ORGANIC LETTERS

2006
Vol. 8, No. 6
1037−1040

Ancisheynine, the First *N,C*-Coupled Naphthylisoquinoline Alkaloid: Total Synthesis and Stereochemical Analysis†

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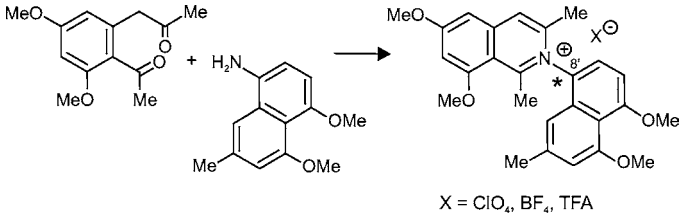
Received December 5, 2005

ABSTRACT



The first total synthesis of an *N,C*-coupled naphthylisoquinoline alkaloid—ancisheynine—was achieved by condensing a monocyclic diketone or the respective benzopyrylium salt with an aminonaphthalene. The presence of a rotationally hindered axis in ancisheynine was demonstrated by resolution of its two atropo-enantiomers by HPLC on a chiral phase with LC-CD coupling. The assignment of their axial configurations succeeded by quantum chemical CD calculations.

The naphthylisoquinoline alkaloids comprise a rapidly growing class of remarkable secondary metabolites from tropical lianas of the Dioncophyllaceae and Ancistrocladaceae families.[1,2] These natural products are of interest for their pharmacological activities,[1,3] e.g., against *Plasmodium falciparum*,[4] and their unprecedented biosynthetic origin via the acetate−malonate pathway.[5] Also remarkable is their structural variety: Besides their variable oxidation states, their oxygenation and *O*-methylation patterns, and their stereostructures (usually involving stereogenic centers and axes), the alkaloids differ in their coupling sites in the isoquinoline part (C5 and C7) and in the naphthalene portion (C1′, C3′, C6′, and C8′). This results in the large number of as yet more than 120 known natural naphthylisoquinolines, among them the 5,1′-linked ancistrocladine (**1**, Figure 1)[6] and the 7,8′-coupled ancistroheynine A (**2**),[7] both from *Ancistrocladus heyneanus*. Recently, the first *N,C*-coupled naphthylisoquinoline, ancisheynine (**3**, natural counteranion, X^-, unknown), was discovered in the same plant.[8] Despite the existence of an apparently rotationally hindered heterobiaryl axis, ancisheynine (**3**) was reported to be optically inactive ($\alpha_D = 0°$), but no stereochemical investigations were performed, e.g., concerning the exact enantiomeric ratio.

In this paper, we describe the convergent first total synthesis of ancisheynine (**3**) and its racemate resolution on a chiral HPLC phase, providing an analytical method, e.g.,

† Acetogenic Isoquinoline Alkaloids. 162. For part 161, see: Bringmann, G.; Dreyer, M.; Kopff, H.; Rischer, H.; Wohlfarth, M.; Hadi, H. A.; Brun, R.; Meimberg, H.; Heubl, G. *J. Nat. Prod.* **2005**, *68*, 686.

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10.1021/ol052946p CCC: $33.50
Published on Web 02/16/2006

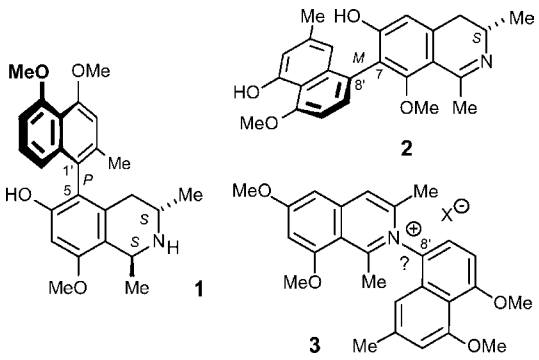
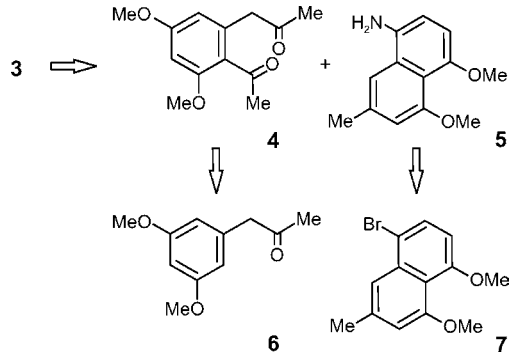


