

A Concise Total Synthesis of (–)-Quinocarcin via Aryne Annulation

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The tetrahydroisoquinoline antitumor antibiotics have received considerable attention over the past several decades owing to their intricate polycyclic architectures and potent broad-spectrum cytotoxicity (e.g., **1–5**, Figure 1).¹ An archetypal member of the 3,8-diaza-

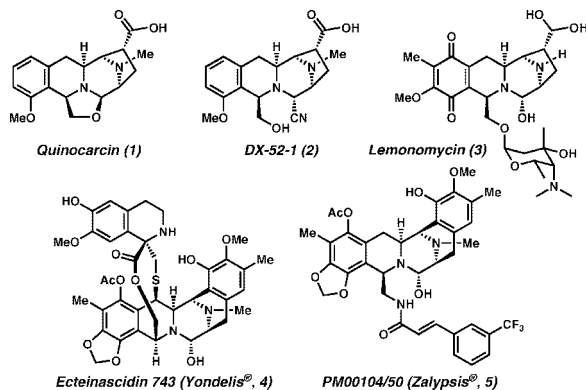
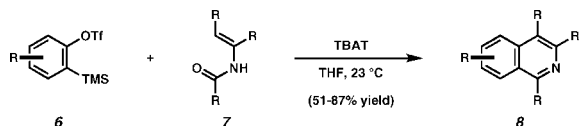


Figure 1. Tetrahydroisoquinoline antitumor antibiotics.

bicyclo[3.2.1]octane subclass, quinocarcin (**1**), has shown remarkable antiproliferative activity against lymphocytic leukemia.² Further in vitro studies involving the more stable citrate salt of **1**³ (KW2152) and the aminonitrile DX-52-1⁴ (**2**) revealed similar inhibition of non-small cell lung cancer and adenocarcinoma. Certain members of this family are currently in advanced human clinical trials in the U.S. as anticancer treatments, notably Ecteinascidin 743⁵ (Yondelis, **4**) and the jorumycin analogue PM00104/50⁶ (Zalypsis, **5**). As part of our ongoing studies directed toward this class of molecules,⁷ we report an 11-step asymmetric total synthesis of (–)-quinocarcin. This represents the shortest synthesis to date and features a key arylene annulation reaction developed in our laboratories to assemble the heterocyclic framework.^{8,9}

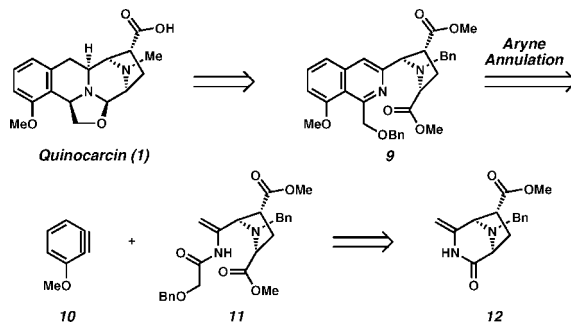
Intriguing structural and biological features of quinocarcin have led to the pursuit of its total synthesis.^{10–12} To date, the Pictet–Spengler condensation has been the most popular procedure used to close the namesake tetrahydroisoquinoline ring system,^{10,11d,e} while alternate strategies centered on the reduction of isoquinolines are noticeably less common.^{11c} We have recently reported a method for the construction of a broad array of substituted isoquinolines **8** that employs a fluoride-induced annulation reaction between arynes derived from silylaryl triflates¹³ **6** and *N*-acyl enamines **7** (Scheme 1).⁸ Isoquinoline

Scheme 1



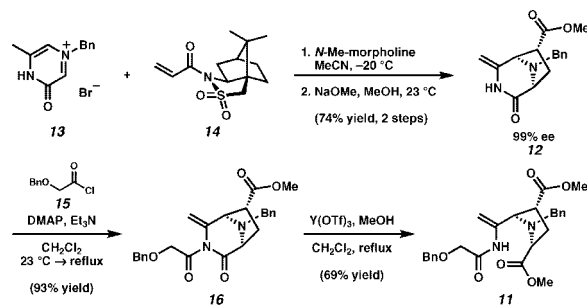
9 was retrosynthetically targeted, for construction through the union of arylene **10** and *N*-acyl enamine **11** (Scheme 2). We ultimately envisioned enamine **11** to arise through functionalization of diazabicyclo **12**, the stereoselective formation of which would impart asymmetry upon our forward route.

Scheme 2



Drawing from our previous total synthesis of the related tetrahydroisoquinoline lemonomycin (**3**),⁷ we chose to build the bridged bicycle using an auxiliary-controlled diastereoselective dipolar cycloaddition between an oxidopyrazinium betaine and a chiral dipolarophile (Scheme 3).¹⁴ Deprotonation of oxidopyrazinium bromide

