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Synthesis of a Tricyclic Mescaline Analogue by Catalytic C–H Bond Activation

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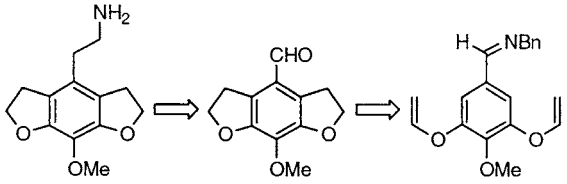
ABSTRACT



A tetrahydrobis(benzofuran) mescaline analogue has been prepared in six steps and 38% overall yield from (4′-*O*-methyl)methyl gallate. The key step in this synthesis is a tandem cyclization reaction via directed C–H activation followed by olefin insertion.

Since its discovery in 1896,[1] mescaline (**1**, Figure 1) has served as a prototypical compound for structure−activity relationship studies linking molecular structure to hallucinogenic activity.[2] Mescaline exerts its behavioral effects primarily through interaction with the 5-hydroxytryptamine$_2$ (5-HT$_2$) receptors.[3] The 5-HT$_2$ family of receptors mediates a number of physiological processes including vascular and nonvascular smooth muscle contraction, platelet aggregation, and modulation of perception, mood, anxiety, and feeding behavior.[4] Furthermore, these receptors are a therapeutic target for the treatment of central nervous system disorders such as schizophrenia and depression.[5]

The synthesis and biological activities of mescaline analogues **2** and **3** (Figure 1), in which one or two of the aromatic methoxy groups of mescaline are tethered into rotationally constrained dihydrobenzofuran rings, has recently been described.[6] Compounds **2** and **3** exhibit increased affinities relative to mescaline for cloned human 5-HT$_{2A}$, 5-HT$_{2B}$, and 5-HT$_{2C}$ receptors as determined through competitive binding studies with radiolabeled agonist and antagonist ligands.[7]

Our interest in compound **3** was generated by the ability to rapidly assemble the tetrahydrobis(benzofuran) functionality utilizing catalytic C−H activation. To date, only a few examples of C−H activation in the synthesis of natural products or biologically active molecules have been re-

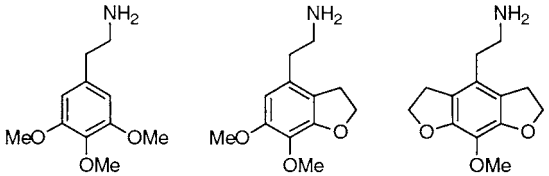


Figure 1. Mescaline (**1**) and dihydrobenzofuran and tetrahydrobis(benzofuran) analogues **2** and **3**.

(1) Heffter, A. *Chem. Ber.* **1896**, *29*, 216.
(2) (a) Nichols, D. E. In *Amphetamine and Its Analogues*; Cho, A. K., Segal, D. S., Eds.; Academic Press: San Diego, CA, 1994; pp 3−41. (b) Nichols, D. E.; Glennon, R. A. In *Hallucinogens: Neurochemical, Behavioral, and Clinical Perspectives*; Jacobs, B. L., Ed.; Raven Press: New York, 1984; pp 95−142.
(3) (a) Aghajanian, G. K.; Marek, G. J. *Neuropsychopharmacology* **1999**, *21*, 16S. (b) Appel, J. B.; Callahan, P. M. *Eur. J. Pharmacol.* **1989**, *159*, 41. (c) Titeler, M.; Lyon, R. A.; Glennon, R. A. *Psychopharmacology* **1988**, *94*, 213. (d) Rasmussen, K.; Aghajanian, G. K. *Brain Res.* **1986**, *385*, 395.
(4) Roth, B. L.; Willins, D. L.; Kristiansen, K.; Kroeze, W. K. *Pharmacol. Ther.* **1998**, *79*, 231 and references therein.
(5) (a) Roth, B. L.; Shapiro, D. A. *Expert Opin. Ther. Targets* **2001**, *5*, 685. (b) Stefanski, R.; Goldberg, S. R. *CNS Drugs* **1997**, *7*, 388.

