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Atroposelective Biaryl Coupling with Chiral Catalysts: Total Synthesis of the Antileishmanial Naphthylisoquinoline Alkaloids Ancistrotanzanine B and Ancistroealaine A†

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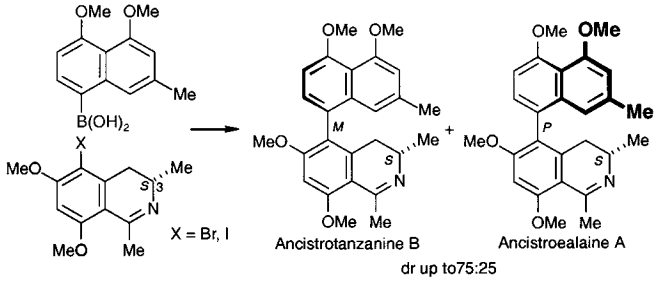
ABSTRACT



The first total synthesis of the naphthylisoquinoline alkaloid ancistrotanzanine B and its atropo-diastereomer, ancistroealaine A, is described. The key step is the construction of the rotationally hindered and thus stereogenic biaryl axis by Suzuki coupling. While only weak internal asymmetric inductions by the stereogenic center in the dihydroisoquinoline part were observed, much better atropisomeric ratios in favor of ancistrotanzanine B were achieved by the use of chiral catalysts. Both alkaloids, in particular ancistrotanzanine B, show high antileishmanial activities.

The naphthylisoquinoline alkaloids constitute a rapidly growing class of structurally[1,2] (presence of both stereogenic centers and chiral axes) and biosynthetically[3,4] (the first polyketide-derived isoquinoline alkaloids) interesting natural biaryl compounds.[5] They have so far been found only in two small tropical plant families, the Ancistrocladaceae and the Dioncophyllaceae.[1] Of particular interest is the antimalarial activity of some of these natural products, both in vitro and in vivo, while, more recently, also other promising antiprotozoal activities have been found.[6,7] Thus, ancistroealaine A (**1a**, see Scheme 1), a naphthylisoquinoline alkaloid recently isolated from the Central African liana *Ancistro-*

† Part 105 of the Series Novel Concepts in Directed Biaryl Synthesis. For part 104, see: Bringmann, G.; Pfeifer, R.-P.; Rummey, C.; Pabst, T.; Leusser, D.; Stalke, D. *Z. Naturforsch.* **2003**, *58b*, 231−236.

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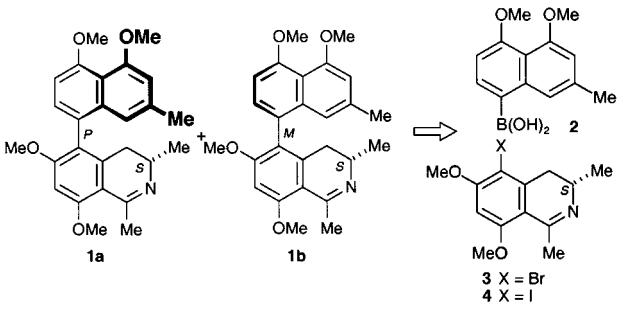
Scheme 1



cladus ealaensis, was found to be highly active in vitro against *Leishmania donovani*, the pathogen of visceral leishmaniasis ("Kala Azar"), even more active than the standard, pentostam.[8] More recently also its atropo-diastereomer, ancistrotanzanine B (**1b**), has been isolated from the East African species *A. tanzaniensis* and has been found to show a still higher activity than **1a**.[9] In this paper, we report on the first total synthesis of ancistrotanzanine B (**1b**) and ancistroealaine A (**1a**).

