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Total Synthesis of the *N,C*-Coupled Naphthylisoquinoline Alkaloids Ancistrocladinium A and B and Related Analogues

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Abstract: The *N,C*-coupled naphthyldihydroisoquinoline alkaloids ancistrocladinium A (**3**) and B (**4**), which possess an unprecedented iminium-aryl axis and show high in vitro antileishmanial activities, have been synthesized via a short sequence of eight linear steps, without the need of protecting groups. Key steps were a Buchwald−Hartwig amination and a Bischler−Napieralski cyclization, preferentially leading to the naturally predominant *M*-atropo-diastereomer in the case of **3**, while the *N,C*-axis is configurationally semistable in **4**. The highly convergent first access to this type of alkaloids will now facilitate the preparation of structural analogues for structure−activity relationship studies. Its general applicability was shown by the preparation of the sterically even more congested, as yet unnatural *N*,3′- and *N*,1′-coupled analogues, ancistrocladinium C (**5**) and D (**6**).

Introduction

Plants of the families Ancistrocladaceae and Dioncophyllaceae are a rich, and the as yet only, source of naphthylisoquinoline alkaloids.[1,2] More than 140 representatives of these structurally and biosynthetically unique, bioactive natural products have so far been isolated from the evergreen vines indigenous to the rainforests of tropical Africa and South-East Asia.[3] Some of them show promising bioactivities against pathogens of severe, and widespread, tropical diseases. As an example, dioncophylline C (**1**, see Figure 1) exhibits a strong activity against different *Plasmodium* species, both in vitro and *in vivo*.[4−6] Butler et al.[7] described the occurrence of a first, apparently racemic, *N,C*-coupled naphthylisoquinoline alkaloid, ancisheynine (**2**), which was synthetically accessed and stereochemically characterized by our group.[8] From an as yet not fully identified, possibly new *Ancistrocladus* species occurring in the rainforest in the Democratic Republic of Congo,[9,10] we have recently discovered the first *N,C*-coupled naphthyldihydroisoquinolines, ancistrocladinium A (**3**), which has an unprecedented rotationally hindered *N,C*-axis, and B (**4**), which is configurationally semistable.[9] Because **3** and **4** display very good antiparasitic properties, especially against the protozoan pathogen *Leishmania major* even in the low micromolar range,[11] these natural products are promising lead structures[12,13] for urgently needed novel anti-infective drugs. The facile availability of these compounds in sufficient quantities for further biological and medicinal studies, for example, by total synthesis, is thus an important task.

Most of the numerous "normal", *C,C*-coupled naphthylisoquinoline alkaloids synthesized so far have been constructed by using the "lactone method",[14−17] an efficient pathway to

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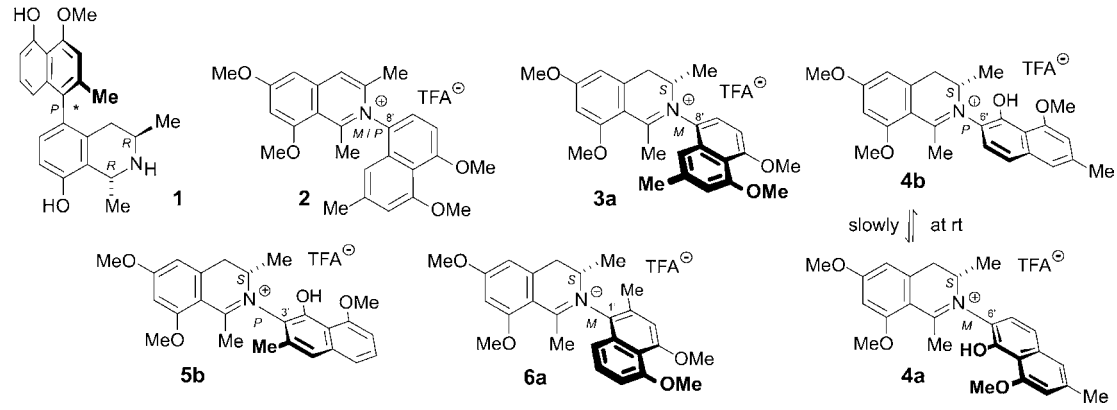

Figure 1. Different coupling types of naphthylisoquinolines: the *C*,*C*-linked dioncophylline C (**1**) and the *N*,*C*-coupled analogues ancisheynine (**2**), ancistrocladinium A (**3**), B (**4**), C (**5**), and D (**6**); for **3**, **5**, and **6**, only the respective main atropo-diastereomers **3a**, **5b**, and **6a** are shown.

rotationally stable biaryls established by our group.[18−20] Basic requirements for the applicability of this approach, however, are the presence of an oxygen function and an (at least cryptic)[14] C_1 group next to the axis, for the construction of the lactone bridge. The latter precondition is not present in ancistrocladinium A (**3**), and because a direct *N*-arylation, for example, by Buchwald−Hartwig amination, is restricted to primary and secondary amines as substrates[21−25] and thus cannot be applied to cyclic imines, it seemed more favorable to prepare the naphthylisoquinolines **3**−**6** through an alternative approach. The only previous total synthesis of an *N*,*C*-coupled naphthylisoquinoline alkaloid, ancisheynine (**2**), was achieved by the condensation of a monocyclic diketone (or the respective benzopyrylium salt) with an aminonaphthalene, leading to a fully dehydrogenated isoquinolinium moiety.[8]

We now report on the first total synthesis of the highly antiinfective *N*,*C*-coupled naphthyldihydroisoquinoline alkaloids ancistrocladinium A (**3**) and B (**4**) by a Buchwald−Hartwig amination → Bischler−Napieralski cyclization sequence. The flexible synthetic strategy also paves the way for the construction of conceivable other members of this class, natural or unnatural, and thus permits easy access to a broad variety of structurally diverse compounds for structure−activity relationship studies (SAR). The general use of the developed method, including sterically even more demanding representatives, was demonstrated by the preparation of the related regioisomeric *N*,3′- and *N*,1′-coupled analogues **5** and **6** (see Figure 1), likewise potential natural products, which have not yet been found in nature so far.

