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Novel Stereoselective Syntheses of the Fused Benzazepine Dopamine D_1 Antagonist (6a*S*,13b*R*)-11-Chloro-6,6a,7,8,9,13b-hexahydro-7-methyl-5*H*-benzo[*d*]naphth[2,1-*b*]azepin-12-ol (Sch 39166): 1. Aziridinium Salt Based Syntheses

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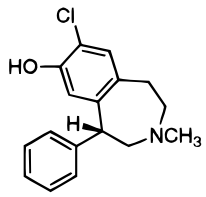
Abstract:

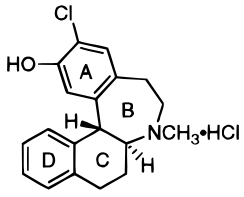
Several novel enantioselective syntheses of the dopamine D_1 antagonist (6a*S*,13b*R*)-11-chloro-6,6a,7,8,9,13b-hexahydro-7-methyl-5*H*-benzo[*d*]naphth[2,1-*b*]azepin-12-ol (2) are described in which the key intermediate was 1-(2,2-dimethoxyethyl)-1-methyl-1a,2,3,7b-tetrahydro-1*H*-naphth[1,2-*b*]aziridinium salt (20). The latter species was prepared either from 1-(2,2-dimethoxyethyl)-1a,2,3,7b-tetrahydro-1*H*-naphth[1,2-*b*]-azirine (18) by methylation or from the tertiary amino alcohols 1-[(2,2-dimethoxyethyl)methylamino]-1,2,3,4-tetrahydro-2-naphthalenol (23) or 2-[(2,2-dimethoxyethyl)methylamino]-1,2,3,4-tetrahydro-1-naphthalenol (24) by tosylation and in situ ring closure. Regioselective trapping of 20 with Grignard reagent (4-chloro-3-methoxyphenyl)magnesium bromide (10) then afforded the trans amine 1-(4-chloro-3-methoxyphenyl)-*N*-(2,2-dimethoxyethyl)-1,2,3,4-tetrahydro-*N*-methyl-2-naphthalenamine (22), which was cyclized to give 11-chloro-6,6a,7,8,9,13b-hexahydro-7-methyl-12-methoxy-5*H*-benzo[*d*]-naphth[2,1-*b*]azepine (9), a known precursor of 2. Several enantioselective syntheses, including a Jacobsen epoxidation route, a *de novo* synthesis from L-homophenylalanine, and a classical salt resolution sequence, were developed for the preparation of the key intermediates in chiral form.

Introduction

The neurotransmitter dopamine is reported to play an important role in several psychiatric and neurological disorders. Parkinson's disease, for example, is associated with an underproduction of this substance in the brain, while an overproduction has been implicated in psychological disorders such as schizophrenia.[1] Consequently, the control of dopamine activity by interception of dopamine receptors with agonists and antagonists is of great interest. 2,3,4,5-Tetrahydro-3-benzazepines have been the subject of much study during the last few decades because of their selective affinity for the D_1 subpopulation[2,3] of dopamine receptors in both the central nervous system and the periphery. For members of this series of compounds, the effects of substitution on antagonist[4] and agonist[5] activity have been reported. The potential of this class of therapeutic agents to exhibit pharmacological properties superior to those already in the marketplace has stimulated considerable research in this field. Our own efforts in this area have led to the discovery of (*R*)-7-chloro-8-hydroxy-1-phenyl-2,3,4,5-tetrahydro-3-methyl-1*H*-3-benzazepine (Sch 23390, **1**)[6] and subsequently the more potent (6a*S*,13b*R*)-11-chloro-6,6a,7,8,9,13b-hexahydro-7-methyl-5*H*-benzo[*d*]naphth[2,1-*b*]azepin-12-ol (Sch 39166, **2**),[7] a compound in which the conformational mobility of the pendant phenyl ring has been restricted and unequivocally fixed by the construction of an ethylene bridge between the latter and the 6a carbon of the benzazepine ring. Immobilization of the phenyl ring maintained the selectivity of **2** for the D_1 receptor versus the D_2 receptor and, more significantly, increased the half-life of **2** relative to **1** in primates, making it potentially a clinically useful drug.[8]



Sch 23390 (1)



Sch 39166 (2)

In vivo, compound **2** exhibited a profile of activity in several species which was indicative of potential antipsy-

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(1) Meltzer, H. Y. *Schizophr. Bull*. **1980**, *6*, 456.
(2) Kebabian, J. W.; Calne, D. B. *Nature (London)* **1979**, *277*, 93.
(3) Goldberg, L. I.; Volkman, P. H.; Kohli, J. D.; Kotake, A. N. *Adv. Biochem. Psychopharmacol*. **1977**, *16*, 251.
(4) Barnett, A. *Drugs Future* **1986**, *11*, 49.
(5) Weinstoch, J.; Heible, J. P.; Wilson, J. W., III. *Drugs Future* **1985**, *10*, 646.
(6) Iorio, L. C.; Barnett, A.; Leitz, F. H.; Houser, V. P.; Korduba, C. *J. Pharmacol. Exp. Ther*. **1983**, *226*, 462. See also: Hyttel, J. *Eur. J. Pharmacol.* **1983**, *91*, 153.
(7) Berger, J. G.; Chang, W. K.; Clader, J. W.; Hou, D.; Chipken, R. E.; McPhail, A. T. *J. Med. Chem*. **1989**, *32*, 1913.
(8) Chipkin, R. E.; Iorio, L. C.; Coffin, V. L.; McQuade, R. D.; Berger, J. G.; Barnett, A. *J. Pharmacol. Exp. Ther*. **1983**, *247*, 1093.

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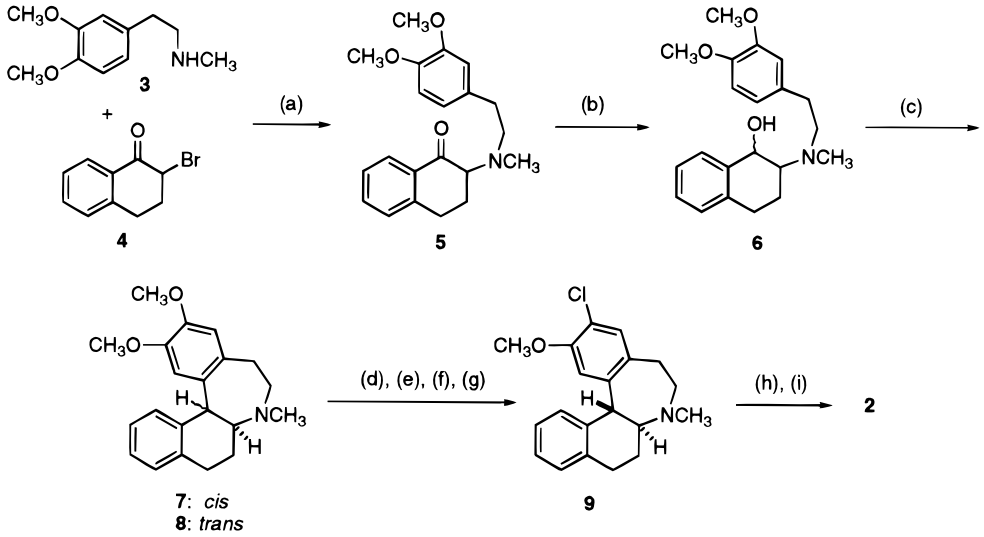
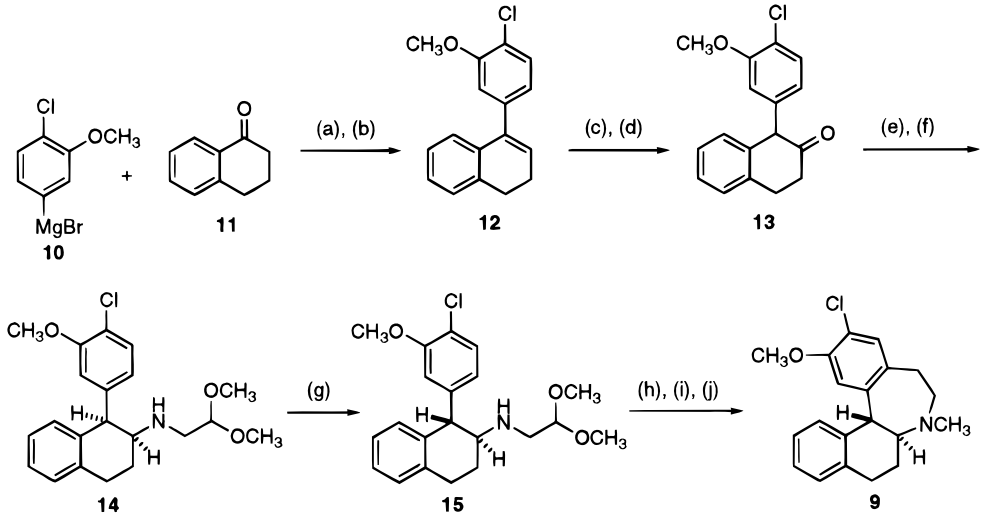
Scheme 1[a]



[a] (a) K_2CO_3, DMF; (b) $NaBH_4$, EtOH; (c) CH_3SO_3H; (d) EtSNa, DMF; (e) 5-chloro-1-phenyltetrazole; (f) H_2, Pd/C; (g) SO_2Cl_2; (h) resolve with (+)-di-*O*,*O*'-*p*-toluyl-L-tartaric acid; (i) HBr, HOAc.

