ORGANIC LETTERS

2013
Vol. 15, No. 12
2942–2945

Asymmetric Synthesis of Vabicaserin via Oxidative Multicomponent Annulation and Asymmetric Hydrogenation of a 3,4-Substituted Quinolinium Salt

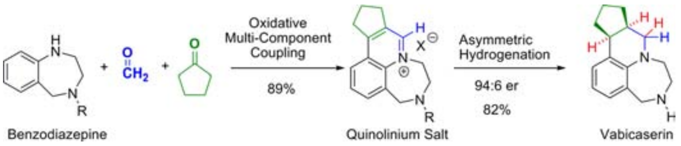
Vladimir Dragan,[*,†,§] J. Christopher McWilliams,[*,†] Ross Miller,[*,†,‖] Karen Sutherland,[†] John L. Dillon,[‡] and Michael K. O'Brien[†]

Pharmaceutical Sciences, Pfizer, Inc., Eastern Point Road, Groton, Connecticut 06340, United States, and Global Supply, Pfizer, Inc., 100 U.S. 206, Peapack, New Jersey 07970, United States

vdragan777@gmail.com; chris.mcwilliams@pfizer.com; rmiller@jstar-research.com

Received April 13, 2013

ABSTRACT



An efficient, asymmetric synthesis of the 5-HT_{2C} agonist vabicaserin in four chemical steps and 54% overall yield from commercially available benzodiazepine was achieved. The synthesis was highlighted by a novel oxidative, multicomponent reaction to affect the quinolinium ring assembly in one step followed by an unprecedented asymmetric hydrogenation of a 3,4-substituted quinolinium salt.

Vabicaserin (SCA-136, **1**) is a potent and selective 5-HT_{2C} receptor full agonist (K_i = 3 nM; EC_{50} = 8 nM), demonstrating efficacy in several animal models predictive of antipsychotic activity.[1] Vabicaserin advanced through phase 2 clinical trials as a potential treatment for schizophrenia, exhibiting positive trends across several PANSS measures.[2] An efficient and scalable synthesis of **1**, containing an unusual cyclopentadiazepinoquinoline ring system with two syn-oriented chiral centers, posed several challenges. In this paper, we describe a four-step, enantioselective synthesis of **1** that was enabled by the discovery of an oxidative, multicomponent reaction yielding two carbon–carbon and two carbon–nitrogen bonds of the pentacylic core structure, and an unprecedented asymmetric hydrogenation of a 1,3,4,8-tetrasubstituted quinolinium salt.

Early pharmaceutical development supplies were provided by the previously disclosed racemic synthetic route to SCA-136 (Scheme 1).[3] A Povarov reaction between benzodiazepine (**2**), cyclopentene, and formaldeyde provided racemic **1**, which was resolved by classical diastereoselective salt resolution. While the synthesis was short, the overall yield for the route was only 23%. Toward a more efficient route to **1**, several asymmetric approaches were pursued. One of the more promising routes consisted of reaction of chiral allylsilane **3** with the in situ generated iminium ion **I**, which gave a highly diastereoselective Povarov product. However, subsequent cleavage of the carbon–silicon bond proved to be difficult.[4] Installation of chirality via asymmetric hydrogenation of a fully assembled pentacyclic core was an attractive route to **1**, and several permutations of this approach were evaluated. The unsaturated amide **4** and the unfunctionalized alkene **5** were found to be either unreactive or nonselective under a variety of reduction conditions. The asymmetric

---

[†] Pharmaceutical Sciences, Pfizer, Inc.

[‡] Global Supply, Pfizer, Inc.

[§] Stepan Co., 100 W Hunter Ave, Maywood, NJ 07026.

[‖] J-Star Research, South Plainfield, NJ 07080.

