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Enantioselective Synthesis of Nicotinic Receptor Probe 7,8-Difluoro-1,2,3,4,5,6-hexahydro-1,5-methano-3-benzazocine

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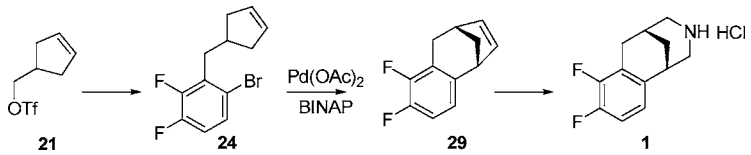
ABSTRACT



The development of a concise enantioselective synthesis of nicotinic alkaloid 1 is presented. The route features the synthesis and use of a "stable" aliphatic triflate 21 in an alkylation step to generate Heck precursor 24 and an enantioselective cyclization to establish a compound with the key [3.2.1]-bicyclic core, 29.

Naturally occurring nicotinic receptor ligands such as nicotine, epibatidine, anatoxin A, cytisine, and their derivatives have been increasingly studied as potential therapeutic agents for cognition, pain, attention-deficit/hyperactivity disorder, schizophrenia, Parkinson's disease, and addiction.[1] Our ongoing pursuit of cholinergic probes necessitated the development of an efficient synthesis of the bicyclic derivative 7,8-difluoro-1,2,3,4,5,6-hexahydro-1,5-methano-3-benzazocine (**1**). Our early approaches, designed for generality, allowed the synthesis of multiple pharmacological targets and utilized triflate intermediates.[2] These compounds were accessed from alkoxy precursors that were incorporated into the initial synthetic design because they displayed robust directing effects in metalation strategies for controlling substituent regiochemistry. Herein, we describe refinements that obviated their use and resulted in a brief enantioselective synthesis of **1**.

The original approach to racemic **1** required multiple steps to prepare Heck precursor **7** (Scheme 1).[3] Metalation of **2** with LDA (1.1 equiv) gave an *ortho*-lithio anisole intermediate, and subsequent low-temperature reaction with aldehyde **3** successfully established the required benzylic C−C bond to provide **4**.[4] Reductive dehydration, anisole deprotection,[5] and triflate formation gave Heck cyclization precursor **7**. Although the overall yield for this sequence was acceptable (∼30%), we believed that the early stages of the synthesis could be improved by a more judicious choice of starting material.

We considered 3,4-difluorobromobenzene **12** to be an ideal alternative. Metalation of **12** gave an anion that reacted

(1) For leading reviews in this area, see: (a) Bunnelle, W. H.; Dart, M. J.; Schrimpf, M. R. *Curr. Med. Chem.* **2004**, *4*, 299−334. (b) Holladay, M. W.; Dart, M. J.; Lynch, J. K. *J. Med. Chem.* **1997**, *40*, 4169−4194. (c) Glennon, R. A.; Dukat, M. *Med. Chem. Res.* **1996**, 465−486.

(2) Coe, J. W.; Vetelino, M. G.; Bashore, C. G.; Wirtz, M. C.; Brooks, P. R.; Arnold, E. P.; Lebel, L. A.; Fox, C. B.; Sands, S. B.; Davis, T. I.; Rollema, H.; Schaeffer, E.; Schulz, D. W.; Tingley, F. D., III; O'Neill, B. T. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 2974−2979.

(3) Coe, J. W. Arylfused Azapolycyclic Compounds. PCT Int. Appl. WO99 55,680, 1999. U.S. Patent 6,462,035, October 8, 2002, and U.S. Patent 6,706,702, March 16, 2004.

(4) The *ortho*-lithio anisole intermediate failed to react with Weinreb amides at low temperature and, upon warming, presumably suffered from benzyne-mediated decomposition before any addition to the amide.

(5) Brooks, P. R.; Wirtz, M. C.; Vetelino, M. G.; Rescek, D. M.; Woodworth, G. F.; Morgan, B. P.; Coe, J. W. *J. Org. Chem.* **1999**, *64*, 9719−9721.

