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Total Synthesis of the 7,3′-Linked Naphthylisoquinoline Alkaloid Ancistrocladidine

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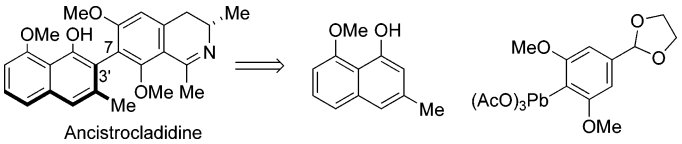

The first total synthesis of ancistrocladidine, a rare 7,3′-linked naphthylisoquinoline alkaloid, has been completed, with the key feature of the synthesis being the formation of the extremely hindered biaryl linkage by *ortho*-arylation of a naphthol with an aryllead triacetate. Initial efforts were focused on the generation of a heteroaryl lead species, which would have allowed a convergent synthesis to be developed. However, it was not possible to generate such a lead species. A simpler aryl lead triacetate was prepared and reacted. The resulting biaryl aldehyde was elaborated in 10 steps to form a 1:1 mixture of ancistrocladidine and its atropisomer. Recrystallization of the mixture afforded ancistrocladidine, which was identical in all respects to the reported data.

Introduction

The naphthylisoquinoline alkaloids are a large group of natural products whose only known sources are the Ancistrocladaceae and the closely related Dioncophyllaceae plant families.[1] Extracts from the tropical Ancistrocladaceae and Dioncophyllaceae plant families have been used in traditional medicines for the treatment of malaria and dysentery.[2] More recently, bioassay-directed isolation has led to the discovery of many structurally related compounds with biological activities such as antimalarial,[3] antifeedant,[4] molluscidal,[5] insect growth-retarding,[6] and anti-HIV activity.[7] Accordingly, structure−activity guided modifications, coupled with chemical syntheses of the natural products, has been a fruitful area of investigation for the development of more selective and active drugs.[2b]

These structurally unique alkaloids are characterized by a naphthalene group, linked to either a dihydro- or tetrahydroisoquinoline moiety, as exemplified by the examples shown in Figure 1. As a result of the hindered nature of the biaryl bond, restricted rotation dictates that many of these compounds exist as thermally stable atropisomers.[8] These natural products can be grouped according to the position of the biaryl bond linking the naphthalene and isoquinoline structural entities, with the 5,1′- and 7,1′-linkages being the most common. Ancistrocladidine (**1a**),[9] ancistroheynine B (**1b**),[10] ancistrotectorine (**2a**),[11] and ancistrotanzanine C (**2b**)[12] are some of the more unusual

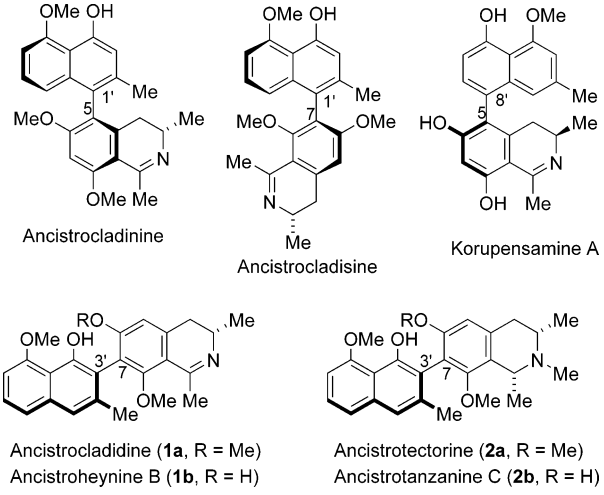

FIGURE 1. Representative examples of naphthylisoquinoline alkaloids.

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members of the naphthylisoquinoline family because of the presence of the highly hindered 7,3′-biaryl linkage.

The challenging architecture of the naphthylisoquinoline alkaloids, combined with their interesting biological activity, has led to considerable interest from the synthetic community.[13] The most successful strategy for the synthesis of these natural products is Bringmann's lactone method,[14] which provides ready access to the 5,1′- and 7,1′- linked members of the family in an atroposelective manner. Direct coupling of the appropriate naphthalene and isoquinoline moieties, under palladium catalysis, has also proved to be a rewarding approach.[13g,15] However, little synthetic attention[16] has been focused on 7,3′-linked systems such as that found in ancistrocladidine **1a** as the highly hindered biaryl system presents a significant challenge to existing methods for the synthesis of the naphthylisoquinoline alkaloids.

Although numerous palladium-catalyzed biaryl cross-couplings have been utilized in the synthesis[17] of biaryls possessing one, two, or three *ortho*-substituents, a common trend in such reactions is a lowering in the yield of coupled product upon an increase in the steric bulk surrounding the resulting biaryl bond.[18,19] For this reason there are only a few examples of couplings resulting in products that contain four *ortho*-substituents, although recent work by Buchwald has begun to rectify this situation.[19] Perhaps more importantly, synthesis of an appropriate naphthalene precursor for the cross-coupling would not be a trivial process.[20] For these reasons, an alternative biaryl coupling methodology for the formation of the 7−3′ linkage of ancistrocladidine was sought.

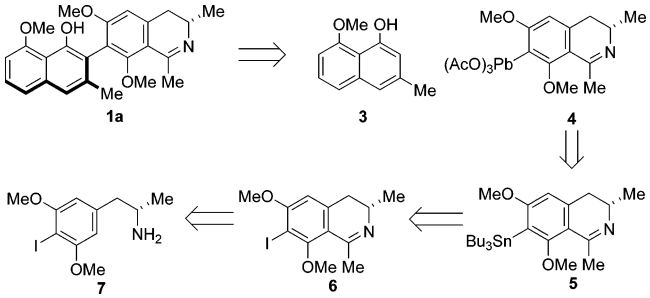

FIGURE 2. Retrosynthetic analysis.

The *ortho*-arylation of phenols with aryllead tricarboxylates is a reaction that is known to proceed on hindered substrates in an efficient manner.[21] Furthermore, Yamamoto and co-workers have extended this *ortho*-arylation methodology even further to allow asymmetric coupling.[22] This *ortho*-arylation chemistry has far-reaching implications with regards to a synthetic approach to a 7−3′ naphthylisoquinoline alkaloid (Figure 2). The possibility exists for direct functionalization of naphthol **3**,[23] which would circumvent the need for preparation of a difficult-to-access naphthalene precursor. In this paper, we present full details of this synthetic strategy and its application to the total synthesis of ancistrocladidine.[24]

Results and Discussion

Our initial efforts focused on the attractive possibility of preparing ancistrocladidine **1a** in a convergent fashion by generating a lead reagent **4** whereby the entire heterocyclic moiety of ancistrocladidine is present (Figure 2). This would allow us to investigate Yamamoto's methodology to control the atroposelectivity.

Organolead compounds may be prepared by two routes, either by direct plumbation or by transmetalation.[21c,f,25] The latter method is the more general route as it exhibits a greater tolerance

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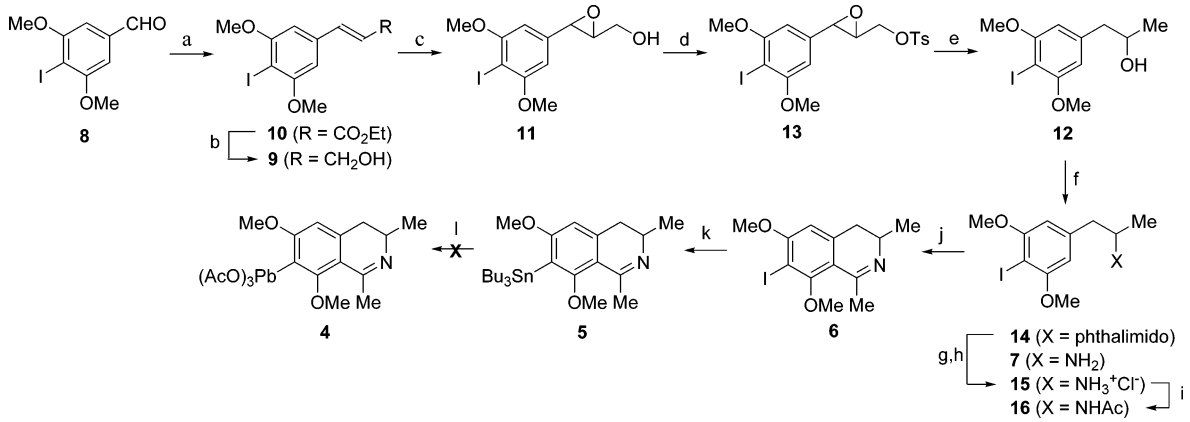
SCHEME 1[a]



[a] Reagents and conditions: (a) $(EtO)_2POCH_2CO_2Et$, NaH, benzene, 0 °C to rt, 100%; (b) DIBAL, CH_2Cl_2, 0 °C, 80%; (c) $VO(acac)_2$, *t*-BuOOH, CH_2Cl_2, rt, 91%; (d) TsCl, NEt_3, DMAP, CH_2Cl_2, 0 °C, 95%; (e) DIBAL, CH_2Cl_2, −20 °C to rt, 94%. (f) phthalimide, PPh_3, DEAD, THF, 0 °C to rt, 81%; (g) $MeNH_2$, H_2O/EtOH, reflux; (h) HCl (g), ether, 0 °C, 91% for 2 steps; (i) CH_3COCl, NEt_3, CH_2Cl_2, 0 °C to rt, 96%; (j) $POCl_3$, 2,4,6-collidine, CH_3CN, reflux, 89%. (k) *t*-BuLi, THF, −95 °C, $ClSnBu_3$, −95 °C to rt, 83%. (l) $Pb(OAc)_4$, cat. $Hg(OAc)_2$, $CHCl_3$.

of functionality. This metal−metal exchange route is normally achieved using either a tin or boron species in the presence of catalytic amounts of mercuric(II) salts.[25c,d] Tin−lead exchange has proven to be the method of choice in many cases because of the ease of purification of the resulting organolead compounds. With this in mind, synthesis of stannane **5** was our first concern (Figure 2). To generate this compound, we required 7-iododihydroisoquinoline **6**. With the Bischler−Napieralski reaction being the standard method[26] for preparing dihydroisoquinolines, access to amphetamine **7** was necessary. Although there are several excellent syntheses[26,27] of such compounds en route to dihydroisoquinolines, the majority are not compatible with the iodo moiety due to the strong reducing agents utilized.

