Convergent Synthesis of Naphthylisoquinoline Alkaloids: Total Synthesis of (+)-*O*-Methylancistrocline

Phung Chau, Ivona R. Czuba, and Mark A. Rizzacasa*

School of Chemistry, The University of Melbourne, Parkville, Victoria 3052, Australia

Gerhard Bringmann, Klaus-Peter Gulden, and Manuela Schäffer

Institut für Organische Chemie der Universität, Am Hubland, D-97074 Würzburg, Federal Republic of Germany

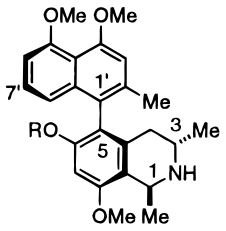
Received April 18, 1996[⊗]

A highly convergent synthesis of the methyl ether derivative **2a** of the naphthylisoquinoline alkaloid ancistrocline (**2**) is described. The key step involves a stereoselective biaryl coupling between the chiral oxazoline **3** and the Grignard reagent **4** derived from the optically active tetrahydroisoquinoline **8**. The atropisomeric mixture was then converted to the separable acetamides **11** and **12**, which were obtained in a ratio of 16:84 and an overall yield of 32% for the three steps. The major atropisomer **12** was then converted into *O*-methylancistrocline (**2a**), which was identical to a semisynthetic sample derived from the related alkaloid ancistrocladinine (**14**).

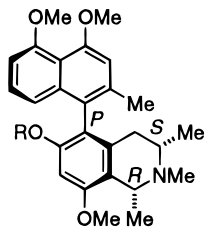
Introduction

The naphthylisoquinoline alkaloids are a group of unique natural products that are found exclusively in two plant families.[1] These compounds are unusual in that they appear to originate, biosynthetically, from the acetate−polymalonate pathway and not from amino acids.[1] Examples include ancistrocladine (**1**),[2] the first naphthylisoquinoline alkaloid to be identified, *O*-methylancistrocladine (**1a**),[3] and ancistrocline (**2**),[4,5] which has been shown to possess some antitumor activity.

The main focus of the synthesis of these natural products is the stereoselective construction of the atropisomeric biaryl linkages by both intra- and intermolecular approaches.[6] To date, the intramolecular approach has been more convergent in that the tetrahydroisoquinoline segments are completed prior to formation of the biaryl linkage. This methodology was utilized by Bringmann in the first total syntheses of (−)-ancistrocladine (**1**)[7] and (+)-ancistrocline (**2**)[8] and has been further expanded by elegant atropdiastereoselective ring-opening of bridged axially prostereogenic lactones.[9]



1 R = H
1a R = Me



2 R = H
2a R = Me

Although a number of intermolecular approaches are now available for the construction of unsymmetrical optically active biaryls,[10] the chiral oxazoline-mediated coupling reaction pioneered by Meyers[11] has become a method of choice for the asymmetric synthesis of a number naphthylisoquinoline alkaloids.[12] More recently, we reported[13] a formal total synthesis of (+)-*O*-methylancistrocladine (**1a**) in which the chiral biaryl linkage was constructed with high stereoselectivity using the oxazoline approach (Scheme 1). The observed stereocontrol can be explained by considering the transition state **A**‡ in which the magnesium atom chelates preferentially to the *o*-methoxy group rather than the $CH_2OTBDMS$ substituent while the isopropyl group on the oxazoline controls the direction of attack of the Grignard reagent.[14] However, the isoquinoline ring still remains to be constructed and this process involves numerous steps.[12]

* Author to whom correspondence should be addressed. Fax: 61 3 9347 5180. E-mail: m.rizzacasa@chemistry.unimelb.edu.au.

[⊗] Abstract published in *Advance ACS Abstracts,* September 1, 1996.

(1) Bringmann, G.; Pokorny, F. In *The Alkaloids*; Cordell, G., Ed.; Academic Press: New York, 1995; Vol. 46, pp 127−271.

(2) Govindachari, T. R.; Parthasarathy, P. C. *Tetrahedron* **1971**, *27*, 1013.

(3) Foucher, J. P.; Pousset, J. L.; Cavé, A.; Bouquet, A.; Paris, R. *Plantes Méd. Phytothér.* **1975**, *9*, 87. Desai, H. K.; Gawad, D. H.; Govindachari, T. R.; Joshi, B. S.; Parthasarathy, P. C.; Ramachandran, K. S.; Ravindranath, K. R.; Sidhaye, A. R.; Viswanathan, N. *Indian J. Chem.* **1976**, *14B*, 473.

(4) Chen, Z. X.; Wang, B. D.; Quin, K. W.; Zhang, B. E.; Su, Q. L.; Lin, Q. C. *Yaoxue Xuebao* **1981**, *16*, 519.

(5) Bringmann, G.; Kinzinger, L. *Phytochemistry* **1992**, *31*, 3297.

(6) Bringmann, G.; Walter, R.; Weirich, R. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 977.

(7) Bringmann, G.; Jansen, J. R.; Rink, H.-P. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 913.

(8) Bringmann, G.; Kinzinger, L.; Busse, H.; Zhao, C. *Planta Med.* **1992**, *58*, 704.

(9) Bringmann, G.; Reuscher, H. *Tetrahedron Lett.* **1989**, *30*, 5249. Bringmann, G.; Reuscher, H. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 1672. Bringmann, G.; Jansen, J. R. *Synthesis* **1991**, 825. Bringmann, G.; Hartung, T. *Synthesis* **1992**, 233. Bringmann, G.; Vitt, D. *J. Org. Chem.* **1995**, *60*, 7674.

