Natural Products

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Total Synthesis of (−)-Quinocarcin by Gold(I)-Catalyzed Regioselective Hydroamination**

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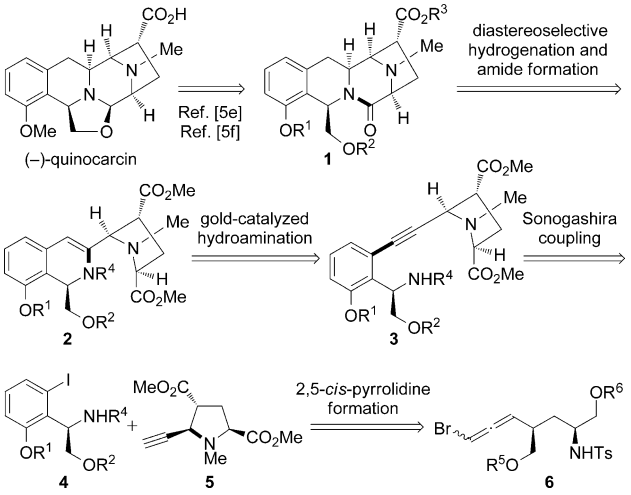
(−)-Quinocarcin is a pentacyclic tetrahydroisoquinoline alkaloid (see Scheme 1 for structure). It has attracted considerable attention from both synthetic and biological chemists interested in its intricate polycyclic architecture and potent broad-spectrum antitumor activity.[1,2] After its isolation from *Streptomyces melanovinaceus* in 1983 by Takahashi, Tomita and co-workers,[3] several efficient syntheses of quinocarcin have been reported by the groups of Fukuyama,[4] Garner, Terashima, Myers, Zhu, and Stoltz.[5] The piperizinohydroisoquinoline motif, the core structure of quinocarcin, appears in a variety of alkaloids such as tetrazomine, lemonomycin, and ecteinascidins.[1] The development of a novel strategy that facilitates convergent assembly of this tetracyclic core unit is therefore desirable.

The tetrahydroisoquinoline ring system can be efficiently constructed by a Pictet–Spengler condensation,[4,5d,e] but we planned an alternative strategy using a gold(I)-catalyzed intramolecular alkyne hydroamination, a simple and atom-economical protocol for the construction of nitrogen-containing heterocycles from free amines, sulfonamides, and carbamates.[6] Combined with a Sonogashira coupling, this strategy provides a convergent approach to the quinocarcin core structure.

Our retrosynthetic analysis is shown in Scheme 1. We expected that the known lactam **1**[5e,f] could be synthesized from the dihydroisoquinoline **2** by a diastereoselective hydrogenation and intramolecular amide formation. The dihydroisoquinoline **2** could be obtained from the alkyne **3** by an intramolecular hydroamination. Although control of the regioselectivity of this hydroamination (6-*endo* versus 5-*exo*) was a challenging issue in this strategy, we hoped that the desired 6-*endo*-*dig*-selective reaction could be achieved by appropriate tuning of the catalyst or substrate structure. The alkyne **3** was retrosynthetically envisioned to arise from the Sonogashira coupling of the phenylglycinol **4** and the 2,5-*cis*-pyrrolidine **5**. We thought that **5** could be stereoselectively prepared by 2,5-*cis*-selective pyrrolidine formation through



Scheme 1. Retrosynthetic analysis of quinocarcin.

intramolecular amination of the bromoallene **6** bearing an amide group, a method originally developed by our group.[7]

Preparation of the bromoallene **6** began with the diastereoselective propargylation of the γ-butyrolactone **8** (Scheme 2). Subsequent reduction of the lactone **9** with $LiBH_4$[8] afforded diol **10**, the primary hydroxy group of which was selectively acetylated to give the alcohol **11**. Introduction of the nitrogen functionality by a Mitsunobu reaction[9] of **11** with TsBocNH and subsequent selenium oxidation produced the propargyl alcohol **13** as a mixture of diastereomers. Treatment of **13** with MsCl and Et_3N gave the corresponding mesylate, which was then reacted with $CuBr{\cdot}Me_2S/LiBr$,[10] followed by removal of the Boc group with TFA to afford the bromoallene **6** as a mixture of diastereomers (d.r. = 55:45; determined by ^1H NMR spectroscopy). We attempted the 2,5-*cis*-selective pyrrolidine formation by intramolecular amination of **6**.[7] Treatment of **6** with NaH in DMF at room temperature successfully produced the desired 2,5-*cis*-pyrrolidine **15** in 95% yield, with excellent diastereoselectivity (*cis*-**15**/*trans*-**15** = 96:4). In contrast, an intramolecular S_N2 reaction using the mesylate **18** under identical reaction conditions afforded almost equal amounts of 2,5-*cis*- and *trans*-**15** (*cis*-**15**/*trans*-**15** = 55:45, Scheme 3). The desired pyrrolidine **5** was then prepared from *cis*-**15** by removal of the TBDPS [TBDPS = *tert*-butyl(diphenyl)silyl] and Ac groups, oxidation, esterification, detosylation, and subsequent *N*-methylation using standard protocols (Scheme 2).