Results and Discussion

Retrosynthetic Analysis. In contrast to the total synthesis of the "normal", *C*,*C*-linked naphthylisoquinoline alkaloids, such as dioncophylline C (**1**),[26,27] in which the key step is the stepwise construction of the central biaryl axis by the "lactone method",[3,18−20] a different approach had to be envisaged for the new alkaloids **3** and **4**. This strategy was also intended to avoid possible problems of regioselectivity and overoxidation as expected from a more biomimetically oriented[28] oxidative *N*,*C*-cross coupling of the corresponding dihydroisoquinoline and naphthalene portions.[29] As exemplarily illustrated for ancistrocladinium A (**3**), a more promising strategy should be based on the transition-metal-mediated coupling of the known[30] *S*-configured amine **8** with the appropriately brominated naphthalene **9**[31] to give the secondary amine **7** (see Figure 2), followed by Bischler−Napieralski ring closure[30,32] to give the target molecule **3**. The late-stage attachment of the isoquinoline precursor to the naphthalene moiety and thus the separate preparation of the two molecular portions (and also the C-1-methyl part, here from acetyl chloride) was expected to permit a high degree of molecular diversity by individual structural variations of these three molecular modules. The strategy should provide the potential to yield a broad variety of structurally diverse analogues for in-depth SAR investigations. To keep the synthesis as short and efficient as possible, only directing groups were used, but no protective groups.

Some of the substituted naphthalenes, such as the 8-bromo compound **9**, can be obtained by literature procedures.[31] The enantiomerically pure amine **8** should be accessible by a regioselective ring-opening of the *N*-Boc-functionalized aziridine **11** using a *C*-nucleophile generated in situ.

Preparation of the Primary Amine 8. A key intermediate in the total synthesis of both alkaloids, ancistrocladinium A (**3**)

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(28) Like for *C*,*C*-coupled analogues,[70] a separate formation of the isoquinoline and naphthalene portion is assumed for the biosynthetic formation of **3** (as also for **2** and **4**), followed by a phenol-oxidative cross coupling.
(29) For a successful biomimetic cross coupling to give *N*,*C*-coupled dimers in the field of carbazole alkaloids, see: Bringmann, G.; Tasler, S.; Endress, H.; Kraus, J.; Messer, K.; Wohlfahrt, M.; Lobin, W. *J. Am. Chem. Soc.* **2001**, *123*, 2703.
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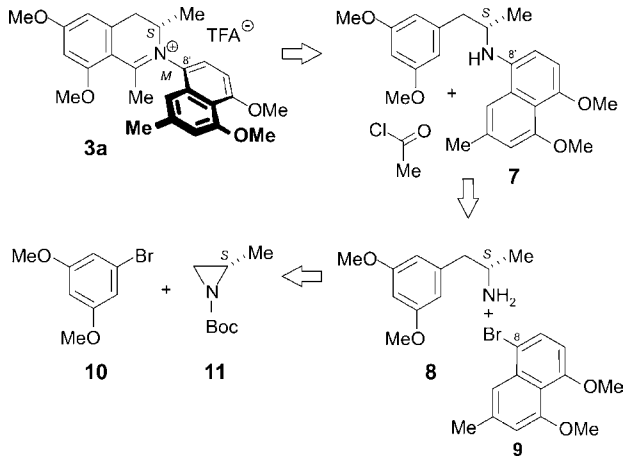
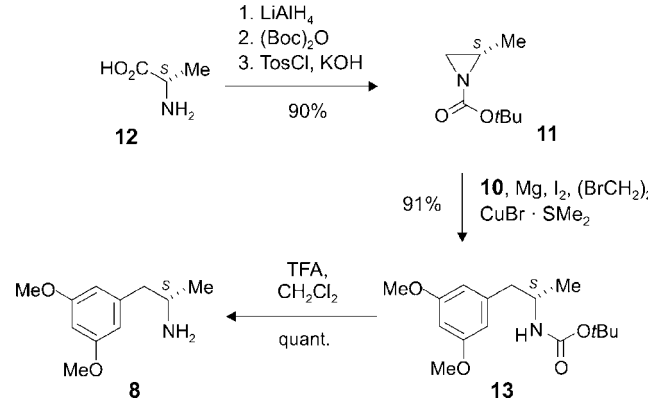


Figure 2. Retrosynthetic analysis of *N*,*C*-linked naphthyldihydroisoquinoline alkaloids, exemplified for ancistrocladinium A (**3**).

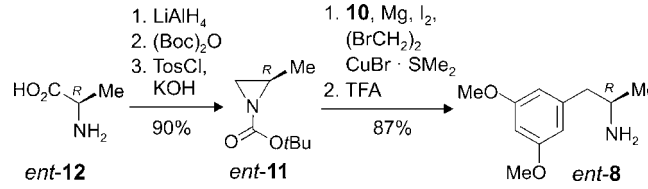
and B (**4**), is the enantiopure 1-aryl-2-propylamine **8**. Different from an enantioselective seven-step synthesis based on the reductive amination of 1-aryl-2-propanones,[30] we have now further developed an approach via chiral aziridines initially used by Hoye et al. for the directed synthesis of, albeit 3*R*-configured, naphthylisoquinoline alkaloids.[33,34] *N*-Tosyl activated aziridines (not shown) have proven to be valuable intermediates in organic synthesis because of their ability to undergo highly regio- and stereoselective ring-opening reactions with a wide variety of nucleophiles.[35,36] Their strain-induced reactivity permits rapid conversion into a wide range of derivatives,[35−40] making the use of an aziridine for the preparation of the enantiopure 2-propylamine **8** a rewarding option. Because of the harsh reaction conditions often required for the subsequent removal of the *N*-substituents,[41−43] like the previously used *N*-tosyl groups,[33,34] we searched for a more suitable directing group that should activate the aziridine toward a nucleophilic ring-opening at the less substituted carbon atom and, simultaneously, would permit its mild cleavage. For this purpose, the *N*-Boc group turned out to be ideally suited.

