the tetrahydroisoquinoline derivatives **16** and **17** in moderate yields.[11]

An intramolecular phenol *ortho*-arylation reaction was attempted with sulfonamides **16** and **17** utilizing previously developed conditions, substoichiometric quantities of palladium acetate (20 mol %) and tricyclohexylphosphine (Cy_3P; 40 mol %) in the presence of cesium carbonate (3.2 equiv) in dimethylacetamide (DMA) at 110 °C for 24 h (Scheme 3).[5,12] In the case of **16** no isolatable product was obtained, apparently due to instability of the *p*-nitrosulfonamide to the basic reaction conditions. However, the tosylsulfonamide **17** readily cyclized to give the aporphine derivative **18** in moderate yield.[13] The hydroxyl group was next converted quantitatively to the aryl triflate **19** in the presence of trifluoromethanesulfonic anhydride (Tf_2O) and 2,6-lutidine in dichloromethane. The aryl triflate was reduced using palladium acetate (10 mol %), a phosphine ligand (10 mol %) and triethylammonium formate at 80 °C.[14] Utilizing triphenylphosphine as ligand gave **20** in low yield (33%). However, with 1,1′-bis(diphenylphosphino)ferrocene (DPPF) as the ligand the yield of **20** was improved to 77%. The tosylamide **20** was reduced using sodium naphthalenide to give **21** in 89% yield.[15] In this reaction, a solution of **20** in dimethoxyethane (DME) was titrated with a dark-green solution of sodium naphthalenide (prepared by stirring a mixture of sodium and naphthalene in DME at room temperature for 3 h)



Scheme 2. Reagents and conditions: (i) 4-R–$PhSO_2Cl$ (R = NO_2 or Me), *i*-Pr_2EtN, DMF, rt, 2 h, 93%; (ii) 2-R–$PhCH_2CHO$ (R = H or Br), 70 °C, 5 h, 51–69%.



Scheme 3. Reagents and conditions: (i) $Pd(OAc)_2$ (20 mol%), Cy_3P (40 mol%), Cs_2CO_3, DMA, 110 °C, 24 h, 56%; (ii) Tf_2O, 2,6-lutidine, CH_2Cl_2, 0 °C, 30 min, 100%; (iii) $Pd(OAc)_2$ (10 mol%), DPPF (10 mol%), Et_3N, HCO_2H, DMF, 80 °C, 24 h, 77%; (iv) Na, N_pH, DME, −56 °C, <5 min, 89%; (v) 37% aq CH_2O, MeOH, rt, 30 min then $NaBH_4$, rt, 1 h, 84%.

at −56 °C. After the endpoint was reached (indicted by a persistent green colour) the reaction mixture was immediately quenched with a saturated aqueous solution of sodium bicarbonate and the resulting mixture was allowed to quickly warm to room temperature. Finally, the amine **21** was converted to (±)-aporphine, **3**, in 84% yield by reductive amination with 37% aqueous formaldehyde in the presence of sodium borohydride.[16] The ^1H NMR spectra of the synthetic product was identical to that previously reported for the natural product.[8a]

In conclusion, a strategy for synthesizing aporphine alkaloids that lack oxygen functionality at the 1- or 2-positions of the 5,6,6a,7-tetrahydro-4*H*-dibenzo-[*de*,*g*]quinoline ring system was described and applied to the synthesis of (±)-aporphine. A Pictet–Spengler cyclization of N-tosyl tyramine with 2-bromophenylacetaldehyde was utilized for assembling a vital benzyl tetrahydroisoquinoline intermediate. Next, a palladium-mediated intramolecular phenol *ortho*-arylation reaction employing tricyclohexylphosphine as co-catalysts in the presence of cesium carbonate provided an aporphine precursor, which was readily converted to the natural product. Further applications of transition-metal mediated intramolecular phenol *ortho*-arylations for the synthesis of other aporphine alkaloids as well as other classes of natural and nonnatural compounds are underway.

Acknowledgements

Financial support was provided by the Harvard Center for Neurodegeneration and Repair (HCNR).

