Total Synthesis of Michellamines A−C, Korupensamines A−D, and Ancistrobrevine B

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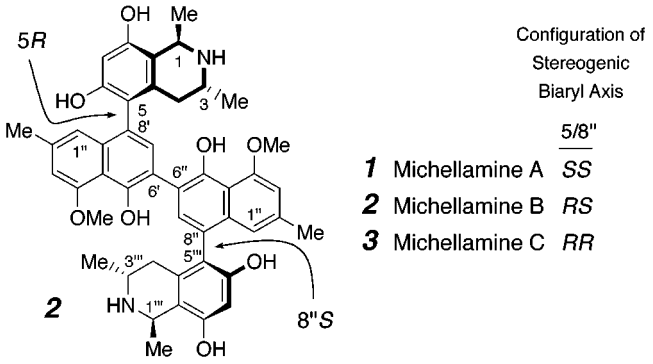
Efficient syntheses of the title compounds have been developed. Several strategies for preparation of each of the naphthalene and tetrahydroisoquinoline (THIQ) portions were developed. Initial attempts to use benzyne plus furan cycloaddition reactions were thwarted by the unfavorable sense of the regiochemical outcome. An interesting annulation reaction of benzynes derived from 2,4-dibromophenol derivatives formed the core of the shortest naphthalene synthesis. An alternative annulation initiated by the addition of a benzylic sulfone anion to methyl crotonate led to an efficient naphthol synthesis amenable to large scale. The THIQ synthesis of Bringmann was used initially and subsequently complemented by a route whose key step involved the opening of *N*-tosyl-2-methylethyleneimine by a 3,5-dimethoxyphenylcuprate reagent. The results from a variety of aryl cross-coupling reactions are described. Suzuki coupling of the boronic acid derived from the naphthalene moiety with a THIQ-iodide was the most generally effective method for forming the hindered biaryl bond. The korupensamines and ancistrobrevine B were then revealed by deprotection. The oxidative coupling of several 4-aryl-1-naphthols to indigoids (cross ring naphthoquinones) with silver oxide effected the critical dimerization reaction needed to establish the michellamine skeleton. For the perbenzylated precursor, hydrogen over palladium on carbon both reductively bleached the indigoid and hydrogenolyzed the benzyl ethers and amines to release the free michellamines. The synthesis of several michellamine analogues, including *ent*-michellamines, is outlined. Results of anti-HIV assays are presented.

Introduction

The identification, isolation, and structures of michellamines A and B (**1** and **2**, respectively) were reported in 1991 by the Boyd laboratory at the National Cancer Institute (NCI).[1] Both isomers were found to be fully protective against both HIV-1 and HIV-2 infected CEM-SS cells. Michellamine B has an EC_{50} value of 1−18 μM for various strains of HIV.[2] Michellamine B (**2**) was identified by the NCI for preclinical development,[2] and numerous related studies have ensued.[3−5] Michellamine B (**2**) has been found to be unique in its ability to completely protect MT-2 cells from both AZT-resistant and pyridone-resistant strains of HIV-1. The fact that "very few known anti-HIV-1 agents demonstrate any activity against HIV-2"[1] raised the question of whether the michellamines may be invoking an unrecognized mechanism of anti-HIV activity. Subsequent studies to elucidate the mode of action of michellamine B (**2**) have indicated that it does not block the initial binding of HIV to target cells, it inhibits cellular fusion and syncytium formation, and it inhibits HIV−RT noncompetitively.[4,5]



Bioassay-guided fractionation of the organic extracts of the vine *Ancistrocladus korupensis*, collected in the Korup National Park in Cameroon, provided a mixture of atropisomeric michellamines A (**1**) and B (**2**). These isomers, formally arising from rotation around the C(5)/C(8′) and C(8″)/C(5‴) bonds, cannot be interconverted thermally. However, they do isomerize when treated with base, a process that also gives rise to the diastereomer michellamine C (**3**). The unsymmetrical (5*R*,8″*S*) isomer, michellamine B (**2**), is typically isolated from plant material in approximately twice the amount of the minor (5*S*,8″*S*) isomer, michellamine A (**1**). Although small amounts of **3** have been obtained during isolation of **1** and **2**, it is believed to arise from atropisomerization of **2** during processing of the biomass.[6] Chemical equilibration studies indicate a **1**:**2**:**3** equilibrium ratio of ∼3:3:1.[2]

The structures of the michellamines are unique among the family of naphthalene−isoquinoline alkaloids.[7] They contain an unprecedented C(5)−C(8′) biaryl linkage; they have a large number of free phenolic hydroxyl groups; and they are the first oxidatively dimerized (binaphthol)

(1) Manfredi, K. P.; Blunt, J. W.; Cardellina, J. H.; McMahon, J. B.; Pannell, L. L.; Cragg, G. M.; Boyd, M. R. *J. Med. Chem.* **1991**, *34*, 3402.

(2) Boyd, M. R.; Hallock, Y. F.; Cardellina, J. H.; Manfredi, K. P.; Blunt, J. W.; McMahon, J. B.; Buckheit, R. W.; Bringmann, G.; Schäffer, M.; Cragg, G. M.; Thomas, D. W.; Jato, J. G. *J. Med. Chem.* **1994**, *37*, 1740.

(3) Supko, J. G.; Malspeis, L. *Antimicrob. Agents Chemother.* **1995**, *39*, 9.

(4) McMahon, J. B.; Currens, M. J.; Gulakowski, R. J.; Buckheit, R. W.; Lackman-Smith, C.; Hallock, Y. F.; Boyd, M. R. *Antimicrob. Agents Chemother.* **1995**, *39*, 484.

(5) Supko, J. G.; Malspeis, L. *Proc. Annual Meet. Am. Assoc. Cancer Res.* ***1994***, *39*, A2520.

(6) Bringmann, G. *Bull. Soc. Chim. Belg.* **1996**, *105*, 601.

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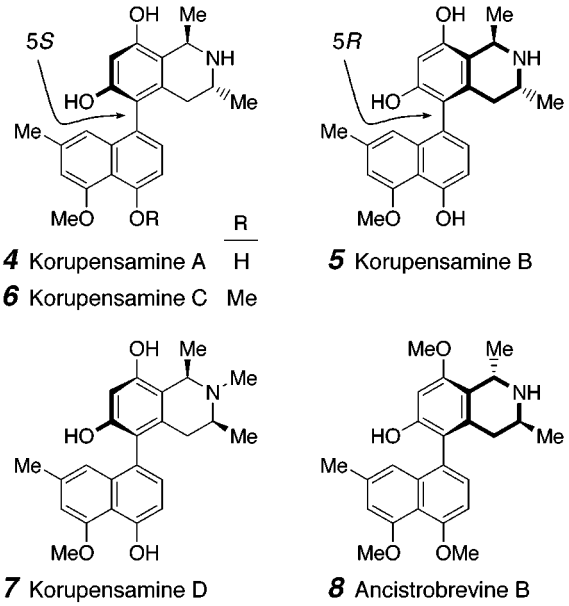
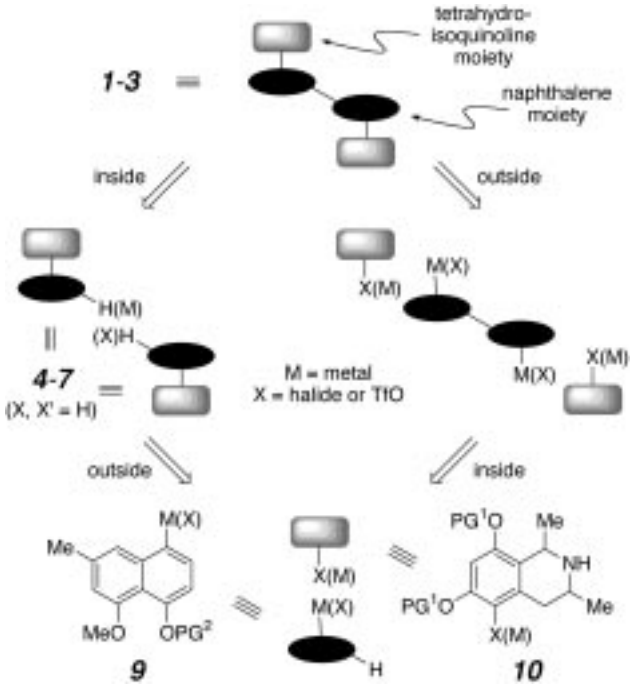
naphthalene−isoquinoline alkaloids. An important degradation [to (*R*)-alanine] study by Bringmann[8] revealed that the configuration at the benzylic C(1) position was opposite to that typically seen in the majority of other naphthalene−isoquinoline alkaloids. The configuration at the stereogenic axis was deduced by NOE studies (cf. below).[1,2]

It was later reported that the extracts of *A. korupensis* also contained four new "monomeric" alkaloids, korupensamines A−D (**4**−**7**, respectively).[9] These are likely biosynthetic precursors to the michellamines; oxidative self-dimerization of **4** or **5** would give michellamines A or C (**1** or **3**, respectively), while cross-coupling of **4** and **5** would give michellamine B (**2**). The korupensamines do not have anti-HIV activity but are antimalarial. The only previously known C(5)−C(8′)-linked naphthalene−isoquinoline alkaloid with a structure similar to **4**−**7** is ancistrobrevine B (**8**),[10] found in *Ancistrocladus abbreviatus*. It is interesting that the configuration at C(3) in **8** is *S* and that **8** is the 5′-*O*-methyl ether of *ent*-korupensamine C (i.e., ***ent*-6**).



Given the promising anti-HIV properties of the michellamines, the potential need for large quantities of michellamine B as it proceeded further in preclinical development studies, the novel structural characteristics of these oxidatively dimerized alkaloids, and the value of being able to access unnatural analogues of this family of lead compounds,[11] several research groups have studied and subsequently reported the synthesis[12a−g] of michellamines A−C (**1**−**3**) and their analogues.[12h−j] The obvious retrosynthetic dissection of the michellamine skeleton can follow two pathways, referred to as outside-in vs inside-out as illustrated in the left vs right half of Scheme 1. These differ in the order in which the C(5)−C(8′)/C(8″)-C(5‴) biaryl bond(s) vs the C(6′)-C(6″) binaphthyl bond are formed in the synthetic direction. Bringmann and Boyd described the first preparation of synthetic michellamine A (**1**). Natural korupensamine A (**4**) was protected as the *N*-formyl di-*O*-acetyl derivative and oxidatively coupled with silver oxide.[12a] Shortly thereafter, Kelly, Bringmann, and Boyd described an inside-out route that employed a Suzuki coupling of a tetrahydroisoquinoline(THIQ)-5-boronic acid with an 8′,8″-bis-trifluorosulfonyloxy-6′,6″-binaphthyl derivative,[12b,13] and we communicated an outside-in total synthesis of michellamines A−C (**1**−**3**, vide infra).[12c] Dawson reported the first synthesis of the unsymmetrical michellamine B (**2**) to the exclusion of michellamines A and C.[12d] It proceeded by an outside-in route that permitted the regiospecific cross-coupling of two differentially functionalized korupensamine derivatives. Bringmann, Kelly, and

Scheme 1



(7) (a) Bringmann, G. The Naphthyl Isoquinoline Alkaloids. In *The Alkaloids;* Brossi, A., Ed.; Academic Press: New York, 1986; Vol. 29, Chapter 3. (b) Bringmann, G.; Pokorny, F. The Naphthylisoquinoline Alkaloids. In *The Alkaloids;* Cordell, G., Ed.; Academic Press: New York, 1995; Vol. 46, Chapter 4.

(8) (a) Bringmann, G.; Zagst, R.; Schäffer, M.; Hallock, Y. F.; Cardellina, J. H., II; Boyd, M. R. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1190. (b) Bringmann, G.; God, R.; Schäffer, M. *Phytochemistry* **1996**, *43*, 1393.

(9) Hallock, Y. F.; Manfredi, K. P.; Blunt, J. W. C.; Cardellina, J. H., II; Schäffer, M.; Gulden, K. P.; Bringmann, G.; Lee, A. Y.; Clardy, J.; François, G.; Boyd, M. R. *J. Org. Chem.* **1994**, *59*, 6349.

(10) Bringmann, G.; Zagst, R.; Reusher, H.; Aké Assi, L. *Phytochemistry* **1992**, *31*, 4011.

(11) Compound supply was problematic, since the only known natural source was the rare *A. korupensis* liana, which is found only in a limited region of the Cameroonian rainforest.

(12) (a) Bringmann, G.; Harmsen, S.; Holenz, J.; Geuder, T.; Götz, R.; Keller, P. A.; Walter, R.; Hallock, Y. F.; Cardellina, J. H., II; Boyd, M. R. *Tetrahedron* **1994**, *50*, 9643. (b) Kelly, T. R.; Garcia, A.; Lang, F.; Walsh, J. J.; Bhaskar, K. V.; Boyd, M. R.; Götz, R.; Keller, P.; Walter, R.; Bringmann, G. *Tetrahedron Lett.* **1994**, *35*, 7621. (c) Hoye, T. R.; Chen, M.; Mi, L.; Priest, O. P. *Tetrahedron Lett.* **1994**, *35*, 8747. (d) Hobbs, P. W.; Upender, V.; Liu, J.; Pollart, D. J.; Thomas, D. W.; Dawson, M. I. *J. Chem. Soc., Chem. Commun.* **1996**, 923. (e) Bringmann, G.; Götz, R.; Harmsen, S.; Holenz, J.; Walter, R. *Liebigs Ann.* **1996**, *12*, 2045. (f) Hobbs, P. W.; Upender, V.; Dawson, M. I. *Synlett* **1997**, 965. (g) Bringmann, G.; Götz, R.; Keller, P. A.; Walter, R.; Boyd, M. R.; Lang, F.; Garcia, A.; Walsh, J. J.; Tellitu I.; Bhaskar, K. V.; Kelly, T. R. *J. Org. Chem.* **1998**, *63*, 1090−1097. (h) Upender, V.; Pollart, D. J.; Liu, J.; Hobbs, P. D.; Olsen, C.; Chao, W.; Bowden, B.; Crase, J. L.; Thomas, D. W.; Pandey, A.; Lawson, J. A.; Dawson, M. I. *J. Heterocycl. Chem.* **1996**, *33*, 1371. (i) Zhang, H. P.; Zembower, D. E.; Chen, Z. D. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 2687. (j) Bringmann, G.; Wenzel, M.; Kelly, T. R.; Boyd, M. R.; Gulakowski, R. J.; Kaminsky, R. *Tetrahedron* **1999**, *55*, 1731−1740. (k) de Koning, C. B.; Michael, J. P.; van Otterlo, W. *Tetrahedron Lett* **1999**, *40*, 3037.

(13) It is interesting that this route ultimately gave rise to michellamines A and B but not C.[12b]

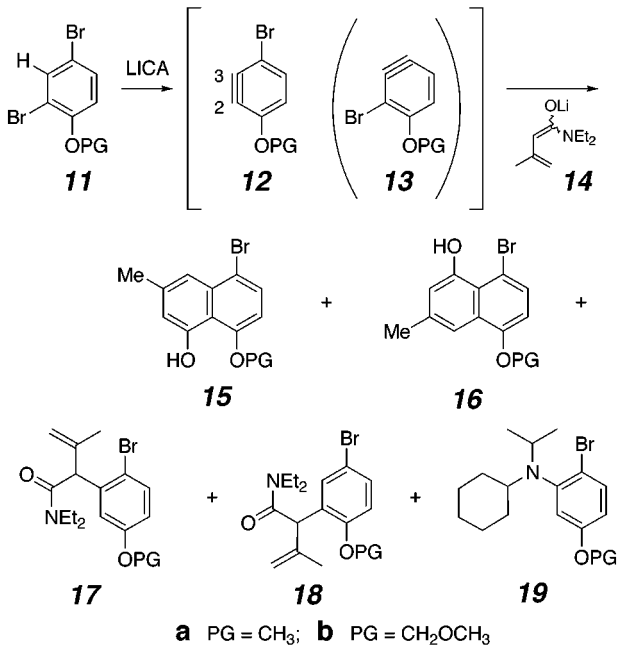
Boyd have reported syntheses of korupensamines A and B (**4** and **5**),[14a,e] Rao has synthesized the *O*,*O*,*O*-trimethyl ethers of korupensamines A and B,[14b] and we have communicated preparations of korupensamines A−D (**4**-**7**) and ancistrobrevine B (**8**).[14c,d]

In this paper, we detail our studies of (i) several approaches to the synthesis of appropriately functionalized naphthalene building blocks **9**, (ii) an aziridine-based synthesis of the THIQ building block **10** that complements the original Bringmann route to these portions,[15] (iii) the synthesis of monomethylated analogues of the THIQ by various stereoselective reductions, (iv) the importance of choice of metal and halogen (or triflate) on the various aryl moieties used in hindered biaryl cross-coupling reactions, (v) the silver oxide oxidative coupling of several relevant naphthalenes, (vi) the successful syntheses of the korupensamines **4**−**7**, ancistrobrevine **8**, and the michellamines **1**−**3**, *ent*-michellamines A−C, and several simpler analogues, and (vii) the anti-HIV activity of several of these synthetic analogues.

Discussion

Naphthalene Synthesis. Preparation of 1-naphthol derivatives such as **9**, bearing 6-methyl and 8-methoxy substituents, became the first goal. After initial unsuccessful attempts to use cycloaddition reactions of benzyne with variously substituted furans,[16] we focused on the benzyne annulation route summarized in Scheme 2. Unsymmetrically substituted benzynes have been trapped previously with dienolate anions,[17] but there are no reports of use of aryl dihalides in this reaction. Thus, it was unclear what regioselectivity would be observed during both benzyne generation and in the subsequent addition of dienolates to the monohalo benzyne when substrates such as **11** were used. We were delighted at the outcome. When 2,4-dibromoanisole (**11a**) was treated with excess amide anion in the presence of the preformed dienolate anion **14**, derived from 3-methyl-2-butenoic acid *N*,*N*-diethylamide, two (and only two) naphthols, **15a** and **16a**, were formed in a ratio of ∼5:1. Both arise by addition of **14** to benzyne **12**. No products arising from the isomeric benzyne **13** have ever been observed. We

Scheme 2



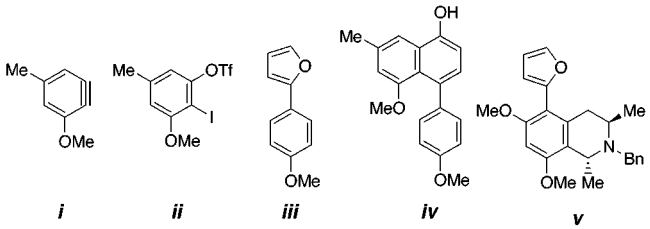
attribute this remarkably regioselective benzyne formation to the ability of the aryl ether oxygen in **11** to coordinate lithium, thereby providing an internal Lewis acid to assist in the unique loss of the 2-bromo substituent. The major and desired naphthol **15** then arises by preferential nucleophilic attack at C(3) rather than C(2) in benzyne **12**. The overall yield of naphthols **15** and **16** was reproducibly ∼25%, regardless of the reaction scale and regardless of considerable attempts at optimization.[18] Several byproducts were identified in these reactions. Amides **17** and **18** arise from α-attack by **14**, and these types of intermediates are known to proceed further[17] to cyclized naphthols such as **15** and **16**, respectively. Amine **19** arises by competitive trapping of benzyne **12** with lithium isopropylcyclohexylamide. The outcome of this reaction, including the formation of an analogous set of byproducts, is quite similar whether one starts with the *O*-methyl ether **11a** or the *O*-methoxymethyl ether **11b**.

Phase-transfer methylation of **15a** or **15b** with tetrabutylammonium bromide and dimethyl sulfate in methylene chloride and aqueous sodium hydroxide gave a high yield of the desired protected naphthalenes **20a** or **20b**. Metalation of either of these bromonaphthalene and subsequent reaction with trimethyl borate gave the naphthalene boronic acids **21a** or **21b** as viscous oils in good yield. The ^{1}H NMR spectrum of the material produced in this fashion was typically quite complex. The samples could be readily dehydrated by precipitation with hexanes from a dry methylene chloride solution. The resulting white solid gave a single set of aromatic and methyl proton resonances, but lacked B(O*H*) resonances. On the other hand, combustion analysis of this material was more consistent with the boronic acid **21b** rather

(14) (a) Bringmann, G.; Götz, R.; Ketter, P. A.; Walter, R.; Henschel, P.; Schäffer, M.; Stablein, M.; Kelly, T. R.; Boyd, M. R. *Heterocycles* **1994**, *39*, 503. (b) Rao, A. V. R.; Gurjar, M. K.; Ramana, D. V.; Chheda, A. K. *Heterocycles* **1996**, *43*, 1. (c) Hoye, T. R.; Mi, L. *Tetrahedron Lett.* **1996**, *37*, 3097. (d) Hoye, T. R.; Chen, M. *Tetrahedron Lett.* **1996**, *37*, 3099. (e) Bringmann G.; Ochse, M. *Synlett* **1998**, 1294.

(15) (a) Bringmann, G.; Jansen, J. R.; Rink, H.-P. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 913−915. (b) Bringmann, G.; Weirich, R.; Reuscher, H.; Jansen, J. R.; Kinzinger, L.; Ortmann, T. *Liebigs Ann. Chem.* **1993**, 877.