(1) (a) Dunlop, J.; Watts, S. W.; Barrett, J. E.; Coupet, J.; Harrison, B.; Mazandarani, H.; Nawoschik, S.; Pangalos, M. N.; Ramamoorthy, S.; Schechter, L.; Smith, D.; Stack, G.; Zhang, J.; Zhang, G.; Rosenzweig-Lipson, S. *J. Pharm. Exp. Tech.* **2011**, *337*, 673. (b) Rosenzweig-Lipson, S.; Dunlop, J.; Marquis, K. L. *Drug News Perspect.* **2005**, *9*, 565–71.

(2) PANSS: Positive and Negative Syndrome Scale used to measure symptom severity of patients with schizophrenia.

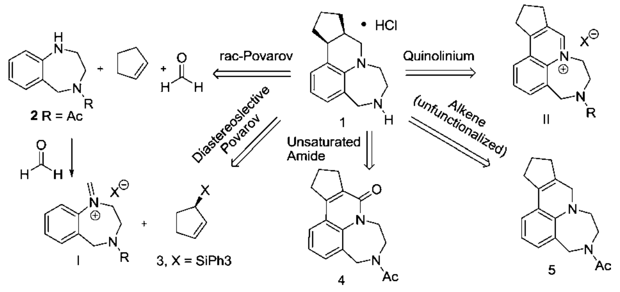
(3) (a) Megati, S.; Bhansali, S.; Dehnhardt, C.; Deshmukh, S.; Fung, P.; Macewan, M.; Tinder, R. J. Chiral Synthesis of Diazepinoquinolines PCT WO 2009/039362; 26 March 2009. (b) Dehnhardt, C. M.; Espinal, Y.; Venkatesan, A. M. *Syn. Comm.* **2008**, 796. (c) Dehnhardt, C.; Megati, S.; Sun, J. Process for Preparing Quinoline Compounds and Products Obtained Therefrom PCT WO 2006/052768; 18 May 2006.

(4) Akiyama, T.; Suzuki, M.; Kagoshima, H. *Heterocycles* **2000**, *52*, 529.

10.1021/ol401029k © 2013 American Chemical Society
Published on Web 06/10/2013

hydrogenation of tetrasubstituted quinolinium salts of type **II** was unprecedented. However, the potential of assembling the quinolinium salt in a single step coupled to an enantioselective hydrogenation made this route a very attractive target for study.

Scheme 1. Retrosynthetic Routes to Vabicaserin (**1**)



Assembly of a quinolinium salt **II** directly from a derivative of readily available benzodiazepine **6**[5] was initially envisioned to occur through an economical multicomponent reaction (MCR) with components at the targeted oxidation state.[6] However, all attempts to produce structures of type **II** with benzodiazepine derivatives in the absence of oxidants were unsuccessful.[7] We then considered a more complex, oxidative MCR sequence, which required annulation, elimination, and oxidation all occurring in the same pot.[8]

The substrate selected for the oxidative MCR study, *N*-tosylbenzodiazepine **7**, was obtained in 95% yield from **6** by treatment with *p*-TsCl and NaHCO$_3$ in EtOAc (Scheme 2). We were encouraged when the oxidative MCR conditions developed by Kozlov were examined.[8d] Accordingly, treating **7** with paraformaldehyde, cyclopentanone, and triflic acid in *n*-butanol at 100 °C yielded the desired quinolinium triflate **8a**. However, an equal amount of the *N*-methyl derivative **9** was also formed. We propose the formation of **9** occurs through hydride transfer from dihydroquinoline intermediate **IV** to iminium ion **III** via an NADH-type redox process, producing equal quantities of **8a** and **9**.[9,10] Several oxidants were tested for their potential to compete with **III**, but most gave only modest improvements in overall conversion. A previous report indicated catalytic iodine alone could effect this transformation, with air as a stoichiometric oxidant.[8c] Applying this protocol to **7** led predominantly to iodination of the aromatic ring, with no product formation.[11] To redirect oxidation, we considered deactivation of the aromatic ring by protonation with acid prior to the addition of iodine. To that effect, the addition of HI prior to iodine not only led to inhibition of ring iodination, observing only trace amounts of **9**, the modified conditions also affected conversion of **7** to **8b** at substantially lower temperature (30 °C). Consequently, the quinolinium salt **8b** was accessed in 89% isolated yield using this new, one-pot annulation/elimination/oxidation MCR sequence.[12]