Investigations into the Preparation of Heterocyclic Lead Triacetates. Rao and co-workers[13a] have reported a synthesis that utilizes mild conditions, which we felt would be amenable to the preparation of the iodide **6**. Furthermore, it would allow for the preparation of chiral material. However, our initial efforts were focused on the preparation of **7** in a racemic form. Starting from aldehyde **8**,[29] the required allylic alcohol **9** was readily prepared in 80% yield by first forming the α,β-unsaturated ester **10** by Horner−Wadsworth−Emmons reaction and then reduction with DIBAL-H (Scheme 1). Treatment of allylic alcohol **9** with catalytic vanadyl acetylacetonate and *t*-BuOOH in dichloromethane gave epoxide **11** in 91% yield after chromatography.[28] Conversion of this epoxide to the secondary alcohol **12** was achieved utilizing a method reported by Chong.[30] Tosylate **13** was readily prepared from epoxyalcohol **11** in 95% yield.

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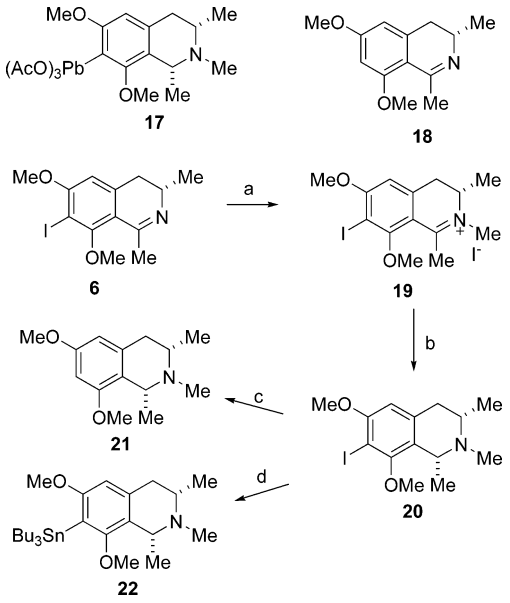
Subsequent reduction with DIBAL-H in dichloromethane gave alcohol **12** in 94% yield after chromatography.

Reaction of alcohol **12** with triphenylphosphine, phthalimide, and diethyl azodicarboxylate in THF gave imide **14** in 81% yield. Deprotection of the phthalmide was readily accomplished by refluxing **14** in an ethanolic solution of aqueous methylamine to give the amine **7**, which was isolated in 91% yield as its hydrochloride salt **15**. Hydrochloride **15** was smoothly acetylated using acetyl chloride and triethylamine in dichloromethane to give acetamide **16** in 96% yield. However, the ensuing Bischler−Napieralski cyclization was problematic. Exposure of **16** to the standard cyclization conditions of phosphorus oxychloride in acetonitrile, at reflux, resulted in varying degrees of deiodination. Addition of 1 equiv of 2,4,6-collidine to the reaction, as reported by Lipshutz and Keith,[26c] afforded the desired dihydroisoquinoline **6** in 89% yield.

The stannane **5** was readily prepared in 83% yield by treatment of iodide **6** with *t*-BuLi at −95 °C in THF, followed by addition of tributyltin chloride. The standard preparation of aryl lead triacetates involves stirring the stannane with freshly purified $Pb(OAc)_4$ in the presence of a catalytic amount of $Hg(OAc)_2$. Unfortunately, exposure of stannane **5** to these conditions resulted in a complex mixture, from which only starting material could be isolated. The reaction was repeated at room temperature, and it was noted that upon addition of **5** to a solution of $Pb(OAc)_4$, red coloration and precipitation of material resulted. The precipitated material appeared to dissolve in water, but no useful information could be gathered from the resulting ^1H NMR spectrum run in D_2O. On the assumption that the $Pb(OAc)_4$ and/or $Hg(OAc)_2$ were reacting with the imine group, it was decided to investigate whether the tetrahydroisoquinoline may be a more suitable compound for the generation of an aryl lead triacetate. Tetrahydroisoquinoline **17** was selected as it is the same as the tetrahydroisoquinoline moiety present in the other 7−3′-linked naphthylisoquinoline alkaloid, ancistrotectorine **2a**, and thus could be utilized in a total synthesis.

It is well documented that reduction of 3,4-dihydroisoquinolines with sodium borohydride in methanol gives *cis*-configured tetrahydroisoquinolines.[26b] These can be converted into their *N*-methyl derivatives by preparation of the carbamate, followed by lithium aluminum hydride reduction.[13c] However, the iodide functionality is not compatible with such a reducing agent, and therefore an alternative method was sought. Rizzacasa and Sargent have shown that upon *N*-methylation of dihydroisoquinoline **18**, reduction of the resulting tetrahydroisoquinolinium salt, with sodium borohydride, affords a 2:1 mixture of tetrahydroisoquinolines in favor of the *trans*-isomer.[26a] As ancistrotectorine contains a *cis* arrangement of the methyl groups, an alternative reducing agent was required. There was evidence to suggest that reduction of isoquinolinium salts with the bulkier diisobutylaluminum hydride should give the desired *cis*-selectivity.[31] Accordingly, *N*-methyldihydroisoquinoline **19** was readily prepared by treating a solution of dihydroisoquinoline **6** in acetone with iodomethane (Scheme 2). The so-obtained salt was reduced with DIBAL-H in dichloromethane at −78 °C to afford a 9:1 ratio of diastereoisomers, which after chromatography afforded the *cis*-diastereoisomer **20** in 85% yield. The relative configuration was confirmed by deiodination, using *t*-BuLi then H_2O, which gave the tetrahydroisoquinoline *cis*-**21**, which had previously been prepared by Sargent and Rizzacasa.[26a] The observed stereoselectivity for the reduction of the isoquinoline could be explained in terms of the bulky reducing agent delivering a hydride from the opposite face with respect to the methyl group at 3-position.

SCHEME 2[a]



[a] Reagents and conditions: (a) MeI, acetone, rt; (b) DIBAL, CH_2Cl_2, −78 °C to rt, 85% for 2 steps; (c) *t*-BuLi/H_2O, THF, −78 °C; (d) *t*-BuLi, THF, −95 °C, $ClSnBu_3$, − 95 °C to rt, 83%.

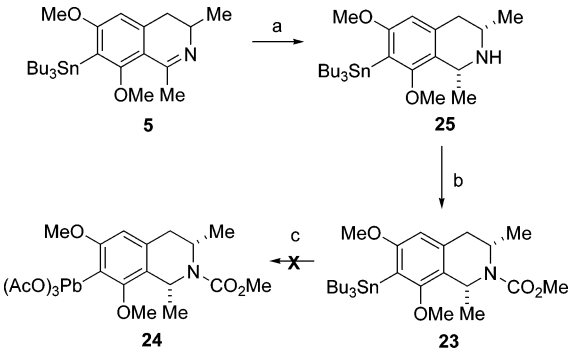
Stannane **22** was prepared in 56% yield from iodide **20** by halogen/metal exchange, followed by addition of tributyltin chloride. Stirring a solution of the stannane **22**, $Pb(OAc)_4$, and $Hg(OAc)_2$ at room temperature gave only recovered starting material and a small amount of demetalated material **21**. Repeating the reaction, but at 40 °C resulted in complete demetalation to form **21**. Barton and co-workers have observed that aryllead reagents can be demetalated by arylamines via an oxidation mechanism.[32] Two potential solutions to this problem were considered at this stage. First, in situ trapping of the aryllead species **17** with naphthol **3**, which may be a faster process than the proposed oxidation, or second, an electron-withdrawing group could be attached to the nitrogen atom of the tetrahydroisoquinoline, thus decreasing the basicity of the lone pair of electrons and slowing the undesired nucleophilic addition to lead. Unfortunately, conducting the plumbation reaction in the presence of naphthol **3** and pyridine resulted in a complex mixture from which only starting materials and demetalated species could be isolated. No trace of a *ortho*-arylated naphthol was found.

Carbamate **23** was chosen as the precursor to aryllead species **24** as the carbamate group would provide significant withdrawal of electron density from the nitrogen and still be readily converted into an *N*-methyl derivative as is required for the synthesis of ancistrotectorine **2a** (Scheme 3). Thus, stannane **5** was readily reduced with sodium borohydride in methanol to give amine **25** in 96% yield. Carbamate **23** was prepared in 77% yield by reacting amine **25** with methyl chloroformate in dichloromethane, in the presence of triethylamine. Interestingly the aliphatic CH signals were significantly broadened in the ^1H

(31) Martens, J. In *Methods of Organic Chemistry*, workbench ed. E21; Georg Thieme Verlag: Stuttgart, 1996; Vol. 7, p 4220.

(32) Barton, D. H.; Donnelly, D. M. X.; Finet, J.-P.; Guiry, P. J. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2095.

