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Total Synthesis of (+)-Korupensamine B via an Atropselective Intermolecular Biaryl Coupling

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Abstract: The asymmetric total synthesis of nonracemic korupensamine B is reported. It includes a newly designed and highly trans-diastereoselective (>20:1 dr) route to the tetrahydroisoquinoline ring and an unprecedented atropdiastereoselective Suzuki−Miyaura coupling for construction of the fully fashioned naphthylisoquinoline framework that invokes π stacking as a possible source of stereocontrol.

Michellamine B (**1**), the heterodimerization product of atropdiastereomeric korupensamines A (**2**) and B (**3**), has received considerable attention as a potent anti-HIV-1 and -2 agent (Figure 1).[1] Korupensamines A and B, which were originally isolated from the Cameroonian liana *Ancistrocladus korupensis*,[2] have a naphthyltetrahydroisoquinoline skeleton with axial chirality between the naphthalene and tetrahydroisoquinoline (THIQ) rings and are presumed to be biosynthetic precursors to the michellamines.[3] Both **2** and **3** themselves exhibit good antimalarial activities in vitro and in vivo.[1,2a] Although their antimalarial properties are no longer being pursued, these targets nonetheless represent a considerable synthetic challenge in stereocontrolled intermolecular biaryl construction between highly functionalized precursors. To date, stereoselective syntheses of either **2** or **3**, notably from the laboratories of Bringmann, Hoye, Kelly, and Uemura, have been completed via *indirect* routes in which either the naphthyl ring or the THIQ ring is installed after formation of the biaryl bond.[4] Alternatively, literature reports describing the formation of the biaryl nucleus directly have led to dr's in the range of 1.5:1.[4f−i] In 1999, we reported a stereospecific, intermolecular biaryl-coupling approach to the biaryl nucleus in **2**.[5] In continued efforts directed toward this class of natural products, we now report an asymmetric total synthesis of (+)-**3** featuring a stereocontrolled biaryl coupling between the highly functionalized naphthyl and THIQ subsections.

Our strategy for the synthesis of **3** was based on the potential for intramolecular π-stacking interactions as a source of stereocontrol in the key Suzuki−Miyaura cross-coupling reaction (Scheme 1). Such a phenomenon has been invoked previously to potentially account for other types of highly stereoselective transformations in asymmetric synthesis.[6] In this case, it was speculated that intramolecular π stacking between the electron-rich THIQ and electron-deficient aryl ester of **5** would orient one face of the THIQ ring as in **7**, thereby positioning the bulky triisopropylsilyl (TIPS) ether to avoid steric interactions with ligands **L** in a square-planar array around the metal. The net effect would be to encourage formation of biaryl **6** with *M* axial chirality.

Naphthylboronic acid **4a** was prepared from commercially available 5-benzyloxy-2-bromobenzaldehyde (**8**) via the known halonaphthol precursor **9**,[5] using a modification of a route by Bringmann toward a related naphthylboronic acid[4a,7] (Scheme 2; also see the Supporting Information).

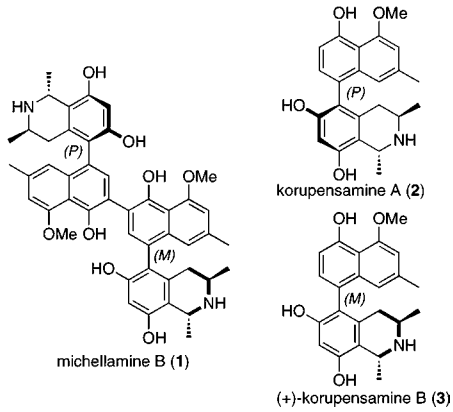
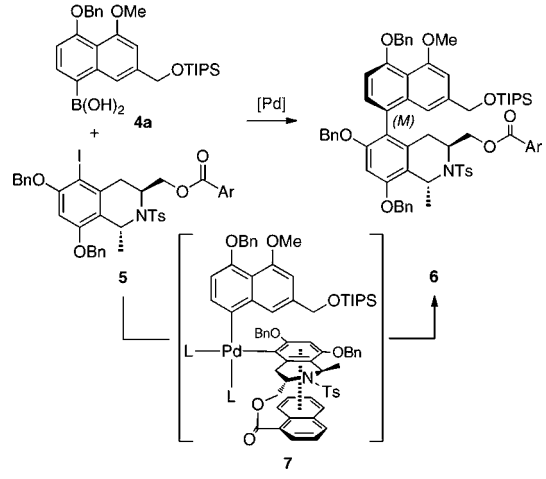
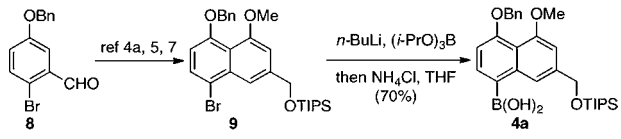


Figure 1. Selected naphthyltetrahydroisoquinoline alkaloids.