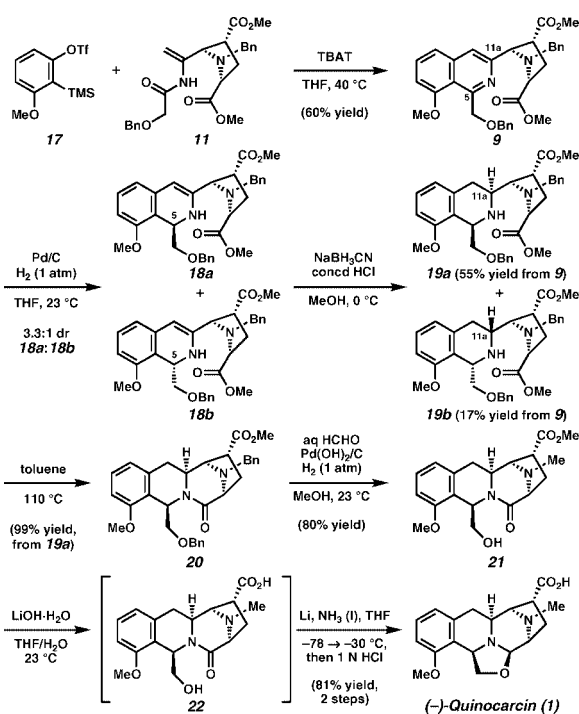
Scheme 3



13¹⁵ to form the putative active dipole in situ followed by subsequent addition of the acrylamide of Oppolzer's sultam (**14**) produced an 11:1 mixture of separable diastereomeric cycloadducts.^{7,11a,b} Purification of the major diastereomer and removal of the auxiliary via basic methanolysis provided methyl ester **12** in 74% yield and 99% ee. Acylation with benzyloxyacetyl chloride (**15**) then afforded imide **16**. To advance this intermediate to enamine **11**, regioselective methanolysis at the lactam carbonyl was required. An extensive screening of additives revealed that several metal triflate salts are capable of inducing this selectivity,¹⁶ and yttrium(III) triflate was eventually found to provide the optimum yield of **11**.

With *N*-acyl enamine **11** in hand, we focused our attention on the key arylene annulation. Using optimized conditions,⁸ enamine **11** and 3-methoxy-2-(trimethylsilyl)phenyl triflate¹⁷ (**17**) were combined in the presence of tetra-*n*-butylammonium difluorotriphenylsilicate (TBAT) at 40 °C to generate isoquinoline **9**, an intermediate comprising the core carbon atoms of quinocarcin (Scheme 4).¹⁸ Having thus assembled the molecular scaffold, our next challenge lay in a diastereoselective reduction of the isoquinoline ring system to introduce the stereocenters at C(5) and C(11a). After exploring several one-step methods to accomplish this transformation,¹⁹ we opted for a two-step sequence beginning with hydrogenation

Scheme 4



over Pd on C that afforded a 3.3:1 mixture of unstable diastereomeric dihydroisoquinolines (**18a** and **18b**).²⁰ Treatment of this mixture with sodium cyanoborohydride resulted in a completely stereoselective reduction to produce an equivalent ratio of separable tetrahydroisoquinolines (**19a** and **19b**), the major diastereomer of which corresponds to the stereochemistry of the target alkaloid.²¹ Upon heating, the newly formed secondary amine selectively condensed with one of the two neighboring esters to form lactam **20** in 99% yield. In light of the slow benzyl group hydrogenolysis implicit in the success of the previous heterogeneous reduction, the more active Pearlman's catalyst was required to remove the two protecting groups and subsequently methylate the unmasked amine, providing tetracycle **21**. In the final two steps, saponification of the methyl ester was followed by a partial reduction of the lactam under dissolving metal conditions.^{11a,b,e,22} Treatment of the resulting hemiaminal with 1 N HCl resulted in closure of the oxazolidine ring and completion of (–)-quinocarcin (**1**).

In summary, we successfully completed a short asymmetric total synthesis of (–)-quinocarcin (**1**) in 10% overall yield via a longest linear sequence of 11 steps from known compounds (13 steps from commercially available materials). By applying our aryne annulation technology toward the construction of key isoquinoline intermediate **9**, we are able to assemble the core of the molecule in only five steps and advance this material to the natural product target along the shortest synthetic route reported to date. We are currently investigating the application of this methodology toward the synthesis of additional members of the tetrahydroisoquinoline antitumor antibiotic family and will report these efforts in due course.

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Supporting Information Available: Experimental details. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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- (17) 3-Methoxy-2-(trimethylsilyl)phenyl triflate (**17**) is prepared in three steps from 3-methoxyphenol; see: Peña, D.; Pérez, D.; Guitián, E.; Castedo, L. *J. Am. Chem. Soc.* **1999**, *121*, 5827–5828.
- (18) Attempts to employ the *N*-methyl analogue of the tertiary amine in **11** resulted in decomposition of the corresponding isoquinoline product, presumably through reaction of this less hindered amine with aryne **10**.
- (19) Under the best one-step conditions, the reduction of isoquinoline **9** with sodium cyanoborohydride in 1:50 HCl/MeOH at 23 °C led to a 1.6:1 mixture of diastereomeric tetrahydroisoquinolines (**19a** and **b**) in 46% yield. For a similar procedure, see ref 11c.
- (20) The diastereomeric ratio was determined by ¹H NMR. Remarkably little hydrogenolysis of the benzyl protecting groups was observed within the first 6 h of this reaction.
- (21) Reduction of either dihydroisoquinoline diastereomer (**18a** or **b**) is observed to be completely stereoselective for the formation of the *syn*-5,11a-tetrahydroisoquinoline (**19a** and **b**) following installation of the stereocenter at C(5). For a similar example of asymmetric induction, see: Ishida, A.; Fujii, H.; Nakamura, T.; Oh-ishi, T.; Aoe, K.; Nishibata, Y.; Kinumaki, A. *Chem. Pharm. Bull.* **1986**, *34*, 1994–2006.
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