SCHEME 3[a]



[a] Reagents and conditions: (a) $NaBH_4$, MeOH, rt, 96%; (b) $ClCO_2Me$, NEt_3, CH_2Cl_2, rt, 77%; (c) $Pb(OAc)_4$, cat. $Hg(OAc)_2$, $CHCl_3$

NMR spectrum of **23**. This may arise from a slowing of the rate of pyramidal inversion at nitrogen by the electron-withdrawing carbamate group

Unfortunately, stirring of **23** with $Pb(OAc)_4$ and $Hg(OAc)_2$ in chloroform at room temperature gave only recovered starting material and a small amount of demetalated material. Conducting the reaction at 40 °C resulted in an increase in the amount of demetalated material.

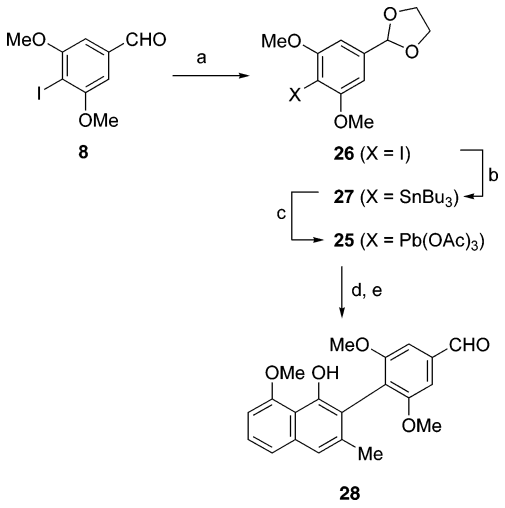
The inability of stannanes **4**, **22**, and **23** to form an aryllead species could be due to a number of factors. The presence of a nitrogen atom containing a basic lone pair of electrons could be detrimental, as it has been shown that nitrogen-containing species such as pyridine interact strongly with aryllead triacetates in solution. A possible steric argument can also be considered when discussing aryllead tricarboxylate **4**. A steric clash between the C8 methoxy group and the C1 methyl group in **4** could cause a subtle compression of the steric environment between the methoxy groups resulting in an inability to form a lead-species. It is possible to remove the issues associated with the nitrogen atom and those associated with steric crowding by investigating the synthesis of aryllead tricarboxylate **25**.

Preparation of an Aryl Lead Triacetate. Iodide **26** was prepared by acetalization of iodobenzaldehyde **8**[28] with ethylene glycol (99%) (Scheme 4). Conversion to the stannane **27** was achieved by halogen−lithium exchange of iodide **26** with *t*-BuLi and subsequent quenching with Bu_3SnCl.

To our delight, stirring the stannane **27** with freshly purified $Pb(OAc)_4$ in the presence of a catalytic amount of $Hg(OAc)_2$ provided aryllead triacetate **25** in 93% yield. Formation of the key biaryl linkage using the Pinhey-Barton methodology was readily achieved by reaction of the lead species **25** with naphthol **3** in the presence of pyridine and CH_2Cl_2 at room temperature. Hydrolysis of the crude reaction mixture with 3% v/v aqueous H_2SO_4 in THF gave the desired biaryl aldehyde **28**, in 67% yield from **3**.

Completion of the Synthesis of Ancistrocladidine. With the successful establishment of the hindered biaryl linkage, aldehyde **28** was then elaborated to the chiral amine **29**, with the Katsuki−Sharpless asymmetric epoxidation being used to set the stereochemistry at C3 (Scheme 5).[13a] The required allylic alcohol **30** was prepared in three steps from biaryl aldehyde **28** in 71% overall yield: (i) protection of the naphthol as its MOM ether, (ii) elaboration of the aldehyde to the α,β-unsaturated ester by Horner−Wadsworth−Emmons reaction, and (iii) reduction with DIBAL-H.

SCHEME 4[a]



[a] Reagents and conditions: (a) 1,2-ethanediol, cat. TsOH, benzene, Dean−Stark, 99%. (b) *t*-BuLi, Bu_3SnCl, THF, −95 °C − rt, 85%; (c) $Pb(OAc)_4$, cat. $Hg(OAc)_2$, CH_2Cl_2, rt, 24 h, 93%; (d) **3**, pyridine, CH_2Cl_2, 24 h, rt; (e) 3% v/v aqueous H_2SO_4, THF, 1 h, rt, 67% yield from **3**.

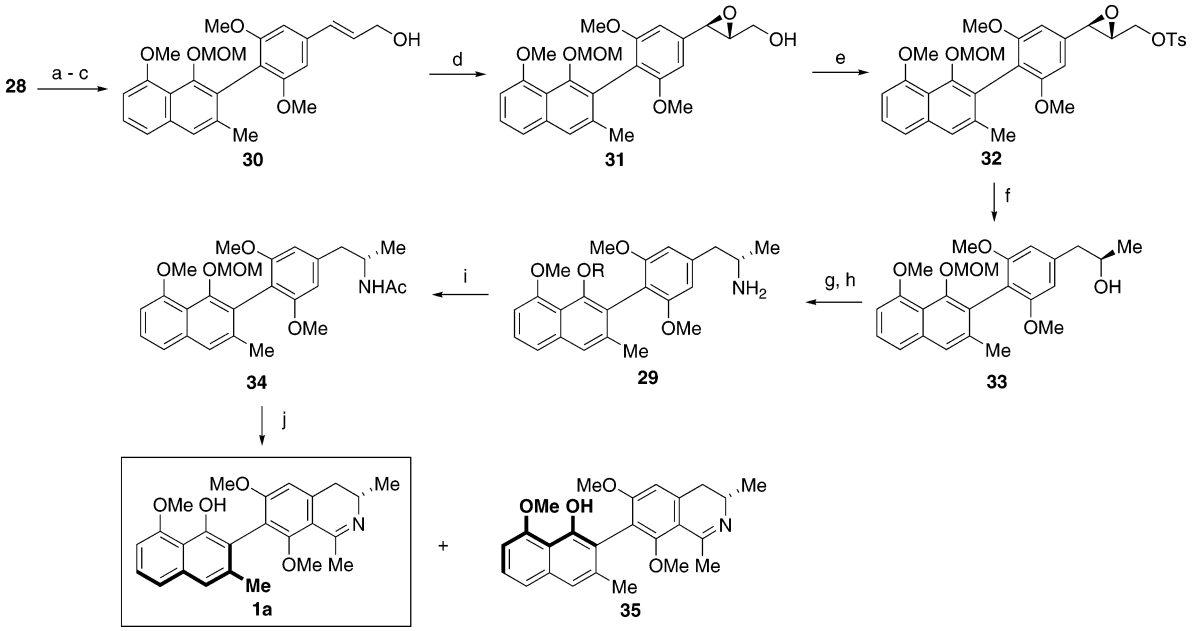
Using the standard Sharpless conditions,[33] the epoxide **31** was obtained in 80% yield and 90% de.[34] This reaction generates diastereomers with respect to the biaryl linkage, but they were not observable. The epoxide was recrystallized from toluene/petroleum ether to provide material with >95% de (63% yield). Tosylation of **31** gave the tosylate **32** in 83% yield. Concomitant cleavage of the tosylate and ring opening of the epoxide to afford alcohol **33**, in 94% yield, was achieved by reaction of tosylate **32** with $LiAlH_4$ in Et_2O. Transformation of the alcohol **33** into the amine **29** was achieved, in 81% overall yield, by reaction of **33** with phthalimide as described earlier, followed by hydrolysis of the phthalimide group with aqueous ethanolic methylamine. Acetylation of the resulting amine **29** with CH_3COCl gave the acetamide **34** in 97% yield. Bischler−Napieralski cyclization was readily achieved by reaction of **34** with $POCl_3$ in the presence of 1.1 equiv of 2,4,6-collidine. During the course of this reaction, the MOM protecting group was cleaved in situ, and thus, ancistrocladidine **1a** was isolated, along with the atropisomer **35**, in a 1:1 ratio, in 74% overall yield. Separation of the atropisomers was readily achieved by recrystallization as the non-natural atropisomer **35** proved to be noncrystalline. While comparison with an authentic sample of ancistrocladidine is not possible as the natural product is no longer available, synthetic ancistrocladidine matches all the reported data for the natural product.[9]

In summary, the first total synthesis of a 7,3′-linked naphthylisoquinoline alkaloid has been completed. The key feature of our synthesis is the formation of the extremely hindered biaryl linkage by *ortho*-arylation of a naphthol with an aryllead triacetate. Future work will involve the application of this strategy to other members of the naphthylisoquinoline alkaloid family, with the ultimate goal being the generation of such compounds as single atropoisomers.

(33) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765−5780.

(34) The diasteromeric excess of this reaction was determined by the method described in Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543−2549. Details are provided in Supporting Information.

SCHEME 5[a]



[a] Reagents and conditions: (a) MOM-Cl, NaH, THF, rt, 81%; (b) NaH, $(EtO)_2POCH_2CO_2Et$, C_6H_6, 0 °C − rt, 99%; (c) DIBAL-H, toluene, −78 °C, 15 min., 89%; (d) 5 mol % $Ti(O^iPr)_4$, 6 mol % D-diisopropyltartrate, TBHP, CH_2Cl_2, −20 °C, 5 h, 80%, 90% ee; (e) TsCl, NEt_3, DMAP, CH_2Cl_2, 1 h, 0 °C, 83%; (f) $LiAlH_4$, Et_2O, 0 °C, 2 h, 94%; (g) phthalimide, DEAD, PPh_3, THF, rt, 16 h, 82%; (h) 40% aq $MeNH_2$, EtOH, reflux, 1 h, 99%; (i) CH_3COCl, NEt_3, CH_2Cl_2, 0 °C − rt, 97%; (j) $POCl_3$, 2,4,6-collidine, CH_3CN, reflux, 4 h, 74% (1:1 mixture of **1a** and **35**).

