DOI: 10.1002/chem.201300687

Convergent Synthesis of (−)-Quinocarcin Based on the Combination of Sonogashira Coupling and Gold(I)-Catalyzed 6-*endo-dig* Hydroamination

Hiroaki Chiba, Yuki Sakai, Ayako Ohara, Shinya Oishi, Nobutaka Fujii,* and Hiroaki Ohno*[a]

Abstract: The total synthesis of the pentacyclic tetrahydroisoquinoline alkaloid quinocarcin, which possesses intriguing structural and biological features, has been achieved through a gold(I)-catalyzed regioselective hydroamination reaction. It is noteworthy that the regioselectivity of the intramolecular hydroamination of an unsymmetrical alkyne could be completely switched through substrate control. Other key features of this synthesis include the highly stereoselective synthesis of 2,5-*cis*-pyrrolidine through the intramolecular amination of the bromoallene and the Lewis acid mediated ring opening of dihydrobenzofuran.

Keywords: allenes · cross-coupling · gold · natural products · total synthesis

Introduction

(−)-Quinocarcin is a pentacyclic tetrahydroisoquinoline alkaloid that was first isolated by Tomita, Takahashi, and Shimizu in 1983 from *Streptomyces melanovinaceus* (Figure 1).[1] This material was reported to exhibit remarkable levels of antiproliferative activity against lymphocytic leukemia. Further in vitro studies with the more stable citrate salt KW2152[2] and the aminonitrile DX-52-1[3] revealed that these compounds exhibited inhibitory activity towards non-small cell-lung cancer and adenocarcinoma. A large number of different natural products within this structural class, from a variety of different environments, have been reported.[4] For example, renieramycin G[5] was obtained from Fijian sea sponges, whereas ecteinascidin 743 (Et-743, Yondelis)[6] was isolated from Caribbean sea squirts. Furthermore, lemonomycin[7] and saframycin B[8] were isolated from the cultures of *Streptomyces* strains. Some of the compounds that belong to this family have been evaluated as anticancer agents in advanced human clinical trials. It is noteworthy that Et-743 exhibited high levels of activity towards a broad range of tumor cell-lines at pM and low nM concentrations.[9] Therefore, this class of tetrahydroisoquinoline alkaloids has been the subject of considerable renewed interest from the drug-discovery community because of their potential use as anti-cancer agents.

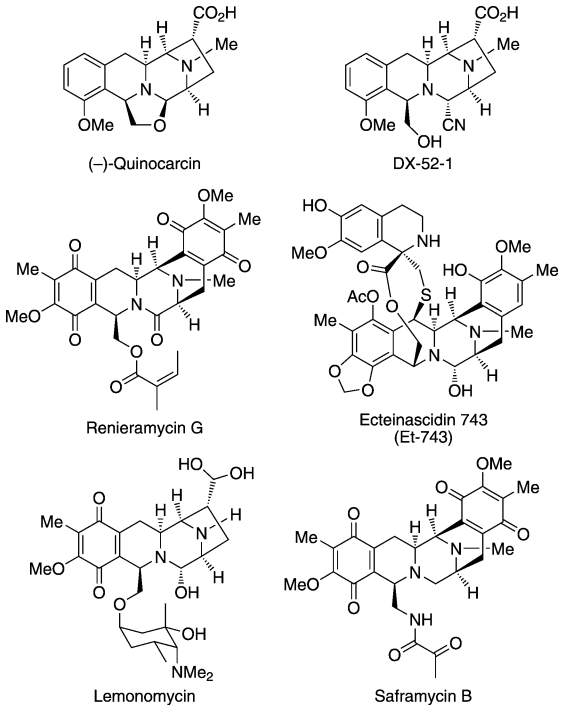
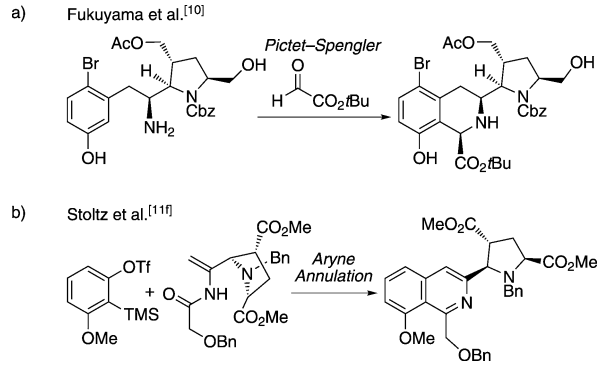


Figure 1. Quinocarcin and related tetrahydroisoquinoline alkaloids.

These tetrahydroisoquinoline alkaloids share a common skeleton that is composed of a piperizinohydroisoquinoline motif. In addition to their potent biological properties, their fascinating and challenging molecular architectures have inspired many synthetic groups to develop creative approaches towards their total synthesis. Although several efficient methods have been reported for the specific synthesis of these alkaloids, the development of a new and convergent route that is capable of providing general access to several tetrahydroisoquinolines in this class is still desirable.

[a] H. Chiba, Y. Sakai, A. Ohara, Dr. S. Oishi, Prof. Dr. N. Fujii, Prof. Dr. H. Ohno
Graduate School of Pharmaceutical Sciences, Kyoto University
Sakyo-ku, Kyoto 606-8501 (Japan)
Fax: (+81) 75-753-4570
E-mail: nfujii@pharm.kyoto-u.ac.jp
hohno@pharm.kyoto-u.ac.jp

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201300687.

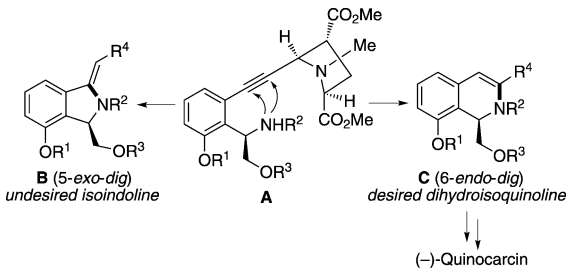


Scheme 1. Total syntheses of quinocarcin, reported by Fukuyama and Nunes[10] and by Allan and Stoltz.[11f] Cbz = benzyloxycarbonyl.

In the majority of the reported syntheses of quinocarcin,[10,11] including the first total synthesis by Fukuyama and Nunes (Scheme 1a),[10] and the syntheses of other related alkaloids, the Pictet–Spengler condensation reaction has been used as one of the most reliable procedures for the construction of the isoquinoline core.[10,11d,e,12] In an alternative strategy, Allan and Stoltz[11f] accomplished their total synthesis based on a unique annulation reaction of an *N*-acyl enamine with an aryne to generate the isoquinoline skeleton (Scheme 1b). It is noteworthy that this new approach allows the development of the shortest synthetic route to the assembly of the core tetrahydroisoquinoline ring system reported to date.