Figure 1. Differently coupled naphthylisoquinoline alkaloids.

for the determination of the enantiomeric purity of this new type of alkaloids in nature. In contrast to the previous total syntheses of "normal", i.e., *C*,*C*-coupled naphthylisoquinolines, in which the key step is the construction of the central biaryl axis,[9] a different approach was envisaged for the new *N*,*C*-coupled naphthylisoquinoline. This strategy avoids problems of regioselectivity as expected from a more biomimetically oriented oxidative *N*,*C*-cross coupling of the corresponding 1,3-dimethylisoquinoline with the respective naphthalene.[10]

The actual synthetic approach (Scheme 1) is based on the cyclocondensation of the diketone **4** with the aminonaphthalene **5**. While **4** is easily available from the propanone **6**, the new amine **5** was obtained by Pd-catalyzed amination of the 1-bromonaphthalene **7**.

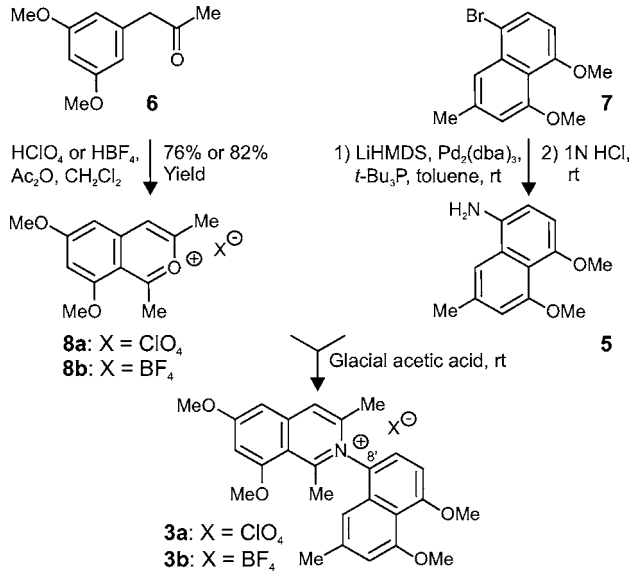
Scheme 1. Retrosynthetic Analysis



Although diketones of type **4** (in their free, phenolic forms) are the presumed biosynthetic precursors to both molecular portions of naphthylisoquinolines (like **1** and **2**),[11] this condensation cannot be considered as biomimetic.[12] Still, it is a useful pathway to isoquinolines and isoquinolinium salts related to **3**.[13]

In analogy to a synthetic pathway described earlier,[14] the diketone **4** was prepared from the arylpropanone **6**, by treatment with acetic anhydride in the presence of perchloric acid to give **8a** in 76% yield (Scheme 2), followed by ring opening with aqueous potassium carbonate. First, exploratory model condensation reactions of **4** using, inter alia, 1-aminonaphthalene as a model amine, revealed that the diketone **4** could be easily replaced by the benzopyrylium salt **8a**, i.e., by its—even more reactive—synthetic precursor. This permitted milder reaction conditions, resulted in better yields (not shown), and in addition, saved one reaction step.

Scheme 2. A First Synthetic Pathway to Ancisheynine (**3a**,**b**)



For the synthesis of the authentic, bis-methoxylated aminonaphthalene **5**, the bromo compound **7**, which was prepared according to a synthetic pathway developed earlier,[15] was transformed into **5** by Buchwald−Hartwig amination.[16] Although the Pd-catalyzed amination of aryl bromides with a variety of *N*-nucleophiles is a standard procedure with no apparent limitations,[17] the reaction does not succeed with ammonia itself,[18] which precluded a direct, one-step preparation of the corresponding aniline. Thus, the

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(10) For a successful *N*,*C*-coupling to give biscarbazole 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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(12) For the biosynthetic formation of **3** (as also of **1** and **2**), a separate formation of the isoquinoline and naphthalene portions is assumed, followed by an oxidative phenolic cross-coupling.