(10) Recent examples include: Aryl imines (with chiral catalyst): Shindo, M.; Koga, K.; Tomioka, K. *J. Am. Chem. Soc.* **1992**, *114*, 8732. Chiral sulfoxides: Baker, R. W.; Pocock, G. R.; Sargent, M. V.; Twiss, E. *Tetrahedron Asymmetry* **1993**, *4*, 2423. 2-Menthoxybenzoates: Miyano, S.; Koike, N.; Hattori, T. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2273. Planar chiral tricarbonyl(arene)chromium complexes: Uemura, M.; Watanabe, T.; Kamikawa, K. *J. Org. Chem.* **1996**, *61*, 1375.

(11) Meyers, A. I.; Lutomski, K. A. *J. Am. Chem. Soc.* **1982**, *104*, 879. Meyers, A. I.; Himmelsbach, R. J. *J. Am. Chem. Soc.* **1985**, *107*, 682. Meyers, A. I.; Flisak, J. R.; Aitken, R. A. *J. Am. Chem. Soc.* **1987**, *109*, 5446. Warshawsky, A. M.; Meyers, A. I. *J. Am. Chem. Soc.* **1990**, *112*, 8090. Meyers, A. I.; Meier, A.; Rawson, D. J. *Tetrahedron Lett.* **1992**, *33*, 853. For a comprehensive account on the chemistry of 2-oxazolines see: Gant, J. G.; Meyers, A. I. *Tetrahedron* **1994**, 2291.

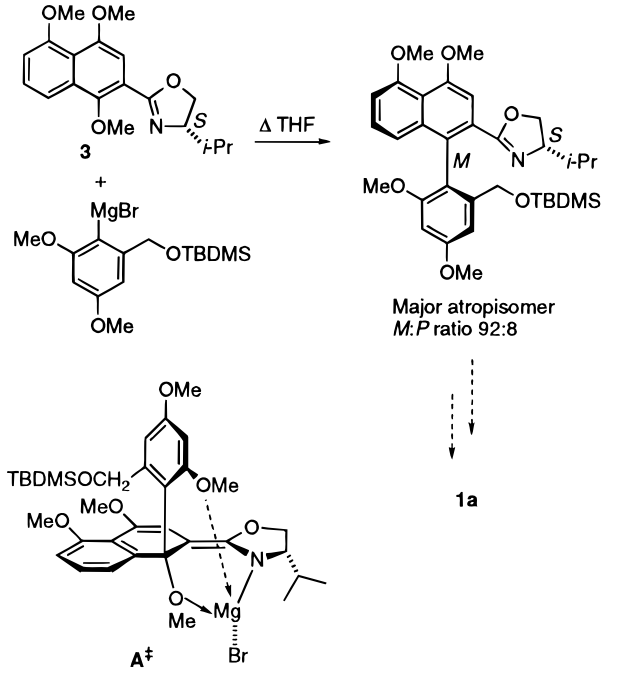
(12) Rizzacasa, M. A.; Sargent, M. V. *J. Chem. Soc., Perkin Trans. 1* **1991**, 845. Rizzacasa, M. A.; Sargent, M. V. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2773. Gable, R. W.; Martin, R. L.; Rizzacasa, M. A. *Aust. J. Chem.* **1995**, *48*, 2013.

(13) Leighton, B. L.; Rizzacasa, M. A. *J. Org. Chem.* **1995**, *60*, 5702.

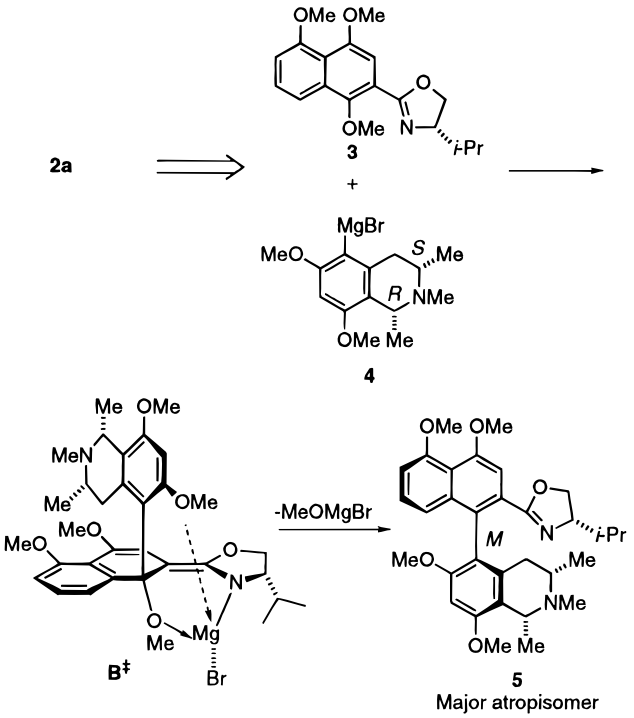
(14) Moorlag, H.; Meyers, A. I. *Tetrahedron Lett.* **1993**, *34*, 6989.

S0022-3263(96)00711-6 CCC: $12.00

Scheme 1



Scheme 2



With a view to developing a highly convergent approach using an *intermolecular* strategy, we envisaged that alkaloids such as **1** and **2** could be constructed stereoselectively by a coupling between a chiral naphthyloxazoline and a Grignard reagent derived from a suitably substituted bromoisoquinoline. In order to rapidly test this proposal we targeted the derivative *O*-methylancistrocline (**2a**) since the requisite isoquinoline segment would be far more accessible. It was hoped that a coupling between the known chiral oxazoline **3**[13] and the Grignard reagent **4** would proceed by an intermediate such as **B**‡ to give the desired atropisomer **5** as the major product (Scheme 2). With the isoquinoline ring complete, a simple conversion of the chiral oxazoline to a methyl group would provide **2a**.