The transition-metal-catalyzed intramolecular hydroamination reaction of alkynes is currently recognized as one of the most synthetically useful and straightforward approaches for the construction of nitrogen-containing heterocycles.[13] Several research groups have made significant contributions to this area, which have resulted in the development of a variety of different catalytic systems. Of the many transition-metal catalysts that are available, gold has been reported to be particularly effective for activating alkynes towards nucleophilic attack.[14] Unfortunately, noble gold was for a long time considered to be catalytically inactive and its potential in organic chemistry was, consequently, overlooked. However, over the course of the last decade, gold catalysis has rapidly become a topic of considerable interest in chemistry. The soft character of this large atom provides a pronounced affinity towards alkynes that ultimately translates into mild reaction conditions and high yields of the desired addition products.[14]

We have designed a new strategy for the preparation of the tetrahydroisoquinoline core of quinocarcin (Scheme 2), based on the idea that the gold-catalyzed hydroamination of an alkyne would provide a powerful alternative to the existing repertoire of synthetic strategies. One of the attractive features of this strategy is that the reactant alkyne **A** could be prepared by using the Sonogashira coupling of two advanced fragments during the latter stages of the synthesis, which would effectively facilitate the preparation of quinocarcin derivatives and other related alkaloids. One of the

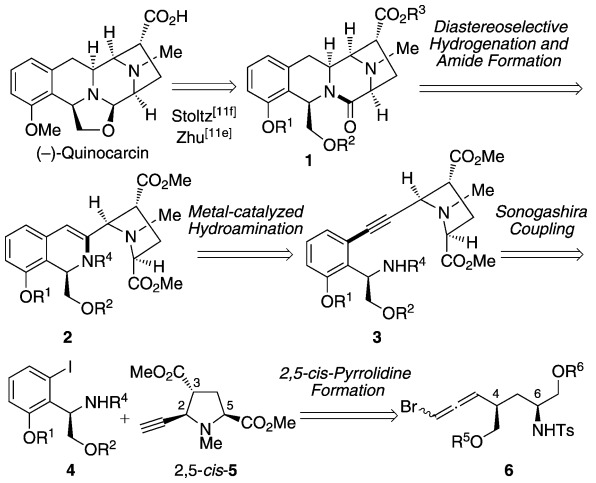


Scheme 2. Regioselectivity issue in the total synthesis of (−)-quinocarcin through the alkyne-hydroamination reaction.

potential issues that were associated with this strategy involved the regioselectivity of the reaction, in that the alkyne carbon atom at the benzylic position would be a highly reactive site for the hydroamination reaction, which would lead to the formation of the undesired isoindoline-type product **B** through a 5-*exo-dig* cyclization reaction. With this issue in mind, a precise optimization of the reaction conditions would be required, in conjunction with any appropriate modifications to the structures of the substrates. Herein, we report a complete account of our investigation towards the construction of the core structure of quinocarcin by using a gold(I)-catalyzed hydroamination reaction, including a description of the complete switch that is observed in the regioselectivity (5-*exo-dig* to 6-*endo-dig*) of the transformation following changes to the substrate structure.[15] The stereoselective construction of an alkyne synthon of type **A**, through a bromoallene-cyclization reaction, and the unusual cleavage of a dihydrobenzofuran moiety, thus allowing for the completion of the total synthesis, are also presented.

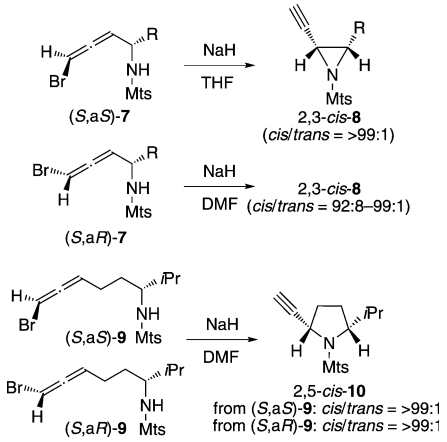
Results and Discussion

Preparation of 2,5-*cis*-pyrrolidine 5 through the highly *cis*-selective intramolecular amination of bromoallene 6: Our retrosynthetic analysis is shown in Scheme 3. It was envisaged that known lactam **1**[11e,f] could be synthesized from dihydroisoquinoline **2** through a diastereoselective hydrogenation reaction, followed by intramolecular amide formation. This strategy is similar to that reported by Fukuyama and Nunes[10] and by Allan and Stoltz[11f] for the late-stage construction of the piperidine ring. As described above, dihydroisoquinoline **2** could be synthesized by using the transition-metal-catalyzed intramolecular hydroamination of alkyne **3**. A review of the literature revealed that no precedent existed for retrosynthetically disconnecting the tetrahydroisoquinoline skeleton of these alkaloids in this particular manner. We envisaged that alkyne **3** could be constructed by the Sonogashira coupling of phenylglycinol **4** with 2,5-*cis*-pyrrolidine **5**. Compound **5** itself could be prepared stereoselectively through a 2,5-*cis*-selective pyrrolidine-formation reaction through the intramolecular amination of bromoallene **6**, which contained a sulfonamide group, according to a method that was originally developed by our group.[16]



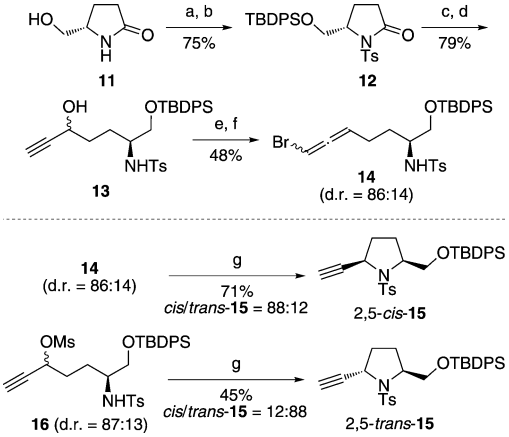
Scheme 3. Retrosynthetic analysis of (−)-quinocarcin.

The development of a highly stereoselective method for the preparation of *cis*-pyrrolidine **5** would be vital to the success of our synthetic strategy. Just over a decade ago, we reported the intramolecular amination reactions of bromoallenes **7** and **9**, as shown in Scheme 4.[16] Thus, 2,3-*cis*-2-ethynylaziridines **8** were obtained from both (*S*,a*S*)- and (*S*,a*R*)-bromoallenes **7**, which contained an N-sulfonylated amino group, following their treatment with NaH in DMF or THF. Although the pyrrolidine formation of bromoallenes **9** also proceeded in a highly *cis*-selective manner (>99:1, Scheme 4), the formation of the five-membered ring was only investigated as an isolated example. Therefore, the effects of the relatively small alkoxymethyl (at the 6-position) and tosyl groups (on the nitrogen atom) of bromoallene **6** (Scheme 3) on this reaction, as well as of the additional substituent at the 4-position, remain unclear.



Scheme 4. Our previous results on the highly *cis*-selective intramolecular amination of bromoallenes.[16] DMF = *N*,*N*-dimethylformamide, Mts = 2,4,6-trimethylbenzenesulfonyl.