Scheme 1. Proposed Intermediate **7** in Biaryl Construction



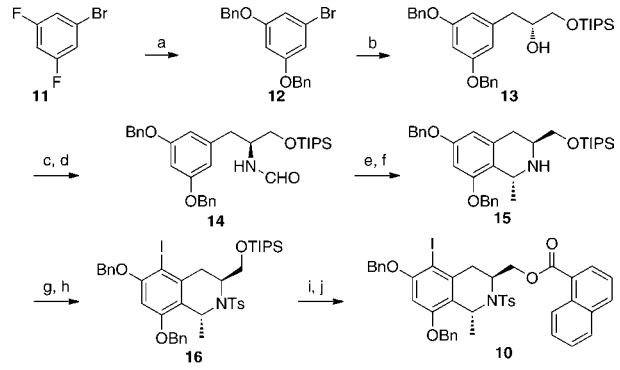
Scheme 2. Synthesis of Naphthylboronic Acid **4a**



The synthesis of THIQ **10** commenced with commercially available 1-bromo-3,5-difluorobenzene (**11**). Nucleophilic aromatic substitution provided bromobenzene **12** (Scheme 3). A copper-catalyzed opening of known (*R*)-TIPS-glycidol[8] with the Grignard reagent derived from **12** led to alcohol **13**. Mitsunobu inversion[9] in **13** with phthalimide followed by hydrazinolysis furnished the

nonracemic primary amine, which was further converted to formamide **14**. Bischler−Napieralski cyclization[10] using $POCl_3$ in combination with 2-methylpyrazine[11] afforded the corresponding imine in 73% yield. Treatment of the imine with MeMgCl in Et_2O initially at low temperature delivered **15** in 85% isolated yield with excellent trans diastereoselectivity (>20:1 dr). By contrast, the alternative route used previously involving the corresponding acetamide analogue of **14** and its subsequent reduction with $LiAlH_4$/$AlMe_3$ or Ru-catalyzed hydrogenation led to poor trans:cis ratios (≤2:1 or <1:20, respectively). N-Sulfonylation and subsequent regiospecific iodination were accomplished without incident. Desilylation followed by esterification with 1-naphthoic acid provided coupling partner **10**. Other benzoic esters **17a**−**h** were synthesized in a similar fashion for cross-coupling studies (also see the Supporting Information).

Scheme 3. Synthesis of Tetrahydroisoquinoline **10**[a]

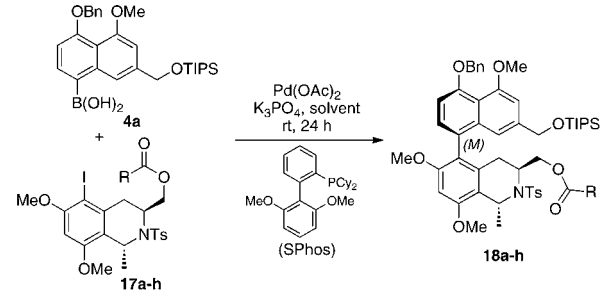


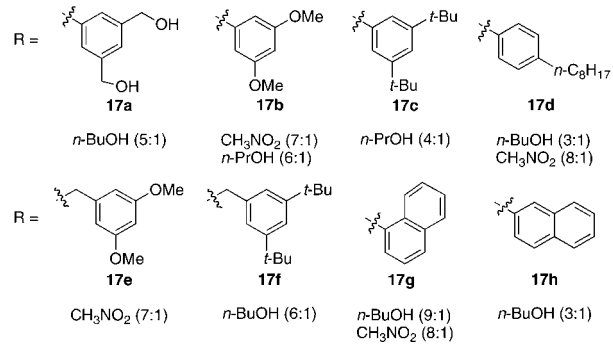
[a] Conditions: (a) NaOBn, NMP, 100 °C, 91%; (b) Mg, THF, reflux; CuI (cat.), (*R*)-triisopropylsilyl glycidyl ether, THF, 64%; (c) Ph_3P, phthalimide, DIAD, THF; $NH_2NH_2 \cdot H_2O$, EtOH, reflux, 74%; (d) AcOH, HCO_2Et, reflux, quant.; (e) $POCl_3$, 2-methylpyrazine, CH_2Cl_2, 0 °C to rt, 73%; (f) MeMgCl, Et_2O, −78 °C to rt, 85% (trans:cis >20:1); (g) TsCl, Et_3N, DMAP, CH_2Cl_2, 88%; (h) $CH(OMe)_3$, I_2, $PhI(O_2CCF_3)_2$, CH_2Cl_2, −10 to 0 °C, 2 h, 94%; (i) TBAF, THF, 97%; (j) 1-naphthoic acid, EDCI, DMAP, Et_3N, CH_2Cl_2, 92%. Abbreviations: Bn = benzyl, NMP = 1-methyl-2-pyrrolidinone, DIAD = diisopropyl azodicarboxylate, TsCl = *p*-toluenesulfonyl chloride, DMAP = 4-*N*,*N*-dimethylaminopyridine, TBAF = tetra-*n*-butylammonium fluoride, EDCI = 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride.

