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*J. Am. Chem. Soc.*, **2008**, 130 (22), 7148-7152 • DOI: 10.1021/ja800662q • Publication Date (Web): 03 May 2008

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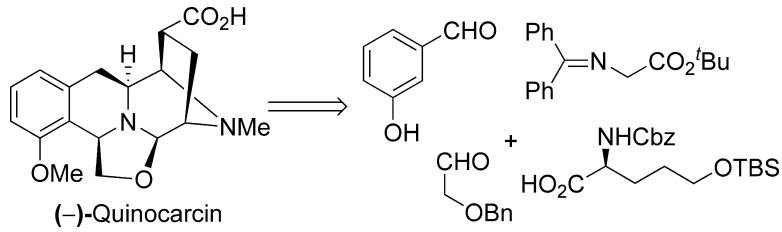


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# Asymmetric Total Synthesis of (−)-Quinocarcin

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***Abstract:*** (−)-Quinocarcin (**1**) has been synthesized in a longest linear sequence of 22 steps from 3-hydroxybenzaldehyde in 16% overall yield. The Pictet−Spengler reaction of L-*tert*-butyl-2-bromo-5-hydroxy phenylalanate (**17**), synthesized according to Corey−Lygo's enantioselective alkylation process, with benzoxyacetaldehyde (**12**) under mild acidic conditions afforded 1,3-*cis* tetrahydroisoquinoline **20** as an only isolable stereomer in 91% yield. The diazabicycle[3,2,1]-octane ring system of **28** was constructed by a silver tetrafluoroborate-promoted intramolecular Mannich reaction using amino thioether as a latent *N*-acyliminium species and tethered silyl enol ether as a nucleophile. Using amino thioether instead of aminal as a precursor of *N*-acyliminium was of high importance to the success of this otherwise disfavored 5-*endo*-Trig cyclization. A $Hf(OTf)_4$-catalyzed (0.1 equiv) transformation of aminal to amino thioether was uncovered in the course of this study, allowing the conversion of tricyclic aminal **24** to amino thioether **25** to be realized in high yield. From the bridged tetracyclic compound **28**, a sequence of oxidation of aldehyde to acid, global deprotection under hydrogenolysis conditions, and one-pot partial reduction of lactam to aminal/oxazolidine formation completed the total synthesis of the pentacyclic (−)-quinocarcine.

## Introduction

(−)-Quinocarcin (**1**) is a pentacyclic tetrahydroisoquinoline alkaloid[1] that was isolated by Takahashi and Tomita in 1983 from the culture broth of *Streptomyces melunovinuceus*.[2] It exhibited potent antitumor activities against a variety of tumor cell lines and its citrate salt (KW2152) had been in clinic trials in Japan.[3,4] The DX-52-1 (**2**), a more stable compound resulting from the ring opening of oxazolidine by cyanide, also has significant antitumor activities.[4] Quinocarcin underwent self-redox disproportionation under anaerobic conditions leading to inactive quinocarcinol (**3**) and quinocarcinamide (**4**).[3d] The structurally related (−)-tetrazomine (**5**) displayed similar antitumor antibiotic activity (see Figure 1).[5] The antiproliferative effect of (−)-quinocarcin was partly accounted for by its ability to inhibit RNA and/or DNA synthesis.[3a] However, it has been suggested that (−)-quinocarcin and (−)-tetrazomine exerted their cytotoxic activity through the expression of multiple mechanisms including the mediation of oxidative damage to DNA via the reduction of molecular oxygen to superoxide by the autoredox disproportionation of the fused oxazolidine.[6]

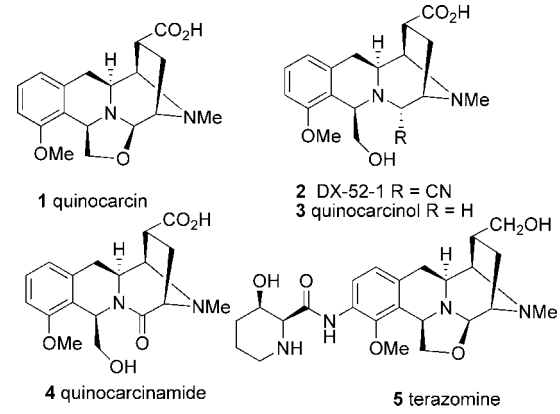


***Figure 1.*** Structures of (−)-quinocarcin (**1**) and related alkaloids.

The fascinating molecular architecture and important biological profile of quinocarcin have attracted significant attention from the synthetic community, culminating in one racemic[7] and three asymmetric synthesis of (−)-quinocarcine.[8–10] Total syntheses of more stable quinocarcinol methyl ester[11] and