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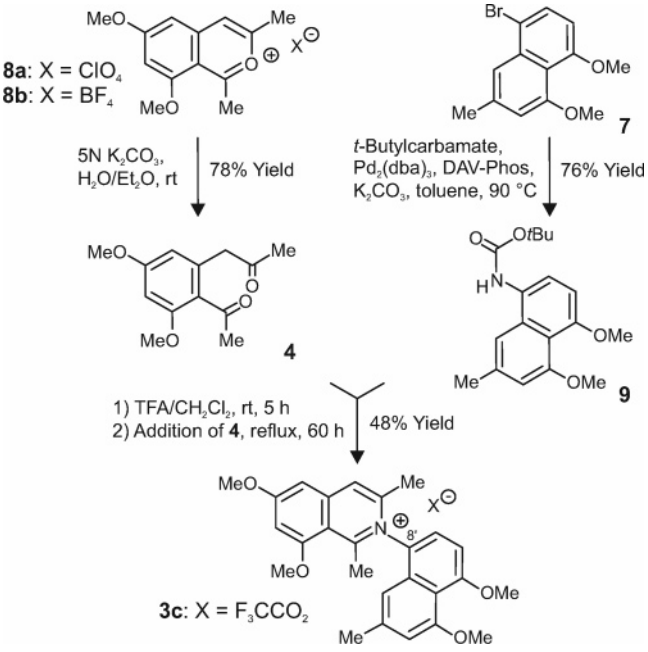
synthesis of **5** with LiHMDS as an ammonia equivalent was attempted with $Pd_2(dba)_3$ and P(*t*-Bu)$_3$ as the catalytic system, followed by an acid-mediated hydrolysis of the silyl groups,[18] to give the free amine **5**. Unfortunately, the isolation and characterization of the electron-rich primary arylamine **5**[19] was impossible due to its decomposition during the purification process. To overcome this problem, freshly prepared **5**, after neutralization of the reaction mixture with aqueous hydrochloric acid, was added immediately to a solution of the benzopyrylium salt **8a** in glacial acetic acid. By ^{1}H NMR spectroscopy of the reaction mixture (after evaporation of the solvent), the desired product, ancisheynine (**3a**), was identified together with different impurities, but no reagents **8a** and **5** were detected anymore. However, attempted chromatographic purification led to complete decomposition of **3a**. Various efforts to isolate the compound under milder conditions resulted in inseparable mixtures of decomposition products. In an attempt to stabilize ancisheynine (**3**) by choosing a more electron-poor anion, the respective benzopyrylium tetrafluoroborate salt **8b** was used, again accessible from the propanone **6** (Scheme 2).[20] Although this resulted in the renewed, yet slower, decomposition of ancisheynine (**3b**), it clearly indicated that its stability depends on the counterion. For the natural product, no such instability was described,[8] raising the question about its natural counteranion.[21]

Since it was not possible to purify the aminonaphthalene **5** either, the nitrogen function was introduced via *tert*-butyl carbamate[22] as a more convenient ammonia equivalent, thus permitting isolation of the more stable *N*-Boc-protected aminonaphthalene **9** prior to the cyclocondensation step (Scheme 3). The best results for the construction of **9** were achieved by using $Pd_2(dba)_3$/DAV-Phos[23] as the catalytic system and potassium carbonate as the base (76% yield). To avoid the necessity of exchanging the perchlorate or the tetrafluoroborate counteranion, the cyclocondensation step was again performed with the diketone **4** instead of the benzopyrylium salt **8**, despite its lower reactivity. Thus, treatment of naphthalene **9** with TFA caused the deprotection of the amino function in **9**, followed by an in situ trapping of the sensitive aminonaphthalene **5** by addition of **4**, with formation of the isoquinolinium salt **3c** in 48% yield.

Due to the presence of trifluoroacetate as an electron-poor counteranion, the stability of the naphthylisoquinolinium salt **3c** was drastically enhanced: No decomposition was observed within 10 days at room temperature. This result

Scheme 3. Completion of the Synthesis of Ancisheynine (**3c**)



emphasizes the important role of the electron-poor or -rich properties of the counteranion for the stability or instability of ancisheynine (**3**).