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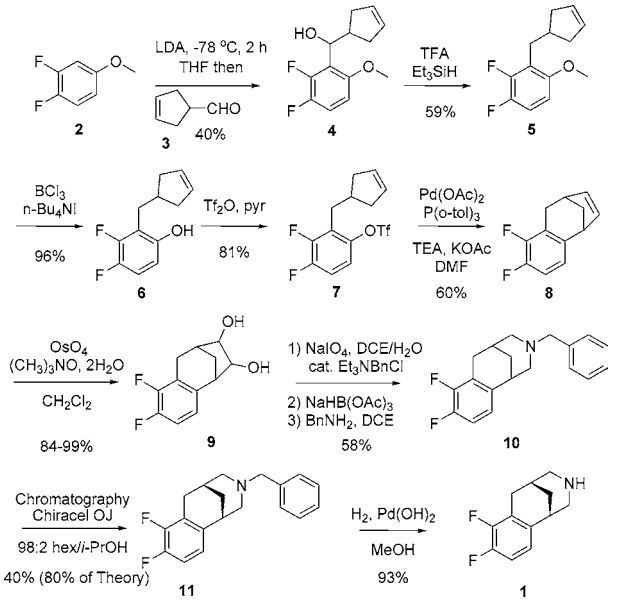
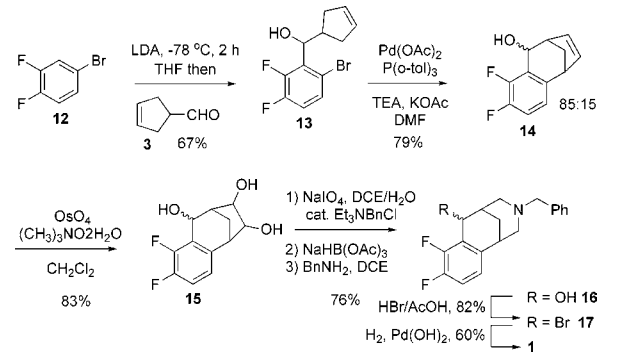
Scheme 1



with aldehyde **3** to afford benzyl alcohol **13**.[6] This intermediate performed well in the Heck reaction to give an 85:15 diastereomeric mixture of products (Scheme 2).[7]

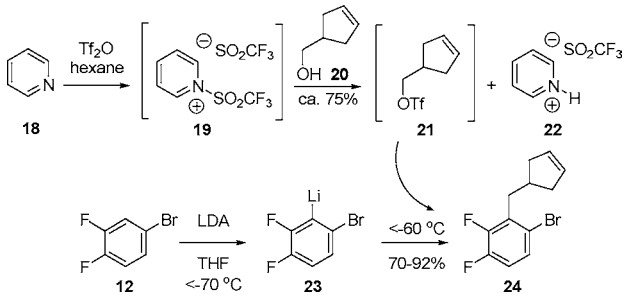
Scheme 2



Conversion of **14** to piperidine **16** proceeded uneventfully as shown in Scheme 2. In the conversion to **1**, the removal of the hindered benzylic alcohol during hydrogenolysis did not occur without prior activation as the corresponding mesylate or bromide.

Removing the benzylic hydroxyl group detracted from this sequence and prompted the study of alkylation methods to introduce the critical benzylic C−C bond. Although there are examples of direct alkylation of aryl anion species flanked by exchangeable halides, as with **12**,[8] we were still concerned that benzyne formation and subsequent decomposition of 2-metalated 3,4-difluoro-1-bromobenzene species would compete with the alkylation process. We found that activated cyclopentene carbinol derivatives of **20** (e.g., Cl, Br, I, OMs) failed to react with aryllithium **23** at low temperature (Scheme 3). Warming the lithio species invariably promoted