The effectiveness of the proposed Suzuki−Miyaura cross-coupling reaction was examined using various aryl-containing esters (R in **17a**−**h**; Table 1) of model methyl ether analogues. These were designed to test several potential factors [e.g., internal hydrogen bonding (**17a**), steric effects (**17c**), and extended conjugation (**17g**, **17h**)] in a variety of polar media. The atropdiastereoselectivity[12] was highest for the bulkier 1-naphthyl ester **17g** (vs the 2-naphthyl case, **17h**) in solvents such as *n*-BuOH (*M*:*P* = 9:1) and CH_3NO_2 (*M*:*P* = 8:1), while alcohols either shorter (*n*-PrOH, *M*:*P* = 8:1) or longer than four carbons (1-hexanol, *M*:*P* = 5:1) did not offer any advantages. In nonpolar solvents, the ratios were noticeably less pronounced (e.g., THF, *M*:*P* = 3:1; toluene, *M*:*P* = 2:1). Interactions of a π-stacking nature may account for the observed selectivity. Coupling of the corresponding non-aromatic acetate derivative **17i** (R = Me) with either boronic acid **4a** or its TBS (rather than TIPS) analogue **4b** led to a 1:1 ratio of *M* and *P* isomers under otherwise identical reaction conditions (Scheme 4).

The coupling of **4a** and **10** as partners en route to korupensamine B could be further optimized (Table 2). Although biaryl formation proceeded smoothly using the conditions described by Buchwald [$Pd(OAc)_2$, SPhos, THF, rt],[13] an initial screening gave a 1:1 mixture of *M* and *P* atropisomers (entry 1). The atropdiastereoselectivity was improved to *M*:*P* = 9:1 when the reaction was run in

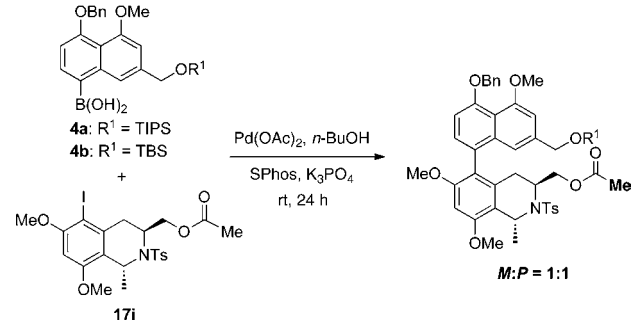
Table 1. *M*:*P* Ratios from Suzuki−Miyaura Couplings of **4a** with **17a**−**h**[a,b]





[a] **4a**, **17a**−**h**, $Pd(OAc)_2$, SPhos, K_3PO_4, rt. [b] *M*:*P* ratios were determined by HPLC (Dupont Instruments Zorbax Sil 4.6 mm × 25 cm).

Scheme 4. Testing the Effect of π Stacking with Acetate **17i**

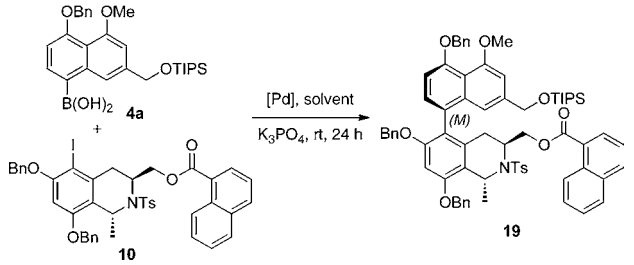


n-BuOH (entry 2). Eventually,[14] the combination of PdI_2/SPhos/K_3PO_4 in *n*-BuOH was identified as the best (*M*:*P* = 11:1; entry 3), leading to pure **19** in 72% isolated yield after chromatographic separation. Other ligands (entry 4) or branching in the alcoholic medium (*s*-BuOH; entry 5) led to low yields of product.