Scheme 2 [a]



[a] (a) THF, 45 °C; (b) *p*-TsOH, toluene, Δ; (c) oxone, acetone; (d) *p*-TsOH, toluene, Δ; (e) $(CH_3O)_2CHCH_2NH_2$, toluene, Δ; (f) *t*-$BuNH_2{\cdot}BH_3$, HOAc, toluene; (g) KO*t*-Bu, DMSO, DMF; (h) CH_3SO_3H, CH_2Cl_2, Δ; (i) *t*-$BuNH_2{\cdot}BH_3$, HOAc, CH_2Cl_2; (j) HCHO, HCO_2H, DMF.

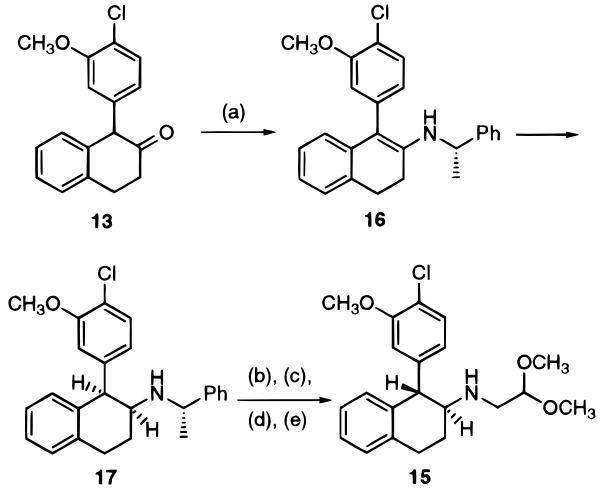
chotic activity in humans, specifically for the treatment of schizophrenia and related major psychoses. Furthermore, these studies indicated that undesirable neurological side effects (such as extrapyramidal side effects) might be mitigated with **2**.[8] These preliminary data were sufficiently encouraging for us to initiate a research program to identify alternative processes for the efficient manufacture of **2**.

The original synthesis[7] of **2** (Scheme 1) commenced with the alkylation of *N*-methylhomoveratrylamine (**3**) with 2-bromo-1-tetralone (**4**) to afford the unstable tertiary amino ketone **5**, which was immediately reduced with $NaBH_4$ to a mixture of amino alcohols **6**. Cyclization in neat CH_3SO_3H produced a 1:1 mixture of the tetracyclic products *cis* **7** and *trans* **8**, which were separated by column chromatography on silica gel. Four further steps were performed on **8** to introduce the appropriate substitution pattern into the D ring, affording racemic **9**. The latter mixture was resolved by crystallization of the (+)-di-*O*,*O*′-*p*-toluyl-L-tartrate salt, which after freebasing followed by demethylation with HBr in HOAc finally produced **2**. This route suffers not only from its length but also from the lack of selectivity in setting the trans stereochemistry between the B and C rings. A further serious defect in this route is the absence of any enantioselectivity, thus requiring the resolution of an expensive intermediate with no opportunity to recycle the unwanted enantiomer.

A more efficient route to **2** (Scheme 2)[9] began by arylation of 1-tetralone (**11**) with the Grignard reagent **10** derived from 5-bromo-2-chloroanisole followed by dehydration of the resulting carbinol to afford the tricyclic olefin **12**. Oxidation of the latter compound and subsequent rearrangement of the derived epoxide afforded the ketone **13**. This ketone was treated with aminoacetaldehyde dimethyl acetal to give an intermediate enamine which was reduced in situ (via the iminium species) with *t*-$BuNH_2{\cdot}BH_3$ to furnish a 9:1 mixture of *cis* **14** and *trans* **15**.

(9) Berger, J.; Chang, W. K.; Gold, E. H.; Clader, J. W. European Patent Application 230270, Jan 15, 1987.

Scheme 3 [a]



[a] (a) Toluene, Δ; (b) $NaCNBH_3$, HOAc; (c) KO^t-Bu, DMSO, DMF; (d) H_2 20% $Pd(OH)_2/C$; (e) $BrCH_2CH(OCH_3)_2$, K_2CO_3, DMF.

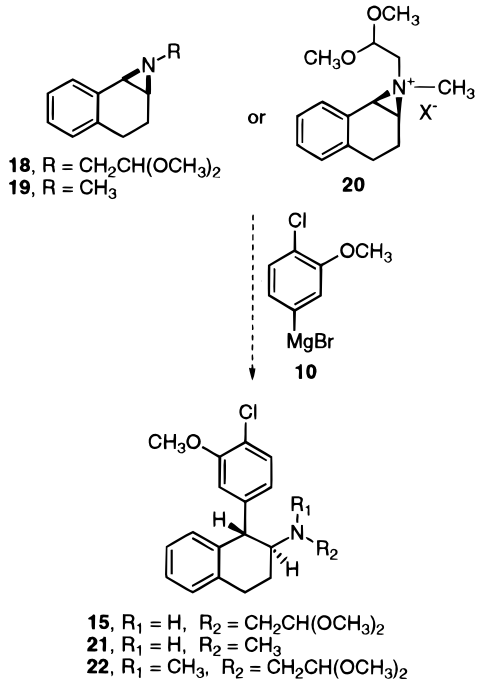
However, this unfavorable result could be improved by epimerization with KO-*t*-Bu in hot DMSO to the desired *trans* isomer as an 85:15 ratio of diastereomers. Cyclization with CH_3SO_3H followed by reduction using *t*-$BuNH_2 \cdot BH_3$ and N-methylation by means of the Eschweiler−Clark reaction gave **9**, which had been previously converted to **2** (See Scheme 1). Although marginally shorter, with higher yields than the previous route and with somewhat better control over the *trans* stereochemistry of the B/C ring junction, this scheme still suffers from total lack of enantioselectivity requiring, as before, a resolution near the end of the synthesis. Nonetheless, this route was used to prepare multikilo quantities of **2**. However, as greater quantities of bulk active were required, the limitations of this route became self-evident.

An enantioselective variation of the latter approach was also developed whereby chirality was introduced by reduction via the iminium species of the chiral enamine **16**, which was prepared by condensation of ketone **13** with (*S*)-(−)-α-methylbenzylamine (Scheme 3).[10] Reduction with $NaCNBH_3$ afforded the diastereomeric amines **17** in 87% de. Epimerization to the trans isomer, hydrogenation to remove the chiral auxiliary, and subsequent N-alkylation gave the known intermediate **15** (87% ee). Although this is a chiral synthesis, the additional steps in this sequence required to induce asymmetric induction and the fact that additional enrichment is essential to obtain **2** of suitable enantiomeric purity detract from the utility of this approach.

The shortcomings for each of the above described routes were such that none of these syntheses was likely to evolve into a commercial process, and therefore alternative routes were sought. Features which we demanded of the new synthesis were that it must be diastereoselective; that is, we desired complete stereocontrol in setting the B/C *trans* ring junction. In addition, we required the synthesis to be enantioselective although it was of no concern whether the enantioselectivity was derived from an inexpensive chiral starting material, perhaps from the chiral pool or generated via an asymmetric reaction. A classical salt resolution procedure would also be acceptable provided it was efficient and performed on a very cheap, early intermediate. Finally, the starting raw materials must be commercially available or readily synthesized.

(10) Berger, J.; Clader, J. European Patent Application 354686, July 27, 1990.

Scheme 4



The first paper in this series describes a synthesis of **2** which proceeds through an appropriately substituted quaternary (1*R*,2*S*)-tetrahydronaphthalene-1,2-aziridinium ion together with various methods of producing the latter intermediate.[11] In Part 2, a number of syntheses are presented which utilize, as the key step, arylations of appropriate substrates derived from L-homophenylalanine with (4-chloro-3-methoxyphenyl)magnesium bromide (**10**). A third enantioselective approach from our laboratories which starts from a chiral amino diol has also recently been published.[12]

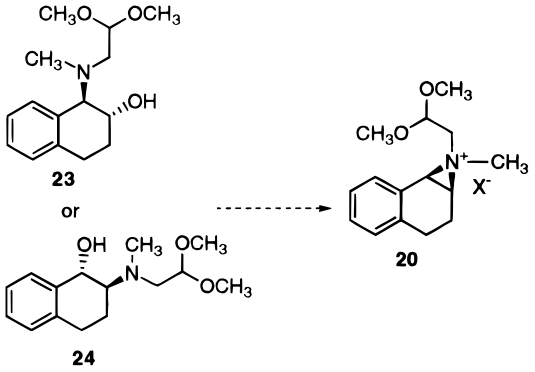
Results and Discussion

In any efficient synthesis of **2**, setting the *trans* stereochemistry of the B/C ring junction is a major hurdle to be surmounted and particular attention must be paid to the choice of strategy used in achieving this goal. The genesis of our first approach (Scheme 4) was founded on the simple premise that opening either an appropriate N-substituted chiral tetrahydronaphthalene-1,2-aziridine **18** or **19** or its N,N-disubstituted aziridinium cation **20**, by a suitable arylmetallic reagent such as Grignard **10**, could occur with high regio- and diastereoselectivity to generate the secondary amines **15** or **21** or the tertiary amine **22**, respectively, bearing the desired *trans* arrangement of substituents. We

(11) This work is part of Schering-Plough Corp. U.S. Patent Application 127,862 (Sept 27, 1993) and covers subsequent U.S. Patents 5,463,051 (Oct 31, 1995) and 5,670,666 (Sept 23, 1997).