For the investigation of the as yet unknown axial chirality of ancisheynine (**3c**), its enantiomers were separated by HPLC on a chiral phase, in conjunction with circular dichroism (CD) spectroscopy. An enantiomeric resolution of **3c** at an analytical level was achieved on a Chiracel OD-RH column at 5 °C, giving the two expected peaks for the enantiomeric forms of **3c**. That these LC-UV peaks (Figure 2a) indeed corresponded to the respective atropo-enantiomers was demonstrated by their opposite CD effects, as measured online (Figure 2b). The racemic synthetic product **3c** gave a negative LC-CD signal for peak A ("faster") and a positive one for peak B ("slower").[24]

In the stopped-flow mode, full LC-CD spectra were recorded, providing mirror-imaged CD curves. Due to the novel-type structure of **3c**, however, a merely empirical interpretation of the CD spectra was impossible, making quantum chemical CD calculations[25] the method of choice.

Starting with (*M*)-**3c**, the conformational space was investigated by means of the PM3[26] method, resulting in six minimum geometries within an energetical array of 0.6 kcal/mol.[27] These structures were submitted to CD calculations,

(19) According to TLC, the bromonaphthalene **7** disappeared within 3 days, with formation of a new substance (with a similar R_f value as compared to 1-aminonaphthalene), turning violet during exposure to air, which hints at the presence of an electron-rich aminonaphthalene.

(20) Bringmann, G.; Pokorny, F.; Wenzel, M.; Wurm, K.; Schneider, C. *J. Labelled Comp. Radiopharm.* **1997**, *39*, 29.

(21) The only information known about the required properties of counteranions of isoquinolinium salts is that they should not be nucleophilic. In this respect, even chloride was reactive enough to compete with the *N*-nucleophile, thus causing decomposition of the isoquinolinium salt, e.g., in Zincke reactions. For details, see: Barbier, D.; Marazano, C.; Das, B. C.; Potier, P. *J. Org. Chem.* **1996**, *61*, 9596.

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(24) Analysis of the er of the isolated enantiomers of **3c** over a period of 600 min showed no atropisomerization.

(25) (a) Wanjohi, J. M.; Yenesew, A.; Midiwo, J. O.; Heydenreich, M.; Peter, M. G.; Dreyer, M.; Reichert, M.; Bringmann, G. *Tetrahedron* **2005**, *61*, 2667. (b) Bringmann, G.; Mühlbacher, J.; Reichert, M.; Dreyer, M.; Kolz, J.; Speicher, A. J. *J. Am. Chem. Soc.* **2004**, *126*, 9283.

(26) Stewart, J. J. P. *J. Comput. Chem.* **1989**, *10*, 209.

(27) The CD spectra of those structures that lie energetically higher than 3 kcal/mol above the global minimum do not significantly contribute to the overall CD curve.