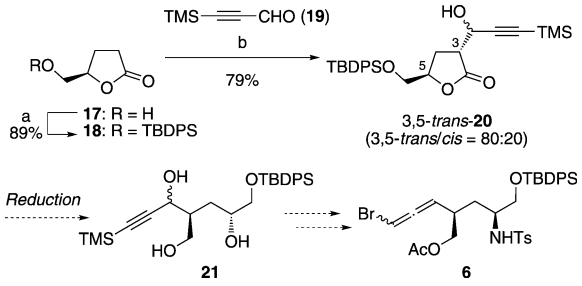
To improve our understanding of the scope of this process, we initially investigated the intramolecular amination reaction by using a simple bromoallene **14** that lacked a C-4 substituent, which was readily prepared from a commercially available pyrrolidinone **11** (Scheme 5). According to a literature report,[17] **11** was converted into compound **12** through the successive protection of the hydroxy and amide functionalities with *tert*-butyldiphenylsilyl (TBDPS) and 4-toluenesulfonyl (Ts) groups, respectively. The subsequent reduction of compound **12** with diisobutylaluminum hydride (DIBAL-H), followed by the addition of ethynylmagnesium bromide to the resulting hemiaminal, afforded the propargyl alcohol **13** in 79% yield as a mixture of diastereomers. Then, the corresponding mesylate, which was prepared by the treatment of **13** with MsCl and Et_3N, was reacted with CuBr·SMe_2/LiBr[18] to give the bromoallene **14**. The ratio of diastereomers was determined to be 86:14 by ^{1}H NMR spectroscopy. The treatment of bromoallene **14** with NaH in DMF afforded the desired 2,5-*cis*-pyrrolidine **15** with good stereoselectivity (*cis*-**15**/*trans*-**15**, 88:12). In contrast, the reaction of the corresponding mesylate **16** under identical conditions gave 2,5-*trans*-pyrrolidine **15** (*cis*-**15**/*trans*-**15** = 12:88), through an inversion of the configuration, which reflected the original ratio of the stereoisomers of mesylate **16** (87:13). This result demonstrated that the *tert*-butyldiphenylsiloxymethyl moiety at the 6-position and the tosyl group on the nitrogen atom effectively induced the *cis*-selective cyclization reaction, although their influences were relatively smaller than those of the isopropyl and/or Mts groups in compound **9** (Scheme 4).



Scheme 5. Model experiment for the cyclization of the bromoallene. Reagents and conditions: a) *tert*-butyldiphenylsilyl chloride (TBDPSCl), imidazole, DMF, 20°C; b) lithium hexamethyldisilazide (LHMDS), TsCl, THF, 20°C; c) DIBAL-H, CH_2Cl_2, 20°C; d) ethynylmagnesium bromide, THF, 20°C; e) MsCl, Et_3N, CH_2Cl_2, 0°C; f) CuBr·SMe_2, LiBr, THF, 20°C; g) NaH, DMF, 20°C.[16] Ms = methanesulfonyl, Ts = 4-toluenesulfonyl.

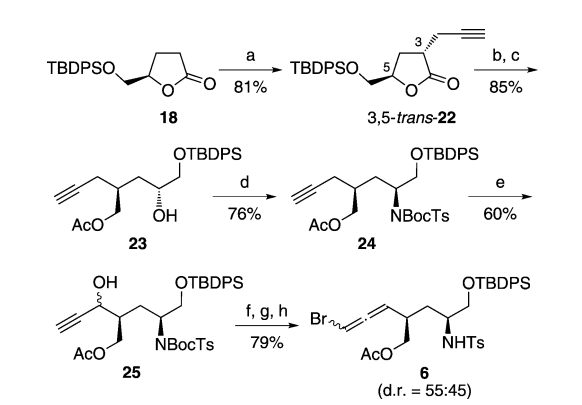
Based on the success of this model reaction, we focused on the preparation of the target pyrrolidine **5** (Scheme 3), which contained an ester functionality at its 3-position. We

initially expected that the diastereoselective aldol reaction of γ-butyrolactone **18** with aldehyde **19** would provide a convenient route to bromoallene **6** with the requisite functionality and stereochemistry (Scheme 6). Disappointingly, the stereoselectivity of this reaction was not satisfactory (3,5-*trans*-**20**/*cis*-**20**, 80:20) and the separation of these isomers was difficult.[19] Therefore, we decided to modify the synthetic route.



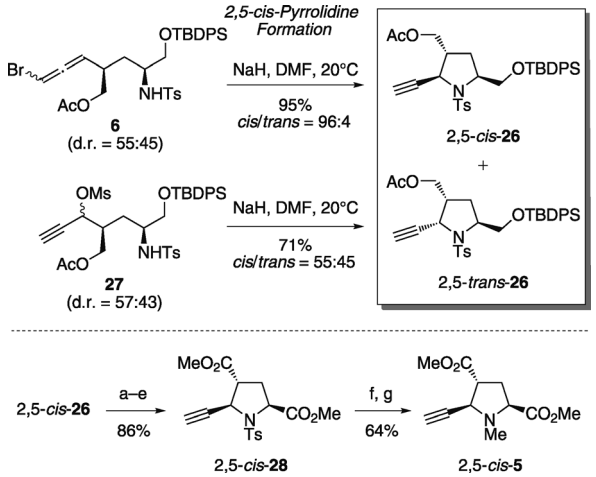
Scheme 6. Attempted synthesis of compound **6** from the aldol reaction of γ-butyrolactone **18**. Reagents and conditions: a) TBDPSCl, imidazole, DMF, 20 °C; b) LHMDS, THF, −78 °C. TMS = trimethylsilyl.

Our modified synthetic route for the construction of bromoallene **6** is shown in Scheme 7. We expected that sequential diastereoselective propargylation and selenium-mediated oxidation reactions would provide access to the desired propargyl alcohol of type **21**. In contrast to the aldol reaction, the propargylation reaction proceeded in a highly stereoselective manner to exclusively afford 3,5-*trans*-lactone **22**. Following the reduction of the lactone **22** with $LiBH_4$,[20] the primary hydroxy group of the resulting diol was selectively acetylated[21] to give alcohol **23**. The Mitsunobu reaction[22] of **23** with TsBocNH allowed for the introduction of a nitrogen functionality and subsequent selenium-mediated oxidation produced propargyl alcohol **25** as a mixture of diastereomers. The treatment of **25** with MsCl and Et_3N gave the corresponding mesylate, which was subsequently reacted with CuBr·SMe_2/LiBr,[18] followed by removal of the *tert*-butoxycarbonyl (Boc) group with trifluoroacetic acid (TFA), to afford bromoallene **6** (d.r. = 55:45; as determined by ^{1}H NMR spectroscopy).