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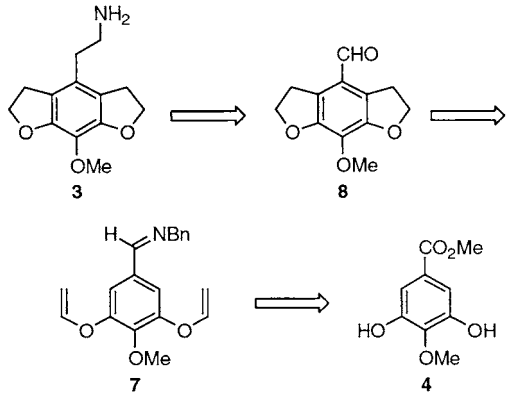
ported.[8,9] Recently, we have described the annulation of aromatic imines, in which an alkene is tethered *meta* to the imine. Rhodium-catalyzed, imine-directed *ortho* C−H activation followed by olefin insertion provides access to functionalized indanes, tetralanes, dihydroindoles, and dihydrobenzofurans.[10] Herein we report the application of our annulation strategy to the concise synthesis of the conformationally restricted tetrahydrobis(benzofuran) mescaline analogue **3**.

Our approach to **3** was based on the elaboration of intermediate **8** (Scheme 1), obtained from the rhodium-catalyzed

Scheme 1

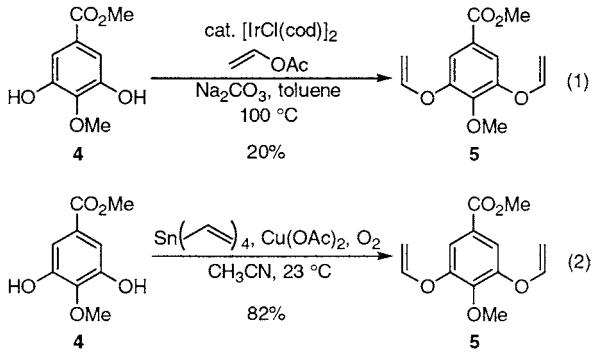


tandem cyclization reaction of aromatic imine **7**. Precursor **7** was prepared from (4′-*O*-methyl)methyl gallate **4**.

The synthesis began with the conversion of bis-phenol **4**[11] to the bis-vinyl ether. The synthesis of phenyl vinyl ethers is generally accomplished by alkylation of phenol with 1,2-dibromoethane followed by elimination with KO*t*Bu, or by subjection of phenol to high pressure of acetylene in the presence of a strong base. These procedures require forcing conditions, and the products are generally obtained in only low to modest yields.

Our initial efforts to form the bis-vinyl ether instead focused on a recently reported procedure for the iridium-catalyzed reaction of alcohols with vinyl pivalate.[12] Unfortunately, subjection of **4** to the reported reaction conditions resulted in low yields of the desired bis-vinyl ether (Scheme 2, eq 1). Modification of reaction parameters, including

Scheme 2

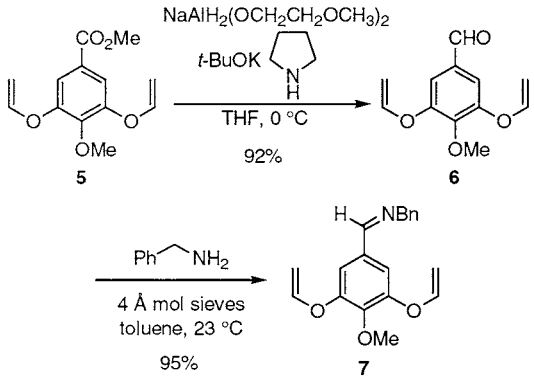


reaction time and temperature, concentration, catalyst loading, and stoichiometry of vinyl acetate, did not improve the yield. Most conditions resulted in poor conversion, and under forcing conditions a significant amount of acetylated rather than vinylated material was observed.

We then investigated an alternative procedure recently described by Blouin and Frenette.[13] Treatment of bis-phenol **4** with tetravinyl tin and copper(II) acetate in the presence of oxygen led to the desired bis-vinyl ether **5** in reproducibly high yield (Scheme 2, eq 2).