The enantioselective reduction of highly substituted heterocycles, such as quinolines or pyridines, remains an elusive target in an active field of research. While there are a variety of methods described for highly selective asymmetric reduction of 2-substituted quinolines, there are only two reports describing substrates with substitution at the 3-position, one report with substitution at the 4-position, and no reports with substitution at the 8-position.[13] Further, while many of the prescribed protocols invoke N-activation, there are no examples of *N*-alkylquinolinium salts as substrates for asymmetric hydrogenation. Consequently, we were not surprised to find that applying the current state of the art reaction conditions to highly substituted **8**, or model substrates thereof, resulted in little or no enantioselectivity. The most promising lead came from the use of the phosphoramidite-iridium catalyst system described by de Vries and Feringa, in which we observed low reactivity and modest enantioselectivity (Figure 1, Table 1, entries 2–4).[13h] Analogous to the findings

---

(5) Bergman, J.; Brynolf, A. *Tetrahedron Lett.* **1989**, *30*, 2979 and references therein.

(6) For MCR reviews, see: (a) Touré, B. B.; Hall, D. G. *Chem. Rev.* **2009**, *109*, 4439. (b) Kumaravel, K.; Vasuki, G. *Curr. Org. Chem.* **2009**, *13*, 1820. (c) Martin, S. F.; Sunderhaus, J. D. *Chem.—Eur. J.* **2009**, *15*, 1300. (d) Ganem, B. *Acc. Chem. Res.* **2009**, *42*, 463. (e) Zhu, J., Bienayamé, H., Eds. *Multicomponent Reactions*; Wiley-VCH: Weinheim, 2005. Recemt examples of MCR, see: (f) Bienayamé, H.; Hulme, C.; Oddon, G.; Schmitt, P. *Chem.—Eur. J.* **2000**, *6*, 3321. (g) Hutt, J. T.; Aron, D. *Org. Lett.* **2011**, *13*, 5256.

(7) Combinations of cyclopentanone with formate derivatives, such as the Vilsmeier reagent or DMF dimethyl acetal, did not yield product. Cyclopentanone-2-carboxaldehyde also did not yield the desired product under a variety of conditions examined.

(8) For recent examples of oxidative MCR, see: (a) Adib, M.; Sheikhi, E.; Bijanzadeh, H. R. *Synlett* **2012**, *23*, 85. (b) Shindoh, N.; Tokuyama, H.; Takemoto, Y.; Takasu, K. *J. Org. Chem.* **2008**, *73*, 7451. (c) Wang, X-S; Li, Q.; Yao, C-S; T, S.-J. *Eur. J. Org. Chem.* **2008**, 3513. (d) Kozlov, N. G.; Gusak, K. N. *Russ. J. Org. Chem* **2008**, *44*, 830. For oxidation of Povarov products, see: (e) Vicente-García, E.; Ramón, R.; Preciado, S.; Lavilla, R. Multicomponent reaction access to complex quinolines via oxidation of the Povarov adducts. *Beilsein J. Org. Chem.* [Online] 2011, *7*, 980, DOI:10.3762/bjoc.7.110 (accessed May 11, 2012).

(9) Meyers, A. I.; Stout, D. M. *Chem. Rev.* **1982**, *82*, 223.