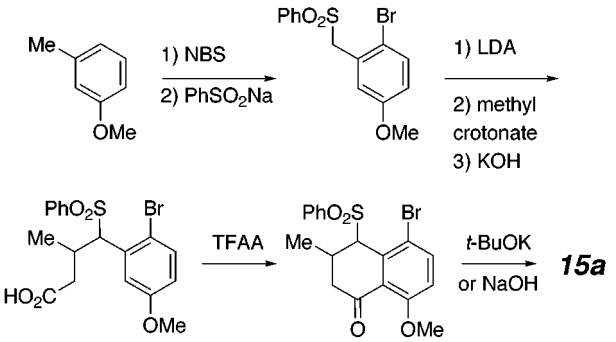
(16) For example, cycloaddition of benzyne **i** (derived from iodotriflate **ii** by treatment with *n*-BuLi) with 4-(2-furyl)anisole (**iii**) gave the undesired regioisomer **iv** as the only product. We also examined the cycloaddition of benzyne **i** with THIQ substituted furan **v**. However, no cycloaddition products were observed, probably because of the hindered nature of **v**.



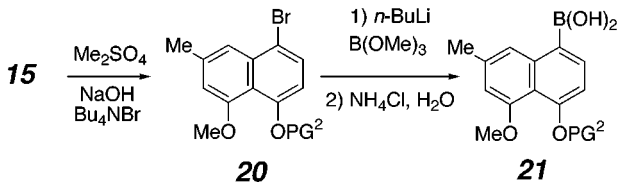
(17) Watanabe, M.; Hisamatsu, S.; Hotokezaka, H.; Furukawa, S. *Chem. Pharm. Bull.* **1986**, *34*, 2810.

(18) Modifications included changing the number of equivalents of dialkylamide anion, the order and rate of addition, the number of equivalents of dibromide precursor, the solvent, the structure of the dialkylamide base, and the temperature of benzyne generation and reaction. *n*-Butyllithium was used for the preliminary deprotonation of *β*,*β*-dimethyl-*N*,*N*-diethylacrylamide (in an attempt to reduce the amount of isopropylcyclohexylamine and the amount of amine-trapped product **19**). However, none of these modifications resulted in significant changes in the yield or ratio of products.

Scheme 3



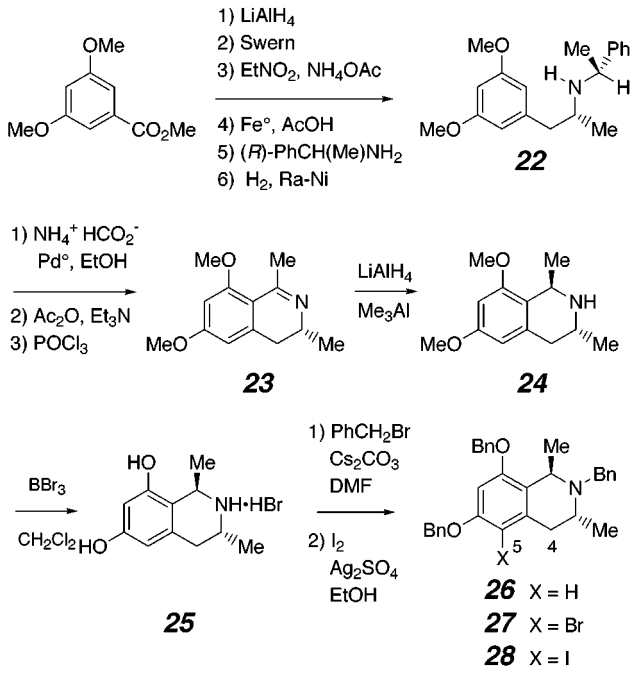
than the corresponding boronic anhydride. Either the crude or the precipitated samples of boronic acids **21** functioned equally well in subsequent, palladium-catalyzed biaryl cross-coupling reactions.



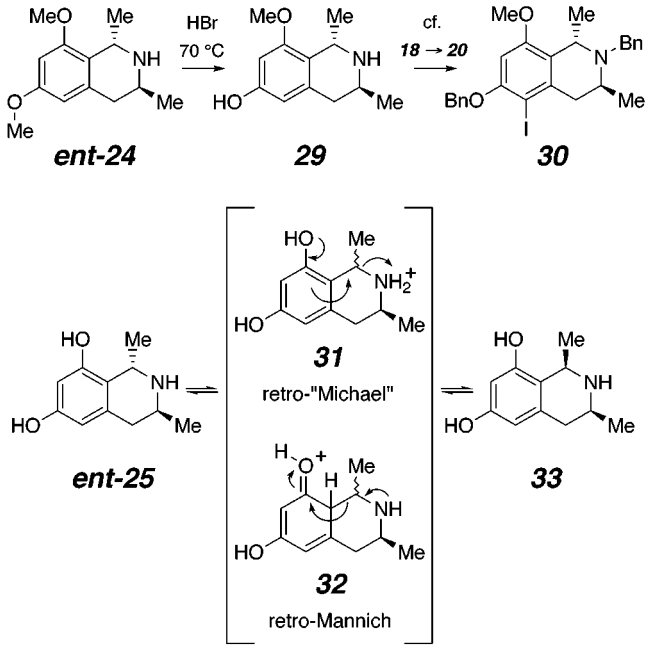
Even though the above route was quite short, the benzyne annulation reaction reproducibly produces **15** in ∼20−25% yield. Chromatographic purification is cumbersome on a large scale (we have prepared up to 10 g of **15b** by this method), and so we decided to develop an alternative, multistep synthesis. If the synthesis was to be competitive we felt it would be desirable to proceed through crystalline derivatives so that chromatographic purifications would not be necessary. The new synthesis is summarized in Scheme 3. We have described the details for this route elsewhere.[19] It proceeds in ∼40% overall yield and is our method of choice for preparing large quantities of naphthalene **15a**.

Tetrahydroisoquinoline (THIQ) Synthesis. In our earliest work aimed at the synthesis of the THIQ fragments such as **10**, we opted to use the sequence pioneered by Bringmann for the synthesis of intermediate **24**,[15] as summarized in the beginning of Scheme 4. Since methyl ether removal at the late stage of a michellamine synthesis was deemed unwise, replacement of the *O*-methyl groups by *O*-benzyl groups was studied at the stage of **24**. Handling of the resultant, amphoteric diphenolic amines such as **25** proved difficult until we developed a nonaqueous workup procedure. Thus, **24** was treated with boron tribromide (6 equiv, −78 °C) in methylene chloride, methanol was added, the mixture was concentrated to remove the volatile $B(OMe)_3$ and HBr byproducts, and the methanol treatment was repeated several times to provide excellent yields of the recrystallizable hydrobromide salt **25**. Tribenzylation of this salt was also problematic until cesium carbonate/DMF was used as the base/solvent system instead of the more common potassium carbonate/MeOH or DMF system. Bromination of the resultant **26** with 1 equiv of Br_2 in methylene chloride or iodination with iodine/silver sulfate in ethanol[20] regiospecifically provided the 5-bromo- or 5-iodo-THIQs **27** or **28**, respectively. A strong NOE between H(5) and $H(4_{eq})$ that is present in **26** is lost in bromide **27**, clearly implicating the site of reaction. These halides were poised for biaryl coupling to the naphthalene unit for establishing the korupensamine and michellamine skeletons and substitution patterns.The ancistrobrevine (**8**) target required the 8-O-monomethylated THIQ **30** (Scheme 5). Partial demethylation of ***ent*-24** (prepared by using the *S*-α-methylbenzylamine chiral auxiliary) with 49% aqueous HBr at 70 °C gave, after quenching with ammonium hydroxide solution, the neutral methoxyaminophenol **29** in 48% yield (Scheme 5). N,O-Bis-benzylation with benzyl bromide and potassium carbonate in 2-butanone and subsequent iodination gave the 6-benzyloxy derivative **30**. Attempts to demethylate both methoxy groups in the amine ***ent*-24** with HBr at

Scheme 4

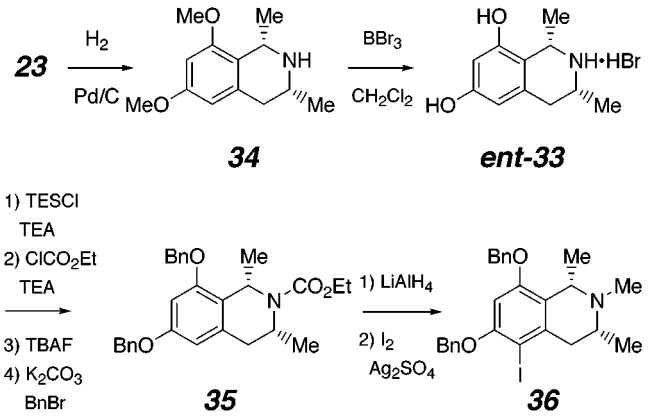


Scheme 5



(19) Hoye, T. R.; Mi, L. *J. Org. Chem.* **1997**, *62*, 8586.
(20) Wy, W.-W. *Tetrahedron Lett.* **1993**, *34*, 6223.

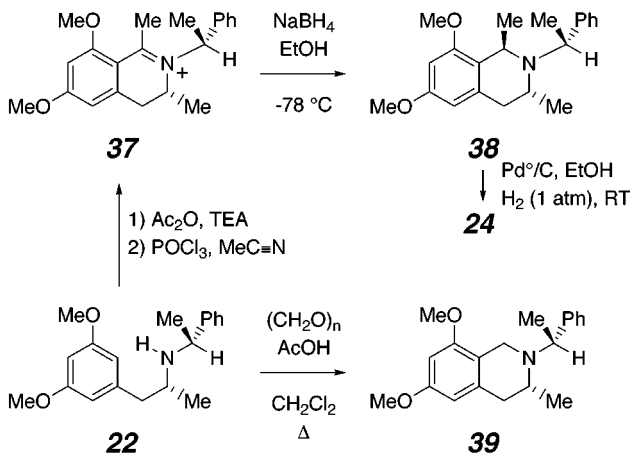
Scheme 6



100 °C both with and without the addition of sodium iodide[21] led to partial isomerization of the *trans*-1,3-dimethyl-THIQ to the cis isomer. This C(1)-epimerization can be viewed as proceeding either through a reverse Michael-like reaction of the ammonium ion **31**[22] or via a reversible retro-Mannich fragmentation of the keto-tautomer **32**.[23]

The key building block we envisioned for korupensamine D was the N-methylated, cis-configured THIQ derivative **36** (Scheme 6). The *cis*-1,3-dimethylated THIQ **34** has been previously prepared by reduction of cyclic imine **23** with $NaBH_4$ with high diastereoselectivity (ds = 94%).[15b] Exposure of **23** to 1 atm of H_2 in the presence of a catalytic amount of 10% Pd/C also gave the cis-configured **34** (93%) as the only observable (^{1}H NMR) diastereomer (Scheme 6). The cis relative configuration was supported by an NOE experiment; irradiation of $H(1)_{ax}$ (δ 4.24) resulted in enhancement of the signal for $H(3)_{ax}$ (δ 2.88). Demethylation of **34** with boron tribromide (4 equiv) almost quantitatively provided the diphenol amine HBr salt ***ent*-33**. O-Silylation of ***ent*-33** and carbamate formation[24] followed by removal of the silyl groups and O-benzylation smoothly afforded compound **35** (~60% overall). Reduction of carbamate **35** with $LiAlH_4$ (94%) followed by regiospecific iodination (80%) provided iodide **36**.

We have studied several reaction sequences designed to take further advantage of the α-methylbenzylamine chiral auxiliary that was incorporated in the original Bringmann synthesis of **22** (Scheme 4). Previously, after serving its role in directing Raney nickel reduction from the α-face to establish the configuration at the newly formed stereocenter in **22**, the α-methylbenzyl moiety was always reductively removed. If, instead, **22** is N-acylated and cyclized with $POCl_3$, the resulting iminium ion **37** can be smoothly reduced with sodium borohydride to give the triply α-branched tertiary amine **38** with high diastereocontrol.[25] The high degree of steric congestion in this molecule is evidenced by the broadened set of resonances for nearly all protons in the ambient temperature ^{1}H NMR spectrum of **38**, presumably because of slow C−N bond rotation and/or nitrogen inversion. This is analogous to the situation known to prevail in triisopropylamine.[26] This severe crowding makes the mild conditions for the subsequent N-debenzylation step remarkable—hydrogenolysis on a palladium catalyst occurred smoothly at room temperature with only 1 atm of hydrogen to give **24**, thereby demonstrating that the α-methylbenzyl moiety can serve both as an initial chiral auxiliary and as a late-stage protecting group. Intermediate **22** was also cyclized in the Pictet−Spengler mode with paraformaldehyde to generate **39**, a THIQ derivative monomethylated only at C(3).

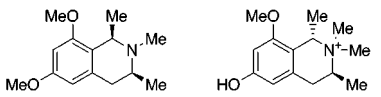


To prepare the analogous C(1)-monomethylated THIQ **41** in nonracemic form, we again relied on the α-methylbenzylamine auxiliary and followed the lead of Polniaszek.[27] We prepared both the 3,5-dimethoxy (**a** series) and 3,5-dibenzyloxy (**b** series) versions of **41**. Thus, the iminium ions **40** could be easily generated by Bischler−Napieralski closure of the *N*-acetyl amide of secondary amines **42** and then reduced with sodium borohydride to give **41** with >95% diastereoselectivity.

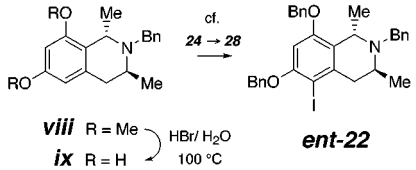
The preparation of the *unsymmetrical* secondary amines **42** was a challenge since all attempts to reduce nitriles **43** to the α-arylacetaldehydes (e.g., DIBALH) as a prelude to reductive amination chemistry were thwarted by rapid aldol dimerizations. The eventual solution took advantage of an underutilized yet powerful in situ

(21) Li, G.; Patel, D.; Hruby, V. J. *Tetrahedron Lett.* **1993**, *34*, 5393.

(22) Cf. the C(1)-epimerization proposed to explain the coexistence of gentryamines A (**vi**) and B (**vii**) in *A. korupensis*: Hallock, Y. F.; Cardellina, J. H.; Korneck, T.; Gulden, K. P.; Bringmann, G.; Boyd, M. R. *Tetrahedron Lett.* **1995**, *36*, 4753.



(23) HBr treatment of the *N*-benzyl derivative of ***ent*-18** (**viii**) at 100 °C was not accompanied by epimerization at C(1). This transformation was also observed by Dawson and co-workers.[12f] The resulting 6,8-dihydroxy-*N*-benzylated THIQ (**ix**) was converted efficiently to ***ent*-22**.



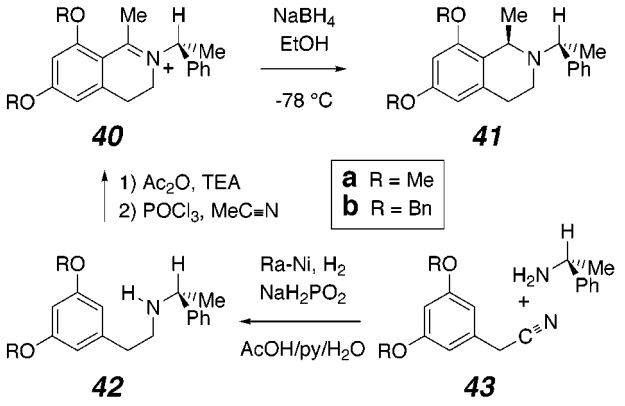
(24) Hoye, T. R.; Renner, M. K.; Vos-Dinardo, T. J. *J. Org. Chem.* **1997**, *26*, 4168.

(25) While the diastereoselectivity favoring the indicated C(1)-epimer of **38** was only 88% de when the reaction was performed at rt, it rose to 96% de for samples arising from reactions begun at −78 °C and then slowly warmed to rt.

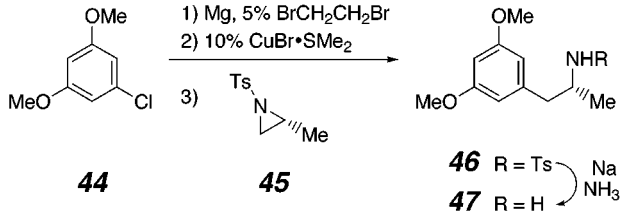
(26) Reny, J.; Wang, C. Y.; Bushweller, C. H.; Anderson, W. G. *Tetrahedron Lett.* **1975**, 503.

(27) Polniaszek, R. P.; McKee, J. A. *Tetrahedron Lett.* **1987**, *28*, 4511.

reductive cross-coupling of nitriles with amines.[28] Specifically, each of the α-arylacetonitriles **43a** and **43b**[29] was reduced over Raney nickel with sodium dihydrogen phosphite and hydrogen gas (1 atm) in acetic acid/pyridine/water (1:2:1) in the presence of 1.2 equiv of (*R*)-α-methylbenzylamine. The secondary amines **42a** and **42b** were isolated in 74% and 72% yields, respectively. There was no evidence (^{1}H NMR or GC/MS) of any symmetrical secondary amine from reductive self-coupling of two nitrile molecules in the crude samples of **42**. Moreover, we are not aware of Raney nickel being previously used for this reductive coupling. Importantly, since Raney nickel does not promote benzylic heteroatom bond hydrogenolysis, this catalyst is both compatible with the use of benzyl ethers as protecting groups in **43b** and **42b** and allows the direct incorporation of the α-methylbenzylamine chiral auxiliary.



An alternative, more efficient sequence for the preparation of the enantiomerically pure primary amine **47**, a valuable intermediate for the construction of nonracemic THIQ **10** as described earlier (**47** is the product of the debenzylation of **22** described in Scheme 4), was also developed. The strategy we envisioned was the ring opening of a properly activated nonracemic aziridine **45** with an aromatic nucleophile derived from commercially available 1-chloro-3,5-dimethoxybenzene (**44**).[30] The Grignard reagent from **44** is difficult to generate, requiring mechanical and chemical (ethylene dibromide) activation of the magnesium turnings and refluxing in THF for extended periods.[31] Under these conditions, the conversion of chloride **44** to the Grignard reagent is 75−100% efficient. Refluxing the aziridine **45**[32] with the Grignard reagent in THF for 3 h only gave ∼10% of the desired product **46**, along with recovered aziridine **45** and several unidentified byproducts. However, when a catalytic amount of $CuBr_2$·SMe_2 was first added to the Grignard reagent, the ring-opened product was formed in almost quantitative yield at 0 °C after 2 h. Removal of the toluenesulfonamide group in **46** provided primary amine **47** in 80% yield. No evidence for Birch reduction of the dimethoxyphenyl ring was seen for this reductive cleavage, which was performed with an excess of sodium in liquid ammonia at −78 °C for 40 min. This concise preparation of **47** compares favorably with the earlier route and is readily amenable to large scales.



Aryl Cross-Coupling Studies While the various pathways to the naphthalene and THIQ building blocks **9** and **10** were being secured, we were also investigating the effectiveness of various mixed aryl coupling reactions on suitable model compounds. We first studied the appealing Lipschutz oxidative cross-coupling of diarylcuprates (method A, Chart 1).[33] This is a technically demanding reaction that had variable outcomes in our hands. Although we were eventually successful in generating the model biaryl **48** in ∼50% yield, which has a similar degree of steric hindrance at the biaryl bond as the michellamines, attempts to apply this coupling to generate the THIQ-containing biaryls **49** were unsuccessful.

We turned to various palladium-mediated couplings. While Stille coupling of arylstannanes was useful in constructing relatively unhindered biaryls such as **50** (method B, Chart 1), it failed in several more sterically demanding instances. Suzuki coupling of aryl boronic acids (or the related cyclic anhydrides) was the most generally successful aryl cross-coupling strategy. Early in our studies aryl bromides, while good substrates for preparation of relatively unhindered biaryls, proved less reliable for the construction of hindered biaryls such as **49** (method C, Chart 1). We settled on the use of aryl iodides, which proved to be versatile precursors for formation of biaryls such as **49**[34] and **51** (method C, Chart

(28) (a) Backeberg, O. G.; Staskun, B. *J. Chem. Soc.* **1962**, 3961. (b) Staskun, B.; Backeberg, O. G. *J. Chem. Soc.* **1964**, 5880. (c) Rylander, P. N.; Hasbrouck, L.; Karpenko, I. *Annals of the New York Academy of Sciences* **1973**, *214*, 100.

(29) Nitriles **43a** and **43b** were prepared from 3,5-dimethoxy- and 3,5-dibenzyloxybenzyl alcohol, respectively, by conversion to the benzylic bromide (PBr_3, ether, *RT*) and displacement with potassium cyanide (aqueous ethanol, reflux).

(30) For a review describing the use of chiral aziridines in synthesis, see: Tanner, D. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 599.

(31) We appreciate Professor Bruce H. Lipshutz sharing his group's expertise in surmounting this problem.

(32) Daub, G. W.; Heerding, D. A.; Overman, L. E. *Tetrahedron* **1988**, *44*, 3919.

(33) Lipshutz, B. H.; Siegmann, K.; Garcia, E. Kayser, F. *J. Am. Chem. Soc.* **1993**, *115*, 9276.

(34) The acetate analogue of **49** (**xiii**) was once prepared by coupling the naphthyl triflate **xi** with the THIQ boronic acid **xii**. The triflate was derived from the naphthalene-1,4-diol **i**, which in turn could be prepared by the indicated Diels−Alder reactions. This strategy was inferior to the THIQ-halide/naphthalene-metal routes we adopted (Chart 1) because the synthesis of **x** was not efficient and the generation of boronic acid **xii** made the sequence less convergent with respect to the more complex THIQ unit.