With the bis-vinyl ether **5** in hand, conversion of the methyl ester to the aldehyde was examined. Preliminary reactions with DIBAl-H were unsuccessful, resulting in over-reduction of the ester to the benzylic alcohol. However, treatment of the ester with a pyrrolidine-modified aluminum hydride reagent according to the procedure of Abe and co-workers[14] provided the desired benzaldehyde in high yield (Scheme 3). The aldehyde was then converted to the benzyl

Scheme 3



imine **7** by treatment with benzylamine in the presence of molecular sieves.

(6) Monte, A. P.; Waldman, S. R.; Marona-Lewicka, D.; Wainscott, D. B.; Nelson, D. L.; Sanders-Bush, E.; Nichols, D. E. *J. Med. Chem.* **1997**, *40*, 2997.

(7) Competition studies employed the agonist ligands [^{125}I]DOI and [^{3}H]-seratonin, and antagonist ligands [^{3}H]ketanserin, [^{3}H]rauwolscine, and [^{3}H]-mesulergine.

(8) For examples of the application of C−H bond activation in target-oriented synthesis, see: (a) Harris, P. W. R.; Woodgate. P. D. *J. Organomet. Chem.* **1997**, *530*, 211. (b) Johnson, J. A.; Sames, D. *J. Am. Chem. Soc.* **2000**, *122*, 6321. (c) Dangel, B. D.; Godula, K.; Youn, S. W.; Sezen, B.; Sames, D. *J. Am. Chem. Soc.* **2002**, *124*, 11856. (d) Wehn, P. M.; Du Bois, J. *J. Am. Chem. Soc.* **2002**, *124*, 12950.

(9) For examples of the application of rhodium−carbenoid insertions into C−H bonds in target-oriented synthesis, see: (a) Taber, D.; Song, Y. *J. Org. Chem.* **1997**, *62*, 6603. (b) Davies, H. M. L.; Stafford, D. G.; Hansen, T. *Org. Lett.* **1999**, *1*, 233. (c) Davies, H. M. L.; Gregg, T. M. *Tetrahedron Lett.* **2002**, *43*, 4951 and references therein.

(10) Thalji, R. K.; Ahrendt, K. A.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2001**, *123*, 9692.

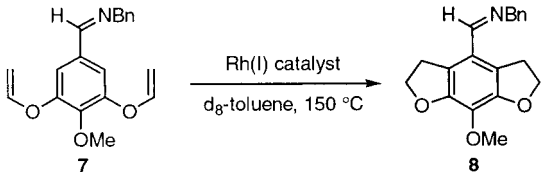
(11) 4-Methoxy-3,5-bis-hydroxy-benzoic acid methyl ester is prepared by alkylation of commercially available methyl benzoate. Cardona, M. L.; Fernandez, M. I.; Garcia, M. B.; Pedro, J. R. *Tetrahedron* **1986**, *42*, 2725.

(12) Okimoto, Y.; Sakaguchi, S.; Ishii, Y. *J. Am. Chem. Soc.* **2002**, *124*, 1590.

(13) Blouin, M.; Frenette, R. *J. Org. Chem.* **2001**, *66*, 9043.

To effect the tandem cyclization reaction, we first examined conditions that we had previously used for the annulation of alkene-substituted aromatic imines. Unfortunately, Wilkinson's catalyst provided only low yields of the desired tetrahydrobis(benzofuran) product after extended heating, as determined by ^{1}H NMR experiments (Table 1, entry 1).

Table 1. Optimization of the Tandem C−H Activation/Olefin Insertion Reaction



entry	Rh catalyst[a]	time (h)	NMR yield (%)[b]
1	$(PPh_3)_3RhCl$[c]	20	10
2	P(*t*-Bu)$_3$, $[RhCl(coe)_2]_2$	3	0
3	P(*n*-Pr)$_3$, $[RhCl(coe)_2]_2$	17	18
4	PCy_3, $[RhCl(coe)_2]_2$	8	48
5	$FcPPh_2$, $[RhCl(coe)_2]_2$	4	34
6	**$FcPCy_2$,$[RhCl(coe)_2]_2$**	**2**	**75**
7	$FcPCy_2$, $[RhCl(coe)_2]_2$[d]	5	52

[a] Reactions were performed with 20 mol % of Rh(I) and 20 mol % of phosphine. [b] Yields were determined by ^{1}H NMR relative to an internal standard. [c] 20 mol % of Wilkinson's catalyst was used. [d] Reaction was performed with 20 mol % of Rh(I) and 40 mol % of phosphine. Abbreviations: coe = cyclooctene; Fc = ferrocenyl.