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(2) (a) Takahashi, K.; Shimizu, K. *J. Antibiot.* **1983**, 463–467. (b) Takahashi, K.; Tomita, F. *J. Antibiot.* **1983**, 468–470. (c) Tomita, F.; Takahashi, K.; Tamaoki, T. *J. Antibiot.* **1984**, 1268–1272.
(3) (a) Fujimoto, K.; Oka, T.; Morimoto, M. *Cancer Res.* **1987**, *47*, 1516–1522. (b) Kanamaru, R.; Konishi, Y.; Ishioka, C.; Kakuta, H.; Sato, T.; Ishikawa, A.; Asamura, M.; Wakui, A. *Cancer Chemother. Pharmacol.* **1988**, *22*, 197–200. (c) Saito, H.; Hirata, T.; Kasai, M.; Fujimoto, K.; Ashizawa, T.; Morimoto, M.; Sato, A. *J. Med. Chem.* **1991**, *34*, 1959–1966. (d) Kahsai, A. W.; Zhu, S. T.; Wardrop, D. J.; Lane, W. S.; Fenteany, G. *Chem. Biol.* **2006**, *13*, 973–983.
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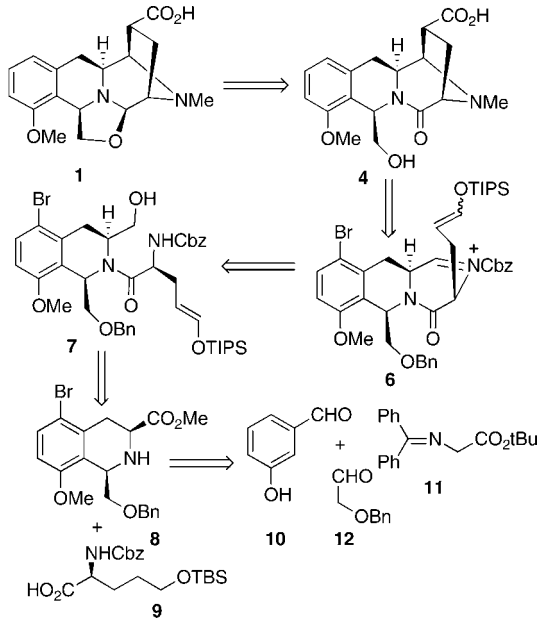
(7) Fukuyama, T.; Nunes, J. J. *J. Am. Chem. Soc.* **1988**, *110*, 5196–5198.
(8) (a) Garner, P.; Ho, W. B.; Shin, H. *J. Am. Chem. Soc.* **1992**, *114*, 2767–2768. (b) Garner, P.; Ho, W. B.; Shin, H. *J. Am. Chem. Soc.* **1993**, *115*, 10742–10753.


**10.1021/ja800662q CCC: $40.75** © **2008 American Chemical Society**

***Scheme 1.*** Retrosynthetic Analysis of **1**[a]



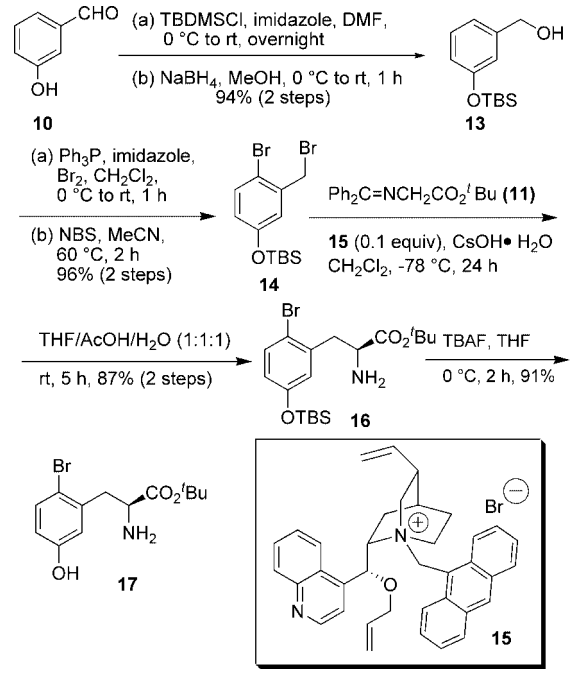
[a] Cbz = benzyloxycarbonyl; TBS = *tert*-butyldimethylsilyl; Bn = benzyl.