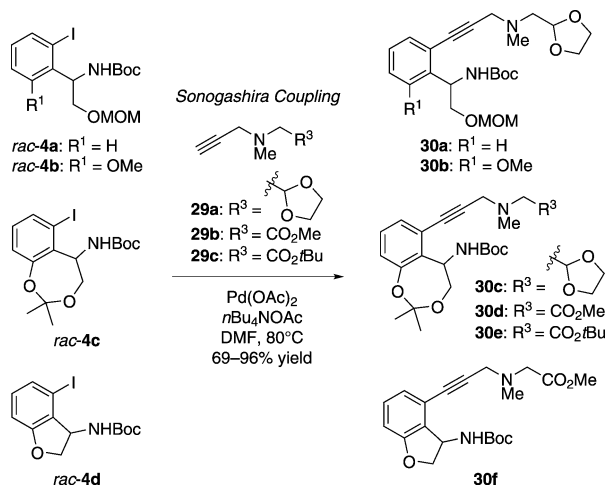
Scheme 7. Modified synthetic route to bromoallene **6**. Reagents and conditions: a) LHMDS, propargyl bromide, THF, −80 °C; b) $LiBH_4$, MeOH, Et_2O, 20 °C; c) AcCl, 2,4,6-collidine, CH_2Cl_2, −20 °C; d) TsBocNH, PPh_3, diisopropyl azodicarboxylate, THF, 20 °C; e) SeO_2, *tert*-butylhydroperoxide, DCE, 60 °C; f) MsCl, Et_3N, CH_2Cl_2, 20 °C; g) CuBr·SMe_2, LiBr, THF, 50 °C; h) TFA, CH_2Cl_2, −20 °C. DCE = 1,2-dichloroethane, TFA = trifluoroacetic acid, Ac = acetyl.

The formation of the 2,5-*cis*-selective pyrrolidine was initially attempted by performing the intramolecular amination[16] of bromoallene **6** (Scheme 8). The treatment of compound **6** with NaH in DMF at room temperature successfully provided the desired 2,5-*cis*-pyrrolidine **26** in 95% yield with excellent diastereoselectivity (*cis*-**26**/*trans*-**26**, 96:4). In a similar manner to the model system shown in Scheme 5, the intramolecular S_N2 reaction of mesylate **27** under identical reaction conditions afforded compound **26** as a mixture of diastereomers in a ratio that corresponded to the initial ratio in the mesylate (*cis*-**26**/*trans*-**26**, 55:45). Then, the desired pyrrolidine **5** was prepared from *cis*-**26** by the removal of the TBDPS and Ac groups, followed by sequential oxidation, esterification, detosylation, and N-methylation reactions by using standard procedures.



Scheme 8. Preparation of 2,5-*cis*-pyrrolidine **5** by the highly *cis*-selective intramolecular amination of bromoallene **6**. Reagents and conditions: a) TBAF, THF, 20 °C; b) K_2CO_3, MeOH, 20 °C; c) Dess–Martin periodinane, CH_2Cl_2, 20 °C; d) $NaClO_2$, 2-methylbut-2-ene, NaH_2PO_4·$2H_2O$, *t*BuOH/CH_2Cl_2/H_2O (8:3:8), 0 °C; e) 1-hydroxybenzotriazole, EDC·HCl, MeOH, 20 °C; f) Mg, MeOH, −20 °C; g) MeI, Cs_2CO_3, acetone, 20 °C. EDC = *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide.

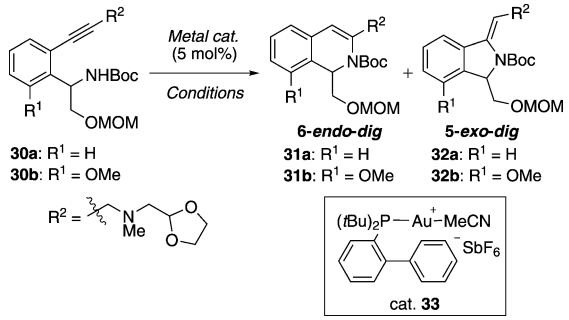
Model experiments for the regioselective hydroamination of the alkyne: With key building block **5** in hand, our attention turned to the regioselective hydroamination reaction. Thus, model substrates **30 a**–**30 f** were prepared by using a copper-free Sonogashira coupling reaction[23] from racemic aryl iodides **4** and readily available propargyl amines **29**, as shown in Scheme 9. It is noteworthy that the application of standard Sonogashira coupling conditions, with a copper co-catalyst, resulted in the generation of significant quantities of the homocoupled alkyne products.



Scheme 9. Preparation of model substrates **30a**–**30f** for the hydroamination reactions of the alkynes. MOM = methoxymethyl.

Our initial efforts were focused on investigating the hydroamination reaction of the alkynes by using simple model substrates **30a** and **30b** (Table 1). Following the optimization of the reaction conditions, cationic gold(I) catalysts were found to be the most efficient among the variety of different transition-metal catalysts that we tested for promoting the hydroamination reaction (Table 1, entries 1–6). However, disappointingly, the undesired 5-*exo-dig* cyclization products **32a** and **32b** were obtained exclusively in most cases.[24] This observed regioselectivity was attributed to the electronic properties of the alkyne, in that the gold(I)-catalyzed C–N bond formation occurred preferentially at the more cationic carbon atom, which contained an aryl substituent.

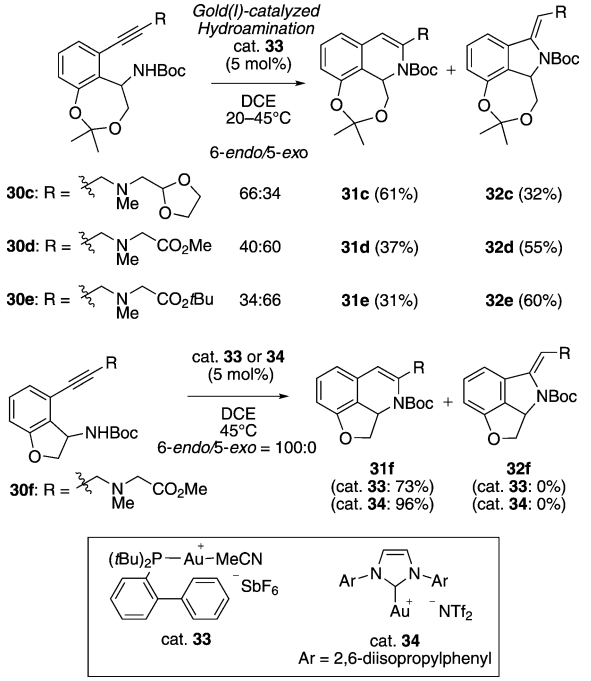
Table 1. Investigation of the regioselective hydroamination reaction (6-*endo-dig* versus 5-*exo-dig*).



Entry	Alkyne	Metal cat.	Solvent	T [°C]	Yield [%][a] 31	32
1[b]	**30a**	CuBr	DMF	100	–	21
2[c]	**30a**	$PtCl_2$	CH_2Cl_2	25	–	–
3[c]	**30a**	PPh_3AuCl	CH_2Cl_2	25	–	43
4[c]	**30a**	JohnPhosAuCl	CH_2Cl_2	25	6	72
5	**30b**	$In(OTf)_3$	DCE	80	–	–
6	**30b**	$[\{RhCl(cod)\}_2]$	DCE	80	–	–
7	**30b**	cat. **33**	DCE	25	–	74

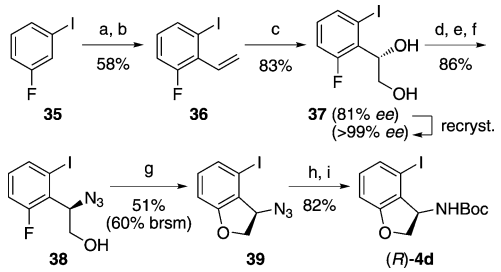
[a] Yield of isolated product. [b] TBAF (5 mol%) was used as an additive. [c] $AgNTf_2$ (5 mol%) was used as an additive. JohnPhos = (2-biphenyl)di-*tert*-butylphosphine.