Experimental Section[35]

(*E*)-3-(4-Iodo-3,5-dimethoxyphenyl)-acrylic Acid Ethyl Ester (10). Triethyl phosphonoacetate (1.58 mL, 7.94 mmol) was added to a suspension of prewashed NaH (208 mg, 8.67 mmol) in dry benzene (20 mL) at 0 °C. The reaction was stirred for 15 min, and then a solution of the aldehyde **8**[28] (2.11 g, 7.22 mmol) in dry benzene (30 mL) was slowly added. The reaction was stirred for 1 h at 0 °C, then 30 min at room temperature, following which H_2O was added. The aqueous layer was extracted with EtOAc (×4) and the combined organic extracts were washed with H_2O (×2). Removal of the solvent under reduced pressure gave the title compound as a white solid (2.62 g, 100%). Mp: 135−136 °C. ^1H NMR (500 MHz, $CDCl_3$): δ 1.34 (t, J = 7.3 Hz, 3H), 3.92 (s, 6H), 4.27 (q, J = 7.3 Hz, 2H), 6.47 (d, J = 16 Hz, 1H), 6.63 (s, 2H), 7.62 (d, J = 16 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.2, 56.4, 60.5, 80.2, 103.2, 118.9, 136.1, 143.7, 159.5, 166.5. IR (KBr): 1703 cm^{-1}. HRMS: calcd for $C_{13}H_{15}IO_4$ (M^+) 362.0014, found 362.0015.

(*E*)-3-(4-Iodo-3,5-dimethoxyphenyl)prop-2-en-1-ol (9). Neat DIBAL-H (2.88 mL, 16.2 mmol) was added dropwise to a solution of the ester **10** (2.34 g, 6.47 mmol) in dry CH_2Cl_2 (40 mL) at 0 °C. The reaction was stirred at 0 °C for 1 h and quenched by dropwise addition of H_2O until coagulation occurred. The suspension was diluted with 1 M aqueous HCl solution and extracted with EtOAc (×4). Removal of the solvent under reduced pressure and purification of the residue by flash chromatography, eluting with 70% EtOAc/petroleum ether, gave the title compound as a white solid (1.65 g, 80%). Mp: 122−123 °C. ^1H NMR (500 MHz, $CDCl_3$): δ 3.89 (s, 6H), 4.34 (d, J = 4.9 Hz, 2H), 6.41 (dt, J = 16, 5.4 Hz, 1H), 6.53 (s, 2H), 6.58 (dd, J = 16, 1.5 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 56.4, 63.1, 76.5, 102.1, 129.5, 130.1, 138.6, 159.2. IR (film): 3209 cm^{-1}. HRMS: calcd for $C_{11}H_{13}IO_3$ (M^+) 319.9908, found 319.9910.

(2*S,3*R**)- (3-[4-Iodo-3,5-dimethoxyphenyl]oxiranyl)-methanol (±11).** Anhydrous TBHP solution (6.1 M, 67.2 mmol) in CH_2Cl_2 (0.52 mL) was added to a solution of the allylic alcohol **9** (500 mg, 1.6 mmol) and $VO(acac)_2$ (8 mg, 3.1 μmol) in dry CH_2Cl_2 (5 mL). The reaction was stirred for 1 h at room temperature, diluted with CH_2Cl_2, and filtered through a plug of Celite. The solvent was removed under reduced pressure, and the residue was purified by flash chromatography, eluting with 70% EtOAc/petroleum ether, to give the title compound as a white solid (480 mg, 91%). Mp: 99−100 °C. ^1H NMR (500 MHz, $CDCl_3$): δ 1.82 (d, J = 7.8 Hz, 1H), 3.17 (m, 1H), 3.82 (m, 1H), 3.88 (s, 6H), 3.94 (d, J = 2.0 Hz, 1H), 4.06 (m, 1H), 6.44 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.3, 56.5, 60.9, 62.6, 76.8, 101.1, 139.3, 159.5. IR (KBr): 3412 cm^{-1}. HRMS: calcd for $C_{11}H_{13}IO_4$ (M^+) 335.9857, found 335.9859.

(2*S,3*R**)-Toluene-4-sulfonic Acid 3-(4-Iodo-3,5-dimethoxyphenyl)oxiranyl-methyl Ester (±13).** Dry NEt_3 (1.69 mL, 12.2 mmol) was added to a solution of the alcohol **11** (0.816 g, 2.43 mmol) and DMAP (0.297 g, 2.43 mmol) in dry CH_2Cl_2 (25 mL) at 0 °C. A solution of TsCl (0.510 g, 2.67 mmol) in dry CH_2Cl_2 (3 mL) was slowly added. The reaction was stirred at 0 °C for 1 h, diluted with CH_2Cl_2, and washed in turn with 1 M aqueous HCl solution and saturated aqueous $NaHCO_3$ solution. Removal of the solvent under reduced pressure gave the title compound as a fluffy white solid (1.13 g, 95%). Mp: 48−49 °C. ^1H NMR (500 MHz, $CDCl_3$): δ 2.45 (s, 3H), 3.19 (m, 1H), 3.80 (d, J = 2.0 Hz, 1H), 3.86 (s, 6H), 4.15 (dd, J = 12, 4.2 Hz, 1H), 4.33 (dd, J = 12, 3.4 Hz, 1H), 6.37 (s, 2H), 7.35 (d, J = 8.3 Hz, 2H), 7.81 (d, J = 8.3 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.5, 56.0, 56.4, 58.5, 69.0, 77.2, 101.0, 127.8, 129.8, 132.3, 138.1, 145.1, 159.4. HRMS: calcd for $C_{18}H_{19}IO_6S$ (M^+) 489.9946, found 489.9947.

1-(4-Iodo-3,5-dimethoxyphenyl)-propan-2-ol (±12). Neat DIBAL (1.23 mL, 6.91 mmol) was added dropwise to a solution of the tosylate 13 (1.13 g, 2.30 mmol) in dry CH_2Cl_2 (35 mL) at 15 °C. The resulting solution was stirred for 2 h at 15 °C and then allowed to warm to room temperature overnight. The reaction was quenched by dropwise addition of H_2O, till coagulation occurred. The suspension was diluted with 1 M aqueous HCl solution and then extracted with EtOAc (×4). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ solution. Removal of the solvent under reduced pressure and purification by flash chromatography, eluting with 60% EtOAc/petroleum ether, gave the title

(35) General procedures are detailed in Supporting Information.

compound as a colorless viscous oil (693 mg, 94%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.25 (d, J = 6.4 Hz, 3H), 2.65 (dd, J = 13, 8.3 Hz, 1H), 2.76 (dd, J = 14, 4.4 Hz, 1H), 3.87 (s, 3H), 4.01 (m, 1H), 6.36 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.7, 45.8, 56.3, 68.4, 74.1, 105.1, 140.9, 159.0. IR (film): 3385, 3547 cm^{-1}. HRMS: calcd for $C_{11}H_{15}IO_3$ (M^+) 322.0066, found 322.0065.

2-(2-(4-Iodo-3,5-dimethoxyphenyl)-1-methylethyl)isoindole-1,3-dione (±14). DEAD (0.422 mL, 0.570 mmol) was added to a solution of the alcohol **12** (693 mg, 2.15 mmol), PPh_3 (0.705 g, 2.69 mmol), and phthalimide (0.396 g, 2.69 mmol) in dry THF (20 mL) at 0 °C. The reaction was protected from light and allowed to warm to room temperature overnight. Saturated aqueous $NaHCO_3$ solution was added, and the product was extracted with EtOAc (×4). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ solution. The solvent was removed under reduced pressure, and purification by flash chromatography, eluting with 25% EtOAc/petroleum ether, gave the title compound as a white solid (786 mg, 81%). Mp: 124−125 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.55 (d, J = 6.8 Hz, 3H), 3.06 (dd, J = 14, 6.4 Hz, 1H), 3.37 (dd, J = 10, 14 Hz, 1H), 3.76 (s, 6H), 4.70 (m, 1H), 6.32 (s, 2H), 7.67 (m, 2H), 7.75 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 18.4, 39.8, 47.8, 56.3, 74.9, 104.7, 122.9, 131.6, 133.8, 140.7, 159.1, 168.2. IR (KBr): 1705 cm^{-1}. HRMS: calcd for $C_{19}H_{18}INO_4$ (M^+) 451.0279, found 451.0281.

2-(4-Iodo-3,5-dimethoxyphenyl)-1-methylethylammonium Chloride (±15). 40% Aqueous $MeNH_2$ solution (33 mL) was added to a solution of the imide **14** (0.786 g, 1.74 mmol) in absolute EtOH (50 mL). The reaction was heated at reflux for 1 h, and then most of the EtOH was removed under reduced pressure. H_2O was added, the product was extracted with Et_2O (×4), and the combined organic extracts were concentrated to a volume of ca. 25 mL. The resulting solution was cooled to 0 °C and purged with gaseous HCl for 15 min. The resulting white precipitate was collected by filtration and dried under reduced pressure to give the title compound as a white solid (566 mg, 91%). Mp: 230−231 °C dec. ^{1}H NMR (500 MHz, CD_3OD): δ 1.30 (d, J = 6.4 Hz, 3H), 2.86 (dd, J = 14, 7.8 Hz, 1H), 2.95 (dd, J = 14, 6.8 Hz, 1H), 3.59 (m, 1H), 3.87 (s, 6H), 6.52 (s, 2H). ^{13}C NMR (75 MHz, CD_3OD): δ 18.9, 42.2, 50.4, 57.4, 76.8, 106.6, 140.2, 161.5. IR (KBr): 1415, 3431 cm^{-1}. HRMS: electrospray calcd for $C_{11}H_{17}INO_2$ (M^+) 322.0304, found 322.0319.