quinocarcinamide[12] have also been reported in the literature.[13] We report herein an efficient and practical synthesis of (−)-quinocarcin following a retro-synthetic analysis shown in Scheme 1.[14] We planned to install the labile oxazolidine ring at the late stage of the synthesis and to construct the strained 3,8-diazabicycle [3.2.1]-octane ring system by an intramolecular nucleophilic attack of the tethered silyl enol ether onto the incipient *N*-acyliminium intermediate. The amino alcohol **7**, a precursor of key cyclization intermediate **6**, could in turn be assembled by coupling of tetrahydroisoquinoline **8** and protected amino acid **9**. Tetrahydroisoquinoline **8** was thought to be prepared from 3-hydroxybenzaldehyde (**10**) via a sequence of enantioselective alkylation and diastereoselective Pictet−Spengler reaction.

## Results and Discussion

Our synthesis started with the preparation of substituted phenylalanine derivative **17** (Scheme 2). 3-Hydroxybenzaldehyde was converted to 2-bromo-5-*tert*-butyldimethylsilyloxybenzyl bromide (**14**) in 4 steps with 90% overall yield.[15]

***Scheme 2.*** Synthesis of Amino Ester **16**[a]



[a] TBSMSCl = *tert*-butyldimethylsilyl chloride; DMF = *N*,*N*-dimethylformamide; NBS = *N*-bromosuccinimide; TBAF = tetrabutylammonium fluoride; rt = room temperature.

Following Corey's procedure,[16] the enantioselective alkylation of *N*-(diphenylmethylene) glycine *tert*-butyl ester **11** by **14** in the presence of Corey−Lygo's phase transfer catalyst[16,17] (**15**, *O*-(9)-ally-*N*-(9′-anthracenylmethyl) cinchonidium bromide, 0.1 equiv) afforded, after chemoselective hydrolysis of the imine function (THF–$H_2O$–AcOH), the amino ester **16** in 87% yield. Cleavage of the silyl ether from **16** gave amino phenol **17** in 91% yield.

The (*S*)-configuration of **16** was assigned, taking for granted the Corey−Lygo's empirical model, and was confirmed by Trost's method.[18] Accordingly, both (*R*)- and (*S*)-*O*-methyl mandelic amides **18** and **19** were prepared by coupling of amine **16** with the respective mandelic acids (Figure 2). The calculated chemical shift differences ($\Delta\delta ArCH_2$ (**19**−**18**) = −0.08 ppm; $\Delta\delta CO_2CMe_3$ (**19**−**18**) = +0.06 ppm) are in accordance with the *S* configuration of amino ester **16**.[18] In addition, analysis of $^1$H NMR spectra of compounds **17** and **18** indicated that the *de* of **17** and **18**, and hence the *ee* of their precursor **16**, is higher than 95%.

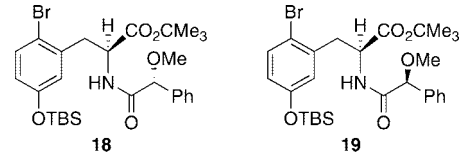


***Figure 2.*** Determination of the absolute configuration and the *ee* of amino ester **16**.

Synthesis of tetrahydroisoquinoline **8** is shown in Scheme 3. The Pictet−Spengler reaction of amino phenol **17** with ben-