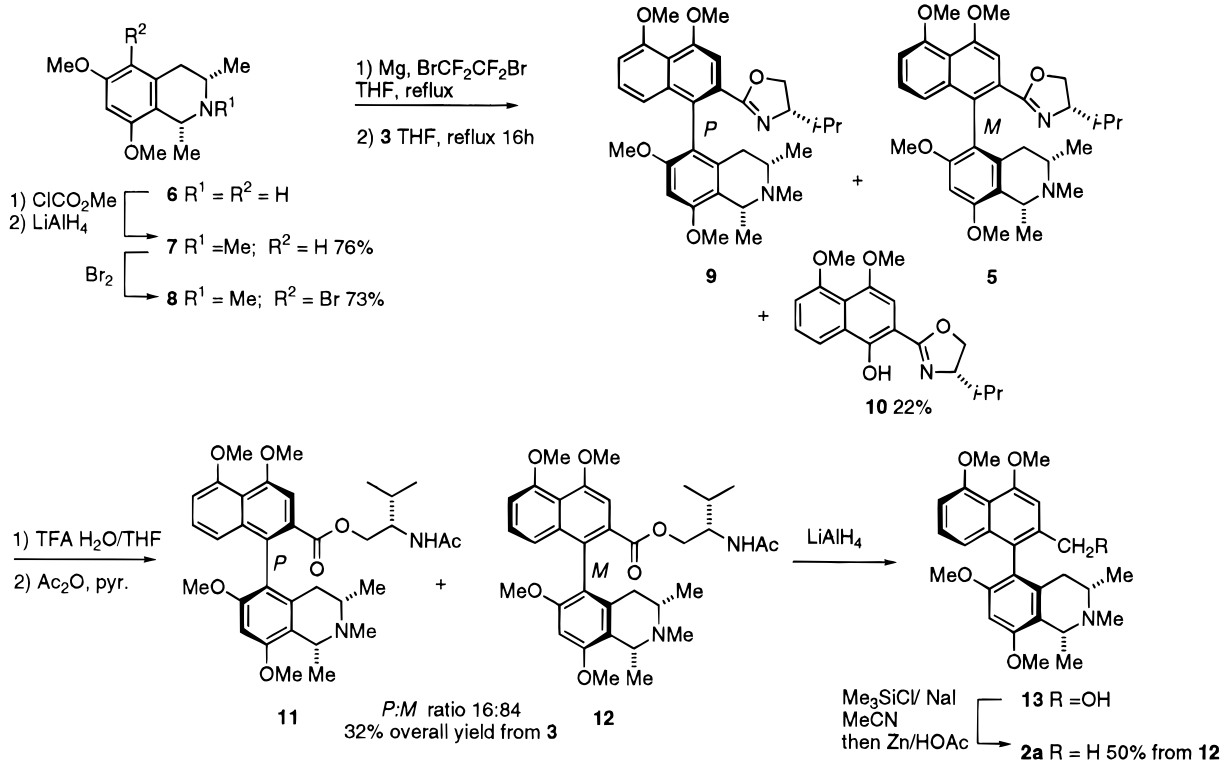
Results and Discussion

The route began with the known *cis*-1,3-dimethyltetrahydroisoquinoline **6**,[15] which is readily available in homochiral form (Scheme 3). Treatment of **6** with methyl chloroformate followed by reduction with $LiAlH_4$ installed the *N*-methyl group to provide **7**. Subsequent bromination then gave the required bromoisoquinoline **8**, which has also been prepared in racemic form.[16] Initial attempts to generate the Grignard reagent of **8** using magnesium metal and catalytic I_2 failed, and we postulated that the amine functionality was hindering the reactivity of the magnesium.[17] Similar difficulties in generating Grignard reagents from bromoindoles have been reported, but these were overcome using 1,2-dibromotetrafluoroethane as an entrainer.[18] When a mixture of the bromoisoquinoline **8** (1 equiv) and magnesium turnings (2 equiv) in THF was treated with 1,2-dibromotetrafluoroethane (1 equiv) the Grignard reagent **4** was formed and allowed to react with the oxazoline **3**[13] in refluxing THF. Examination of the crude product by ^{1}H NMR spectroscopy revealed that coupling had taken place (diagnostic resonance due to shielded C-6 methoxy group at δ 3.56) and that one atropisomer had predominated (ratio 82:18 by integration of the signals due to the C-7 protons). Silica gel chromatography gave a higher R_f material **10**, resulting from demethylation of **3** by $MgBr_2$[12] and a lower R_f mixture consisting of compound **7** and the biaryls **9** and **5**. This lower R_f mixture was then subjected to acid treatment (TFA, H_2O/THF)[14] followed by immediate acetylation to provide acetamides **11** and **12**, which were easily separated by flash chromatography.

