

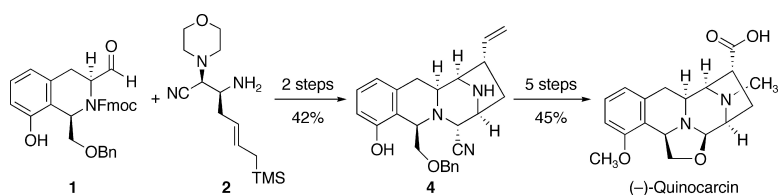
Communication

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J. Am. Chem. Soc., **2005**, 127 (48), 16796-16797 • DOI: 10.1021/ja056206n • Publication Date (Web): 10 November 2005

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Synthesis of (–)-Quinocarcin by Directed Condensation of α -Amino Aldehydes

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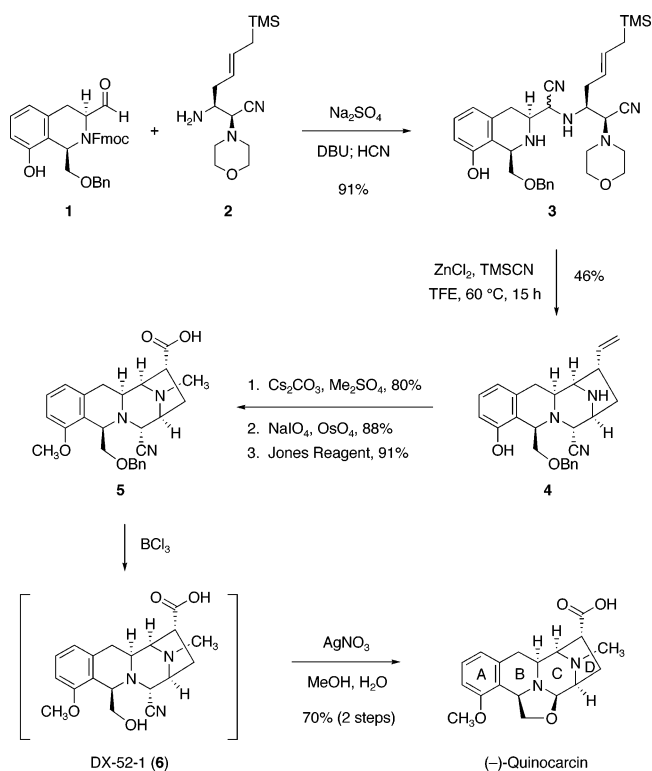
Received September 9, 2005; E-mail: myers@chemistry.harvard.edu

(–)-Quinocarcin is a pentacyclic alkaloid with antiproliferative effects.^{1,2} It is structurally similar to the saframycins³ and ecteinascidins⁴ in the A-, B-, and C-rings, but differs from these molecules in the D-ring, which is five-membered rather than six-membered. We sought to extend to the synthesis of quinocarcin an approach we had earlier used to prepare (–)-saframycin A, involving the directed condensation of C- and N-protected α -amino aldehyde derivatives.⁵ To achieve this it was necessary to devise chemistry to synthesize the five-membered D-ring of quinocarcin that was compatible with the planned condensation-based approach, and to determine an effective sequence for its implementation. We describe here the realization of these objectives in a synthetic route to (–)-quinocarcin.⁶ The major bond formations were achieved using simple condensation reactions of α -amino aldehyde derivatives.

The synthetic sequence to (–)-quinocarcin developed is illustrated in Scheme 1 and employs as starting materials the N-protected α -amino aldehyde component **1**, comprising the A- and B-rings of the target and synthesized in eight steps from (*R,R*)-pseudoephedrine glycinamide⁷ (19% yield, see Supporting Information), and the C-protected α -amino aldehyde component **2**, also synthesized from (*R,R*)-pseudoephedrine glycinamide (seven steps, 34% yield, see Supporting Information).⁸ Condensation of **1** and **2** in dichloromethane in the presence of sodium sulfate afforded the corresponding imine. Without isolation, the imine intermediate was treated with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 1.1 equiv), cleaving the fluorenylmethoxycarbonyl (Fmoc) protective group, and to the resulting product was added methanolic hydrogen cyanide (prepared in situ), leading to Strecker addition. This sequence, conducted as one operation, afforded the bis-amino nitriles **3** as a mixture of diastereomers, as indicated, in 91% yield after flash-column chromatography.