(12) Wu, G.; Wong, Y.-S.; Steinman, M.; Tormos, W.; Schumacher, D. P.; Love, G. M.; Shutts, B. *Org. Proc. Res. Dev.* **1997**, *1*, 359.

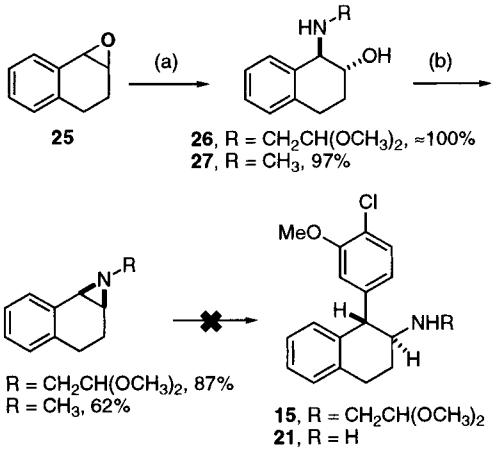
Scheme 5



anticipated that scission of the aziridine C−N bond in **18**, **19**, or **20** would be concerted with attack of the incoming nucleophile and, further, the latter would approach the more electrophilic benzylic carbon. Synthon **15** could then be converted to **2** following the route depicted in Scheme 2. Alternatively, intermediate **21** could be N-alkylated to **22**, and subsequent cyclization of this synthon would afford an enantiomerically pure tetracyclic compound containing the desired trans B/C ring junction. The synthesis of aziridines **18** and **19** is straightforward, and in principle, the required quaternary aziridinium salt **20** might be conveniently obtained either from an aziridine precursor such as **18** or from one of two regioisomeric tertiary 1,2-amino alcohols **23** or **24** via a Gabriel-type cyclization reaction of their corresponding *p*-toluenesulfonates or other derivative (Scheme 5). The potential of this approach was further enhanced as the aziridine precursors or the two tertiary amino alcohols **23** and **24** could be derived from a variety of sources, for example, from (1*S*,2*R*)-1,2,3,4-tetrahydronaphthalene 1,2-oxide or by amination of the racemic epoxide followed by resolution of either a secondary or tertiary amino alcohol or, in the case of the tertiary amino alcohol **24**, from the commercially available L-homophenylalanine.

We were encouraged in our selection of this approach when a search of the prior art revealed numerous precedents for the formation of aziridinium salts from β-substituted tertiary amines and their use in synthesis including natural products.[13] Of concern was the mechanism of ring opening of the aziridine or aziridinium salt. If bond breaking occurs via an S_N1 mechanism leading to a discrete benzyl carbonium ion, then the inherent risk of destroying diastereoselectivity is high. However, there are many examples in which the preferred pathway of ring cleavage can be determined by judicial choice of conditions, and with nucleophiles under basic conditions, including carbanions, the usual mode of reaction is S_N2 during which complete stereochemical control is maintained.[13−15]

Scheme 6 [a]



[a] (a) $(CH_3O)_2CHCH_2NH_2$ or CH_3NH_2, 100 °C. (b) PPh_3Br_2, NEt.

Synthesis and Reactions of Aziridines 18 and 19

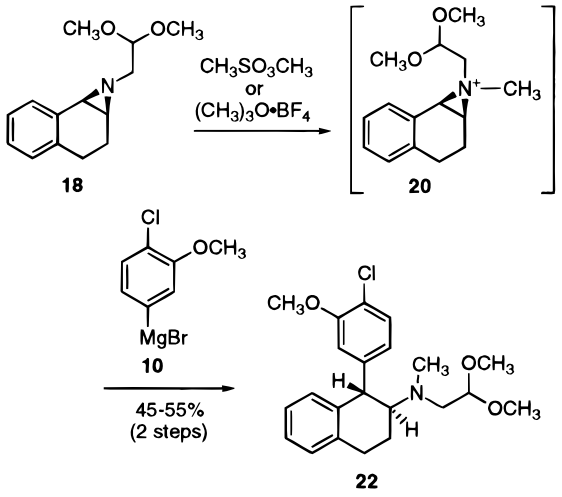
To determine the feasibility of this chemistry, we carried out our initial work using racemic epoxide **25**, which was easily prepared using $H_2O_2/KHCO_3/CH_3CN$ as described in the literature.[16] Conversion of **25** to amino alcohols **26** and **27** was accomplished in >95% yield by treatment with either aminoacetaldehyde dimethyl acetal or methylamine, respectively (Scheme 6). As expected, on the basis of literature precedents, only the desired regioisomer was obtained.[14a] Closure to the aziridines **18** and **19** was accomplished using a Mitsunobu type promoted cyclization using PPh_3Br_2 and NEt_3,[17] in which case the desired aziridines were obtained in 87 and 62% yields, respectively.

A number of attempts were made to open the aziridines **18** and **19** with a nucleophilic anion generated from 5-bromo-2-chloroanisole. Both the Grignard and the organolithium species, directly or after conversion to the cuprates[15] or cerium species,[18] either by themselves or with additives such as TMEDA, $BF_3{\cdot}OEt_2$,[14d] and Lewis acids such as $TiCl_4$, $ZnCl_2$, $AlEt_3$, $AlEt_2Cl$, and $MgBr_2{\cdot}OEt_2$, did not afford any of the desired addition products **15** or **21**. Instead, recovery of starting material was generally observed.

We reasoned that the low reactivity of aziridines **18** and **19** toward the carbanion derived from 5-bromo-2-chloroanisole might be overcome if they were "activated" as their quaternary aziridinium species. To this end, aziridine **18** was treated with a number of methylating agents prior to the addition of Grignard reagent **10** (Scheme 7). Methyl iodide and dimethyl sulfate failed to effect any reaction, but to our delight, both methyl triflate and the Meerwein reagent $Me_3O{\cdot}BF_4$[19] gave the desired amine **22** in 45−55% yield, and as expected, only the trans isomer was obtained. It was also found that the aziridinium species **20**, when generated with $Me_3O{\cdot}BF_4$, could be isolated as its tetrafluoroborate salt in 76% yield. Like many similar compounds prepared

(13) (a) Freedman, J.; Vaal, M. J.; Huber, E. W. *J. Org. Chem.* **1991**, *56*, 670. (b) Heller, M.; Bernstein, S. *J. Org. Chem.* **1971**, *36*, 1386.
(14) (a) Perrone, R.; Berardi, F.; Bettoni, G.; Tortorella, V. *Farmaco, Ed. Sci.* **1988**, *43*, 61. (b) Sugihara, H.; Ukawa, K.; Miyake, A.; Itoh, K.; Sanno, Y. *Chem. Pharm. Bull.* **1978**, *26*, 394. (c) Yamada, K.; Takeda, M.; Iwakuma, T. *J. Chem. Soc., Perkin Trans. 1* **1983**, 265. (d) Eis, M. J.; Ganem, B. *Tetrahedron Lett.* **1985**, *26*, 1153.
(15) Kozikowski, A. P.; Ishida, H.; Isobe, K. *J. Org. Chem.* **1979**, *44*, 2788. See also: Martin, L. D.; Stille, J. K. *J. Org. Chem.* **1982**, *47*, 3630.
(16) Bach, R. D.; Knight, J. W. *Org. Synth.* **1981**, *60*, 63. See also: Imuta, M.; Ziffer, H. *J. Org. Chem.* **1979**, *44*, 1351.
(17) Okada, I.; Ichimura, K.; Sudo, R. *Bull. Chem. Soc. Jpn.* **1970**, *43*, 1185.
(18) Imamoto, T.; Takiyama, N.; Nakamura, K. *Tetrahedron Lett.* **1985**, *26*, 4763.
(19) Earle, M. J.; Fairhurst, R. A.; Giles, R. G.; Heaney, H. *Synth. Lett.* **1991**, 728.

Scheme 7



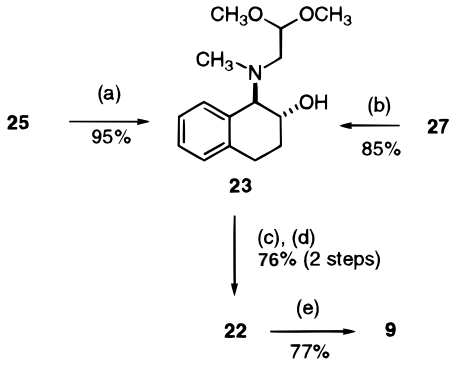
through the pioneering work of Leonard,[20] this salt is quite stable in air at room temperature. A number of other Meerwein type reagents such as $C(OMe)_3 \cdot BF_4$,[21] $HC(OMe)_2 \cdot BF_4$[21] and $PhC(OMe)_2 \cdot BF_4$[22] were also tried but did not work as well. Attempted activation of aziridine **19** with bromoacetaldehyde dimethyl acetal was also unsuccessful. Although **20** did react with Grignard reagent **10**, the fact that potent methylating reagents such as methyl triflate and $Me_3O \cdot BF_4$ were required seriously detracts from the usefulness of this sequence, given the high cost and/or toxicity associated with these reagents. Therefore, an alternative method for forming the aziridinium cation **20** was investigated.