(9) (a) Katoh, T.; Kirihara, M.; Nagata, Y;.; Kobayashi, Y.; Arai, K.; Minami, J.; Terashima, S. *Tetrahedron* **1994**, *50*, 6239–6258. (b) Katoh, T.; Terashima, S. *Pure Appl. Chem.* **1996**, *68*, 703–706.
(10) Kwon, S.; Myers, A. G. *J. Am. Chem. Soc.* **2005**, *127*, 16796–16797.
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(12) Flanagan, M. E.; Williams, R. M. *J. Org. Chem.* **1995**, *60*, 6791–6797.
(13) (a) Saito, H.; Hirata, T. *Tetrahedron Lett.* **1987**, *28*, 4065–4068. (b) Lessen, T. A.; Demko, D. M.; Weinreb, S. M. *Tetrahedron Lett.* **1990**, *31*, 2105–2108. (c) Allway, P. A.; Sutherland, J. K.; Joule, J. A. *Tetrahedron Lett.* **1990**, *31*, 4781–4784. (d) McMills, M. C.; Wright, D. L.; Zubkowski, J. D.; Valente, E. J. *Tetrahedron Lett.* **1996**, *37*, 7205–7208. (e) Wipf, P.; Hopkins, C. R. *J. Org. Chem.* **2001**, *66*, 3133–3139. (f) Koepler, O.; Laschat, S.; Baro, A.; Fischer, P.; Miehlich, B.; Hotfilder, M.; le Viseur, C. *Eur. J. Org. Chem.* **2004**, 3611–3614. (g) Schneider, U.; Pannecoucke, X.; Quirion, J.-C. *Synlett* **2005**, 1853–1856.
(14) Liron, M. Ph.D. Dissertation, University of Paris XI, 2006.
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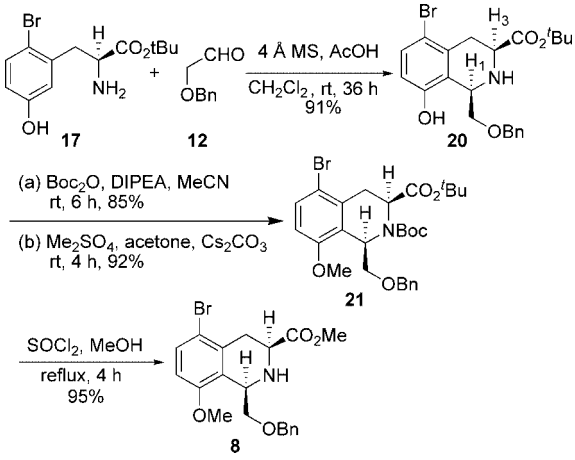
(16) Corey, E. J.; Xu, F.; Noe, M. C. *J. Am. Chem. Soc.* **1997**, *119*, 12414–12415.
(17) (a) Lygo, B.; Wainwright, P. G. *Tetrahedron Lett.* **1997**, *38*, 8595–8598. (b) Lygo, B.; Andrews, B. I. *Acc. Chem. Res.* **2004**, *37*, 518–525.

