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The Imidato-Alkenyllithium Route for the Synthesis of the Isoquinocycline-Pyrrolopyrrole Substructure

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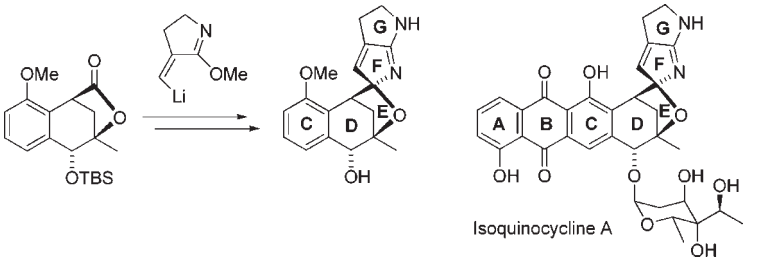
ABSTRACT



A convergent and effective synthesis of the pyrrolopyrrole substructure (CDEFG) of the isoquinocyclines is reported. A key step is a tin−lithium exchange of an imidato-alkenyltin compound (a ring G equivalent) and the subsequent acylation with a lactone. The resulting acetal is used successfully for the ring F closure to the pyrrolopyrrole. The sole formation of the isoquinocycline *N,O*-acetal epimer is in accordance with the proposed mechanism for the isomerization of quinocyclines to isoquinocyclines.

Strepomyces aureofaciens produces the four antibiotic compounds quinocycline A, quinocycline B, isoquinocycline A, and isoquinocycline B (Figure 1).[1] The quinocyclines were isolated in 1957 and microbiological testing was conducted.[1,2] The γ-branched octoses of the quinocyclines were isolated through hydrolysis under protic conditions.[3,4] The structure of isoquinocycline A was confirmed by Tulinsky via X-ray crystal structure analysis.[5] Quinocycline B and isoquinocycline B were also isolated from *micromonspora sp.*[6] and *streptomyces violaceusniger*.[7] Quinocycline B possesses a strong cytotoxicity against human myeloid leukemia U937 cells (IC_{50} = 0.09 μM).[6]

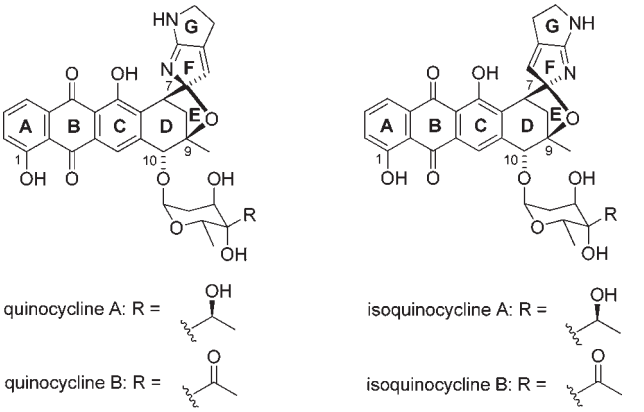


Figure 1. Quinocycline structures.

(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) 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. (c) 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.

(2) McBride, T. J.; English, A. R. *Antibiotics Annual 1957−1958*; Medical Encyclopedia Inc.: New York, 1955; pp 493−501.

(3) Isolation of the anhydro sugar: Webb, J. S.; Broschard, R. W.; Cosulich, D. B.; Mowat, J. H. *J. Am. Chem. Soc*. **1962**, *84*, 3183–3184.

(4) (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.

(5) Tulinsky, A. *J. Am. Chem. Soc*. **1964**, *86*, 5368–5369.

(6) (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.

