A convenient formation of aporphine core via benzyne chemistry: conformational analysis and synthesis of (*R*)-aporphine

Givago P. Perecim, Alessandro Rodrigues, Cristiano Raminelli

PII: S0040-4039(15)30280-X
DOI: http://dx.doi.org/10.1016/j.tetlet.2015.10.083
Reference: TETL 46912

To appear in: *Tetrahedron Letters*

Received Date: 24 September 2015
Revised Date: 21 October 2015
Accepted Date: 26 October 2015

Please cite this article as: Perecim, G.P., Rodrigues, A., Raminelli, C., A convenient formation of aporphine core via benzyne chemistry: conformational analysis and synthesis of (*R*)-aporphine, *Tetrahedron Letters* (2015), doi: http://dx.doi.org/10.1016/j.tetlet.2015.10.083

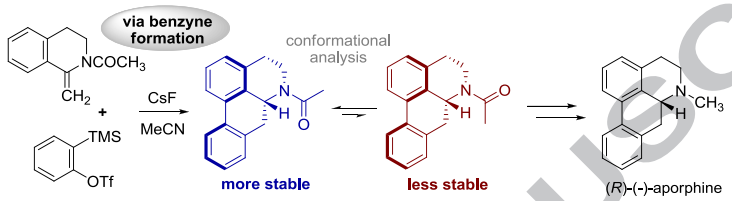
Graphical Abstract

∗To create your abstract, type over the instructions in the template box below.
Fonts or abstract dimensions should not be changed or altered.

A convenient formation of aporphine core via benzyne chemistry: conformational analysis and synthesis of (*R*)-aporphine

Leave this area blank for abstract info.

Givago P. Perecim, Alessandro Rodrigues, Cristiano Raminelli*



∗ Corresponding author. Tel.: +55 11 3385 4137; fax: +55 11 4043 6428; e-mail: raminelli@unifesp.br

Tetrahedron Letters
journal homepage: www.elsevier.com

A convenient formation of aporphine core via benzyne chemistry: conformational analysis and synthesis of (*R*)-aporphine

Givago P. Perecim, Alessandro Rodrigues, Cristiano Raminelli*

Instituto de Ciências Ambientais, Químicas e Farmacêuticas, Universidade Federal de São Paulo, Rua Prof. Artur Riedel, 275, Diadema 09972-270, SP, Brazil

ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
(*R*)-aporphine
Aporphine core
Benzyne chemistry
Conformational analysis
1D gradient NOE experiment

ABSTRACT

Total synthesis of (*R*)-aporphine has been accomplished by an approach that employs in the key step a sequence of transformations involving a [4+2] cycloaddition reaction followed by a hydrogen migration, leading to aporphine core in good yield, which was subjected to a 1D gradient NOE experiment, conformational analysis, and simple transformations, including a small scale resolution process, to afford enantiomerically enriched aporphine alkaloid.

* Corresponding author. Tel.: +55 11 3385 4137; fax: +55 11 4043 6428; e-mail: raminelli@unifesp.br

Aporphine alkaloids compose a class of isoquinoline alkaloids which can be found in several families of plants.[1] Considering structural features, aporphine skeletons are constituted by four rings (A-D), with a nitrogen atom present in the B ring. Besides, aporphine alkaloids can be classified into at least five groups, namely, aporphines, oxoaporphines, aristolactams, azafluoranthenes and proaporphines.[2]

From the pharmacological perspective, aporphinoids present important biological properties, involving, for example, anti-HIV activity,[3] anticancer activity,[4] and dopaminergic activities.[5] In this sense, (*R*)-(-)-apomorphine hydrochloride, an example of an aporphine prototype, has currently been employed in erectile dysfunction treatment[6] and Parkinson's disease therapy.[7]