Synthesis and Reaction of Tertiary Amino Alcohol 23

As proposed earlier (*vide supra*), the aziridinium species could quite likely also be generated from an appropriately substituted tertiary amino alcohol precursor by means such as sulfonylation and ring closure. The requisite tertiary amino alcohol **23** was prepared by treatment of epoxide **25** with *N*-methylaminoacetaldehyde dimethyl acetal, which proceeded in excellent yield (95%). Alternatively, **23** could be obtained in 85% yield by alkylation of the previously prepared amino alcohol **27** with bromoacetaldehyde dimethyl acetal (Scheme 8). Initial attempts to form the aziridinium intermediate **20** using Mitsunobu conditions (PPh_3, DEAD) were not successful. However, it was found that a one-pot sequence, where deprotonation of **23** was effected by the addition of 1 equiv of *n*-BuLi (titration with 1,10-phenanthroline allowed for addition of the precise amount of base required), followed by reaction with either mesyl chloride or *p*-TsCl, allowed for subsequent in situ generation of the aziridinium cation **20**. Addition of the Grignard reagent **10** then gave the desired *trans* amine **22** in 45−76% overall yield.

With a good synthesis of **22** in hand, it only remained to complete the synthesis by converting it to a known intermediate. This was accomplished by acid-catalyzed cyclization using either CH_3SO_3H or H_2SO_4 to the intermediate enamine and subsequent reduction with $t\text{-}BuNH_2 \cdot BH_3$ to give **9** in 77% yield for the sequence. The reduction was also accomplished using $NaBH_4$. This completes a formal synthesis since **9** has previously been converted to **2** (Scheme 1).

Scheme 8 [a]



[a] (a) $(CH_3O)_2CHCH_2NHCH_3$, 100 °C; (b) $(CH_3O)_2CHCH_2Br$, KF on Al_2O_3; (c) *n*-BuLi, *p*-TsCl, 1,10-phenanthroline, THF; (d) **10**, THF; (e) (i) CH_3SO_3H or H_2SO_4, CH_2Cl_2, 40 °C; (ii) $t\text{-}BuNH_2 \cdot BH_3$.

Enantioselective Syntheses of Amino Alcohol (+)-23

Having demonstrated that the aziridinium synthetic sequence is viable, we next focused attention on preparing a single enantiomer of the desired amino alcohol **23**. Two routes were developed: the first via a resolution of an appropriate amino alcohol precursor with a chiral acid and the second by asymmetric epoxidation of 1,2-dihydronaphthalene.

In the classical resolution sequence (Scheme 9), racemic *trans* amino alcohol **27** was prepared in high yield by reaction of the corresponding racemic *trans* bromohydrin **30** with aqueous methylamine using a modification of the procedure originally described by Lukes et al.[23] The transfer of oxygen from C-1 to C-2 of the substrate with retention of the trans stereochemistry is effected through the intermediacy of epoxide **25**, which is formed as an intermediate and can be followed by HPLC. Bromohydrin **30** is prepared either by hydrolysis of the *trans* dibromide **29**, which is available from the 1,2,3,4-tetrahydronaphthalene (**28**),[24] or directly from 1,2-dihydronaphthalene (**31**) by treatment of the latter with *N*-bromosuccinimide in the presence of moist DMSO.[25]

We were extremely fortunate to effect an efficient resolution of *N*-methylamino alcohol **27** on our first attempt at salt formation with the readily available natural (+)-L-tartaric acid and even more fortunate to obtain directly the "anti-Murphy" [26] (1*R*,2*R*) enantiomer. After isolation, the oily crude racemic **27** was treated in MeOH with 0.25 molar equiv of L-(+)-tartaric acid, whereupon crystals of the (1*R*,2*R*)-2-hydroxy-1-(methylamino)-1,2,3,4-tetrahydronaphthalene semi (+)-L-tartrate salt [(+)-**32**] were isolated in 46%

(20) Leonard, N. J.; Paukstelis, J. V. *J. Org. Chem.* **1965**, *30*, 821 and references therein.
(21) Meerwein, H.; Bodenbenner, K.; Borner, P.; Kunert, F.; Wunderlich, K. *Justus Liebigs Ann. Chem.* **1960**, *632*, 38. See also: Kollonitsh, U.S. Patent 3,891,668, 1975.
(22) Dimroth, K.; Heinrich, P. *Angew. Chem., Int. Ed. Eng.* **1966**, *5*, 676.
(23) Lukes, R.; Pitha, J.; Kovár, J.; Blaha, K. *Collect. Czech. Chem. Commun.* **1960**, *25*, 492.
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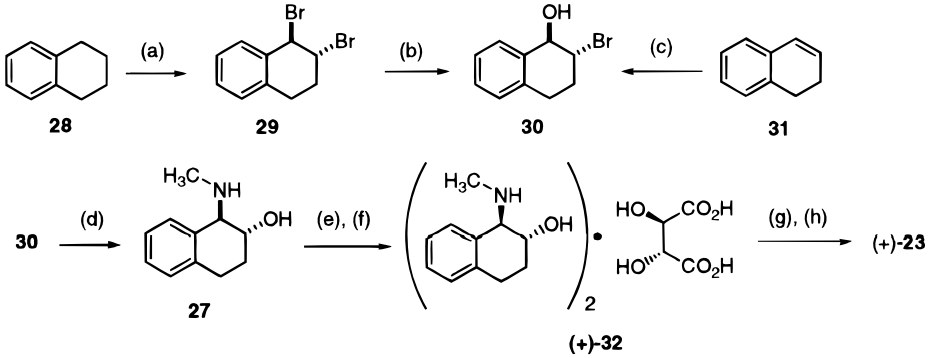
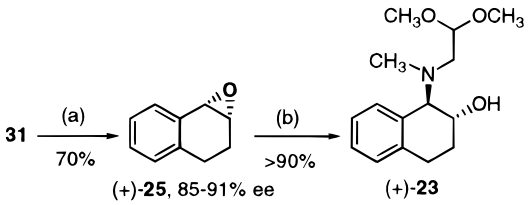
Scheme 9 [a]



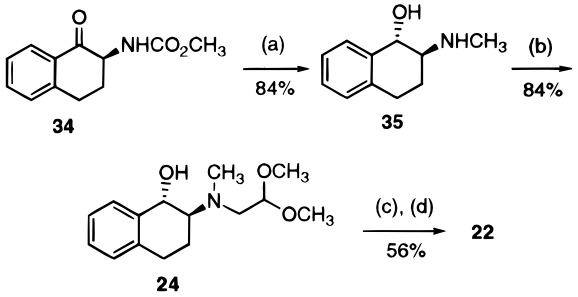
[a] (a) Br_2, hexane; (b) acetone, H_2O, $NaHCO_3$; (c) 1,3-dibromo-5,5-dimethylhydantoin, $HClO_4$, THF; (d) 40% aqueous CH_3NH_2; (e) (+)-L-tartaric acid, MeOH; (f) recrystallize; (g) NH_4OH, CH_2Cl_2; (h) $BrCH_2CH(OCH_3)_2$, K_2CO_3, CH_3CN.

Scheme 10 [a]



[a] (a) Mn(III) Salen complex (cat.), NaOCl, NMNO; (b) $(CH_3O)_2CHCH_2NCH_3$, 95 °C (sealed reactor).

Scheme 11 [a]



[a] (a) $LiAlH_4$, THF, Δ; (b) $BrCH_2CH(CH_3O)_2$, K_2CO_3, CH_3CN; (c) *n*-BuLi, *p*-TsCl, THF; (d) THF, **10**.

yield (overall yield from the bromohydrin **30**) with a de of 94%. Two further slurries in refluxing MeOH raised the de to 100%. The 2:1 amine/acid structure of (+)-**32** was established by combustion analysis and confirmed by integration of the appropriate ^1H NMR (DMSO-d_6) signals, which also corroborated the *trans* relationship of the vicinal substituents (J_{H1}, J_{H2} = 6.17 Hz). The diastereomeric excess of salt (+)-**32** was originally determined by NMR in combination with the chiral shift reagent (*R*)-(−)-2,2,2-trifluoro-1-(9-anthryl)ethanol, the addition of which produced a separation and baseline resolution of the diastereomeric *N*-methyl signals. Subsequently, the ee of (+)-**23** was more accurately determined by chiral HPLC using a Chiracel ODR column, which indicated 99% ee. The absolute configuration of the free base from (+)-**32** is 1*R*,2*R* since this material was ultimately converted into **2** (*vide infra*).

Optically pure (1*R*,2*R*)-2-hydroxy-1-(methylamino)-1,2,3,4-tetrahydronaphthalene [(+)-**27**], produced by free-basing of salt (+)-**32**, was alkylated with bromoacetaldehyde dimethyl acetal (potassium carbonate in acetonitrile) to produce the tertiary amino alcohol (+)-**23** with $[\alpha]_D^{22} = +31°$ (c = 0.5, MeOH), and chiral HPLC (Chiracel ODR column) indicated 99% ee. Finally, (+)-**22** prepared from (+)-**23** had a 99.6% ee as determined by chiral HPLC (Chiracel ODR column).

