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Discovery of μ-opioid selective ligands derived from 1-aminotetralin scaffolds made via metal-catalyzed ring-opening reactions

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ABSTRACT

A series of 1-aminotetralin scaffolds was synthesized via metal-catalyzed ring-opening reactions of heterobicyclic alkenes. Small libraries of amides and amines were made using the amino group of each scaffold as a handle. Screening of these libraries against human opioid receptors led to the identification of (*S*)-(*S*)-**5.2a** as a high-affinity selective μ ligand (IC_{50} μ = 5 nM, κ = 707 nM, δ = 3,795 nM) displaying μ-agonist/antagonist properties due to its partial agonism (EC_{50} = 2.6 μM; E_{max} = 18%).

Opioid receptor ligands (opiates) have been used medicinally for thousands of years, and work continues to identify and develop selective, well-tolerated molecules for several different indications. During the course of an ongoing search for potent and selective novel opioid receptor ligands, it was recognized that tetrahydronaphthalenes (tetralins) such as the κ-agonist **1**[1] (Scheme 2) could be conveniently accessed by new metal-catalyzed ring-opening methods developed in our labs.[2] A variety of other tetralins also have important and diverse bioactivities, including morphine, sertraline, and podophyllotoxin. We were thus inspired to initiate a program to synthesize gram-scale quantities of 1,2-disubstituted tetralin scaffolds which could be utilized in drug discovery efforts. This paper describes the synthesis of several of these scaffolds and their application in library synthesis, which has led to the identification of a selective and high-affinity μ-opioid receptor ligand with low μ-efficacy. Such compounds are clinically important as analgesics (e.g., meperidine (Demerol®) and dezocine (Dalgan®)), and for the treatment of drug addiction (e.g., methadone and buprenorphine[3]).

At the outset of this project, we decided to focus on making 1-aminotetralin scaffolds with diverse substitution patterns and stereochemistry. We accessed these structures via rhodium-catalyzed ring-opening of oxabenzonorbornadienes with a variety of nucleophiles,[4] followed by displacement of the resulting hydroxyl groups with azide, followed by reduction (Scheme 1). A number of developments in our labs have enabled the use of alcohol,[5] carboxylate,[5] phenol,[5] amine,[5] and sulfide[6] nucleophiles with rhodium (I) catalysts, which generally lead to ring-opened products of exclusive *trans* stereochemistry with excellent enantioselectivities. Concurrently, several metals have been reported to enable ring-openings of oxabicyclic alkenes with alkyl,[7] aryl,[8] and alkenyl[7] nucleophiles,[9] which generally give exclusively *cis* configured products.[10]

Subsequent to our initial synthetic studies, it was found that ring-opening reactions of less-reactive azabenzonorbornadienes are possible under appropriate conditions, with both heteroatom[2,11] and carbon-based[12] nucleophiles (Scheme 2). These reactions have the advantage of giving a direct synthesis of 1-aminotetralin scaffolds, in general with complementary relative stereochemistry to the products of the sequences outlined in Scheme 1.[13] This approach has additionally been used for the synthesis of several libraries not described in this communication.

According to the chemistry outlined in Schemes 1 and 2, both di- and tetrahydronaphthalenes are accessible. Tetrahydronaphthalenes are generally more stable (less prone to oxidation and elimination reactions), but several examples of dihydronaphthalene scaffolds were used for library synthesis. In the reactions outlined in Scheme 2, hydrogenation of the olefin generally preceeds deprotection, except in the case of nosyl-protected products.

With scaffolds of types **4.1**–**4.6** in hand (Schemes 1 and 2), we prepared a number of secondary scaffolds by acylating the amine