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

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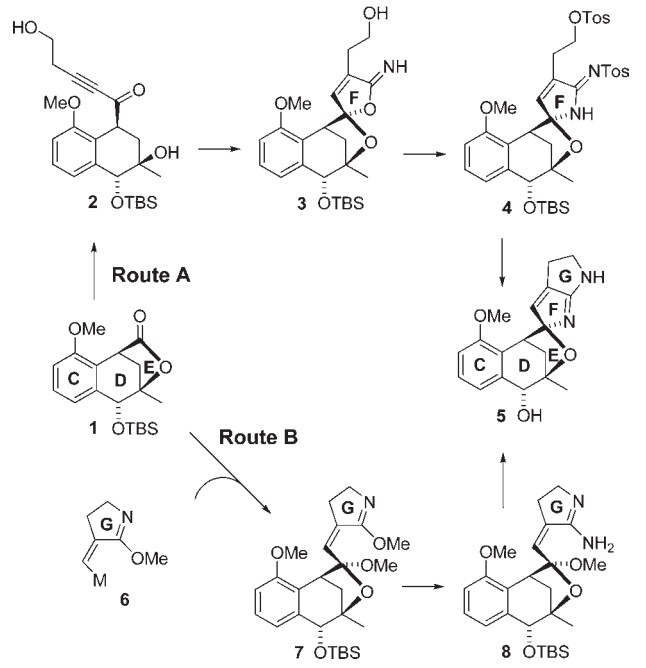
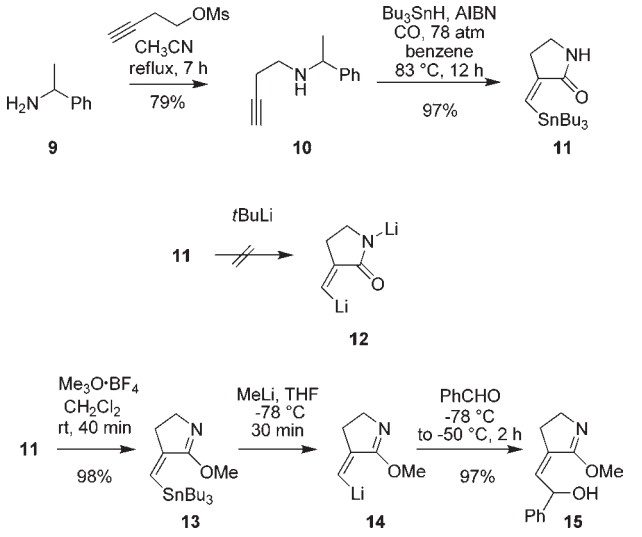
Scheme 1. Synthetic Routes to the Pyrrolopyrrole Substructure



Scheme 2. Synthesis of a Metalated Ring G Equivalent



A synthetic challenge of the quinocyclines is the bicyclic amidine (rings FG), which is connected to the rest of the molecule via an *N*,*O*-spiro acetal. One synthetic access to the isoquinocycline-pyrrolopyrrole substructure was reported recently (route A in Scheme 1).[8] After conversion of the lactone **1**[8] into the ketone **2**, a Ni(0)-mediated cyanation gave the imino ether **3**. *N*,*O*-Tosylation and conversion of the *O*,*O*-acetal into an *N*,*O*-acetal (**4**) afforded the ring F first. Ring G was closed at last in route A by intramolecular *N*-alkylation and subsequent deprotection (**4** → **5**). Considering shorter, even more efficient solutions for the introduction of the pyrrolopyrrole substructure (**1** → **5**) we devised an alternative synthetic solution (route B in Scheme 1). Here, an already formed ring G would be added to the lactone first. The exocyclic metalated olefin **6** carrying an imino ether could be a key reagent for this transformation. The resulting imino ether **7** should be convertible into the amidine **8**. At last, the attack of the amidine at the *O*,*O*-acetal should lead to the closure of ring F.

A tin−lithium exchange was chosen to access a metalated ring G equivalent of type **6** (Scheme 2). The corresponding organostannyl lactam **11** was prepared according to Ryu's procedure[9] by using acyl-radical chemistry in two steps with 77% overall yield (**9** → **10** → **11**). Attempts for a tin−lithium exchange reaction with the stannyl lactam **11** to prepare a dilithium reagent **12** failed.