References and notes

1. Ríos, J. L.; Máñez, S.; Giner, R. M.; Recio, M. C. In *The Alkaloids*; Cordell, G. A., Ed.; Academic: New York, 2000; Vol. 53, pp 57–117.
2. Guinaudeau, H.; Lebœuf, M.; Cavé, A. *J. Nat. Prod.* **1994**, *57*(8), 1033–1135, and reference cited therein.
3. (a) Phillipson, J. D.; Thomas, O. O.; Gray, A. I.; Sariyar, G. *Planta Med.* **1981**, *41*(2), 105–118; (b) Ziyaev, R.; Abdusamatov, A.; Yunusov, S. Y. *Chem. Nat. Prod. (Engl. Transl.)* **1973**, (6), 727–729; *Khimiya Prirodnykh Soedinenii* **1973**, (6), 760–763.
4. Věžník, F.; Táborská, E.; Sedmera, P.; Dolejš, L.; Slavík, J. *Collect. Czech. Chem. Commun.* **1986**, *51*(8), 1752–1763.
5. Cuny, G. D. *Tetrahedron Lett.* **2003**, *44*(44), 8149–8152.
6. For examples of Pd-mediated *ortho*-arylation reactions see: (a) Kitamura, M.; Ohmori, K.; Kawase, T.; Suzuki, K. *Angew. Chem., Int. Ed.* **1999**, *38*(9), 1229–1232; (b) Satoh, T.; Inoh, J.; Kawamura, Y.; Kawamura, Y.; Miura, M.; Nomura, M. *Bull. Chem. Soc. Jpn.* **1998**, *71*(9), 2239–2246; (c) Satoh, T.; Kawamura, Y.; Miura, M.; Nomura, M. *Angew. Chem., Int. Ed.* **1997**, *36*, 1740–1742; (d) Hennings, D. D.; Iwasa, S.; Rawal, V. *J. Org. Chem.* **1997**, *62*(1), 2–3; (e) Wiegand, S.; Schäfer, H. J. *Tetrahedron* **1995**, *51*(18), 5341–5350.
7. For examples of Rh-mediated *ortho*-arylation reactions see: (a) Bedford, R. B.; Limmert, M. E. *J. Org. Chem.* **2003**, *68*(22), 8669–8682; (b) Bedford, R. B.; Coles, S.; Hursthouse, M. B.; Limmert, M. E. *Angew. Chem., Int. Ed.* **2003**, *42*(1), 112–114; (c) Oi, S.; Watanabe, S.; Fukita, S.; Inoue, Y. *Tetrahedron Lett.* **2003**, *44*(48), 8665–8668.
8. For other syntheses of aporphine see: (a) Hedberg, M. H.; Linnanen, T.; Jansen, J. M.; Nordvall, G.; Hjorth, S.; Unelius, L.; Johansson, A. M. *J. Med. Chem.* **1996**, *39*(18), 3503–3513; (b) Cannon, J. G.; Raghupathi, R.; Moe, S. T.; Johnson, A. K.; Long, J. P. *J. Med. Chem.* **1993**, *36*(10), 1316–1318; (c) Gadamer, J.; Oberlin, M.; Schoeler, A. *Arch. Pharm.* **1925**, *263*, 81–99.
9. Barn, D. R.; Caulfield, W. L.; Cottney, J.; McGurk, K.; Morphy, J. R.; Rankovic, Z.; Roberts, B. *Bioorg. Med. Chem.* **2001**, *9*(10), 2609–2624.
10. Hartman, G. D.; Phillips, B. T.; Halczenko, W. *J. Org. Chem.* **1985**, *50*(14), 2423–2427.
11. A mixture of **13** (1.45 g, 5.0 mmol) and 2-bromophenylacetaldehyde (1.97 g, 10 mmol)[10] in TFA (8.5 mL) was heated at 70 °C for 5 h. The reaction mixture was allowed to cool and then concentrated to a dark oil. The oil was suspended in water (50 mL) and solid sodium bicarbonate was carefully added (CAUTION: gas evolution!) in small portions until the mixture was neutralized. The mixture was extracted with ethyl acetate (2 × 100 mL). The organic