With the key building block **5** secured, efforts were directed toward a model study for construction of the isoquinoline skeleton through gold(I)-catalyzed intramolecular hydroamination (Scheme 4). The model substrates **19a–d**

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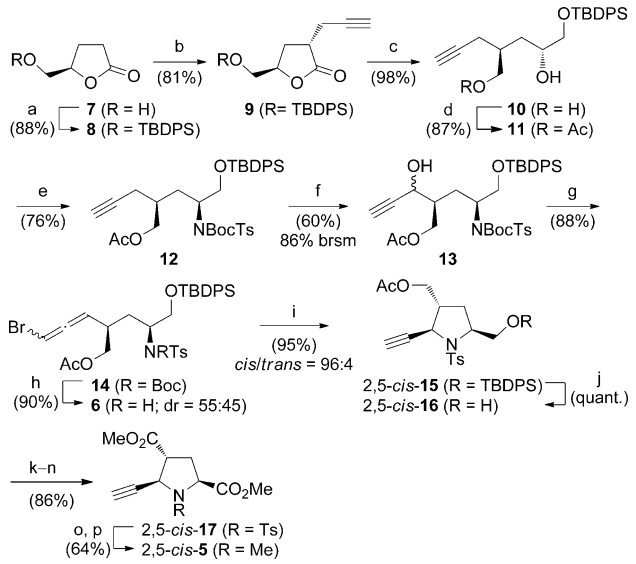
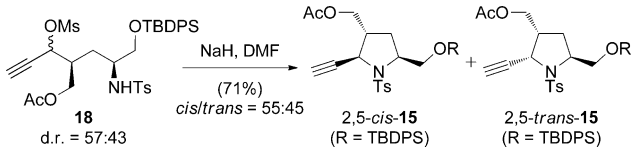
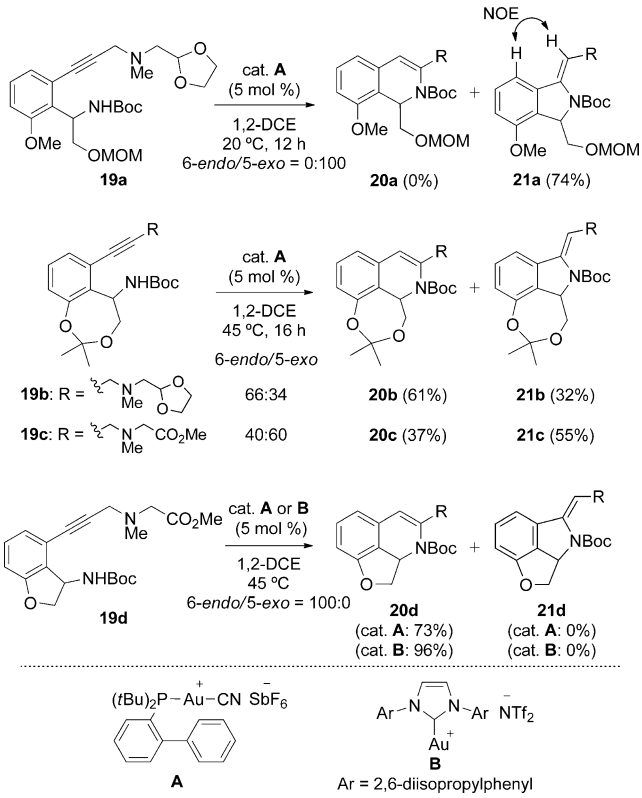