***Scheme 3.*** Synthesis of Tetrahydroisoquinoline **8**[a]

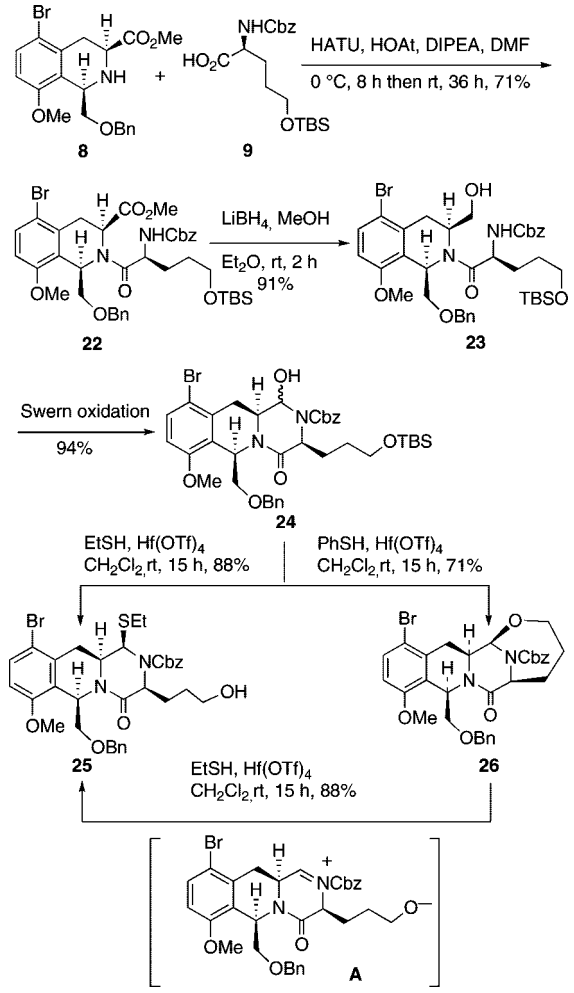



[a] TBAF = tetrabutylammonium fluoride; Boc = *tert*-butylcarbonyl; DIPEA = *N*,*N*-diisopropylethylamine; TBAF = tetrabutylammonium fluoride.

zoxyacetaldehyde (**12**) under mild acidic conditions provided tetrahydroisoquinoline **20** as a single diastereomer. A slow addition of a dichloromethane ($CH_2Cl_2$) solution of **12** to the reaction mixture containing **17**, acetic acid (1.1 equiv), and 4 Å molecular sieves in $CH_2Cl_2$ was found to be important to ensure a good yield of the desired tetrahydroisoquinoline **8** (91%). The 1,3-*cis* relative stereochemistry of **20** was deduced from the observed NOE correlation between $H_1/H_3$ and was in accordance with literature precedents.[19] The presence of a 2-bromo substituent effectively obviated the regioselectivity issue during the Pictet−Spengler reaction.[20] Masking the secondary amine as *N*-*tert*-butoxycarbamate followed by methylation of the phenol provided compound **21** in 78% overall yield. Transesterification of a *tert*-butyl ester to a methyl ester with concurrent removal of the *N*-Boc function from **21** were realized in a one-pot fashion to afford the desired tetrahydroisoquinoline **8** in 95% yield.

Acylation of 1,3-*cis*-disubsituted tetrahydroisoquinoline was known to be difficult.[21] After much experimentation, coupling of bulky amine **8** with amino acid **9**, synthesized from glutamic aicd following literature procedure (see Supporting Information),[22] was realized by aminolysis of the in situ generated activated ester of **9** (Scheme 4). Thus, reaction of **9** with 1-hydroxy-7-azabenzotriazol (HOAt, HATU, DIPEA, DMF, 0 °C) afforded the corresponding HOAt ester. By raising the temperature to room temperature, the subsequent amidation with **8** took place smoothly to provide amide **22** in 71% yield (86%

***Scheme 4.*** Synthesis of Amino Thioether **25**[a]




[a] HATU = *O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate; HOAt = 1-hydroxy-7-azabenzotriazole.

based on conversion) without detectable epimerization. Reduction of **22** with lithium borohydride gave primary alcohol **23**, which upon Swern oxidation afforded directly hemiaminal **24** as a mixture of two diastereomers (ratio 3/2). Attempt to convert the hemiaminal to amino ether or to aminonitrile by reacting **24** with methanol (MeOH), or trimethylsilyl cyanide (TMSCN) in the presence of a variety of Lewis acids and Brønsted acids led either to no reaction, or, if forcing conditions were used, to destruction of the molecule. Fortunately, we found that hafnium trifluoromethanesulfonate, known to be highly oxophilic,[23] was able to catalyze the reaction of **24** with ethanethiol to afford the amino thioether **25** in 88% yield [$Hf(OTf)_4$, 0.1 equiv]. Under these conditions, the *O*-TBS function was simultaneously removed, setting the stage for the subsequent oxidation step. The use of EtSH as trapping agent is important because **24** was converted to cyclic amino ether **26** in 71% yield when benzenethiol (PhSH) was employed as a nucelophile under otherwise identical conditions. It is reasonable to assume that both reactions went through the *N*-acyliminium intermediate (**A**). In the presence of a strong external nucleophile (EtSH), intermolecular trapping occurred to afford **25**. However, with

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(19) For 1,3-cis selective Pictet−Spengler reactions, see: (a) (b) Massiot, G.; Mulamba, T. *J. Chem. Soc., Chem. Commun.* **1983**, 1147–1149. (c) Bailey, P. D.; Hollinshead, S. P.; McLay, N. R.; Morgan, K.; Palmer, S. J.; Prince, S. N.; Reynolds, C. D.; Wood, S. D. *J. Chem. Soc., Perkin Trans. 1,* **1993**, 431–439. (d) Myers, A. G.; Kung, D. W.; Zhong, B.; Movassaghi, M.; Kwon, S. *J. Am. Chem. Soc.* **1999**, *121*, 8401–8402. (e) Myers, A. G.; Kung, D. W. *J. Am. Chem. Soc.* **1999**, *121*, 10828–10829. (f) Chen, J.; Chen, X.; Bois-Choussy, M.; Zhu, J. *J. Am. Chem. Soc.* **2006**, *128*, 87–89.