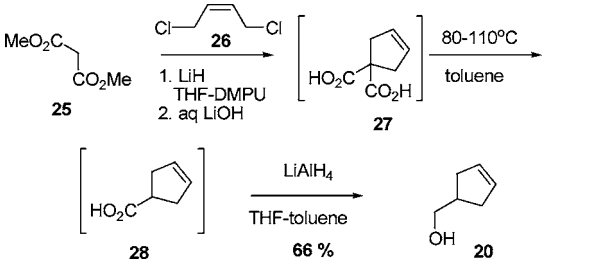
Scheme 3



decomposition, presumably as a result of benzyne formation under the reaction conditions; the alkylating agents were stable and recovered unchanged. Triflate **21**, however, proved uniquely suited to this alkylation,[9] giving advanced Heck intermediate **24** in one step from 3,4-difluorobromobenzene **12** (Scheme 3). Our emphasis, therefore, shifted to this promising methodology, which was further developed to support multikilogram-scale preparations.

Although alcohol **20** is known in the literature,[10] a number of modifications were introduced to support pilot plant processing requirements and to avoid the isolation of oils or low-melting solids (Scheme 4). The base-mediated alkylation

Scheme 4



of 25 kg of dimethyl malonate (**25**) with *cis*-1,4-dichloro-2-butene (**26**) was accomplished with LiH between 25 and 40 °C in 9:1 (v/v) THF−1,3-dimethyl-3,4,5,6-tetrahydro-2-(1*H*)-pyrimidinone (DMPU). Although exothermic, the dialkylation was relatively slow and easily controlled. The resulting diester was saponified directly by the addition of aqueous LiOH to give diacid **27**. After workup, the decar-

(6) Lithiated 3,4-difluorobromobenzene failed to react with the corresponding Weinreb amide.

(7) In theory, with optically enriched alcohol, chiral induction in the Heck cyclization step should be possible.

(8) Hayan, S. E.; Domagala, J. M.; Heifetz, C. L.; Johnson, J. *J. Med. Chem.* **1991**, *34*, 1155−1161.

(9) Bashore, C. G.; Samardjiev, I. J.; Bordner, J.; Coe, J. W. *J. Am. Chem. Soc.* **2003**, *125*, 3268−3272. Vedejs, E.; Engler, D. A.; Mullins, M. J. *J. Org. Chem.* **1977**, *42*, 3102−3113.

(10) (a) Deprés, J.-P.; Greene, A. E. *J. Org. Chem.* **1984**, *49*, 928−931. (b) Deprés, J.-P.; Greene, A. E. *Org. Synth.* **1997**, *75*, 195−200. (c) Johnson, C. R.; Keiser, J. E.; Sharp, J. C. *J. Org. Chem.* **1969**, *34*, 860−864.

boxylation proceeded smoothly in toluene at 80−120 °C to give monoacid **28**. A 9:1 (v/v) THF−toluene solution of **28** was added to 1 M $LiAlH_4$/THF at 20−25 °C. After an aqueous workup, alcohol **20** was isolated by fractional distillation (81 °C/29 mmHg) in 66% overall yield.

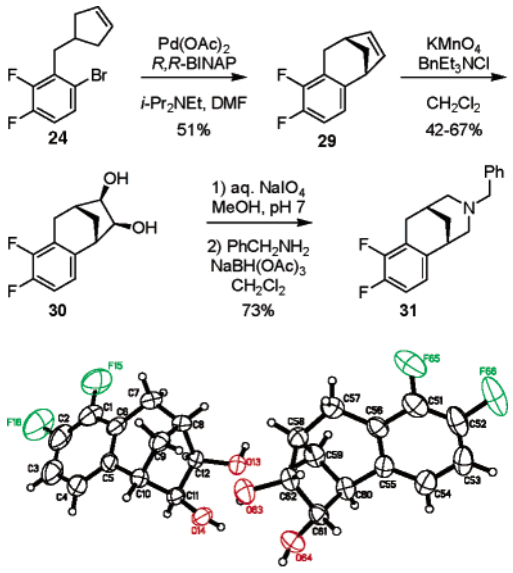
Typically, the generation of trifluoromethane sulfonates involves aqueous workup procedures. We suspected that under these conditions trace amounts of triflic acid, either from the workup or from a slower adventitious hydrolysis of unreacted triflic anhydride and trace levels of water, could compromise the stability of the resulting trifluoromethane sulfonate esters. In the Schleyer procedure, for example, the conversion of alcohol **20** to triflate **21**[11] invariably led to solutions with dramatic differences in stability from batch to batch. Such instability was unsuitable for further scale-up, and a protocol to eliminate residual triflic anhydride/acid from the isolated reaction solution was developed (Scheme 3). The reaction of pyridine and triflic anhydride in hexanes generated a sparingly soluble slurry of pyridinium triflate salt **19**, effectively consuming the highly organic-soluble triflic anhydride. This salt is an effective agent for converting alcohol **20** to triflate **21**.