Although the overall yield of **11** and **12** (32% for three steps) was modest and could not be improved, the byproduct **10** could easily be recycled to **3** by methylation.[12] The major isomer **12** was tentatively assigned the *M* configuration[19] about the biaryl linkage on the basis of previous observations,[13,14,20] which was indeed confirmed on the level of the final target molecule **2a** (see below). Of note was the fact that the ^{1}H NMR spectra of **12** and subsequent compounds displayed considerable broadening of the signals due to the protons in close proximity to the isoquinoline nitrogen unless the $CDCl_3$ solutions were first treated with K_2CO_3 to remove all traces of acid. Reduction of **12** provided alcohol **13**, which was converted into the corresponding mesylate. All attempts at further reduction ($LiAlH_4$ or $LiBEt_3H$) failed to provide **2a**. Finally, one pot hydroxy−halogen exchange−Zn/AcOH reduction[21] of **13** furnished *O*-methylancistrocline (**2a**). For rapid confirmation of the absolute

(15) Bringmann, G.; Weirich, R.; Reuscher, H.; Jansen, J. R.; Kinzinger, L.; Ortmann, T. *Liebigs Ann. Chem.* **1993**, 877.
(16) Rizzacasa, M. A.; Sargent, M. V. *Aust. J. Chem.* **1990**, *43*, 79.
(17) Lai, Y.-H. *Synthesis* **1981**, 585.
(18) Meyers, A. I.; Hutchings, R. H. *Tetrahedron Lett.* **1993**, *34*, 6185. Meyers, A. I.; Hutchings, R. H. *J. Org. Chem.* **1996**, *61*, 1004.
(19) More recently, the use of *M* and *P* (rather than *R* and *S*) descriptors has been recommended for the denotion of axial configurations; see: Helmchen, G. In *Houben-Weyl, Methods in Organic Chemistry*, 4th ed.; Helmchen, G., Hoffmann, R. W., Mulzer, J., Schaumann, E., Eds.; Thieme: Stuttgart, 1995; Vol. E21a, p 13.
(20) In a preliminary study on the coupling reaction using racemic bromide **8** with optically pure oxazoline **3**, acetamide **12** and 1,3-*epi*-**12** were the major atropisomers (*M* configured) isolated. This result demonstrated that the chirality at C-1 and -3 of the isoquinoline ring appears to have little, if any, influence on the stereoselectivity of the coupling. Chau, P.; Rizzacasa, M. A. Unpublished results.
(21) Morita, T.; Okamoto, Y.; Sakurai, H. *Synthesis* **1981**, 32. Rizzacasa, M. A.; Sargent, M. V. *J. Chem. Soc., Perkin Trans. 1* **1991**, 841.

Scheme 3

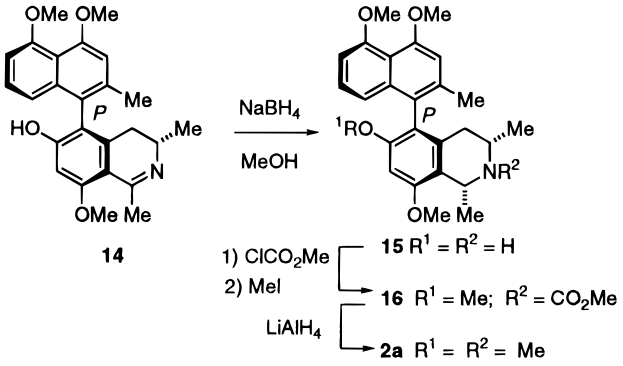


configurations at the stereocentres and at the axis, the synthetic compound **2a** was investigated using degradative and CD methods previously introduced for naphthylisoquinoline analysis.[1] Also, synthetic **2a** was found to be identical to semisynthetic **2a** prepared from an authentic sample of the related alkaloid ancistrocladinine (**14**)[22] as detailed below.

Ruthenium-mediated oxidative degradation[23] of **2a** followed by Mosher-type derivatization and GC-analysis provided (*S*)-*N*-methyl-3-aminobutyic acid, clearly indicating the 3*S*-configuration in **2a**. This configuration was further confirmed by the identification of the (*S*)-*N*-unsubstituted 3-aminobutyric acid arising from an additional *C*,*N*-bond cleavage. As to C-1, the (*R*)-*N*-methylalanine and (*R*)-alanine were formed in agreement with the proposed 1*R*-configuration in the synthetic compound.

To investigate the absolute configuration at the biaryl axis, we compared the CD spectrum calculated for the proposed absolute stereostructure **2a** with the experimental spectrum obtained for the synthetic product.[24] The conformational space of **2a** was investigated by varying the dihedral angle at the stereogenic axis and at the 8-*O*-methyl group using *AdaptivSearch*, a novel scanning mode for energy hypersurfaces recently developed.[25] For all the conformations within 1.5 kcal mol^{-1} of the absolute minimum of **2a**, single CD spectra were calculated and added in a Boltzmann-weighted manner to give the theoretical overall spectrum. The calculated spectrum (Figure 1a) compared very well to the experimental spectrum of synthetic **2a** (Figure 1b) when the expected[24] bathochromic shift of *ca.* $\Delta\lambda = 13$ nm was taken into account.

Scheme 4



The semisynthesis of **2a** began with $NaBH_4$ reduction[5,22] of ancistrocladinine **14** to provide isoancistrocladine (**15**), which upon treatment with methyl chloroformate and $NaHCO_3$ followed by *O*-methylation gave the carbamate **16** (Scheme 4). Reduction with $LiAlH_4$ provided semisynthetic **2a**, which was identical to the synthetic material by all the usual criteria.

Conclusion

In conclusion, a highly convergent synthesis of *O*-methylancistrocline (**2a**) has been achieved in a stereoselective manner. Since chiral 1,3-dimethyltetrahydroisoquinolines are now readily available,[15] this methodology can easily be utilized for the synthesis of other members of this alkaloid family.