The second enantioselective route to chiral amino alcohols (+)-**23**, (+)-**26**, and (+)-**27** is via amination of (1*S*,2*R*)-1,2-epoxy-1,2,3,4-tetrahydronaphthalene [(+)-**25**], readily available from olefin **31** by Jacobsen chiral epoxidation chemistry[27] (Scheme 10). Following the conditions described by Jacobsen, the 1*S*,2*R* enantiomer of epoxide (+)-**25** was prepared with an ee of about 85−90%. Interestingly, we found some variation in the results from the Jacobsen epoxidation reaction and in several cases obtained **25** with superior ee (>97%) but in low yield (20−30%).[28] To verify that the major enantiomer obtained from the Jacobsen epoxidation had the requisite 1*S*,2*R* configuration, an early sample of (+)-**25** (65% ee) was converted, utilizing the methods of Crabb and Robinson,[29] to the previously prepared tertiary amino alcohol (+)-**23** (65% ee), which also exhibited a positive rotation $[\alpha]_D^{22} = +21°$ (c = 0.5, MeOH). Therefore, (+)-**23** synthesized by this route has the same (1*R*,2*R*) configuration as (+)-**23** prepared via resolution of **27** with (+)-L-tartaric acid, and the precursor epoxide (+)-**25** must be 1*S*,2*R*. These comparative configurational assignments were confirmed by chiral HPLC (Chiracel ODR column) on a sample of (+)-**27** derived from epoxide (+)-**25** where the retention time of the major enantiomer was identical to that of (+)-**27** obtained through resolution. For purposes of a practical process, the enantioenriched epoxide **25** can be converted to the tartrate salt **32**, whose enantiopurity can be raised by recrystallization (*vide supra*).

Enantioselective Synthesis of Amino Alcohol 24

In principle, the aziridinium cation **20** could also be produced from the regioisomeric tertiary amino alcohol **24**. A hybrid route was developed for its synthesis which starts from the known ketocarbamate **34** (Scheme 11), which was prepared from (+)-L-homophenylalanine following the pro-

(27) Jacobsen, E. N.; Zhang, W. *J. Org. Chem.* **1991**, *56*, 2296. Lee, N. H.; Muci, A. R.; Jacobsen, E. N. *Tetrahedron Lett*. **1991**, *32*, 5055. The chiral epoxidation chemistry has also been licensed for commercial use by ChiRex, Boston, MA.

(28) Larrow, J. F.; Jacobsen, E. N. *J. Am. Chem. Soc*. **1994**, *116*, 12129.

(29) Crabb, T. A.; Robinson, P. *Magn. Reson. Chem*. **1986**, *24*, 798.

cedure of McClure et al.[30,31] Reduction of **34** with $LiAlH_4$ afforded primarily the *trans* amino alcohol **35** in 84% yield (*trans*:*cis* ratio >39:1). Alkylation with bromoacetaldehyde dimethyl acetal then produced **24** in 84% yield. As expected, the deprotonation, tosylation, Grignard "one-pot" sequence similarly afforded the chiral *trans* amine (+)-**22** in 56% (solution) overall yield. Finally, conversion of (+)-**22** to (+)-**9** following the previously described procedures and subsequent examination by chiral HPLC indicated that no racemization had occurred during the sequence (99% ee for **9**).

Conclusions

A number of stereoselective syntheses of **2** have been developed. The key intermediate in these routes is the "activated" aziridinium cation **20**, which can be prepared either from aziridine **18** by methylation or from the tertiary amino alcohols (+)-**23** or (+)-**24** by tosylation and in situ ring closure. Selective trapping of **20** exclusively at the benzylic position with Grignard reagent **10** then gives *trans* amine **22**, which was cyclized to give **9**, a known precursor of **2**, in good yields. Several enantioselective syntheses, a Jacobsen epoxidation route to give epoxide (+)-**25** and its conversion to (+)-**23**, a classical salt resolution sequence to prepare (+)-**23**, and a *de novo* synthesis starting from (+)-L-homophenylalanine to afford (+)-**24** were developed for preparing the key intermediates in chiral form.

Experimental Section

General. Melting points are uncorrected. ^{1}H NMR (400 and 300 MHz) and ^{13}C NMR (100 MHz) spectra were recorded in $CDCl_3$ or $(CD_3)_2SO$ solutions with Me_4Si as the internal standard, unless specified otherwise. IR spectra were obtained using a Matteson Galaxy 7000 IR spectrometer. Unless specified otherwise, all reagents and solvents were used as supplied by the manufacturer. All reactions were run under an inert atmosphere. Retention times for the chiral HPLC are provided in the Supporting Information. Flash chromatography refers to the procedure developed by Still et al.[32]

***trans*-(±)-(1*RS*,2*RS*)-1-[(2,2-Dimethoxyethyl)amino]-1,2,3,4-tetrahydro-2-naphthalenol [(±)-26].** A mixture of (±)-**25**[16] (4.745 g, 32.460 mmol) and $NH_2CH_2CH(OMe)_2$ (4.720 g, 44.893 mmol) was added to a 30 mL Teflon acid digestion bomb, sealed, placed in a stainless steel closed system reactor (bomb), and heated with stirring for 16 h (oil bath temperature about 100 °C). After cooling to rt and removal of excess $NH_2CH_2CH(OMe)_2$ by high vacuum, (±)-**26** was obtained in quantitative yield (8.204 g, 32.644 mmol). The product was used without further purification for the subsequent step.

^{1}H NMR ($CDCl_3$): δ 7.10−7.37 (m, 4H); 4.47 (t, 1H, J = 6.8 Hz); 3.65−3.81 (m, 2H); 3.42 (s, 3H); 3.40 (s, 3H); 2.75−2.90 (m, 4H); 2.12 (m, 1H); 1.60−1.90 (m, 3H).

(±)-(1*RS*,2*SR*)-1-(2,2-Dimethoxyethyl)-1a,2,3,7b-tetrahydro-1*H*-naphth[1,2-*b*]azirine [(±)-18]. A mixture of (±)-**26** (3.647 g, 14.512 mmol), 75 mL of CH_3CN, and $PPh_3{\cdot}Br_2$ (9.472 g, 22.439 mmol) was cooled to about 0 °C (ice/water bath), and then a solution of NEt_3 (6.50 mL, 46.635 mmol) in 5.5 mL of CH_3CN was added dropwise over 10 min. After stirring for 90 min, the reaction mixture was filtered and concentrated, at which point additional solids precipated. The mixture was slurried with 20 mL of *n*-hexane, filtered, and concentrated using a Büchi rotavapor. Flash chromatography (20−60% EtOAc/hexanes) afforded (±)-**18** in 87% yield (2.944 g, 12.618 mmol).

^{1}H NMR ($CDCl_3$): δ 7.10−7.35 (m, 4H); 4.51 (t, 1H, J = 6.8 Hz); 3.40 (2s, 6H); 2.65−2.87 (m, 2H); 2.42−2.55 (m, 3H); 2.21−2.31 (m, 2H); 1.53 (dd, 1H J = 6.8, 11.3 Hz).

(±)-(1*RS*,2*SR*)-1-(2,2-Dimethoxyethyl)-1-methyl-1a,2,3,-7b-tetrahydro-1*H*-naphth[1,2-*b*]aziridinium Tetrafluoroborate [(±)-20]. A solution of (±)-**18** (12.60 g, 51.30 mmol) and 200 mL of dry CH_2Cl_2 was cooled to −20 °C (dry ice/acetone bath), and then $Me_3O{\cdot}BF_4$ (12.00 gm, 81.00 mmol, Fluka[33]) was added in two portions. After stirring for 20 h at −20 °C, the excess $Me_3O{\cdot}BF_4$ was filtered off under conditions of moisture exclusion, and then the filtrate was treated with 200 mL of Et_2O at −20 °C. The precipitate that formed was collected under argon, washed with cold Et_2O, and dried under vacuum at rt to afford the aziridinium tetrafluoroborate salt as white crystals in 76% yield (13.70 g, 38.6 mmol).

^{1}H NMR ($CDCl_3$): δ 7.60 (dd, 1H); 7.30 (m, 3H); 4.80 (t, 1H); 4.45 (d, 1H); 4.00 (m, 1H); 3.80 (dd, 1H); 3.50 (d, 6H); 3.35 (dd, 1H); 2.80−3.05 (m, 1H); 2.55−2.75 (m, 2H); 2.50 (s, 3H); 2.10−2.40 (m, 1H).

The reagents $C(OMe)_3BF_4$,[21] $HC(OMe)_2BF_4$,[21] and $PhC(OMe)_2BF_4$,[22] were prepared according to the literature procedures and then were tried following the procedure indicated above for $Me_3O{\cdot}BF_4$, but they were not as efficient.

4-(Chloro-3-methoxyphenyl)magnesium bromide (10). To a slurry of magnesium turnings (1.16 g, 47.70 mmol) in 30 mL of dry THF was added a solution of 5-bromo-2-chloroanisole (10.48 g, 47.30 mmol) in 30 mL of dry THF over a 10 min period, the reaction temperature being maintained at 40−45 °C, and then the mixture was stirred for 90 min. The solution of Grignard reagent **10** was used as is (0.79 M in THF).

***trans*-(±)-(1*RS*,2*SR*)- and (+)-(1*R*,2*S*)-1-(4-Chloro-3-methoxyphenyl)-*N*-(2,2-dimethoxyethyl)-1,2,3,4-tetrahydro-*N*-methyl-2-naphthalenamine [(±)-22 and (+)-22].** *Method A. (±)-22 from (±)-18.* A solution of (±)-**18** (0.500 g, 2.144 mmol) in 4 mL of THF was cooled to about −15 °C (dry ice/acetone bath), and then $CF_3SO_3CH_3$ (0.250 mL,

(30) McClure, D. E.; Lumma, P. K.; Arison, B. H.; Jones, J. H.; Baldwin, J. J. *J. Org. Chem.* **1983**, *48*, 2675.