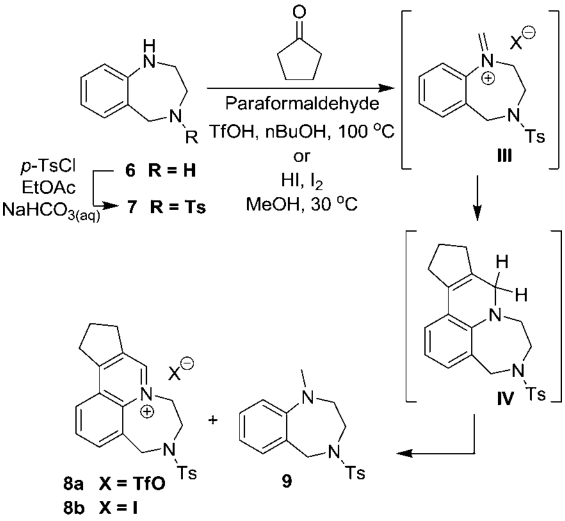
(10) When the reaction was run using paraformaldehyde-d_2, **9** was formed with incorporation of three deuterium atoms (94% of theoretical) and **8a** with one deuterium atom, consistent with single deuterium transfer from the intermediate hydroquinoline **IV** to the iminium ion **III**. For a related example of an imine acting as an oxidant, see ref 8b.

(11) Iodination was not noted in ref 8c, although the authors indicate the reaction was limited in scope to a single substrate, 2-aminonaphthalene.

(12) In this unoptimized process, an excess of cyclopentanone and paraformaldedyde was used to drive the reaction to completion.

(13) For a recent review article, see: (a) Maj, A. M.; Suisse, I.; Méliet, C.; Hardoin, C.; Agbossou-Neidercorn, F. *Tetrahedron Lett.* **2012**, *53*, 4747. (b) Wang, D.-S.; Chen, Q.-A.; Lu, S.-M.; Zhou, Y.-G. *Chem. Rev.* **2012**, *112*, 2557. Representative examples: (c) Wang, T.-L.; Zhuo, L. G.; Li, Z.-W.; Chen, F.; Ding, Z.-Y.; He, Y.-M.; Fan, Q.-H.; Xiang, J.-F.; Yu, Z.-X.; Chan, A. S. C. *J. Am. Chem. Soc.* **2011**, *133*, 9878. (d) Dobereiner, G. E.; Nova, A.; Schley, N. D.; Hazari, N.; Miller, S.; Eisenstein, O.; Crabtree, R. H. *J. Am. Chem. Soc.* **2011**, *133*, 7547. (e) Tang, W.-J.; Tan, J.; Xu, L.-J.; Lam, K.-H.; Fan, Q.-H.; Chan *Adv. Synth. Catal.* **2010**, *352*, 1055. (f) Wang, D.-S.; Zhou, Y.-G. *Tetrahedron Lett.* **2010**, *51*, 3014. (g) Wang, C.; Li, C.; Wu, X.; Pettman, A.; Xiao, J. *Angew. Chem., Int. Ed.* **2009**, *48*, 6524. (h) Mršić, N.; Lefort, L.; Boogers, J. A. F.; Minnaard, A. J.; Feringa, B. L.; de Vries, J. G. *Adv. Synth. Catal.* **2008**, *350*, 1081. (i) Lu, S.-M.; Bolm, C. *Adv. Synth. Catal.* **2008**, *350*, 1101. (j) Lu, S.-M.; Wang, Y.-Q.; Han, X.-W.; Zhou, Y.-G. *Angew. Chem., Int. Ed.* **2006**, *45*, 2260. (k) Rueping, M.; Antonchick, A. P.; Theissmann, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 3683. (l) Wang, W.-B.; Lu, S.-M.; Yang, P.-Y.; Han, X.-W.; Zhou, Y.-G. *J. Am. Chem. Soc.* **2003**, *125*, 10536. Example of quinoline *N*-oxide: (m) Gou, F.-R.; Li, W.; Zhang, X.; Liang, Y.-M. *Adv. Synth. Catal.* **2010**, *352*, 2441. For reduction of 4-substituted quinolines, see: (n) Rueping, M.; Theissmann, T.; Stoekel, M.; Antonchick, A. P. *Org. Biomol. Chem.* **2011**, *9*, 6844. For a related reduction of a 1-hydro-2,2,4,7-tetramethylquinoline, see: (o) Sumerin, V.; Chernichenko, K.; Nieger, M.; Leskilä, M.; Rieger, B.; Repo, T. *Adv. Synth. Catal.* **2011**, *353*, 2093.

