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Scalable Formal Synthesis of (−)-Quinocarcin

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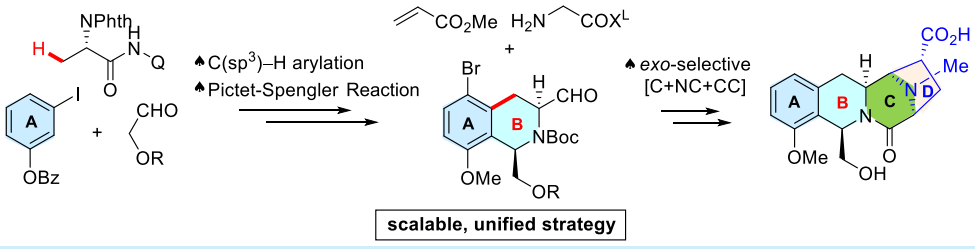
Supporting Information

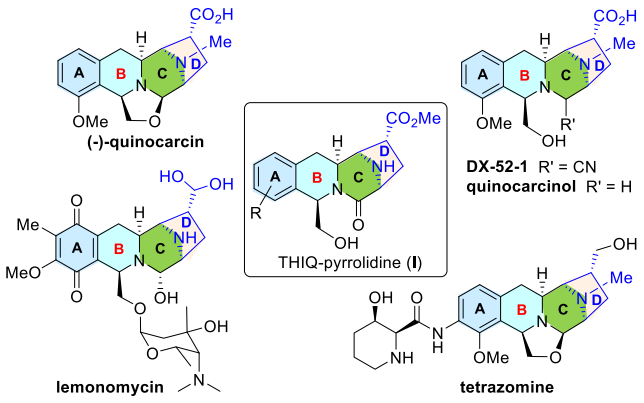


ABSTRACT: A scalable and unified strategy is described for the synthesis of (−)-quinocarcin, an important tetrahydroisoquinoline antitumor alkaloid. The strategy allows the practical formal synthesis of (−)-quinocarcin in 13 steps and 4.8% overall yield using *N*-phthaloyl-L-alanine as a chiral pool. It features the gram-scale and stereoselective synthesis of the tetrahydroisoquinoline moiety (AB ring) via Pd-catalyzed C(sp^3)−H arylation and Pictet−Spengler condensation and a Cu(I)-catalyzed *exo*-selective [C + NC + CC] coupling reaction to generate the chiral pyrrolidine motif (D ring).

(−)-Quinocarcin is a potent antitumor antibiotic first isolated from *Streptomyces melanovinaceus* by Takahashi and Tomita.[1] It belongs to an important subclass of the large family of tetrahydroisoquinoline (THIQ) alkaloids.[2] The main representatives of this subclass are (−)-quinocarcin, DX-52-1, quinocarcinol, tetrazomine, and lemonomycin, which share a common tetracyclic THIQ-pyrrolidine core scaffold (**I**) containing a THIQ as the AB ring and a chiral 3,8-diazabicyclo[3.2.1]octane skeleton as the CD ring (Scheme 1).[2] Quinocarcin exhibited remarkable antiproliferative activity against lymphocytic leukemia.[3] Its intricate polycyclic structure and promising biological activities make quinocarcin an attractive synthetic target.[4,5] The first racemic total synthesis of (±)-quinocarcin was reported by Fukuyama in 1988. Several asymmetric syntheses of (−)-quinocarcin have been elegantly demonstrated by the groups of Garner, Terashima, Myers, Zhu, Stoltz, Fujii, and Ohno.[5] Total syntheses of the racemic form of the more stable quinocarcinol methyl ester and quinocarcinamide have also been achieved.[6] The THIQ alkaloids hold great potential as anticancer agents and have triggered ongoing synthetic endeavors, as exemplified by recent achievements on the concise and practical total syntheses of those families compounds by the groups of Stoltz and Ma.[7] However, the medicinal applications have somehow been restricted by their natural availability and synthetic efficiency and scalability. Therefore, the development of a practical and unified strategy to facilitate the convergent assembly of this core tetracyclic scaffold (**I**) in sufficient quantity is highly desirable. Undoubtedly, such a strategy might offer a great opportunity to discover some new and promising anticancer agents. As part of our continuous endeavors to promote practical synthesis of natural products via C−H activation,[8,9] we report herein a scalable synthesis of (−)-quinocarcin based on the Pd(II)-catalyzed C(sp^3)−H arylation, Pictet−Spengler condensation, and Cu^I-catalyzed *exo*-selective asymmetric multicomponent [C + NC + CC] coupling reaction.