(31) A detailed discussion of the conversion of (+)-L-homophenylalanine to **34**, including modifications of the literature procedures, is contained in the following paper: Draper, R. W.; Hou, D.; Iyer, R.; Lee, G. M.; Liang, J. T.; Mas, J. L.; Vater, E. J. *Org. Process Res. Dev.* **1998**, *2*, 186.

(32) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

(33) Commercially available $Me_3O{\cdot}BF_4$ was slurried under argon in dry CH_2Cl_2 (2 vol) at 0 °C and stirred for 30 min. The mixture was filtered under argon, washed with dry CH_2Cl_2 and dry Et_2O, and then dried in vacuo at rt for 3 h. The solid was stored at 5 °C in a desiccator over P_4O_{10} under argon.

(34) For a preparation of **27** from 1,2-dihydronaphthalene and *N*,*N*-dibromomethylamine, see: Schmitz, E.; Bicker, U.; Schramm, S.; Dietz, K.-P. *J. Prakt. Chem.* **1978**, *320*, 413.

(35) A stock solution of NaOCl was prepared by adjusting the pH of 500 mL of NaOCl (Clorox) to pH 11.3 using 0.05 M $NaHPO_4$ and 1 M NaOH solutions.

0.363 g, 2.210 mmol) was added. After stirring for 20 min, the Grignard reagent **10** (4.0 mL, 3.16 mmol, 0.79 M in THF) prepared as described above was then added. The reaction mixture was stirred for 17 h at rt, and then 50 mL of H_2O, 25 mL of saturated $NaHCO_3$, and 50 mL of EtOAc were added. The layers were separated, the aqueous layer was extracted with 1 × 50 mL of EtOAc, and the combined organic layers were washed with 1 × 10 mL of saturated NH_4Cl and 1 × 10 mL of saturated NaCl solution, dried over $MgSO_4$, and concentrated using a Büchi rotavapor to yield an oil. Flash chromatography (20−40% EtOAc/hexanes) then afforded (±)-**22** in 41% yield (0.345 g, 0.886 mmol).

^{1}H NMR ($CDCl_3$): δ 6.65−7.30 (m, 7H); 4.12 (t, 1H, J = 5.6 Hz); 4.09 (d, 1H, J = 11.3 Hz); 3.82 (s, 3H); 3.21 (s, 3H); 3.12 (s, 3H); 2.95 (m, 3H); 2.60 (dd, 2H, J = 5.6, 11.3 Hz); 2.31 (s, 3H); 2.08 (m, 1H); 1.70−1.80 (m, 1H).

*Method B. (±)-**22** from (±)-**20**.* A slurry of (±)-**20** (12.20 g, 36.40 mmol) suspended in 60 mL of dry THF was cooled to −20 to −30 °C (dry ice/acetone bath), and then the Grignard reagent **10** (60 mL, 47.70 mmol, 0.795 M in THF) was added over a 30 min period. The reaction mixture was stirred at −20 °C for 5 h, warmed to rt, stirred for 15 h, and then adjusted to pH 11 using 8.6% aqueous $NaHCO_3$ at 0−10 °C. The layers were separated, the aqueous layer was extracted with 2 × 100 mL of Et_2O, and the combined organic layers were washed with 2 × 50 mL of H_2O, dried over Na_2SO_4, and concentrated using a Büchi rotavapor to an oil to afford (±)-**22** in 64% yield (16.1 g, 56% pure, HPLC, external standard). A pure sample was prepared by flash chromatography (2−10% EtOAc/*n*-hexane; 73% recovery). The ^{1}H NMR spectrum was identical to that for the material prepared by method A.

*Method C. (+)-**22** from (+)-**23**.* A solution of (+)-**23** (81.0 g, 0.305 mol), 1,10-phenanthroline (0.040 g, 0.222 mmol), and 305 mL of anhydrous THF was cooled to about 0 °C (ice/water bath), and then *n*-BuLi (191 mL, 0.306 mol, 1.6 M in hexanes) was added. After stirring for 20 min, a solution of *p*-toluenesulfonyl chloride (63.7 g, 0.334 mol) in 200 mL of anhydrous THF was added, and the mixture was stirred for 1 h to form the aziridinium intermediate. The reaction mixture was cooled to about −30 °C (dry ice/acetone bath), and a solution of **10** (654 mL, 0.641 mol, 0.98 M in THF) was then added. After stirring for 24 h at room temperature, 250 mL of saturated NH_4Cl solution was added, and the reaction mixture was filtered and concentrated to a residue using a Büchi rotavapor. The residue was dissolved in 230 mL of *t*-BuOMe and washed with 1 × 100 mL of H_2O, 1 × 200 mL of 5% HCl, and 1 × 300 mL of 5% HCl, and the combined acidic washes were extracted with 230 mL of *t*-BuOMe. The combined acidic washes were then adjusted to pH 4.9 with aqueous saturated $NaHCO_3$ and extracted with 1 × 300 mL of *t*-BuOMe. The combined organic layers were washed with NaCl solution, dried over Na_2SO_4, and concentrated using a Büchi rotavapor to afford (+)-**22** in 76% yield (90.8 g, 0.232 mol). Chiral HPLC (Chiracel ODR, 250 × 4.6 mm) indicated 99.6% ee. The ^{1}H NMR spectrum was identical to that for the material prepared by method A.

*Method D. (+)-**22** from Chiral 24.* A solution of **24** (633.3 mg, 2.387 mmol) in 2 mL of dry THF was cooled to about 0 °C (ice/H_2O bath), and *n*-BuLi (1.20 mL, 2.45 mmol, 2.04 M in hexane) was added. The reaction mixture was stirred for 10 min, and *p*-toluenesulfonyl chloride (456.4 mg, 2.394 mmol) was added. The reaction mixture was stirred for a further 15 min, and a solution of Grignard **10** (5.8 mL, 4.8 mmol, 0.83 M in THF) was then added. After stirring at rt for 17 h [capillary GC analysis indicated a 54% solution yield (pyrene, internal standard)], 10 mL of saturated NH_4-Cl solution and 25 mL of EtOAc were added, the reaction mixture was filtered, and the solids were washed with 10 mL of EtOAc. The layers were separated, and the organic layer was washed with 1 × 10 mL of saturated NaCl solution, dried over anhydrous $MgSO_4$, and concentrated using a Büchi rotavapor. Flash chromatography (5−100% EtOAc/hexanes) afforded (+)-**22** in 44% yield (411.4 mg, 1.055 mmol). The ^{1}H NMR spectrum was identical to that for the material prepared by method A.

***trans*-(±)-(6a*SR*,13b*RS*)- and (+)-(6a*S*,13b*R*)-11-Chloro-6,6a,7,8,9,13b-hexahydro-7-methyl-12-methoxy-5*H*-benzo[*d*]naphth[2,1-*b*]azepine [(±)-9 and (+)-9].** *Method A. From (±)-**22** Prepared from (±)-**20**.* A solution of CH_3SO_3H (5.2 g, 54.1 mmol) in 25 mL of CH_2Cl_2 was cooled to 0−5 °C (ice/water bath), and then a solution of (±)-**22** (2.34 g, 3.96 mmol; HPLC assay: 66% pure) in 25 mL of CH_2Cl_2 was added over a 5 min period. The reaction mixture was stirred at 20−25 °C for 24 h and then at 40 °C for 45 h. To the reaction mixture was added *t*-$BuNH_2 \cdot BH_3$ (0.70 g, 8.0 mmol), and after 1 h, the reaction mixture was cooled to rt and a solution of Na_2CO_3 (5.50 g, 51.89 mmol) in 120 mL of H_2O was then added. The layers were separated, the aqueous layer was extracted with 2 × 30 mL of CH_2Cl_2, and the combined organic layers were washed with 2 × 30 mL of H_2O, dried over anhydrous $MgSO_4$, and concentrated using a Büchi rotavapor to afford (±)-**9** in 77% yield (2.14 g, 3.05 mmol; HPLC assay: 46.4% pure). An analytical sample was prepared by flash chromatography (70:30 EtOAc/*n*-hexane).

Note: Sulfuric acid was also used instead of methanesulfonic acid with the same results.

^{1}H NMR ($CDCl_3$): δ 6.95−7.19 (m, 5H); 5.88 (s, 1H); 4.78 (d, 1H, J = 7.5 Hz); 3.5−3.62 (m, 1H); 3.49 (s, 3H); 3.2 (dd, 1H, J = 3.75, 11.3 Hz); 2.65−2.86 (m, 4H); 2.51 (s, 3H); 2.41 (dd, 1H, J = 5.6, 11.3 Hz); 1.98−2.18 (m, 1H); 1.6−1.8 (dq, 1H, J = 5.6, 11.3 Hz).

*Method B. From (+)-**22** Prepared from **24**.* The procedure described above in method A was followed, and in this manner (+)-**22** (2.59 g, 6.642 mmol) was converted to (+)-**9** (1.62 g, 4.941 mmol) in 74% yield (isolated by column chromatography). The ^{1}H NMR spectrum was identical to that for the material prepared by method A.

Chiral HPLC (Chiracel OD column, 250 × 4.6 mm) indicated 99% ee. $[\alpha]_D^{20}$ = +63.53° (*c* 1.49, EtOH).

