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Synthesis of the Isoquinocycline−Pyrrolopyrrole Substructure

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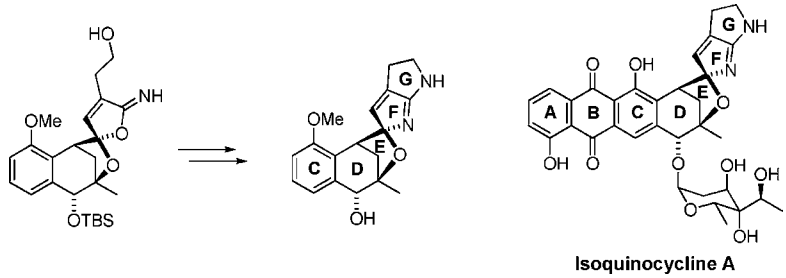
ABSTRACT



The synthesis of the pyrrolopyrrole substructure of the isoquinocyclines is reported. The pentacyclic (CDEFG) substructure of isoquinocycline A and B, which contains an unusual 2,4,5,6-tetrahydropyrrolo[2,3-*b*]pyrrole (FG) connected via an *N,O*-spiro acetal to the anthraquinoid core of the isoquinocycline aglycon has been synthesized. Key steps were a nickel(0)-mediated hydrocyanation of an alkynone, the conversion of an *O,O*-acetal into an *N,O*-acetal, and an intramolecular amidine alkylation.

Quinocyclines[1] are a class of anthracycline related natural products[2] consisting of the four compounds quinocycline A, quinocycline B, isoquinocycline A, and isoquinocycline B (Figure 1). All four substances were first isolated in the 1950s from *Streptomyces aureofaciens*.[1] Quinocycline B, also known as kosinostatin,[3] was also isolated from *Micromonospora sp.* (TP-A0468, along with isoquinocycline B)[3] and *Streptomyces violaceusniger* (HAL64).[4]

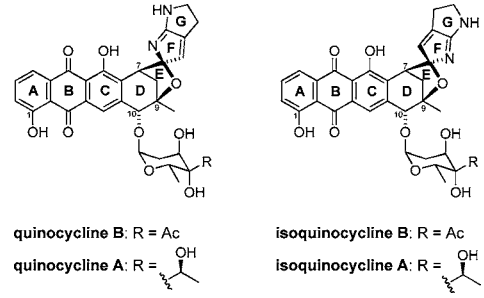


Figure 1. Quinocyclines.

Apart from their antibiotic and cytotoxic activities, some unusual structural characteristics of the quinocyclines make

(1) (a) Celmer, W. D.; Murai, K.; Rao, K. V.; Tanner, F. W.; Marsh, W. S. *Antibiotics Annual 1957−1958*; Medical Encyclopedia Inc.: New York, 1958; pp 484−492. (b) McBride, T. J.; English, A. R. *Antibiotics Annual 1957−1958*; Medical Encyclopedia Inc.: New York, 1955; pp 493−501. (c) Martin, J. H.; Shay, A. J.; Pruess, L. M.; Porter, J. N.; Mowat, J. H.; Bohonos, N. *Antibiotics Annual 1954−1955*; Medical Encyclopedia Inc.: New York, 1955; pp 1020−1024. (d) Cosulich, D. B.; Mowat, J. H.; Broschard, R. W.; Patrick, J. B.; Meyer, W. E. *Tetrahedron Lett.* **1963**, *7*, 453–458. Erratum: *Tetrahedron Lett.* **1964**, *13*, 750. (e) Tulinsky, A. *J. Am. Chem. Soc.* **1964**, *86*, 5368–5369.

(2) For a review on naturally occurring anthracyclines, see: Laatsch, H.; Fotso, S. *Top. Curr. Chem.* **2008**, *282*, 3–74.

(3) (a) Furumai, T.; Igarashi, Y.; Higuchi, H.; Saito, N.; Oki, T. *J. Antibiot.* **2002**, *55*, 128–133. Corrections: *J. Antibiot.* **2003**, *56*, C1. (b) Igarashi, Y.; Higuchi, H.; Oki, T.; Furumai, T. *J. Antibiot.* **2002**, *55*, 134–140. Corrections: *J. Antibiot.* **2003**, *56*, C1.