Scheme 2. Stereoselective synthesis of **5**. Reagents and conditions: a) TBDPSCl, imidazole, DMF, 20 °C; b) LHMDS, propargyl bromide, THF, −80 °C; c) $LiBH_4$, MeOH, Et_2O, 20 °C; d) AcCl, 2,4,6-collidine, CH_2Cl_2, −20 °C; e) TsBocNH, DIAD, PPh_3, THF, 20 °C; f) SeO_2, TBHP, 1,2-DCE, 60 °C; g) MsCl, Et_3N, CH_2Cl_2, 20 °C; then $CuBr\cdot Me_2S$, LiBr, THF, 50 °C; h) TFA, CH_2Cl_2, −20 °C; i) NaH, DMF, 20 °C; j) TBAF, THF, 20 °C; k) K_2CO_3, MeOH, 20 °C; l) DMP, CH_2Cl_2, 20 °C; m) $NaClO_2$, 2-methylbut-2-ene, NaH_2PO_4, *t*BuOH/CH_2Cl_2/H_2O (8:3:8), 0 °C; n) HOBt, EDC·HCl, MeOH, 20 °C; o) Mg, MeOH, −20 °C; p) MeI, Cs_2CO_3, acetone, 20 °C. Boc = *tert*-butoxycarbonyl, 1,2-DCE = 1,2-dichloroethane, DIAD = diisopropyl azodicarboxylate, DMF = *N*,*N*-dimethylformamide, DMP = Dess–Martin periodinane, EDC = *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide, HOBt = 1-hydroxybenzotriazole, LHMDS = lithium hexamethyldisilazide, Ms = methanesulfonyl, TBAF = tetra-*n*-butylammonium fluoride, TBDPS = *tert*-butyldiphenylsilyl, TBHP = *tert*-butylhydroperoxide, TFA = trifluoroacetic acid, THF = tetrahydrofuran, Ts = 4-toluenesulfonyl.



Scheme 3. Intramolecular S_N2 reaction of mesylate **18**.

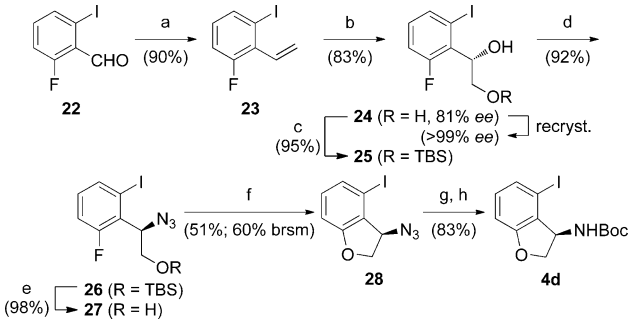
were prepared by copper-free Sonogashira coupling[11] using the racemic aryl iodides **4**.[12] After optimization of the reaction conditions using **19a**, a cationic gold(I) catalyst was found to be the most efficient catalyst for promotion of the hydroamination among the various transition-metal catalysts tested (Cu, Rh, In, Pt, and Au).[12] However, the undesired 5-*exo-dig* cyclization product **21a** was obtained exclusively in most cases (74% when using the cationic gold catalyst **A**).[13] The observed regioselectivity can be rationalized by the electronic properties of the alkyne: a new C–N bond was formed at the cationic carbon atom bearing an aryl substituent when activated by the gold catalyst. We thought that substrate modification would affect the regioselectivity of the hydroamination. Use of the seven-membered acetonide-type substrate **19b** overcame the inherent preference for 5-*exo-dig* cyclization, thereby leading to the desired 6-*endo-dig* product



Scheme 4. Model study of the gold(I)-catalyzed intramolecular hydroamination (6-*endo* versus 5-*exo*). Tf = trifluoromethanesulfonyl.

20b in 61% yield, along with the 5-*exo-dig* product **21b** (32% yield). However, the regioselectivity decreased when the acetonide-type substrate **19c** bearing a methyl ester was used. The desired 6-*endo-dig* product **20d** was exclusively obtained in 73% yield using the dihydrobenzofuran-type substrate **19d** and the catalyst **A**, presumably as a result of the ring strain of the 5-*exo-dig* product **21d**. Changing the ligand showed that the cationic gold catalyst **B**, generated in situ from IPr/AuCl and $AgNTf_2$, in 1,2-DCE afforded **20d** in 96% yield. Encouraged by this substrate-controlled switch in the regioselectivity, we proceeded to prepare an optically active dihydrobenzofuran-type substrate for the total synthesis.