Taking into account the pharmacological properties exhibited by aporphinoids, several synthetic approaches have been reported allowing access to aporphine cores.[8-11] The most widespread approaches are those based on biosynthetic routes, having in common the formation of the C ring, employing 1-benzyltetrahydroisoquinoline intermediates,[8-10] which are well exemplified by the Pschorr reaction.[8] In addition, over the last decades, approaches based on benzyne chemistry, involving reactions between 1-methyleneisoquinolines and arenediazonium-2-carboxylates, which provide dehydroaporphines in moderate yields, have experienced a remarkable development.[11] However, the formation of dehydroaporphines can be pointed as a negative aspect related with the use of arynes to synthesize aporphinoids, once the reduction of dehydroaporphines to aporphines is not a well-documented transformation and the procedures reported in the literature involve expensive metal[9d] or harsh conditions.[9e] Moreover, some researchers have discouraged the use of arenediazonium-2-carboxylates for safety reasons.[11a] In this context, our research group has explored an approach that employs reactions between isoquinoline derivatives and silylaryl triflates in the presence of CsF, providing aporphine cores instead of dehydroaporphines, under mild reaction conditions, through [4+2] cycloaddition reactions followed by hydrogen migrations,[12] in total syntheses of aporphine alkaloids (**Figure 1**).

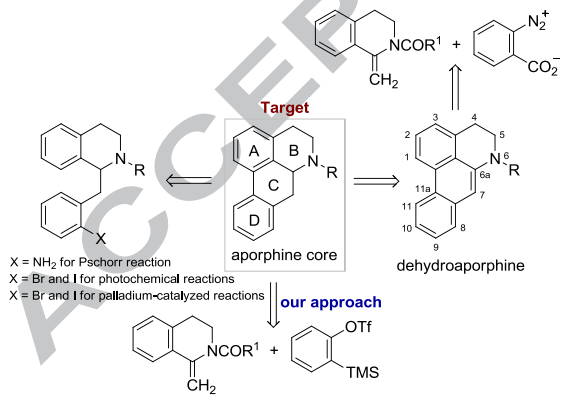
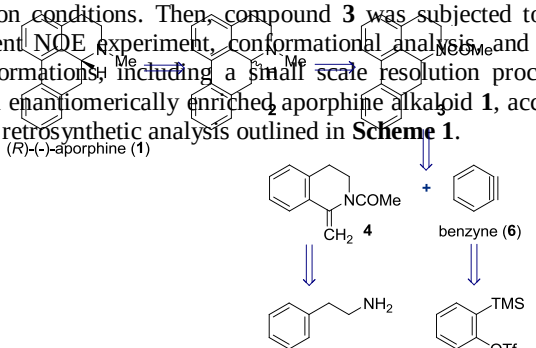


Figure 1. Approaches to produce aporphine compounds.

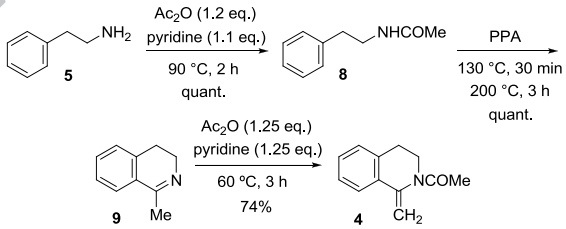
Accordingly, herein we wish to report the total synthesis of (*R*)-aporphine (**1**), employing as key step the reaction between 1-methyleneisoquinoline (**4**), which can be considered a relatively nonpolar diene, and 2-(trimethysilyl)phenyl triflate (**7**) in the presence of CsF, to produce aporphine core **3**, under mild reaction conditions. Then, compound **3** was subjected to a 1D gradient NOE experiment, conformational analysis, and simple transformations, including a small scale resolution process, to afford enantiomerically enriched aporphine alkaloid **1**, according to the retrosynthetic analysis outlined in **Scheme 1**.



Scheme 1. Retrosynthetic analysis for (*R*)-aporphine (**1**).