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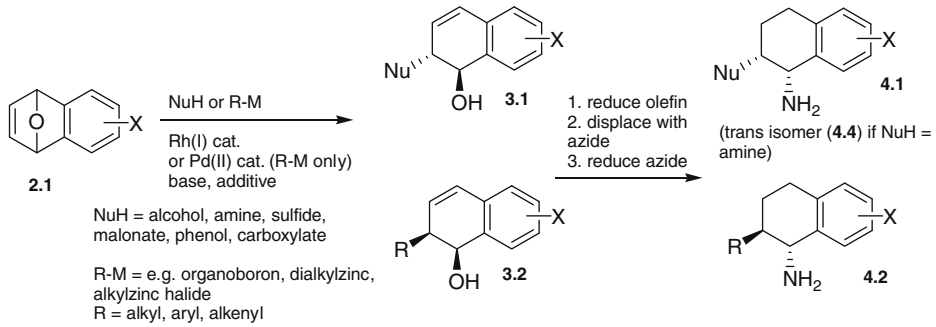
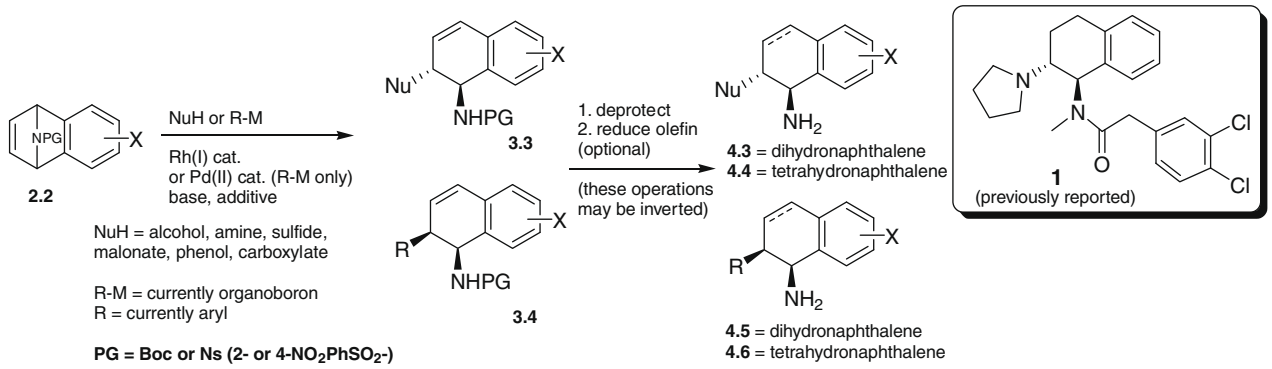


Scheme 1. Synthesis of 1-aminotetralin ligands via ring-opening of oxabicylic alkenes.

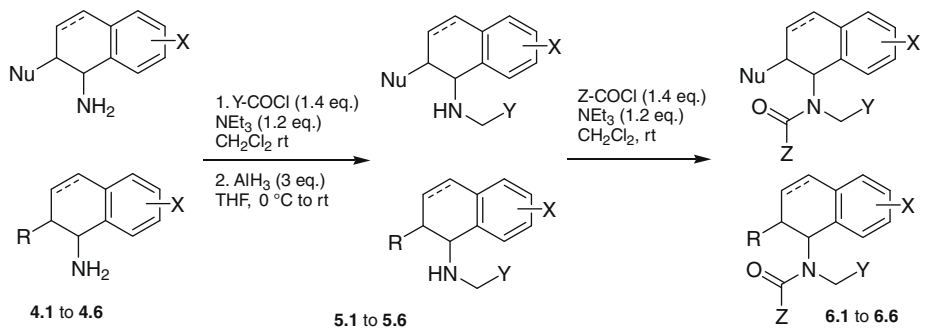


Scheme 2. Synthesis of 1-aminotetralin ligands via ring-opening of azabicylic alkenes.

moieties with several acid chlorides and reducing the resulting amide carbonyl groups with alane (AlH_3).[14] These were then acylated with a set of commercially available acid chlorides to give a series of focused libraries (Scheme 3). A selection of racemic compounds of types **5.1**–**5.6** was made, along with amide libraries composed of compounds of types **6.1**–**6.6**. These were screened against cloned human opioid receptors. Initial screening was performed at a concentration of 10 μM for each library member. Competitive binding studies with standard radiolabelled ligands were used for each receptor. Compounds showing greater than 50% inhibition were re-synthesized, purified and underwent further measurements to calculate IC_{50} values, of which selected results are presented in Table 1.