The key to the practical syntheses of quinocarcin family lies in the development of a scalable and unified strategy to the asymmetric construction of THIQ (AB ring) and pyrrolidine (D ring). To date, the Pictet−Spengler condensation is one of

Scheme 1. Quinocarcin Family Alkaloids Featuring a Common Tetracyclic THIQ−Pyrrolidine Core Scaffold (I)



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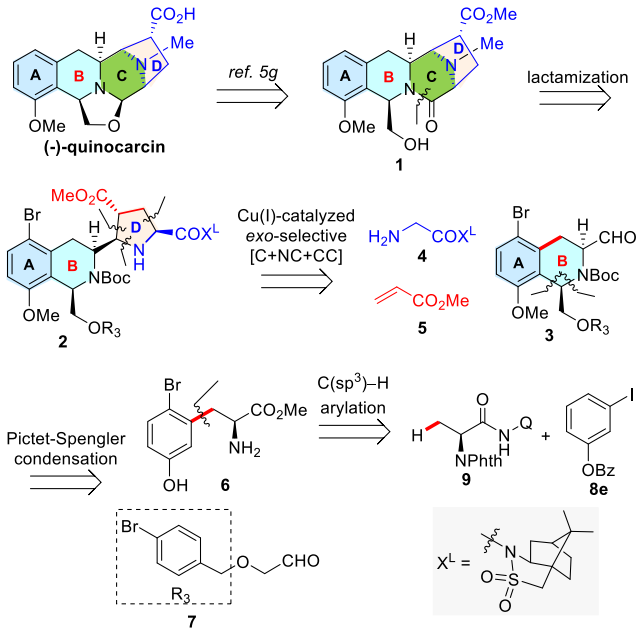
the most popular strategies for the assembly of the THIQ moiety. The pivotal point of this strategy relies on the use of properly substituted chiral β-aryl-α-amino acids as general precursors (**6** + **7** → **3**). Thus, the synthetic challenge shifted to the stereoselective synthesis of β-aryl-α-amino acids. We envisioned that our recently developed Pd-catalyzed mono-arylation of β-methyl C−H of alanine could provide a practical access to this general precursor (**8e** + **9** → **6**).[10,11] Different from the conventional synthetic methods, this protocol uses readily available L-alanine as a chiral pool and avoid the use of expensive chiral auxiliaries or catalysts. For the D-ring featuring a densely functionalized 4,5-*trans*-pyrrolidine, the asymmetric 1,3-dipolar cycloaddition has been recognized as an ideal strategy.[5a,b,12] In particular, we realized that a Cu(I)-catalyzed *exo*-selective asymmetric multicomponent [C + NC + CC] coupling reaction developed by Garner would be perfect for setting up the three chiral centers of the D ring (**3** + **4** + **5** → **2**).[13,14] Specifically, the 4,5-*trans*-pyrrolidine in **2** could be synthesized by Cu(I)-catalyzed asymmetric coupling of THIQ−aldehyde **3**, methyl acrylate **5**, and Oppolzer's L-glycylsultam **4** (X^L = Oppolzer's L-camphorsultam).[13] The quinocarcinol methyl ester **1**, an advance intermediate in Stoltz's total synthesis of (−)-quinocarcin,[5g] could be obtained from **2** by lactamization/ester cyclization. Our detailed retrosynthetic analysis and envisions are shown in Scheme 2.

Scheme 2. Retrosynthetic Analysis



The combination of Pd-catalyzed C(sp^3)−H arylation/Pictet−Spengler condensation to construct the THIQ moiety (AB ring) and a Cu(I)-catalyzed exo-selective [C + NC + CC] coupling reaction to generate the chiral pyrrolidine motif (D ring) might offer a unified strategy to access a diversity of quinocarcin family compounds and elucidate their biological activities.