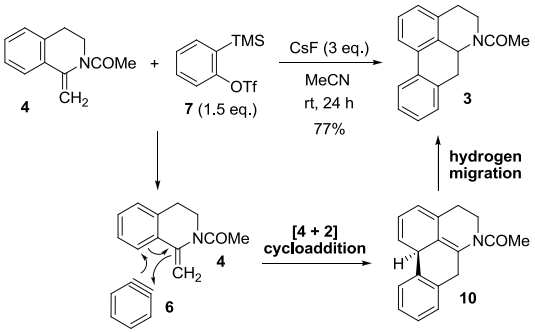
(*R*)-Aporphine (**1**) was planned by small scale resolution process from (±)-aporphine (**2**) obtained by transformations employing aporphine core **3** achieved by [4+2] cycloaddition reaction followed by hydrogen migration between 1-methyleneisoquinoline **4** and benzyne **6** formed under mild reaction conditions (**Scheme 1**).

Intermediate **4** was obtained by minor modifications of well-established transformations.[13-14] Commercially available amine **5** was allowed to react with acetic anhydride in pyridine, leading to the formation of the corresponding amide **8** in quantitative yield.[13] Amide **8** was converted by Bischler-Napieralski reaction to heterocyclic intermediate **9** in a quantitative yield.[13] Compound **9** was treated with acetic anhydride in pyridine to produce intermediate **5** in an isolated yield of 74%[14] (**Scheme 2**).



Scheme 2. Synthesis of intermediate **5**.

Allowing the reaction between isoquinoline derivative **4** and 1.5 equiv of benzyne precursor **7** in the presence of 3 equiv of CsF at room temperature for 24 h, intermediate **3** was obtained in an isolated yield of 77%. In this transformation, compounds **4** and **7** were partially recovered and the corresponding dehydroaporphine was not observed (**Scheme 3**).



Scheme 3. Preparation and proposed mechanisms for the aporphine core **3**.

Reaction involving relatively nonpolar diene **4** and benzyne **6** resulted in compound **3** presumably by a sequence of transformations involving a [4+2] cycloaddition reaction followed by a hydrogen migration (**Scheme 3**).

By performing ^{1}H and ^{13}C NMR spectra for intermediate **3**, we observed a mixture of rotamers or diastereomers in $CDCl_3$

solution at room temperature (please, see Supplementary Material). To distinguish between the existence of rotamers or diastereomers, we carried out a 1D gradient NOE experiment for compound **3**, in $CDCl_3$ solution at room temperature, irradiating one of two signals corresponding to hydrogens attached to the 6a position and observed two negative peaks at 5.31 ppm (**A**) and 4.78 ppm (**B**), confirming the existence of equilibrating rotamers, instead of a mixture of diastereomers, in a ratio of 2:1 (**Figure 2**).[15]

Figure 2. 1D gradient NOE experiment for the compound **3** in $CDCl_3$ solution at room temperature in a NMR spectrometer operating at 600 MHz.

In an attempt to understand the fluxional behavior of **3** in solution, we carried out a computational analysis to identify energetically viable conformers for **3**.[16] Conformational analysis was performed by DFT calculations at M062X/6-311+G(d,p) theory level employing SCIPCM method to evaluate the solvent effect.[17] Taking into consideration the conformational equilibrium, rotamer **3a** appeared as the global energy minimum with populations of 65.7 and 68.2% in the gas phase and chloroform, respectively (**Figure 3**). Conversion of rotamer **3a** to rotamer **3d**, the second most stable conformer, presenting populations of 34.2% and 31.8% in the gas phase and chloroform, respectively, takes place through rotamers **3b** and **3c**, i.e., two other less stable local minima (**Figure 3**). In addition, B ring flipping (**3a** to **3b** and **3c** to **3d**) and the rotation around the N–CO bond (**3a** to **3d** and **3b** to **3c**) are presented in **Figure 3**.

Figure 3. Conformational analysis for the aporphine core **3**.

Boltzmann distribution calculations provided a ratio of 2:1 for rotamers **3a** and **3d**, respectively, both in the gas phase and chloroform, which is according to the ratio obtained by ^{1}H NMR experiment performed in $CDCl_3$. Similar dipole moment values, namely, 3.7 and 3.5 D, calculated for structures **3a** and **3d**, respectively, can give some support to the absence of solvent effect observed.