(20) In the absence of a 2-bromo substituent, the Pictet−Spengler reaction afforded the wrong regioisomer as a major product, see ref 10.

(21) Lane, J. W.; Chen, Y.; Williams, R. M. J. *Am. Chem. Soc.* **2005**, *127*, 12684–12690.

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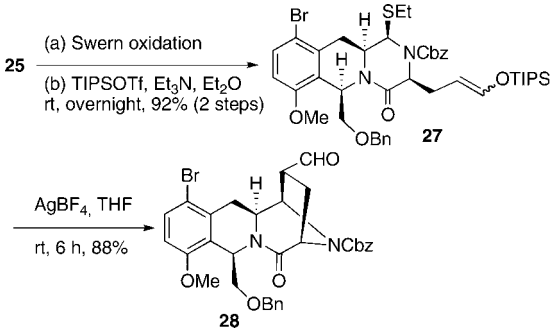
(23) (a) Kobayashi, S.; Ogawa, C.; Kawamura, M.; Sugiura, M. *Synlett* **2001**, 983–985. (b) Noji, M.; Ohno, T.; Fuji, K.; Futaba, N.; Tajima, H.; Ishii, K. *J. Org. Chem.* **2003**, *68*, 9340–9347. (c) Sakai, N.; Asano, J.; Shimano, Y.; Konakahara, T. *Synlett* **2007**, 2675–2678.

***Scheme 5.*** Construction of Tetracyclic Ring of Quinocarcin[a]

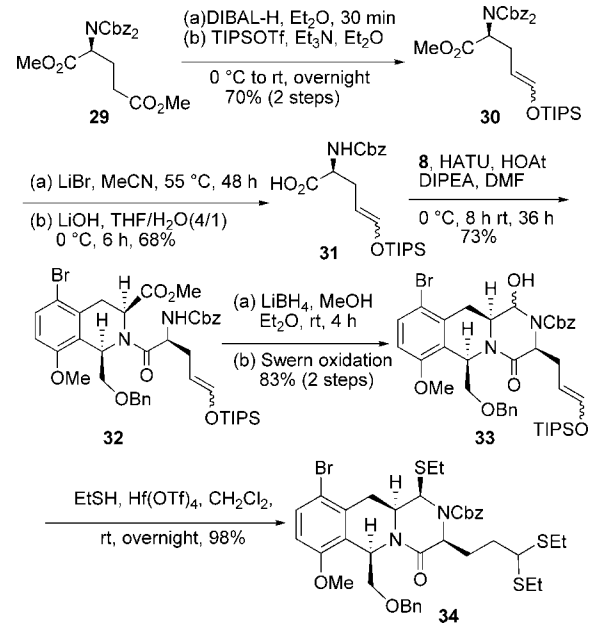



[a] TIPSOTf = triisopropylsilyl trifluoromethanesulfonate.

a weaker nucleophile such as PhSH, nucleophile attack of tethered alcohol prevailed over intermolecular process leading to cyclic amino ether **26**. Interestingly, compound **26** was converted to **25** with EtSH in the presence of $Hf(OTf)_4$ in 88% yield. These results indicated that 1,3-oxazepine **26** was in equilibrium with the *N*-acyliminium under these conditions. Due to the low thiophilicity of $Hf(OTf)_4$, amino thioether **25** was apparently stable under the reaction conditions providing thus the deriving force for its formation. Interestingly, if other Lewis acids ($BF_3 \bullet Et_2O$, $Bu_3SnF$) or Brønsted acids (*p*TSA, HF) were used instead of $Hf(OTf)_4$, the 1,3-oxazepine **26** was produced even in the presence of EtSH. Presumably, the amino thioether **25** underwent rapid equilibrium with the incipient *N*-acyliminium species under these conditions. The high tendency to form the 1,3-oxazepine **26** could be accounted for by the conformational preference of the iminium **A**. Due to the inherent allylic $A^{1,3}$ interaction,[24] the alkyl side chain might adopt preferentially a pseudoaxial position, favoring thus the formation of 1,3-oxazepine **26** for the entropic reason.[25]

