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First Asymmetric Synthesis of *trans*-3,4-Dimethyl-4-arylpiperidines

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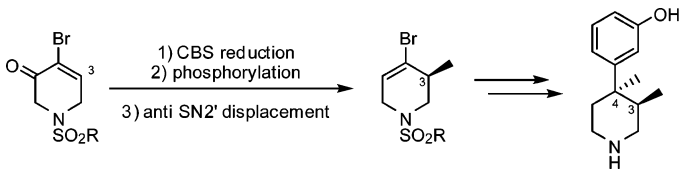
ABSTRACT



The first asymmetric synthesis of the *trans*-3,4-dimethyl-4-arylpiperidine opioid antagonist scaffold is reported. C-3 stereochemistry was established via CBS reduction and stereoselective *anti*-S_N2' cuprate displacement of the derived allylic phosphonate. The resultant vinyl bromide was then elaborated to the target compound by Suzuki coupling and *trans*-selective 4-methylation. Extension of this methodology should allow general enantioselective access to highly substituted piperidine ring systems.

trans-3,4-Dimethyl-4-(3-hydroxyphenyl)piperidines are an important class of non-morphinoid compounds that exhibit pure antagonist activity at opioid receptors.[1] Since their initial discovery in 1978, extensive study of ligands derived from the basic piperidine scaffold (**1**, Figure 1) has delivered several promising drug candidates including JDTic (**2**)[2] for treatment of drug abuse and Alvimopan (**3**)[3] for prevention of gastrointestinal side effects of opioid analgesia.

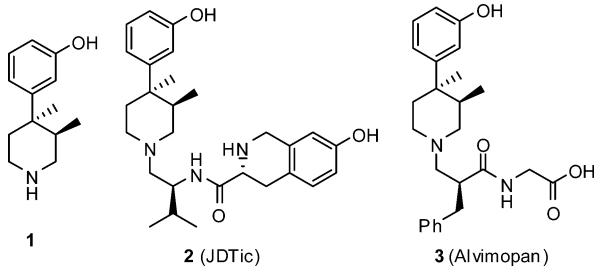


Figure 1. Selective opioid antagonists based on the 3,4-*trans*-dimethyl-4-(3-hydroxyphenyl)piperidine scaffold.

To date, only racemic syntheses of **1** have been reported, and consequently, enantiomeric resolution of chiral salts is required to deliver optically pure material.[4] Although this approach is convenient for large-scale production, an asymmetric synthesis would avoid the loss of material represented by the unwanted stereoisomer and potentially allow access to novel chemical entities for pharmacological study.

From a retrosynthetic point of view, metalation and alkylation of 4-arylpiperidines such as **4** (Figure 2) is known to afford exclusively the *trans*-3,4-dimethyl product **1** after reduction of the initially obtained enamine.[5] We expected that enantiopure **4** should in turn be available from **5** via Pd-catalyzed coupling with an arylboronic acid and appropriate protecting group manipulation.

Unsaturated piperidines such as **5** are not well-known in the literature,[6] but we anticipated that their assembly might

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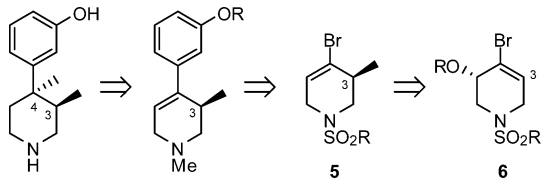
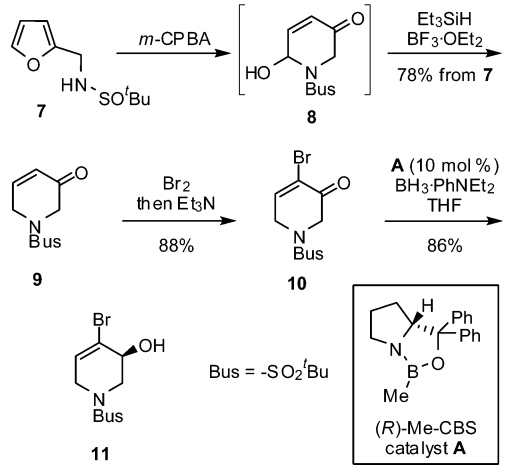


Figure 2. Retrosynthetic analysis of **1**.

be accomplished by an approach beginning with *aza*-Achmatowicz reaction of α-furfuryl amine **7** (Scheme 1) to