After reduction of L-alanine (**12**) with $LiAlH_4$[44] and *N*-functionalization with $(Boc)_2O$,[45] cyclization was achieved by intramolecular S_N2 displacement of the likewise, in situ, generated *O*-tosyl group,[46] giving the aziridine **11** in 90% overall yield. The Grignard reagent prepared in situ from **10**[47] was

Scheme 1. Improved Synthesis of the *S*-Configured Primary Amine **8**



Scheme 2. Analogous Preparation of the *R*-Configured Amine *ent*-**8**



reacted with **11** in the presence of catalytic $CuBr \cdot SMe_2$ (10 mol %), furnishing the *N*-Boc amine **13** in an excellent yield of 91%, without any loss of optical purity. Final removal of the *N*-Boc directing group of **13** yielded the primary amine **8** in quantitative yield (Scheme 1). Enantiomerically pure **8** was thus available in five steps and 81% overall yield, which constitutes a significant improvement over previously established pathways to **8** (seven and five steps in 33%[30] and 36% yield,[33,34] respectively).

Hence, a short and practicable procedure for the preparation of 1-aryl-2-propyl amines of type **8** as the central precursor for the planned first total synthesis of *N*,*C*-coupled naphthyldihydroisoquinolines on a multigram scale had become available, utilizing cheap optically pure starting material from the chiral pool. The strategy should also permit variation of the absolute configuration and of the identity of the eventual C-3 substituent (here Me) by using configurationally or constitutionally different amino acids. This was demonstrated by the analogous preparation of the enantiomeric primary amine *ent*-**8** from D-alanine (*ent*-**12**) (Scheme 2) in a similar yield (78%).

Synthesis of Ancistrocladinium A (3). For the synthesis of the *N*,8′-coupled alkaloid ancistrocladinium A (**3**), the bromonaphthalene **9**[31] had to be transformed into the secondary amine **7** by Buchwald−Hartwig amination with **8** (Scheme 3). The use of chelating ligands such as BINAP[48,49] or DPPF[50] for the nitrogen−carbon bond formation is known to provide high yields for the reaction of primary alkylamines and arylbromides,[49] as these ligands prevent rapid β-hydrogen elimination[24] and diarylation[48] of the amine. On the other hand, intermolecular palladium-catalyzed *N*-arylation can proceed with loss of optical purity for substrates bearing a stereogenic center in the α-position to the nitrogen atom, such as the amine **8**, if monodentate

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(46) Wessig, P.; Schwarz, J. *Synlett* **1997**, 893.
(47) By using dimethoxybromobenzene **10** instead of the corresponding chlorobenzene derivative, as applied by Hoye et al.,[33,34] the reaction time for generating the Grignard reagent was reduced from 12 to 2.5 h.
(48) Wolfe, J. P.; Wagaw, S.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 7215.
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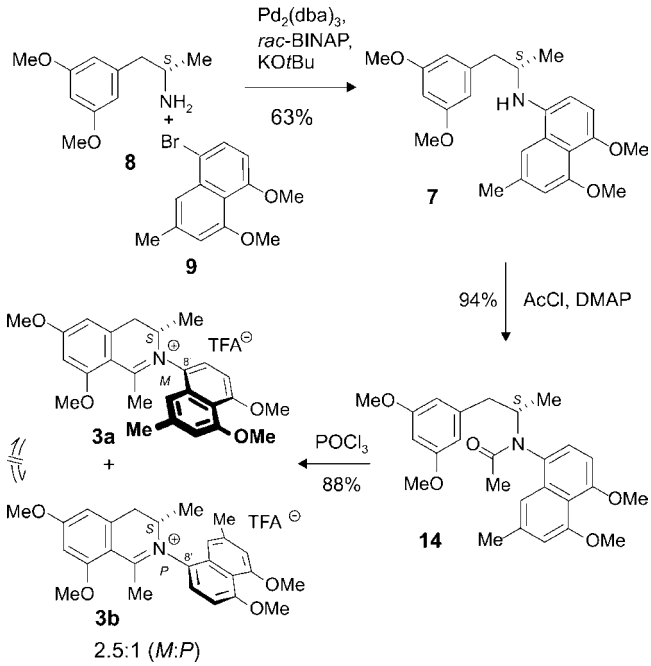
(50) Driver, M. S.; Hartwig, J. F. *J. Am. Chem. Soc.* **1996**, *118*, 7217.

Scheme 3. Synthesis of Ancistrocladinium A (**3**) by a Buchwald−Hartwig Amination → Bischler−Napieralski Ring Closure Sequence



ligands are utilized.[48] The use of a chelating ligand like *rac*-BINAP was thus necessary for the *N*-arylation of the chiral amine **8** with the bromonaphthalene **9**. Despite the electron-rich character of this arylhalide, the secondary amine **7** was obtained in as much as 63% yield when using $Pd_2(dba)_3$ as the transition-metal catalyst and KO*t*Bu as the base.[51] The catalyst loading was decreased to 1 mol % without diminishing the chemical yield if the reaction was run in refluxing toluene. *N*-Acetylation of amine **7** gave the amide **14**, whose Bischler−Napieralski cyclization afforded ancistrocladinium A (**3**) as a 2.5:1 mixture of atropo-diastereomers in an excellent yield (83%). Despite extensive variations of the reaction parameters (temperature, Lewis acid, and solvent), the diastereomeric excess could not be changed substantially during the cyclization reaction. As already reported for the isolated natural product **3**,[9] all attempts to resolve the atropo-diastereomers, **3a** and **3b**, failed, even on chiral HPLC phases.