Scalable synthesis of (−)-quinocarcin is shown in Scheme 3. First, we focused our attention on the palladium-catalyzed C(sp^3)−H arylation reaction.[10] We were delighted to find that our previous protocol was quite robust, and several aryl iodides were compatible with this protocol.[10] After extensive investigations of various 3-iodophenols bearing different protecting groups (**8a**−**e**), we finally chose the use of 3-iodophenyl benzoate **8e** as the arylation reagent since it gave the optimal results regarding both yield and scalability. Thus, the arylation reaction was subjected to the following conditions, that is, $Pd(OAc)_2$ (10 mol %), $AgBF_4$ (1.5 equiv), alanine derivative **9** (1.0 equiv) ,and 3-iodophenyl benzoate **8e** (1.2 equiv) in *t*-BuOH/DCE at 78 °C under N_2 for 12 h, providing **10e** in 82% yield on a 22.18 g scale. The main advantage of this reaction is the robustness, which could be repeated on a large scale. Removal of the 8-aminoquinoline group and esterification of **10e** was achieved in the presence of TsOH in methanol, leading to the corresponding methyl ester **11** in 76% yield (9.88 g), with the benzoyl group simultaneously removed. Bromination of **11** with DMSO/HBr, an elegant procedure developed by Jiao and co-workers, provided the desired bromination product **13** in 92% yield, with 7% yield of **12**.[15] It is worth noting that **12** could be reduced to **11** by hydrogenation over Pd on C in 99% yield. The phthalimide group of **13** was removed in the presence of ethylenediamine to afford the free amine **6** in 64% yield with complete retention of chirality from alanine derivative **9** (**9**, 96% ee; **6**, 97% ee). The Pictet−Spengler reaction of amido phenol **6** with acetaldehyde **7**[16] under mild acidic conditions gave tetrahydroisoquinoline **14** in 69% yield (dr, 7:1).[5f,17] Although attempts to improve the yield failed, we were glad that THIQ **14** could be obtained in multigram scale (3.13 g). It is worth noting that the multigram-scale synthesis of THIQ **14** could be achieved in five steps from alanine derivative **9**. Protecting the secondary amine as the *N*-*tert*-butoxycarbamate gave **15** in 74% yield. Subsequent methylation of phenol **15** with $TMSCHN_2$ afforded **16** in 95% yield. Treatment of **16** with $LiBH_4$ led to the reduction of ester to primary alcohol, providing **17** in 95% yield. THIQ−aldehyde **3** was obtained by Dess−Martin oxidation in 93% yield.

With the key building block THIQ−aldehyde **3** secured, efforts were directed toward the asymmetric synthesis of functionalized pyrrolidine. The [C + NC + CC] coupling reaction proceeded smoothly by combining THIQ−aldehyde **3**, Oppolzer's L-glycylsultam **4**, and methyl acrylate **5** with $Cu(CH_3CN)_4PF_6$/dppb at room temperature, giving the desired 4,5-*trans*-pyrrolidine **2** in 68% yield on a 1.22 g scale.[13] To ensure the scalability, a slightly modification of Garner's procedure was used with increased loading of copper catalyst and bisphosphine (10 mol % $Cu(CH_3CN)_4PF_6$ and 11 mol % dppb). The stereochemistry of the newly generated pyrrolidine of **2** could not be clearly determined simply using standard NMR techniques. The expected configurations were tentatively assigned on the basis of Garner's precedent[13] and later confirmed by correlation with an established intermediate **1**.

Transesterification of the chiral sultam moiety to methyl ester[18] with concurrent removal of the *N*-Boc function from **2** were realized in a one-pot fashion to afford the desired **18** in 61% yield. Upon heating, the newly formed secondary amine selectively condensed with esters to form lactams **19** in 96% yield. We expected that the aryl bromide and the OBn protecting group could potentially be removed under the same conditions as that for the N-reductive methylation, by judicious choice of reaction conditions. Indeed, simultaneous deprotection and *N*-methylation of the unmasked amine was realized under over Pd on C in the presence of aqueous solution of formaldehyde,[5f] giving quinocarcinol methyl ester **1** in 86% yield on a 0.25 g scale. Compound **1** is an established