A gradual increase in energy was observed when the dihedral angle (C^1–C^{16}–C^{15}–C^{14}) of biphenyl system present in the rotamer **3a** was varied from -23° to +6° (**Figure 4a**). Structure optimizations for the boat conformer **3e** showed relatively high energies in gas phase and chloroform (**Figure 4b**).

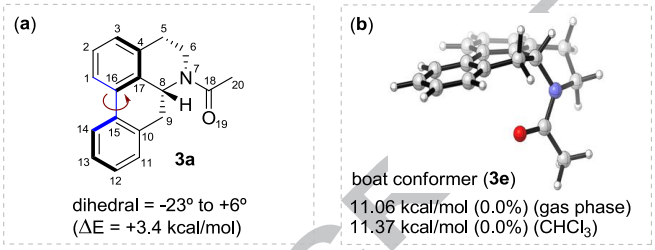
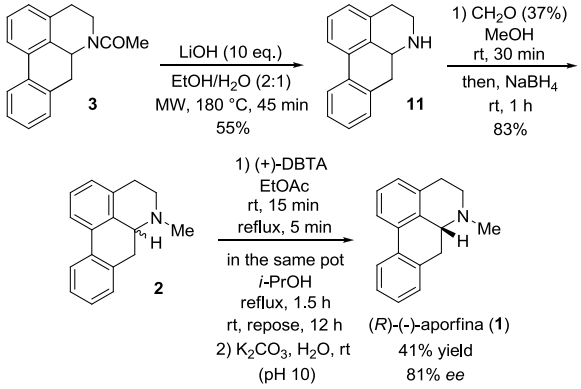


Figure 4. (**a**) Variation of axial dihedral angle for the rotamer **3a**. (**b**) Energies for the boat conformer **3e** in the gas phase and chloroform.

Total synthesis of (*R*)-(-)-aporphine (**1**) was archived from aporphine core **3** by modifications of published procedures.[18-20] (±)-Noraporphine (**11**) was obtained by hydrolysis of intermediate **3** employing lithium hydroxide in a mixture of ethanol/water (2:1) under microwave heating in a moderate yield of 55%.[18] Compound **11** was *N*-alkylated by reaction with a 37% aqueous solution of formaldehyde followed by reduction with sodium borohydride, to afford (±)-aporphine (**2**) in 83% yield.[19] Alkaloid **2** was subjected to a small scale resolution process employing (+)-DBTA,[20] which provided (*R*)-(-)-aporphine (**1**) in an isolated yield of 41% and with 81% *ee* (**Scheme 4**).



Scheme 4. Synthesis of (*R*)-(-)-aporphine (**1**).

The structures of compounds **1**, **2**, **4**, **8**, **9**, and **11** were assigned according to their GC/MS, IR, ^{1}H and ^{13}C NMR spectra. The structure of compound **3** was assigned according to its GC/MS, IR, ^{1}H, ^{13}C, DEPT, COSY, and HSQC NMR spectra. All substances produced (**1**-**4**, **8**, **9**, and **11**) are known and their spectral data are in accordance with those already published.

In summary, we have employed a concise route toward the synthesis of (*R*)-(-)-aporphine (**1**). Our approach involves the formation of aporphine core (**3**) by reaction between relatively nonpolar isoquinoline derivative (**4**) and 2-(trimethysilyl)phenyl triflate (**7**) promoted by CsF. The formation of aporphine core (**3**) proceeded under mild reaction conditions and in good yield presumably through [4+2] cycloaddition reaction followed by hydrogen migration. 1D gradient NOE experiment and conformational analysis provided significant details about structural features for compound **3**. The chemistry disclosed

represents an advance for the synthesis of aporphine alkaloids emerging as a trustworthy alternative to produce aporphinoids.