Based on the unsuccessful results of these model experiment, we turned our attention towards modifying the substrate structure (Scheme 10). The use of seven-membered acetonide-type substrate **30c** partially overcame the inherent preference for the 5-*exo-dig* cyclization, thereby leading to the desired 6-*endo-dig* product **31c** in 61% yield, together with the 5-*exo-dig* product **32c** (32% yield). However, disappointingly, the regioselectivities were decreased when acetonide-type substrates **30d** and **30e**, which contained methyl and *tert*-butyl ester groups, respectively, were used. In sharp contrast, the desired 6-*endo-dig* product **31f** was obtained exclusively in 73% yield when dihydrobenzofuran-type substrate **30f** was used with gold catalyst **33**. This difference in reactivity was attributed to the ring strain in the 5-*exo-dig* product **32f**. Gold catalyst **34**, which was generated in situ from IPrAuCl (IPr = 1,3-bis(diisopropylphenyl)imidazol-2-ylidene) and $AgNTf_2$ in DCE afforded compound **31f** in 96% yield. These model experiments demonstrated that a dihydrobenzofuran-type aryl iodide would be the target building block for the phenylglycinol derivative **4** for this synthesis.



Scheme 10. Substrate-controlled 6-*endo-dig* hydroamination of alkynes.

Our efforts towards the preparation of optically active dihydrobenzofuran (*R*)-**4d** began with the formylation of 3-fluoroiodobenzene **35** through its treatment with lithium diisopropylamide (LDA) and DMF (Scheme 11). A subsequent Wittig reaction of the resulting aldehyde afforded dihalostyrene **36**, which was subjected to an asymmetric dihydroxylation reaction. Following Sharpless's procedure,[25]

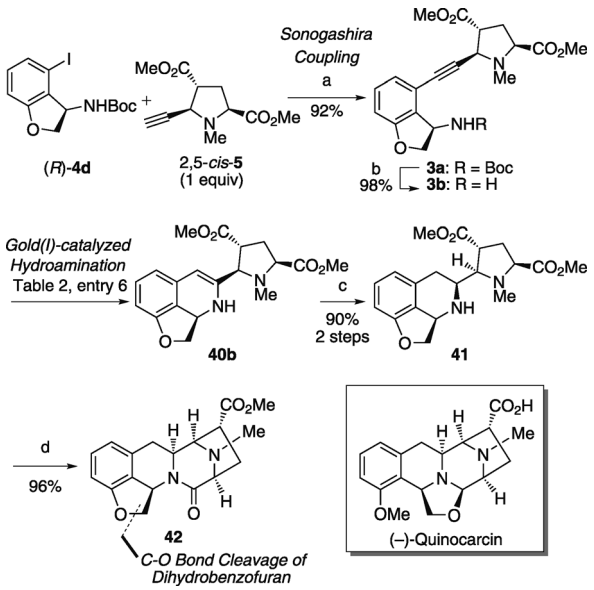


Scheme 11. Preparation of optically active dihydrobenzofuran (*R*)-**4d**. Reagents and conditions: a) LDA, DMF, THF, 20 °C; b) $MePPh_3Br$, LHMDS, THF, 0 °C; c) OsO_4, hydroquinine 1,4-phthalazinediyl diether, K_2CO_3, $[K_3Fe(CN)_6]$, $MeSO_2NH_2$, *t*BuOH/H_2O (1:1), 0 °C; d) TBSCl, 4-(dimethylamino)pyridine, Et_3N, CH_2Cl_2, 20 °C; e) DPPA, diethyl azodicarboxylate, PPh_3, THF, 0 °C; f) TBAF, THF, 0 °C; g) *t*BuOK, THF, 20 °C; h) PhSH, $SnCl_2$, Et_3N, THF, 20 °C; i) Boc_2O, Et_3N, CH_2Cl_2, 20 °C. brsm = based on recovered starting material.

diol **37** was obtained in good yield and moderate enantioselectivity (83% yield, 81% *ee*). Pleasingly, diol **37** was obtained with an excellent level of optical purity (>99% *ee*), following a single recrystallization from $CHCl_3$. The silylation of the primary alcohol of compound **37** by its treatment with *tert*-butyldimethylsilyl chloride (TBSCl) and Et_3N, followed by a Mitsunobu reaction with diphenylphosphoryl azide (DPPA)[26] and the removal of the TBS group with tetra-*n*-butylammonium fluoride (TBAF), afforded azide alcohol **38** in excellent yield. The desired dihydrobenzofuran derivative **39** was obtained in 51% yield through the intramolecular S_NAr reaction of alcohol **38** in the presence of *t*BuOK in THF at room temperature.[27] Although the Staudinger reduction[28] of azide **39** did not provide satisfactory results, the treatment of compound **39** with PhSH, $SnCl_2$, and Et_3N in THF[29] successfully afforded the corresponding amine, which was subsequently converted into optically pure compound (*R*)-**4d** in 82% yield by treatment with Boc_2O/Et_3N.

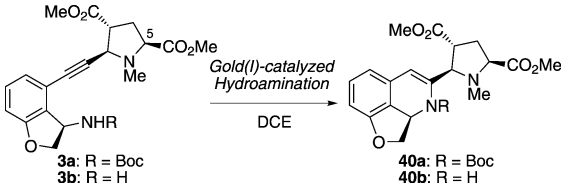
Total synthesis of (−)-quinocarcin through a gold(I)-catalyzed 6-*endo-dig* selective hydroamination reaction: With both of the building blocks, that is compounds (*R*)-**4d** and 2,5-*cis*-**5**, in hand, the stage was set for their coupling and for the construction of the quinocarcin core structure. Thus, the treatment of compounds (*R*)-**4d** and 2,5-*cis*-**5** with $[Pd(PPh_3)_4]$, $CuSO_4$, and sodium ascorbate[30] in DMF and Et_3N at 80 °C provided the coupling product (**3a**) in 92% yield (Scheme 12). It is noteworthy that the use of $CuSO_4$/sodium ascorbate, in an equimolar amount to alkyne **5**, was critical to the success of this coupling reaction and it effectively prevented the generation of the undesired homocoupled alkyne product.

Then, we proceeded with the construction of the dihydroisoquinoline skeleton according to our established gold(I)-catalyzed hydroamination of compound **3a** (Table 2). Our initial attempt at the hydroamination of compound **3a** by using gold catalyst **34**, which was the most efficient catalyst for the hydroamination of model substrate **30f**, resulted in the substantial decomposition of compound **3a** (Table 2,



Scheme 12. Construction of the core structure of quinocarcin (**42**). Reagents and conditions: a) $[Pd(PPh_3)_4]$, $CuSO_4$, sodium ascorbate, DMF/Et_3N (3:2), 80 °C. b) TFA, CH_2Cl_2, 0 °C; c) $NaBH_3CN$, DCE/MeOH (2:1), 1 M HCl, 0 °C; d) AcOH, toluene, 80 °C.