extracts were combined, washed with brine (50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. The product was purified by column chromatography on silica gel using hexane/ethyl acetate (70:30) as eluant to give 1.31 g of **17** (55%) as a pale yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.32 (s, 3H); 2.56–2.60 (m, 1H); 2.69–2.76 (m, 1H); 3.11–3.22 (m, 2H); 3.57–3.63 (m, 1H); 3.88 (ddd, 1H, $J_1 = 14.0$ Hz, $J_2 = 6.0$ Hz, $J_3 = 2.0$ Hz); 4.65 (b s, 1H); 5.24 (dd, 1H, $J_1 = 9.5$ Hz, $J_2 = 5.0$ Hz); 6.53 (d, 1H, $J = 3.0$ Hz); 6.62 (dd, 1H, $J_1 = 8.0$ Hz, $J_2 = 2.5$ Hz); 6.86 (d, 1H, $J = 8.5$ Hz); 7.03 (d, 2H, $J = 8.5$ Hz); 7.10 (d, 2H, $J = 8.0$ Hz); 7.20 (dt, 1H, $J_1 = 7.5$ Hz, $J_2 = 1.5$ Hz); 7.39 (dd, 2H, $J_1 = 7.5$ Hz, $J_2 = 1.5$ Hz); 7.47 (d, 1H, $J = 8.0$ Hz); ^{13}C NMR (100.5 MHz, $CDCl_3$): δ 21.69, 26.38, 39.50, 43.55, 56.18, 113.63, 114.79, 125.31, 125.47, 127.31, 127.52, 128.58, 129.52, 130.33, 132.34, 132.91, 137.13, 137.28, 143.05, 153.77; HRESMS $[M+Na]^+$: 494.0396 (calculated for $[C_{23}H_{22}BrNO_3S+Na]^+$: 494.0396). Compound **16** was prepared in a similar manner in 51% yield as a white solid. ^{1}H NMR (400 MHz, d_6-acetone): δ 2.63–2.81 (m, 2H); 3.15–3.26 (m, 2H); 3.58–3.86 (m, 1H); 4.01–4.06 (m, 1H); 5.33 (dd, 1H, $J_1 = 9.6$ Hz, $J_2 = 5.2$ Hz); 6.66 (dd, 1H, $J_1 = 8.0$ Hz, $J_2 = 2.4$ Hz); 6.77 (d, 1H, J = 2.4 Hz); 6.87 (d, 1H, $J = 8.4$ Hz); 7.10–7.23 (m, 3H); 7.47 (dd, 1H, $J_1 = 7.6$ Hz, $J_2 = 0.8$ Hz); 7.72 (d, 2H, $J = 8.8$ Hz); 8.14 (d, 2H, $J = 8.8$ Hz); 8.29 (s, 1H); ^{13}C NMR (100.5 MHz, d_6-acetone): δ 26.94, 40.19, 43.48, 57.17, 113.76, 115.70, 124.35, 124.87, 125.34, 128.43, 128.97, 129.50, 130.98, 133.26, 133.44, 137.59, 138.08, 147.17, 150.52, 156.45. Compound **15** was prepared in a similar manner (eluent was hexane/ethyl acetate 85:15) in 69% yield as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.34 (s, 3H); 2.42–2.47 (m, 1H); 2.59–2.66 (m, 1H); 3.07 (dd, 1H, $J_1 = 14.0$ Hz, $J_2 = 6.5$ Hz); 3.19 (dd, 1H, $J_1 = 13.5$ Hz, $J_2 = 6.5$ Hz); 3.39–3.45 (m, 1H); 3.56–3.60 (m, 1H); 3.61 (s, 3H); 5.16 (t, 1H, $J = 7.0$ Hz); 6.23 (d, 1H, $J = 3.0$ Hz); 6.67 (dd, 1H, $J_1 = 8.5$ Hz, $J_2 = 2.5$ Hz); 6.87 (d, 1H, $J = 8.5$ Hz); 7.04–7.06 (m, 2H); 7.11 (d, 2H, $J = 7.5$ Hz); 7.20–7.24 (m, 3H); 7.49 (d, 2H, $J = 7.5$ Hz).

12. For an example of a Pd-mediated intramolecular aniline *ortho*-arylation utilizing trialkylphosphines see: Harayama, T.; Hori, A.; Abe, H.; Takeuchi, Y. *Heterocycles* **2003**, *60*(11), 2429–2434.
13. A mixture of **17** (271 mg, 0.576 mmol), tricyclohexylphosphine (69 mg, 0.246 mmol), anhydrous cesium carbonate (600 mg, 1.84 mmol, finely ground powder) and palladium acetate (28 mg, 0.123 mmol) in DMA (10 mL) under an argon atmosphere was heated at 110 °C for 24 h. The reaction mixture was allowed to cool and then carefully diluted with 1 N HCl (50 mL). The reaction mixture was extracted with ethyl acetate (3 × 50 mL). The organic extracts were combined, washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The product was purified by column chromatography on silica gel using CH_2Cl_2/hexane/ethyl acetate (60:35:5) as eluant to give 125 mg of **18** (56%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.31–2.36 (m, 1H); 2.38 (s, 3H); 2.44–2.47 (m, 1H); 3.03 (t, 1H, $J = 13.5$ Hz); 3.16 (dd, 1H, $J_1 = 14.5$ Hz, $J_2 = 4.0$ Hz); 3.24 (dt, 1H, $J_1 = 12.8$ Hz, $J_2 = 2.5$ Hz); 4.07–4.12 (m, 1H); 4.66 (dd, 1H, $J_1 = 14.0$ Hz, $J_2 = 4.5$ Hz); 5.31 (b s, 1H); 6.75 (d, 1H, $J = 8.0$ Hz); 6.85 (d, 1H, $J = 8.0$ Hz); 7.23–7.29 (m, 3H); 7.34–7.37 (m, 2H); 7.69 (d, 2H, $J = 8.0$); 8.15 (d, 1H, $J = 8.0$ Hz); ^{13}C NMR (100.5 MHz, $CDCl_3$): δ 21.70, 28.24, 37.65, 41.25, 53.72, 116.15, 121.10, 125.86, 127.11, 127.19, 127.39, 127.92, 128.94, 129.16, 130.07, 131.58, 134.20, 136.68, 138.16, 143.54, 151.44; HRESMS $[M+Na]^+$: 414.1127 (calculated for $[C_{23}H_{21}NO_3S+Na]^+$: 414.1134).
14. Cacchi, S.; Ciattini, P. G.; Morera, E.; Ortar, G. *Tetrahedron Lett.* **1986**, *27*(45), 5541–5544.
15. Heathcock, C. H.; Blumenkopf, T. A.; Smith, K. M. *J. Org. Chem.* **1989**, *54*(7), 1548–1562.
16. Bick, I. R. C.; Sevenet, T.; Sinchai, W.; Skelton, B. W.; White, A. H. *Aust. J. Chem.* **1981**, *34*(1), 195–207.