Treatment of the lactam **11** with trimethyloxonium tetrafluoroborate gave the imino ether **13** in excellent yield. The formation of an imino ether in the presence of a vinyl stannane is noteworthy, without precedence, and should be applicable in general. A tin−lithium exchange (**13** → **14**) was achieved by using methyl lithium at −78 °C.[10] The resulting *Z*-alkenyl lithium compound **14**, which corresponds to key reagent **6**, was allowed to react with benzaldehyde to afford the addition product **15** in 97% yield.

The addition of the ring G equivalent to the lactone **1** was examined next (Scheme 3). Reaction of **1** with the lithiated alkene **13** led to a ketone/hemiacetal mixture that was converted into the mixed acetal **7** upon treatment with trimethyl orthoformate and *p*-TosOH. Only one epimer was observed in the mixed acetal formation. The imino ether **7** could be transformed smoothly into the amidine **8** with ammonium chloride in refluxing methanol. Attempts to achieve a closure of ring F at the stage of the amidine **8** (CSA; *p*-TosOH; $AlMe_3$) led to decomposition of the starting material only. To disfavor amidine protonation, which may prevent nucleophilic *N*-attack at the acetal, the amidine functionality was tosylated (**8** → **16**). With the increased acidity of the tosylated amidine, the reaction of a base like lutidine[8] with compound **16** was of interest. When the tosylated amidine **16** was heated to 155 °C in lutidine two stereoisomeric nitriles **17** and **18** were obtained, which could be separated by chromatography. The stereochemical assignment was possible by NOE measurements and the later X-ray structural analysis.

Nitrile formation by tosylation of an amide and heating up under basic conditions is already known in literature.[11] In the present case a migration of the tosyl group from the

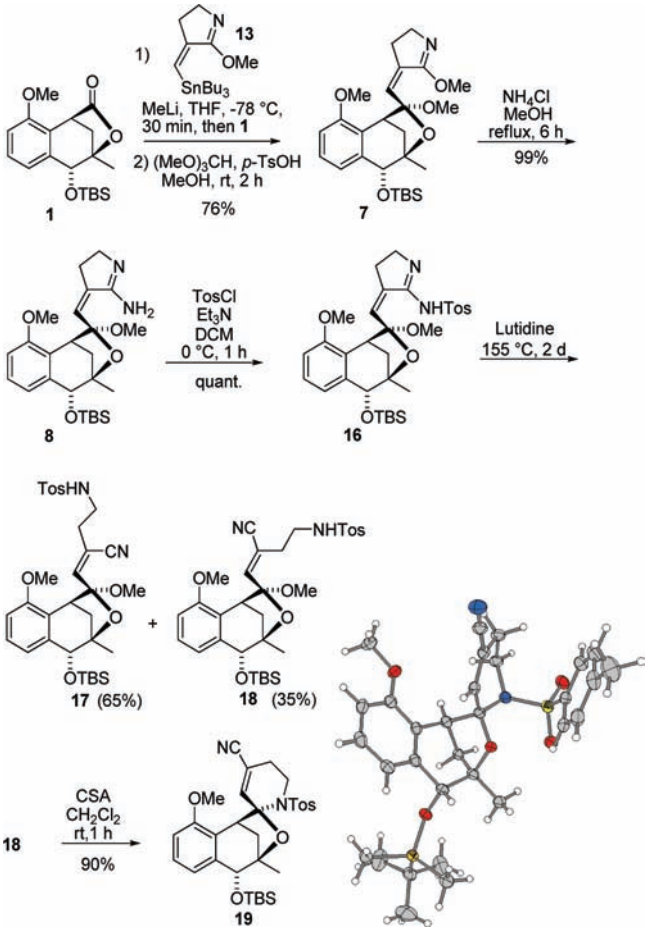
(8) Cordes, J.; Harms, K.; Koert, U. *Org. Lett.* **2010**, *12*, 3808–3811. For synthesis of the quinocycline A sugar moiety see: König, C. M.; Harms, K.; Koert, U. *Org. Lett.* **2007**, *9*, 4777–4779.

