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Total synthesis of the antimalarial naphthylisoquinoline alkaloid 5-*epi*-4′-*O*-demethylancistrobertsonine C by asymmetric Suzuki cross-coupling

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ABSTRACT

The first total synthesis of the antimalarial naphthylisoquinoline alkaloid 5-*epi*-4′-*O*-demethylancistrobertsonine C (**1a**) and its—as yet unnatural—atropo-diastereomer, **1b**, is described. The key step of the synthesis is the construction of the rotationally hindered and thus stereogenic biaryl axis, which was built up by a Suzuki reaction. The use of chiral ligands in the palladium-catalyzed cross-coupling permitted to increase the low internal asymmetric induction up to a diastereomeric ratio of 74:26. The assignment of the axial configurations of the atropo-diastereomers was achieved by 2D NMR experiments and corroborated by quantum chemical CD calculations.

1. Introduction

Tropical lianas belonging to the plant families Dioncophyllaceae and Ancistrocladaceae are the only plants known to produce naphthylisoquinoline alkaloids,[1,2] a rapidly growing class of remarkable secondary metabolites: biosynthetically, since these are the only acetogenic tetrahydroisoquinoline alkaloids,[3–5] pharmacologically, because of their pronounced bioactivities (among them antimalarial,[6,7] antileishmanial,[8] and antitrypanosomal[9] effects), and structurally, due to the presence of a usually rotationally hindered and thus stereogenic biaryl axis.[1,10] One of the alkaloids of this type, 5-*epi*-4′-*O*-demethylancistrobertsonine C (**1a**, Scheme 1), which has recently been isolated from a Congolese *Ancistrocladus* species related to *Ancistrocladus congolensis*,[11] has been found to exhibit promising activities (IC_{50}=0.27 μg/mL) against *Plasmodium falciparum*, the pathogen of malaria tropica. For more detailed structure–activity relationship (SAR) investigations, in particular with respect to the influence of the configuration at the biaryl axis, the availability of the other atropo-diastereomer, **1b**, would be of importance. Since **1b** has so far not yet been found in nature, both **1a**, with its proven activity, and **1b** constitute rewarding synthetic targets. In this paper, we report on the total synthesis, stereochemical analysis, and bioactivities of 5-*epi*-4′-*O*-demethylancistrobertsonine C (**1a**) and its atropo-diastereomer, **1b**.

2. Results and discussion

The stereoselective construction of a stereogenic biaryl axis has, over the past years, attracted a lot of interest, making use of both intramolecular and intermolecular C–C coupling reactions.[12–14] One of the most successful concepts that have, finally, proven applicable to the total synthesis of concrete natural products, is the 'lactone method',[15–17] which permits the directed synthesis of either of the two atropisomers in excellent chemical and optical yields and asymmetric inductions.[18] This concept has been successfully applied to the total synthesis of a broad number of naphthylisoquinoline alkaloids (also including representatives with large steric hindrance at the axis).[19] A certain drawback is the required presence of a C_1 unit next to the coupling position. Although examples have been described that succeeded in circumventing the problem, such solutions may prolong the synthesis of target molecules that lack an *ortho*-C_1 substituent. For this reason, alternatives involving intermolecular cross-coupling reactions with different metal catalysts have been used for the total synthesis of such particular naphthylisoquinoline alkaloids, too, examples being korupensamines A and B[20–24] and dioncophylline B.[25] These intermolecular alternatives are, however, less generally applicable, due to their sensitivity toward major steric hindrance. Moreover, they usually lack any significant stereocontrol (or even atropodiastereodivergence) because of the use of achiral catalysts, thus restricting any asymmetric induction to the influence of the inherent chirality as resulting from stereogenic centers present in the isoquinoline portion.[26] After some early pioneering work in

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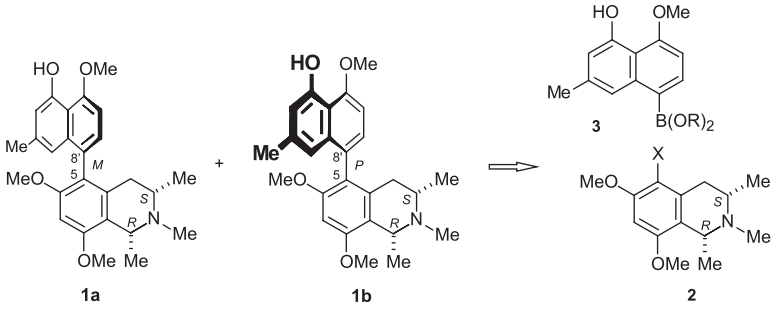


Scheme 1. Retrosynthetic disconnection of the alkaloid **1a** and its atropo-diastereomer **1b**.