In the key transformation of the synthetic route, the mixture of diastereomers **3** was warmed in 2,2,2-trifluoroethanol (TFE) in the presence of trimethylsilyl cyanide (3.6 equiv) and zinc chloride (3.3 equiv) at 60 °C for 15 h, forming the tetracyclic ring system of quinocarcin in the form of the cyanopiperazine intermediate **4** (46% from **3**).⁹ This process, which forms two of the four rings of the target and three of its six stereocenters, proceeds by initial cyclization of the C-ring in an intramolecular amino nitrile exchange and then by closure of the D-ring in an allyl silane-imine addition reaction.⁹ steps discussed in greater detail below. To complete the synthesis of quinocarcin, the tetracyclic cyanopiperazine intermediate **4** was bis-methylated and the olefinic side-chain of the resulting product was subjected to oxidative cleavage. The aldehyde formed was then oxidized with Jones reagent in acetone to furnish the intermediate **5** (64% over the three steps).¹⁰ Debenzylation of **5** with boron trichloride (5 equiv) produced quinocarcin and a small amount of its noncyclized precursor **6**, also known as DX-52-1. By treating the crude mixture with silver nitrate in aqueous methanol, complete conversion to quinocarcin was achieved (70% yield, two steps). The synthetic material was identical to an authentic

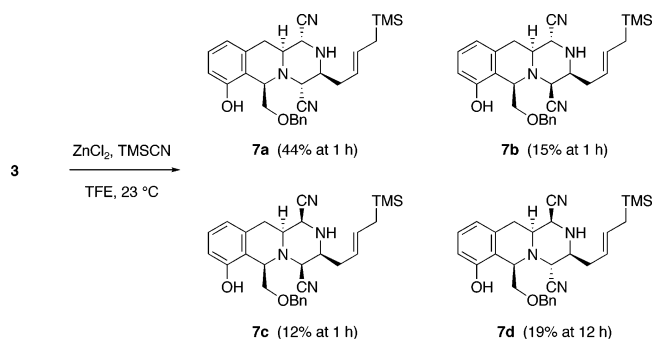
Scheme 1



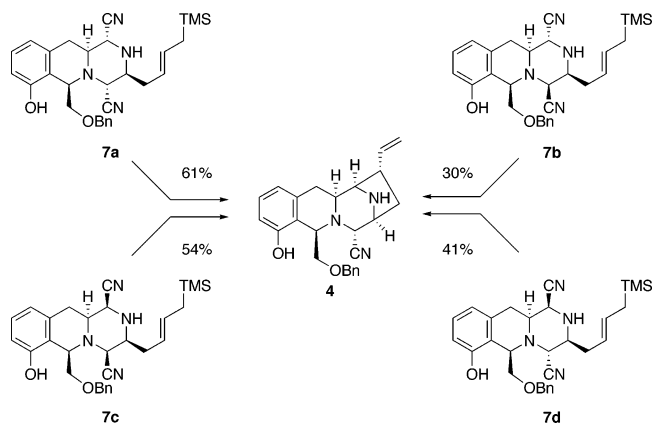
sample of the natural product, as determined by ¹H NMR and HPLC analysis, and by optical rotation measurements. The entire sequence from **1** and **2** proceeds in 19% yield (7 steps); the yield from pseudoephedrine glycinamide is approximately 4% (15 steps).