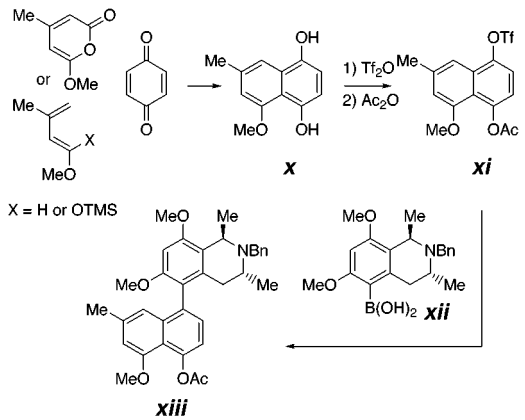
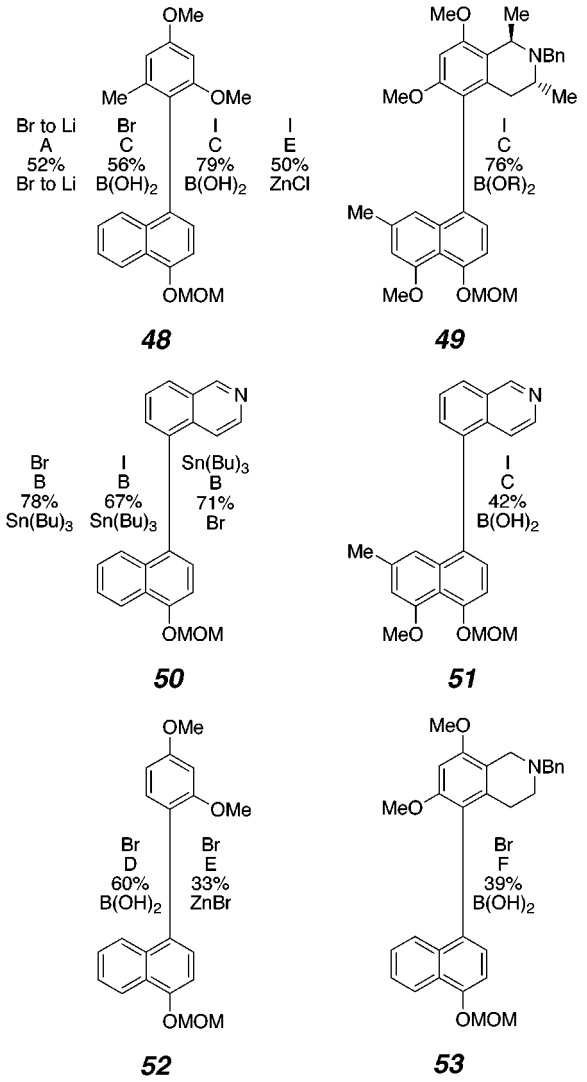


Chart 1. Some Unsymmetrical Biaryls Constructed by Various Aryl Coupling Reactions[a]



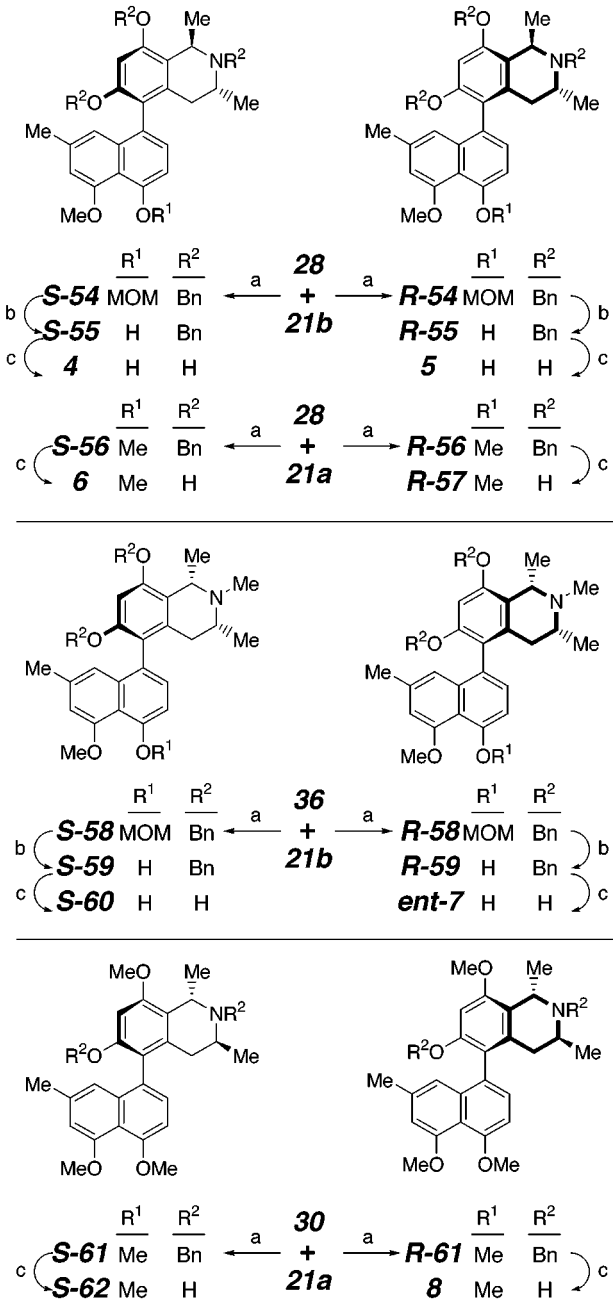
[a] Descriptors indicate (from top to bottom) the precursor substituent on the THIQ surrogate, the catalytic method, the yield of coupled product, and the precursor substituent on the naphthalene moiety. [b] Method A: ArLi + CuCN + Ar′Li, −130 °C, dry O_2. Method B: $Pd(PPh_3)_4$, CuBr, PhMe, 100 °C. Method C: $Pd(PPh_3)_4$, PhMe/EtOH/satd $NaHCO_3$, 100−110 °C. Method D: $Pd(PPh_3)_4$, acetone/H_2O/Na_2CO_3, degassing, 100 °C. Method E: ArBr + *n*-BuLi + ZnX_2 in THF, −78 °C; $Pd(PPh_3)_4$, Ar′Br, 80 °C. Method F: $Pd(PPh_3)_4$, PhMe/EtOH/Na_2CO_3, degassing, 100 °C.

1). Use of basic aqueous sodium carbonate in thoroughly degassed acetone or toluene/ethanol has provided the biaryls **52** and **53**. Finally, we have also recently shown that Negishi coupling of aryl zinc halides is a useful method for construction of biaryls **48**, **52**, and others.[35]

Completion of Korupensamines and Ancistrobrevine Syntheses. With the appropriate building blocks and a reliable aryl coupling method in hand, we were positioned to complete syntheses of the monomeric alkaloids korupensamines A−C (**4**−**6**), *ent*-korupensamine D (***ent*-7**), and ancistrobrevine B (**8**). All followed similar paths as indicated in Scheme 7. In every case, (i) aryl coupling was effected between a THIQ-iodide (**28**, **36**, or **30**) and either the *O*-MOM or *O*-methylnaphthalene **21b** or **21a**; (ii) the yield of coupled products was in

(35) Hoye, T. R.; Chen, M. *J. Org. Chem.* **1996**, *61*, 7490.

Scheme 7



[a] $Pd(PPh_3)_4$, PhMe/EtOH/satd $NaHCO_3$, 100−110 °C. [b] HCl (concd), MeOH/CH_2Cl_2, rt. [c] 10% Pd/C, H_2 (1 atm), MeOH, rt.

the range of 65−86%; (iii) the diastereoselectivity was minimal (typically between 1.25 and 1.5:1); (iv) the atropisomeric adducts had very similar HPLC (SiO_2) retention behavior; (v) MOM ethers (when present) could be easily and subsequently removed at room temperature using methanolic hydrochloric acid; (vi) the *O*- and *N*-benzyl protecting groups were trivial to remove in a single hydrogenolytic treatment with 1 atm of hydrogen over 10% palladium on carbon (but prolonged reaction times should be avoided to minimize formation of byproducts that may arise by cleavage of the N−C(1) bond); and (vii) the atropisomers were separated by HPLC either following MOM removal (SiO_2) or after debenzylative conversion to the natural products (amino-bonded SiO_2).

Stereochemical Assignments of Atropisomers. The assignment of configuration of axial chirality in the

Table 1. Chemical Shifts of Axial and Equatorial Protons H(4) Correlate with the Diastereomeric Relationship between the C(3) Methyl-Bearing Carbon and the C(5) Biaryl Axis

compd	3,5-rel config[a]	$\delta_{H(4ax)}$[b]	$\delta_{H(4eq)}$[b]	$\Delta\delta_{4ax}$[c]	$\Delta\delta^{4eq}$[d]	$\Delta\delta_{4ax-eq}$[e]
michellamine A (**1**)	unlike	2.15	2.81	−0.46	0.46	-0.66
michellamine C (**3**)	like	2.61	2.35			0.26
michellamine B (**2**)						
S-biaryl	unlike	2.11	2.78	−0.41	0.43	-0.66
R-biaryl	like	2.52	2.35			0.17
korupensamine A (**4**)	unlike	2.05	2.62	−0.33	0.39	-0.57
korupensamine B (**5**)	like	2.38	2.23			0.15
korupensamine C (**6**)	unlike	2.06	2.59	−0.33	0.37	-0.53
***R*-57**	like	2.39	2.22			0.17
(*ent*)-korupensamine D (***ent*-7**)	like	2.25	1.91	−0.24	0.17	0.34
***S*-59**	unlike	2.01	2.08			−0.07
ancistrobrevine B (**8**)	unlike	1.77	2.29	−0.50	0.24	-0.52
***S*-62**	like	2.27	2.05			0.22

[a] The relative configuration between C(3) and the biaryl axis [at C(5)]. [b] Data in CD_3OD solution except for **8** and ***S*-62**, which were determined in $CDCl_3$. [c] $\Delta\delta_{4ax} = \delta_{H(4ax)unlike} - \delta_{H(4ax)like}$ = the chemical shift of the axial proton in the *unlike* (*ul*) diastereomer minus that in the *like* (*l*). [d] $\Delta\delta_{4eq} = \delta_{H(4eq)unlike} - \delta_{H(4eq)like}$ = the chemical shift of the equatorial proton in the *unlike* (*ul*) diastereomer minus that in the *like* (*l*). [e] $\Delta\delta_{4ax-4eq} = \delta_{H(4ax)} - \delta_{H(4eq)}$ = the chemical shift of the axial proton minus that of the equatorial proton in the same compound.

THIQ-naphthalene alkaloids presents an interesting challenge. The problem was solved in the initial studies of Boyd, Cardellina, Manfredi, and co-workers by a clever NOE study.[1,2] Specifically, the assignment of relative configuration of each stereogenic biaryl axis vis-à-vis the adjacent C(1)/C(3) stereocenters followed from the enhancements observed between the naphthalene protons H(1′)/H(7′) and the corresponding diastereotopic methylene protons at C(4). The latter were identified as axial or equatorial, respectively, on the basis of their large vs small vicinal coupling constants to H(3). Circular dichroism methods have also been developed to address this question.[36]

We have identified an even more straightforward basis for making this configurational assignment. The method relies on chemical shift differences of the diastereotopic C(4) methylene protons (Table 1). The example of *ent*-korupensamine D (***ent*-7**) and its stereogenic axis epimer ***S*-60** is detailed in Figure 1. $H(4_{eq})$, distinguished again from $H(4_{ax})$ by its characteristic coupling patterns, is more highly shielded in ***ent*-7** than in ***S*-60** because it is adjacent to the "long" side of the naphthalene ring. The inverse is true for $H(4_{ax})$. This relationship holds for all of the atropisomeric pairs of natural products and their stereogenic axis epimers; i.e., $\Delta\delta_{4ax}$ (defined and recorded in Table 1) is always negative and $\Delta\delta_{4eq}$ is always positive. It is also the case that $H(4_{ax})$ is always downfield of $H(4_{eq})$ (i.e., $\Delta\delta_{4ax-4eq}$ is positive) in diastereomers having the *like* relative configuration between C(3) and the stereogenic axis (cf. ***ent*-7**), but upfield of $H(4_{eq})$ (i.e., $\Delta\delta_{4ax-4eq}$ is negative) in the *unlike* isomers (cf., ***S*-60**). That is, the relative shifts of these diastereotopic protons are inverted in the two isomers. These two trends appear to hold in both methanol and chloroform solution as well as for many of the diastereomeric pairs of synthetic intermediates enroute to the natural products. We suggest that these correlations can be used as convenient and reliable empirical relationships for assigning relative configuration in this class of naphthalene-3-alkyltetrahydroisoquinoline alkaloids.

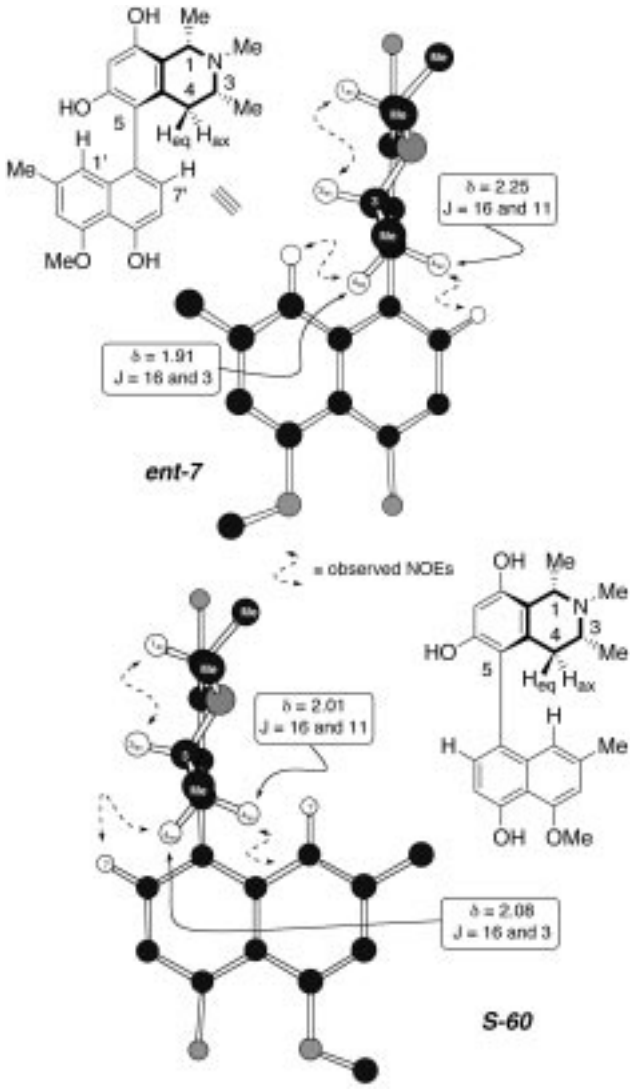
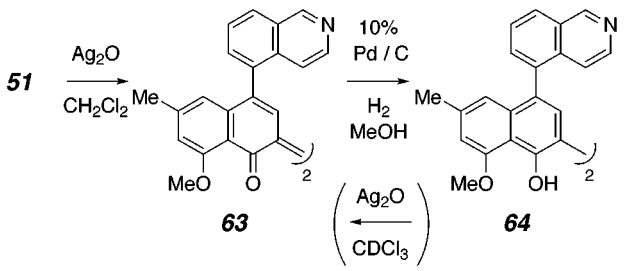


Figure 1. Diagnostic chemical shift differences for the diastereotopic C(4) methylene protons in the representative mixture of atropisomers ***ent*-7** and ***S*-60**; the long side of the naphthalene ring shields the nearby H(4) more strongly than the short side of the naphthalene.

1-Naphthol Oxidative Couplings to 2,2′-Bi-1-naphthols. Although a variety of oxidative methods can be imagined for self-coupling of 1-naphthols at the 2-position, we were attracted to the silver oxide-induced

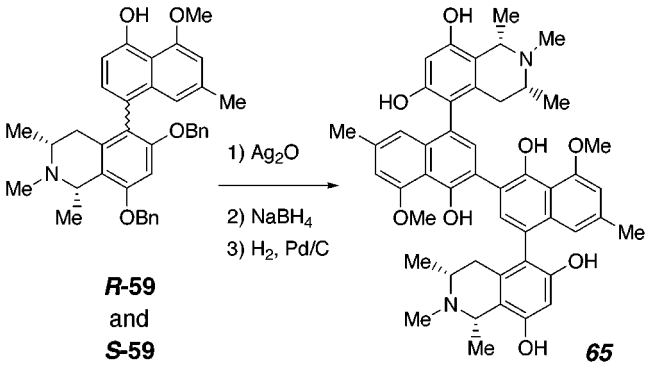
(36) (a) Bringmann, G.; Gulden, K. P.; Hallock, Y. F.; Manfredi, K. P.; Cardellina, J. H.; Boyd, M. R.; Kramer, B.; Fleischhauer, J. *Tetrahedron* **1994**, *50*, 7807. (b) Bringmann, G.; Stahl, M.; Gulden, K. P. *Tetrahedron* **1997**, *53*, 2817.

Scheme 8



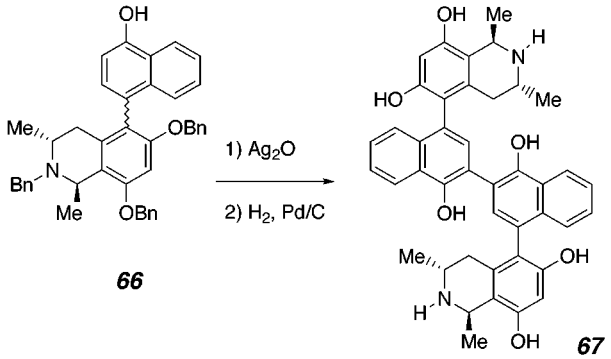
dimerizations that Laatsch and co-workers had described for an array of similarly substituted naphthol derivatives.[37] When applied to the quinoline **51**, the silver oxide coupling method worked splendidly; the cross-ring naphthoquinone **63** was smoothly and quickly produced at room temperature when **51** was stirred with a slurry of Ag_2O in methylene chloride (Scheme 8). Moreover, the quinone chromophore in similar compounds could be readily bleached by a variety of reducing agents (sodium borohydride or sodium dithionite). Catalytic hydrogenation was also useful for this purpose; **63** easily accepted 1 equiv of H_2 (1 atm) over palladium on charcoal at room temperature to give the cross-ring hydroquinone (or 2,2′-bi-1-naphthol) **64**. This same oxidative coupling/reduction sequence also worked for simpler, less-electron rich naphthols lacking the 6-methyl and 8-methoxy substituents,[38] suggesting that this same chemistry would be useful for the preparation of structural analogues of the michellamines.

The silver oxide coupling was also compatible with the THIQ moiety. Specifically, the mixture of atropisomeric *O,O*-dibenzyl ether derivatives of korupensamine D (***R*-59** and ***S*-59**) was readily coupled and immediately reduced with sodium borohydride to a mixture of intermediate 2,2′-bi-1-naphthols. Subsequent removal of four



O-benzyl groups occurred under mild conditions to provide an atropisomeric mixture of three korupensamine D dimers **65**. It is interesting to speculate whether **65** exists in nature, especially in light of the recent discovery of michellamine E, which contains one each of 1,3-cis- and 1,3-trans-dimethylated THIQ's.[6,7b]

Related naphthol derivatives with oxidation potentials lower than those present in substrates **51** and **59** can also be oxidatively coupled with silver oxide. The simple 4-THIQ-1-naphthol **66** was coupled to generate the corresponding cross-ring naphthoquinone. This was directly treated under very mild conditions (rt, 1 atm H_2, 10% Pd/C) both to reduce the quinone chromophore and to cleave all six benzyl groups, including the hindered *N*-benzyl substituents. The resulting mixture of the known[12h] atropisomeric binaphthols **67** was isolated in 75% yield.



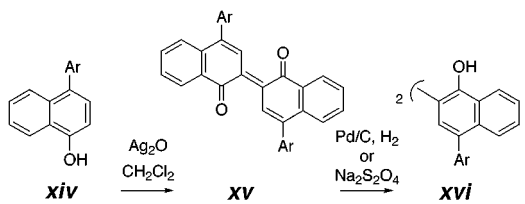
Completion of Syntheses of Michellamines A−C. We were delighted when the silver oxide coupling worked equally well on the *N,O,O*-tribenzyl-4-tetrahydroisoquinolinyl-1-naphthol derivative ***S*-55** to produce the symmetrical quinone ***S,S*-68** (Scheme 9) as the only observed product. At the end of the coupling reaction, the silver salts were removed by filtration, and methanol was added to the methylene chloride solution. Addition of 10% Pd/C and exposure to an atmosphere of hydrogen not only resulted in reductive bleaching of the indigoid but also readily removed all six benzyl protecting groups to produce michellamine A (**1**).

A sample of the 5:4 mixture of ***S*-55** and ***R*-55** was subjected to the same coupling/reduction procedure to efficiently generate an ∼1:2:1 mixture of the atropisomeric michellamines A−C (**1**−**3**). The crude product mixture from this two-step sequence is remarkably clean by ^{1}H NMR spectroscopy. The individual michellamine atropisomers can be separated by the NCI HPLC protocol[2] [amino-bonded column with a 7:1 mixture of CH_2Cl_2:3% methanolic $(NH_4)_2CO_3$].