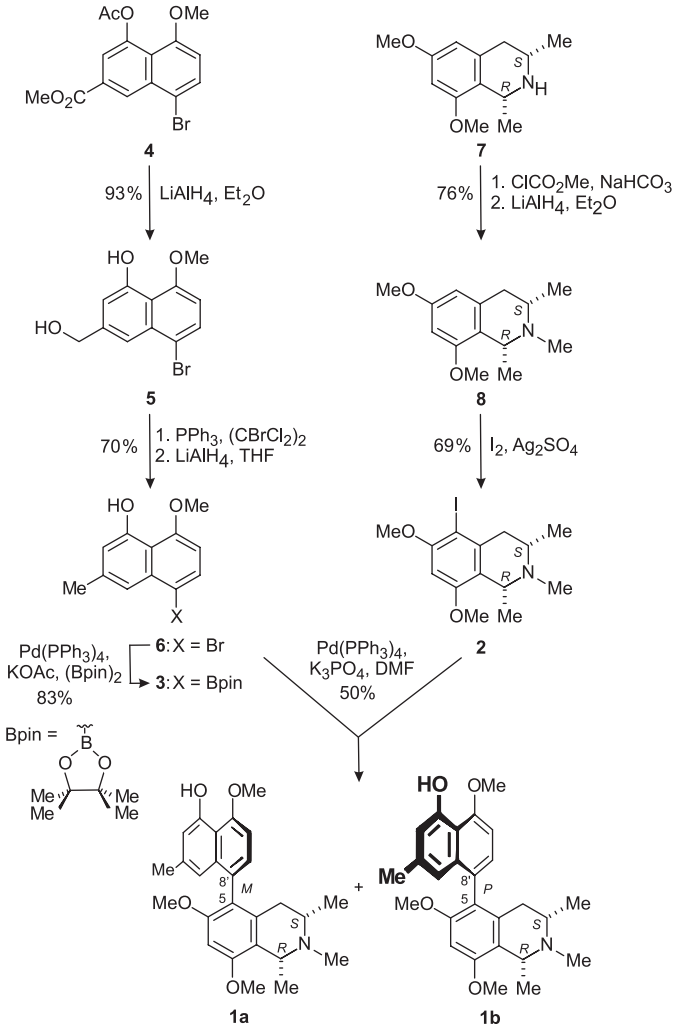
enantioselective biaryl Suzuki coupling,[27–29] the first efficient examples of atropo-enantioselective Suzuki couplings were reported in 2000 by Cammidge and Buchwald,[30,31] but still only few applications of this concept to the total synthesis of natural products are known,[32] among them the synthesis of the naphthylisoquinoline alkaloids ancistroealaine A and ancistrotanzanine B.[33] Like in that case, the presence of a 5,8′-linkage (i.e., only three *ortho*-substituents next to the axis, in particular without a C_1 unit) in **1a** and **1b** should offer the possibility to construct the stereogenic biaryl axis by a Suzuki cross-coupling. Before evaluating the use of chiral ligands in the asymmetric construction of the biaryl axis, however, achiral catalysts were utilized to gain a rapid access to both atropo-diastereomers for biological testing.

In order to keep the synthesis as short and efficient as possible and to further explore the scope and limitations of the method,[34] the use of any protective groups was avoided. For this purpose, the naphthalene moiety was activated as a boronic ester, which would permit both, boronation and cross-coupling by palladium-catalyzed reactions in the presence of the free phenolic function at C-4′. Thus, the known[35] naphthalene bicycle **4** was built up by a Wittig reaction with subsequent ring closure (Scheme 2),[35] then both ester groups were reduced with lithium aluminum hydride, and deoxygenation of the benzylic alcohol (by hydroxy–halogen exchange followed by renewed $LiAlH_4$ reduction) eventually furnished the brominated naphthalene **6**, which was further converted into the pinacol boronic ester **3** following the conditions reported by Miyaura.[36]

The isoquinoline portion, in turn, was iodinated, since it was known from previous work on a similar system[33] that the use of a less reactive brominated derivative leads to much lower yields in the cross-coupling step.[33] Therefore, the tetrahydroisoquinoline **7**, with its quite sensitive cis-configuration, was prepared as described before[37] and was then *N*-methylated by reaction with methyl chloroformate and subsequent reduction of the carbamate with lithium aluminum hydride to give **8**[38] in 76% yield. Despite its electron-rich character, iodination of **8** turned out to be difficult. After careful optimization of the reaction conditions, treatment of **8** with I_2 and Ag_2SO_4[39] gave **2** in 69% yield. Attempts to perform the iodination under less rigorous conditions (e.g., by using NIS and TFA[40]) gave no reaction or resulted in mixtures of difficult-to-separate regioisomers.

With the two building blocks available, a first Suzuki cross-coupling of the two moieties was achieved in DMF with K_3PO_4 as the base (see Table 2, entry 1), which (according to ^1H NMR) resulted in a 62:38 mixture of the two expected atropisomers in 50% yield. Although the two diastereomers showed a very similar chromatographical behavior on reversed-phase HPLC, they were easily separable by simple silica gel column chromatography, in contrast to more difficult previous separations of other, related atropo-diastereomers (which could only be resolved on a chiral phase, as if they were enantiomers).[33,41] Similar to related other cases,[42–44] this atropisomer-differentiating chromatographical behavior is presumably due to interactions of the free phenolic group at C-4′ with the silica gel. The more rapidly eluting isomer proved to be identical in all spectroscopic, chromatographical, and physical properties with the authentic natural product, 5-*epi*-4′-*O*-demethylancistrobertsonine C, thus confirming the structure previously published,[11] in all details.

The assumption that the two obtained products were really atropo-diastereomers, was demonstrated by their mirror-shaped circular dichroism (CD) curves (Fig. 1b), as measured offline. The spectrum of the more rapidly eluting isomer (peak A) perfectly matched the one of the natural product and was also in a good agreement with that of the structurally related, likewise 5,8′-



Scheme 2. Synthetic pathway to 5-*epi*-4′-*O*-demethylancistrobertsonine C (**1a**) and its atropo-diastereomer **1b**.