(4) El-Naggar, M. Y. *J. Microbiol.* **2007**, *45*, 262–267.

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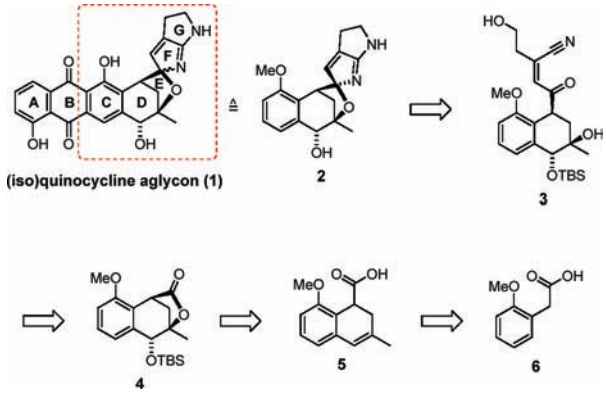
them interesting synthetic targets. All quinocyclines show an anthraquinoid tetracycle (ABCD) and are glycosylated at C10 with γ-branched octoses. These are trioxacarcinose B for (iso)quinocycline B and dihydro-trioxacarcinose B for (iso)quinocycline A.[5]

The most remarkable substructure of the (iso)quinocycline aglycon is the bicyclic amidine (FG) that connects C7 and C9O via an *N*,*O*-spiro center. This heterocycle, a 2,4,5,6-tetrahydropyrrolo[2,3-*b*]pyrrole, is unique among natural products and has so far only been found in the quinocyclines.

Having completed the stereoselective synthesis of dihydro-trioxacarcinose B,[6] we report here a synthetic access to the pyrrolopyrrole substructure as the next step toward the total synthesis of the quinocyclines.

A retrosynthetic analysis (Scheme 1) of the CDEFG-substructure **2** of the (iso)quinocycline aglycon (**1**) reveals

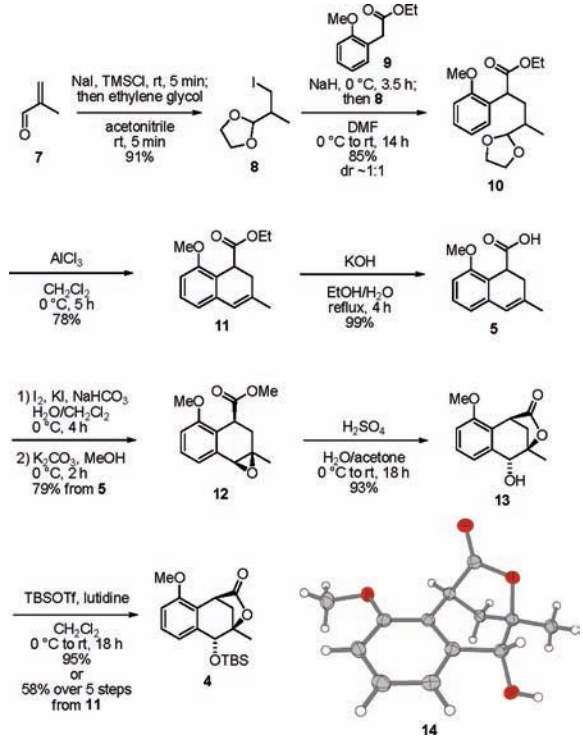
Scheme 1. Retrosynthetic Analysis of the CDEFG-Substructure of the (Iso)quinocycline Aglycon



the possibility to construct the pyrrolopyrrole (FG) from the (*Z*)-β-nitrilo alkenone **3**. By converting the nitrile to an amidine and the alcohol to a leaving group, the G-ring could be closed by intramolecular substitution, while the F-ring is established by formation of an *N*,*O*-acetal. Enone **3** should be accessible by a cyanide addition to the corresponding alkynone, which originates from lactone **4**. The diol motif in **4** leads to the olefin precursor **5**, which could be prepared from the arylacetic acid **6**. This results in a synthetic strategy that starts with the ring C and adds all other rings sequentially. This approach should be applicable to the isoquinocycline and quinocycline series.