Scheme 1

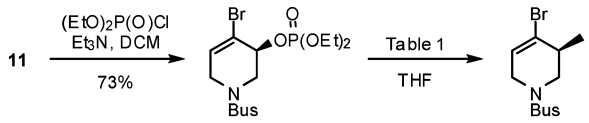


establish the 3-piperidinone ring system.[7] The cyclohexyl analogue of **11** has previously been prepared enantioselectively via CBS reduction of the corresponding ketone,[8] and although stereoselective S_N2' displacements involving derivatives of **11** are unreported, we had reason to believe that the reaction might be successful based on the reports of the Knochel group involving vinyl iodides and zinc cuprate nucleophiles.[9]

Upon treatment with slightly more than 2 equiv of *m*-CPBA, protected α-furfuryl amine **7** was smoothly converted to intermediate hydroxyaminal **8** with concomitant oxidation of the sulfinamide (Scheme 1). In our hands however, **8** proved particularly unstable and resisted all attempts at purification or isolation. Combining the two steps into a one-pot operation[10] was unsuccessful, but further investigation revealed that basic aqueous workup *without removal of solvent* allowed the subsequent reduction to proceed to afford 3-piperidinone **9** in good yield. One-pot bromination−elimination gave α-bromoenone **10** which was conveniently purified by recrystallization from methanol. Luche reduction of **10** proceeded quantitatively to give *rac*-**11**, and we were pleased to find that CBS reduction of **10** using the catalyst derived from (*R*)-(+)-diphenylprolinol and methylboronic acid[8] provided (+)-**11** in high yield with excellent enantioselectivity (96% ee by chiral HPLC).

To effect the S_N2' displacement, **11** was transformed into the corresponding diethylphosphonate **12**.[11] Treatment of **12** with dialkyl cuprates (Scheme 2, entries 1 and 2) proved

Scheme 2



	RM[a]	equiv[b]	Cu source	time (h)	temp (°C)	yield (%)
1	MeLi	2	CuCN.2LiCl	0.1	-78	-[c]
2	MeMgCl	2	CuCN.2LiCl	0.1	-78	-[c]
3	MeZnCl	2	CuCN.2LiCl	48	-10 to 0	-[d]
4	MeLi	1	CuCN.2LiCl	16	-10 to 0	57[e]
5	MeMgBr	1	CuCN.2LiCl	6	-10 to 0	62
6	MeMgBr	1	CuBr.Me_2S	0.3	-10	83
7	MeMgBr	1	CuBr.Me_2S	6	-35	93

[a] **12** (1 equiv) added to preformed organocuprate (2 equiv) in THF. [b]Equivalents of RM relative to the copper source. [c]Complex mixture. [d]No reaction. [e]Plus 30% recovered starting material.

disappointing, however. Starting material was rapidly consumed at low temperature to provide an inseparable mixture of many products, possibly containing **13**, in addition to compounds obtained via other reaction pathways. Use of the organozinc-derived copper reagent (entry 3) did not result in any reaction even after prolonged reaction times. We were finally pleased to discover that use of the monoalkyl cuprate derived from methyllithium and CuCN·2LiCl (entry 4) led to the slow formation of the desired product **13** in reasonable yield, the remainder of the mass balance being unreacted starting material which could be recovered and reused.

Further investigation of the nucleophilic component (entries 5 and 6) revealed that the combination of methyl Grignard and the copper bromide−dimethyl sulfide complex was most effective, leading to rapid and complete consumption of starting material. To confirm the exact mechanism of the displacement, *d*-**12** was prepared by Luche reduction of **10** with $NaBD_4$ and submitted to the optimized reaction conditions (Scheme 3).

Examination of the deuterium ^{2}D NMR spectra of the product mixtures revealed that at −10 °C the displacement proceeded with S_N2':S_N2 selectivity of only ca. 3.5:1, as determined by the ratio of products **13b**/**13c**.[12] Lowering the

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(7) Zhou, W.-S.; Lu, Z.-H.; Xu, Y.-M.; Liao, L.-X.; Wang, Z.-M. *Tetrahedron* **1999**, *55*, 11959.
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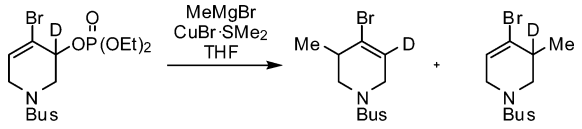
(11) Yanagisawa, A.; Noritake, Y.; Nomura, N.; Yamamoto, H. *Synlett* **1991**, 251.