(22) Govindachari, T. R.; Parthasarathy, P. C.; Desai, H. K. *Indian J. Chem.* **1971**, *9*, 1421.
(23) Bringmann, G.; Geuder, T.; Rübenacker, M.; Zagst, R. *Phytochemistry* **1991**, *30*, 2067. Bringmann, G.; God, R.; Schäffer, M. *Phytochemistry* **1996**, in press.
(24) Bringmann, G.; Gulden, K.-P.; Busse, H.; Fleischhauer, J.; Kramer, B.; Zobel, E. *Tetrahedron* **1993**, *49*, 3305. Bringmann, G.; Gulden, K.-P.; Hallock, Y. F.; Manfredi, K. P.; Cardellina, J. H., II; Boyd, M. R.; Kramer, B.; Fleischhauer, J. *Tetrahedron* **1994**, *50*, 7807. Hallock, Y. F.; Cardellina, J. H., II; Kornek, T.; Gulden, K.-P.; Bringmann, G.; Boyd, M. R. *Tetrahedron Lett.* **1995**, *36*, 4753.
(25) Bringmann, G.; Gulden, K.-P.; Vitt, D.; Birken, K.; Helf, C. *J. Mol. Model.* **1995**, *1*, 153.

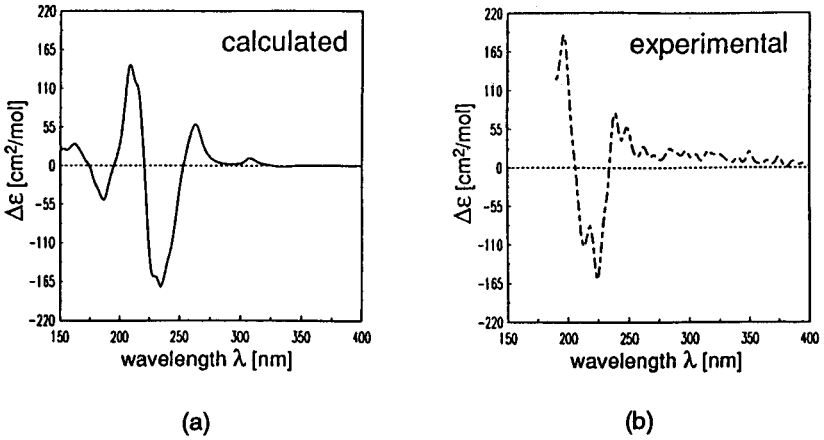


Figure 1. Calculated (a) and experimental (b) CD spectra of *O*-methylancistrocline (**2a**).

Experimental Section

^{1}H NMR (300 MHz) and proton-decoupled ^{13}C NMR spectra (75.5 MHz) were recorded for K_2CO_3–treated deuteriochloroform solutions with residual chloroform as internal standard. Authentic ancistrocladinine was available from previous synthetic and isolation work.[1] Experimental CD spectra were recorded in ethanolic solution at room temperature. Other general methods have been given previously.[13]

(+)-(1*R*,3*S*)-6,8-Dimethoxy-1,2,3-trimethyl-1,2,3,4-tetrahydroisoquinoline (7). To a solution of the tetrahydroisoquinoline **6**[15] (4.41 g, 20.0 mmol) in CH_2Cl_2 (129 mL) was added $NaHCO_3$ (8.9 g) and methyl chloroformate (3.30 mL, 42.7 mmol) at rt, and the mixture was stirred under a nitrogen atmosphere overnight. The ppt was removed by filtration, and the filtrate was evaporated to give a yellow oil that was chromatographed on silica gel with 20% EtOAc/petroleum ether as eluent to give the carbamate (5.01 g, 90%) as an oil. To a solution of the carbamate (4.82 g, 17.3 mmol) in dry THF (182 mL) was added $LiAlH_4$ (2.70 g, 71.1 mmol), and the mixture was heated at reflux under nitrogen for 4 h and then cooled to 0 °C. Aqueous NaOH (10 M) was added until coagulation ceased, and the precipitated salts were removed by filtration. Concentration of the filtrate provided the crude product, which was purified by distillation (Kugelrohr) to give the isoquinoline **7** (3.75 g, 92%) as a pale yellow oil: $[\alpha]^{19}_D$ +120.0° (*c* 1.08, $CHCl_3$); ^{1}H NMR δ 1.21 (d, J = 6.2 Hz, 3H), 1.36 (d, J = 6.3 Hz, 3H), 2.42 (ddq, J = 10.2, 6.2, 2.7 Hz, 1H), 2.45 (s, 3H), 2.53 (dd, J = 15.4, 2.7 Hz, 1H), 2.68 (ddd, J = 15.4, 10.2 Hz, 1H) 3.61 (q, J = 6.2 Hz, 1H), 3.78 (s, 6H), 6.21 (d, J = 2.4 Hz, 1H), 6.30 (d, J = 2.4 Hz, 1H); ^{13}C NMR δ 21.2, 22.6, 39.2, 41.1, 54.9, 55.1, 55.2, 56.9, 96.5, 103.4, 121.2, 137.6, 157.0, 158.4. Anal. Calcd for $C_{14}H_{21}NO_2$: C, 71.46; H, 8.99; N, 5.95. Found: C, 70.80; H, 9.19; N, 5.99.