The synthesis of the racemic lactone **4** is outlined in Scheme 2. The starting point was the conversion of methacrolein (**7**) to the iodo dioxolane **8**.[7] Fischer esterification of **6** afforded the ethyl ester **9**, which was alkylated with the iodide **8** to obtain the dioxolane **10**. Friedel−Crafts cyclization and subsequent elimination resulted in the formation of

Scheme 2. Synthesis of the Lactone **4**



the dihydronaphthalene **11**. The ethyl ester could be hydrolyzed to the γ,δ-unsaturated carboxylic acid **5**, which was suitable for an iodolactonization. The resulting iodolactone proved to be unstable and was therefore converted directly with potassium methoxide into the epoxide **12**. Under aqueous acidic conditions, the epoxide was opened regioselectively at the benzylic position, yielding a *trans*-diol that underwent a subsequent lactonization to form the hydroxylactone **13**. The configuration of this compound could be confirmed by an X-ray crystal structure (**14**). The TBS-protection of the alcohol finally lead to the lactone **4**.

It turned out that the reaction sequence from **11** to **4** works quite well without intermediate chromatography. As compounds **9**, **10**, and **11** can be purified by distillation, the TBS-ether **4** can be prepared on a gram scale with only one final chromatographic purification step.

The next steps of the synthesis are shown in Scheme 3. The lactone **4** was allowed to react with double lithiated 3-butyn-1-ol to give the alkynone **15**. No hemiacetal formation was observed for the case of the hydroxy alkynone **15**. The hydrocyanation of this alkynone was conducted according to a method developed by Arzoumanian et al.[8] By generating $[Ni^0(CN)_4]^{4-}$ from a nickel precursor, potassium cyanide, and zinc as a reducing agent, Arzoumanian et al. were able to convert non-4-yn-3-one to 3-butyl-5-ethyl-5-hydroxy-1*H*-pyrrol-2(5*H*)-one in 65% yield.[8] By applying these conditions to our alkynone **15**, we therefore expected to get the hydroxypyrrolone **17** or its condensation product

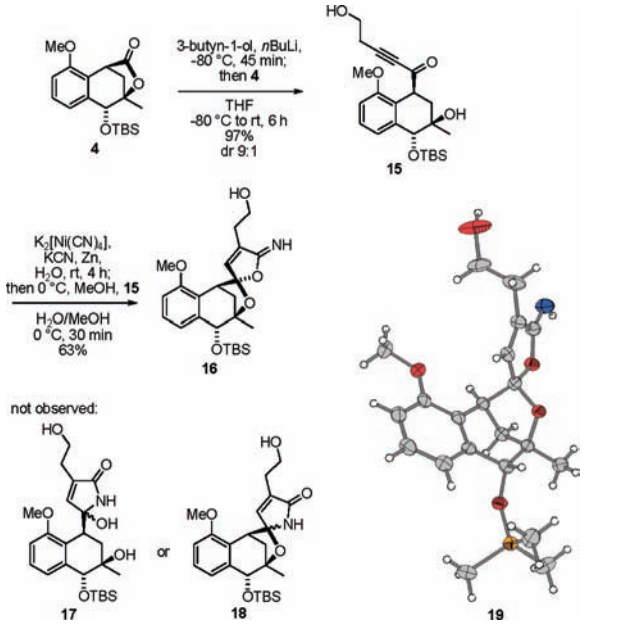
(5) (a) Matern, U.; Grisebach, H.; Karl, W.; Achenbach, H. *Eur. J. Biochem.* **1972**, *29*, 1–4. (b) Matern, U.; Grisebach, H. *Eur. J. Biochem.* **1972**, *29*, 5–11.

(6) König, C. M.; Harms, K.; Koert, U. *Org. Lett.* **2007**, *9*, 4777–4779.

(7) Larson, G. L.; Klesse, R. *J. Org. Chem.* **1985**, *50*, 3627.

(8) Arzoumanian, H.; Jean, M.; Nuel, D.; Garcia, J. L.; Rosas, N. *Organometallics* **1997**, *16*, 2726–2729.

Scheme 3. Nickel(0)-Mediated Hydrocyanation Leading to the Formation of the Cyclic Imidate **16**

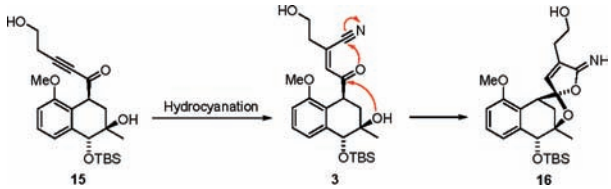


18 each with an *N*,*O*-acetal. Instead, the cyclic imidate **16** with an *O*,*O*-acetal was formed.