On a range of scales, treatment of the slurry of **19** with alcohol **20** generated hexane-soluble triflate **21** and the pyridinium hydrogen triflate salt. All salts (**19** and **22**) were conveniently removed by filtering the reaction mixture through a pad of activity I neutral alumina. These conditions effectively maintained anhydrous processing conditions while eliminating residual triflic anhydride, the suspected source of adventitious triflic acid. This process routinely gave colorless solutions of **21** that were stable at 0 to −15 °C for 8−16 h without observable decomposition. The improved stability was effectively established using differential scanning calorimetry measurements (see Supporting Information). Samples prepared by this nonaqueous Tf_2O/pyr method had a much higher decomposition onset temperature (202 °C) than products derived from the Schleyer methodology (46 °C).

Confident in our ability to prepare acceptably stable solutions of triflate **21**, we began investigating the alkylation of 2-lithio-3,4-difluoro-1-bromobenzene **23** (Scheme 3). Anion formation was effected with LDA in THF at −60 to −78 °C. The lithiation was indirectly monitored by in situ IR spectroscopy by observing the appearance/disappearance of absorbance bands attributable to diisopropylamine. On the basis of the IR data, upon addition of LDA, proton transfer was immediate, and the resulting solutions showed little change over the next 2 h (IR). The triflate **21**/hexanes solution was then added to the aryllithium solution at a rate that maintained the internal temperature below −70 °C (Scheme 3). This procedure provided good conversion to the desired product, as indicated by the ratio of product to 4-bromo-1,2-difluorobenzene (from anion protonation): by NMR, **24**/**12** ratios were typically 15−35:1 in yields of 70−92%.

Palladium-mediated Heck cyclization reactions of **24** with $Pd(OAc)_2$/P(*o*-tol)$_3$ provided racemic material in 77% yield. An enantioselective process to prepare olefin **29** was subsequently developed using chiral ligands. From initial screenings, 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (BINAP), $Pd(OAc)_2$, and DMF emerged as attractive components for this reaction (Scheme 5). Under controlled

Scheme 5



Single crystal X-ray structure of **30**

conditions on the gram scale, high levels of enantioselectivity [enantiomeric excess (ee) > 93%] were seen using 1−10 mol % $Pd(OAc)_2$/BINAP levels.[12] Purging and sparging with N_2 were found to be critical to achieve high levels of enantioselectivity. When the reaction was insufficiently purged, the rate slowed and the ee was reduced to 60% (see Supporting Information). This latter result was observed during a single large-scale run (51% yield, 60% ee on an 18-kg scale) and reflects the importance of effective purging of process reactors.