Acknowledgments

We are grateful to FAPESP (Brazil) (Fundação de Amparo à Pesquisa do Estado de São Paulo - Brazil) for financial support. G.P.P. thanks CAPES (Brazil) (Coordenação de Aperfeiçoamento de Pessoal de Nível Superior - Brazil) for fellowship.

References and notes

1. (a) *Natural Compounds (Alkaloids): Plant Sources, Structure and Properties*; Azimova, S. S.; Yunusov, M. S., Eds.; Springer: New York, 2013; pp 336. (b) Osorio, E. J.; Robledo, S. M.; Bastida, J. In *The Alkaloids*; Cordell, G. A., Ed.; Academic Press: San Diego, 2008; Vol. 66, pp 126.
2. Shamma, M.; Guinaudeau, H. *Nat. Prod. Res.* **1984**, 201.
3. (a) Singh, I. P.; Bodiwala, H. S. *Nat. Prod. Rep.* **2010**, *27*, 1781. (b) Kashiwada, Y.; Aoshima, A.; Ikeshiro, Y.; Chen, Y.-P.; Furukawa, H.; Itoigawa, M.; Fujioka, T.; Mihashi, K.; Cosentino, L. M.; Morris-Natschke, S. L.; Lee, K.-H. *Bioorg. Med. Chem.* **2005**, *13*, 443.
4. (a) Wiart, C. *Lead Compounds from Medicinal Plants for the Treatment of Cancer*; Academic Press: Waltham, 2013, pp 35. (b) Suresh, H. M.; Shivakumar, B.; Shivakumar, S. I. *Int. J. Plant Res.* **2012**, *2*, 57. (c) Ponnala, S.; Chaudhary, S.; González-Sarrias, A.; Seeram, N. P.; Harding, W. W. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 4462. (d) Stévigny, C.; Bailly, C.; Quetin-Leclercq, J. *Curr. Med. Chem. Anti-Cancer Agents*, **2005**, *5*, 173.
5. (a) Booth, R. G. In *Foye´s Principles of Medicinal Chemistry*, 7th ed; Lemke, T. L.; Williams, D. A.; Roche, V. F.; Zito, S. W., Eds.; Lippincott Williams & Wilkins: Philadelphia, 2013, pp 430. (b) Zhang, A.; Zhang, Y.; Branfman, A. R.; Baldessarini, R. J.; Neumeyer, J. L. *J. Med. Chem.* **2007**, *50*, 171.
6. (a) Eardley, I.; Donatucci, C.; Corbin, J.; El-Meliegy, A.; Hatzimouratidis, K.; McVary, K.; Munarriz, R.; Lee, S. W. J. *Sex. Med.* **2010**, *7*, 524. (b) Hatzimouratidis, K.; Amar, E.; Eardley, I.; Giuliano, F.; Hatzichristou, D.; Montorsi, F.; Vardi, Y.; Wespes, E. *Eur. Urol.* **2010**, *57*, 804. (c) Hatzimouratidis, K.; Hatzichristou, D. G. *Drugs* **2005**, *65*, 1621. (d) Hatzichristou, D. G.; Pescatori, E. S. *BJU Int.* **2001**, *88*, 11.
7. (a) Tyne, H. L.; Parsons, J.; Sinnott, A.; Fox, S. H.; Fletcher, N. A.; Steiger, M. J. *J. Neurol.* **2004**, *251*, 1370. (b) Poewe, W.; Wenning, G. K. *Mov. Disord.* **2000**, *15*, 789.
8. (a) Li, J. J. *Name Reactions: A Collection of Detailed Mechanisms and Synthetic Applications*, 4th ed; Springer-Verlag: Berlin-Heidelberg, 2009, pp 450. (b) Smith, M. B.; March, J. *March's Advanced Organic Chemistry: Reactions, Mechanisms and Structure*, 6th ed; John Wiley & Sons: Hoboken, 2007, pp 925. (c) Laali, K. K.; Shokouhimehr, M. *Curr. Org. Synth.* **2009**, *6*, 193. (d) Leake, P. H. *Chem. Rev.* **1956**, *56*, 27.