The chromatographic, physical, and spectroscopic properties of synthetic **3** were identical to those of the authentic natural product in all respects, including the prevalence of the naturally predominant *M*-atropo-diastereomer **3a** in the synthetic product, so that the only difference in the NMR spectra was the relative intensity of the signals of **3a** versus those of **3b** due to a different diastereomeric ratio of synthetic and natural **3**, which was 10:1 (*M*:*P*) for ancistrocladinium A (**3**) isolated from *Ancistrocladus ikela*.[9] The circular dichroism (CD) spectrum of ancistrocladinium A (**3**) obtained by total synthesis was in good agreement with the CD curve of isolated **3** (Figure 3), thus confirming the absolute configuration at the iminium-carbon axis of the major synthetic diastereomer, **3a**, as *M*.

In a similar way, by applying the same strategy as above, yet starting from *ent*-**8** instead of **8**, the synthesis of the unnatural

(51) For further, more recent Buchwald−Hartwig aminations on likewise electron-rich substrates, see: Organ, M. G.; Abdel-Hadi, M.; Avola, S.; Dubovyk, I.; Hadei, N.; Kantchev, E. A. B.; O'Brien, C. J.; Sayah, M.; Valente, C. *Chem.-Eur. J.* **2008**, *14*, 2443. Saelinger, D.; Brueckner, R. *Synlett* **2009**, 109.

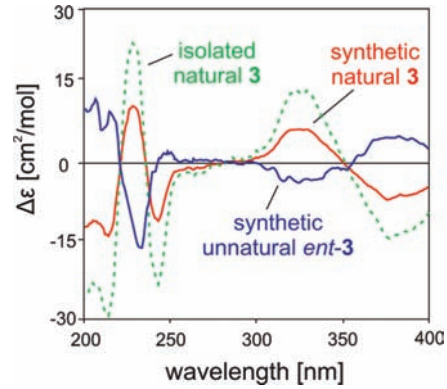
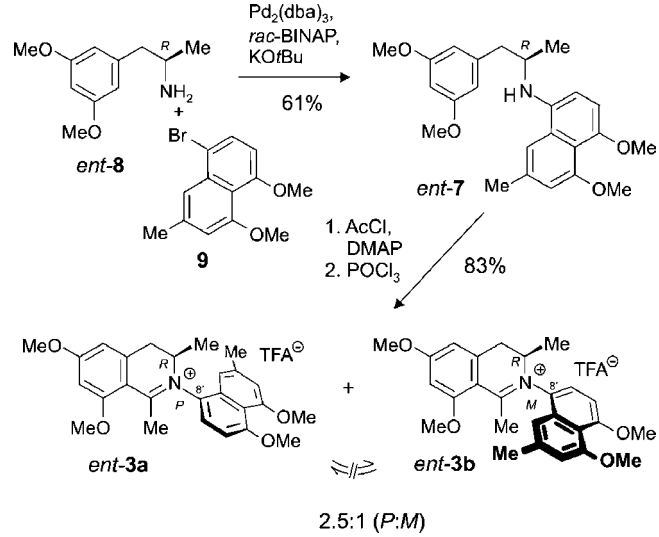


Figure 3. Comparison of the CD spectrum of synthetic ancistrocladinium A (**3**) and its enantiomer, *ent*-**3**, with that of the natural-derived alkaloid **3** to confirm the absolute configuration of the major atropo-diastereomers.

Scheme 4. Preparation of the Unnatural (3*R*)-Enantiomers of Ancistrocladinium A



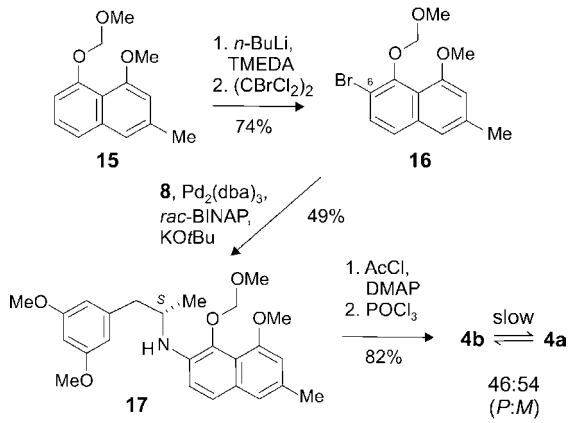
enantiomer *ent*-**3** of ancistrocladinium A (**3**), now with *R*-configuration at C-3, succeeded (Scheme 4). Pd-catalyzed Buchwald−Hartwig *N*,*C*-coupling of the two molecular portions, *ent*-**8** and **9**, gave the secondary amine *ent*-**7** in 61% yield. Formation of the acetamide and Bischler−Napieralski cyclization delivered *ent*-**3** in 83% yield, again in a 2.5:1-ratio of the respective atropo-diastereomers, *ent*-**3a** and *ent*-**3b**.

As expected, the CD spectrum of synthetic *ent*-**3** was opposite to the curves of both, natural and synthetic ancistrocladinium A (**3**), confirming the absolute configuration at the *N*,*C*-axis of *ent*-**3** to be *P* in its major atropo-diastereomer (see Figure 3). The total synthesis of both, **3** and *ent*-**3**, fully corroborates the previous structural assignment[9] of the isolated natural product.

Synthesis of Ancistrocladinium B (4). With this first synthetic route to an *N*,*C*-coupled naphthyldihydroisoquinoline alkaloid, ancistrocladinium A (**3**), elaborated, we focused on the construction of other members of this novel subclass of alkaloids, such as the antileishmanial[11] alkaloid ancistrocladinium B (**4**).[9] Because **3** and **4** just differ by their coupling positions (*N*,8′ vs *N*,6′) and their *O*-methylation patterns (OH instead of OMe at C-5′), only the naphthalene module (i.e., **9** for the synthesis of **3** above) had to be replaced by the 6-bromonaphthalene **16**.