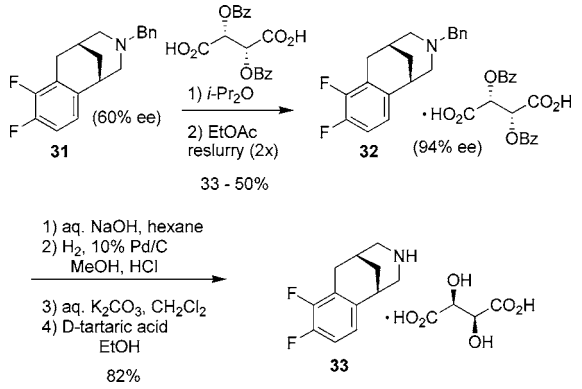
Although the catalytic dihydroxylation of olefin **29** could be effectively accomplished with osmium tetroxide, concern over the monitoring and control of residual osmium led us to use an alternate reagent during scale-up. We found that stoichiometric potassium permanganate performed well for this conversion, as reported by Ogino and Mochizuki.[13] An aqueous $NaHSO_3$ workup followed by a filtration of the organic phase through two weight equivalents of silica gel with dichloromethane−ethyl acetate provided diol **30** as an oil, which crystallized upon standing (42−78% yield). The structure shown in Scheme 5 was obtained by X-ray crystal analysis of **30**, confirming that dihydroxylation had occurred from the less-hindered exo face.

(11) (a) Su, T. M.; Sliwinski, W. F.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1969**, *91*, 5386−5388. (b) Stang, P. J.; Hanack, M.; Subramanian, L. R. *Synthesis* **1982**, 85−126. (c) Bashore, C. G.; Samardjiev, I. J.; Bordner, J.; Coe, J. W. *J. Am. Chem. Soc.* **2003**, *125*, 3268−3272.

(12) Gas-phase calculations of carbopallidation adducts before β-hydride elimination were performed, but the results did not align with the observed sense of enantiofacial induction.

(13) Ogino, T.; Mochzuki, K. *Chem. Lett.* **1979**, 443−446.

Scheme 6



Conversion of diol **30** to benzyl amine **31** (Scheme 5) was accomplished by initial cleavage of the diol, with sodium periodate in buffered methanol, to form the dialdehyde (which existed as a mixture of hydrated cyclic hemiacetals by ^{1}H NMR analysis). The dichloromethane extracts from this reaction were added to a cold dichloromethane slurry containing benzyl amine (2 equiv) and $NaBH(OAc)_3$ (3.3 equiv) to complete the *N*-benzyl piperidine formation, **31**. The reaction was quenched after 1−2 h; prolonged reaction times (>12 h) generated an impurity corresponding to *N*-benzylacetamide by MS analysis.

To enrich the desired enantiomer from racemic and nonracemic mixtures, a dibenzoyl-L-tartaric acid resolution with **31** was developed. The formation of salt **32** using isopropyl ether served as an initial purification step. Two additional reslurries in ethyl acetate drove the chiral purity to 94% ee. Hydrogenolysis cleaved the benzyl amine to give free base **31**, and conversion to D-tartrate salt **33** completed the synthesis of the desired active pharmaceutical ingredient (Scheme 6).

We have described an efficient enantioselective synthesis of **1** using a six-step sequence. A series of process improvements were introduced that supported an effective large-scale synthesis. Adopting an alkylation strategy eliminated the need to remove a pendant hydroxyl group thus streamlining the process from the original approach. Key observations were made that enhanced our understanding and supported large-scale processing. First, we found that lithiation of **12** by LDA is rapid, and this allowed us to remove any unnecessary reaction hold times. This, in conjunction with a novel procedure to produce stable solutions of the highly reactive triflate **21**, provided a consistently reproducible procedure for the critical alkylation C−C bond-forming step to produce **24**. Studies of the BINAP/$Pd(OAc)_2$-mediated Heck cyclization reaction revealed that greatly improved enantioselectivities to product **29** result from control of adventitious oxygen. Resolution with dibenzoyl-L-tartaric acid effectively enhanced the chiral purity of **31**, and final cleavage of the benzyl protecting group provided **1**, which was isolated as a D-tartrate salt.

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Supporting Information Available: Experimental procedures and spectral data for all new compounds, differential scanning calorimetry, and enantiomeric ratio experiments. This material is available free of charge via the Internet at http://pubs.acs.org.

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