Anti-HIV Activities: *ent*-Michellamines A−C, Korupensamine D Dimer 65, and Desmethoxy/Desmethyl Michellamines 67. We have used the same chemistry just described to prepare an ∼1:2:1 mixture of *ent*-michellamines A−C (***ent*-1**, ***ent*-2**, and ***ent*-3**). The enantiomeric series of intermediates was reached simply by using *S*-α-methylbenzylamine to prepare the intermediate imine en route to ***ent*-22** (see Scheme 4), the first important chiral intermediate from which all of the remaining stereochemistry is derived. The mixture of ***ent*-1**−***ent*-3** has been examined for activity.[39] The EC_{50}

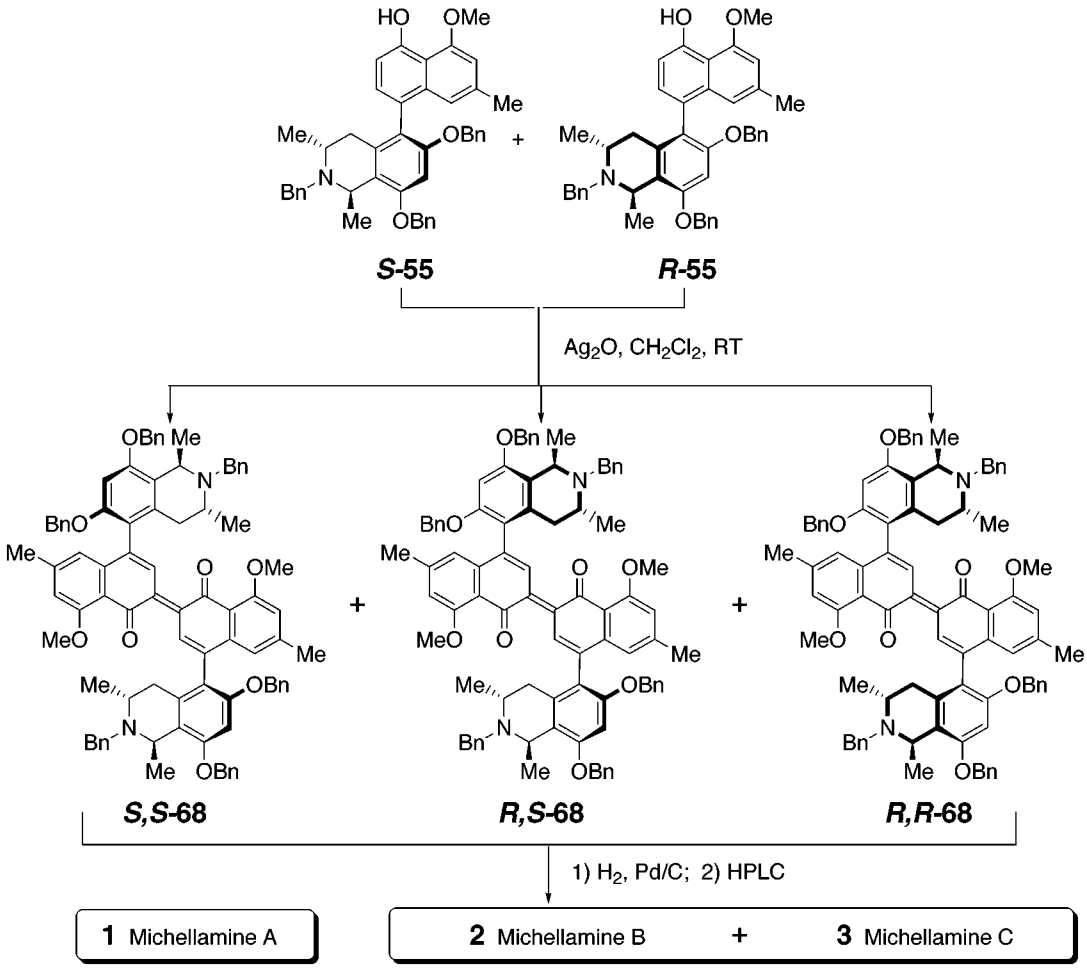
(37) Laatsch, H. *Liebigs Ann. Chem.* **1980**, 1321.

(38) The 4-aryl-substituted 1-naphthol (Ar = 2,4-dimethoxy-6-methylphenyl) **xiv** was readily coupled by silver oxide to the indigo-blue cross-ring quinone **xv** and then reduced to the binaphthol derivative **xvi**.



(39) Assays were performed under the Developmental Therapeutics Program at the National Cancer Institute. Protection of CEM-SS cells toward infection by HIV-1 was monitored by quantifying the number of viable cells using XTT/formazin colorimetric detection. Weislow, O. W.; Kiser, R.; Fine, D.; Bader, J.; Shoemaker, R. H.; Boyd, M. R. *J. Natl. Cancer Inst.* **1989**, *81*, 577.

Scheme 9



value for protection of infected CEM-SS cells was 5.8−9.5 μM (quadruplicate assays), and the in vitro therapeutic index (TI_{50} = IC/EC) ranged from 5.5 to 10.4. Both sets of numbers are strikingly similar to those for each of the natural michellamines. The mixture of korupensamine D dimers **65** showed marginal activity; the EC_{50} values ranged from 11.5 to 13.7 μM and the TI_{50} was ~2 in four separate runs. Finally, the desmethyl/desmethoxy analogue of michellamines A−C (**67**) showed no protective ability in each of four separate assays.

The fact that each of the samples of **1**−**3** and the mixture of ***ent*-1**−***ent*-3** show similar activity suggests that neither the absolute configuration of the methyl-bearing centers [and, therefore, the presence of each or both of the C(1) and C(3) methyl groups] nor the overall topology of the molecule (which is dramatically different for the individual atropisomers) is critical to imparting anti-HIV properties to the michellamines. The fact that compound **65** showed some activity but the analogue **67** was inactive suggests that the presence of the methoxy and or methyl groups on the binaphthol core is a required structural feature for activity. It is tempting to speculate that redox chemistry within the more electron-rich binaphthol—perhaps related to the events used in the synthesis itself—may play a role in generating active species. It is relevant that none of a series of simpler analogues of michellamines, containing less easily oxidized biphenolic and biphenyl core structures, possessed any anti-HIV activity.[12i]

Model Oxidation. One problem encountered during preclinical development studies of michellamine B has been the propensity of various formulations of the drug to develop purple discoloration during storage and handling. While we have not observed this problem in solid samples of the michellamines stored for extensive periods at <−25 °C, silica gel TLC plates spotted with the michellamines turn purple-black when left exposed to air and ambient light, suggestive of air oxidation of the 2,2′-bi-1-naphthol moiety to the corresponding cross-ring naphthoquinone. It is conceivable that such oxidation might play a role in the mechanism of action of the michellamines. To demonstrate the chemical viability of this redox cycle in a simple analogue, we exposed the isoquinoline containing 2,2′-bi-1-naphthols **64** to silver oxide at room temperature (Scheme 7). It was easily and efficiently oxidized back to the cross-ring naphthoquinone **63** by stirring room temperature in the presence of Ag_2O. Thus, **64** and **63** can be reversibly interconverted by facile oxidation and reduction events that may be relevant to the biosynthesis and or biological activity of the michellamines.

Experimental Section

[(1*R*),1*R,3*R**,5*S**,1′*R**,3′*R**,5′*S**]-, [(1*R*),1*R**,3*R**,5*S**,1′*R**,3′*R**,5′*R**]-, and [(1*R*),1*R**,3*R**,5*R**,1′*R**,3′*R**,5′*R**]-5,5′-[1,1′-Dihydroxy-8,8′-dimethoxy-6,6′-dimethyl(2,2′-binaphthalene)-4,4′-diyl]-bis-1,2,3,4-tetrahydro-1,3-dimethyl-6,8-isoquinolinediol (Michellamines A−C; 1−3).** Silver oxide (68 mg, 0.25 mmol) was added to a 5:4 mixture of biaryls ***S*-55** and ***R*-55** (13 mg,

0.02 mmol) dissolved in CH_2Cl_2 (10 mL). The mixture was stirred at room temperature in the dark until TLC and ^1H NMR analyses showed complete transformation (usually 54−72 h). The reaction mixture was passed through a bed of Celite, and the filtrate was concentrated to give a mixture of purple indigoid compounds. The mixture was dissolved in CH_2Cl_2 (5 mL) and diluted with methanol (25 mL). Palladium on carbon (10 mg) was added, and the reaction mixture was stirred under a hydrogen atmosphere (1 atm) at room temperature for 7 h. The mixture was filtered through a bed of Celite and concentrated to provide a mixture of michellamines A−C (**1**−**3**) (7.6 mg, 100%) in an ∼1:2:1 ratio. The mixture was separated by HPLC [Microsorb amino-bonded column, 7:1 CH_2Cl_2/3% methanolic $(NH_4)_2CO_3$] to give michellamine A (**1**) (∼2 mg), michellamine B (**2**), and michellamine C (**3**). The peak for michellamine C partially overlapped that for michellamine B. **1**: ^1H NMR (500 MHz, CD_3OD) δ 7.30 (s, 2H), 6.85 (s, 2H), 6.74 (s, 2H), 6.44 (s, 2H), 4.76 (q, J = 7.0 Hz, 2H), 4.10 (s, 6H), 3.69 (ddq, J = 12.0, 4.3, 6.5 Hz, 2H), 2.81 (dd, J = 18.0, 4.3 Hz, 2H), 2.34 (s, 6H), 2.15 (dd, J = 18.0, 12.0 Hz, 2H), 1.64 (d, J = 6.5 Hz, 6H), and 1.24 (d, J = 6.5 Hz, 6H). **2**: ^1H NMR (500 MHz, CD_3OD) δ 7.31/7.26 (s, 1H), 6.86/6.74 (s, 1H), 6.85/6.83 (s, 1H), 6.45/6.44 (s, 1H), 4.76/4.72 (q, J = 7.0/6.7 Hz, 1H), 4.10/4.09 (s, 3H), 3.65 (m, 2H), 2.78 (dd, J = 18.0, 4.9 Hz, 1H), 2.52 (dd, J = 18.0, 11.9 Hz, 1H), 2.36/2.33 (s, 3H), 2.35 (dd, J = 17.4, 4.9 Hz, 1H), 2.11 (dd, J = 18.0, 11.3 Hz, 1H), 1.68/1.64 (d, J = 6.7/7.0 Hz, 3H), and 1.26/1.22 (d, J = 6.4/6.4 Hz, 3H). **3**: ^1H NMR (500 MHz, CD_3OD, from a mixture of **2** and **3**) δ 7.28 (s, 2H), 6.85 (s, 4H), 6.44 (s, 2H), 4.74 (q, J = 6.7 Hz, 2H), 4.10 (s, 6H), 3.65 (m, 2H), 2.61 (dd, J = 18.0, 11.6, 2H), 2.36 (s, 6H), 2.35 (dd, J = 18.0, 4.5 Hz, 2H), 1.68 (d, J = 6.7 Hz, 6H), and 1.30 (d, J = 6.1 Hz, 6H).

Using the same procedure, a sample of ***S*-55** was converted into michellamine A (**1**).

[(1*R*),1*R,3*R**,5*S**]- and [(1*R*),1*R**,3*R**,5*R**]-1,2,3,4-Tetrahydro-5-(4-hydroxy-5-methoxy-7-methyl-1-naphthalenyl)-1,3-dimethyl-6,8-isoquinolinediol (Korupensamine A, 4, and Korupensamine B, 5).** A mixture of biaryls ***S*-55** and ***R*-55** (21 mg, 0.032 mmol) was dissolved in a 2:1 mixture of MeOH/CH_2Cl_2 (15 mL) with 10% Pd/C (40 mg). The reaction mixture was stirred under an H_2 atmosphere (1 atm) for 12 h. The reaction mixture was filtered through a bed of Celite, and the filtrate was concentrated to yield a mixture of korupensamines A (**4**) and B (**5**) (10 mg, 87%) in a 4:3 ratio. Separation of a portion of the mixture by HPLC [amino-bonded column, 19:1 $CHCl_3$/3% methanolic $(NH_4)_2CO_3$] provided a pure sample of korupensamines A (**4**) and B (**5**). **4**: ^1H NMR (HOAc Salt) (500 MHz, CD_3OD) δ 7.09 (d, J = 8.0 Hz, 1H), 6.80 (d, J = 8.0 Hz, 1H), 6.78 (s, 1H), 6.69 (s, 1H), 6.44 (s, 1H), 4.75 (q, J = 7.0 Hz, 1H), 4.08 (s, 3H), 3.65 (ddq, J = 12.0, 5.0, 6.5 Hz, 1H), 2.62 (dd, J = 18.0, 5.0 Hz, 1H), 2.30 (s, 3H), 2.05 (dd, J = 18.0, 12.0 Hz, 1H), 1.64 (d, J = 7.0 Hz, 3H), and 1.19 (d, J = 6.5 Hz, 3H). **5**: ^1H NMR (HOAc Salt) (500 MHz, CD_3OD) δ 7.02 (d, J = 8.0 Hz, 1H), 6.80 (d, J = 8.0 Hz, 1H), 6.80 (s, 1H), 6.78 (s, 1H), 6.44 (s, 1H), 4.74 (q, J = 7.0 Hz, 1H), 4.08 (s, 3H), 3.62 (ddq, J = 12.0, 5.0, 6.5 Hz, 1H), 2.38 (dd, J = 18.0, 12.0 Hz, 1H), 2.33 (s, 3H), 2.23 (dd, J = 18.0, 5.0 Hz, 1H), 1.67 (d, J = 6.5 Hz, 3H), and 1.23 (d, J = 6.5 Hz, 3H). By the same procedure, a sample of ***S*-55** (separated from the ***R*-55** atropisomer by HPLC on SiO_2) was converted into **4**.

[(1*R*),1*R,3*R**,5*S**]- and [(1*R*),1*R**,3*R**,5*R**]-1,2,3,4-Tetrahydro-5-(4,5-dimethoxy-7-methyl-1-naphthalenyl)-1,3-dimethyl-6,8-isoquinolinediol (Korupensamine C, 6, and *R*-57).** A mixture of compounds ***S*-56** and ***R*-56** (20 mg, 0.03 mmol) was dissolved in a mixture of CH_2Cl_2 and MeOH (2 mL and 10 mL). Pd/C (10%, 3 mg) was added, and the reaction mixture was stirred under an H_2 atmosphere (1 atm) for 4 h. The mixture was passed through a bed of Celite, and evaporation of the filtrate gave korupensamine C (**6**) and its atropisomer ***R*-57** as a white solid (12 mg, 100%). Separation of a portion of this mixture by HPLC [amino-bonded column, 19:1 $CHCl_3$/3% methanolic $(NH_4)_2CO_3$] provided korupensamine C (**6**) and the atropisomer ***R*-57** as white solids. **6**: ^1H NMR (500 MHz, CD_3OD) δ 7.14 (d, J = 8.0 Hz, 1H), 6.92 (d, J = 8.0 Hz, 1H), 6.78 (s, 1H), 6.69 (s, 1H), 6.45 (s, 1H), 4.75 (q, J = 6.5 Hz, 1H), 3.93 (s, 3H), 3.91 (s, 3H), 3.64 (ddq, J = 11.5, 3.0, 6.5 Hz, 1H), 2.59 (dd, J = 17.5, 3.0 Hz, 1H), 2.29 (s, 3H), 2.06 (dd, J = 17.5, 11.5 Hz, 1H), 1.65 (d, J = 6.5 Hz, 3H), and 1.18 (d, J = 5.5 Hz, 3H). ***R*-57**: ^1H NMR (500 MHz, CD_3OD, from the mixture) δ 7.08 (d, J = 8.0 Hz, 1H), 6.91 (d, J = 8.0 Hz, 1H), 6.78 (s, 1H), 6.76 (s, 1H), 6.45 (s, 1H), 4.74 (q, J = 7.0 Hz, 1H), 3.94 (s, 3H), 3.91 (s, 3H), 3.64 (ddq, J = 11.0, 4.5, 7.0 Hz, 1H), 2.39 (dd, J = 17.5, 11.0 Hz, 1H), 2.31 (s, 3H), 2.22 (dd, J = 17.5, 4.5 Hz, 1H), 1.68 (d, J = 7.0 Hz, 3H), and 1.22 (d, J = 6.5 Hz, 3H).

[(1*S*),1*R,3*S**,5*S**]- and [(1*S*),1*R**,3*S**,5*R**]-1,2,3,4-Tetrahydro-5-(4-hydroxy-5-methoxy-7-methyl-1-naphthalenyl)-1,2,3-trimethyl-6,8-isoquinolinediol [(*ent*)-Korupensamine D, 7, and *S*-60].** To a stirred solution of ***R*-59** and ***S*-59** (37 mg, 0.065 mmol) in a 4:1 mixture of MeOH/CH_2Cl_2 (5 mL) was added a catalytic amount of 10% Pd/C. The reaction mixture was stirred under an H_2 atmosphere (1 atm) for 2 h, and the catalyst was removed by passing the mixture through a bed of Celite. Purification via flash chromatography (hexanes/EtOAc 1:4 with 5% Et_3N) provided a mixture of ***ent*-7** and ***S*-60** (25 mg, 100%) as a white powder. A pure sample of ***ent*-7** was obtained from ***R*-59** following the same procedure. ***ent*-7**: ^1H NMR (500 MHz, CD_3OD) δ 7.08 (d, J = 8.0 Hz, 1H), 6.76 (d, J = 8.0 Hz, 1H), 6.76 (s, 1H), 6.74 (s, 1H), 6.34 (s, 1H), 4.07 (s, 3H), 3.84 (br m, 1H), 2.49 (s, 3H), 2.38 (br m, 1H), 2.31 (s, 3H), 2.25 (dd, J = 16.0, 10.5 Hz, 1H), 1.91 (dd, J = 16.0, 2.5 Hz, 1H), 1.51 (d, J = 6.5 Hz, 3H), and 1.00 (d, J = 6.5 Hz, 3H). ***S*-59**: ^1H NMR (from the mixture of ***ent*-7** and ***S*-59**) (500 MHz, CD_3OD) δ 7.06 (d, J = 8.0 Hz, 1H), 6.83 (s, 1H), 6.76 (d, J = 8.0 Hz, 1H), 6.74 (s, 1H), 6.36 (s, 1H), 4.07 (s, 3H), 3.74 (q, J = 6.5 Hz, 1H), 2.41 (s, 3H), 2.34 (m, 1H), 2.30 (s, 3H), 2.08 (dd, J = 16.0, 3.0 Hz, 1H), 2.01 (dd, J = 16.0, 10.5 Hz, 1H), 1.52 (d, J = 6.5 Hz, 3H), and 0.97 (d, J = 6.5 Hz, 3H).

[(1*S*),1*R,3*R**,5*S**]- and [(1*S*),1*R**,3*R**,5*R**]-1,2,3,4-Tetrahydro-5-(4,5-dimethoxy-7-methyl-1-naphthalenyl)-8-methoxy-1,3-dimethyl-6-isoquinolinol (Ancistrobrevine B, 8, and *S*-62).** A mixture of compounds ***R*-61** and ***S*-61** (18 mg, 0.03 mmol) was dissolved in CH_2Cl_2 (2 mL). The solution was diluted with MeOH (10 mL), and 10% Pd/C (3 mg) was added. The reaction mixture was stirred under an H_2 atmosphere (1 atm) for 3 h. The mixture was passed through a bed of Celite, and the filtrate was concentrated to cleanly give a mixture of ancistrobrevine B (**8**) and its atropisomer ***S*-62** (12 mg, 98%) as a white solid. Separation of a portion of the mixture by HPLC [amino-bonded column, 100:1 $CHCl_3$/3% methanolic $(NH_4)_2CO_3$] provided ancistrobrevine B (**8**) and its atropisomer ***S*-62** as white solids. **8**: ^1H NMR (500 MHz, $CDCl_3$) δ 7.25 (d, J = 8.0 Hz, 1H), 6.87 (d, J = 8.0 Hz, 1H), 6.75 (bs, 1H), 6.71 (bs, 1H), 6.49 (s, 1H), 4.62 (bs, 1H), 4.40 (q, J = 6.5 Hz, 1H), 4.01 (s, 3H), 3.98 (s, 3H), 3.87 (s, 3H), 3.16 (ddq, J = 11.0, 7.0, 4.0 Hz, 1H), 2.33 (s, 3H), 2.29 (dd, J = 17.5, 4.0 Hz, 1H), 1.77 (dd, J = 17.5, 11.0 Hz, 1H), 1.45 (d, J = 7.0 Hz, 1H), and 0.96 (d, J = 6.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.6, 157.3, 156.7, 152.4, 137.3, 136.7, 135.6, 129.8, 123.2, 121.0, 117.7, 117.2, 116.3, 109.0, 105.1, 95.7, 56.4, 56.3, 55.2, 47.3, 41.9, 35.2, 22.8, 22.1, and 21.7; FABMS calcd for $C_{25}H_{30}NO_4$ 408.2175, found 408.2180. ***S*-62**: ^1H NMR (500 MHz, $CDCl_3$) δ 7.20 (d, J = 8.5 Hz, 1H), 6.86 (d, J = 8.5 Hz, 1H), 6.81 (d, J = 1.0 Hz, 1H), 6.73 (d, J = 1.0 Hz, 1H), 6.49 (s, 1H), 4.46 (q, J = 6.5 Hz, 1H), 4.01 (s, 3H), 3.99 (s, 3H), 3.87 (s, 3H), 3.12 (ddq, J = 11.0, 4.5, 6.0 Hz, 1H), 2.33 (s, 3H), 2.27 (dd, J = 17.0, 11.0 Hz, 1H), 2.05 (dd, J = 17.0, 4.5 Hz, 1H), 1.52 (d, J = 6.5 Hz, 3H), and 1.05 (d, J = 6.0 Hz, 3H); FABMS calcd for $C_{25}H_{30}NO_4$ 408.2175, found 408.2173.