***N*-(2-(4-Iodo-3,5-dimethoxyphenyl)-1-methylethyl)acetamide (±16).** Dry NEt_3 (0.722 mL, 5.18 mmol) was added to a suspension of the hydrochloride **15** (842 mg, 2.35 mmol) in dry CH_2Cl_2 (20 mL) at 0 °C. Freshly distilled acetyl chloride (194 μL, 2.71 mmol) was slowly added, and the reaction was warmed to room temperature overnight. The resulting solution was diluted with CH_2Cl_2 and washed with 1 M aqueous HCl solution (×3). Removal of the solvent under reduced pressure gave the title compound as a white solid (817 mg, 96%). Mp: 142−143 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.12 (d, J = 6.4 Hz, 3H), 1.94 (s, 3H), 2.65 (dd, J = 14, 7.8 Hz, 1H), 2.87 (dd, J = 14, 5.4 Hz, 1H), 3.86 (s, 6H), 4.26 (m, 1H), 5.33 (d, J = 7.3 Hz, 1H), 6.33 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.8, 23.2, 42.5, 45.8, 56.3, 74.8, 105.1, 140.5, 159.0, 169.2. IR (KBr): 1570, 1630, 3076, 3242 cm^{-1}. HRMS: calcd for $C_{13}H_{19}INO_3$ (M^+) 364.0410, found 364.0411.

7-Iodo-6,8-dimethoxy-1,3-dimethyl-3,4-dihydroisoquinoline (±6). 2,4,6-Collidine (173 μL, 1.30 mmol) was added to a solution of the amide **16** (429 mg, 1.18 mmol) in dry CH_3CN (6 mL). Freshly distilled $POCl_3$ (121 μL, 1.30 mmol) was added, and the reaction was heated at reflux for 3 h. The resulting solution was poured into saturated aqueous $NaHCO_3$ solution and extracted with EtOAc (×4). The solvent was removed under reduced pressure, and purification by flash chromatography on alumina, eluting with 30% EtOAc/petroleum ether, gave the title compound as a light tan solid (364 mg, 89%). Mp: 91−92 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.37 (d, J = 6.8 Hz, 3H), 2.30 (dd, J = 16, 13 Hz, 1H), 2.45 (d, J = 2.0 Hz, 3H), 2.61 (dd, J = 16, 4.4 Hz, 1H), 3.33 (m, 1H), 3.73 (s, 3H), 3.90 (s, 3H), 6.47 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.6, 25.7, 34.6, 51.3, 56.5, 61.9, 82.4, 105.9, 117.3, 142.5, 159.0, 160.2, 161.7. HRMS: calcd for $C_{13}H_{16}INO_2$ (M^+) 345.0225, found 345.0226.

6,8-Dimethoxy-1,3-dimethyl-7-tributylstannanyl-3,4-dihydroisoquinoline (±5). A solution of *t*-BuLi in pentane (1.5 M, 0.707 mL, 1.06 mmol) was added dropwise to a solution of the iodide **6** (154 mg, 0.424 mmol) in dry THF (4 mL) at −95 °C. The reaction was stirred at −95 °C for 15 min, then $ClSnBu_3$ (0.288 mL, 1.06 mmol) was slowly added, and the reaction allowed to warm to room temperature overnight. The resulting solution was poured into saturated aqueous $NaHCO_3$ solution and extracted with EtOAc (×4). Removal of the solvent under reduced pressure and purification by flash chromatography on alumina, eluting with 15% EtOAc/petroleum ether, gave the title compound as a colorless oil (179 mg, 83%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.88 (m, 9H), 1.07 (m, 6H), 1.32 (m, 6H), 1.39 (d, J = 6.8 Hz, 3H), 1.51 (m, 6H), 2.33 (dd, J = 16, 14 Hz, 1H), 2.43 (d, J = 2.0 Hz, 3H), 2.60 (dd, J = 16, 4.4 Hz, 1H), 3.32 (m, 1H), 3.56 (s, 3H), 3.77 (s, 3H), 6.44 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 11.2, 13.6, 22.0, 25.5, 27.3, 29.1, 35.2, 51.6, 55.2, 63.1, 104.5, 117.0, 121.0, 144.0, 163.2, 164.9, 165.9. HRMS: calcd for $C_{25}H_{43}NSnO_2$ (M^+ − Bu) 452.1612, found 452.1612.

(1*R,3*S**)-7-Iodo-6,8-dimethoxy-1,2,3-trimethyl-1,2,3,4-tetrahydroisoquinoline (±20).** Iodomethane (212 μL, 3.40 mmol) was added to a solution of the dihydroisoquinoline **6** (235 mg, 0.680 mmol) in dry acetone (7 mL), followed by stirring at room temperature for 48 h. The solvent was removed under reduced pressure and the residue dissolved in dry CH_2Cl_2 and cooled to −78 °C. Neat DIBAL (145 μL, 0.816 mmol) was added, and the reaction allowed to warm to room temperature overnight. The reaction was quenched by dropwise addition of H_2O till coagulation occurred. The suspension was diluted with 1 M aqueous HCl solution, stirred for 5 min, and then neutralized with 1 M aqueous NaOH solution. The product was extracted with CH_2Cl_2 (×4), and the solvent was removed under reduced pressure. Purification by flash chromatography on alumina, eluting with 15% EtOAc/petroleum ether, gave the title compound as a pale yellow solid (209 mg, 85%). Mp: 79−80 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.23 (d, J = 6.4 Hz, 3H), 1.40 (d, J = 6.8 Hz, 3H), 2.44 (m, 1H), 2.45 (s, 3H), 2.59 (dd, J = 16, 2.9 Hz, 1H), 2.67 (dd, J = 10, 16 Hz, 1H), 3.68 (q, J = 6.4 Hz, 1H), 3.79 (s, 3H), 3.85 (s, 3H), 6.38 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.3, 23.2, 38.3, 41.4, 55.0, 56.4, 57.5, 60.5, 81.2, 106.6, 126.7, 138.5, 157.0, 157.6. HRMS: calcd for $C_{14}H_{19}INO_2$ (M^+) 360.0459, found 360.0461.

(1*R,3*S**)-6,8-Dimethoxy-1,2,3-trimethyl-7-tributylstannanyl-1,2,3,4-tetrahydroisoquinoline (±22).** A solution of *t*-BuLi in pentane (1.5 M, 0.489 mL, 0.734 mmol) was added dropwise to a solution of the iodide **20** (0.106 g, 0.293 mmol) in dry THF (3 mL) at −95 °C. The reaction was stirred at −95 °C for 15 min then $ClSnBu_3$ (0.200 mL, 0.734 mmol) was slowly added, and the reaction was allowed to warm to room temperature overnight. The resulting solution was poured into saturated aqueous $NaHCO_3$ solution and extracted with EtOAc (×4). The solvent was removed under reduced pressure and purification by flash chromatography on alumina, eluting with 5% EtOAc/petroleum ether, gave the title compound as a colorless oil (87 mg, 56%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.88 (m, 9H), 1.07 (m, 6H), 1.23 (d, J = 6.4 Hz, 1H), 1.32 (m, 6H), 1.41 (d, J = 6.4 Hz, 3H), 1.51 (m, 6H), 2.44 (m, 1H), 2.45 (s, 3H), 2.58 (dd, J = 16, 2.6 Hz, 1H), 2.71 (dd, J = 16, 11 Hz, 1H), 3.62 (s, 3H), 3.63 (m, 1H), 3.72 (s, 3H), 6.34 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 11.2, 13.7, 21.4, 23.3, 27.4, 29.2, 39.0, 41.4, 55.0, 55.2, 57.6, 61.8, 104.9, 119.7, 125.4, 139.3, 162.8, 163.5. HRMS: calcd for $C_{26}H_{47}NSnO_2$ (M^+ − CH_3) 510.2394, found 510.2394.

(1*R,3*S**)-6,8-Dimethoxy-1,3-dimethyl-7-tributylstannanyl-1,2,3,4-tetrahydroisoquinoline (±25).** $NaBH_4$ (78 mg) was added to a solution of the dihydroisoquinoline **5** (179 mg, 0.353 mmol) in MeOH (35 mL). The reaction was stirred for 30 min at room temperature, following which the solvent was removed under

reduced pressure. The residue was dissolved in CH_2Cl_2 and filtered through a plug of Celite. Removal of the solvent under reduced pressure gave the title compound as a colorless oil (173 mg, 96%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.87 (m, 9H), 1.04 (m, 6H), 1.21 (d, J = 6.4 Hz, 3H), 1.30 (m, 6H), 1.48 (d, J = 5.9 Hz, 3H), 1.50 (m, 6H), 2.48 (dd, J = 16, 11 Hz, 1H), 2.69 (dd, J = 16, 2.4 Hz, 1H), 2.91 (m, 1H), 3.57 (s, 3H), 3.70 (s, 3H), 4.25 (q, J = 6.4 Hz, 1H), 6.32 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 11.2, 13.7, 22.4, 22.6, 27.3, 29.2, 39.8, 48.3, 50.1, 55.0, 60.7, 105.8, 120.2, 125.3, 139.6, 162.8, 164.2. HRMS: calcd for $C_{17}H_{45}NO_2Sn$ (M^+ − Bu) 454.1768, found 454.1768.