Among the methods[10−14] developed for the directed, i.e., regio- and stereoselective construction of biaryl systems, only a few have so far proven suited for the synthesis of naphthylisoquinoline alkaloids.[15−18] The first total syntheses in this field—and by far the largest number of successful examples—were achieved by using the "lactone method",[17,18] which allows the atropo-divergent construction of any of the two possible atropo-diastereomers in high chemical and optical yields. Within this concept, however, the target molecule should ideally have a C_1 unit and an oxygen function in opposite ortho-positions next to the biaryl axis, to be used as the "bridge heads" for the prefixation of the two molecular moieties via an ester bridge, for the subsequent intramolecular biaryl coupling. Although several examples have meanwhile been accomplished without these requirements,[19,20] we decided to try a direct, intermolecular biaryl coupling for the synthesis of **1a** and **1b**, also because the presence of only three ortho-substituents next to the axis should make it possible to use methods such as the Suzuki coupling[10−12] (which is more sensitive to steric hindrance) for the construction of the axis. Thus, the use of the lactone methodology, which can even build up 4-fold ortho-substituted biaryls with the largest steric hindrance next to the axis,[21,22] would not be necessary for a first rapid construction of **1a** and **1b** for further pharmacological investigations. Moreover, we found it interesting to test how far it would be possible to control the axial configuration of the product by an internal asymmetric induction by the stereogenic center at C-3; in previous cases, using related tetrahydroisoquinoline moieties, atropisomeric ratios of only 55:45 to 60:40 had been attained.[23−25] In addition, the example seemed of interest to check whether in this case the atropisomeric selectivities might be improved by chiral catalysts, applying enantioselective coupling techniques, e.g., by Buchwald and Cammidge,[26,27] which, however, had so far been applied mainly to simple, not sterically hindered, electron-poor model compounds, none of them containing nitrogen, while Nicolaou et al. had used related catalysts in the synthesis of a vancomycin-related compound,[28] but without larger steric hindrance. But even in those cases, the coupling yields were decreased as compared to the nonselective coupling reaction, and still the atropisomeric ratios obtained were often only moderate.

As the immediate precursors for the biaryl coupling, we chose the naphthalene building block **2**, activated as a boronic acid, and the heterocyclic portion **3** in the form of a halogen-substituted (initially brominated) dihydroisoquinoline (see Scheme 1), even though no such coupling reaction in the presence of a free iminic nitrogen in any of the coupling partners had so far succeeded. On the other hand, to protect this nitrogen at the same oxidation level (e.g., as an *N*-acylenamide) would have caused additional problems.

By contrast, previous strategies to do the coupling at the level of the corresponding 1,3-dimethyltetrahydroisoquinoline would have required either the respective *N*-protected (yet quite unstable[29]) cis-diastereomer or the corresponding trans-isomer, which, however, can be oxidized to the respective dihydroisoquinolines only under drastic conditions and with extremely low yields.[30]

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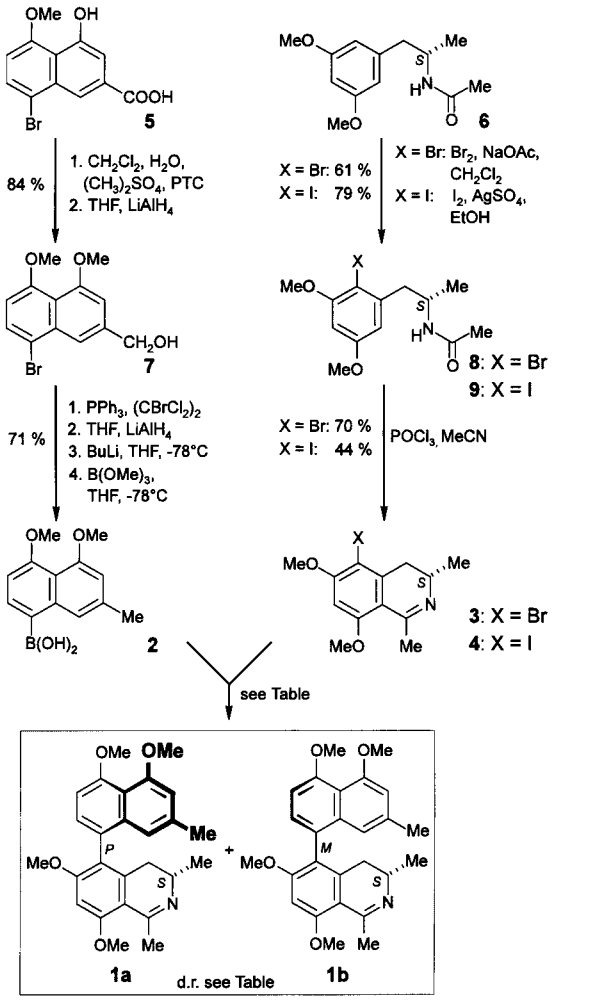
In analogy to a reaction sequence described earlier for a related *O*-isopropyl derivative,[31] the naphthylboronic acid **2** was prepared from the bromo compound **5** by phase-transfer-catalyzed *O*-methylation of the phenolic OH-function, LAH reduction of the carboxylate, and deoxygenation of the resulting primary alcohol **7** (by hydroxy-halogen exchange and subsequent renewed alanate reduction), followed by lithiation and subsequent reaction with trimethyl borate. The brominated dihydroisoquinoline **3** was prepared from the known[29] acetamide **6**, which was brominated and cyclized by the Bischler−Napieralski reaction.