Table 2. Gold(I)-catalyzed hydroamination of alkynes.



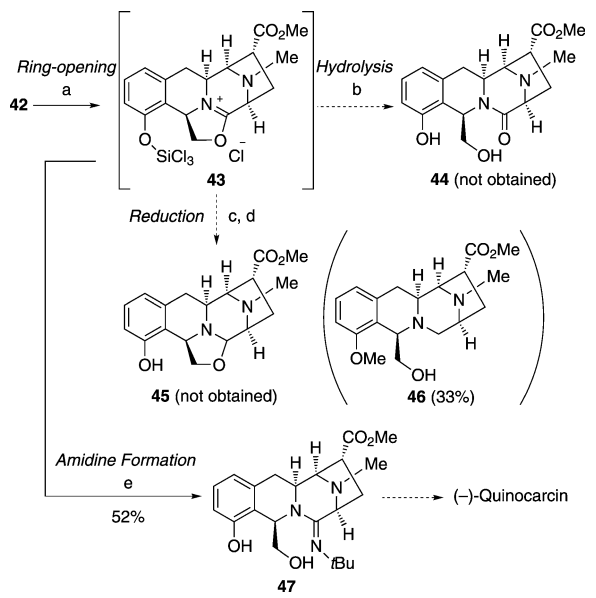
Entry	Alkyne	Gold cat. [mol%]	*T* [°C]	Yield [%][a]	Recovery [%][a]
1	**3a**	**34** (10)	45	3	9
2	**3a**	**33** (10)	70	17	37
3	**3a**	**33** (25)	70	38	–
4	**3a**	**33** (40)	60	46	–
5	**3b**	**33** (10)	45	61[b]	–
6	**3b**	**33** (20)	45	90[b]	–

[a] Yield of isolated compound. [b] Yield after reduction with $NaBH_3CN$ (Scheme 12).

entry 1). Although some improvement was observed in the hydroamination reaction by using gold catalyst **33**, the desired dihydroisoquinoline **40a** was obtained in a low yield of 17% (Table 2, entry 2). Increased loading of the gold catalyst was unsuccessful and resulted in poor levels of catalyst turnover (Table 2, entries 3 and 4). It was assumed that the methoxycarbonyl group at the C-5 position of the 2,5-*cis*-pyrrolidine was located near to the *N*-Boc group in the conformer required for the hydroamination reaction and this steric repulsion could have impaired the formation of compound **40a**. Therefore, we examined the reaction of the corresponding amine **3b**. Fortunately, the desired 6-*endo-dig* hydroamination reaction proceeded efficiently upon the treatment of compound **3b** with gold catalyst **33** (>90% yield; Table 2, entry 6). The desired 6-*endo-dig* product was

isolated in 90% yield as its tetrahydroisoquinoline form **41**, following the stereoselective reduction of compound **40b** with $NaBH_3CN$ (Scheme 12), because the resulting enamine product **40b** was found to be particularly unstable. When compound **41** was heated in the presence of AcOH at 80°C, the secondary amine underwent a selective condensation reaction with one of the ester groups to form **42** bearing the diazabicyclo[3.2.1]octane core in 96% yield. For the completion of the total synthesis, we had to overcome the newly and challenging task of cleaving the C–O bond of the dihydrobenzofuran and converting it into the phenylglycinol moiety of quinocarcin.

In a related transformation, Zewge et al.[31] reported the LiI-mediated ring-opening halogenation of dihydrobenzofuran in the presence of $SiCl_4$ and BF_3·AcOH. With this procedure in mind, we envisaged that the treatment of lactam **42** with a Lewis acid would afford oxazolidinium intermediate **43**, which would result from the cleavage of the C–O bond of the dihydrobenzofuran, assisted by the neighboring lactam carbonyl group in compound **42**. The resulting intermediate **43** could then be converted into phenylglycinol derivative **44** by hydrolysis (Scheme 13). Our initial synthetic

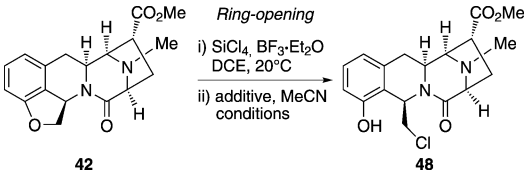


Scheme 13. Unsuccessful results of the Lewis acid mediated ring-opening of dihydrobenzofuran (**42**). Reagents and conditions: a) BF_3·Et_2O, $SiCl_4$, DCE, 20°C; b) $NaHCO_3$, H_2O, 0°C; c) Et_3SiH, MeCN, 0°C; d) Me_2SO_4, Cs_2CO_3, acetone, 20°C; e) *t*$BuNH_2$, 0°C.

efforts revealed that the exposure of compound **42** to BF_3·Et_2O and $SiCl_4$ in DCE afforded a suspension that could potentially contain the expected oxazolidinium intermediate **43**. However, disappointingly, the aqueous workup of this suspension only resulted in the recovery of the starting material **42**. This disappointing result was attributed to the hydrolysis of the transient silyl ether in compound **43** prior to the required cleavage of the oxazolidinium species, thus promoting the reverse reaction (dihydrobenzofuran formation) to afford lactam **42**. The use of other silyl chlorides, such as TMSCl and TESCl, also led to the recovery of dihydrobenzofuran **42**. Although the reduction of compound **43** with Et_3SiH for the preparation of the *N*,*O*-acetal **45** represented another attractive approach, over-reduction of compound **45** occurred and the resulting phenol was isolated as its methyl ether **46** following methylation with Me_2SO_4. In contrast, treatment of the suspension with *tert*-butylamine afforded amidine **47**. However, disappointingly, all of our attempts to convert compound **47** into quinocarcin were unsuccessful.

Despite these unsuccessful results, the formation of oxazolidinium intermediate **43** was supported by the isolation of alcohol **46** and amidine **47**. We envisaged that the trapping of intermediate **43** with an external nucleophile would prevent the reverse reaction. In practice, the treatment of the ring-opening reaction mixture with LiOAc in MeCN provided chlorinated phenol **48** in 20% yield, together with the recovery of compound **42** in 57% yield (Table 3,

Table 3. Lewis acid mediated ring-opening chlorination of dihydrobenzofuran **42**.