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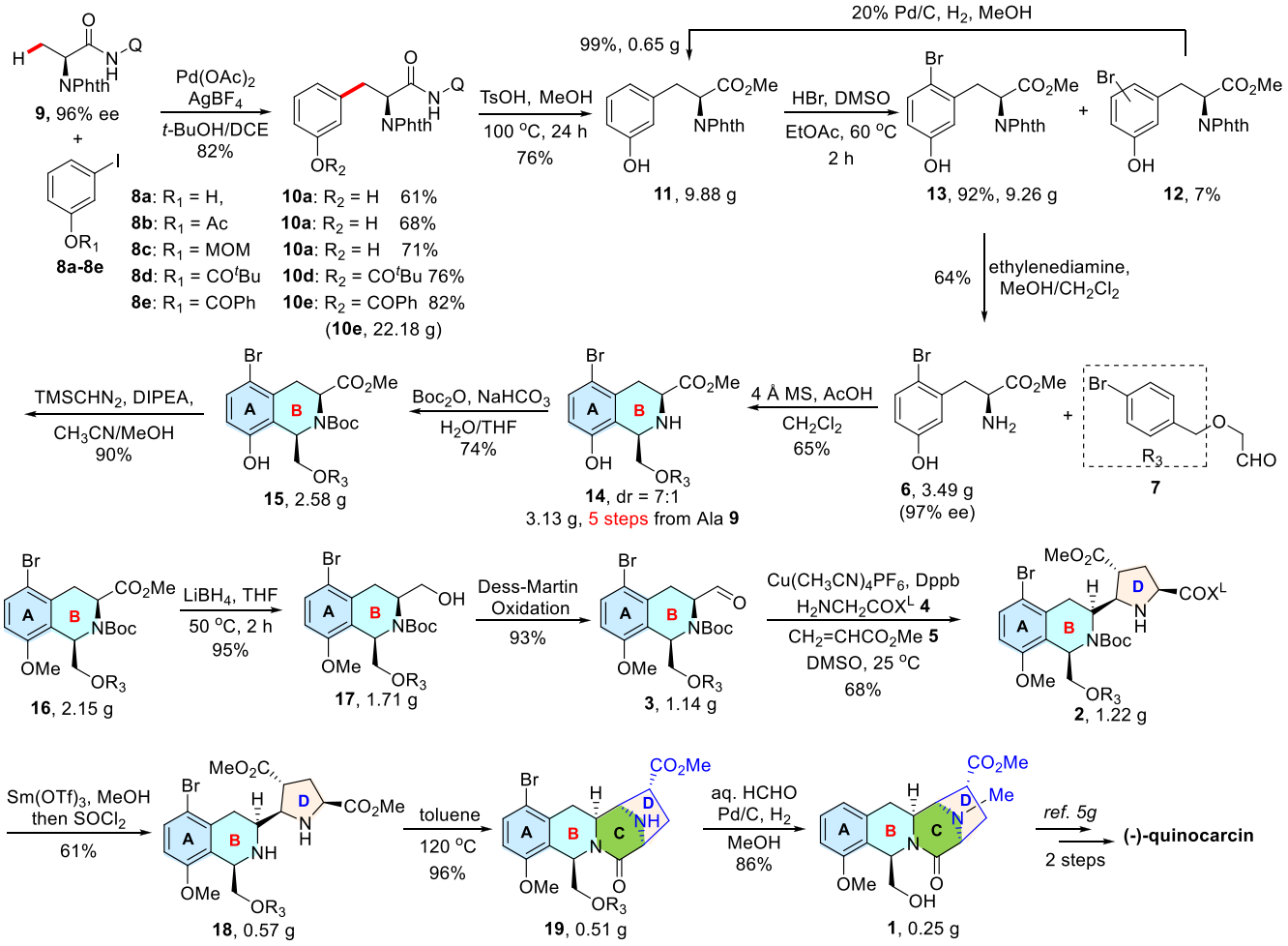
Scheme 3. Scalable Formal Synthesis of Quinocarcin



precursor in Stoltz's total synthesis of (−)-quinocarcin, and the spectroscopic data are identical to those reported.[5g]

In conclusion, a scalable formal synthesis of (−)-quinocarcin has been achieved in 13 linear steps with 4.8% overall yield. Pd(II)-catalyzed C(sp^3)−H arylation has provided an efficient and robust method to access the general precursor of THIQ core. Subsequent scalable Pictet−Spengler condensation and Cu(I)-catalyzed *exo*-selective asymmetric multicomponent [C + NC + CC] coupling reaction led to the success of practical synthesis. We believe this approach would serve as a unified strategy to facilitate the total synthesis of other natural products containing the THIQ−pyrrolidine tetracyclic core unit, such as tetrazomine, lemonomycin, and their analogues. Related studies are currently underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b01511.

Experimental details and spectral data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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