The required naphthalene precursor **15** (Scheme 5) was obtained in analogy to a literature procedure.[52−54] Introduction

Scheme 5. Preparation of Ancistrocladinium B (**4**)



of the bromine at C-6 was attained by applying the "directed *ortho*-metalation" (D*o*M) strategy,[55,56] assisted by the methoxymethyl (MOM) ether group at C-5. Thus, treatment of **15** with *n*-butyllithium/*N*,*N*,*N*′,*N*′-tetramethylethylendiamine (TMEDA) at −10 °C, followed by careful addition of 1,2-dibromotetrachloroethane to the C-6 metalated intermediate, gave the desired building block **16** exclusively (Scheme 5). 2D-NOESY investigations confirmed the bromo substituent of **16** to be located at the 6-position of the naphthalene, without any regioisomeric or overhalogenated byproduct. At lower temperatures, the reaction proceeded very slowly, while inseparable mixtures of the differently halogenated products were obtained at room temperature.

Nitrogen−carbon bond formation of the primary amine **8** with the 6-bromonaphthalene **16** utilizing $Pd_2(dba)_3$/*rac*-BINAP as the catalytic system and KO*t*Bu as the base gave amine **17** in a satisfying yield (49%, Scheme 5). *N*-Acetylation of **17** and Lewis-acid mediated ring closure with concomitant cleavage of the MOM directing group in the naphthalene portion yielded ancistrocladinium B (**4**) in 82% yield and as a 46:54 mixture (see Figure 4) of atropo-diastereomers. NMR investigations and comparison of the chromatographic and physical data of the obtained product with those of the natural alkaloid **4** revealed the major diastereomer to be *M*-configured at its iminium-aryl axis. The slight preference for **4a** is in agreement with the thermodynamically controlled equilibrium of the two configurationally semistable atropo-diastereomers of **4**, which slowly interconvert at room temperature, by rotation about the *N*,*C*-axis.[9]

The assignment of the absolute axial configuration of the two atropo-diastereomers of ancistrocladinium B (**4**) was further corroborated by their HPLC resolution in hyphenation with CD spectroscopy (Figure 4a). As already described for the authentic natural product,[9] this separation succeeds easily. The CD spectra of peaks I (rapid) and II (slow, Figure 4b), which were recorded in the stopped-flow mode,[57] were almost mirror-imaged, although derived from diastereomers and not from enantiomers, showing that the iminium-carbon linkage and thus the orientation of the major aryl chromophores dominates the CD curve over

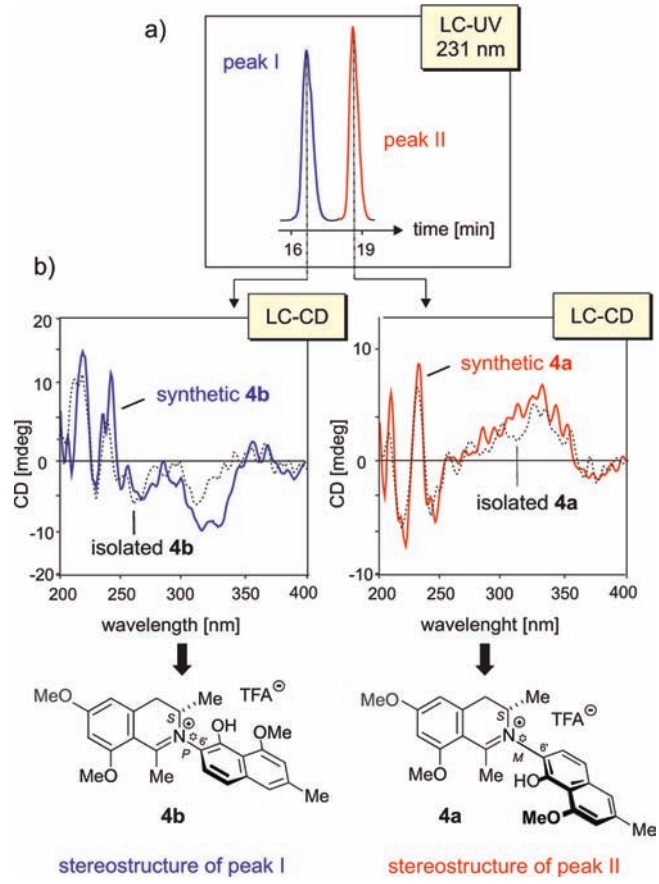


Figure 4. Stereochemical assignment of the two diastereomers of synthetic ancistrocladinium B (**4**) by LC−CD coupling and comparison of the obtained CD spectra with those of the isolated alkaloid **4**.

the chiroptical contribution of the stereogenic carbon center. A similar phenomenon is known for many "normal", *C*,*C*-linked naphthylisoquinoline alkaloids.[58,59] The spectrum of the more rapidly eluting isomer (peak I) perfectly matched the CD curve of the *P*-isomer of the natural alkaloid, **4b**, while the curve of the slower isomer (peak II) was in excellent agreement with that of the *M*-atropo-diastereomer of isolated **4**. By this comparison, and by the chromatographic and spectroscopic identity of **4** from synthetic and natural origins, the structure of the natural product[9] was fully confirmed, including the absolute configuration.

Synthesis of Ancistrocladinium C (5) and D (6). To validate the general applicability of the developed first synthetic pathway to *N*,*C*-coupled naphthyldihydroisoquinolines, to even sterically more congested representatives, the *N*,3′- and *N*,1′-linked analogues **5** and **6** were prepared, too. The synthesis of **5** and **6**, which are as yet unknown as natural products, should, simultaneously, facilitate the directed search for these compounds in nature and permit studies on the impact of the coupling position in the naphthalene moiety on the anti-infective activity.