Scheme 2. Multicomponent Reaction Annulation/Oxidation



of de Vries and Feringa, a mixed ligand system provided the best results with regard to enantioseletivity. In contrast to the decreased enantioselectivity observed by de Vries, the addition of iodide salts had a positive effect on enantioselectivity with this substrate (Table 1, entries 5–6). Although promising, the catalyst loading was too high to be a practical synthetic method, and further optimization based upon these leads was pursued.

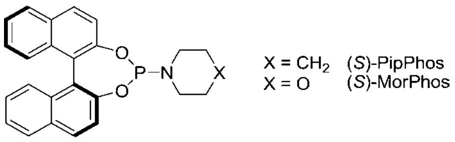
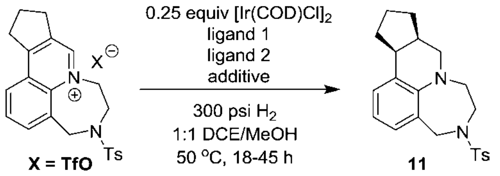


Figure 1. Structures of Monophos ligands.

Table 1. Representative Examples of the Initial Catalyst Screen[a]

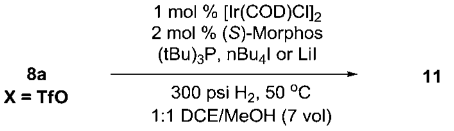


entry	ligand 1	ligand 2	additive	conv (%)	er
1	Josiphos[b]	none	Pip-HCl	99	50:50
2	(*S*)-PipPhos	(o-Tol)$_3$P	Pip-HCl	28	75:25
3	(*S*)-MorPhos	(o-Tol)$_3$P	Pip-HCl	57	70:30
4	(*S*)-MorPhos	(t-Bu)$_3$P	Pip-HCl	99	76:24
5[c]	(*S*)-MorPhos	(o-Tol)$_3$P	nBu_4I	39	91:09
6[c]	(*S*)-MorPhos	(t-Bu)$_3$P	nBu_4I	35	90:10

[a] 2:1:5:1 ratio of ligand 1/ligand 2/additive/$[Ir(COD)Cl]_2$. [b] 0.5 equiv relative to Ir. [c] 0.10 equiv of $[Ir(COD)Cl]_2$

Optimization of the achiral phosphine loading yielded a key observation; increasing the concentration of the achiral phosphine led to an increase in reactivity (Table 2, entries 1–4). We postulated that the role of the excess phosphine may be to act as a base in addition to serving as a ligand for iridium. Apparent confirmation of this conclusion is evidenced by the analogous effect of added base at low phosphine charge (Table 2, entries 5–7), yielding high conversion without significant loss in enantioselectivity. With the addition of 2,6-di-*tert*-butylpyridine (2,6-DtBP), catalyst loading could be reduced to ≤0.5 mol %, making this the first practical method for the enantioselective hydrogenation of highly substituted *N*-alkylquinolinium salts.[14]

Table 2. Impact of Achiral Phosphine Loading and Bases on Conversion and Enantioselectivity[a]

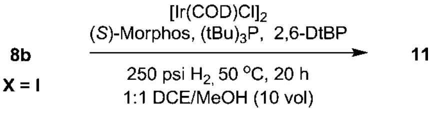


entry	(t-Bu)$_3$P (mol %)	additive (equiv)	conv (%)	er
1	1	none	22	90:10
2	40	none	50	87:13
3	80	none	85	85:15
4	100	none	78	83:17
5	3	DBU (1.3)	81	89:11
6	3	KO-*t*-Bu (1.3)	75	89:11
7	3	2,6-DtBP (2)[b]	99	89:11
8[c]	1.5	2,6-DtBP (4)[b]	96	89:11

[a] 5 mol % of n-Bu_4I for entries 1–4; 1.3 equiv of LiI for entries 5–8. [b] 2,6-di-*tert*-butylpyridine. [c] 0.5 mol % of $[Ir(COD)Cl]_2$, 1 mol % of Morphos.

