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

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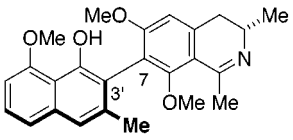
ABSTRACT



(-)-Ancistrocladidine (**1**)

The first total synthesis of the rare 7,3′-linked naphthylisoquinoline alkaloid, ancistrocladidine, has been completed. The key feature of the synthesis is the formation of the extremely hindered biaryl linkage by Pinhey−Barton *ortho*-arylation of a naphthol with an aryllead triacetate. The biaryl aldehyde formed is 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.

Extracts from the tropical *Ancistrocladaceae* and *Dioncophyllaceae* plant families have been used in traditional medicines for the treatment of malaria and dysentery.[1] Recent examination of these extracts has revealed that the profound biological activity is due to the presence of naphthylisoquinoline alkaloids. These structurally unique alkaloids are characterized by a naphthalene group, linked to either a dihydro- or tetrahydroisoquinoline moiety as exemplified in the examples shown in Figure 1.[2] While significant advances have been made in the syntheses[3] of 5,1′-, 7,1′-, and 5,8′-linked naphthylisoquinoline alkaloids, little synthetic attention[4] has been focused on 7,3′-linked systems such as that found in ancistrocladidine **1**.[5] The 7,3′-biaryl bond in

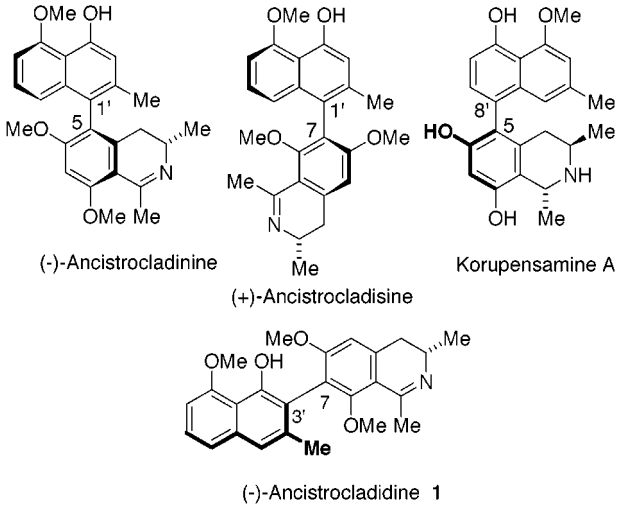


Figure 1. Representative examples of naphthylisoquinoline alkaloids.

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

(3) (a) Rao, A. V. R.; Gurjar, M. K.; Ramana, D. V.; Chheda, A. K. *Heterocycles* **1996**, *43*, 1−6. (b) Hobbs, P. D.; Upender, V.; Dawson, M. I. *Synlett* **1997**, 965−967. (c) Rizzacasa, M. A. In *Studies in Natural Product Synthesis, Structure and Chemistry* (Part F); Atta-ur-Rahman, Ed.; Elsevier: Amsterdam, 1998; Vol. 20, pp 407−455 and references therein. (d) Bringmann, G.; Breuning, M.; Tasler, S. *Synthesis* **1999**, 525−558 and references therein. (e) Lipshutz, B. H.; Keith, J. M. *Angew. Chem., Int. Ed.* **1999**, *38*, 3530−3533. (f) Hoye, T. R.; Chen, M.; Hoang, B.; Mi, L.; Priest, O. P. *J. Org. Chem.* **1999**, *64*, 7184−7201. (g) Kamikawa, K.; Watanabe, T.; Daimon, A.; Uemura, M. *Tetrahedron* **2000**, *56*, 2325−2337. (h) Bringmann, G.; Menche, D. *Acc. Chem. Res.* **2001**, *34*, 615−624 and references therein.

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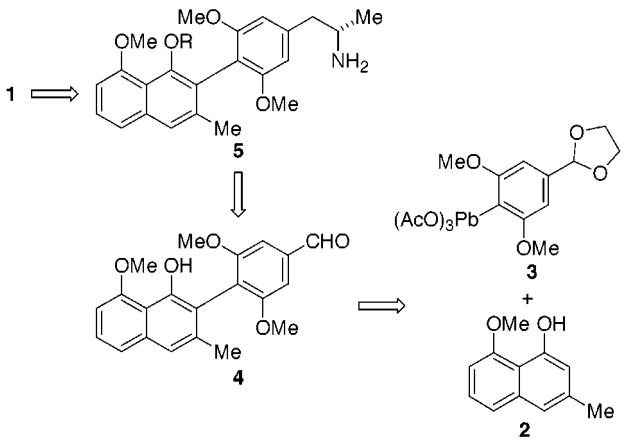
ancistrocladidine represents a particular challenge to contemporary cross-coupling methods as a result of the presence of four ortho substitutents. Despite the many advances[6] in transition metal catalyzed cross-coupling methodology, relatively few biaryl linkages with four ortho-substituents have been synthesized in this way.[7] In this Letter, we report a new strategy that has resulted in the first total synthesis of ancistrocladidine.