The naphthalene building block **20**, with the halogen atom now at C-3, was obtained from the known[60] naphthol **18**, which

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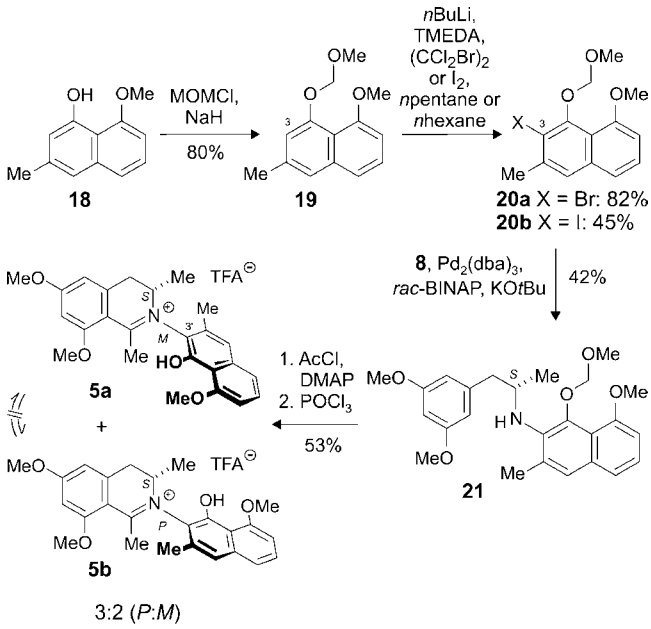
Scheme 6. Synthesis of the *N*,3′-Coupled Naphthyldihydroisoquinoline Ancistrocladinium C (**5**), an As Yet Unknown but Imaginable Natural Product



was accessible by Diels−Alder reaction of 2-bromoanisole and *N*,*N*′-diethyl-3,3-dimethylacrylamide (not shown).[61] After formation of the methoxymethylether **19**, the bromide was introduced selectively by a D*o*M reaction (Scheme 6). By using THF as a strongly coordinating solvent, the bromonaphthalene **20a** was obtained, but only in 42% yield. Replacing the THF by a nonpolar and thus noncoordinative solvent, such as *n*-pentane, the bromination was achieved in 82% yield.

Linkage of the amine **8** and the naphthalene **20a** under the same Buchwald−Hartwig conditions as described for the synthesis of ancistrocladinium A (**3**) and B (**4**) unfortunately did not give the desired product **21**, despite extended variations of the reaction parameters such as palladium source, ligand, base, and solvent, but only resulted in the reisolation of starting materials. This lack of reactivity can be explained by the substantially higher steric hindrance and the further increased electron density at the coupling site of the naphthalene substrate **20a** as compared to the above reacted arylbromides, **9** and **16**. To facilitate the oxidative addition of the naphthalene **20**, and thus the successful formation of **21**, the more reactive iodonaphthalene **20b** was used as a substrate, which was also accessible from **19** using a D*o*M reaction (45% yield). Amination of the building block **20b** with **8** gave **21** in 42% yield after 3 d (Scheme 6). This secondary amine was further transformed into the final product **5** by *N*-acetylation followed by cyclization of the resulting acetamide. The isoquinoline **5** was obtained as a 3:2-mixture of, in this case configurationally stable, atropodiastereomers (*P*:*M*) and in 53% chemical yield.

In accordance with the known representatives of this class of isoquinolines, ancistrocladinium A (**3**) and B (**4**), and due to its *N*,3′-coupling of the two molecular portions, compound **5** was henceforth given the name ancistrocladinium C.

The configuration at the axis relative to the stereogenic centers at C-3 was deduced from an NOE correlation between the protons of the methyl group at C-2′ and at H-3, which, in view

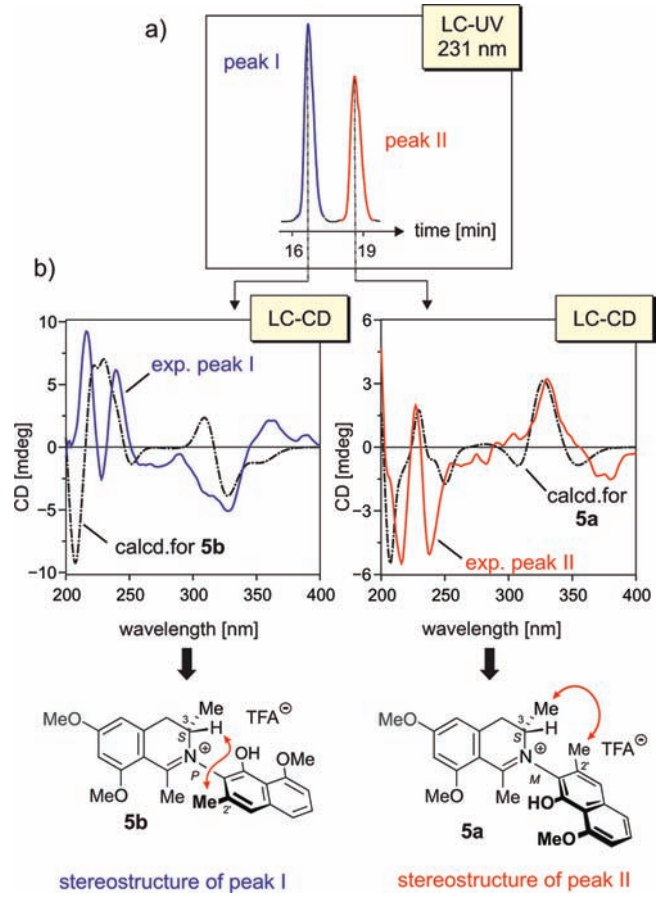


Figure 5. Assignment of the relative and absolute axial configurations of the two atropo-diastereomers of ancistrocladinium C (**5**) by NOE investigations and quantum chemical CD calculations, respectively (for the respective offline CD spectra of the pure isolated atropo-diastereomers, see the Supporting Information).

of the *S*-configuration at C-3, indicated an absolute *P*-configuration at the *N*,*C*-axis for peak I (Figure 5a, left). In a complementary way, an NOE interaction between the methyl groups at C-3 and C-2′ revealed an axial *M*-configuration for peak II (Figure 5a, right). These assignments were further corroborated by the individual CD spectra of the two atropodiastereomers recorded online, by HPLC-CD in the stopped flow mode.[57] The two spectra were found to be virtually opposite to each other, again due to the dominant CD effect of the element of axial chirality (Figure 5b),[58,59] and showed a strong analogy to the spectra recorded for the regioisomeric alkaloids **4a** and **4b** (Figure 4).