(1*R,3*S**)-6,8-Dimethoxy-1,3-dimethyl-7-tributylstannanyl-3,4-dihydro-1*H*-isoquinoline-2-carboxylic Acid Methyl Ester (±23).** NEt_3 (190 μL, 1.36 mmol) was added to a solution of the amine **25** (178 mg, 0.339 mmol) in dry CH_2Cl_2 at 0 °C. Methyl chloroformate (53 μL, 0.678 mmol) was added slowly added, and the reaction was allowed to warm to room temperature overnight. The resulting solution was diluted with CH_2Cl_2 and washed with water. The solvent was removed under reduced pressure, and the residue was purified by flash chromatography, eluting with 15% EtOAc/petroleum ether, to give the title compound as a colorless oil (148 mg, 77%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.87 (m, 9H), 1.08 (m, 6H), 1.31 (m, 6H), 1.38 (d, J = 6.4 Hz, 3H), 1.44 (d, J = 7.3 Hz, 3H), 1.50 (m, 6H), 2.88 (dd, J = 16, 8.8 Hz, 1H), 2.96 (dd, J = 16, 6.8 Hz, 1H), 3.67 (s, 3H), 3.71 (s, 3H), 3.72 (s, 3H), 4.16 (br m, 1H), 5.54 (br m, 1H), 6.41 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 11.1, 13.5, 22.0 (br), 24.0(br), 27.3, 29.2, 35.6, 46.5, 47.3, 52.3, 55.1, 62.6, 105.4, 120.0, 125.0 (br), 137.0, 156.1 (br), 162.2, 163.5. IR (KBr): 1699 cm^{-1}. HRMS: calcd for $C_{27}H_{47}NO_4Sn$ (M^+ − Bu) 512.1823, found 512.1823.

2-(4-Iodo-3,5-dimethoxy-phenyl)-(1,3)-dioxolane (26). A solution of the aldehyde **8** (3.42 g, 11.7 mmol), 1,2-ethanediol (0.98 mL, 17.6 mmol), and *p*-toluenesulfonic acid (40 mg, 0.21 mmol) in benzene (80 mL) was heated at reflux under Dean−Stark conditions for 20 h. After this time Et_2O (100 mL) and saturated aqueous $NaHCO_3$ solution were added. The organic extract was washed with water, and the solvent was removed under reduced pressure to give the title compound as a white solid (3.89 g, 99%). Mp: 82−83 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.91 (s, 3H), 4.00−4.17 (m, 4H), 5.80 (s, 1H), 6.64 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 56.6, 65.3, 78.2, 102.0, 103.1, 140.3, 159.4. HRMS: calcd for $C_{11}H_{13}IO_4$ (M^+) 335.9857, found 335.9859.

Tributyl-(4-(1,3)-dioxolan-2-yl-2,6-dimethoxy-phenyl)stannane (27). A solution of *t*-BuLi in pentane (1.5 M, 10.2 mL, 15.2 mmol) was added dropwise via syringe to a stirred solution of the iodide **26** (2.05 g, 6.10 mmol) in dry THF (60 mL) at −95 °C. The resulting solution was stirred at −95 °C for 15 min, then $ClSnBu_3$ (4.13 mL, 15.2 mmol) was slowly added, and the reaction was allowed to warm slowly to room temperature overnight. The resulting solution was poured into saturated aqueous $NaHCO_3$ solution and extracted with EtOAc (×4). Evaporation of the solvent under reduced pressure gave the crude product, which was purified by flash chromatography on alumina, eluting with 5% ethyl acetate/petroleum ether, to give the title compound as colorless oil (2.58 g, 85%). ^{1}H NMR (500 MHz, $CDCl_3$): δ ?0.87 (m, 9H), 1.01 (m, 6H), 1.30 (m, 6H), 1.48 (m, 6H), 3.75 (s, 3H), 4.00−4.17 (m, 4H), 5.80 (s, 1H), 6.62 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 11.2, 13.7, 27.3, 29.1, 55.1, 65.2, 100.9, 103.7, 117.8, 140.8, 165.1. HRMS: calcd for $C_{23}H_{40}O_4{}^{120}Sn$ (M^+ − Bu) 443.1245, found 443.1244.

4-[(1,3)-Dioxolan-2-yl]-2,6-dimethoxyphenyl Lead Triacetate (25). $Pb(OAc)_4$ (95%, 3.02 g) was protected from light and stirred under high vacuum for 30 min. A solution of the stannane **27** (2.69 g, 5.39 mmol) and $Hg(OAc)_2$ (86 mg, 0.27 mmol) in dry CH_2Cl_2 (55 mL) was added via cannula, and the reaction was stirred at room temperature for 24 h. After this time the solution was diluted with CH_2Cl_2 and rinsed through a plug of Celite. The solvent was removed under reduced pressure to give a residue, which was washed with petroleum ether (×4). The resulting solid was dried under high vacuum to give the title compound as a light yellow solid (2.98 g, 93%), which was used immediately in the next reaction. ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.08 (s, 9H), 3.90 (s, 6H), 4.03−4.10 (m, 4H), 5.81 (s, 1H), 6.82 (s, 2H).

3,5-Dimethoxy-4-(1-hydroxy-8-methoxy-3-methylnaphthalen-2-yl)benzaldehyde (28). Dry pyridine (1.34 mL) was added dropwise to a solution of the aryllead compound **25** (2.98 g, 5.02 mmol) and the naphthol **3** (0.945 g, 5.02 mmol) in dry CH_2Cl_2 (50 mL). The reaction was stirred at room temperature, protected from light, for 24 h. After this time saturated aqueous NH_4Cl solution was added, and the aqueous layer was extracted with EtOAc (×4). The combined organic extracts were washed with 1 M aqueous HCl solution. The solvent was removed under reduced pressure, and the residue was dissolved in THF (100 mL). A solution of 3% v/v aqueous H_2SO_4 solution (25 mL) was added, and the reaction was stirred vigorously for 1 h. The resulting solution was diluted with 1 M aqueous HCl solution and extracted with EtOAc (×4). Removal of the solvent under reduced pressure and purification by flash chromatography, eluting with 40% ethyl acetate/petroleum ether, gave the title compound as pale yellow solid (1.18 g, 67%). Mp: 196−197 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.09 (s, 3H), 3.81 (s, 6H), 3.98 (s, 3H), 6.71 (d, J = 7.8 Hz, 1H), 7.22 (s, 2H), 7.24 (s, 1H), 7.27 (m, 1H), 7.35 (d, J = 8.3 Hz, 1H), 9.41 (s, 1H), 10.01 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.1, 55.8, 56.1, 103.1, 105.3, 113.2, 116.0, 118.5, 121.1, 122.0, 125.5, 136.1, 137.1, 137.2, 150.7, 156.0, 158.5, 191.9. IR (KBr): 1697, 3500 cm^{-1}. HRMS: calcd for $C_{21}H_{20}O_5$ (M^+) 352.1311, found 352.1311.

(*E*)-3-(3,5-Dimethoxy-4-(8-methoxy-1-methoxymethoxy-3-methylnaphthalen-2-yl)-phenyl)prop-2-en-1-ol (30). (a) A solution of the naphthol **28** (1.18 g, 3.34 mmol) in dry THF (45 mL) was added to a suspension of prewashed NaH (0.160 g, 6.68 mmol) in dry THF (10 mL). The reaction was stirred for 1 h at room temperature, resulting in a turbid red solution. MOM-Cl (1.27 mL, 16.7 mmol) was added dropwise, and the reaction was stirred at room temperature overnight. The reaction was poured into saturated aqueous $NaHCO_3$ solution and extracted with EtOAc (×4). The solvent was removed under reduced pressure and the residue purified by flash chromatography, eluting with 50% EtOAc/petroleum ether, to give 3,5-dimethoxy-4-(8-methoxy-1-methoxymethoxy-3-methylnaphthalen-2-yl)benzaldehyde as a white solid (1.08 g, 81%). Mp: 177−178 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.09 (s, 3H), 2.80 (s, 3H), 3.79 (s, 6H), 3.95 (s, 3H), 4.86 (s, 2H), 6.80 (d, J = 6.8 Hz, 1H), 7.19 (s, 2H), 7.34 (dd, J = 8.3, 7.8 Hz, 1H), 7.38 (dd, J = 8.3, 1.5 Hz), 1H), 7.52 (s, 1H), 10.01 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.0, 55.9, 56.0, 56.1, 100.3, 104.8, 104.9, 118.6, 120.4, 122.9, 124.3, 126.0, 126.1, 136.1, 136.9, 137.1, 149.7, 155.8, 158.9. IR (KBr): 1693 cm^{-1}. HRMS: calcd for $C_{23}H_{24}O_6$ (M^+) 396.1573, found 396.1573.

(b) Triethyl phosphonoacetate (592 μL, 2.98 mmol) was added to a suspension of prewashed NaH (78 mg, 3.25 mmol) in dry benzene (8 mL) at 0 °C. The reaction was stirred for 15 min, and then a solution of the aldehyde (1.08 g, 2.71 mmol) in dry benzene (15 mL) was slowly added. The reaction was stirred for 1 h at 0 °C, warmed to room temperature, and stirred for a further 30 min, following which H_2O was added. The aqueous layer was extracted with EtOAc (×4) and the combined organic extracts were washed with H_2O (×2). Removal of the solvent under reduced pressure gave (*E*)-3-(3,5-dimethoxy-4-(8-methoxy-1-methoxymethoxy-3-methylnaphthalen-2-yl)-phenyl)acrylic acid ethyl ester as a white solid (1.26 g, 100%). Mp: 181−182 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.37 (t, J = 7.1 Hz, 3H), 2.12(s, 3H), 2.84 (s, 3H), 3.74 (s, 6H), 3.94 (s, 3H), 4.30 (q, J = 7.1 Hz, 2H), 4.86 (s, 2H), 6.50 (d, J = 16 Hz, 1H), 6.78 (d, J = 7.3 Hz, 1H), 6.83 (s, 2H), 7.32 (dd, J = 8.3, 7.3 Hz, 1H), 7.35 (d, J = 7.3 Hz, 1H), 7.51 (s, 1H), 7.73 (d, J = 16 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.1, 20.0, 55.6, 55.7, 55.9, 60.3, 100.0, 103.3, 104.7, 117.8, 118.3, 118.6, 120.3, 124.0, 125.7, 126.4, 134.9, 136.5, 136.7, 144.8, 149.6, 155.6, 158.4, 166.7. IR (KBr): 1709 cm^{-1}. HRMS: calcd for $C_{27}H_{30}O_7$ (M^+) 466.1992, found 466.1992.