5-Bromo-8-(methoxymethoxy)-3-methyl-1-naphthalenol (15), 8-Bromo-5-(methoxymethoxy)-3-methyl-1-naphthalenol(16), *N,N*-Diethyl2-[2-Bromo-5-(methoxymethoxy)phenyl]-3-methyl-3-butenoic Acid Amide (17), *N,N*-Diethyl-2-[5-bromo-2-(methoxymethoxy)phenyl]-3-methyl-3-butenoic Acid Amide (18), and 1-Bromo-2-(*N*-cyclohexyl-*N*-methylethyl)amino-4-methoxymethoxybenzene (19). At −78 °C and under nitrogen *n*-butyllithium (2.5 M in hexane, 16.8 mL, 42 mmol) was added to a solution of *N,N*-diethyl-3,3-dimethylacrylic amide (6.20 g, 40 mmol) in THF

(40 mL). The mixture was stirred for 2 h while warming to room temperature. A solution of lithium isopropyl cyclohexylamide (40 mmol), made from *n*-BuLi (16 mL, 2.5 M in hexanes) and isopropyl cyclohexylamine at 0 °C in THF (70 mL), was added. This mixture was cooled to 0 °C, and a solution of dibromide **11b** (11.84 g, 40 mmol) in THF (50 mL) was added. The mixture was stirred at 0 °C for 14 h, quenched with aqueous ammonium chloride, and concentrated. The residue was mixed with ether (500 mL) and the organic layer was separated, washed with water and brine, dried with sodium sulfate, and concentrated. Flash chromatography (SiO_2, hexanes/EtOAc 6:1) yielded, in order of elution, naphthalenol **16b** (844 mg, 7%), naphthalenol **15b** (3.72 g, 31%, as a pale yellow oil), aniline **19b** (∼5%), and amides **17b** and **18b** (627 mg, 4%, as a 3:4 mixture). **16b**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.0 (bs, 1H), 7.69 (d, J = 1.0 Hz, 1H), 7.39 (d, J = 8.5 Hz, 1H), 6.93 (d, J = 1.0 Hz, 1H), 6.84 (d, J = 8.5 Hz, 1H), 5.32 (s, 2H), 3.51 (s, 3H), and 2.45 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 152.6, 152.2, 137.3, 129.9, 129.4, 119.3, 115.6, 114.1, 108.4, 106.9, 94.7, 56.3, and 21.7; FABMS calcd for $C_{13}H_{13}BrO_3$ 296.0048, found 296.0053. **15b**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.29 (s, 1H), 7.50 (d, J = 8.0 Hz, 1H), 7.46 (d, J = 2.0 Hz, 1H), 6.79 (d, J = 2.0 Hz, 1H), 6.76 (d, J = 8.0 Hz, 1H), 5.34 (s, 2H), 3.52 (s, 3H), and 2.45 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.2, 153.4, 139.4, 134.4, 129.6, 118.1, 115.4, 114.4, 113.5, 107.2, 95.8, 56.9, and 22.0; IR (KBr) 3412, 2966, 2919, 1635, 1602, 1571, 1385, 1164, and 1046 cm^{-1}; GC/MS *m*/*z* (relative intensity) 298 (M^+, 9), 296 (M^+, 9). Anal. Calcd for $C_{13}H_{13}BrO_3$: C, 52.55; H, 4.41. Found: C, 52.63; H, 4.26. **19b**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49 (d, J = 8.7 Hz, 1H), 6.96 (d, J = 3.0 Hz, 1H), 6.77 (dd, J = 8.7, 3.0 Hz, 1H), 5.14, (s, 2H), 3.75 (septet, J = 7 Hz, 1H), 3.5 (m, 1H), 3.48 (s, 3H), 1.5−2.0 (m, 10H), and 1.02 (d, J = 6.6 Hz, 6H). **17b**: ^{1}H NMR (500 MHz, $CDCl_3$, from the mixture) δ 7.44 (d, J = 9.0 Hz, 1H), 7.11 (d, J = 3.0 Hz, 1H), 6.86 (dd, J = 9.0, 3.0 Hz, 1H), 5.12 (s, 2H), 5.08 (s, 1H), 4.76 (bs, 1H), 4.72 (bs, 1H), 3.44 (s, 3H), 3.33 (q, J = 7.0 Hz, 2H) 3.23 (q, J = 7.0 Hz, 2H), 1.80 (s, 3H), 1.20 (t, J = 7.0 Hz, 3H), and 1.12 (t, J = 7.0 Hz, 3H). **18b**: ^{1}H NMR (500 MHz, $CDCl_3$, from the mixture) δ 7.43 (d, J = 2.5 Hz, 1H), 7.30 (dd, J = 9.0, 2.5 Hz, 1H), 6.94 (d, J = 9.0 Hz, 1H), 5.16 (d, J = 7.0 Hz, 1H), 5.13 (d, J = 7.0 Hz, 1H), 5.08 (bs, 1H), 4.83 (bs, 1H), 4.79 (bs, 1H), 3.41 (q, J = 7.5 Hz, 2H) 3.25 (q, J = 7.0 Hz, 2H), 3.42 (s, 3H), 1.78 (s, 3H), 1.22 (t, J = 7.5 Hz, 3H), and 1.11 (t, J = 7.0 Hz, 3H).

5-Bromo-1-methoxy-8-(methoxymethoxy)-3-methylnaphthalene (20). A solution of dimethyl sulfate (2.52 g, 20 mmol) in CH_2Cl_2 (20 mL) was mixed with a solution of tetrabutylammonium bromide (2.25 g, 7 mmol) and sodium hydroxide (400 mg, 10 mmol) in water (15 mL). A solution of naphthalenol **15** (1.50 g, 5 mmol) in CH_2Cl_2 (10 mL) was added. The mixture was stirred at room temperature for 18 h and diluted with CH_2Cl_2 (10 mL). The aqueous layer was separated and extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were washed with water (2 × 15 mL), dried with sodium sulfate, and evaporated to dryness. The residue was purified by flash chromatography (SiO_2, hexanes/EtOAc 9:1) to give methyl ether **20** (1.49 g, 96%) as a white solid: mp 84.5−85.5 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62 (d, J = 1.0 Hz, 1H), 7.61 (d, J = 8.5 Hz, 1H), 6.85 (d, J = 8.5 Hz, 1H), 6.74 (d, J = 1.0 Hz, 1H), 5.22 (s, 2H), 3.93 (s, 3H), 3.57 (s, 3H), and 2.50 (s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.7, 153.8, 137.7, 134.9, 130.3, 119.3, 118.0, 115.2, 112.8, 109.2, 96.7, 56.4, 56.3, and 22.1; IR (KBr) 2999, 2900, 1625, 1594, 1597, 1363, 1273, 1060, and 970 cm^{-1}; LRMS *m*/*z* (relative intensity) 312 (M^+, 100), 310 (M^+, 83). Anal. Calcd for $C_{14}H_{15}BrO_3$: C, 54.04; H, 4.86. Found: C, 54.15; H, 5.01.

[5-Methoxy-4-(methoxymethoxy)-7-methyl-1-naphthalenyl]boronic Acid (21). In a flame-dried flask bromonaphthalene **20** (1.10 g, 3.54 mmol) was dissolved in freshly distilled THF (10 mL). The solution was kept at − 78 °C and under nitrogen. *n*-Butyllithium (2.5 M in hexane, 1.7 mL, 4.24 mmol) was added. The mixture was stirred at − 78 °C for 30 min. Freshly distilled trimethyl borate (1.7 mL, 14.45 mmol) was added. The mixture was stirred at − 78 °C for 30 min and at room temperature for 2 h. The mixture was quenched with saturated aqueous $(NH_4)Cl$ (10 mL), concentrated, and mixed with ether (15 mL). The aqueous layer was separated and extracted with ether (2 × 10 mL). The combined organic layers were washed with water (2 × 15 mL) and dried with sodium sulfate. Evaporation of the solvent gave boronic acid **21** (980 mg, 100%) as a caramel: ^{1}H NMR (200 MHz, DMSO) δ 8.16 (s, 2H), 7.71 (bs, 1H), 7.52 (d, J = 8.0 Hz, 1H), 6.91 (d, J = 8.0 Hz, 1H), 6.78 (bs, 1H), 5.21 (s, 2H), 3.87 (s, 3H), 3.48 (s, 3H), and 2.50 (s, 3H). Boronic acid **21** was dissolved in a minimum amount of CH_2Cl_2 and precipitated by addition of hexanes to give the corresponding boronic anhydride (660 mg, 72%) as a white solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.73 (s, 1H), 8.52 (d, J = 8.0 Hz, 1H), 7.08 (d, J = 8.0 Hz, 1H), 6.77 (s, 1H), 5.37 (s, 2H), 3.97 (s, 3H), 3.62 (s, 3H), and 2.49 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.1, 157.0, 142.0, 139.0, 136.9 (b), 120.4, 116.4, 109.7, 108.4, 95.6, 56.5, 56.3, and 22.3; IR (KBr) 2943, 2909, 1622, 1579, 1350, 1279, 1053, and 968 cm^{-1}.

(1*R*-*trans*)-1,2,3,4-Tetrahydro-1,3-dimethyl-6,8-isoquinolinediol Hydrobromide (25). Tetrahydroisoquinoline **24** (50.7 mg, 0.23 mmol) was dissolved in CH_2Cl_2 (1 mL). Under a nitrogen atmosphere, the reaction mixture was cooled to −78 °C and a BBr_3 solution (1 mL, 4.3 equiv, 1 M in CH_2Cl_2) was added via syringe. The reaction mixture was immediately allowed to warm to room temperature and stirred. After 10 h, the flask was cooled to −78 °C and carefully quenched with 1.5 mL of MeOH. The reaction mixture was concentrated in vacuo to yield a brown oil. MeOH (3.5 mL) was added to dissolve the oil, and the reaction mixture was concentrated again. This quenching procedure was repeated six to eight times until product **25** (62.86 g, 100%) was isolated as brown crystals: mp 140−143 °C; $[\alpha]_D^{rt}$ −16.4 (c = 2.16, MeOH); ^{1}H NMR (500 MHz, CD_3OD) δ 6.23 (d, J = 1.8 Hz, 1H), 6.12 (d, J = 2.1 Hz, 1H), 4.64 (q, J = 6.7 Hz, 1H), 3.75 (ddq, J = 11.6, 4.6, 6.5 Hz, 1H), 2.98 (dd, J = 17.4, 4.6 Hz, 1H), 2.75 (dd, J = 17.4, 11.6 Hz, 1H), 1.59 (d, J = 7.0 Hz, 3H), and 1.46 (d, J = 6.4 Hz, 3H); ^{13}C NMR (125 MHz, CD_3OD) δ 158.97, 156.10, 133.65, 112.61, 107.01, 101.94, 49.35, 45.35, 34.59, 19.23, and 18.33. Anal. Calcd for $C_{11}H_{16}NO_2Br$: C, 48.19; H, 5.88. Found: C, 48.35; H, 5.69.

(1*R*-*trans*)-1,2,3,4-Tetrahydro-1,3-dimethyl-6,8-bis(phenylmethoxy)-2-phenylmethylisoquinoline (26). To a stirred solution of compound **25** (0.39 g, 1.4 mmol) in dry DMF (15 mL) was added benzyl bromide (1.2 mL, 1.7 g, 10 mmol), followed by the addition of cesium carbonate (2.4 g, 7.4 mmol). The reaction mixture was stirred for 6 h at room temperature and poured into H_2O (100 mL). The reaction mixture was extracted with EtOAc (2 × 25 mL), and the combined organics were washed with brine (2 × 10 mL) and dried over Na_2SO_4. Purification via flash chromatography (SiO_2, hexanes/EtOAc 9:1, with 1% Et_3N) afforded compound **26** (0.57 g, 86%) as a thick yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42−7.21 (m, 15H), 6.42 (d, J = 2.0 Hz, 1H), 6.34 (d, J = 2.0 Hz, 1H), 4.99 (s, 2H), 4.98 (d, J = 12.0 Hz, 1H), 4.95 (d, J = 12.0 Hz, 1H), 4.01 (q, J = 7.0 Hz, 1H), 3.82 (d, J = 14.0 Hz, 1H), 3.52 (ddq, J = 10.5, 4.5, 6.5 Hz, 1H), 3.32 (d, J = 14.0 Hz, 1H), 2.63 (dd, J = 17.0, 10.5 Hz, 1H), 2.58 (dd, J = 17.0, 4.5 Hz, 1H), 1.34 (d, J = 6.5 Hz, 3H), and 1.26 (d, J = 6.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.6, 157.1, 137.1, 136.7, 129.0, 128.7, 128.5 (5C), 128.4 (2C), 128.3, 128.0 (2C), 127.9, 127.6 (2C), 126.9 (2C), 126.4, 105.5, 98.3, 70.0, 69.6, 51.2, 50.0, 45.7, 32.6, 19.9, and 19.5; IR (neat) 2967, 1603, 1454, and 1149 cm^{-1}. Anal. Calcd for $C_{32}H_{33}NO_2$: C, 82.90; H, 7.17. Found: C, 82.89; H, 6.95.

(1*R*-*trans*)-5-Bromo-1,2,3,4-tetrahydro-1,3-dimethyl-6,8-bis(phenylmethoxy)-2-(phenylmethyl)isoquinoline (27). To a stirred solution of compound **26** (45 mg, 0.091 mmol) in CH_2Cl_2 (3 mL) was slowly added Br_2 (6 μL, 0.1 mmol). The resulting mixture was stirred for 0.5 h. The reaction mixture was washed with saturated $NaHCO_3$ (3 mL), 20% $Na_2S_2O_3$ (3 mL), and brine (3 mL) before being dried over $MgSO_4$. The crude product was purified by flash chromatography (SiO_2, hexanes/EtOAc 9:1, with 1% Et_3N) to provide amine **27** (37 mg, 71%) as a brown oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43−7.19 (m, 15H), 6.44 (s, 1H), 5.06 (s, 2H), 4.96 (d, J = 12.5 Hz, 1H), 4.92 (d, J = 12.5 Hz, 1H), 4.02 (q, J = 6.5 Hz, 1H), 3.82 (d, J = 14.0 Hz, 1H), 3.51 (ddq, J = 12.0, 4.0, 7.0 Hz, 1H),

3.20 (d, J = 14.0 Hz, 1H), 2.73 (dd, J = 18.0, 4.5 Hz, 1H), 2.45 (dd, J = 18.0, 11.5 Hz, 1H), 1.33 (d, J = 7.0 Hz, 3H), and 1.31 (d, J = 6.5 Hz, 3H).

(1*R-trans*)-1,2,3,4-Tetrahydro-5-iodo-1,3-dimethyl-6,8-bis(phenylmethoxy)-2-phenylmethylisoquinoline (28). A solution of compound **26** (0.48 g, 1.0 mmol) in EtOH (10 mL) and CH_2Cl_2 (2 mL) was slowly added to a stirred mixture of iodine (0.53 g, 2.1 mmol) and silver sulfate (0.69 g, 2.2 mmol) in EtOH (10 mL). The reaction mixture was stirred at room temperature for 16 h. The solids were removed by filtration, and the residue was dissolved in CH_2Cl_2 (100 mL). This organic solution was washed with saturated $NaHCO_3$ (2 × 50 mL) and H_2O (1 × 50 mL), dried over Na_2SO_4, and concentrated. The residue was purified by flash chromatography (SiO_2, hexanes/EtOAc 9:1) to yield **28** (0.40 g, 66%) as a thick oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49−7.18 (m, 15H), 6.41 (s, 1H), 5.07 (s, 2H), 4.98 (d, J = 12.0 Hz, 1H), 4.94 (d, J = 12.0 Hz, 1H), 4.01 (q, J = 6.5 Hz, 1H), 3.82 (d, J = 14.0 Hz, 1H), 3.51 (ddq, J = 12.0, 4.0, 6.5 Hz, 1H), 3.20 (d, J = 14.0 Hz, 1H), 2.66 (dd, J = 17.5, 4.0 Hz, 1H), 2.42 (dd, J = 17.5, 12.0 Hz, 1H), 1.34 (d, J = 6.5 Hz, 3H), and 1.31 (d, J = 6.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.4, 156.1, 141.3, 139.5, 137.1 (2C), 128.9 (7C), 128.5 (2C), 128.2, 127.4 (2C), 127.2 (3C), 126.9, 124.3, 97.7, 71.6, 70.3, 51.9, 50.1, 46.9, 39.3, 20.2, and 20.1; IR (neat) 2971, 1585, 1324, and 1062 cm^{-1}. Anal. Calcd for $C_{32}H_{32}INO_2$: C, 65.20; H, 5.47. Found: C, 65.39; H, 5.73.

(1*S-trans*)-1,2,3,4-Tetrahydro-8-methoxy-1,3-dimethyl-6-isoquinolinol (29). Tetrahydroisoquinoline ***ent*-24** (442 mg, 2.0 mmol) was dissolved in 49% aqueous hydrobromic acid (20 mL). The mixture was heated to 70 °C and stirred for 7 h. The mixture was transferred to a flask with methanol and concentrated. At 0 °C, CH_2Cl_2 (1 mL) and concentrated aqueous ammonia (1 mL) were added to the residue. The CH_2Cl_2/NH_3 residue was loaded on a neutral alumina column and eluted with hexanes/EtOAc (9:1 with 3% Et_3N) to give the starting material ***ent*-24** (203 mg, 46%). Subsequent elution with CH_2Cl_2/MeOH (98:2) provided mono-demethylated product **29** (200 mg, 48%) as a white solid: ^{1}H NMR (500 MHz, CD_3OD, referenced to CHD_2OD at 3.30 ppm) δ 6.21 (d, J = 2.0 Hz, 1H), 6.10 (d, J = 2.0 Hz, 1H), 4.20 (q, J = 7.0 Hz, 1H), 3.74 (s, 3H), 3.24 (ddq, J = 11.0, 4.5, 6.5 Hz, 1H), 2.63 (dd, J = 17.0, 4.5 Hz, 1H), 2.37 (dd, J = 17.0, 11.0 Hz, 1H), 1.34 (d, J = 7.0 Hz, 3H), and 1.17 (d, J = 6.0 Hz, 3H); ^{13}C NMR (125 MHz, CD_3OD, referenced to CD_3OD at49.0 ppm) δ 158.3, 157.9, 136.8, 120.0, 107.9, 97.7, 55.5, 54.8, 43.0, 37.9, 22.2, and 20.9; IR (KBr) 3392, 3248, 2970, 2624, 1666, 1603, 1147, and 842 cm^{-1}; LRMS m/z (relative intensity) 207 (M^+, 4), 192 (100), and 177 (10).

(1*S-trans*)-1,2,3,4-Tetrahydro-5-iodo-8-methoxy-1,3-dimethyl-6-(phenylmethoxy)-2-(phenylmethyl)isoquinoline (30). Tetrahydroisoquinoline **29** (207 mg, 1.0 mmol) and benzyl bromide (410 mg, 2.4 mmol) were dissolved in methyl ethyl ketone (20 mL). Potassium carbonate (552 mg, 4 mmol) was added, and the reaction mixture was stirred at room temperature for 16 h. The mixture was passed through a bed of Celite. The filtrate was washed with H_2O (2 × 10 mL), and the organic layer was dried over Na_2SO_4 and concentrated. Flash chromatography of the residue (SiO_2, hexanes/EtOAc 9:1, with 3% Et_3N) afforded the dibenzylated derivative of **29** [(1*S-trans*)-1,2,3,4-tetrahydro-8-methoxy-1,3-dimethyl-6-(phenylmethoxy)-2-(phenylmethyl)isoquinoline, 317 mg, 82%] as a pale yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43−7.18 (m, 10H), 6.36 (d, J = 2.0 Hz, 1H), 6.31(d, J = 2.0 Hz, 1H), 4.99 (s, 3H), 3.89 (q, J = 7.0 Hz, 1H), 3.80 (d, J = 14.0 Hz, 1H), 3.64 (s, 3H), 3.49 (ddq, J = 11.0, 4.5, 7.0 Hz, 1H), 3.28 (d, J = 14.0 Hz, 1H), 2.61 (dd, J = 16.5, 11.0 Hz, 1H), 2.54 (dd, J = 16.5, 4.5 Hz, 1H), 1.30 (d, J = 7.0 Hz, 3H), and 1.24 (d, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.2, 157.6, 141.3, 137.1, 136.6, 128.5, 128.3, 128.0, 127.9, 127.5, 126.2, 120.7, 104.9, 97.0, 70.0, 55.0, 51.3, 49.7, 45.7, 32.4, 19.9, and 19.5; IR (neat) 3028, 2964, 1594, 1453, 1148, and 826 cm^{-1}. Anal. Calcd for $C_{26}H_{29}NO_2$: C, 80.59, H, 7.54. Found: C, 80.64, H, 7.48. This tetrahydroisoquinoline (279 mg, 0.72 mmol) and iodine (348 mg, 1.37 mmol) were dissolved in ethanol (10 mL). Silver sulfate (427 mg, 1.37 mmol) was added, and the reaction mixture was stirred at room temperature for 14 h. The mixture was passed through a bed of Celite. The filtrate was concentrated. The resulting residue was dissolved in CH_2Cl_2 (40 mL), washed with 10% aqueous NaOH (2 × 15 mL) and water (1 × 20 mL), and dried over $MgSO_4$. Purification by flash chromatography (SiO_2, hexanes/EtOAc 9:1, with 3% Et_3N) provided iodide **30** (307 mg, 83%) as a pale yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54 (d, J = 7.5 Hz, 2H), 7.40 (t, J = 7.5 Hz, 2H), 7.34 (d, J = 7.0 Hz, 2H), 7.32 (t, J = 7.5 Hz, 1H), 7.29 (t, J = 7.0 Hz, 2H), 7.22 (t, J = 7.0 Hz, 1H), 6.39 (s, 1H), 5.15 (s, 2H), 3.89 (q, J = 7.0 Hz, 1H), 3.81 (d, J = 14.5 Hz, 1H), 3.49 (ddq, J = 11.5, 4.5, 6.5 Hz, 1H), 3.17 (d, J = 14.5, 1H), 2.65 (dd, J = 12.5, 4.5 Hz, 1H), 2.41 (dd, J = 14.5, 11.5 Hz, 1H), 1.33 (d, J = 6.5, 3H), and 1.28 (d, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 158.3, 155.8, 141.0, 139.0, 136.8, 128.5, 128.3, 128.0, 127.8, 127.1, 126.3, 123.5, 95.7, 83.3, 71.3, 55.2, 51.7, 49.5, 46.5, 38.7, and 19.8; IR (neat) 3028, 2964, 1594, 1453, 1148, and 826 cm^{-1}. Anal. Calcd for $C_{26}H_{28}INO_2$: C, 60.83, H, 5.50, N, 2.73. Found: C, 61.00, H, 5.71, N, 2.66.