(9) (a) Uenoyama, Y.; Fukuyama, T.; Ryu, I. *Org. Lett.* **2007**, *9*, 935–937. (b) Tojino, M.; Uenoyama, Y.; Fukuyama, T.; Ryu, I. *Chem. Commun.* **2004**, *21*, 2482–2483.

(10) (a) Piers, E.; Karunaratne, V. *J. Org. Chem.* **1983**, *48*, 1774–1776. (b) Piers, E.; Yeung, B. W. A. *J. Org. Chem.* **1984**, *49*, 4567–4569. (c) Johnson, C. R.; Penning, T. D. *J. Am. Chem. Soc.* **1986**, *108*, 5655–5656.

(11) (a) Boshta, N. M.; Bomkamp, M.; Waldvogel, S. R. *Tetrahedron* **2009**, *65*, 3773–3779. (b) Wright, K.; Dutot, L.; Wakselman, M.; Mazaleyrat, J.-P.; Crisma, M.; Formaggio, F.; Toniolo, C. *Tetrahedron* **2008**, *64*, 4416–4426. (c) Carlier, P. R.; Zhang, Y. *Org. Lett.* **2007**, *9*, 1319–1322.

Scheme 3. Addition of the Ring G Equivalent to Lactone **1**, Amidine Formation and Conversion to Nitrile, and X-ray Structure of Nitrile **19**



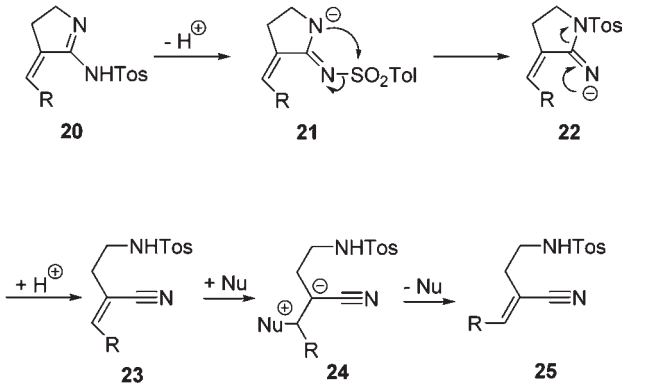
exocyclic amidine nitrogen to the endocyclic nitrogen has to occur before sulfonamide elimination leads to the nitrile. A mechanistic view for the reaction (**16** → **17** + **18**) is given in Scheme 4: Deprotonation of the tosylated amidine **20** results in the anion **21**, which after 1,3-*N*-tosyl migration leads to **22**. An elimination results in the *Z*-unsaturated nitrile **23**. The subsequent *Z*,*E*-isomerization can be explained by nucleophilic addition (**23** → **24**) followed by elimination (**24** → **25**). While the formation of amidines by addition of amines to nitriles is standard, this observed elimination of a tosylated amidine to form a nitrile is a rare example.[12]

A cyclization of the *E*-nitrile **18** to form the *N*,*O*-acetal **19** was possible under acidic conditions. Only that epimer of the *N*,*O*-acetal is formed, which corrresponds to the isoquinocycline series. NOE data and an X-ray crystal structure were used for the structural and stereochemical assignment of compound **19** (Scheme 3).

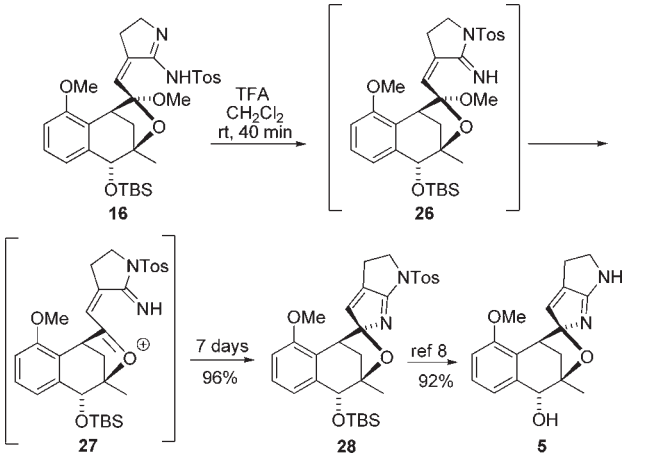
The closure of the ring F starting with the tosylated amidine **16** was examined under acidic conditions (Scheme 5). Five

(12) Golec reported formation of nitriles out of alkylated isothiazole amines that is compareable to our results: Golec, J. M. C.; Scrowston, R. M. *J. Chem. Res. (S)* **1988**, *1*, 46.