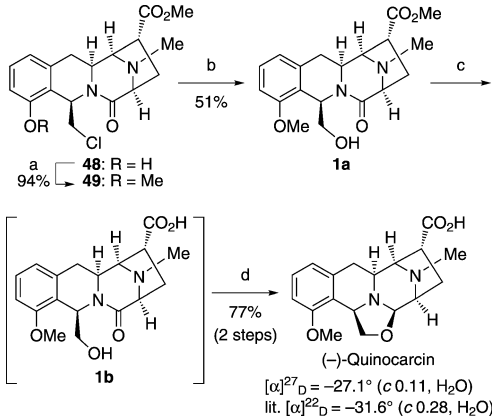


Entry	Additive [equiv]	*T* [°C]	*t* [h]	Yield [%][a]	Recovery [%][a]
1	LiOAc (10)	45	33	20	57
2	LiOAc (20)	60	24	45	50
3	LiOAc (50)	80	12	–	89
4	CsOAc (10)	60	20	86	trace
5	CsCl (10)	60	10	92	–

[a] Yield of isolated compound.

entry 1). Following optimization of the reaction conditions, the use of CsCl gave the most promising result and phenol **48** was obtained in 92% yield (Table 3, entry 5). NOE experiments on this compound confirmed the relative stereochemistry.

With phenol **48** in hand, only a short sequence of functional manipulations was required to complete the total synthesis of quinocarcin. The methylation of phenol **48** with dimethyl sulfate afforded methyl ether **49** in 94% yield (Scheme 14). Then, compound **49** was converted into alcohol **1a** by using acetone/water in the presence of $AgNO_3$ and Et_3N and compound **1a** was successfully converted into quinocarcin by using the procedure reported by Allan and Stoltz.[11f] The spectroscopic data for our synthetic (−)-quinocarcin were identical to those in the original isolation report[1] and to those provided in the reports concerning synthetic quinocarcin.[11]



Scheme 14. Total synthesis of quinocarcin. Reagents and conditions: a) Me_2SO_4, Cs_2CO_3, acetone, 20 °C; b) $AgNO_3$, Et_3N, acetone/H_2O (3:1), 50 °C; c) LiOH·H_2O, THF/H_2O (2:1), 20 °C; d) Li, NH_3 (liq.), THF, −80 °C to −30 °C.

Conclusion

We have achieved an asymmetric total synthesis of quinocarcin, according to a new and convergent strategy that is based on a combination of Sonogashira coupling and gold(I)-catalyzed hydroamination reactions. The alkyne unit for the coupling reaction was stereoselectively prepared through a bromoallene-cyclization reaction. The troublesome issue of the regioselectivity of the intramolecular hydroamination reaction was completely resolved by the substrate-controlled inversion of the selectivity and by a chlorine-mediated benzofuran cleavage. This strategy is considerably different from the many other existing syntheses, which predominantly involved the application of the Pictet–Spengler condensation reaction for the construction of the core tetrahydroisoquinoline structure. These findings could potentially lead to the development of a general and divergent synthetic strategy for the synthesis of related tetrahydroisoquinoline alkaloids.

Acknowledgements

This work was supported by a Grant-in-Aid for the Encouragement of Young Scientists (A) (H.O.) and a Strategic Young Researcher Overseas Visits Program for Accelerating Brain Circulation from the Japan Society for the Promotion of Science (JSPS) and a Platform for Drug Design, Discovery, and Development from the Ministry of Education, Culture, Sports, Science and Technology (MEXT) of Japan. H.C. is grateful for Research Fellowships for Young Scientists from JSPS.

[1] a) F. Tomita, K. Takahashi, K. Shimizu, *J. Antibiot.* **1983**, *36*, 463; b) K. Takahashi, F. Tomita, *J. Antibiot.* **1983**, *36*, 468; c) F. Tomita, K. Takahashi, T. Tamaoki, *J. Antibiot.* **1984**, *37*, 1268.

[2] a) K. Fujimoto, T. Oka, M. Morimoto, *Cancer Res.* **1987**, *47*, 1516; b) S. Inaba, M. Shimoyama, *Cancer Res.* **1988**, *48*, 6029; c) J. R. Jett, N. Saijo, W.-S. Hong, Y. Sasaki, H. Takahashi, H. Nakano, K. Nakagawa, M. Sakurai, K. Suemasu, M. Tesada, *Invest. New Drugs* **1987**, *5*, 155; d) C. D. Chiang, F. Kanzawa, Y. Matsushima, H. Nakano, K. Nakagawa, H. Takahashi, M. Tesada, S. Morinaga, R. Tsuchiya, Y. Sasaki, *J. Pharmacobio-Dyn.* **1987**, *10*, 431.

[3] a) J. Plowman, D. J. Dykes, V. L. Narayanan, B. J. Abbott, H. Saito, T. Hirata, M. R. Grever, *Cancer Res.* **1995**, *55*, 862; b) C. A. Bunnell, J. G. Supko, J. P., Jr. Eder, J. W. Clark, T. J. Lynch, D. W. Kufe, L. N. Shulman, *Cancer Chemother. Pharmacol.* **2001**, *48*, 347.

[4] For comprehensive reviews on the chemistry and biology of tetrahydroisoquinoline-based antitumor antibiotics, see: a) J. D. Scott, R. M. Williams, *Chem. Rev.* **2002**, *102*, 1669; b) P. Siengalewicz, U. Rinner, J. Mulzer, *Chem. Soc. Rev.* **2008**, *37*, 2676; c) M. Chrzanowska, M. D. Rozwadowska, *Chem. Rev.* **2004**, *104*, 3341.

[5] B. S. Davidson, *Tetrahedron Lett.* **1992**, *33*, 3721.

[6] a) K. L. Rinehart, T. G. Holt, N. L. Fregeau, J. G. Stroh, P. A. Kieffer, F. Sun, L. H. Li, D. G. Martin, *J. Org. Chem.* **1990**, *55*, 4512; b) K. L. Rinehart, T. G. Holt, N. L. Fregeau, J. G. Stroh, P. A. Kieffer, F. Sun, L. H. Li, D. G. Martin, *J. Org. Chem.* **1991**, *56*, 1676.

[7] H. A. Whaley, E. L. Patterson, M. Dann, A. J. Shay, J. N. Porter, *Antimicrob. Agents Chemother.* **1964**, *8*, 83.

[8] T. Arai, K. Takahashi, A. Kubo, *J. Antibiot.* **1977**, *30*, 1015.

[9] a) D. P. Ryan, J. G. Supko, J. P. Eder, M. V. Seiden, G. Demetri, T. J. Lynch, A. J. Fischman, J. Davis, J. Jimeno, J. W. Clark, *Clin. Cancer Res.* **2001**, *7*, 231; b) C. Sessa, F. De Braud, A. Perotti, J. Bauer, G. Curigliano, C. Noberasco, F. Zanaboni, L. Gianni, S. Marsoni, J. Jimeno, M. D'Incalci, E. Dall'ó, N. Colombo, *J. Clin. Oncol.* **2005**, *23*, 1867; c) D. G. Soares, A. E. Escargueil, V. Poindessous, A. Sarasin, A. De Gramont, D. Bonatto, J. A. P. Henriques, A. Larsen, *Proc. Natl. Acad. Sci. USA* **2007**, *104*, 13062.

[10] For the total synthesis of (±)-quinocarcin, see: T. Fukuyama, J. J. Nunes, *J. Am. Chem. Soc.* **1988**, *110*, 5196.