An overview of our retrosynthetic analysis is depicted in Scheme 1 and is based on the formation of the key biaryl

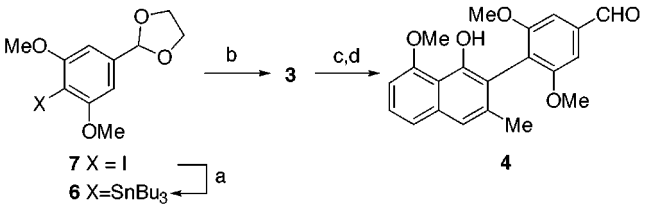
Scheme 1



linkage by Pinhey−Barton *ortho*-arylation[8] of naphthol **2** with aryllead triacetate **3**. Elaboration of the biaryl **4** to amphetamine **5** would allow for the use of a Bischler−Napieralski cyclization to form the 3,4-dihydroisoquinoline ring system.[9]

In light of these plans, our initial goal was the synthesis of aryllead triacetate **3**. While there are a variety of methods[8c] for the preparation of aryllead triacetates, perhaps the most general method involves a tin-to-lead transmetalation using $Pb(OAc)_4$ in the presence of a catalytic amount of a mercury salt. Accordingly, stannane **6** was prepared in 85% yield by halogen−lithium exchange of iodide **7**[10] with *t*-BuLi and subsequent quenching with Bu_3SnCl (Scheme 2).

Scheme 2[a]



[a] Reagents: (a) ^{t}BuLi, Bu_3SnCl, THF, −95 °C to rt, 85%; (b) $Pb(OAc)_4$, cat. $Hg(OAc)_2$, CH_2Cl_2, rt, 24 h, 93%; (c) **2**, pyridine, CH_2Cl_2, 24 h, rt; (d) 3% v/v aqueous H_2SO_4, THF, 1 h, rt, 67% yield from **3**.

Stirring the stannane **6** with freshly purified $Pb(OAc)_4$ in the presence of a catalytic amount of $Hg(OAc)_2$ provided aryllead triacetate **3** in 93% yield. Formation of the key biaryl linkage using the Pinhey−Barton methodology was readily achieved by reacting the lead species **3** with naphthol **2**[11] 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 **4**, in 67% yield from **3**.

With the successful establishment of the hindered biaryl linkage, aldehyde **4** was then elaborated to the chiral amine **5** (R = MOM) by use of the Katsuki−Sharpless epoxidation[12] (Scheme 3).

The required allylic alcohol **8** was prepared in three steps from biaryl aldehyde **4** 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.

Epoxide **9** was obtained in 80% yield and 90% de[14] using the standard Sharpless catalytic conditions.[15] Tosylation of **9** gave the primary tosylate **10** in 83% yield. Concomitant cleavage[16] of the tosylate and ring opening of the epoxide to afford alcohol **11**, in 94% yield, was achieved by reaction of tosylate **10** with $LiAlH_4$ in Et_2O.Transformation of the alcohol **11** into the amine **5** (R = MOM) was achieved, in 81% overall yield, by reaction of **11** with phthalimide under Mitsunobu conditions,[17] followed by hydrolysis of the

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(5) (a) Govindachri, T. R.; Parthsarathy, P. C.; Desai, H. K. *Indian J. Chem.* **1973**, *11*, 1190. (b) Govindachri, T. R.; Parthsarathy, P. C.; Rajagopalan, T. G.; Desai, H. K.; Lee, E. *J. Chem. Soc., Perkin Trans. 1*, **1975**, 2134−2136. (c) Meksuriyen, D.; Ruangrungsi, N.; Tantivatana, P.; Cordell, G. A. *Phytochemistry*, **1990**, *29*, 2750−2752.

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(8) The groups of Pinhey and Barton have shown that this is an efficient method for the generation of extremely hindered biaryl linkages: (a) Bell, H. C.; Pinhey, J. T.; Sternhell, S. *Aust. J. Chem.* **1979**, *32*, 1551−1560. (b) Morgan, J.; Hambley, T. W.; Pinhey, J. T. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2173−2177. (c) Pinhey, J. T. *Aust. J. Chem.* **1991**, *44*, 1353−1382. (d) Barton, D. H. R.; Donnelly, D. M. X.; Guiry, P. J.; Finet, J.-P. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2921−2926.

(9) Bringmann, G.; Weirich, R.; Reuscher, H.; Jansen, J. R.; Kinzinger, L.; Ortmann, T. *Liebigs Ann. Chem.* **1993**, 877−888.

(10) Iodide **7** is prepared by acetalization of 3,5-dimethoxy-4-iodobenzaldehyde with ethylene glycol (99%). The aldehyde is readily available from 3,5-dihydroxybenzoic acid as described in (a) Gray, J. S.; Martin, G. C. J.; Rigby, W. *J. Chem. Soc. C* **1967**, 2580−2587. (b) Kompis, I.; Wick, A. *Helv. Chim. Acta* **1977**, *8*, 3025−3034.

(11) Watanabe, M.; Hisamatsu, S.; Hotokezaka, H.; Furukawa, S. *Chem. Pharm. Bull.* **1986**, *34*, 2810−2820.