(c) Neat DIBAL-H (1.00 mL, 5.61 mmol) was added dropwise to solution of the ester (1.05 g, 2.24 mmol) in dry toluene (25 mL) at −78 °C. The reaction was stirred for 15 min at this temperature. After this time EtOAc (100 mL) was added, and the solution was allowed to warm to room temperature. Saturated aqueous $NaHCO_3$ solution was added, and the solution swas tirred vigorously for 5 min, followed by filtration and separation of the layers. The aqueous layer was further extracted with EtOAc (×3), and the organic extracts combined. Removal of the solvent under reduced pressure and purification by flash chromatography, eluting with 60% EtOAc/petroleum ether, gave the title compound **30** as a white solid (844 mg, 89%). Mp: 154−155 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.11 (s, 3H), 2.87 (s, 3H), 3.72 (s, 6H), 3.94 (s, 3H), 4.36 (d, J = 4.9 Hz, 2H), 4.84 (s, 2H), 6.42 (m, 1H), 6.65 (d, J = 16 Hz, 1H), 6.69 (s, 2H), 6.77 (d, J = 6.8 Hz, 1H), 7.31 (m, 1H), 7.36 (d, J = 7.3 Hz, 1H), 7.50 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.1, 55.6, 55.7, 56.1, 63.1, 99.8, 101.9, 104.6, 115.2, 118.7, 120.3, 124.0, 125.6, 127.0, 128.5, 130.9, 136.6, 136.9, 137.5, 149.4, 155.6, 158.1. IR (KBr): 3500 cm^{-1}. HRMS: calcd for $C_{25}H_{28}O_6$ (M^+) 424.1886, found 424.1886.

(+)-(2*S*,3*R*)-{3-(3,5-Dimethoxy-4-(8-methoxy-1-methoxymethoxy-3-methyl-naphthalen-2-yl)-phenyl)-2,3-oxiranyl}-methanol (31). $Ti(O^iPr)_4$ (20 μL, 0.068 mmol) was added to a solution of diisopropyl-D-tartrate (19 mg, 0.081 mmol) and powdered 4 Å molecular sieves (40 mg) in dry CH_2Cl_2 (5 mL) at −20 °C. An anhydrous solution of TBHP in dry CH_2Cl_2 (6.1 M, 439 μL, 2.69 mmol) was added at a rate that maintained the internal temp at −20 °C. The reaction was stirred for 30 min at this temperature, following which a solution of the allylic alcohol **30** (568 mg, 1.34 mmol) in dry CH_2Cl_2 (6 mL), previously stirred over 4 Å sieves for 30 min, was added at a rate as to maintain the internal temperature between −15 and −20 °C. The reaction was stirred for 5 h at −20 °C, and then 10% aqueous NaOH solution, saturated with brine, was added, followed by Et_2O (15 mL). The solution was warmed to room temperature, and then dry $MgSO_4$ (2.6 g) and Celite (0.33 g) were added. The suspension was stirred for 15 min, diluted with CH_2Cl_2, and filtered through a pad of Celite, eluting with CH_2Cl_2. Removal of the solvent under reduced pressure and purification by flash chromatography, eluting with 60% EtOAc/petroleum ether, gave the title compound as a white solid (474 mg, 80%, 90% de). Recrystallization from toluene/petroleum ether gave material (372 mg, 63%) of >95% de. $[\alpha]^{20}_D$ +13.8 (*c* 3.99, $CHCl_3$). Mp: 174−175 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.83 (m, 3H), 2.09 (s, 3H), 2.86 (s, 3H), 3.25 (m, 1H), 3.71 (s, 6H), 3.85 (m, 1H), 3.94 (s, 3H), 3.99 (d, J = 2.0 Hz, 1H), 4.09 (m, 1H), 4.83 (s, 2H), 6.585 (s, 1H), 6.590 (s, 1H), 6.78 (d, J = 7.3 Hz, 1H), 7.31 (m, 1H), 7.36 (d, J = 7.3 Hz, 1H), 7.50 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.1, 55.7, 56.0, 56.1, 61.20, 61.25, 62.5, 99.8, 100.8, 104.7, 115.5, 118.7, 120.3, 124.1, 125.6, 126.8, 136.6, 136.8, 137.9, 149.4, 155.6, 158.2. IR (KBr): 3485 cm^{-1}. HRMS: electrospray calcd for $C_{25}H_{28}O_7$ (M^+ + Cl) 475.1524, found 475.1524.

(+)-(2*S*,3*R*)-Toluene-4-sulfonic Acid 3-(3,5-Dimethoxy-4-(8-methoxy-1-methoxy-methoxy-3-methyl-naphthalen-2-yl)-phenyl)-2,3-oxiranylmethyl Ester (33). Dry NEt_3 (433 μL, 3.12 mmol) was added dropwise to a solution of the epoxy alcohol **31** (275 mg, 0.623 mmol) and DMAP (76 mg, 0.623 mmol) in dry CH_2Cl_2 (6 mL) at 0 °C. A solution of TsCl (131 mg, 0.686 mmol) in dry CH_2Cl_2 (2 mL) was slowly added, and the reaction was stirred at 0 °C for 1 h. Saturated aqueous $NaHCO_3$ solution was added, and the product was extracted with EtOAc (×4). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ solution. Removal of the solvent under reduced pressure gave the title compound as a fluffy white solid (307 mg, 83%). $[\alpha]^{20}_D$ +29.3 (*c* 2.39, $CHCl_3$). Mp: 80−81 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.07 (s, 3H), 2.47 (s, 3H), 2.84 (s, 3H), 3.29 (m, 1H), 3.685 and 3.687 (s, 3H), 3.84 (d, J = 2.0 Hz, 2H), 3.94 (s, 3H), 4.16 (dd, J = 11, 5.4 Hz, 1H), 4.39 (dd, J = 11, 3.4 Hz, 1H), 4.82 (s, 2H), 6.51 (s, 1H), 6.53 (s, 1H), 6.77 (d, J = 7.8 Hz, 1H), 7.31 (t, J = 7.8 Hz, 1H), 7.36 (d, J = 7.8 Hz), 7.38 (d, J = 8.3 Hz, 2H), 7.49 (s, 1H), 7.85 (d, J = 8.3 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.1, 21.5, 55.7, 56.1, 56.6, 58.6, 69.2, 99.9, 100.6, 101.0, 104.7, 116.0, 118.7, 120.3, 124.1, 125.7, 126.7, 127.8, 129.9, 132.4, 136.6, 136.7, 136.8, 145.1, 149.6, 155.7, 158.3, 158.4. HRMS: calcd for $C_{32}H_{35}O_9$ (M^+ + H) 595.2002, found 595.1981.

(−)-(2*R*)-1-(3,5-Dimethoxy-4-(8-methoxy-1-methoxymethoxy-3-methylnaphthalen-2-yl)-phenyl)-propan-2-ol (32). A solution of $LiAlH_4$ (1.0 M, 1.55 mL, 1.55 mmol) in THF was added dropwise to a solution of the tosylate **33** (307 mg, 0.516 mmol) in dry Et_2O (50 mL) at 0 °C. The reaction was stirred for 2 h at 0 °C, then 30 min at room temperature. The resulting solution was diluted with EtOAc and washed with saturated aqueous $NaHCO_3$ solution. Removal of the solvent under reduced pressure and purification by flash chromatography, eluting with 80% EtOAc/petroleum ether, gave the title compound as a fluffy white solid (206 mg, 94%). $[\alpha]^{20}_D$ −14.0 (*c* 4.10, $CHCl_3$). Mp: 94−95 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.29 (d, J = 6.4 Hz, 3H), 2.11 (s, 3H), 2.73 (dd, J = 13, 8.3 Hz, 1H), 2.85 (dd, J = 13, 4.9 Hz, 1H), 2.88 (s, 3H), 3.70 (s, 6H), 3.94 (s, 3H), 4.07 (m, 1H), 4.84 (s, 2H), 6.51 (s, 2H), 6.78 (d, J = 7.3 Hz, 1H), 7.31 (m, 1H), 7.36 (d, J = 7.8 Hz, 1H), 7.51 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.2, 22.6, 46.5, 55.8, 55.9, 56.1, 68.9, 99.9, 104.6, 104.7, 104.8, 113.9, 118.9, 120.4, 124.1, 125.6, 127.1, 136.7, 137.1, 139.5, 149.5, 155.8, 158.2, 158.3. IR (film): 3427 cm^{-1}. HRMS: calcd for $C_{25}H_{30}O_6$ (M^+) 426.2042, found 426.2042.