***trans*-(±)-(1*RS*,2*RS*)- and (+)-(1*R*,2*R*)-1-(Methylamino)-1,2,3,4-tetrahydro-2-hydroxynaphthalene [(±)-27 and (+)-27].** To a 120 mL Teflon acid digestion bomb was added

(±)-**25** (20.086 g, 0.137 mol) followed by liquid $MeNH_2$ (≈25 mL). The digestion bomb was sealed, placed in a stainless steel closed system reactor (bomb), and then placed in a preheated oil bath at 100 °C for 22 h. After the bomb had been cooled to rt, the excess $MeNH_2$ was allowed to boil off, and the residue was then Kugelrohr distilled (160−175 °C/1 Torr) to afford (±)-**27**[34] in 97% yield (23.545 g, 0.133 mmol).

^{1}H NMR ($CDCl_3$): δ 7.30 (m, 4H); 3.86 (m, 1H); 3.64 (d, 1H, J = 8 Hz); 2.89 (dd, 2H, J = 5.4, 7.9 Hz); 2.42 (s, 3H); 2.25 (m, 3H); 1.86 (m, 1H). MS (CI): m/z 178 (M^+ + 1), 160 (M^+ − 17, OH), 147 (M^+ − 30, $NHCH_3$).

An analytical sample of (+)-**27** was prepared by free-basing the tartrate salt (+)-**32** with K_2CO_3, H_2O, and CH_2Cl_2. The ^{1}H NMR spectrum was identical to that of the racemic material. $[\alpha]_D^{21.5}$ = +36° (*c* 1.00, MeOH).

***trans*-(±)-(1*RS*,2*RS*)-1-Methyl-(1a,2,3,7b-tetrahydro-1*H*-naphth[1,2-*b*]azirine [(±)-19].** A slurry of (±)-**27** (24.049 g, 0.136 mol), 400 mL of CH_3CN, and $PPh_3{\cdot}Br_2$ (86.0 g, 0.204 mol) was cooled to about 0 °C (ice/water bath), and then a solution of NEt_3 (43.5 mL, 0.430 mol) in 100 mL of CH_3CN was added dropwise over 30 min. After stirring for 2 h, 250 mL of EtOAc was added, the slurry filtered and the filtrate concentrated to a residue using a Büchi rotavapor. The residue was slurried with 500 mL of hexanes and filtered and the filtrate concentrated using a Büchi rotavapor. The residue was Kugelrohr distilled (110−125 °C/1 Torr) to yield (±)-**19** in 62% yield (13.40 g, 0.084 mol).

^{1}H NMR ($CDCl_3$): δ 7.00−7.35 (m, 4H); 2.75 (m, 1H); 2.50 (dd, 1H, J = 7 Hz); 2.42 (s, 3H); 2.3 (m, 2H); 2.01 (bd, 1H, J = 5 Hz), 1.52 (m, 1H). MS (EI): m/z 159 (M^+), 144 (M^+ − 15, CH_3).

***trans*-(±)-(1*RS*,2*RS*)- and (+)-(1*R*,2*R*)-1-[(2,2-Dimethoxyethyl)methylamino]-1,2,3,4-tetrahydro-2-naphthalenol [(±)-23 and (+)-23].** *Method A. From (±)-27 from (±)-25*. A slurry of (±)-**27** (85.8 g, 0.484 mol), K_2CO_3 (133.8 g, 0.968 mol), $BrCH_2CH(OMe)_2$ (123.0 g, 0.726 mol), and 484 mL of CH_3CN was refluxed for 6 days. After cooling to rt, the reaction mixture was decanted and then concentrated to a residue using a Büchi rotavapor. The residue was dissolved in 750 mL of H_2O and washed with 350 mL of EtOAc, and the organic layer was washed with 2 × 160 mL of 2.5% HCl. The combined acidic washes were adjusted to pH 8.8 with saturated Na_2CO_3 and extracted with 250 mL of EtOAc. The combined organic extracts were washed with 50 mL of saturated NaCl solution, dried over anhydrous $MgSO_4$, and concentrated using a Büchi rotavapor to give (±)-**23** in 78% yield (100.2 g, 0.378 mol)

^{1}H NMR ($CDCl_3$): δ 7.12 (m, 4H); 4.50 (t, 1H, J = 7 Hz); 4.13 (s, 1H); 3.72 (m, 2H); 3.40 (s, 6H); 3.08 (d, 2H, J = 7 Hz); 3.86 (m, 2H); 2.48 (S, 3H); 2.22 (m, 1H); 1.80 (m, 1H). IR (film): 3440, 2920, 1450, 1130, 1070, 740 cm^{-1}.

Method B. (±)-23 from (±)-25. A solution of (±)-**25** (2.613 g, 17.872 mmol) and $CH_3NCH_2CH(OMe)_2$ (2.747 g, 23.055 mmol) was added to a 30 mL Teflon acid digestion bomb, sealed, placed in a stainless steel closed system reactor (bomb), and then heated with stirring for 20 h (oil bath temperature about 95 °C). After cooling to rt, flash chromatography of the crude product (2−5% MeOH/CH_2Cl_2) afforded (±)-**23** in 94% yield (4.478 g, 16.877 mmol). The ^{1}H NMR spectrum was identical to that of the material prepared by method A.

Method C. Enantioenriched (+)-23 from Enantioriched (+)-25. An enantioenriched sample of (+)-**25** (4.650 g, 31.804 mmol; prepared by Jacobsen asymmetric epoxidation, ≈65% ee) was reacted with $CH_3NCH_2CH(OMe)_2$ (5.693 g, 47.78 mmol) following the procedure described in method B to afford, after flash chromatography, (+)-**23** in 57% yield (4.807 g, 18.114 mmol). The ^{1}H NMR spectrum was identical to that of the material prepared by method A. $[\alpha]_D^{22}$ = +21° (*c* 0.50, MeOH).

Method D. (+)-23 from (+)-32. A slurry of (+)-**32** (12.6 g, equivalent to 0.05 mol of free amine), K_2CO_3 (13.8 g, 0.1 mol), and 30 mL of H_2O was stirred for 30 min and then extracted with 3 × 100 mL of CH_2Cl_2. The combined organic extracts were dried over Na_2SO_4 and concentrated using a Büchi rotavapor to an oil, which was then dissolved in 50 mL of CH_3CN. To this solution of the free amine (+)-**27** were added K_2CO_3 (13.8 g, 0.1 mol) and $BrCH_2CH(OMe)_2$ (7.09 mL, 0.06 mol), and the mixture was refluxed overnight. The reaction mixture was cooled to rt, diluted with H_2O, and extracted with 2 × 100 mL of CH_2Cl_2. The combined organic extracts were concentrated using a Büchi rotavapor and chromatographed over silica gel [CH_2Cl_2 containing 2% MeOH/H_2O (10:1)] to give (+)-**23** in 46% yield (6.12 g, 0.023 mol). The ^{1}H NMR spectrum was identical to that of the material prepared by method A. Chiral HPLC (Chiracel ORD) indicated 99% ee. $[\alpha]_D^{21.5}$ = +30.9° (*c* 0.51, MeOH).

(±)-(1*RS*,2*SR*) and (+)-(1*R*,2*R*)-1a,2,3,7b-Tetrahydronaphth[1,2-*b*]oxirene [(±)-25 and (+)-25]. *Method A. (±)-25*. The procedure of Bach and Knight was followed.[16] To a solution of **31** (26.00 g; GC assay: 93% pure, 0.186 mol) in 70 mL of MeOH and 60 mL of CH_3CN was added $KHCO_3$ (2.00 g, 0.020 mol). The slurry was stirred for 5 min, and then 30% H_2O_2 (45.00 g, 0.400 mol, 30% solution in H_2O) was added at a rate such that the reaction temperature was maintained between 25 and 30 °C. After stirring for 17 h at rt, the reaction mixture was quenched with 40% sodium bisulfite. The reaction mixture was concentrated using a Büchi rotavapor to an oil (40−45 °C/60 Torr), which was dissolved in 50 mL of CH_2Cl_2 and 150 mL of H_2O, and the layers were separated. The organic layer was washed with 2 × 50 mL of H_2O, dried over anhydrous Na_2SO_4, and concentrated using a Büchi rotavapor. The residue was distilled (70−76 °C/0.05 Torr) to afford (±)-**25** in 94% yield (26.70 g, HPLC assay, 95.3% pure). A reference sample was obtained by distillation (70−76 °C/0.05 Torr).

^{1}H NMR ($CDCl_3$): δ 7.42 (dd, 1H, J = 1, 5 Hz); 7.24 (m, 2H), 7.10 (d, 1H, J = 5 Hz); 3.85 (d, 1H, J = 3 Hz); 3.72 (m, 1H); 2.80 (m, 1H); 2.56 (dd, 1H, J = 6, 11 Hz); 2.42 (m, 1H); 1.86 (m, 1H).