By conducting the key cyclization reaction of the bis-amino nitriles **3** at 23 °C (1 h, ZnCl₂, TMSCN, TFE) rather than at 60 °C, it was possible to isolate and characterize three of the four possible diastereomeric tricyclic bis-amino nitrile intermediates **7** (**7a**, 44%; **7b**, 15%; **7c**, 12%, Scheme 2), as well as a small amount of the bicyclization product **4** (18%) that predominates at higher temperature. The fourth diastereomer (**7d**) could also be isolated, after longer treatment at 23 °C (12 h, 19%, see Scheme 2). Each of the individual diastereomeric tricyclic amino nitriles **7a–d** was transformed into the tetracyclic product **4** upon subjection to the cyclization medium for 19 h at 61 °C, albeit at different rates and with different efficiencies (see Scheme 3). These experiments leave little doubt that the sequence of bicyclization to form product **4** involves initial formation of the C-ring followed by formation of the D-ring. This proves to be critical to achieving proper stereochemistry of the D-ring; in one alternative sequence that we investigated, where D-ring formation preceded C-ring formation, the allyl silane-imine addition reaction did not provide the necessary stereochemistry for synthesis of quinocarcin.¹¹

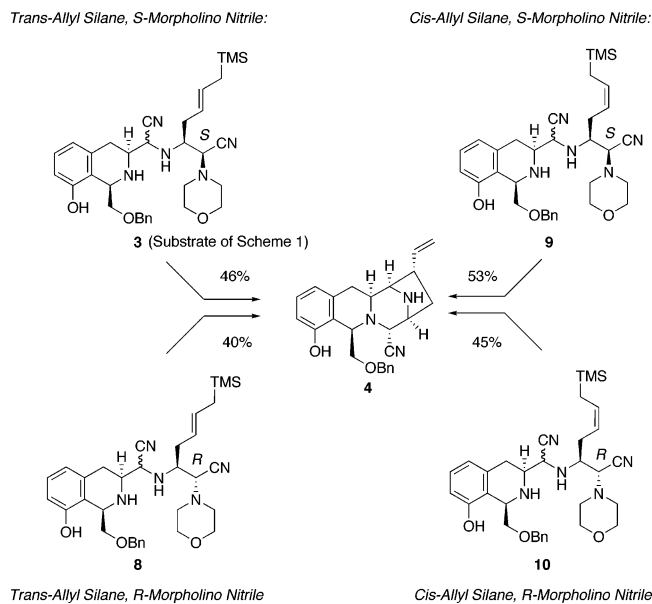
Scheme 2



Scheme 3



Scheme 4



We investigated the influence of modification of the stereochemistry of the morpholino nitrile group upon the key cyclization reaction (using as starting material the diastereomer produced in the synthesis of the C-protected α -amino aldehyde derivative **2**; see structure **8**, Scheme 4, and the Supporting Information) as well as the influence of modification of the geometry of the allyl silane

appendage in both diastereomeric morpholino nitrile series (see structures **9** and **10**, Scheme 4). In brief, when each of the four pairs of diastereomeric starting materials was subjected to cyclization conditions (40–60 °C, ~15 h) the tetracycle **4** was formed as the major product, but the substrate **9**, containing a *cis*-allyl silane appendage and an *S*-configured morpholino nitrile group, formed **4** most efficiently (53% yield). In both the *cis*- and *trans*-substrate series the *S*-morpholino nitrile stereochemistry correlated with a slightly greater efficiency of product formation (Scheme 4).

Acknowledgment. Financial support from the National Institutes of Health is gratefully acknowledged. S.K. acknowledges a postdoctoral fellowship from Eli Lilly. We thank Dr. Richard Staples for the X-ray analyses, and Kyowa Hakko Kogyo Co., Ltd. for an authentic sample of quinocarcin.

Supporting Information Available: Detailed experimental procedures and tabulated spectroscopic data (^1H and ^{13}C NMR, FT-IR and HRMS) for all new compounds, and the X-ray analysis of the aldehyde intermediate referred to in reference 10. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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JA056206N