An efficient and reliable method for the assignment of absolute stereostructures is the combination of experimental CD investigations with quantum chemical CD calculations.[62] With the stereogenic center at C-3 known to be *S*-configured, theoretical investigations concentrated on the absolute configuration at the chiral axes, that is, on the two possible atropodiastereomers of **5**. The analysis of the conformational space based on DFT (B3LYP/6-31G*)[63−66] led to four relevant

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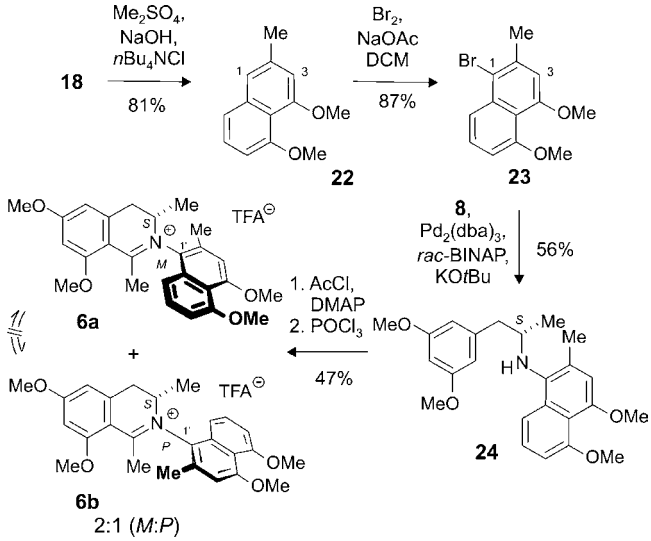
Scheme 7. Synthesis of the *N*,1′-Coupled Naphthyldihydroisoquinoline Ancistrocladinium D (**6**)



conformers (within a range of 3 kcal mol^{-1}) for each of the isomers. These structures were subjected to RI-SCS-MP2/TZVP[67,68] single-point energy calculations to provide more reliable values for the enthalpy of formation. On the basis of these conformers, CD calculations were now carried out with TDB3LYP using the 6-31G* basis set. The curve calculated for **5b** was found to match with the experimental one of peak I (Figure 5b, left), while peak II gave a match with the CD curve predicted for **5a** (Figure 5b, right). This led to the clear attribution of the absolute configurations of the two atropo-diastereomers of ancistrocladinium C (**5**), finally confirming the results of the NOE correlations above.

For the synthesis of the sterically even more hindered *N*,1′-linked naphthylisoquinoline **6**, a regioselective introduction of the bromine substituent at C-1 was required after *O*-methylation of **18** (Scheme 7). In this case, the method of choice was an electrophilic bromination reaction with Br_2, directly on **22**, which occurred predominantly at C-1, leading to the desired bromonaphthalene **23**. Optimum reaction conditions were found by using a slight excess of bromine at −40 °C in the presence of sodium acetate (1.2 equiv), giving **23** together with a small amount of dibrominated product. The latter was easily removed by column chromatography, yielding pure **23** in 87% yield.

Amination of the building block **23** with the primary amine **8** was achieved under the same conditions as described for the synthesis of ancistrocladinium A (**3**) and B (**4**), giving the amine **24** in an initially unsatisfactory 31% yield after 2 d (Scheme 7). The low conversion can be explained by the substantially higher steric hindrance and the further increased electron density at the coupling site of the naphthalene substrate **23** as compared to the above reacted arylbromides **9** and **16**. By addition of a second portion of catalyst after 48 h (1 mol % $Pd_2(dba)_3$ and 2 mol % BINAP) and refluxing for another 24 h, the yield was improved to 56%. Conversion of **24** into the *N*,1′-naphthyldihydroisoquinoline **6** succeeded by *N*-acetylation and Bischler−Napieralski cyclization in 47% chemical yield to furnish the target molecule **6** as a 2:1-mixture of its, configurationally stable, atropo-diastereomers, **6a** and **6b**. Remarkably, and in contrast to the closely related regioisomeric natural product ancistrocladinium A (**3a/b**), resolution of **6a** and **6b** succeeded on a Waters Symmetry C_{18} column. Because of its coupling type, **6** was named ancistrocladinium D.