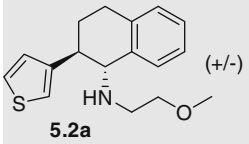
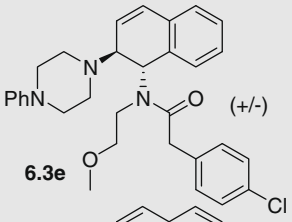
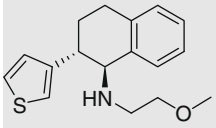
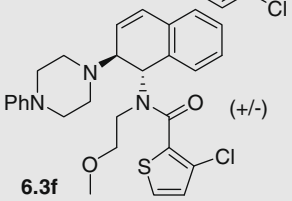
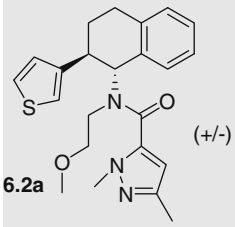
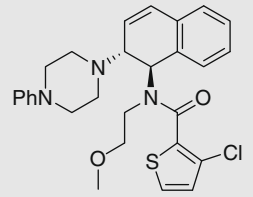
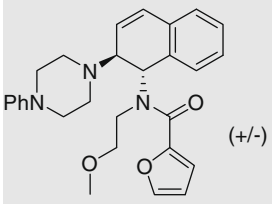
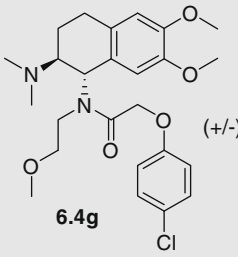
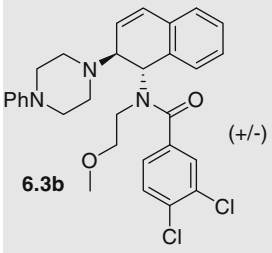
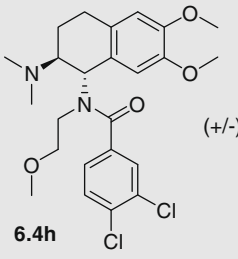
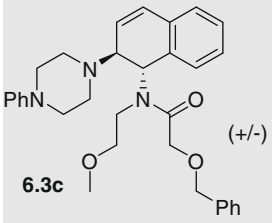
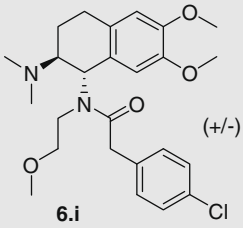
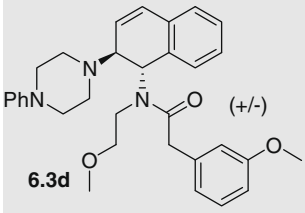
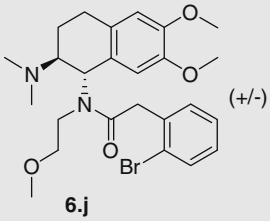
Prompted by the initial screening results (vide infra), we re-synthesized compounds **5.2a** and **6.3f** in enantiopure form, which provide good illustrations of the specific synthetic sequences discussed in general terms previously. The single enantiomers of **5.2a** were made as outlined in Scheme 4. We have found that the rhodium-catalyzed ring-opening reactions with heteroaryl nucleophiles have often been problematic due to insertion of the rhodium into one of the aromatic C–H bonds from a catalytic intermediate after addition of Rh–Ar across the olefin, which leads to unopened and/or oligomeric adducts.[15] However, we were pleased to find that in this case the ring-opening reaction with thiophene-3-boronic acid proceeded in moderate yield with excellent enantioselectivity using the Josiphos-type ligand PPF-P(t-Bu)$_2$, in accordance with our original report.[8b] The intermediate dihydronaphthalene was hydrogenated using diimide generated *in-situ* from the oxidation ($NaIO_4$) of hydrazine, giving the *cis*-tetrahydronaphthol **3.2a**. Mitsunobu inversion proceeded to give azide **3.2b** in moderate yield. Staudinger reduction of **3.2b** with PPh_3 in THF with an excess of water proceeded quantitatively, and the resulting crude amine **4.2a** was acylated to give amide **4.2b**. An X-ray crystal structure of this intermediate confirmed the expected absolute configuration.[16] Reduction with alane[14] gave the desired single enantiomers of **5.2a** in excellent yield.