This result, the formation of a cyclic imidate via a β-nitrilo-carbonyl intermediate instead of the formation of a pyrrolone, is in contrast to almost all examples in the literature.[8,9] There is only one example for the formation of a benzannelated cyclic imidate starting from 2-cyano-benzaldehyde.[10] The structural assignment of the imidate formation was confirmed by an X-ray crystal structure (**19**) which was obtained from the TMS-analogue of TBS-ether **16**.

A mechanistic explanation for the formation of the unusual imidate is possible from considering the structural context of the intermediate β-nitrilo-ketone **3**. The tertiary alcohol of the β-nitrilo-ketone **3** (Scheme 4) is in close proximity to

Scheme 4. Plausible Mechanism for the Formation of the Imidate **16** from Alkynone **15**

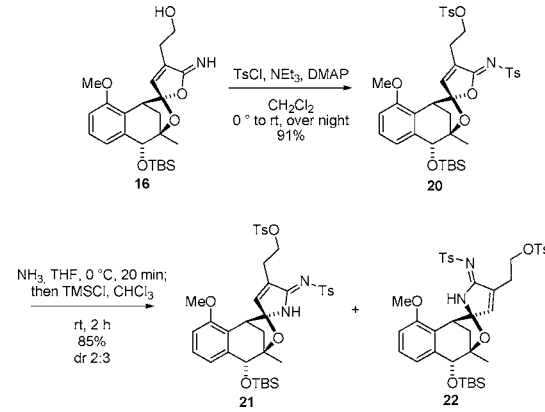


the ketone, which allows easy formation of a hemi acetal via a five-membered ring. On the other hand, the ketone is already preorientated for an attack on the nitrile to form a second five-membered ring. These two ring formations may occur in concerted or sequential fashion; in any case, the intramolecular attack of the OH group should be favored compared to the proposed mechanism for the formation of pyrrolones, which begins with a partial hydrolysis of the nitrile group by water.[8]

While compound **16** contained all carbon atoms of the target already, two problems still remained to be solved: the conversion of the *O*,*O*-acetal into an *N*,*O*-acetal and the closure of the G ring.

N- and *O*-tosylation of compound **16** gave compound **20** in very good yield (Scheme 5). The tosylated imidate **20**

Scheme 5. Synthesis of the Amidines **21** and **22**



was easily attacked by ammonia. If this addition was carried out in the presence of TMSCl, the two *N*,*O*-acetals **21** and **22** could be obtained.

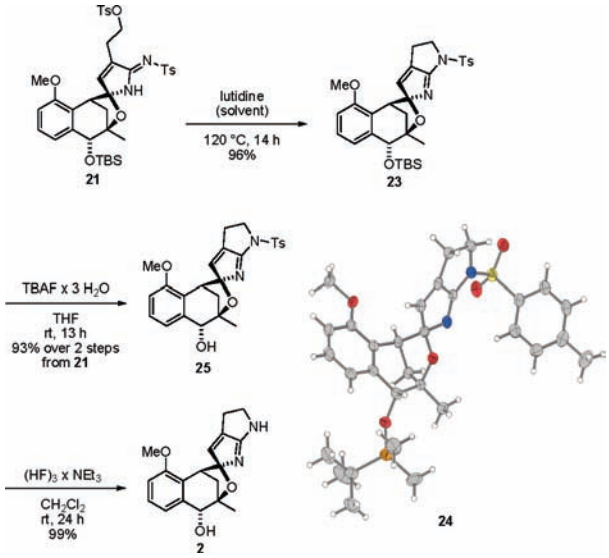
Throughout the synthesis so far, only one single diastereomer was obtained for the spiro center at the *O*,*O*-acetal. At this point, two epimeric *N*,*O*-acetals **21** and **22** were formed. Compound **21** corresponds to the configuration of isoquinocycline A/B, while compound **22** exhibits the configuration of quinocycline A/B. The two epimers could be separated by chromatography. A slow epimerization of quinocycline into the more stable isoquinocycline was reported for the natural product.[1,3] No epimerization at the *N*,*O*-acetal was observed during the purification and storage of compounds **21** and **22**.