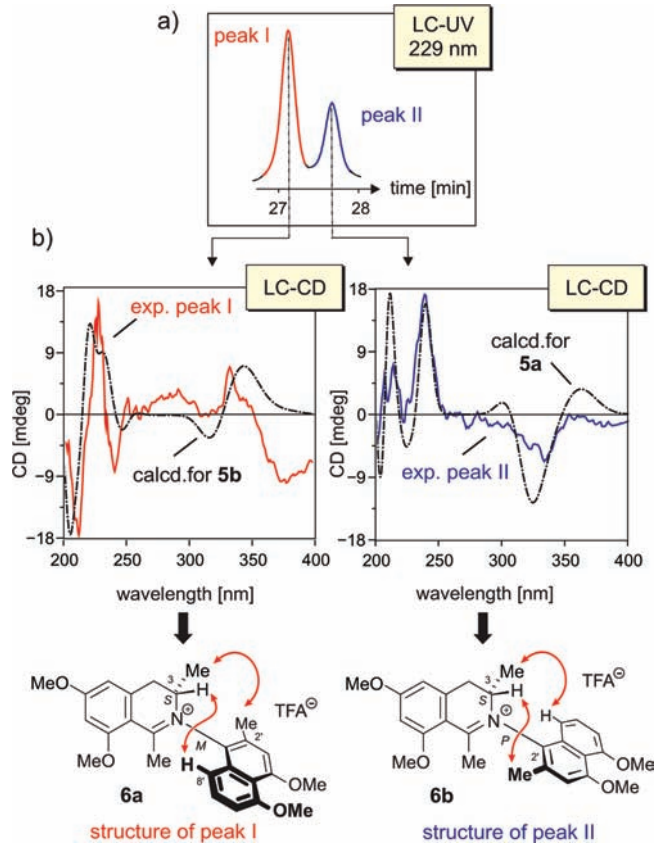


Figure 6. Stereochemical assignment of the axial configurations of the two atropo-diastereomers of ancistrocladinium D (**6**) by NOE investigations and LC−CD coupling in combination with quantum chemical CD calculations. Similar CD spectra were obtained offline, after preparative resolution of **6a** and **6b** (see the Supporting Information).

The axial configurations of the two atropo-diastereomeric products relative to the stereocenters were established by 2D-NOESY investigations on the pure isolated isomers. Interactions between H-8′ and the proton at C-3 (Figure 6b, bottom left) of the major diastereomer of **6** revealed that these spin systems were on the same side of the isoquinoline "plane", while the interactions between the methyl groups at C-2′ and C-3 indicated that these groups were both located on the other side. This, in combination with the known absolute *S*-configuration of the stereogenic center at C-3, permitted assignment of the absolute configuration at the axis of the major diastereomer of ancistrocladinium D, **6a**, as *M*. In a similar way, NOESY correlations between H-3 and the Me-2′ and between the methyl substituent at C-3 and the proton at H-8′ for the minor diastereomer, **6b** (Figure 6b, bottom right), again in conjunction with the known *S*-configuration at C-3, revealed a *P*-configuration at its iminium-aryl axis, thus also corroborating the above assignment for **6a**.

To further confirm the absolute axial configuration of ancistrocladinium D (**6**), LC−CD investigations were carried out in the stopped-flow mode (Figure 6b). Because **6** constitutes the first representative of an *N*,1′-coupled naphthyldihydroisoquinoline, again quantum chemical CD calculations were performed. Given the known absolute configuration at the stereogenic center at C-3, only the two possible 3*S*-diastereomers of **6** were investigated. As for **5a** and **5b** (see above), the same conformational investigations, DFT geometry optimizations, and

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single-point energy calculations were performed on the two atropisomers of **6**, again leading to four relevant conformers each. For these conformers, CD calculations by TDB3LYP permitted a first assignment of the absolute configurations, but the agreement between the theoretical spectra and the experimental ones, especially in the case of **6b**, was not perfect over the whole range of wavelengths. Slightly improved results were achieved when taking into account solvent effects, by using the COSMO approach, but still the shorter-wavelength region (210−230 nm) in the experimental curve of the more slowly eluting atropo-diastereomer (peak II) provisionally assigned as **6b** (see above) was not reproduced. Therefore, a combined approach of DFT (B3LYP/SVP) and MRCI methods[69] was pursued, resulting in much more accurate excitation energies and a nearly perfect match between peak I and the CD curve predicted for **6a** (Figure 6b, left), on the one hand, and between peak II and the curve computated for **6b** (Figure 6b, right), on the other. This permitted an unambiguous assignment of the absolute configurations of the two atropo-diastereomers of ancistrocladinium D (**6**), thus leading to the same results as deduced from the observed NOE correlations for the two signal sets in ^{1}H NMR (see Figure 6, bottom).

Conclusion

Because of their unprecedented molecular architectures, their potent activities against several pathogens of infectious diseases, and their difficult availability from plant resources, the *N*,*C*-linked naphthyldihydroisoquinolinium alkaloids ancistrocladinium A (**3**) and B (**4**) are valuable synthetic targets. We have therefore developed effective and convergent synthetic pathways to prepare these plant metabolites, and the not (yet) isolated *N*,3′- and *N*,1′-coupled analogues **5** and **6**, accessible in larger quantities, including the possibility to produce a plethora of structurally diverse analogues and derivatives. Starting from L-alanine (**12**), the first *N*-naphthyldihydroisoquinoline alkaloids were synthesized, via the key precursor **8**, in only eight linear steps and good yields, for example, in 43% overall yield in the case of ancistrocladinium A (**3**), and without the need of protective groups. The coupling of the two molecular portions at a late stage of the synthesis by Buchwald−Hartwig amination, followed by *N*-acetylation and cyclization to the *N*-aryldihydroisoquinoline, furthermore makes this convergent approach a versatile strategy for generating structurally diverse analogues of these natural products. This was demonstrated in the likewise successful first total synthesis of the related alkaloid ancistrocladinium B (**4**) and the as yet unknown, sterically even more hindered regioisomers ancistrocladinium C (**5**) and D (**6**). The presented work paves the way for ongoing studies on this promising class of anti-infective lead compounds, which will help to gain deeper insight into their structure−activity relationships, and, thus, to improve their activity and selectivity, and to decrease their cytotoxicity against mammalian cells. For the future, more detailed investigations on the stereochemical course of the Bischler−Napieralski ring closure and the improvement of the stereoselectivity, or even a directed, diastereo-divergent preparation of any of the respected atropoisomers, will be of high interest. This work is currently in progress.

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Supporting Information Available: Full characterization, including copies of ^{1}H and ^{13}C NMR spectra, and experimental procedures for selected compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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