The synthesis of the enantiomers of **6.3f** (Scheme 5) began with the Rh-catalyzed asymmetric ring-opening of *N*-Boc azabenzonor-

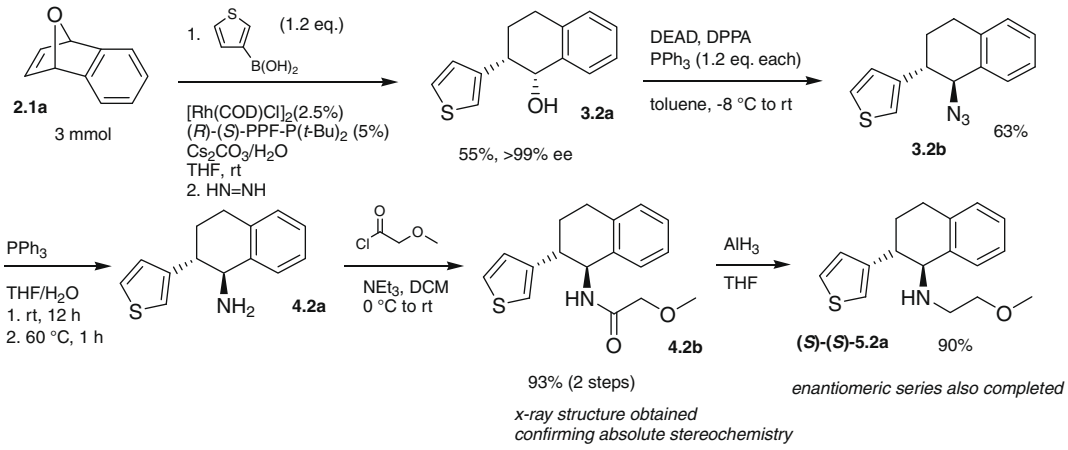


Scheme 3. Functionaliztion of 1-aminotetralins and library synthesis.

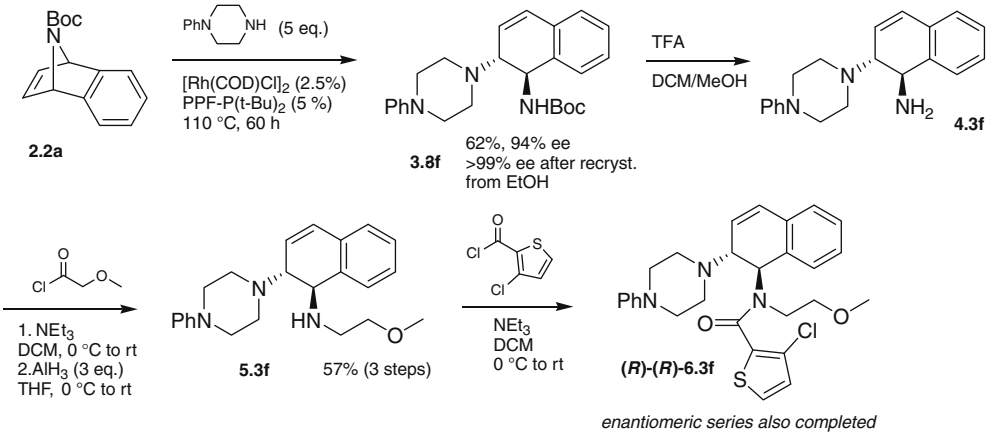
Table 1
Binding and μ functional data for selected compounds active against human opioid receptors

Compound	μ IC_{50} (nM)	κ IC_{50} (nM)	δ IC_{50} (nM)	μ EC_{50} (nM)	μ E_{max} (%)	Compound	μ IC_{50} (nM)	κ IC_{50} (nM)	δ IC_{50} (nM)	μ EC_{50} (nM)	μ E_{max} (%)
 **5.2a**	69	2209	7161	>90,000	15	 **6.3e**	181	7993	1955	>90,000	0
 (*S*)-(*S*)-**5.2a**	5.3	707	3795	2600	18	 **6.3f**	100	7136	2289	>90,000	0
 **6.2a**	4862	>10,000	1274	N.T.	N.T.	 (*R*)-(*R*)-**6.3f**	58	1324	1243	N.T.	N.T.
 **6.3a**	126	>10,000	3947	>90000	5	 **6.4g**	245	155	>10,000	>90,000	0
 **6.3b**	443	>10,000	3620	>90,000	60	 **6.4h**	351	6002	3501	>90,000	0
 **6.3c**	211	6121	3887	>90,000	10	 **6.i**	1122	922	>10,000	>90,000	0
 **6.3d**	151	>10,000	1467	>90,000	10	 **6.j**	4828	1005	>10,000	N.T.	N.T.