(+)-(1*R*,3*S*)-5-Bromo-6,8-dimethoxy-1,2,3-trimethyl-1,2,3,4-tetrahydroisoquinoline (8). A solution of bromine (1.38 g, 8.60 mmol) in CH_2Cl_2 (11 mL) was added dropwise to a stirred solution of compound **7** (1.83 g, 7.78 mmol) in CH_2Cl_2 (80 mL) at 0 °C. When the addition was complete the solution was shaken in turn with aqueous NaOH solution (2.5 M), $Na_2S_2O_3$, water, and finally with brine. Purification of the crude product by flash chromatography with EtOAc/diethyl ether (3:2) as eluent gave the bromide **8** (1.65 g, 67%) as pale yellow prisms after recrystallization from petroleum ether: mp 81−84 °C (lit.[16] mp 103−104 °C (for racemate)); $[\alpha]^{20}_D$ +145.2° (*c* 1.11, $CHCl_3$); ^{1}H NMR δ 1.23 (d, J = 4.7 Hz, 3H), 1.33 (d, J = 4.7 Hz, 3H), 2.42 (m, 1H), 2.43 (s, 3H), 2.50 (m, 1H), 2.90 (dd, J = 1.8, 12.3 Hz, 1H), 3.63 (dq, J = 6 Hz, 1H), 3.83 (s, 3H), 3.88 (s, 3H), 6.38 (s, 1H); ^{13}C NMR δ 21.0, 22.5, 38.9, 40.9, 54.7, 55.3, 56.4, 56.8, 94.4, 103.6, 122.9, 137.1, 154.3, 155.8. Anal. Calcd for $C_{14}H_{20}BrNO_2$: C, 53.51; H, 6.42; Br, 25.43; N, 4.40. Found: C, 53.66; H, 6.66; Br, 25.30; N, 4.64.

Coupling Reaction: *N*-Acetates (+)-11 and (+)-12. A mixture of bromide **8** (510 mg, 1.62 mmol) and magnesium turnings (78 mg, 3.52 mmol) in anhydrous THF (2 mL) was heated under reflux under argon, and a solution of 1,2-dibromotetrafluoroethane (194 μL, 1.62 mmol) in anhydrous THF (2 mL) was added dropwise over 30 min. To the resulting Grignard reagent was added a solution of the oxazoline **3**[13] (486 mg, 1.48 mmol) in THF (2.5 mL) via cannula. The solution was then heated under reflux for 23 h, cooled, and then quenched with saturated NH_4Cl, and the product was extracted with EtOAc. After removal of the solvent the crude product was purified by flash chromatography with EtOAc as eluent. The band of higher R_f was recrystallized from petroleum ether to give the oxazoline **10** (170 mg, 22%) as pale yellow needles: mp 115−117 °C; $[\alpha]^{20}_D$ +9.7° (*c* 1.02, $CHCl_3$); ^{1}H NMR δ 0.97 (d, J = 6.6 Hz, 3H), 1.05 (d, J = 6.0 Hz, 3H), 1.84 (m, 1H), 3.93 (s, 3H), 3.98 (s, 3H), 4.19 (m, 2H), 4.44 (m, 1H), 7.01 (d, J = 7.5 Hz, 1H), 7.01 (s, 1H), 7.45 (t, J = 8.1 Hz, 1H), 8.03 (d, J = 8.1 Hz, 1H); ^{13}C NMR δ 18.6, 18.7, 33.1, 56.5, 57.3, 70.0, 71.4, 103.0, 103.6, 109.2, 116.3, 126.2, 128.0, 148.8, 152.6, 156.6, 165.5. Anal. Calcd for $C_{18}H_{21}NO_4$: C, 68.55; H, 6.71; N, 4.44. Found: C, 68.63, H, 6.59, N, 4.35. The band of lower R_f (390 mg) consisted of a mixture of the biaryls **5** and **9** as well as quenched Grignard reagent **7** as deduced by ^{1}H NMR spectroscopy.

To a solution of the above mixture of **5**, **9**, and **7** in anhydrous THF (4 mL) were added powdered anhydrous Na_2SO_4 (2.7 g), H_2O (0.35 mL), and trifluoroacetic acid (150 μL). The yellow suspension was stirred at rt for 26 h, and then an additional amount of anhydrous Na_2SO_4 (1 g) was added. Filtration and concentration under reduced pressure at 25 °C gave an ammonium salt that was dissolved in CH_2Cl_2 (6 mL), cooled to 0 °C, and treated sequentially with acetic anhydride (1.3 mL) and pyridine (1.9 mL) under nitrogen. The reaction mixture was allowed to warm to rt over 4 h and then washed with H_2O, saturated aqueous $NaHCO_3$ and then H_2O, saturated aqueous $CuSO_4$, H_2O, and brine. Removal of the solvent left a brown viscous oil that was purified by flash chromatography with 10% MeOH/$CHCl_3$ as eluent to afford **12** (236 mg, 27%) as a foam: $[\alpha]^{20}_D$ +47.6° (*c* 1.03, $CHCl_3$); ^{1}H NMR δ 0.82 (d, J = 6.6 Hz, 3H), 0.83 (d, J = 6.6 Hz, 3H), 0.89 (d, J = 5.7 Hz, 3H), 1.4 (m, 1H), 1.43 (d, J = 6.3 Hz, 3H), 1.76 (d, J = 13 Hz, 1H), 1.94 (s, 3H), 2.07−2.22 (m, 3H), 2.38 (s, 3H), 3.58 (s, 3 H), 3.71 (q, J = 6.3 Hz, 1H), 3.82 (m, 1H), 3.92 (s, 3 H), 3.94 (m, 1H), 3.98 (s, 3H), 4.05 (s, 3 H), 4.31 (dd, J = 11.4, 5.7 Hz, 1H), 5.39 (br d, J = 9.3 Hz, 1H), 6.47 (s, 1H), 6.81 (d, J = 8.4 Hz, 1H), 6.91 (d, J = 7.5 Hz, 1H), 7.23 (app t, J = 8.1 Hz, 1H), 7.37 (s, 1H). ^{13}C NMR δ 19.0, 19.2, 21.1, 22.7, 23.3, 28.8, 36.3, 40.9, 53.4, 54.7, 55.1, 55.8, 56.3, 56.6, 57.0, 65.2, 93.2, 105.9, 108.1, 118.5, 119.3, 119.5, 121.0, 126.9, 128.7, 129.3, 136.4, 136.8, 155.8, 156.3, 156.4, 157.2, 168.4, 169.7; EIMS *m*/*e* (rel intensity) 592 (1.1, M^+), 577 (39), 576 (100, $M^+ - CH_3$), 449 (31); HRMS (FAB) calcd for $C_{24}H_{45}N_2O_7$ (MH^+) 593.3232, found 593.3227.