The first coupling reactions of the two building blocks **2** and **3** thus prepared, using $Pd(PPh_3)_4$, gave the desired biaryl **1** in traces only (see Table, entry 1), while under other reaction conditions, no product was observed (not shown). As indicated by the formation of the hydro-deboronation product of **2**, the palladium had indeed been inserted, but apparently the bromide **3** was not reactive enough for the final coupling to proceed in good yields (see Table 1). For this reason, iodide **4**, as prepared from acetamide **6** in a similar reaction sequence (see Scheme 2), gave much better coupling yields, straightaway, e.g., 50% again with $Pd(PPh_3)_4$ (see Table 1, entry 2). To avoid the still occurring hydro-deboronation reaction, water-free conditions were likewise tested, but did not yield any coupling product **1**.

Table 1. Coupling Conditions, Yields, and Diastereomeric Ratios in the Suzuki Coupling Reactions of **2** with the Dihydroisoquinolines **3** or **4**

entry	compds	conditions	yield (%)	*M*:*P*
1	**2** + **3**	toluene; 5 equiv of K_3PO_4; 0.1 equiv of $Pd(PPh_3)_4$	traces	n.d.
2	**2** + **4**	toluene/H_2O; $NaHCO_3$; 0.1 equiv of $Pd(PPh_3)_4$	50	45:55
3	**2** + **4**	toluene/H_2O; $NaHCO_3$; 0.05 equiv of $Pd_2(dba)_3$; (R_c,S_p)-**10**	38	75:25
4	**2** + **4**	toluene/H_2O; $NaHCO_3$; 0.05 equiv of $Pd_2(dba)_3$; (S_c,R_p)-**10**	34	51:49
5	**2** + **4**	toluene/H_2O; $NaHCO_3$; 0.1 equiv of $Pd_2(dba)_3$; (*M*)-**11**	45	61:39
6	**2** + **4**	toluene/H_2O; $NaHCO_3$; 0.1 equiv of $Pd_2(dba)_3$; (*P*)-**11**	50	75:25

Scheme 2



Given the stereogenic center (C-3) in the isoquinoline portion, it was of interest how far this element of chirality would govern the stereoisomeric ratio at the biaryl axis. The stereoanalysis of **1a**/**1b** was, however, hampered by the fact that these two atropo-diastereomers behaved chromatographically identically, both on normal and reversed-phase silica gel, so that, as already seen in previous cases,[32,33] the best approach for their separation was to actually treat them as enantiomers, here by chromatography on a chiral phase. This was achieved, analytically, by using a Chiracel OD-H 250 column (4.6 mm; 5 μm; 0.5 mL/min; A, *n*-hexane (with 0.1% TFA); B, 2-propanol (with 0.1% TFA); gradient = 0 min 10% B, 10 min 10% B, 30 min 50% B, 60 min 50% B), which gave the two expected peaks for the diastereomeric products obtained above, in this case revealing a disappointing isomeric ratio of 55:45 in favor of the *P*-atropisomer, i.e., ancistroealaine A (**1a**). That the two peaks thus obtained in the LC-UV chromatogram were indeed the corresponding atropisomers was evident from their opposite circular dichroism (CD) effect as easily measured online, right from the peaks, by LC-CD coupling, here by simply monitoring the CD effect at one favorable wavelength, in this case the best wavelength was 230 nm, where the CD spectrum of **1a** has a minimum and that of **1b** a maximum. Thus, the LC-CD chromatogram of the reaction product obtained above gave the expected positive peak for **1b** and a negative one for **1a**.