(1*S-cis*)-1,2,3,4-Tetrahydro-1,3-dimethyl-6,8-isoquinolinediol Hydrobromide (*ent*-33). To a stirred solution of compound **34** (0.79 g, 3.57 mmol) in CH_2Cl_2 (50 mL) at −78 °C under N_2 was added BBr_3 (15 mL of a 1.0 M solution in CH_2Cl_2, 15 mmol). The reaction mixture was warmed to room temperature, stirred for 24 h, and quenched by careful addition of MeOH (30 mL). After all solvents were removed, MeOH (30 mL) was added and then removed on a rotary evaporator. This procedure was repeated three times to yield amine ***ent*-33** (0.97 g, 99%) as a brown solid (pure by ^{1}H NMR analysis). A pure sample for data analysis was obtained by recrystallization of a small portion from MeOH and CH_2Cl_2: mp > 220 °C; $[\alpha]_D^{rt}$ −94.4 (c = 2.32, MeOH); ^{1}H NMR (500 MHz, CD_3OD) δ 6.21 (d, J = 2.0 Hz, 1H), 6.12 (d, J = 2.0 Hz, 1H), 4.64 (q, J = 6.5 Hz, 1H), 3.77 (ddq, J = 11.5, 4.5, 6.5 Hz, 1H), 3.00 (dd, J = 17.0, 4.5 Hz, 1H), 2.73 (dd, J = 17.0, 11.5 Hz, 1H), 1.59 (d, J = 6.5 Hz, 3H), and 1.45 (d, J = 6.5 Hz, 3H). Anal. Calcd for $C_{11}H_{16}BrNO_2$: C, 48.19; H, 5.88. Found: C, 48.27; H, 6.00.

(1*S-cis*)-1,2,3,4-Tetrahydro-6,8-dimethoxy-1,3-dimethylisoquinoline (34). Cyclic imine **23** (308 mg, 1.41 mmol) was dissolved in MeOH (10 mL) with 10% Pd/C (65 mg). The reaction mixture was stirred under a hydrogen atmosphere (1 atm) at room temperature for 5 h. The reaction mixture was filtered through a plug of silica and purified by column chromatography (SiO_2, hexanes/EtOAc 1:2, with 3% Et_3N) to give tetrahydroisoquinoline **34** (276 mg, 89%) as an amber oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.31 (d, J = 2.5 Hz, 1H), 6.21 (d, J = 2.4 Hz, 1H), 4.22 (q, J = 6.1 Hz, 1H), 3.78 (s, 6H), 2.86 (ddq, J = 11.0, 2.4, 6.1 Hz, 1H), 2.62 (dd, J = ∼15.0, 2.4 Hz, 1H), 2.44 (dd, J = ∼15.0, 11.0 Hz, 1H), 1.43 (d, 7.5 Hz, 3H), and 1.21 (d, J = 6.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.23, 157.83, 137.93, 121.20, 104.30, 96.52, 55.06, 54.86, 49.29, 48.09, 39.76, 22.74, and 22.34; IR (neat) 3287, 2997, 2957, 2836, 2360, 2340, and 1606 cm^{-1}. Anal. Calcd for $C_{13}H_{19}NO_2$: C, 70.56; H, 8.65. Found: C, 70.36; H, 8.84.

(1*S-cis*)-*N*-Carbethoxy-1,2,3,4-tetrahydro-1,3-dimethyl-6,8-bis(phenylmethoxy)isoquinoline (35). To a stirred mixture of ammonium bromide **33** (0.28 g, 1.0 mmol) in CH_2Cl_2 (10 mL) was added Et_3N (0.70 mL, 5.1 mmol), followed by TESCl (0.36 mL, 2.1 mmol). After 2 h, Et_3N (0.60 mL, 4.3 mmol) and ethyl chloroformate (0.18 mL, 1.9 mmol) were added. The reaction mixture was stirred for another 2 h, and TBAF (4.0 mL of a 1.0 M solution in THF, 4.0 mmol) was added. The reaction mixture was stirred for 0.5 h and then diluted with Et_2O (30 mL). The organic layer was washed with saturated NH_4Cl (2 × 15 mL), H_2O (1 × 20 mL), and brine (1 × 20 mL) and dried over $MgSO_4$. Purification by MPLC (SiO_2, hexanes/EtOAc 1:4) afforded the ethylcarbamate derivative of ***ent*-33** [(1*S-cis*)-*N*-carbethoxy-1,2,3,4-tetrahydro-1,3-dimethyl-6,8-isoquinolinediol, 0.24 g, 87%) as a white solid: ^{1}H NMR (300 MHz, CD_3OD) δ 6.16 (d, J = 2.1 Hz, 1H), 6.10 (d, J = 2.1 Hz, 1H), 5.39 (br m, 1H), 4.22 (ddq, J = 7.2, 6.6, 6.6 Hz, 1H), 4.13 (br m, J = 6.9 Hz, 2H), 2.81 (dd, J = 15.9, 6.6 Hz, 1H), 2.64 (dd, J = 15.9,d 7.2 Hz, 1H), 1.40 (d, J = 6.9 Hz, 3H), 1.32 (d, J = 6.6 Hz, 3H), and 1.26 (t, J = 6.9 Hz, 3H); IR (neat) 3327, 2977, 2470, 1660, 1607, 1076, and 774 cm^{-1}. Anal. Calcd

for $C_{14}H_{19}NO_4$: C, 63.38; H, 7.22. Found: C, 63.16; H, 7.32. To a stirred solution of this ethylcarbamate derivative (145 mg, 0.55 mmol) and benzyl bromide (0.16 mL, 1.35 mmol) in methyl ethyl ketone (10 mL) was added K_2CO_3 (0.30 g, 2.17 mmol). The reaction mixture was refluxed for 4 h. The solid was removed by filtration. The filtrate was concentrated. The residue was purified by MPLC (SiO_2, hexanes/EtOAc 6:1, with 2% Et_3N) to afford amide **35** (174 mg, 72%) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43−7.32 (m, 10H), 6.47 (d, J = 2.5 Hz, 1H), 6.39 (d, J = 2.5 Hz, 1H), 5.57 (br m, 1H), 5.07 (d, J = 12.0 Hz, 1H), 5.05 (d, J = 12.0 Hz, 1H), 5.01 (s, 2H), 4.40 (br m, 1H), 4.20 (m, 2H), 2.96 (dd, J = 15.5, 6.5 Hz, 1H), 2.72 (dd, J = 15.5, 6.5 Hz, 1H), 1.47 (d, J = 7.0 Hz, 3H), 1.37 (d, J = 6.0 Hz, 3H), and 1.28 (t, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.4, 155.7, 155.4, 137.1, 135.1, 128.7 (3C), 128.6 (2C), 128.1, 127.9, 127.6 (2C), 127.1 (3C), 105.7, 98.6, 70.2, 70.0, 61.1, 46.4, 45.9, 35.4, 21.8, and 14.8 (2C); IR (neat) 2973, 1686, 1605, 1151, and 736 cm^{-1}; HRMS (FAB) calcd for $C_{28}H_{32}NO_4$ $(M + H)^+$ 446.2331, found 446.2332.

(1*S-cis*)-1,2,3,4-Tetrahydro-5-iodo-1,2,3-trimethyl-6,8-bis(phenylmethoxy)isoquinoline (36). Amide **35** (184 mg, 0.41 mmol) dissolved in Et_2O (5 mL) was added to a stirred mixture of $LiAlH_4$ (81 mg, 2.1 mmol) in Et_2O (5 mL). The reaction mixture was refluxed under N_2 for 5 h and quenched by careful addition of H_2O (180 μL), 15% NaOH (180 μL), and H_2O (540 μL). The solids were removed by filtration, and the filtrate was purified by flash chromatography (SiO_2, hexanes/EtOAc 9:1, with 3% Et_3N) to afford the *N*-methyl analogue of **35** [(1*S-cis*)-1,2,3,4-tetrahydro-1,2,3-trimethyl-6,8-bis(phenylmethoxy)isoquinoline, 151 mg, 94%] as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45−7.33 (m, 10H), 6.49 (d, J = 2.5 Hz, 1H), 6.35 (d, J = 2.5 Hz, 1H), 5.06 (d, J = 11.5 Hz, 1H), 5.02 (d, J = 11.5 Hz, 1H), 5.02 (s, 2H), 3.73 (q, J = 6.5 Hz, 1H), 2.73 (dd, J = 15.0, 10.5 Hz, 1H), 2.56 (dd, J = 15.0, 2.5 Hz, 1H), 2.47 (ddq, J = 10.5, 2.5, 6.5 Hz, 1H), 2.47 (s, 3H), 1.46 (d, J = 6.5 Hz, 3H), and 1.24 (d, J = 6.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.7, 156.2, 137.8, 137.2, 128.6 (5C), 128.5, 128.0, 127.9, 127.6(2), 127.3 (2C), 104.9, 98.5, 70.2, 69.9, 57.0, 55.0, 41.2, 39.3, 22.8, and 21.3; IR (neat) 2965, 1607, 1150, and 735 cm^{-1}; HRMS (FAB) calcd for $C_{26}H_{30}NO_2$ $(M + H)^+$ 388.2276, found 388.2280. To a stirred solution of iodine (0.16 g, 0.63 mmol) and silver sulfate (0.20 g, 0.62 mmol) in EtOH (5 mL) was added a solution of this *N*-methylamine (0.11 g, 0.29 mmol) in EtOH (5 mL). The reaction mixture was stirred at room temperature for 5 h. The formed solid was removed by filtration, and the filtrate was purified by flash chromatography (SiO_2, hexanes/EtOAc 9:1, with 2% Et_3N) to yield amine **36** (0.12 g, 80%) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49−7.30 (m, 10H), 6.42 (s, 1H), 5.07 (s, 2H), 5.03 (d, J = 12.0 Hz, 1H), 5.00 (d, J = 12.0 Hz, 1H), 3.70 (q, J = 6.5 Hz, 1H), 2.86 (dd, J = 16.0, 3.0 Hz, 1H), 2.56 (dd, J = 16.0, 10.5 Hz, 1H), 2.44 (s, 3H), 2.40 (ddq, J = 10.5, 3.0, 6.5 Hz, 1H), 1.39 (d, J = 6.0 Hz, 3H), and 1.26 (d, J = 6.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.2, 155.8, 140.6, 136.8, 128.7 (3C), 128.6 (3C), 128.1, 127.9, 127.2 (2C), 127.1 (2C), 124.2, 97.2, 71.4, 70.3, 57.1, 55.3, 44.6, 41.0, 22.9, and 21.2; IR (neat) 2967, 1585, 1056, and 736 cm^{-1}; HRMS (FAB) calcd for $C_{26}H_{29}INO_2$ $(M + H)^+$ 514.1245, found 514.1230.

[*R*-[*R,(*R**),*R**]]-1,2,3,4-Tetrahydro-6,8-dimethoxy-1,3-dimethyl-2-(1-phenylethyl)isoquinoline (38).** Amine **22** (771.0 mg, 2.58 mmol) and Et_3N (2.23 mL, 6.2 equiv) were stirred in CH_2Cl_2 (10.0 mL). After 5 min, acetic anhydride (0.97 mL, 4.0 equiv) was slowly added, and the reaction mixture was stirred at room temperature overnight. The reaction was quenched with saturated NH_4Cl (4 mL) and extracted with CH_2Cl_2 (2 × 10 mL). The combined organics were washed with water, dried over $MgSO_4$, and concentrated in vacuo. The resulting solid was recrystallized (hexanes/MeOH) to yield the acetamide derivative of **22** [[*R*-(*R**,*R**)]-[2-(3,5-dimethoxyphenyl)-1-methylethyl]-*N*-[1-phenylethyl)acetamide, 823 mg, 94%] as a white solid: mp 123−124 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41−7.35 (m, 5H), 6.18 (s, 1H), 5.70 (s, 2H), 5.08 (q, J = 6.8 Hz, 1H), 3.63 (s, 6H), 3.17 (dd, J = 10.6, 5.0 Hz, 1H), 3.15−3.03 (m, 1H), 2.33 (dd, J = 10.6, 5.0 Hz, 1H), 2.29 (s, 3H), 1.59 (d, J = 6.8 Hz, 3H), and 1.29 (d, J = 6.2 Hz,3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.7, 160.2 (2C), 142.3, 139.6, 128.3 (2C), 127.5 (2C), 127.4, 106.6 (2C), 98.2, 56.3, 54.9 (2C), 53.5, 41.2, 23.7, 17.1, and 16.9; IR (KBr) 3005, 2979, 2958, 2932, 2838, 1637, 1596, and 1460 cm^{-1}. Anal. Calcd for $C_{14}H_{21}NO_2$: C, 73.87; H, 7.97. Found: C, 73.76; H, 8.00. To a well-stirred solution of this acetamide (277.7 mg, 0.81 mmol) in benzene (8.0 mL) was added $POCl_3$ (306 μL, 4.0 equiv). The mixture was refluxed under argon for 5 h, cooled, and concentrated in vacuo. The concentrated solution was dried in a vacuum oven to remove traces of $POCl_3$. The resulting residue was dissolved in EtOH (5 mL) and cooled to −78 °C. Sodium borohydride (123 mg, 3.25 mmol, 4.0 equiv) was added with stirring, and the solution was allowed to immediately warm to room temperature. Stirring was continued for 0.5 h after which time the reaction mixture was quenched with HCl (1 M, 40 drops). After 5 min, the mixture was concentrated in vacuo. The resulting residue was dissolved in CH_2Cl_2 (4 mL) and basified with 15% NaOH. The aqueous layer was extracted with CH_2Cl_2 (2 × 4 mL), and the combined organics were dried over $MgSO_4$. Concentration in vacuo and purification via column chromatography (SiO_2, hexanes/EtOAc 6:1, with 3% Et_3N) provided amine **38** (235.5 mg, 89%) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28 (nfom, 2H), 7.11 (nfom, 3H), 6.22 (d, J = 2.3 Hz, 1H), 6.04 (s, 1H), 4.35 (q, J = 5.8 Hz, 1H), 4.17 (q, J = 6.8 Hz, 1H), 3.74 (s, OCH_3), 3.72 (s, OCH_3), 3.52 (nfom, 1H), 2.56 (d, J = 13.4 Hz, 1H), 2.34 (d, J = 13.4 Hz, 1H), 1.48 (broad s, 3H), 1.29 (d, J = 5.6 Hz, 3H), and 1.19 (bs, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.03, 156.45, 146.16, 136.62, 127.42 (2C), 127.29 (2C), 126.05, 122.49, 103.91, 95.81, 56.21, 54.89 (2C), 47.86, 46.22, 35.75, 21.28, 21.00, and 19.93; IR (neat) 3066, 2968, 2836, 1601, 1489, and 1423 cm^{-1}; LRMS *m/z* (relative intensity) 310 (M^+ − 15, 100), 309 (2), 308 (7), 207 (8), 206 (57), 205 (3), 204 (16), 191 (2), 190 (4), 189 (3), 176 (2), 175 (2), 163 (2), 135 (2), 106 (3), 105 (34), 104 (7), 103 (5), 91 (2), 79 (5), 78 (2), and 77 (5).

[*R*-(*R,*R**)]-1,2,3,4-Tetrahydro-6,8-dimethoxy-3-methyl-2-(1-phenylethyl)isoquinoline (39).** Amine **22** (186 mg, 0.62 mmol), paraformaldehyde (28 mg, 1.5 equiv), and glacial acetic acid (350 μL, 10 equiv) were dissolved in CH_2Cl_2 (2.5 mL) and heated to 40 °C. After being stirred for 6 h, the reaction mixture was cooled, washed with water (3 mL), dried over $MgSO_4$, and concentrated in vacuo. Purification via column chromatography (SiO_2, hexanes/EtOAc 6:1, with 3% Et_3N) yielded an amber oil. The oil was triturated from hexanes with EtOAc to afford amine **39** (193 mg, mp = 115−116 °C, 99%) as a white solid: mp 115−116 °C; ^{1}H NMR (500 MHz, C_6D_6): δ 7.45 (d, J = 7.6 Hz, 1H), 7.18 (dd, J = 7.9, 7.6 Hz, 2H), 7.07 (dd, J = 7.0, 7.0 Hz, 3H), 6.31, (d, J = 2.1 Hz, 1H), 6.24 (d, J = 2.1 Hz, 1H), 4.01 (d, J = 16.5 Hz, 1H), 3.69 (q, J = 6.7 Hz, 1H), 3.54 (d, J = 16.5 Hz, 1H), 3.42 (s, 3H), 3.22 (dd, J = 16.0, 5.0 Hz, 1H), 3.05 (s, 3H), 3.43 (nfom, 1H), 2.46 (dd, J = 16.0, 3.0 Hz, 1H), 1.28 (d, J = 6.7 Hz, 3H), and 0.95 (d, J = 6.7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.77, 146.05, 135.38, 128.19 (2C), 127.33 (2C), 126.52, 116.00, 104.17, 95.56, 60.58, 55.21, 54.97, 47.06, 42.54, 36.41, 19.97, and 12.66; IR (KBr) 3026, 3010, 2977, 2958, 2783, 1601, 1497, and 1461 cm^{-1}. Anal. Calcd for $C_{20}H_{25}NO_2$: C, 77.10; H, 8.10. Found: C, 77.26; H, 8.05.

[*R*-(*R,*R**)]-1,2,3,4-Tetrahydro-6,8-dimethoxy-1-methyl-2-(1-phenylethyl)isoquinoline (41a).** Amine **42a** (887 mg, 3.1 mmol) and Et_3N (2.7 mL, 6.2 equiv) were dissolved in CH_2Cl_2 (16 mL). Ac_2O (1.1 mL, 3.8 equiv) was added slowly via syringe, and the reaction mixture was stirred at room temperature overnight. The reaction was quenched by pouring into water (10 mL), and the organic phase was washed with aqueous ammonium chloride (2 × 10 mL) and brine (1 × 10 mL). The organic phase was dried over $MgSO_4$ and purified via column chromatography (SiO_2, hexanes/EtOAc 1:1) to afford the acetamide derivative of **42a** [(*R*)-*N*-(1-phenylethyl)-*N*-2-(3,5-dimethoxyphenyl)ethyl acetamide, 1.02 g, 100%] as a yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 (m, 3H), 7.29 (dd, J = 9.1 and 7.6 Hz, 2H), 6.29/6.27 (s, 1H), 6.20/6.06 (s, 2H), 6.28/5.20 (q, J = 7.0 Hz, 1H), 3.75/3.23 (t, J = 8.0 Hz, 2H), 3.73/3.72 (s, 6H), 3.34/2.74/2.57 and 2.43 (m, 2H), 2.27/2.20 (3H), and 1.60/1.54 (d, J = 7.0 Hz, 3H); ^{13}C NMR (125

MHz, $CDCl_3$) δ 170.29/170.13, 160.71/160.48 (2C), 141.84/140.60, 140.38/140.10, 128.49/128.28 (2C), 127.80/127.53 (2C), 127.42/126.78, 106.35/106.31 (2C), 98.11/97.92, 56.08/50.76, 55.02/55.01 (2C), 46.05/44.79, 37.04/35.22, 22.11/21.76, and 17.86/16.38; IR (neat) 2970, 2941, 2838, 1736, 1639, 1601, 1459, 1421, 1204, and 1155 cm^{-1}; LRMS *m*/*z* (relative intensity) 327 (M^+, 4), 284 (4), 222 (2), 176 (1), 166 (2), 164 (45), 152 (2), 151 (4), 135 (2), 134 (5), 120 (2), 106 (8), 105 (100), 103 (3), 91 (4), 79 (4), 78 (2), 77 (5), and 72 (8). To a solution of this acetamide (820 mg, 2.5 mmol) in benzene (25.0 mL) was added $POCl_3$ (0.58 mL, 2.5 equiv). The reaction mixture was refluxed under argon for 3 h. The mixture was cooled and concentrated in vacuo to remove excess $POCl_3$. The iminium residue was dissolved in dry MeOH (25.0 mL) and cooled to −78 °C. $NaBH_4$ (946 mg, 10 equiv) was added in portions, and the mixture was allowed to stir at −78 °C for 30 min. The mixture was slowly warmed to room temperature and then concentrated in vacuo. The resulting residue was dissolved in CH_2Cl_2 (25 mL), washed with aqueous NaOH (2 × 15 mL), dried over $MgSO_4$, and purified via column chromatography (SiO_2, hexanes/EtOAc 9:1, with 3% Et_3N) to provide tetrahydroisoquinoline **41a** (595 mg, 76%) as a colorless oil: ^1H NMR (300 MHz, $CDCl_3$) δ 7.37−7.18 (m, 5H), 6.28 (d, J = 2.2 Hz, 1H), 6.23 (d, J = 2.2 Hz, 1H), 4.25 (q, J = 6.6 Hz, 1H), 3.75 (s, 3H), 3.72 (s, 3H), 3.68 (q, J = 6.4 Hz, 1H), 2.95−2.80 (m, 3H), 2.49−2.43 (m, 1H), 1.39 (d, J = 6.4 Hz, 3H), and 1.23 (d, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.27, 157.10, 146.77, 136.09, 128.08 (2C), 126.90 (2C), 126.39, 121.70, 103.76, 95.98, 59.64, 54.81, 54.74, 47.95, 39.59, 27.08, 21.98, and 15.06; LRMS (EI) *m*/*z* 297 (M^+ − 14, 18), 296 (91), 193 (12), 192 (100), 191 (4), 190 (6), 177 (7), 176 (4), 148 (3), 141 (4), 106 (4), 105 (41), 103 (6), 91 (5), 79 (7), and 77 (7).