(12) For a related example, see ref 3a. For other methods for the introduction of chirality into biaryl systems, see refs 3e, 3g, and 13.

(13) (a) Bringmann, G.; Jansen, J. R.; Rink, H. P. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 913−915. (b) Hoye, T. R.; Chen, M. *Tetrahedron Lett.* **1996**, *37*, 3099−3100.

(14) This reaction generates diastereomers with respect to the biaryl linkage, but they are not observable. The epoxide was recrystallized from toluene/petroleum ether to provide material with >95% de, as determined by the method described in Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543−2549.

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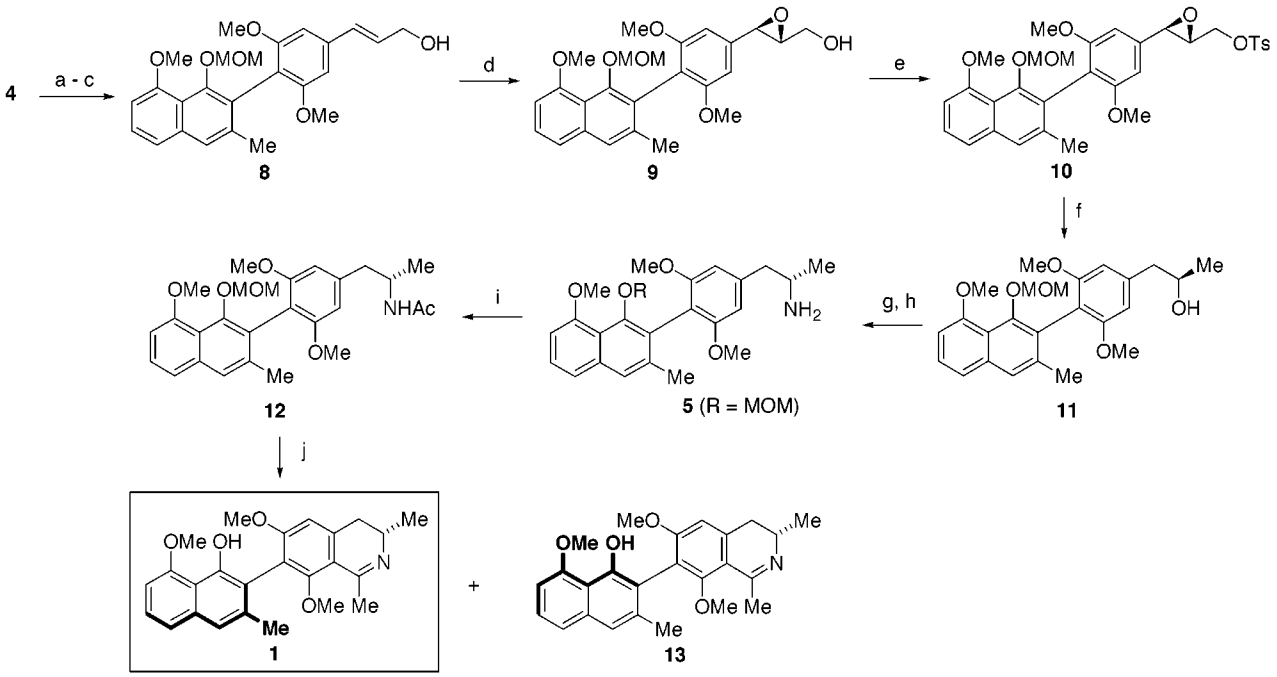
Scheme 3[a]



[a] Reagents: (a) MOM-Cl, NaH, THF, rt, 81%; (b) NaH, $(EtO)_2POCH_2CO_2Et$, C_6H_6, 0 °C to 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 to rt, 97%; (j) $POCl_3$, 2,4,6-collidine, CH_3CN, reflux, 4 h, 74% (1:1 mixture of **1** and **13**).

phthalimide group with aqueous ethanolic methylamine. Acetylation of the amine **5** (R = MOM) with CH_3COCl gave the acetamide **12** in 97% yield. Bischler−Napieralski cyclization was readily achieved by reaction of **12** 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 **1** was isolated, along with the atropisomer **13**, in a 1:1 ratio, in 74% overall yield. Separation of the atropisomers was readily achieved by recrystallization from toluene/petroleum ether. Comparison with an authentic sample of ancistrocladidine is not possible as the natural product is no longer available, but synthetic ancistrocladidine matches all the reported data for the natural product.[5a,5c,18]

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. The formation of such a hindered bond under very mild conditions, coupled with the recent report that this chemistry can be carried out in an atroposelective fashion,[19] indicates that this new strategy could be applied to the synthesis of other members of the naphthylisoquinoline alkaloid family.

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Supporting Information Available: Characterization data for natural ancistrocladidine, synthetic ancistrocladidine, and atropisomer **13**, and copies of ^1H 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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(18) Professor Geoffrey Cordell (Illinois) has indicated that the 1.8 Hz coupling constant reported for the signal at δ 2.42 (dd, J = 15.5, 1.8 Hz, 1H) is a misprint in the original paper (ref 5c). (Personal communication)

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