Scheme 3*



-10 °C[a]	68%	19%
-35 °C[b]	83%	<1%

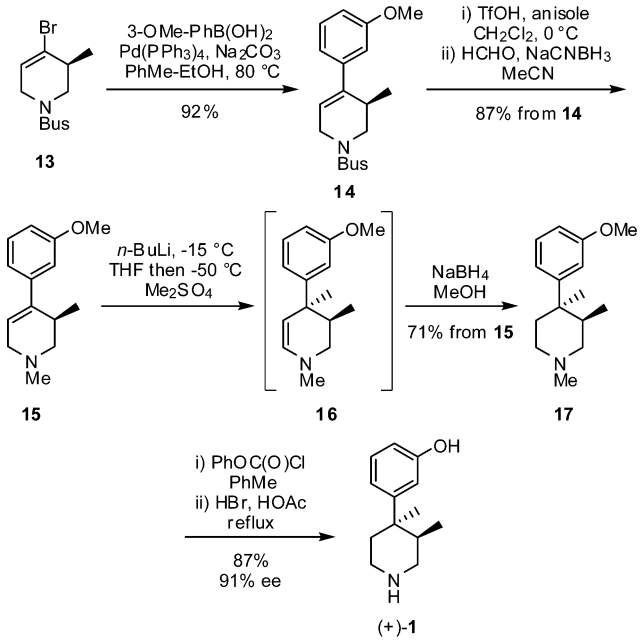
* Ratio **13b**/**13c** determined by deuterium ^{2}D NMR. [a] Complete in 30 min. [b]Complete in 4 h.

temperature to −35 °C extended the reaction time to 4 h and resulted in almost exclusive preference for the S_N2' pathway.

Compound **13** exhibited an optical rotation of $[\alpha]_D$ −9.0 (*c* 0.062, $CHCl_3$), but to assess the enantiomeric excess obtained, it proved necessary to carry this material forward through the synthesis for comparison with previously reported data.

Our attention now turned to preparation of the complete 3,4-*trans*-dimethyl-4-arylpiperidine system (Scheme 4). Suzuki coupling of **13** with 3-methoxybenzeneboronic acid afforded **14** in high yield, contaminated by a small amount (<5%) of inseparable homocoupling product, which could be readily separated at the next step. The coupling product was then transformed into the required *N*-methyl alkylation substrate **15** by quantitative removal of the *N*-*tert*-butylsulfonamide group with triflic acid in the presence of anisole as a cation scavenger[13] and reductive amination of the free amine.

Scheme 4



Metalation of **15** with butyllithium at −15 °C according to a literature procedure[4b] followed by quenching of the resultant stabilized anion with dimethylsulfate at −50 °C led to 4-alkylation exclusively *trans* to the 3-methyl substituent. Reduction of the crude enamine product **16** with sodium borohydride in methanol gave amine **17** in 71% yield over the two steps.

We were pleased to find that NMR analysis of **17** with the chiral complexing agent (*S*)-(+)-1-(9-anthryl)-2,2,2-trifluoroethanol[4a,14] indicated the presence of only one enantiomer to the limits of NMR detection. Comparison of the measured optical rotation ($[\alpha]_D$ +69.3, *c* 0.021, MeOH) with the literature value for the ^{i}Pr ether analogue ($[\alpha]_D$ +76.2, *c* 1.01, MeOH)[4b] suggested that the key S_N2' displacement had indeed occurred stereoselectively *anti* to the phoshonate in **12** to eventually afford the desired enantiomer (+)-**17**.

Finally, deprotection of the *N*- and *O*-methyl groups was achieved in two operations under standard conditions to give the target 4-(3-hydroxyphenyl)-3,4-*trans*-dimethylpiperidine (+)-**1** in excellent yield. Chiral HPLC analysis in comparison with a racemic sample confirmed an enantiomeric excess of 91.1%.

In conclusion, the first asymmetric synthesis of the pharmaceutically important 4-aryl-3,4-dialkylpiperidine opioid antagonist scaffold is reported via the unprecedented stereoselective displacement of an enantiopure α-bromo allylic phosphonate. Due to the variety of reactions possible starting from 4-brominated unsaturated piperidines such as **10** or **11**, we hope this chemistry will prove useful for enantioselective synthesis of natural products and pharmaceutical target compounds containing highly substituted piperidine ring systems.

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

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(12) Determined by the relative integrals of the signals due to deuterium in the vinylic (**13b**) and allylic (**13c**) positions (δ 6.00 and 2.59 ppm, respectively).

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(14) Doubling of signals due to the three methyl groups was observed with a racemic sample.