[*R*-(*R,*R**)]-1,2,3,4-Tetrahydro-1-methyl-2-(1-phenylethyl)-6,8-bis(phenylmethoxy)isoquinoline (41b).** Amine **42b** (1.12 g, 2.56 mmol) and Et_3N (2.14 mL, 6 equiv) were dissolved in CH_2Cl_2 (35.0 mL). The reaction mixture was stirred at room temperature, and after 5 min acetic anhydride (965 μL, 4 equiv) was slowly added. The reaction mixture was stirred under a nitrogen atmosphere at room temperature for 12 h. The reaction was quenched with water (20 mL) and extracted with CH_2Cl_2 (2 × 15 mL). The combined organic extracts were washed with saturated NH_4Cl (1 × 20 mL), dried over $MgSO_4$, and concentrated to an oil. Purification via column chromatography (SiO_2, hexanes/EtOAc 1:1) yielded the acetamide derivative of **42b** [(*R*)-*N*-(1-phenylethyl)-*N*-2-[3,5-bis(phenylmethoxy)phenyl]ethyl acetamide, 956 mg, 78%] as a straw yellow oil: ^1H NMR (500 MHz, $CDCl_3$) δ 7.40−7.34 (m, 10H), 7.32−7.24 (m, 5H, Ar−H), 6.44 (dd, J = 2.14, 2.13 Hz, 1H), 6.43 (dd, J = 2.14, 2.13 Hz, 1H), 6.29 (d, J = 2.13 Hz, 2H), 6.13 (d, J = 2.14 Hz, 2H), 6.07 (q, J = 7.0 Hz, 1H), 5.06 (q, J = 7.0 Hz, 1H), 4.95 (s, 4H, 2H), 3.33 (ddd, J = 16.2, 11.6, 4.6 Hz, 1H), 3.19−3.13 (m, 2H), 3.19−3.13 (m, 2H), 2.72 (ddd, J = 12.2, 11.6, 5.5 Hz, 1H), 2.53 (ddd, J = 13.1, 9.2, 7.9 Hz, 1H), 2.51 (s, 3H), 2.45 (ddd, J = 12.2, 11.6, 4.6 Hz, 2H), 2.16 (s, 3H), 2.11 (ddd, J = 13.1, 8.2, 8.2 Hz, 2H), 1.56 (d, J = 7.0 Hz, 3H), and 1.51 (d, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.49 and 170.36 (1C), 159.96 and 159.78 (2C), 141.99 and 140.50 (2C), 140.70 and 140.21 (1C), 136.83 and 136.61 (1C), 128.61 and 128.38 (2C), 128.50 and 128.43 (4C), 127.94 and 126.81 (2C), 127.85 and 127.80 (2C), 127.63 and 127.52 (1C), 127.41 and 127.38 (4C), 107.69 and 107.64 (2C), 99.91 and 99.83 (1C), 69.93 and 69.84 (2C), 56.19 and 50.85 (1C), 46.10 and 44.89 (1C), 37.15 and 35.29 (1C), and 17.99 and 16.49 (1C); IR (neat) 3062, 3030, 2976, 2872, 1636, and 1593 cm^{-1}; HRMS (FAB) calcd for $C_{32}H_{33}NO_3$ $(M + H)^+$ 480.2539, found 480.2565. To this acetamide (657 mg, 1.4 mmol) in benzene (20.0 mL) was added $POCl_3$ (0.26 mL, 2 equiv). The reaction mixture was refluxed under argon for 3 h and was cooled and concentrated in vacuo. The concentrated solution was dried in a vacuum oven to remove traces of $POCl_3$. The iminium residue was dissolved in dry MeOH (15.0 mL) and cooled to −78 °C. $NaBH_4$ (518 mg, 10 equiv) was added in portions, and the mixture was allowed to stir at −78 °C for 0.5 h. The mixture was slowly warmed to room temperature and then concentrated in vacuo. The resulting residue was dissolved in CH_2Cl_2 (20 mL), washed with aqueous NaOH (2 × 10 mL), and dried over $MgSO_4$. Purification via column chromatography (SiO_2, hexanes/EtOAc 6:1, with 3% Et_3N) afforded tetrahydroisoquinoline **41b** (476 mg, 75%) as an orange-yellow oil: ^1H NMR (300 MHz, $CDCl_3$) δ 7.41−7.20 (m, 15H), 6.41 (d, J = 2.2 Hz, 1H), 6.34 (d, J = 2.2 Hz, 1H), 4.98 (4H), 4.35 (q, J = 6.4 Hz,1H), 3.69 (q, J = 6.4 Hz, 1H), 3.05−2.80 (m, 3H), 2.47 (ddd, J = 14.1, 3.8, 2.7 Hz, 1H), 1.40 (d, J = 6.5 Hz, 1H), and 1.28 (d, J = 6.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.52, 156.23, 146.73, 137.13, 137.02, 136.37, 128.41 (2C), 128.31 (2C), 128.22 (2C), 127.77, 127.42 (2C), 127.10 (2C), 126.65 (2C), 126.56, 122.35, 105.40, 98.12, 69.84, 69.47, 59.65, 48.17, 39.58, 26.81, 22.00, and 15.77; IR (neat) 3061, 3029, 2971, 2825, 1735, 1602, 1491, 1455, 1279, and 1147 cm^{-1}; LRMS *m*/*z* (relative intensity) 448 (M^+ − 15, 100), 446 (8), 344 (5), 252 (3), 164 (3), 106 (5), 105 (50), 104 (5), 103 (6), 92 (6), 91 (70), 79 (8), 78 (4), 77 (8), 65 (7), 51 (3), and 44 (5).

(*R*)-*N*-2-(3,5-Dimethoxyphenyl)ethyl-*N*-1-phenylethylamine (42a). α-Methylbenzylamine (1.6 mL, 1.5 equiv) was added to a mixture of pyridine (82 mL), glacial acetic acid (41 mL), water (41 mL), and activated Raney Ni (200 mg). The reaction mixture was stirred, and NaH_2PO_2 (9.46 g, 13 equiv) and nitrile **43a** (1.46 g, 8.27 mmol) were sequentially added. The reaction mixture was stirred under a hydrogen atmosphere (1 atm) at room temperature for 24 h. The solids were filtered off, and the filtrate was washed with CH_2Cl_2 (2 × 100 mL) and washed with water (2 × 50 mL). Purification via column chromatography (hexanes/ethyl acetate 6:1, with 3% Et_3N) afforded amine **42a** (1.75 g, 74%) as a yellow oil: ^1H NMR (300 MHz, $CDCl_3$) δ 7.33−7.22 (m, 5H), 6.32 (m, 3H), 3.78−3.74 (m, 2H), 3.75 (6H), 2.75−2.69 (m, 4H), and 1.33 (d, J = 6.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.50 (2C), 145.36, 142.18, 128.12 (2C), 126.57, 126.26 (2C), 106.34 (2C), 97.79, 57.92, 54.85 (2C), 48.37, 36.39 and 24.12; IR (neat NaCl plates) 3059 (w), 2997 (w), 2956 (m), 2937 (m), 2837 (w), 1599 (s), 1461 (s), 1431 (m), 1203 (s) and 1154 (s) cm^{-1}; FAB-HRMS calcd for $C_{18}H_{23}NO_2$ acc mass $(M + H)^+$ 286.1807, obsd mass $(M + H)^+$ 286.1819.

(*R*)-*N*-1-Phenylethyl-*N*-2-[3,5-bis(phenylmethoxy)phenyl]ethylamine (42b). α-Methylbenzylamine (1.5 mL, 2 equiv) was added to a mixture of pyridine (19 mL), glacial acetic acid (9.5 mL), water (9.5 mL), and activated Raney Ni (250 mg). The reaction mixture was stirred, and NaH_2PO_2 (6.60 g, 13 equiv) and nitrile **43b** (1.89 g, 5.74 mmol) were sequentially added. The reaction mixture was stirred under a hydrogen atmosphere (1 atm) at room temperature for 12 h. The solids were filtered off, and the filtrate was washed with $CHCl_3$ (2 × 50 mL). The combined organics were washed with water (50 mL) and dried over $MgSO_4$. Purification via column chromatography (SiO_2, hexanes/EtOAc 6:1, with 3% Et_3N) yielded ethylamine **42b** (1.81 g, 72%) as an amber oil: ^1H NMR (300 MHz, $CDCl_3$) δ 7.42−4.22 (m, 15H), 6.47 (dd, J = 2.2, 2.2 Hz, 1H), 6.42 (d, J = 2.2 Hz, 1H), 4.98 (s, 4H), 3.74 (q, J = 6.5 Hz, 1H), 2.74−2.66 (m, 4H), and 1.31 (d, J = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.88 (2C), 142.32, 136.83 (3C), 128.48 (4C), 128.35 (2C), 127.87 (2C), 127.44 (4C), 126.85, 126.50 (2C), 107.77 (2C), 99.77, 69.89 (2C), 58.13, 48.43, 36.45, and 24.18; IR (neat) 3063, 3030, 2926, 2867, 1594, 1450, 1375, and 1155 cm^{-1}; HRMS (FAB) calcd for $C_{30}H_{32}NO_2$ $(M + H)^+$ 438.2433, found 438.2417.

(−)-(*R*)-*N*-2-(3,5-Dimethoxyphenyl)-1-methylethyl (4-Methylphenyl)sulfonamide (46). 1-Chloro-3,5-dimethoxybenzene (9.12 g, 53 mmol), Mg turnings (5.12 g, 0.21 mol), and 1,2-dibromoethane (150 μL) were mixed in freshly distilled THF (45 mL). The mixture was refluxed for 12 h and then cooled to 0 °C. $CuBr{\cdot}SMe_2$ (0.60 g, 3.0 mmol) was added, and the resulting mixture was stirred for 20 min. A solution of **45** (6.12 g, 29 mmol) dissolved in THF (20 mL) was added. The mixture was stirred at 0 °C for 2 h. The reaction was quenched by careful addition of saturated $NaHCO_3$ (100 mL) and was diluted with Et_2O (200 mL). The aqueous layer was extracted with Et_2O (2 × 150 mL). The combined organics were washed with brine (2 × 100 mL) and dried over $MgSO_4$. The crude product was purified by flash chromatography (SiO_2, hexanes/EtOAc 3:1, with 3% Et_3N) to afford **46** (10.5 g, 100%) as a pale

yellow oil: $[\alpha]_D^{rt}$ −19 (*c* = 1.8, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57 (d, *J* = 8.1 Hz, 2H), 7.18 (d, *J* = 8.1 Hz, 2H), 6.26 (t, *J* = 2.1 Hz, 1H), 6.12 (d, *J* = 2.1 Hz, 2H), 4.65 (d, *J* = 6.9 Hz, 1H), 3.70 (s, 6H), 3.44 (dddq, *J* = 6.9, 6.9, 6.9, 6.6 Hz, 1H), 2.57 (d, *J* = 6.9 Hz, 2H), 2.38 (s, 3H), and 1.12 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.8, 143.1, 139.5, 137.5, 129.5, 127.0, 107.2, 98.7, 55.2, 50.9, 43.7, 21.7, and 21.5; LRMS *m*/*z* (intensity) 349 (M^+, 10), 198 (100), 155 (84), and 91 (54); IR (neat) 3283, 2967, 2935, 1598, 1430, 1159, and 834 cm^{-1}. Anal. Calcd for $C_{18}H_{23}NO_4S$: C, 61.87; H, 6.64. Found: C, 61.85; H, 6.66.

(1*R*)-2-(3,5-Dimethoxyphenyl)-1-methylethylamine (47). To a stirred solution of **46** (0.51 g, 1.5 mmol) in freshly distilled THF (5 mL) at −78 °C was added anhydrous ammonia (10 mL). Small pieces of sodium (0.32 g, 14 mmol) were added, and the resulting blue mixture was stirred for 40 min and quenched by addition of MeOH (1 mL). After the ammonia had evaporated, Et_2O (50 mL) and 5% HCl (100 mL) were added. The aqueous layer was basified with 5% NaOH. The aqueous solution was extracted with Et_2O (3 × 50 mL), and the combined organics were washed with brine (2 × 100 mL), dried over anhydrous $MgSO_4$, and concentrated to give **47** (0.22 g, 79%) as a pale yellow oil (pure by ^{1}H NMR analysis): ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.36 (d, *J* = 2.0 Hz, 2H), 6.34 (t, *J* = 2.0 Hz, 1H), 3.78 (s, 6H), 3.26 (ddq, *J* = 8.0, 6.0, 6.5 Hz, 1H), 2.68 (dd, *J* = 13.5. 6.0 Hz, 1H), 2.61 (dd, *J* = 13.5. 8.0 Hz, 1H), and 1.18 (d, *J* = 6.5 Hz, 3H); LRMS *m*/*z* (intensity) 195 (M^+, 9), 152 (100), 91 (10), 77 (13), and 65 (11). The **47·HCl** was crystallized from CH_2Cl_2/cyclohexane: mp 148–150 °C (lit.[15b] mp 151 °C); $[\alpha]_D^{rt}$ −14.1 (*c* =2.29, MeOH) [lit.[15b] $[\alpha]_D^{rt}$ −14.1 (*c* = 0.89, MeOH)].

5-[(1*R*, 3*R*)-2-Phenylmethyl-6,8-bis-phenylmethoxy-1,3-dimethyl-1,2,3,4-tetrahydroisoquinolin-5-yl]-1-methoxy-8-methoxymethoxy-3-methylnaphthalene (*S*-54 and *R*-54). THIQ **28** (200 mg, 0.34 mmol), boronic acid **21b** (222 mg, 0.82 mmol), and $Pd(PPh_3)_4$ (77 mg, 0.067 mmol) were dissolved in a mixture of toluene (10 mL) and saturated $NaHCO_3$ (5 mL). The reaction mixture was sealed under N_2 and heated at 110 °C for 20 h. The reaction mixture was cooled to room temperature and diluted with EtOAc (20 mL). The organic layer was washed with brine (2 × 10 mL) and dried over $MgSO_4$. Purification via column chromatography (SiO_2, hexanes/EtOAc 3:1 with 3% Et_3N) provided a mixture of atropisomers ***S*-54** and ***R*-54** (190 mg, 81%) in a 5:4 ratio. ***S*-54**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39–6.90 (m, 17H), 6.77 (s, 1H), 6.69 (s, 1H), 6.53 (s, 1H), 5.31 (s, 2H), 5.02 (s, 2H), 4.87 (d, *J* = 12.5 Hz, 1H), 4.81 (d, *J* = 12.5 Hz, 1H), 4.12 (q, *J* = 6.5 Hz, 1H), 3.98 (s, 3H), 3.72 (d, *J* = 14.5 Hz, 1H), 3.65 (s, 3H), 3.37 (ddq, *J* = 11.5, 4.0, 6.5 Hz, 1H), 3.30 (d, *J* = 14.5 Hz, 1H), 2.36 (s, 3H), 2.22 (dd, *J* = 17.5, 4.0 Hz, 1H), 2.00 (dd, *J* = 17.5, 11.5 Hz, 1H), 1.41 (d, *J* = 6.5 Hz, 3H), and 1.01 (d, *J* = 6.5 Hz, 3H). ***R*-54**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39–6.90 (m, 17H), 6.86 (s, 1H), 6.70 (s, 1H), 6.51 (s, 1H), 5.31 (s, 2H), 5.03 (d, *J* = 12.0 Hz, 1H), 4.97 (d, *J* = 12.0 Hz, 1H), 4.86 (d, *J* = 12.5 Hz, 1H), 4.81 (d, *J* = 12.5 Hz, 1H), 4.11 (q, *J* = 6.5 Hz, 1H), 3.98 (s, 3H), 3.77 (d, *J* = 14.5 Hz, 1H), 3.65 (s, 3H), 3.37 (ddq, *J* = 14.0, 4.0, 6.5 Hz, 1H), 3.35 (d, *J* = 14.0 Hz, 1H), 2.36 (s, 3H), 2.25 (dd, *J* = 17.0, 14.0 Hz, 1H), 1.92 (dd, *J* = 17.0, 4.0 Hz, 1H), 1.39 (d, *J* = 6.5 Hz, 3H), and 1.05 (d, *J* = 6.5 Hz, 3H); HRMS (FAB) calcd for $C_{46}H_{48}NO_5$ $(M + H)^+$ 694.3532, found 694.3546.

44-[(1*R*, 3*R*)-2-Phenylmethyl-6,8-bis-phenylmethoxy-1,3-dimethyl-1,2,3,4-tetrahydroisoquinolin-5-yl]-8-methoxy-5-methylnaphthalen-1-ol (*S*-55 and *R*-55). The 5:4 mixture of atropisomers **54** (180 mg, 0.26 mmol) was dissolved in a 10:1 mixture of MeOH–CH_2Cl_2 (20 mL). Concentrated HCl (1 mL) was added, and the reaction mixture was stirred at room temperature for 16 h. The organic solvent was then removed under reduced pressure. Saturated $NaHCO_3$ (20 mL) was added, and the mixture was extracted with EtOAc (2 × 15 mL). The combined organics were washed with brine (2 × 10 mL) and dried over $MgSO_4$. Purification via column chromatography (SiO_2, hexanes/EtOAc 3:1, with 3% Et_3N) provided a mixture of atropisomers ***S*-55** and ***R*-55** (120 mg, 71%), with a 4:3 ratio. ***S*-55**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.40 (s, 1H), 7.39–6.95 (m, 16H), 6.91 (d, *J* = 8.0 Hz, 1H), 6.76 (s, 1H), 6.62 (s, 1H), 6.52 (s, 1H), 5.01 (s, 2H), 4.88 (d, *J* = 13.0 Hz, 1H), 4.82 (d, *J* = 13.0 Hz, 1H), 4.08 (q, 1H), 4.08 (s, 1H), 3.72 (d, *J* = 14.0 Hz, 1H), 3.37 (ddq, *J* = 11.5, 4.0, 6.5 Hz, 1H), 3.29 (d, *J* = 14.0 Hz, 1H), 2.36 (s, 3H), 2.21 (dd, *J* = 17.5, 4.0 Hz, 1H), 1.90 (dd, *J* = 17.5, 11.5 Hz, 1H), 1.40 (d, *J* = 6.5 Hz, 3H), and 1.01 (d, *J* = 6.5 Hz, 3H). ***R*-55**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.42 (s, 1H), 7.39–6.95 (m, 16H), 6.90 (d, *J* = 8.0 Hz, 1H), 6.85 (s, 1H), 6.63 (s, 1H), 6.50 (s, 1H), 5.03 (d, *J* = 11.5 Hz, 1H), 4.97 (d, *J* = 11.5 Hz, 1H), 4.87 (d, *J* = 13.0 Hz, 1H), 4.82 (d, *J* = 13.0 Hz, 1H), 4.08 (q, 1H), 4.08 (s, 3H), 3.77 (d, *J* = 14.0 Hz, 1H), 3.37 (ddq, *J* = 11.5, 4.0, 6.5 Hz, 1H), 3.34 (d, *J* = 14.0 Hz, 1H), 2.36 (s, 3H), 2.24 (dd, *J* = 17.5, 11.5 Hz, 1H), 1.90 (dd, *J* = 17.5, 4.0 Hz, 1H), 1.38 (d, *J* = 6.5 Hz, 3H), and 1.05 (d, *J* = 6.5 Hz, 3H); HRMS (FAB) calcd for $C_{44}H_{44}NO_4$ $(M + H)^+$ 650.3270, found 650.3251.