9. For photochemical reactions, please see: (a) Bach, T.; Hehn, J. P. *Angew. Chem. Int. Ed.* **2011**, *50*, 1000. (b) Chuang, T.-H.; Li, C.-F.; Lee, H.-Z.; Wen, Y.-C. *J. Org. Chem.* **2013**, *78*, 4974. (c) Barolo, S. M.; Teng, X.; Cuny, G. D.; Rossi, R. A. *J. Org. Chem.* **2006**, *71*, 8493. (d) Lenz, G. R. *J. Org. Chem.* **1988**, *53*, 4447. (e) Cava, M. P.; Stern, P.; Wakisaka, K. *Tetrahedron* **1973**, *29*, 2245. (f) Kupchan, S. M.; Moniot, J. L.; Kanojia, R. M.; O´Brien, J. *J. Org. Chem.* **1971**, *36*, 2413.
10. For palladium-catalyzed reactions, please see: (a) Hellal, M.; Singh, S.; Cuny, G. D. *Tetrahedron* **2012**, *68*, 1674. (b) Lee, K. M.; Kim, J. C.; Kang, P.; Lee, W. K.; Eum, H.; Ha, H.-J. *Tetrahedron* **2012**, *68*, 883. (c) Lafrance, M.; Blaquière, N.; Fagnou, K. *Eur. J. Org. Chem.* **2007**, 811. (d) Campeau, L.-C.; Fagnou, K. *Chem. Commun.* **2006**, 1253. (e) Lafrance, M.; Blaquière, N.; Fagnou, K. *Chem. Commun.* **2004**, 2874.
11. (a) Tadross, P. M.; Stoltz, B. M. *Chem. Rev.* **2012**, *112*, 3550. (b) Atanes, N.; Castelo, L.; Guitián, E.; Saá, C.; Saá, J. M.; Suau, R. *J. Org. Chem.* **1991**, *56*, 2984. (c) Gómez, B.; Martín, G.; Guitián, E.; Castedo, L.; Saá, J. M. *Tetrahedron* **1993**, *49*, 1251. (d) Atanes, N.; Castedo, L.; Cobas, A.; Guitián, E.; Saá, C.; Saá, J. M. *Tetrahedron* **1989**, *45*, 7947.
12. Rossini, A. F. C.; Muraca, A. C. A.; Casagrande, G. A.; Raminelli, C. *J. Org. Chem.* **2015**, *80*, 10033.
13. Liu, D.; Venhuis, B. J.; Wikström, H. V.; Dijkstra, D.; *Tetrahedron* **2007**, *63*, 7264.
14. (a) Leroy, C.; Dupas, G.; Bourguignon, J.; Quéguiner, G. *Tetrahedron* **1994**, *50*, 13135. (b) Brossi, A.; Dolan, L. A.; Teitel, S. *Org. Synth.* **1988**, *Coll. Vol. 6*, 1.
15. Hu, D. X.; Grice, P.; Ley, S. V. *J. Org. Chem.* **2012**, *77*, 5198.
16. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A., Jr.; Vreven, T.; Kudin, K. N.; Burant, J. C. et al. *Gaussian 09*; Gaussian, Inc.: Wallingford, CT, **2009**.
17. Zhao, Y.; Truhlar, D. G. *Acc. Chem. Res.* **2008**, *41*, 157.
18. Lee, K. M.; Kim, J. C.; Kang, P.; Lee, W. K.; Eum, H.; Ha, H.-J. *Tetrahedron* **2012**, *68*, 883.
19. Jones, K. M.; Karier, P.; Klussmann, M. *ChemCatChem* **2012**, *4*, 51.
20. Shi, X.-X.; Ni, F.; Shang, H.-X.; Yan, M.-L.; Su, J.-Q. *Tetrahedron: Asymmetry* **2006**, *17*, 2210.

Supplementary Material

Supplementary data (experimental procedures, computational details, characterization data and RMN spectra) associated with this article can be found, in the online version, at http://dx.doi.org/XXX.