Further elution yielded the minor biaryl **11** (47 mg, 5%) as a cream foam: $[\alpha]^{17}_D$ +39.7° (*c* 0.58, $CHCl_3$); ^{1}H NMR δ 0.84 (d, J = 6.6 Hz, 6H), 1.15 (d, J = 6.6 Hz, 3H), 1.49 (m, 1H), 1.63 (d, J = 6.6 Hz, 3H), 1.99 (s, 3H), 2.63 (s, 3H), 3.58 (s, 3H), 3.91 (s, 3H), 3.98 (s, 3H), 4.46 (s, 3H), 6.49 (s, 1H), 6.94

(d, J = 7.8 Hz, 1H), 6.95 (d, J = 7.8 Hz, 1H), 7.28 (app t, J = 8.1 Hz, 1H), 7.35 (s, 1 H); ^{13}C NMR δ 18.7, 19.5, 21.1, 23.2, 28.5, 34.2, 40.7, 53.4, 55.1, 56.3, 56.4, 56.6, 56.9, 65.1, 93.9, 105.8, 108.2, 119.3, 119.5, 127.3, 127.8, 128.7, 136.0, 136.6, 156.1, 156.3, 156.6, 157.3, 168.1, 169.6; EIMS m/e (rel intensity) 592 (3, M^+), 577 (38), 576 (100, $M^+ - CH_3$), 450 (27).

(*M*,1*R*,3*S*)-5-[(2-Hydroxymethyl)-4,5-dimethoxy-1-naphthyl]-6,8-dimethoxy-1,2,3-trimethyl-1,2,3,4-tetrahydroisoquinoline (13). A solution of **12** (101 mg, 0.17 mmol) in THF (2 mL) was added dropwise to a stirred suspension of $LiAlH_4$ (27 mg, 0.71 mmol) in THF (2 mL) at 0 °C under nitrogen. After being stirred for 22 h at rt, the mixture was treated with aqueous NaOH (5 M) until a white precipitate had formed. The salts was removed by filtration, and the filtrate was concentrated. Purification of the crude product by flash chromatography with 10% MeOH/$CHCl_3$ as eluent afforded the alcohol **13** (75 mg). NMR analysis indicated the presence of a small amount of byproduct (reduced chiral auxiliary), and this material was used in the next step without further purification: ^{1}H NMR δ 1.02 (d, J = 6 Hz, 3H), 1.53 (d, J = 6 Hz, 3H), 1.92 (dd, J = 2.8, 16.8 Hz, 1H), 2.23 (m, 1H), 2.48 (m, 1H), 2.52 (s, 3H), 3.59 (s, 3H), 3.89 (m, 1H), 3.91 (s, 3H), 3.96 (s, 3H), 4.03 (s, 3H), 4.37 (ABq, J = 10.8 Hz, 2H), 6.49 (s, 1H), 6.72 (d, J = 8 Hz, 1H), 6.80 (d, J = 5.4 Hz, 1H), 7.08 (s, 1H), 7.17 (t, J = 8.0 Hz, 1H); EIMS m/e (rel intensity) 451 (1.3, M^+), 436 (31), 435 (100, $M^+ - CH_3$), 419 (3), 421 (18).

(+)-(*P*,1*R*,3*S*)-5-(4,5-dimethoxy-2-methyl-1-naphthyl)-6,8-dimethoxy-1,2,3-trimethyl-1,2,3,4-tetrahydroisoquinoline [(+)-*O*-Methylancistrocline] (2a). Chlorotrimethylsilane (54 μL, 0.43 mmol) was added dropwise to a stirred mixture of the alcohol **13** (75 mg, 0.17 mmol) and anhydrous NaI (65 mg, 0.43 mmol) in dry acetonitrile (5 mL) at rt under nitrogen. After 2 h, acetic acid (303 μL) and zinc dust (76 mg) were added, and the colorless mixture was stirred at 80 °C for 1 h. The cooled mixture was diluted with saturated aqueous $NaHCO_3$ and extracted with EtOAc, and the organic layer was washed with water and brine. Removal of the solvent and purification of the crude product by flash chromatography using 10% MeOH/$CHCl_3$ as eluent afforded *O*-methylancistrocline (**2a**) (39 mg, 53%) as a white foam: $[\alpha]^{20}_D$ +80.2° (*c* 0.54, $CHCl_3$); ^{1}H NMR δ 0.94 (d, J = 6.3 Hz, 3H), 1.43 (d, J = 6.6 Hz, 3H), 1.89 (dd, J = 15.9, 3.0 Hz, 1H), 2.08 (dd, J = 8.7, 15.9 Hz, 2H), 2.12 (s, 3H), 2.26 (m, 1H), 2.42 (s, 3H), 3.60 (s, 3H), 3.75 (q, J = 6.3 Hz, 1H), 3.92 (s, 3H), 3.97 (s, 3H), 4.01 (s, 3H), 6.49 (s, 1H), 6.75 (d, J = 7.8 Hz, 1H), 6.78 (d, J = 8.7 Hz, 1H), 6.81 (s, 1H), 7.19 (app t, J = 8.1 Hz, 1H); ^{13}C NMR δ 20.5, 21.1, 22.9, 35.8, 41.2, 54.9, 55.1, 56.0, 56.3, 56.6, 57.0, 93.7, 105.4, 109.1, 116.2, 118.4, 118.8, 121.4, 125.5, 126.0, 135.6, 136.6, 137.2, 155.9, 156.1, 157.3; EIMS m/e (rel intensity) 435 (2.3, M^+), 419 (100, $M^+ - CH_3$), 405(13); HRMS (FAB) calcd for $C_{27}H_{34}NO_4$ (MH^+) 436.2495, found 436.2488.