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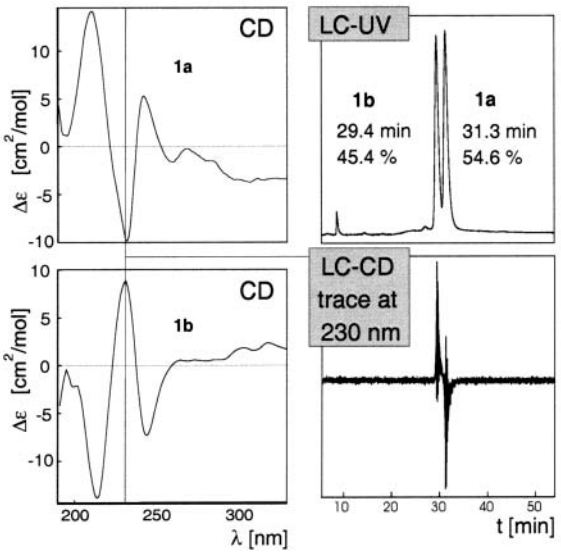
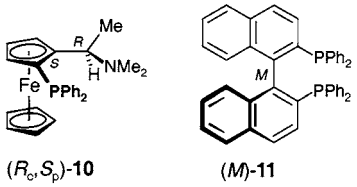


For the likewise difficult preparative separation of two atropo-diastereomeric products, **1a** and **1b**, a similar chromatographic device was applied, this time by using a semipreparative Chiracel OD column (250 × 10 mm; 10 μm; 3.0 mL/min; see above for solvents and gradient).[34] The two pure products, **1a** and **1b**, proved to be identical in all spectroscopic, chromatographic, and physical (in particular chiroptical) properties with the authentic natural products, ancistroealanine A and ancistrotranzanine B, thus completing the first total synthesis of these two natural products, which, in addition, confirms the structures of these bioactive alkaloids.

Still, in view of the nearly equal formation of **1a** and **1b** and the hence lacking internal asymmetric induction,[35] it seemed rewarding to try chiral catalysts, thus hopefully influencing the atropisomeric ratio more efficiently. Attempts to generate chiral catalysts first from $PdCl_2$ by addition of the previously successful[27] chiral ligands **10** or **11** failed, while with catalysts prepared from $Pd_2(dba)_3$ and those ligands, the biaryl coupling worked well (see Table 1, entries 3−6). For each of these cases, the ligand−palladium ratio was optimized (not shown) since different metal−ligand ratios can provide different selectivities in such analytical processes.[36] In the case of ferrocene **10** as the ligand, the complex was first prepared and even purified by column filtration prior to use. By using the (R_c,S_p)-enantiomer of **10**, the two alkaloids **1a** and **1b** were obtained in as much as 52% yield and in an atropisomeric ratio of 75:25, i.e., with a preference opposite to that with an achiral catalyst, giving rise to the hope that this would be the "mismatched" case and that the (S_c,R_p)-enantiomer of **10** would give an even better ratio, now in favor of the *P*-enantiomer, **1a**. This, however, was not the case, since (besides delivering a lower chemical yield of only 34%) the reaction did not provide any preference for one of the diastereomers (dr 51:49). The catalyst derived from (*M*)-**11**, by contrast, gave a yield of 45%, with a dr of 61:39 in favor of the *M*-isomer, again suggesting that the use of (*P*)-**11** would permit an even higher diastereomeric ratio in favor of *P*. Indeed, an isomeric ratio of 75:25 was obtained, with an even higher chemical yield (now 50%), but unexpectedly again in favor of *M*.



(R_c,S_p)-**10** (*M*)-**11**

In summary, the work described in this paper constitutes the first total synthesis of the two bioactive naphthylisoquinoline alkaloids ancistroealaine A (**1a**) and ancistrotanzanine B (**1b**) via a short and efficient synthetic pathway. Particularly remarkable is the fact that the Suzuki coupling still worked in the presence of a free imino function and when using chiral palladium catalysts and even gave quite good asymmetric inductions, leading to atropisomeric ratios of up to 75:25, in favor of ancistrotanzanine B (**1b**), although it was not yet possible to likewise produce the other atropisomer, **1a**, preferentially, by using the other reagent enantiomers. The reasons for this absence of atropodivergence[16] remain to be investigated.

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Supporting Information Available: Experimental procedure and characterization data for compounds **1**−**9**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(34) Different from previous preparative atropo-diastereomeric separations by enhancing the diastereomeric differentiation through attachment of a chiral electrophile, this approach was not possible here due to the absence of free OH- or NH-functions.

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