[11] For the total syntheses of (−)-quinocarcin, see: a) P. Garner, W. B. Ho, H. Shin, *J. Am. Chem. Soc.* **1992**, *114*, 2767; b) P. Garner, W. B. Ho, H. Shin, *J. Am. Chem. Soc.* **1993**, *115*, 10742; c) T. Katoh, M. Kirihara, Y. Nagata, Y. Kobayashi, K. Arai, J. Minami, S. Terashima, *Tetrahedron* **1994**, *50*, 6239; d) S. Kwon, A. G. Myers, *J. Am. Chem. Soc.* **2005**, *127*, 16796; e) Y.-C. Wu, M. Liron, J. Zhu, *J. Am. Chem. Soc.* **2008**, *130*, 7148; f) K. M. Allan, B. M. Stoltz, *J. Am. Chem. Soc.* **2008**, *130*, 17270.

[12] For other recent examples, see: a) W. Dong, W. Liu, X. Liao, B. Guan, S. Chen, Z. Liu, *J. Org. Chem.* **2011**, *76*, 5363; b) A. Yoshida, M. Akaiwa, T. Asakawa, Y. Hamashima, S. Yokoshima, T. Fukuyama, T. Kan, *Chem. Eur. J.* **2012**, *18*, 11192; c) P. Magnus, K. S. Matthews, *Tetrahedron* **2012**, *68*, 6343; for reviews, see ref. [4].

[13] For reviews on the transition-metal-catalyzed hydroamination of alkynes, see: a) F. Alonso, I. P. Beletskaya, M. Yus, *Chem. Rev.* **2004**, *104*, 3079; b) R. Severin, S. Doye, *Chem. Soc. Rev.* **2007**, *36*, 1407; for selected publications by ourselves on the hydroamination of alkynes, see: c) H. Ohno, Y. Ohta, S. Oishi, N. Fujii, *Angew. Chem.* **2007**, *119*, 2345; *Angew. Chem. Int. Ed.* **2007**, *46*, 2295; d) Y. Ohta, H. Chiba, S. Oishi, N. Fujii, H. Ohno, *Org. Lett.* **2008**, *10*, 3535; e) Y. Ohta, H. Chiba, S. Oishi, N. Fujii, H. Ohno, *J. Org. Chem.* **2009**, *74*, 7052; f) Y. Ohta, Y. Kubota, T. Watabe, H. Chiba, S. Oishi, N. Fujii, H. Ohno, *J. Org. Chem.* **2009**, *74*, 6299; g) K. Hirano, Y. Inaba, N. Takahashi, M. Shimano, S. Oishi, N. Fujii, H. Ohno, *J. Org. Chem.* **2011**, *76*, 1212; h) K. Hirano, Y. Inaba, K. Takasu, S. Oishi, Y. Takemoto, N. Fujii, H. Ohno, *J. Org. Chem.* **2011**, *76*, 9068; i) S. Naoe, Y. Suzuki, K. Hirano, Y. Inaba, S. Oishi, N. Fujii, H. Ohno, *J. Org. Chem.* **2012**, *77*, 4907.

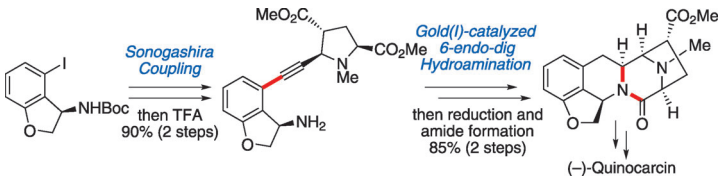
[14] For reviews on the gold-catalyzed hydroamination of alkynes, see: a) A. S. K. Hashmi, G. J. Hutchings, *Angew. Chem.* **2006**, *118*, 8064; *Angew. Chem. Int. Ed.* **2006**, *45*, 7896; b) A. Fürstner, P. W. Davies, *Angew. Chem.* **2007**, *119*, 3478; *Angew. Chem. Int. Ed.* **2007**, *46*, 3410; c) D. J. Gorin, B. D. Sherry, F. D. Toste, *Chem. Rev.* **2008**, *108*, 3351; d) S. F. Kirsch, *Synthesis* **2008**, 3183; e) A. Das, S. M. A. Sohel, R.-S. Liu, *Org. Biomol. Chem.* **2010**, *8*, 960; f) N. Krause, C. Winter, *Chem. Rev.* **2011**, *111*, 1994.

[15] For our preliminary communication, see: H. Chiba, S. Oishi, N. Fujii, H. Ohno, *Angew. Chem.* **2012**, *124*, 9303; *Angew. Chem. Int. Ed.* **2012**, *51*, 9169.

[16] H. Ohno, K. Ando, H. Hamaguchi, Y. Takeoka, T. Tanaka, *J. Am. Chem. Soc.* **2002**, *124*, 15255.
[17] J. Cossy, M. Cases, D. G. Pardo, *Tetrahedron* **1999**, *55*, 6153.
[18] a) M. Montury, J. Goré, *Synth. Commun.* **1980**, *10*, 873; b) C. J. Elsevier, J. Meijer, G. Tadema, P. M. Stehouwer, H. J. T. Bos, P. Vermeer, *J. Org. Chem.* **1982**, *47*, 2194.
[19] The relative stereochemistry of 3,5-*trans*-**20** and 3,5-*cis*-**20** was confirmed by NOE experiments.
[20] H. Driguez, B. Henrissat, *Tetrahedron Lett.* **1981**, *22*, 5061.
[21] K. Ishihara, H. Kurihara, H. Yamamoto, *J. Org. Chem.* **1993**, *58*, 3791.
[22] O. Mitsunobu, M. Yamada, *Bull. Chem. Soc. Jpn.* **1967**, *40*, 935.
[23] S. Urgaonkar, J. G. Verkade, *J. Org. Chem.* **2004**, *69*, 5752.
[24] The *Z* configuration of 5-*exo-dig* product **32b** was determined by NOE analysis.
[25] a) S. G. Hentges, K. B. Sharpless, *J. Am. Chem. Soc.* **1980**, *102*, 4263; b) H. C. Kolb, M. S. VanNieuwenhze, K. B. Sharpless, *Chem. Rev.* **1994**, *94*, 2483.
[26] B. Lal, B. N. Pramanik, M. S. Manhas, A. K. Bose, *Tetrahedron Lett.* **1977**, *18*, 1977.
[27] Shielding of light was necessary to the success of the reaction.
[28] H. Staudinger, J. Meyer, *Helv. Chim. Acta* **1919**, *2*, 635.
[29] M. Bartra, V. Bou, J. Garcia, F. Urpi, J. Vilarrasa, *J. Chem. Soc., Chem. Commun.* **1988**, 270.
[30] S. S. Bag, R. Kundu, M. Das, *J. Org. Chem.* **2011**, *76*, 2332.
[31] D. Zewge, A. King, S. Weissman, D. Tschaen, *Tetrahedron Lett.* **2004**, *45*, 3729.

Received: February 21, 2013
Published online: ■■ ▮▮, 0000

Total Synthesis



Golden(I): A convergent asymmetric total synthesis of quinocarcin employed Sonogashira and Au-catalyzed hydroamination reactions (see scheme). The regioselectivity of the intramolecular hydroamination of an unsymmetrical alkyne was switched by substrate control.