After the naphthylisoquinoline framework in **19**, including all of the stereocenters in the natural configuration, had been assembled, the remaining transformations focused mainly on deoxygenation of the two side chains and ultimately on removal of the *N*-tosyl protecting group. Coupling product **19** was first transformed into diol **20** via saponification and then desilylation (Scheme 5). After hydroxyl-to-halogen exchange by treatment with $(Cl_2BrC)_2/Ph_3P$,[15,16] a two-step sequence involving debromination of **21** with Zn (nanopowder) in acetic acid at 40 °C followed by removal of the tosyl group with $LiAlH_4$[17] led to tri-O-benzylated korupensamine B (**22**).[18] Hydrogenolysis of crude **22** afforded korupensamine B (**3**), $[\alpha]_D^{23}$ = +68.0 (*c* 0.182, MeOH; lit.[2a] +65, *c* 0.76, MeOH), which was found to be identical in all respects to natural[2] and previously synthesized material.[4]

In summary, the asymmetric total synthesis of (+)-korupensamine B (**3**) has been completed in 7% overall yield, with a longest

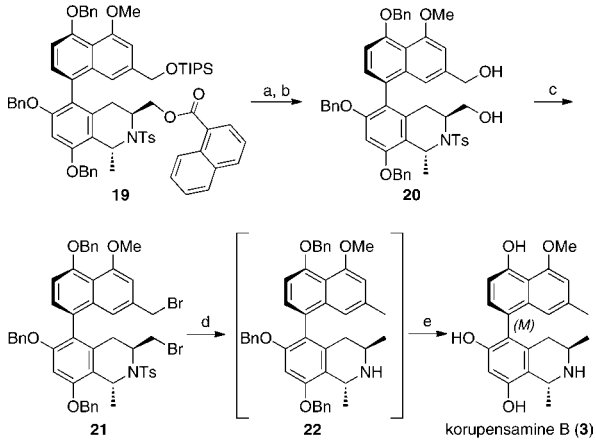
Table 2. Optimization of Suzuki−Miyaura Coupling Between **4a** and **10**[a]



entry	catalyst	solvent	*M*:*P*[b]	yield (%)[c]
1	$Pd(OAc)_2$, SPhos	THF	1:1	n.d.[d]
2	$Pd(OAc)_2$, SPhos	*n*-BuOH	9:1	52
3	**PdI_2, SPhos**	***n*-BuOH**	**11:1**	**72**
4	$Pd(t\text{-}Bu_3P)_2$	*n*-BuOH	10:1	31
5	$Pd(OAc)_2$, SPhos	*s*-BuOH	n.d.[d]	30

[a] Conducted at rt for 24 h with 4 mol % Pd, 8 mol % ligand, K_3PO_4 (3 equiv), **4a** (1.5 equiv), and **10** (1 equiv). [b] Determined by ^1H NMR spectroscopy. [c] Isolated yield of *M* atropisomer. [d] Not determined.

Scheme 5. Completion of the Synthesis of Korupensamine B (**3**)[a]



[a] Conditions: (a) NaOH, MeOH/THF, 88%; (b) TBAF, THF, 83%; (c) $(Cl_2BrC)_2$, Ph_3P, KOAc, CH_2Cl_2, reflux, 80%; (d) (i) Zn, AcOH, 40 °C; (ii) $LiAlH_4$, THF, rt; (e) Pd/C, H_2, $MeOH/CH_2Cl_2$, 8 h, 63% from **21**.

linear sequence of 18 steps from commercially available materials. Prominent features of this route include (i) a two-step sequence from formamide **14** to give tetrahydroisoquinoline **15** with noteworthy trans diastereoselectivity (>20:1 dr) and (ii) an unprecedented atropdiastereoselective Suzuki−Miyaura biaryl coupling (up to 11:1 dr) for construction of the naphthylisoquinoline framework in polar media that invokes π-stacking interactions as a potential source of stereocontrol.

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Note Added after ASAP Publication. Table 2 footnote contained an error in the version published ASAP September 17, 2010; the correct version and an updated SI file were reposted September 22, 2010.

Supporting Information Available: Experimental procedures, copies of spectral data, and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) The choice of base is crucial. A very low yield of the desired dihydroisoquinoline was obtained using 2,6-lutidine as the base.

(12) The diastereomers can be separated by chromatography in most cases, and the stereochemistry can be assigned by saponification to the reported compound. See the Supporting Information. Also see ref 5.

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