(+)-(1*S*)-2-(3,5-Dimethoxy-4-(8-methoxy-1-methoxymethoxy-3-methylnaphthalen-2-yl)-phenyl)-1-methylethylamine (29). (a) DEAD (90 μL, 0.570 mmol) was added to a solution of the alcohol **32** (194 mg, 0.456 mmol), PPh_3 (0.149 g, 0.570 mmol), and phthalimide (84 mg, 0.570 mmol) in dry THF (6 mL) at 0 °C. The reaction was protected from light and allowed to warm to room temperature overnight. Saturated aqueous $NaHCO_3$ solution was added, and the product extracted with EtOAc (×4). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ solution. The solvent was removed under reduced pressure, and the residue was passed through a short column of alumina, eluting with 25% EtOAc/petroleum ether. Removal of the solvent under reduced pressure and purification of the residue by flash chromatography, eluting with 40% EtOAc/petroleum ether, gave (1*S*)-2-{2-(3,5-dimethoxy-4-(8-methoxy-1-methoxymethoxy-3-methyl-naphthalen-2-yl)-phenyl)-1-methylethyl}isoindole-1,3-dione as a white solid (207 mg, 82%). $[\alpha]^{20}_D$ +120 (*c* 3.05, $CHCl_3$). Mp: 82−85 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.60 (d, J = 5.9 Hz, 3H), 1.88 (s, 3H), 2.61 (s, 3H), 3.12 (dd, J = 14, 5.9 Hz, 1H), 3.43 (dd, J = 11, 14 Hz, 1H), 3.54 (s, 3H), 3.60 (s, 3H), 3.90 (s, 3H), 4.70−4.80 (overlapping m, 2H and 1H), 6.44 (s, 1H), 6.47 (s, 1H), 6.74 (d, J = 7.3 Hz, 1H), 7.27 (dd, J = 7.8, 7.3 Hz, 1H), 7.32 (d, J = 7.8 Hz, 1H), 7.43 (s, 1H), 7.67 (m, 2H), 7.75 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 18.5, 19.8, 40.1, 48.2, 55.5, 55.6, 55.7, 55.8, 99.6, 104.0, 104.4, 104.5, 113.6, 118.6, 120.2, 122.7, 123.9, 125.4, 126.9, 131.6, 133.7, 136.5, 136.9, 139.2, 149.4, 155.6, 157.7, 157.8, 168.1. IR (KBr): 1709, 1770 cm^{-1}. HRMS: calcd for $C_{33}H_{33}O_7$ (M^+) 555.2257, found 555.2257.

(b) A 40% aqueous $MeNH_2$ soution (8 mL) was added to a solution of the phthalimide (234 mg, 0.420 mmol) in abs EtOH (10 mL). The reaction was heated at reflux for 1 h, following which most of the EtOH was removed under reduced pressure. Saturated aqueous $NaHCO_3$ solution was added, and the product was extracted with EtOAc (×4). Removal of the solvent under reduced pressure gave amine (**29**) as a white solid (179 mg, 100%). $[\alpha]^{20}_D$ +13.8 (*c* 3.58, $CHCl_3$). Mp: 45−46 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.18 (d, J = 6.4 Hz, 3H), 2.11 (s, 3H), 2.60 (dd, J = 13, 8.3 Hz, 1H), 2.78 (dd, J = 13, 5.4 Hz, 1H), 2.88 (s, 3H), 3.26 (m, 1H), 3.70 (s, 6H), 3.94 (s, 3H), 4.84 (s, 2H), 6.49 (s, 1H), 6.50 (s, 1H), 6.77 (d, J = 7.3 Hz, 1H), 7.30 (m, 1H), 7.36 (d, J = 7.8 Hz, 1H), 7.50 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.1, 23.0, 46.8, 48.4, 55.6, 55.7, 56.0, 99.7, 104.4, 104.5, 104.6, 113.5, 118.8, 120.3, 124.0, 125.5, 127.1, 136.5, 137.0, 140.4, 149.4, 155.7, 157.9, 158.0.

IR (KBr): 3416, 3551 cm^{-1}. HRMS: electrospray calcd for $C_{25}H_{31}NO_5$ ($M^+ - CH_3OH$) 393.1940, found 393.1940.

(+)-(1*S*)-*N*-{2-(3,5-Dimethoxy-4-(8-methoxy-1-methoxymethoxy-3-methyl-naphthalen-2-yl)-phenyl)-1-methylethyl}-acetamide (34). Dry NEt_3 (129 μL, 0.924 mmol) was added to a solution of the amine **29** (179 mg, 0.420 mmol) in dry CH_2Cl_2 at 0 °C. Freshly distilled AcCl (36 μL, 0.504 mmol) was added dropwise, and the reaction was allowed to warm slowly to room temperature overnight. The resulting solution was diluted with CH_2Cl_2 and washed with saturated aqueous $NaHCO_3$ solution. Removal of the solvent under reduced pressure gave the title compound as a white solid (191 mg, 97%). $[\alpha]^{20}_D$ +16.7 (*c* 1.10, $CHCl_3$). Mp: 200−202 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ1.15(d, J = 6.8 Hz, 3H), 1.96 (s, 3H), 2.09 (s, 3H), 2.68 (dd, J = 14, 7.8 Hz, 1H), 2.87 (s, 3H), 2.94 (dd, J = 13, 5.4 Hz, 1H), 3.69 (s, 3H), 3.70 (s, 3H), 3.94 (s, 3H), 4.30 (m, 1H), 4.84 (m, 2H), 5.35 (d, J = 7.8 Hz, 1H), 6.46 (s, 1H) and 6.49 (s, 1H), 6.77 (d, J = 6.8 Hz, 1H), 7.31 (m, 1H), 7.36 (d, J = 7.3 Hz, 1H), 7.50 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.7, 20.1, 23.3, 43.2, 46.2, 55.7, 55.7, 56.1, 83.2, 99.8, 104.6, 104.6, 104.7, 113.7, 118.8, 120.3, 124.0, 125.5, 127.1, 136.6, 137.0, 139.2, 149.4, 155.7, 157.9, 158.0, 169.2. IR (KBr): 1568, 1636, 3061, 3242, 3416 cm^{-1}. HRMS: calcd for $C_{27}H_{33}NO_6$ (M^+) 467.2308, found 467.2308.

(−)-*M*-(3*S*)-2-(6,8-Dimethoxy-1,3-dimethyl-3,4-dihydroisoquinolin-7-yl)-8-methoxy-3-methyl-naphthalen-1-ol (1a) and (+)-*P*-atropisomer (35). 2,4,6-Collidine (58 μL, 0.437 mmol) was added to a solution of the amide **34** (186 mg, 0.397 mmol) in dry CH_3CN (2 mL). Freshly distilled $POCl_3$ (41 μL, 0.437 mmol) was added, and the reaction was heated at reflux for 4 h. The resulting solution was cooled to room temperature, poured into saturated aqueous $NaHCO_3$ solution, and extracted with EtOAc (×4). Removal of the solvent under reduced pressure and purification by flash chromatography on alumina, eluting with 50% EtOAc/petroleum ether, gave the title compound as a 1:1 mixture of diastereoisomers (119 mg, 74%). The mixture was crystallized from toluene/petroleum ether. Concentration of the mother liquor and repeated crystallization gave a further crop of crystals. The combined crops of crystals from above were recrystallized from toluene/petroleum ether to give ancistrocladidine **(1a)** as a single diastereoisomer as determined by ^{1}H NMR spectroscopy. $[\alpha]^{20}_D$ −136 (*c* 1.84, $CHCl_3$). Mp: 253−254 °C dec (lit.[9a] 245−247 °C dec; lit.[9b] 255−258 °C dec). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.42 (d, J = 6.8 Hz, 3H), 2.16 (s, 3H), 2.45 (dd, J = 15, 13 Hz, 1H), 2.48 (d, J = 2.0 Hz, 3H), 2.68 (dd, J = 15, 4.4 Hz, 1H), 3.37 (s, 3H), 3.43 (m, 1H), 3.75 (s, 3H), 4.01 (s, 3H), 6.63 (s, 1H), 6.72 (d, J = 7.3 Hz, 1H), 7.25 (s, 1H), 7.28 (dd, J = 8.3, 7.3 Hz, 1H), 7.36 (d, J = 8.3 Hz, 1H), 9.61 (s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 20.5, 22.0, 26.9, 35.2, 51.5, 55.8, 56.0, 60.9, 103.1, 105.9, 113.3, 116.9, 117.1, 118.7, 118.8, 121.1, 125.6, 136.2, 137.8, 141.3, 151.3, 156.1, 157.7, 159.2, 163.1. IR (KBr): 3361 cm^{-1}. HRMS: calcd for $C_{25}H_{27}NO_4$ (M^+) 405.1940, found 405.1940.

Concentration of the mother liquor gave atropisomer **35** as a colorless gum shown to be 90% diastereomerically pure by ^{1}H NMR spectroscopy. $[\alpha]^{20}_D$ +40.4 (*c* 0.292, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.44 (d, J = 6.8 Hz, 3H), 2.19 (s, 3H), 2.43 (dd, J = 15, 14 Hz, 1H), 2.47 (d, J = 2.0 Hz, 3H), 2.67 (dd, J = 16, 4.4 Hz, 1H), 3.41 (s, 3H), 3.41 (m, 1H), 3.76 (s, 3H), 4.01 (s, 3H), 6.64 (s, 1H), 6.73 (d, J = 7.3 Hz, 1H), 7.27 (s, 1H), 7.29 (dd, J = 8.3, 7.3 Hz, 1H), 7.37 (d, J = 8.3 Hz, 1H), 9.59 (s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 20.6, 22.4, 26.6, 35.3, 51.5, 55.9, 56.0, 61.2, 103.1, 105.9, 113.3, 117.0, 117.3, 118.8, 118.9, 121.3, 125.6, 136.2, 138.0, 141.5, 151.1, 156.1, 157.7, 159.3, 163.2. IR (film): 3381 cm^{-1}. HRMS: calcd for $C_{25}H_{27}NO_4$ (M^+) 405.1940, found 405.1940.

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Supporting Information Available: Characterization data for natural ancistrocladidine, synthetic ancistrocladidine, and atropisomer **35**. Experimental details on the determination of diastereomeric excess. Copies of ^{1}H and ^{13}C NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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