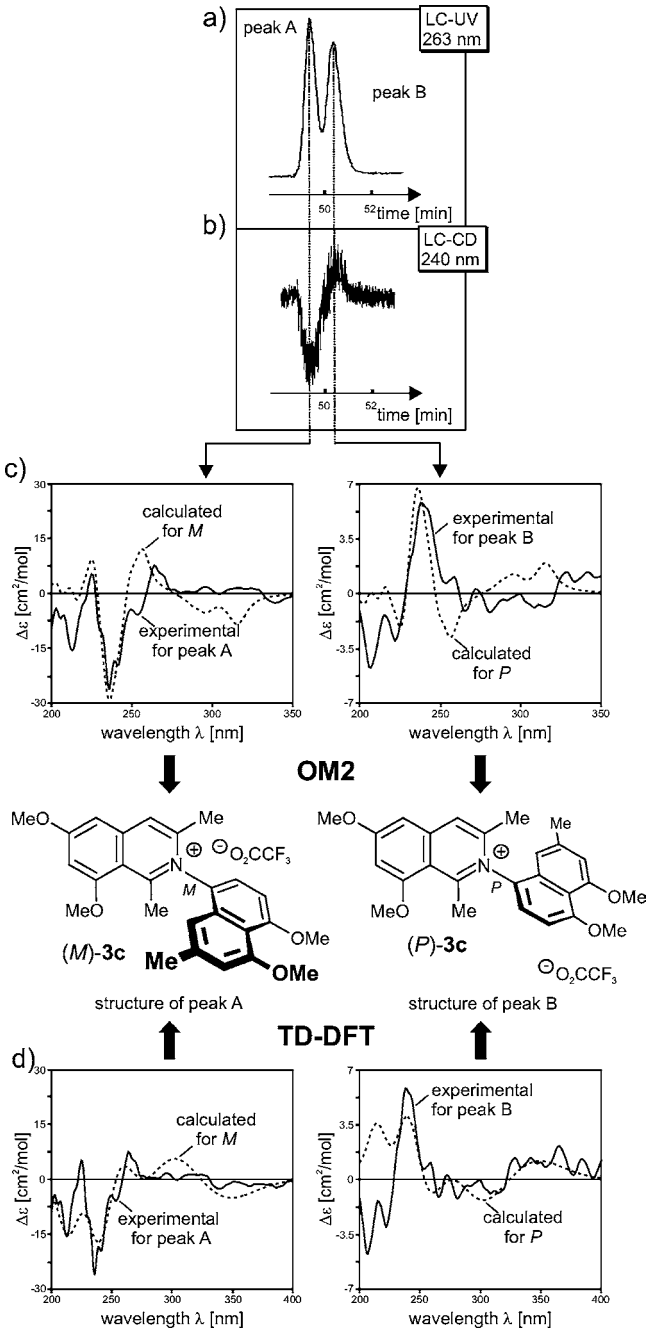

Figure 2. Stereochemical assignment of the two enantiomers of ancisheynine (**3c**), by LC-CD coupling and quantum chemical CD calculations.

using the OM2[28] Hamiltonian. The single spectra received were added following the Boltzmann statistics. The theoretical CD spectrum of the other atropo-enantiomer, (*P*)-**3c**, was obtained by reflection of the spectrum of (*M*)-**3c** on the wavelength axis. The predicted overall CD curves thus obtained were UV-corrected[29] and compared with the experimental spectra of the "faster" (peak A) and the "slower" (peak B) eluting atropo-enantiomers of **3c**. The comparison revealed quite good agreements between (*M*)-**3c** and peak A (Figure 2c, left) and between (*P*)-**3c** and peak B (Figure 2c, right), thus permitting assignment of the absolute configurations to the corresponding atropo-enantiomer.

Since the calculated spectra failed to match the experimental curves at wavelengths >280 nm, a confirmation of the results seemed desirable. For this purpose, the six minimum structures found with PM3 were further optimized using DFT (B3LYP[30]/6-31G*[31]), thus converging to only two minimum geometries. For these, CD calculations by means of TDDFT (B3LYP/TZVP[32]) were carried out. The resulting CD curves for (*M*)-**3c** and (*P*)-**3c** again showed a good agreement with the measured spectra of peaks A (Figure 2d, left) and B (Figure 2d, right), respectively, now over the complete range of wavelength under investigation, thus fully confirming the results described above.

This paper reports on the first total synthesis of an *N*,*C*-coupled naphthylisoquinoline. The introduction of the amino function at C8 of the naphthalene core was achieved by Buchwald−Hartwig amination with *tert*-butyl carbamate as an ammonia equivalent. The best yields were obtained by using $Pd_2(dba)_3$ and DAV-Phos as the catalytic system and potassium carbonate as the base. The electronic property of the counteranion has a substantial impact on the stability of ancisheynine (**3**), with the electron-poor trifluoroacetate as the best counterion.On the basis of this synthetic material, the first stereochemical investigation of an *N*,*C*-coupled naphthylisoquinoline was performed. The two atropo-enantiomers of **3c** were analytically resolved by HPLC on a chiral phase. Their absolute configurations were established by comparison of the LC-CD spectra recorded in the stopped-flow mode, with the ones quantum chemically calculated. The methodology developed constitutes an efficient tool for the stereochemical analysis of natural ancisheynine (**3**) as produced by the plant. This work is in progress.

Acknowledgment. This work is dedicated to Prof. Wolfgang Kiefer on the occasion of his 65th birthday. It was supported by the Fonds der Chemischen Industrie (fellowship to T.G. and research funds) and the DFG (SFB 630 and SPP 1152).

Supporting Information Available: Experimental procedures and NMR spectra for obtained compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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