Oxidative Degradation of Synthetic *O*-Methylancistrocline. Synthetic **2a** (0.37 mg, 0.85 μmol) was degraded in 107 mL of a 1:1:2 (two phase) mixture of MeCN/CCl_4/aqueous phosphate buffer (pH = 6) at rt, using $RuCl_3 \cdot 3H_2O$ (0.1 mg) and $NaIO_4$ (3 mg). After esterification with $SOCl_2$ (140 μL)/MeOH (1.5 mL) and subsequent derivatization with (*R*)-α-methoxy-α-(trifluoromethyl)phenylacetic acid chloride [1.27 μmol, prepared from the corresponding (*S*)-acid] as previously described,[23] the GC−MSD analysis was done on a nonpolar fused silica capillary column Hewlett-Packard Ultra 2, 25 m × 0.32 mm (i.d.) × 0.52 μm (film thickness), cross-linked 5% diphenyl- and 95% dimethylpolysiloxane, with a temperature program of 100 to 160 °C at 30° min^{-1} and then 160 to 190 °C at 1° min^{-1}, and finally increased at 40 °C min^{-1} to 270 °C. This analysis gave peaks with retention times identical to the derivatives of authentic (*S*)-*N*-methyl-3-aminobutyric acid, (*S*)-3-aminobutyric acid, D-*N*-methylalanine, and D-alanine.

Calculation of the CD Spectrum of 2a. The computational generation of the theoretical spectrum of **2a** consisted of three crucial steps:[24]

(1) The conformational analysis of **2a** was performed using the program package VAMP 5.5[26] and *AdaptivSearch*[25] on an IBM-compatible PC equipped with a Pentium processor (Intel) using LinuX as the operating system.

(2) The rotational strength values $R_{0\rightarrow a}$ for electric transitions $0\rightarrow a$ were calculated according to the equation

$$R_{0\rightarrow a} = Im\left\{\frac{-e\hbar}{2\pi m \nu_a}\langle\Psi_0|\hat{\nabla}|\Psi_a\rangle\langle\Psi_a|\hat{m}|\Psi_0\rangle\right\}$$

which is the origin-independent formalism of the rotational strength. The wave functions of the excited states were obtained by CNDO/2S calculation,[27] in which the CI expansion consists of 400 singly occupied configurations and the ground state determinant.

(3) All calculated single CD spectra were added to provide the theoretical overall spectrum for **2a** (Figure 1a) by means of the Boltzmann statistic in order to simulate the distribution of the ensemble of conformations over the conformational space at rt.

Semisynthesis of 2a from Isoancistrocladine 15. To a solution of isoancistrocladine (**15**)[22] (~70% pure by ^{1}H NMR, 14.9 mg, 37 μmol, prepared[5] from an authentic sample of ancistrocladinine) in dry CH_2Cl_2 was added anhydrous $NaHCO_3$ (19 mg) followed by $ClCO_2Me$ (10 μL) at 0 °C. After the mixture was stirred at rt for 16 h the solids were removed by filtration and the filtrate was concentrated *in vacuo*. Chromatography on silica gel with 40% EtOAc/petroleum ether as eluent gave a yellow oil (13.5 mg) that was dissolved in anhydrous DMF (1 mL) and treated with K_2CO_3 and MeI (18 μL) at rt for 2 h. Water was added, and the product was extracted with diethyl ether. Purification by preparative TLC using 40% EtOAc/petroleum ether as eluent gave essentially pure carbamate **16** (3.3 mg, 26%) as an oil that was dissolved in anhydrous THF (3 mL) and heated under reflux with $LiAlH_4$ (10 mg, 0.26 mmol) for 2 h. Aqueous NaOH (5 M) was added until a white precipitate had formed and the salts were removed by filtration. Preparative TLC with 10% MeOH/$CHCl_3$ as eluent gave *O*-methylancistrocline (**2a**) (2.1 mg, 64%), which was identical to the synthetic sample (R_f in three solvent systems, NMR, $[\alpha]_D$).

Acknowledgment. We thank the Australian Research Council as well as the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie for generous financial support. Furthermore, we thank S. Busemann and R. God for skillful help in the degradative and chiroptical analyses.

Supporting Information Available: Copies of the 300 MHz ^{1}H NMR spectra of compounds **10**−**13** and **2a** (5 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO9607119

(26) Rauhut, G.; Chandrasekhar, J.; Alex, A.; Beck, B.; Sauer, W.; Clark, T.; VAMP 5.5, available from Oxford Molecular Limited, The Magdalen Centre, Oxford Science Park, Sandford on Thames, Oxford OX4 4GA, England.

(27) The CD programs used, BDZDO and MCD3SP, were written by J. Downing and J. Michl (University of Colorado at Bolder), modified by J. Fleischhauer, W. Schleker, and B. Kramer (RWTH Aachen), and ported to LinuX by K.-P. Gulden (University of Würzburg).