Method B. Enantioenriched (+)-25 from 31 ("Jacobsen Epoxidation Procedure"[27]). A solution of **31** (5.00 g, 38.405

mmol), 4-phenylpyridine *N*-oxide (1.32 g, 7.71 mmol), (*S*,*S*)-chloro[2,2′-[1,2-cyclohexanediylbis(nitrilomethylidyne)]bis-[4,6-bis(1,1-dimethylethyl)phenolato]](2−)-*N*,*N*′,*O*,*O*′-manganese[27] (0.98 g, 1.60 mmol) and 40 mL of toluene was cooled to 0 °C (ice/water bath), and then a cooled solution (0 °C) of NaOCl[35] (135 mL, 7.147 g, 96.013 mmol, ≈5% NaOCl in H_2O) was added. After stirring for 3 h at 0 °C, 300 mL of hexanes was added and the layers were separated. The organic layer was washed with 2 × 150 mL of water and 1 × 100 mL of saturated NaCl solution. The combined aqueous washes were extracted with 2 × 50 mL of hexanes, and the combined organic layers were then dried over anhydrous $MgSO_4$ and concentrated using a Büchi rotavapor to afford (+)-**25** in 83% yield [6.12 g, 75% pure by capillary GC (dodecane, internal standard), actual amount is 4.65 g]. Naphthalene was also observed in 15% yield.[36] The ^{1}H NMR spectrum was identical to that of the racemic material prepared by method A. Chiral HPLC (Daicel OB column) indicated the product to have an ee of 86%. Similar experiments typically afforded (+)-**25** with ee's of 85−90%, although in one instance an ee of 97% was observed, but with low yield (≈30%).[28]

***trans*-(±)-(1*RS*,2*SR*)-1,2-Dibromo-1,2,3,4-tetrahydronaphthalene [(±)-29].** This compound was prepared following the procedure of v. Braun and Kirschbaum.[24] To a refluxing solution of **28** (66.1 g, 0.5 mol) in 50 mL of hexane was added Br_2 (51.52 mL, 1.0 mol) at such a rate as to maintain reflux. Heating was continued after the addition was complete until the Br_2 color was discharged. The solution was cooled to 20 °C, sparged with N_2 to purge HBr, and diluted with 20 mL of hexane. After the solution had been chilled overnight in the refrigerator, the crystals of **29** were separated by filtration, washed with cold hexane, and dried to afford **29** in 55% yield (79.7 g, 0.28 mol).

^{1}H NMR (DMSO-d_6): δ 7.12−7.42 (m, 4H); 5.95 (m, 1H); 5.14 (m, 1H), 3.03 (m, 2H); 2.68 (m, 1H); 2.15 (m, 1H).

***trans*-(±)-(1*RS*,2*SR*)-2-Bromo-1-hydroxy-1,2,3,4-tetrahydronaphthalene [(±)-30].** This compound was prepared following a modified procedure of Lukes.[23] To a solution of **29** (503 g, 1.73 mol) in 2.25 L of acetone and 1.5 L of H_2O was added $NaHCO_3$ (145.5 g, 1.73 mol). The reaction mixture was refluxed under N_2 for 2.5 h, cooled, and concentrated using a Büchi rotavapor until crystals formed. H_2O (1 L) was added, and the product was separated by filtration, washed with H_2O, and dried to afford **30** in 93% yield (366 g, 1.61 mol).

^{1}H NMR (DMSO-d_6): δ 7.08−7.40 (m, 4H); 5.91 (d, 1H, J = 6.5 Hz); 4.66 dd, 1H, J = 6.5, 6.5 Hz), 4.46 (m, 1H); 2.85 (m, 2H); 2.45 (m, 1H); 2.13 (m, 1H).

***trans*-(+)-(1*R*,2*R*)-2-Hydroxy-1-(methylamino)-1,2,3,4-tetrahydronaphthalene) Semi L-(+)-Tartrate Salt [(+)-32].** A suspension of (±)-**30** (471.8 g, 2.08 mol) in $MeNH_2$ (40% aqueous solution, 1.85 L) was stirred at rt for 24 h, during which time solution occurred. The mixture was saturated with NaCl and extracted with 4 × 1 L portions of CH_2Cl_2. The extracts were combined and concentrated using a Büchi rotavapor to an oil, which was diluted with 400 mL of MeOH. To this solution of racemic **27** was added a solution of L-(+)-tartaric acid (77.9 g, 0.52 mol) in 400 mL of MeOH with good agitation. After stirring overnight at −5 °C the crystals were collected by filtration, washed with MeOH, and dried to afford (+)-**32** in 46% yield [243 g; 94% de (by HPLC)]. This material was slurried in refluxing MeOH (600 mL) for 4 h. Filtration and washing with MeOH afforded 202 g (0.4 mol); 98% de. Similarly, one further slurry gave material of 100% de. Mp: 214−216 °C. $[\alpha]_D^{20}$ = +33.7° (c = 1.0, H_2O). Anal. Calcd for ($C_{26}H_{36}N_2O_8$): C, 61.89; H, 7.19; N, 5.55. Found: C, 61.89; H, 7.12; N, 5.59.

^{1}H NMR (DMSO-d_6): δ 7.06−7.46 (m, 8H); 4.00 (ddd, 2H, J = 3.1, 6.1, 8.2 Hz); 3.88 (s, 2H); 3.82 (d, 2H, J = 6.1 Hz); 2.75 (m, 4H); 2.37 (s, 6H); 2.00 (m, 2H); 1.71 (m, 2H).

***trans*-(1*S*,2*R*)-1,2,3,4-Tetrahydro-2-(methylamino)-1-naphthalenol (35).** A solution of **34**[30,31] (81.18 g, 0.370 mol) and 300 mL of dry THF was cooled to about 0 °C (ice/H_2O bath), and then $LiAlH_4$ (24.914 g, 0.656 mol) dissolved in 300 mL of dry THF was added over 50 min. The reaction mixture was refluxed for 2 h and cooled to rt, and a mixture of 600 mL of saturated NH_4Cl/ice was added followed by 300 mL of CH_2Cl_2. The reaction mixture was allowed to warm to rt and filtered. The solids were washed with 2 × 100 mL of CH_2Cl_2, and the layers were separated. The aqueous layer was extracted with 2 × 50 mL of CH_2Cl_2, and the combined organic layers were dried over anhydrous $MgSO_4$ and concentrated using a Büchi rotavapor to afford **35** in 84% yield (55.312 g, 0.312 mol).

Trans: ^{1}H NMR ($CDCl_3$): δ 7.68 (d, 1H, J = 7.5 Hz); 7.10−7.30 (m, 3H); 4.50 (d, 1H, J = 7.5 Hz); 2.90 (m, 2H); 2.67 (m, 1H); 2.55 (s, 3H); 2.27 (m, 1H); 2.00 (br s, 2H); 1.60 (m, 1H).

^{13}C NMR ($CDCl_3$): δ 138.1, 135.8, 128.3, 127.2, 127.1, 126.2, 72.7, 62.4, 33.4, 27.9, 25.2. MS (EI): m/z 177 (M^+).

A small amount of the *cis* diastereomer was also isolated (>39:1 *trans*:*cis* ratio).

Cis: ^{1}H NMR ($CDCl_3$): δ 7.48 (m, 1H); 7.10−7.30 (m, 3H); 4.71 (d, 1H, J = 3.8 Hz); 2.75−3.00 (m, 3H); 2.55 (br s, 5H); 1.95 (m, 1H); 1.75 (m, 1H).

***trans*-(1*S*,2*R*)-2-[(2,2-Dimethoxyethyl)methylamino]-1,2,3,4-tetrahydro-1-naphthalenol (24).** A slurry of **35** (1.010 g, 5.698 mmol), 10 mL of anhydrous CH_3CN, and KF over alumina (3.050 g, 19.06 mmol) was stirred for 5 min, and $BrCH_2CH(OMe)_2$ (1.4 mL, 11.8 mmol) was then added. The reaction mixture was refluxed for 2 days and cooled to rt, and 25 mL of EtOAc was added. The slurry was filtered though a pad of Celite, the solids were washed with 10 mL of EtOAc and 10 mL of CH_2Cl_2, and the combined filtrate was concentrated on a Büchi rotavapor. The residue was flash chromatographed (30−100% EtOAc/hexanes and then 60% MeOH saturated with NH_3/EtOAc) to afford **24** in 94% yield (1.264 g, 4.764 mmol). MS (CI): m/z 266 (M^+ + 1), 248 (M^+ − 17, OH), 234 (M^+ − 31, OCH_3), 190 (M^+ − 75, $CH(OCH_3)_2$). IR (CH_2Cl_2): 3450, 2940, 1458, 1190, 1125, 1070 cm^{-1}.

(36) The actual mechanism for formation of naphthalene was not investigated, but one possible mechanism is hydrolysis of epoxide **25** to its diol followed by a double dehydration.

^{1}H NMR ($CDCl_3$): δ 7.65 (d, 1H, J = 7.5 Hz); 7.05−7.30 (m, 3H); 4.65 (d, 1H, J = 11.3 Hz); 4.55 (br m, 1H); 4.10 (br s, 1H); 3.45 (s, 3H); 3.10 (s, 3H); 2.53−3.00 (m, 5H); 2.47 (s, 3H); 2.05 (m, 1H); 1.61 (m, 1H).

^{13}C NMR ($CDCl_3$): δ 138.3, 134.8, 128.0, 126.8, 126.7, 126.1, 103.2, 68.7, 67.1, 54.5, 54.0, 53.6, 38.7, 29.2, 19.4.

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Supporting Information Available

^{1}H NMR spectra for **9**, **18**−**20**, **22**−**27**, **29**, **30**, **32**, and **35**. SINEPT and APT ^{1}H NMR experiments for **24**, COSY ^{1}H NMR experiment for **26**, chiral HPLC conditions for **9**, **22**, **23**, **25**, **27**, and **32**, and capillary GC conditions for **22** and **25** (20 pages). See any current masthead page for ordering and Internet access instructions.

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