The preparation of the optically active **4d** was initiated by Wittig reaction of the aldehyde **22** (Scheme 5). Following Sharpless's protocol for the dihydroxylation,[14] the diol **24** was obtained from the resulting dihalostyrene **23** in good yield with moderate enantioselectivity (83% yield, 81% *ee*). A single recrystallization from chloroform provided the optically pure diol **24** (> 99% *ee*). Regioselective silylation of **24** followed by a Mitsunobu reaction with diphenylphosphoryl azide (DPPA)[15] afforded the azide **26** in excellent yield. After removing the TBS group with TBAF, an intramolecular S_NAr reaction of the resulting alcohol **27** using *t*BuOK in THF at room temperature provided the dihydrobenzofuran **28** in 51% yield (60%, based on recovered starting material).[16] Although the Staudinger reduction of the azide **28**[17] did not give satisfactory results, treatment of **28** with PhSH, $SnCl_2$, and Et_3N in THF[18] successfully afforded the corresponding

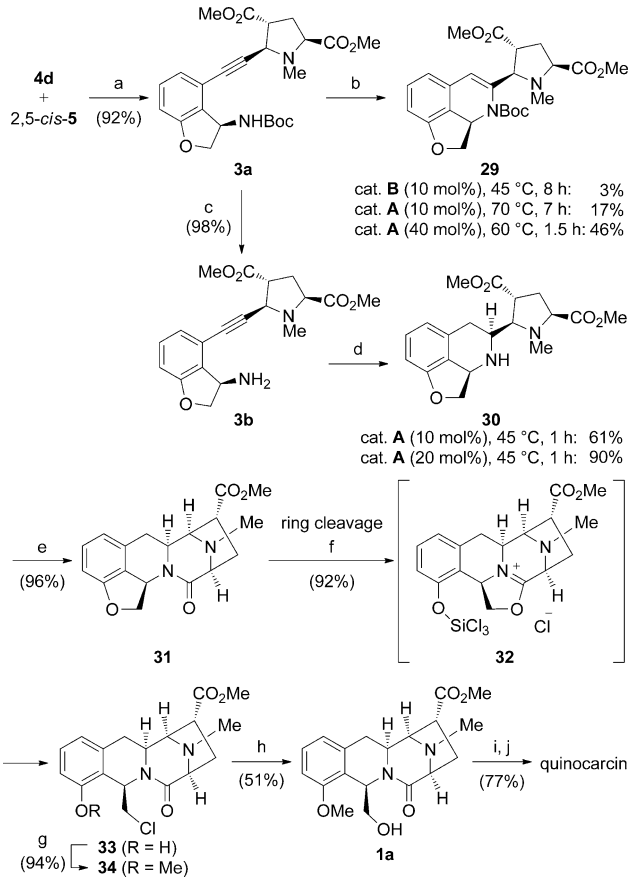


Scheme 5. Synthesis of optically active dihydrobenzofuran **4d**. Reagents and conditions: a) $MePPh_3Br$, LHMDS, THF, 0 °C; b) OsO_4, $(DHQ)_2PHAL$, K_2CO_3, $[K_3Fe(CN)_6]$, $MeSO_2NH_2$, *t*BuOH/H_2O (1:1), 0 °C; c) TBSCl, DMAP, Et_3N, CH_2Cl_2, 20 °C; d) DPPA, DEAD, PPh_3, THF, 0 °C; e) TBAF, THF, 0 °C; f) *t*BuOK, THF, 20 °C; g) PhSH, $SnCl_2$, Et_3N, THF, 20 °C; h) Boc_2O, Et_3N, CH_2Cl_2, 20 °C. DEAD = diethyl azodicarboxylate, $(DHQ)_2PHAL$ = hydroquinine 1,4-phthalazinediyl diether, DMAP = 4-(dimethylamino)pyridine, TBS = *tert*-butyldimethylsilyl.

amine, which was converted into the optically pure **4d** in 83 % yield by treatment with Boc_2O/Et_3N.

With both the building blocks, **4d** and **5**, in hand, the stage was set for their coupling and elaboration into quinocarcin (Scheme 6). The treatment of equimolar amounts of **4d** and **5** with $[Pd(PPh_3)_4]$, $CuSO_4$, and sodium ascorbate[19] in DMF and Et_3N at 80 °C provided the coupling product **3a** in 92 % yield. It is noteworthy that the use of $CuSO_4$/sodium ascorbate was vital to prevent the generation of undesired homocoupling products of the terminal alkyne **5**. We then began construction of the dihydroisoquinoline structure through the established gold(I)-catalyzed hydroamination of **3a**. Our initial attempt at the hydroamination of **3a** resulted in substantial decomposition of **3a** under the reaction conditions that were optimized for the model substrate **19d**. Further investigations using the catalyst **B** and increased loadings of catalyst **A** were unsuccessful, thus resulting in recovery of the starting material and a poor catalyst turnover (46 % yield using 40 mol % catalyst **A**), respectively. Considering that the serious steric repulsion between the methyl ester and Boc groups would impair formation of the required conformer for the hydroamination, we prepared the corresponding amine **3b** by cleavage of the Boc group. The desired 6-*endo-dig* cyclization proceeded efficiently upon treatment of **3b** with the catalyst **A**. Because the resulting enamine product was unstable, we isolated the desired 6-*endo-dig* product **30** in the tetrahydroisoquinoline form after stereoselective reduction with $NaBH_3(CN)$ (90 % yield after 2 steps). Upon heating in the presence of AcOH at 80 °C, the secondary amine selectively condensed with one of the ester groups to form the diazabicyclo[3.2.1]octane core **31** in 96 % yield. This is a related strategy to that of the late-stage construction of the piperadine ring reported by Fukuyama and Nunes[4] and Allan and Stoltz.[5f]