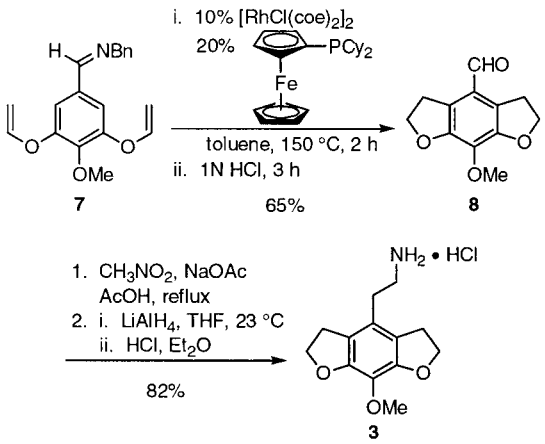
Consequently, a number of phosphines were screened in the presence of $[RhCl(coe)_2]_2$ in an effort to improve the reaction efficiency (Table 1).[15] Higher yields were obtained with the use of more electron-rich phosphines, with the exception of the bulky P(*t*-Bu)$_3$ ligand (entries 2−7). In the cases of the electron-rich phosphines, the optimal ratio of ligand to rhodium(I) for generating the bis-cyclization product was 1:1 (entry 6 versus entry 7). We were pleased to find that employing catalytic $[RhCl(coe)_2]_2$ with the electron-rich dicyclohexyl ferrocenyl phosphine ligand led to the desired bis-cyclization product in good yield (entry 6).[16]

(14) Abe, T.; Haga, T.; Negi, S.; Morita, Y.; Takayanagi, K.; Hamamura, K. *Tetrahedron* **2001**, *57*, 2701.

(15) $[RhCl(coe)_2]_2$ is commercially available from Aldrich Chemical Co., though for these studies it was prepared in one step from $RhCl_3{\cdot}(H_2O)_3$ and cyclooctene: van der Ent, A.; Onderdelinden, A. L. *Inorg. Synth.* **1973**, *14*, 92.

(16) Lowering the catalyst loading to 5 mol % of $[RhCl(coe)_2]_2$ resulted in reduced product yield (60% NMR yield).

Scheme 4



Having identified an efficient catalyst system for the annulation reaction, the tetrahydrobis(benzofuran) **8** was isolated in 65% yield after acidic workup (Scheme 4).[17] Aldehyde **8** was then converted to the target mescaline analogue **3** via a Henry reaction followed by reduction of the intermediate nitroalkene.

In summary, tetrahydrobis(benzofuran) mescaline analogue **3** has been prepared in six steps and 38% overall yield from (4′-*O*-methyl)methyl gallate **4**. The key step in this synthesis is a rhodium-catalyzed tandem C−H activation/C−C bond forming reaction. The bis-vinylation of **4** is also noteworthy. Importantly, this efficient annulation sequence can potentially be applied to the synthesis of other biologically relevant dihydrobenzofurans.

Acknowledgment. This work was supported by the National Institutes of Health Grant GM50353 (to J.A.E.), and by the Director, Office of Energy Research, Office of Basic Energy Sciences, Chemical Sciences Division, U.S. Department of Energy, under Contract No. DE-AC03-76SF00098 (to R.G.B). K.A.A. thanks Pharmacia for a graduate fellowship. The Center for New Directions in Organic Synthesis is supported by Bristol-Myers Squibb as a sponsoring member and Novartis as a supporting member.

Supporting Information Available: Experimental procedures and characterization of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) No starting material or side products were isolated after silica gel chromatography. The remaining material is attributed to intractable mixtures of oligomers or polymers. Lowering the concentration of the reaction improved the product yield.