[(1*R*),1*R,3*R**,5*R**]- and [(1*R*),1*R**,3*R**,5*S**]-1,2,3,4-Tetrahydro-5-(4,5-dimethoxy-7-methyl-1-naphthalenyl)-1,3-dimethyl-6,8-bis(phenylmethoxy)-2-(phenylmethyl)isoquinoline (*S*-56) and (*R*-56).** Iodide **28** (294 mg, 0.50 mmol) and boronic acid **21a** (160 mg, 0.65 mmol) were dissolved in toluene (10 mL). Saturated aqueous $NaHCO_3$ (10 mL) and $Pd(PPh_3)_4$ (58 mg, 0.05 mmol) were added, and the mixture was stirred at 110 °C for 12 h. The aqueous layer was separated and extracted with ether (2 × 15 mL). The combined organic layers were washed with brine, dried with sodium sulfate, and concentrated. The residue was dissolved in a minimum amount of CH_2Cl_2 and passed through a short SiO_2 column with hexanes/ethyl acetate (9:1, with 3% Et_3N). Subsequent purification by MPLC with the same solvent gave the 5:4 mixture of product (***S*-56**) and (***R*-56**) as a light yellow solid (272 mg, 82%). ***S*-56**: ^{1}H NMR (500 MHz, $CDCl_3$, from the mixture) δ 7.39–6.90 (m, 15H), 7.21 (d, *J* = 8.0 Hz, 1H), 6.88 (d, *J* = 8.0 Hz, 1H), 6.75 (bs, 1H), 6.69 (d, *J* = 1.0 Hz, 1H), 6.54 (s, 1H), 5.02 (s, 2H), 4.87 (d, *J* = 12.5 Hz, 1H), 4.82 (d, *J* = 12.5 Hz, 1H), 4.10 (q, *J* = 6.5 Hz, 1H), 4.02 (s, 3H), 4.00 (s, 3H), 3.72 (d, *J* = 14.0 Hz, 1H), 3.36 (ddq, *J* = 11.0, 4.5, 6.5 Hz, 1H), 3.30 (d, *J* = 14.0 Hz, 1H), 2.35 (s, 3H), 2.21 (dd, *J* = 18.0, 4.5 Hz, 1H), 2.00 (dd, *J* = 18.0, 11.0 Hz, 1H), 1.41 (d, *J* = 6.5 Hz, 3H), and 1.00 (d, *J* = 6.5, 3H); ^{13}C NMR (125 MHz, $CDCl_3$, from the mixture) δ 157.2, 156.3, 156.2, 155.2, 154.3, 137.6, 137.3, 137.7, 136.5, 135.8, 128.6, 128.4, 128.2, 128.0, 127.6, 127.3, 127.0, 126.7, 126.3, 122.4, 120.9, 117.7, 116.0, 108.2, 105.3, 97.3, 70.8, 69.8, 56.5, 56.4, 51.5, 46.2, 45.8, 30.1, 22.1, 20.3, and 19.2. ***R*-56**: ^{1}H NMR (500 MHz, $CDCl_3$, from the mixture) δ 7.39–6.90 (m, 15H), 7.16 (d, *J* = 8.0 Hz, 1H), 6.87 (d, *J* = 8.0 Hz, 1H), 6.84 (bs, 1H), 6.70 (d, *J* = 1.0 Hz, 1H), 6.52 (s, 1H), 5.04 (d, *J* = 12.0 Hz, 1H), 4.98 (d, *J* = 12.0 Hz, 1H), 4.87 (d, *J* = 12.5 Hz, 1H), 4.82 (d, *J* = 12.5 Hz, 1H), 4.12 (q, *J* = 6.0 Hz, 1H), 4.02 (s, 3H), 4.00 (s, 3H), 3.77 (d, *J* = 14.0 Hz, 1H), 3.36 (ddq, *J* = 12.0, 4.5, 6.5 Hz, 1H), 3.36 (d, *J* = 14.0 Hz, 1H), 2.35 (s, 3H), 2.24 (dd, *J* = 17.5, 12.0 Hz, 1H), 1.92 (dd, *J* = 17.5, 4.5 Hz, 1H), 1.39 (d, *J* = 6.0 Hz, 3H), and 1.05 (d, *J* = 6.5, 3H); ^{13}C NMR (125 MHz, $CDCl_3$, from the mixture) δ 157.1, 156.3, 156.1, 155.1, 141.2, 131.6, 137.3, 136.5, 136.4, 135.9, 128.4, 128.3, 128.2, 128.0, 127.6, 127.2, 127.0, 126.9, 126.6, 126.3,122.1, 121.2, 117.9, 116.0, 108.4, 105.3, 97.0, 70.6, 69.8, 56.5, 56.3, 51.4, 46.2, 45.9, 30.9, 22.1, 20.0, and 19.8; IR of the mixture (thin film) 3029, 2965, 1621, 1584, 1382, 1119, 1095, 1070, 1028, and 966 cm^{-1}. Anal. Calcd for the mixture $C_{45}H_{45}NO_4$: C, 81.42; H, 6.83; N, 2.21. Found: C, 81.22; H, 6.84; N, 2.21.

5-[(1*S*, 3*R*)-5-Methoxy-4-methoxymethyl-7-methylnaphthalen-1-yl)-1,2,3-trimethyl-6,8-bis-phenylmethoxy-1,2,3,4-tetrahydroisoquinoline (*S*-58 and *R*-58). Iodide **36** (0.10 g, 0.19 mmol), boronic acid **21b** (0.10 g, 0.36 mmol), and $Pd(PPh_3)_4$ (50 mg, 0.048 mmol) were dissolved in a mixture of toluene (5 mL) and saturated aqueous $NaHCO_3$ (2 mL). The reaction mixture was sealed under N_2 and heated to 110 °C for 15 h. The reaction mixture was extracted with EtOAc (2 × 10 mL), and the combined organics were washed with brine (2 × 5 mL) and dried over $MgSO_4$. Purification via column chromatography (SiO_2, hexanes/EtOAc 6:1, with 3% Et_3N) provided biaryls ***S*-58** and ***R*-58** (85 mg, 73%) in an ∼5:4 ratio. This mixture of atropisomers elutes as a single spot on SiO_2

TLC and shows a symmetrical peak on MPLC. Spectral data were collected for the mixture of ***S*-58** and ***R*-58**. ***S*-58**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46−6.90 (m, 12H), 6.85 (s, 1H), 6.69 (s, 1H), 6.59 (s, 1H), 5.30 (s, 2H), 5.09 (d, J = 12.0 Hz, 1H), 5.04 (d, J = 12.0 Hz, 1H), 4.84 (d, J = 12.5 Hz, 1H), 4.78 (d, J = 12.5 Hz, 1H), 3.97 (s, 3H), 3.80 (q, J = 6.5 Hz, 1H), 3.64 (s, 3H), 2.42 (s, 3H), 2.37−2.28 (m, 1H), 2.34 (s, 3H), 2.19 (dd, J = 15.5, 6.0 Hz, 1H), 2.16 (dd, J = 15.5, 6.0 Hz, 1H), 1.49 (d, J = 6.5 Hz, 3H), and 0.99 (d, J = 6.5 Hz, 3H). ***R*-58**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46−6.90 (m, 12H), 6.79 (s, 1H), 6.67 (s, 1H), 6.52 (s, 1H), 5.30 (s, 2H), 5.05 (s, 2H), 4.86 (d, J = 12.5 Hz, 1H), 4.80 (d, J = 12.5 Hz, 1H), 3.98 (s, 3H), 3.81 (q, J = 6.5 Hz, 1H), 3.65 (s, 3H), 2.42 (s, 3H), 2.37−2.33 (m, 1H), 2.37−2.28 (m, 1H), 2.31 (s, 3H), 2.04 (dd, J = 15.5, 2.0 Hz, 1H), 1.52 (d, J = 6.5 Hz, 3H), and 0.99 (d, J = 6.5 Hz, 3H); IR (neat) 2965, 1584, 1049, and 734 cm^{-1}; HRMS (FAB) calcd for $C_{40}H_{44}NO_5(M + H)^+$ 618.3219, found 618.3249.

5-[(1*S*, 3*R*)-4-Hydroxy-5-methoxy-7-methylnaphthalen-1-yl)-1,2,3-trimethyl-6,8-bis-phenylmethoxy-1,2,3,4-tetrahydroisoquinoline (*S*-59 and *R*-59). Biaryl **58** (35 mg, 0.057 mmol) was dissolved in a 4:1 mixture of MeOH/CH_2Cl_2 (10 mL), and 10% HCl (1 mL) was added. The reaction mixture was stirred at room temperature for 16 h. The organic solvent was then removed under reduced pressure. Saturated $NaHCO_3$ (20 mL) was added, and the mixture was extracted with EtOAc (2 × 15 mL). The combined organics were washed with brine (2 × 10 mL) and dried over $MgSO_4$. Purification via column chromatography (SiO_2, hexanes/EtOAc 2:1, with 3% Et_3N) provided a mixture of atropisomers ***S*-59** and ***R*-59** (30 mg, 92%) with an ∼5:4 ratio. The slightly faster eluting isomer, ***R*-59**, could be partially separated from the mixture under these chromatography conditions. Thus, a pure sample of ***R*-59** was also obtained. ***R*-59**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.41 (s, 1H), 7.46−6.96 (m, 11H), 6.89 (d, J = 8.0 Hz, 1H), 6.79 (s, 1H), 6.63 (s, 1H), 6.52 (s, 1H), 5.04 (s, 2H), 4.88 (d, J = 13.0 Hz, 1H), 4.82 (d, J = 13.0 Hz, 1H), 4.08 (s, 3H), 3.82 (br m, 1H), 2.44 (br s, 3H), 2.36−2.28 (m, 1H), 2.36−2.28 (m, 1H), 2.35 (s, 3H), 2.02 (dd, J = 15.5, 2.0 Hz, 1H), 1.48 (d, J = 6.5 Hz, 3H), and 0.98 (d, J = 6.5 Hz, 3H). ***S*-59**: ^{1}H NMR (from the mixture of ***S*-59** and ***R*-59**) (500 MHz, $CDCl_3$) δ 9.44 (s, 1H), 7.46−6.96 (m, 11H), 6.89 (d, J = 8.0 Hz, 1H), 6.84 (s, 1H), 6.61 (s, 1H), 6.59 (s, 1H), 5.09 (d, J = 12.0 Hz, 1H), 5.04 (d, J = 12.0 Hz, 1H), 4.86 (d, J = 12.5 Hz, 1H), 4.80 (d, J = 12.5 Hz, 1H), 4.07 (s, 3H), 3.82 (br m, 1H), 2.44 (br s, 3H), 2.36−2.28 (m, 1H), 2.32 (s, 3H), 2.18 (br s, 2H), 1.51 (d, J = 6.5 Hz, 3H), and 0.98 (d, J = 6.5 Hz, 3H); IR (neat) 3398, 2968, 1587, 1256, and 735 cm^{-1}; HRMS (FAB) calcd for $C_{38}H_{40}NO_4$ $(M + H)^+$ 574.2957, found 574.2985.

[(1*R*),1*R,3*R**,5*R**]- and [(1*R*),1*R**,3*R**,5*S**]-1,2,3,4-Tetrahydro-5-(4,5-dimethoxy-7-methyl-1-naphthalenyl)-1,3-dimethyl-6-(phenylmethoxy)-8-methoxy-2-(phenylmethyl)-isoquinoline (*S*-61 and *R*-61).** Aryl iodide **30** (110 mg, 0.214 mmol) and boronic acid **21a** (105 mg, 0.428 mmol) were dissolved in toluene (15 mL), and saturated aqueous $NaHCO_3$ (10 mL) and $Pd(PPh_3)_4$ (53 mg, 0.050 mmol) were added. The mixture was heated at 120 °C and stirred under N_2 for 12 h. The aqueous layer was separated and extracted with ether (2 × 25 mL). Purification via flash chromatography (SiO_2, hexanes/EtOAc 6:1, with 3% Et_3N) gave the products ***S*-61 and *R*-61**(107 mg, 86%) as a 5:4 mixture and as a light yellow solid. ***S*-61**: ^{1}H NMR (500 MHz, $CDCl_3$, from the mixture) δ 7.40−6.93 (m, 11H), 6.89 (d, J = 8.0 Hz, 1H), 6.76 (d, J = 1.0 Hz, 1H), 6.69 (d, J = 1.0 Hz, 1H), 6.49 (s, 1H), 4.92 (d, J = 12.5 Hz, 1H), 4.87 (d, J = 12.5 Hz, 1H), 4.02 (s, 3H), 4.00 (s, 3H), 3.99 (q, J = 6.0 Hz, 1H), 3.76 (s, 3H), 3.72 (d, J = 14.5 Hz, 1H), 3.36 (ddq, J = 11.5, 4.5, 6.5 Hz, 1H), 3.27 (d, J = 14.5 Hz, 1H), 2.35 (s, 3H), 2.19 (dd, J = 17.5, 4.5 Hz, 1H), 2.00 (dd, J = 17.5, 11.5 Hz, 1H), 1.38 (d, J = 6.0 Hz, 3H), and 1.00 (d, J = 6.5 Hz, 3H). ***R*-61**:^{1}H NMR of (500 MHz, $CDCl_3$, from the mixture) δ 7.40−6.93 (m, 11H), 6.88 (d, J = 8.0 Hz, 1H), 6.84 (d, J = 1.0 Hz, 1H), 6.70 (d, J = 1.0 Hz, 1H), 6.48 (s, 1H), 5.28 (s, 2H), 4.02 (s, 3H), 4.01 (s, 3H), 3.99 (q, J = 6.0 Hz, 1H), 3.75 (s, 3H), 3.71 (d, J = 14.5 Hz, 1H), 3.36 (ddq, J = 11.5, 4.0, 6.5 Hz, 1H), 3.30 (d, J = 14.5 Hz, 1H), 2.35 (s, 3H), 2.23 (dd, J = 17.5, 11.5 Hz, 1H), 2.00 (dd, J = 17.5, 4.0 Hz, 1H), 1.37 (d, J = 6.0 Hz, 3H), and 1.04 (d, J = 6.5 Hz, 3H). Anal. Calcd for $C_{39}H_{41}NO_4$: C, 79.70; H, 7.03; N, 2.38. Found: C, 79.74; H, 7.20; N, 2.44.

4,4′-(Bis-isoquinolin-5-yl)-8,8′-dimethoxy-6,6′-dimethyl-[2,2′]binaphthalenylidene-1,1′-dione (63). Naphthol **51** (126 mg, 0.4 mmol) was dissolved in CH_2Cl_2 (4 mL). Ag_2O (278 mg, 3 eq) was added, and the reaction mixture was stirred at room temperature for 12 h. After passage through a plug of Celite and concentration in vacuo, the residue was chromatographed (CH_2Cl_2/MeOH 95:5) and yielded dione **63** (119 mg, 95%) as a purple solid: mp > 200 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.35 (d, J = 6.7 Hz, 1H), 8.48 (d, J = 5.8 Hz, 1H), 8.09 (d, J = 8.2 Hz, 1H), 7.97 (s, 1H), 7.79−7.77 (m, 2H), 7.61 (d, J = 5.8 Hz, 1H), 6.73 (s, 1H), 6.12 (s, 1H), 3.90 (s, 3H), and 2.14 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 189.57, 160.46, 152.77, 145.59, 143.41, 140.34, 138.68, 137.97, 136.37, 134.95, 131.72, 130.34, 127.94, 127.10, 120.39, 118.91, 118.31 and 113.12; IR (KBr) 3367, 3065, 2931, 2850, 1612, 1582, 1558, and 1240 cm^{-1}; HRMS (FAB) calcd for $C_{42}H_{30}N_2O_4$ $(M + H)^+$ 627.2284, found 629.2444. The mass spectral data are very similar to those of the dihydro (leuco) form **64**, suggestive of in situ reduction during the FAB-MS determination.

4′,4″-(Bis-isoquinolin-5-yl)-8′,8″-dimethoxy-6′,6″-dimethyl-[2′,2″]-binaphthalene-1′,1″-diol (64). Dione **63** (55 mg, 0.09 mmol) was dissolved in MeOH (25 mL). The reaction mixture was stirred, and $NaBH_4$ (10 mg, 3 equiv) was added in small portions. The reaction mixture was stirred at room temperature for 15 min and was then concentrated in vacuo. The residue was dissolved in CH_2Cl_2 (20 mL) and washed with H_2O (2 × 10 mL) before being dried over $MgSO_4$. Concentration in vacuo and purification via column chromatography (CH_2Cl_2/MeOH 98:2) afforded diol **64** (30 mg, 55%) as an amber oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.99 (s, 1H), 9.30 (s, 1H), 8.34 (d, J = 6.0 Hz, 1H), 8.01 (d, J = 7.8 Hz, 1H), 7.75 (d, J = 7.0 Hz, 1H), 7.69 (dd, J = 7.8 and 7.0 Hz, 1H), 7.51 (s, 1H), 7.37 (d, J = 6.0 Hz, 1H), 6.65 (br s, 2H), 4.07 (s, 3H), and 2.23 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.40, 152.51, 151.56, 142.90, 138.20, 135.86, 135.73, 135.03, 133.21, 132.37, 128.70, 126.96, 126.85, 126.01, 119.40, 118.75, 113.45, 106.61, 56.17, and 22.00; HRMS (FAB) calcd for $C_{42}H_{32}N_2O_4(M + H)^+$ 629.2440, found 629.2444.

4,4′-(Bis-isoquinolin-5-yl)-8,8′-dimethoxy-6,6′-dimethyl-[2,2′]binaphthalenylidene-1,1′-dione (63) by Oxidation of 64. 2,2′-Bi-1-naphthol **64** (2 mg, 3 μmol) was dissolved in $CDCl_3$ (1 mL). Ag_2O (0.4 mg, 20 μmol) was added, and the reaction mixture was stirred at room temperature for 6 h. The mixture was filtered through a syringe with a plug of Celite, and the ^{1}H NMR spectrum of the resulting indigoid solution was obtained. The spectrum was identical to that obtained for **64** by oxidative coupling of the monomeric 1-naphthol **51,** and no other significant resonances were observed.

[(1*S*),1*R,3*S**,5*S**,1′*R**,3′*S**,5′*S**]-, [(1*S*),1*R**,3*S**,5*S**,1′*R**,3′*S**,5′*R**]-, and [(1*S*),1*R**,3*S**,5*R**,1′*R**,3′*S**,5′*R**]-5,5′-[1,1′-Dihydroxy-8,8′-dimethoxy-6,6′-dimethyl(2,2′-binaphthalene)-4,4′-diyl]-bis-1,2,3,4-tetrahydro-1,2,3-trimethyl-6,8-isoquinolinediol (65).** To a stirred solution of **59** (20 mg, 0.031 mmol) in CH_2Cl_2 (2 mL) was added Ag_2O (10 mg, 0.043 mmol). The resulting mixture was stirred in the dark at room temperature for 48 h. The mixture was passed through a plug of cotton, and the filtrate was concentrated to yield a dark blue solid. The dark blue solid was dissolved in MeOH (2 mL), and $NaBH_4$ (5 mg, 0.13 mmol) was added to the stirred solution. The dark blue color of the solution disappeared in less than 5 min. After 0.5 h, the reaction was quenched by addition of saturated $NaHCO_3$ (2 mL). MeOH was removed under reduced pressure, and Et_2O (5 mL) was added. The organic layer was washed with H_2O (2 mL) and brine (2 mL), dried over $MgSO_4$, and purified by column chromatography (SiO_2, hexanes/EtOAc 6:1, with 3% Et_3N) to provide a brown oil. The oil was dissolved in a 2:1 mixture of MeOH/CH_2Cl_2 (15 mL), and 10% Pd/C (20 mg) was added. The reaction mixture was stirred under an hydrogen atmosphere (1 atm) for 4 h. The reaction mixture was filtered through a bed of Celite, and the filtrate was concentrated to yield a mixture of **65** (7 mg, 60%) as a white solid: ^{1}H NMR of (500 MHz, CD_3OD) δ 7.32/7.32/7.31/7.29 (s, 1/2H each), 6.86−

6.78 (m, 4H), 6.49/6.48/6.46/6.46 (1/2 each), 4.63−4.58 (m, 2H), 4.10/4.09 (s, 3H each), 3.26−3.18 (m, 2H), 2.82(dd, J = 18.0, 12.0 Hz, 1/2H), 2.80 (dd, J = 18.0, 11.0 Hz, 1/2H), 2.69 (dd, J = 18.0, 11.0 Hz, 1/2H), 2.69 (dd, J = 18.0, 4.5 Hz, 1/2H), 2.63 (dd, J = 18.0, 4.0 Hz, 1/2H), 2.45−2.25 (m, 3/2H), 2.36/2.35 (s, 3H each), 1.81 (d, J = 7.0 Hz, 3/2H), 1.80 (d, J = 7.0 Hz, 3/2H), 1.79 (d, J = 7.0 Hz, 3/2H), 1.76 (d, J = 6.5 Hz, 3/2H), 1.35 (d, J = 6.5 Hz, 3/2H), 1.34 (d, J = 6.5 Hz, 3/2H), 1.32 (d, J = 6.5 Hz, 3/2H), and 1.31 (d, J = 6.5 Hz, 3/2H); HRMS (FAB) calcd for $C_{48}H_{53}N_2O_8$ $(M + H)^+$ 785.3802, found 785.3752.

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Supporting Information Available: Experimental procedures for the 10 reactions leading to tetrahydroisoquinoline **24** and preparations of **43a**,**b** and **49**−**53**. This material is available free of charge via the Internet at http://pubs.acs.org.

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