All compounds are ⩾95% pure. Inhibition binding assays were performed against [^{125}I]-FK33824, [^{125}I]-deltorphin II, and [^{125}I]-U69593 for μ, δ, and κ, respectively.Values are means of 3 measurements. N.T., not tested.



Scheme 4. Enantioselective synthesis of **5.2a**.



Scheme 5. Enantioselective synthesis of **6.3f**.

bornadiene **2.2a** with *N*-phenylpiperazine, using PPF-P(*t*-Bu)$_2$ as ligand. Dihydronaphthalene **3.3f** was obtained in 62% yield, 94% ee, and >99% ee after recrystallization. It was necessary to heat the reaction in neat *N*-phenylpiperazine at 110 °C for an extended period (60 h) for good conversion. Since this work was performed, our lab has reported improved results (92%,93% ee) using C_2-Ferriphos as the ligand.[11] Deprotection with TFA, acylation with methoxyacetyl chloride, reduction of the intermediate amide with alane, and acylation with 3-chlorothiophene-2-carbonyl chloride proceeded smoothly to give the individual enantiomers of **6.3f**.

Binding and μ functional data for selected tetralin compounds is given in Table 1. The *N*-phenylpiperazine dihydronaphthalenes (**6.3a-6.3f**) are μ-selective ligands that are weakly sensitive to the acyl side chain employed, with μ potencies ranging from 100–440 nM. The most potent and selective compound from this subclass is **6.3f** which shows μ IC_{50} of 100 nM and is >20-fold selective versus κ and δ-opioid receptors. In the case of dimethylamino analogues (**6.4g-6.4j**) with the tetrahydronaphthalene core, μ affinity was found to be sensitive to the acyl side chain employed (e.g., **6.4g** and **6.4h** vs. **6.4i** and **6.4j**). Moreover, depending on the acyl group, it is possible to introduce activity at the κ-opioid receptor thereby affording mixed μ/κ activity (e.g., **6.4g**). Overall, tetralin **5.2a**, derived from the ring-opening of oxabenzonorbornadiene with thiophene-3-boronic acid, showed the most active binding to the μ-opioid receptor (IC_{50} = 69 nM) and selectivity versus δ- and κ-opioid receptors (>30-fold).

We were pleased to observe that the (*S*)–(*S*) enantiomer of 5.2a (IC_{50} μ = 5 nM, κ = 707 nM, δ = 3795 nM) and the (*R*)–(*R*) enantiomer of 6.3f (IC_{50} μ = 58 nM, κ = 1324 nM, δ = 1243 nM,) both displayed high affinity and excellent selectivity for the human μ-opioid receptor.[17]

Selected compounds in Table 1 were tested for agonist activity at the human μ-receptor, using [^{35}S]-GTPγS binding as the functional endpoint, as described elsewhere.[18,19] Compound **5.2a** displayed measurable agonist efficacy. Its weak EC_{50}, shifted to the right compared to its IC_{50}, may be due at least in part to the requirement of sodium in the functional assay (sodium decreases the affinity of opioid agonists[20]). The more active enantiomer, (*S*)–(*S*)-**5.2a**, was characterized further by [^{35}S]-GTPγS binding assay. (*S*)–(*S*)-**5.2a** yielded low efficacy (E_{max} 18% at 100 μM; EC_{50} = 2.6 μM), and was shown to reverse DAMGO in a dose dependent manner, down to the level of its own intrinsic efficacy (Fig. 1).