The initial asymmetric hydrogenation was performed using the triflate salt **8a**. The iodide **8b** acquired by the oxidative MCR conditions provided similar results. However, we found that added chloride increased enantioselecivity (Table 3). This is consistent with recent reports implicating the involvement of mixed halide catalysts.[15] This procedure now provided conditions to achieve up to 94% of the desired enantiomer in the asymmetric

Table 3. Impact of LiCl on Enantioselective Hydrogenation of **8b**[a]



entry	mol % Ir	additive	equiv	conv (%)	er
1	0.5	none	N/A	99	90:10
2	0.5	LiCl	3	99	93:07
3	0.75	LiCl	3	99	94:06

[a] 2:3:1 ratio of (*S*)-Morphos/(t-Bu)$_3$P/$[Ir(COD)Cl]_2$, 2.5 equiv of 2,6-DtBP.

hydrogenation of a tetrasubstituted quinolinium salt. Crystalline **11** was isolated from the hydrogenation mixture in 82% yield.

The final conversion of **11** to **1** consisted of deprotection with HCl in acetic acid, yielding vabicaserin **1** in 92% yield and 92% ee after crystallization (eq 1). An additional recrystallization from EtOH/MTBE provided the target compound in 86% yield and 99.9+% ee.

$$\mathbf{11} \xrightarrow[\text{2) 95\% EtOH, MTBE}]{\text{1) HCl, AcOH, 115 }^{\circ}\text{C}} \underset{\substack{\text{79\% yield} \\ \text{99.9+\% ee}}}{\mathbf{1}} \qquad (1)$$

In summary, we have developed an efficient, asymmetric synthesis of the 5-HT$_{2c}$ agonist vabicaserin in four chemical steps and 54% overall yield from commercially available benzodiazepine, a >2 fold increase compared to the resolution approach to **1**. The short synthesis was enabled by the discovery of two new reaction processes: an oxidative, multicomponent reaction to affect the quinolinium ring assembly in one step, and an unprecedented asymmetric hydrogenation of a highly substituted quinolinium salt. Notably, this work provides the first example of an enantioselective reduction of a quinoline heterocycle with substitution at the 4 position.

Acknowledgment. We thank Thomas Storz (Pfizer, Inc.) for providing samples of the unsaturated amide **4**. We thank Joel Hawkins, Javier Magano, and Sebastien Monfette (Pfizer, Inc.) for helpful comments in the preparation of the manuscript.

Note Added after ASAP Publication. References 13n−o were added on June 12, 2013.

Supporting Information Available. Copies of ^{1}H NMR and ^{13}NMR, as well as experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org

---

(14) The role of added base is under investigation and may be critical to enabling enamine ↔ iminium ion equilibria (we have detected partially reduced intermediates that accumulate in the absence of added base) or to remove hydrogen from an unreactive iridium complex.

(15) Wang, D.-W.; Wang, X.-B.; Wang, D.-S.; Lu, S.-W.; Zhou, Y. G.; Li, Y.-X. *J. Org. Chem.* **2009**, *74*, 2780. For an example of mixed halide acceleration in rhodium transfer hydrogenation, see: Wu, J.; Wang, C.; Tang, W.; Pettman, A.; Xiao, J. *Chem.—Eur. J.* **2012**, *18*, 9525.

The authors declare no competing financial interest.