Scheme 4. Mechanistic View for the Nitrile Formation and *E*,*Z*-Isomerization



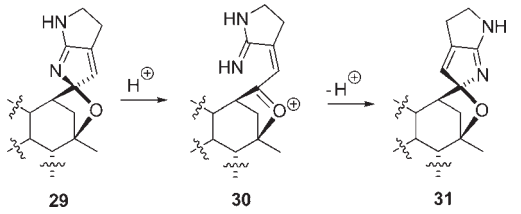
Scheme 5. Closure of Ring F and Formation of the Pyrrolopyrrole Isoquinocycline Substructure



equivalents of TFA at ambient temperature in methylene chloride were found to be optimal conditions. NMR control of the reaction progress showed a nearly complete migration of tosyl group from the exocyclic nitrogen to the endocyclic position (**16** → **26**) after 30−45 min. The ring F closure to the desired pyrrolopyrrole substructure **28** required prolonged reaction times (7 d). The yield for the TFA-mediated ring F closure (**16** → **28**) was 96%. The structural assigment of compound **28** was possible by comparison with the spectroscopic data of this compound obtained by route A, which are secured by an X-ray crystal structure.[8] After deprotection (TBAF, HF-Et_3N) the amidine **5** is accessible.

Noteworthy is the sole formation of the isoquinocycline epimer **28** in the ring F closure reaction. Celmer[1] observed isomerization of quinocycline A into isoquinocycline A under protic conditions. Igarashi and Furumai proposed a mechanism for this isomerization: protonation of the amidine **29** and subsequent ring-opening to the oxonium ion **30** (Scheme 6);[6b] attack of the amidine from the

Scheme 6. Proposed Mechanism for Isomerization of Quinocycline A to Isoquinocycline A Adapted from Igarashi and Furumai[6b]



opposite side of the oxonioum ion leads to the isoquinocycline compound **31**.

The ring closure of the tosylated amidine under acidic conditions (**16** → **26** → **28**) should follow a related reaction pathway via formation of the oxonium ion intermediate **27**. The fact that in our case only the isoquinocycline and no quinocycline substructure was observed is in accordance with the proposed mechanism for isomerization of the natural products.

A comparison of the two routes A and B from the lactone **1** to the isoquinocycline substructure **5** gives the following result: Route A (first ring F closure, then ring G closure) has 7 steps with 17% overall yield; route B (premade ring G and final ring F closure) has 7 steps with 67% overall yield. Clearly, the novel route B is more efficient.

In summary, a novel efficient synthesis for the CDEFG substructure of isquinocyclines was developed. Key steps of the synthesis were the reaction of the alkenyllithium iminoether **14** with lactone **1** and the acid-catalyzed F-ring closure of a tosylated amidine. The sole formation of the isoquinocycline *N*,*O*-acetal epimer supports the presence of an oxonium ion intermediate during the isomerization of quinocyline to isoquinocycline. Of mechanistic interest is the base-mediated *N*-tosyl migration followed by nitrile formation.

Future work will concern the extension of the novel developed route B to the stereoselective total synthesis of isoquinocycline A and B.

Acknowledgment. Generous support by the Deutsche Forschungsgemeinschaft (KO1349/8-2) is gratefully acknowledged.

Supporting Information Available. Full experimental and characterization details for all new compounds and X-ray crystallographic data of **19**. This material is available free of charge via the Internet at http://pubs.acs.org.