In summary, we have utilized several metal-catalyzed ring-opening reactions developed in our laboratories to synthesize a variety of 1-aminotetralin-type scaffolds. Several examples of rhodium-catalyzed additions of carbon and heteroatom nucleophiles to heterobicyclic alkenes were presented. These scaffolds were used to make libraries of amines and amides, which have been

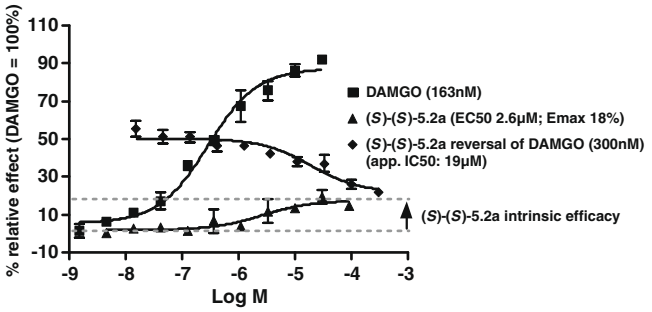


Figure 1. Reversal of DAMGO by (*S*)–(*S*)-**5.2a** in a [^{35}S]-GTPγS binding assay. Average of two experiments performed in duplicate. Data points are displayed as the arithmetic mean value ± SD; maximal effect (100%) is relative to DAMGO (30 μM).

screened against cloned human opioid receptors. The high-affinity μ-selective ligand (*S*)–(*S*)-**5.2a** emerged as a molecule displaying partial μ-agonist/antagonist properties. The maximal effect of (*S*)–(*S*)-**5.2a** as a partial agonist on human μ-opioid receptor-mediated [^{35}S]-GTPγS binding (18% E_{max}, with EC_{50} = 2.6 μM) was slightly below that of meperidine (28% E_{max} and 9.4 μM EC_{50}).[19] However, we found that (*S*)–(*S*)-**5.2a** had higher μ-efficacy than the clinically used μ-opioid partial agonist dezocine, which showed only 6% E_{max} and 38 nM EC_{50} in our μ [^{35}S]-GTPγS functional assay).[21] Drugs with a similar profile have proved beneficial in the treatment of pain as well as for the treatment of drug addiction, particularly due to their low dependence-inducing potential.[3]

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2008.12.095.