The completion of the synthesis of amidine **2** (the CDEFG-substructure of the aglycon of isoquinocycline A and B) is outlined in Scheme 6. The desired ring closure to the pyrrolopyrrole substructure via an intramolecular amidine alkylation was achieved by the treatment of the amidine **21** with lutidine at 120 °C for several hours. The structural assignment of the resulting pyrrolopyrrole **23** was confirmed by an X-ray crystal structure (**24**). The deprotection of **23**

(9) (a) Rosas, N.; Cabrera, A.; Sharma, P.; Arias, J. L.; García, J. L.; Arzoumanian, H. *J. Mol. Catal. A: Chem.* **2000**, *156*, 103–112. (b) Zanatta, N.; Rosa, L. S.; Cortelini, M. F. M.; Beux, S.; Santos, A. P. D.; Bonacorso, H. G.; Martins, M. A. P. *Synthesis* **2002**, *16*, 2404–2408. (c) Nenajdenko, V. G.; Druzhinin, S. V.; Balenkova, E. S. *Russ. Chem. Bull., Int. Ed.* **2003**, *52*, 2467–2472. (d) Martins, M. A. P.; Pereira, C. M. P.; Zimmermann, N. E. K.; Cunico, W.; Moura, S.; Beck, P.; Zanatta, N.; Bonacorso, H. G. *J. Fluorine Chem.* **2003**, *123*, 261–265.

(10) Sato, R.; Ohmori, M.; Kaitani, F.; Kurosawa, A.; Senzaki, T.; Goto, T.; Saito, M. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 2481–2485.

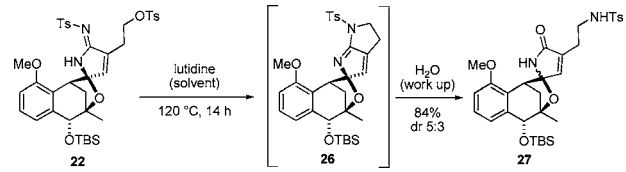
Scheme 6. Completion of the Synthesis of Amidine **2**, the CDEFG-Substructure of Isoquinocycline A and B



with TBAF gave alcohol **25**, which was further deprotected with HF-triethylamine to deliver the free amidine **2**.

In contrast to the smooth conversion of amidine **21** to the CDEFG-substructure of the isoquinocyclines, the analogue conversion of amidine **22** to the CDEFG-quinocycline substructure proved to be problematic. Under the same conditions that allowed the synthesis of pyrrolopyrrole **23** from amidine **21**, the epimeric amidine **22** gave the lactam **27** as the main product. The isolated compound **27** represents the hydrolysis product of the desired pyrrolopyrrole **26** (Scheme 7). One possible explanation for this failure could be that, after successful ring closure, the less stable *N*-tosylated amidine with the quinocycline configuration hydrolyzed easily during workup and purification. Optimal

Scheme 7. Attempted Synthesis of the Pyrrolopyrrole **26**



cyclization conditions for the intramolecular amidine alkylation in the quinocycline series remain to be elaborated.

Future work will be directed at the extension of the present synthesis to the complete heptacyclic aglycon of the (iso)-quinocyclines and its application to a stereoselective total synthesis of (iso)quinocycline A and B.

In conclusion, an efficient synthesis for the CDEFG-substructure of isoquinocycline A and isoquinocycline B was developed. Key steps were a nickel(0)-mediated hydrocyanation of an alkynone to install the carbon skeleton, the conversion of a cyclic imidate to an amidine (*O*,*O*- to *N*,*O*-acetal), and the intramolecular amidine alkylation for the final G-ring closure. A synthetic solution for the long-standing problem of 2,4,5,6-tetrahydropyrrolo[2,3-*b*]pyrrole, which is connected via an *N*,*O*-spiro acetal to the anthraquinoid core of the quinocyclines, has been found.

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Supporting Information Available: Experimental procedures and analytical data for all new compounds and single X-ray crystallographic data (CIF) for **14**, **19**, and **24**. This material is available free of charge via the Internet at http://pubs.acs.org.

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