For the completion of the total synthesis, we had to overcome the newly generated and challenging task of cleaving the dihydrobenzofuran ring for construction of the phenylglycinol moiety of quinocarcin. On the basis of the LiI-



Scheme 6. Total synthesis of quinocarcin. Reagents and conditions: a) $[Pd(PPh_3)_4]$, $CuSO_4$, sodium ascorbate, DMF/Et_3N (3:2), 80 °C; b) cat. **A** or **B**, 1,2-DCE; c) TFA, CH_2Cl_2, 0 °C; d) cat. **A** or **B**, 1,2-DCE; then $NaBH_3(CN)$, MeOH, 1 N HCl, 0 °C; e) AcOH, toluene, 80 °C; f) $BF_3{\cdot}Et_2O$, $SiCl_4$, 1,2-DCE, 20 °C; then CsCl, MeCN, 60 °C; g) Me_2SO_4, Cs_2CO_3, acetone, 20 °C; h) $AgNO_3$, Et_3N, acetone/H_2O (3:1), 50 °C; i) LiOH·H_2O, THF/H_2O (2:1), 20 °C; j) Li, NH_3(l), THF, −78 °C → −30 °C.

mediated ring-opening halogenation of benzofurans in the presence of $SiCl_4$ and $BF_3{\cdot}AcOH$,[20] we expected that the neighboring lactam carbonyl group of **31** would assist the benzofuran cleavage to provide the oxazolidinium intermediate **32**, which could be converted into the phenylglycinol derivative through hydrolysis. Our initial attempt revealed that the exposure of **31** to $BF_3{\cdot}Et_2O$ and $SiCl_4$ in 1,2-DCE afforded a suspension, which possibly contained the expected oxazolidinium intermediate **32**.[21] However, aqueous workup of this suspension only resulted in recovery of the starting material (68 %). This disappointing result can be attributed to hydrolysis of the transient silyl ether in **32** prior to the required cleavage of the oxazolidinium ring, thus promoting the reverse reaction (benzofuran formation) to lactam **31**. After optimization of the workup procedure, use of CsCl gave the desired result and produced the phenol **33** in 92 % yield. NOE experiments on this compound confirmed the relative stereochemistry. Methylation of **33** with dimethyl sulfate afforded the lactam **34** in 94 % yield. After conversion of **34** into the alcohol **1a** using acetone/H_2O in the presence of $AgNO_3$ and Et_3N, **1a** was successfully converted into quino-

carcin using procedure reported by Allan and Stoltz.[5f] The spectroscopic data for our synthetic (−)-quinocarcin were identical to those of the original isolation report and to the reports on synthetic quinocarcin.[5]

In conclusion, we have achieved the asymmetric total synthesis of quinocarcin. Notably, the regioselectivity of intramolecular hydroamination of **19a–d** could be completely switched by substrate control. This novel and concise construction of the tetrahydroisoquinoline core structure of quinocarcin using the combination of a Sonogashira coupling and an intramolecular hydroamination will enable the syntheses of a variety of related tetrahydroisoquinoline alkaloids.

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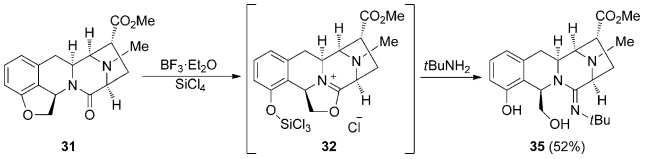
[21] The formation of the oxazolidinium intermediate **32** was supported by isolation of the amidine derivative **35** after treatment of the suspension with *tert*-butylamine. Unfortunately, all our attempts to convert **35** into quinocarcin were unsuccessful.



31 **32** **35** (52%)