References and notes

1. (a) Freeman, J. P.; Michalson, E. T.; D'Andrea, S. V.; Baczynskyj, L.; Von Voigtlander, P. F.; Lahti, R. A.; Smith, M. W.; Lawson, C. F.; Scahill, T. A.; Mizsak, S. A.; Szmuszkovicz, J. *J. Med. Chem.* **1991**, *34*, 1891; (b) Rajagopalan, P.; Scribner, R. M.; Pennev, P.; Schmidt, W. K.; Tam, S. W.; Steinfels, G. F.; Cook, L. *Bioorg. Med. Chem. Lett.* **1992**, *2*, 715.
2. Lautens, M.; Fagnou, K.; Zunic, V. *Org. Lett.* **2002**, *4*, 3465.
3. Buprenorphine is a partial mu agonist used in both analgesia and the treatment of heroin addiction. See for example Tzschentke, T. M. *Psychopharmacology* **2002**, *161*, 1.
4. (a) Lautens, M.; Fagnou, K.; Hiebert, S. *Acc. Chem. Res.* **2003**, *36*, 48; (b) Lautens, M.; Fagnou, K.; Yang, D. *J. Am. Chem. Soc.* **2003**, *125*, 14884.
5. See Ref. 4 and references therein.
6. Leong, P.; Lautens, M. *J. Org. Chem.* **2004**, *69*, 2194.
7. For selected examples, see Ref. 4a and references therein, as well as: Scope studies (a) Lautens, M.; Hiebert, S. *J. Am. Chem. Soc.* **2004**, *126*, 1437; Application in total synthesis (b) Lautens, M.; Colucci, J. T.; Hiebert, S.; Smith, N. D.; Bouchain, G. *Org. Lett.* **2002**, *4*, 1879; (c) Mechanism: Lautens, M.; Hiebert, S.; Renaud, J. -L. **2001**, *123*, 6834.; With organozinc halides (d) Zhang, T. K.; Yuan, K.; Hou, X.-L. *J. Organomet. Chem.* **2007**, *692*, 1912.
8. (a) Murakami, M.; Igawa, H. *Chem. Comm.* **2002**, 390; (b) Lautens, M.; Dockendorff, C.; Fagnou, K.; Malicki, A. *Org. Lett.* **2002**, *4*, 1311.
9. It should also be noted that Cheng and coworkers have synthesized a variety of dihydronaphthalenes from metal-catalyzed ring-opening reactions with electrophilic partners (e.g. aryl halides) under reductive conditions. See for example (a) Wu, M.-S.; Rayabarapu, D. K.; Cheng, C.-H. *J. Org. Chem.* **2004**, *69*, 8407. and references therein; For variations reported by Martin, see (b) Chen, C.-L.; Martin, S. F. *J. Org. Chem.* **2006**, *71*, 4810. and references therein.
10. An exception is the Cu-catalyzed alkylative ring-opening reactions reported by Feringa which provide selectively trans adducts Bertozzi, F.; Pineschi, M.; Macchia, F.; Arnold, L. A.; Minnaard, A.; Feringa, B. L. *Org. Lett.* **2002**, *4*, 2703; See also Zhang, W.; Wang, L.-X.; Shi, W.-J.; Zhou, Q.-L. *J. Org. Chem.* **2005**, *70*, 3734.
11. Cho, Y.-H.; Zunic, V.; Senboku, H.; Olsen, M.; Lautens, M. *J. Am. Chem. Soc.* **2006**, *128*, 6837.
12. See for example (a) Lautens, M.; Hiebert, S.; Renaud, J.-L. *Org. Lett.* **2000**, *2*, 1971; (b) Lautens, M.; Dockendorff, C. *Org. Lett.* **2003**, *5*, 3695; (c) Carretero, J. C.; Cabrera, S.; Arrayás, R. G. *Angew. Chem. Int. Ed.* **2004**, *43*, 3944; (d) Arrayás, R. G.; Cabrera, S.; Carretero, J. C. *Org. Lett.* **2005**, *7*, 219; (e) Arrayás, R. G.; Cabrera, S.; Carretero, J. C. *Synthesis* **2006**, 1205; (f) McManus, H. A.; Fleming, M. J.; Lautens, M. *Angew. Chem. Int. Ed.* **2007**, *46*, 433.
13. An exception involves the ring-opening of oxabenzonorbornadienes with secondary amines. Displacement of the resulting hydroxyl group proceeds with retention of configuration, thus only trans products are normally accessible via this sequence. See: Lautens, M.; Schmid, G. A.; Chau, A. *J. Org. Chem.* **2002**, *67*, 8043.
14. (a) Brown, H. C.; Yoon, N. M. *J. Am. Chem. Soc.* **1968**, *90*, 2927; (b) Cha, J. S.; Brown, H. C. *J. Org. Chem.* **1993**, *58*, 3974.
15. (a) Dockendorff, C.; Lautens, M.; Lough, A. *J. Acta Cryst.* **2006**, *E62*, o1601; (b) Oguma, K.; Miura, M.; Satoh, T.; Nomura, M. *J. Am. Chem. Soc.* **2000**, *122*, 10464; (c) Menard, F.; Lautens, M. *Angew. Chem. Int. Ed.* **2008**, *47*, 2085.
16. Dockendorff, C.; Lautens, M.; Lough, A. J. *Acta Cryst.* **2006**, *E62*, o639 (X-ray coordinates were also deposited in the Cambridge Crystallographic Data Centre, deposition number 298396).
17. The IC_{50} at the μ-receptor for (*S*)–(*S*)-**6.3f** = 2.8 μM, and for (*R*)–(*R*)-**5.2a** = 772 nM.
18. The methods used to determine receptor binding and function values were similar to those used in previous reports by AstraZeneca. See Plobeck, N. et al *J. Med. Chem.* **2000**, *43*, 3878.
19. K. Payza, Binding and activity of opioid ligands at the cloned human delta, mu, and kappa receptors. In *The Delta Receptor*; K. -J. Chang, F. Porreca, J. H. Woods, Eds.; Marcel Dekker, New York, pp. 261.
20. Pfeiffer, A.; Sadée, W.; Herz, A. *J. Neurosci.* **1982**, *2*, 912.
21. Payza, K.; St-Onge, S.; LaBarre, M.; Godbout, C.; Wahlestedt, C. *Abstracts of Papers, 26th Annual Meeting of the Society of Neuroscience*; Washington, DC; 1996 (Abstract 695.14).