Construction of the 3,8-diazabicycle [3.2.1]-octane ring system was depicted in Scheme 5. A chemoselective Swern oxidation of **25** followed by silyl enol ether formation afforded compound **27** (E/Z = 8/1) in 92% overall yield. The amino thioether function was perfectly stable in the presence of TIPSOTf, a Lewis acid that is frequently used for the generation of *N*-acyliminium from the aminal or aminonitrile.[26] The intramolecular Mannich reaction of **27** was realized in the presence of silver tetrafluoroborate to furnish the tetracyclic compound **28** with an *exo*-oriented aldehyde function in 88% yield.[27,28] In this cyclization, silver tetrafluoroborate served as an activator of both electrophile and nucleophile leading to an efficient, although disfavored 5-*endo*-Trig cyclization.[29]

***Scheme 6.*** Synthesis of Thiohemiaminal **34**[a]




[a] TIPS = triisopropylsilyl.

Parallel to this approach, we have developed an alternative synthesis of functionalized tricycle **33** using a preformed enol ether **31** as a coupling partner of **8** (Scheme 6). Selective reduction of L-methyl-*N*,*N*-dibenzoxycarbamoyl-glutamate (**29**, see Supporting Information) afforded the corresponding aldehyde,[22] which after treatment with TIPSOTf and $Et_3N$ afforded the silyl enol ether **30**. Mono *N*-deprotection of **31** followed by selective hydrolysis of the methyl ester provided the amino acid **31**. The protection of amine as imide in **29** was found to be important for both the regioselective reduction of $\delta$-ester and for avoiding the formation of 5-hydroxy proline derivative.[30] Coupling of **31** with tetrahydroisoquinoline **8** went smoothly to afford the amide **32** in 73% yield, which after a sequence of reduction and oxidation provided the cyclization precursor **33** in 83% overall yield. However, cyclization of **33** under a variety of acidic conditions failed to produce the desired tetracyclic skeleton. Under the conditions developed for the cyclization of **27** [EtSH/$Hf(OTf)_4$ or EtSH/$AgBF_4$], the enol silyl ether **33** was converted to the thioacetal **34** in almost quantitative yield. The rapid and irreversible conversion of enol ether to thioacetal hampered thus the desired cyclization.

With the tetracyclic compound **28** in hand, the total synthesis of (−)-quinocarcin was realized as shown in Scheme 7. Jones oxidation of **28** afforded the carboxylic acid **35** in 93% yield. The *N*-Cbz and the *O*-Bn protective groups were selected based on the consideration that they could potentially be removed under the same conditions as that for the reduction of aryl bromide. Indeed, global deprotection was realized in a one-pot fashion under hydrogenolysis conditions. Selective *N*-methylation of the resultant amino acid was realized under reductive alkylation conditions to provide quinocarcinamide (**4**) in 95% overall yield. The labile oxazolidine ring of quinocarcin has previously been installed in a three-step sequence via aminal and aminonitrile intermediates. By modifying the workup procedure, we found that this can be realized in a one-pot fashion. Thus, partial lactame reduction of **4** with an excess of

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(25) Blankenstein, J.; Zhu, J. *Eur. J. Org. Chem.* **2005**, 1949–1964.
(26) For reviews on *N*-acyliminium chemistry, see: (a) Hiemstra, H.; Speckamp, W. N. *Comprehensive Organic Synthesis*; Trost, B., Fleming, I., Heathcock, C. H., Eds.; Pergmon: Oxford, 1991; Vol. 2, pp 1047−1082. (b) Maryanoff, B. E.; Zhang, H.-C.; Cohen, J. H.; Turchi, I. J.; Maryanoff, C. A. *Chem. Rev.* **2004**, *104*, 1431–1628. (c) Royer, J.; Bonin, M.; Micouin, L. *Chem. Rev.* **2004**, *104*, 2311–2352.
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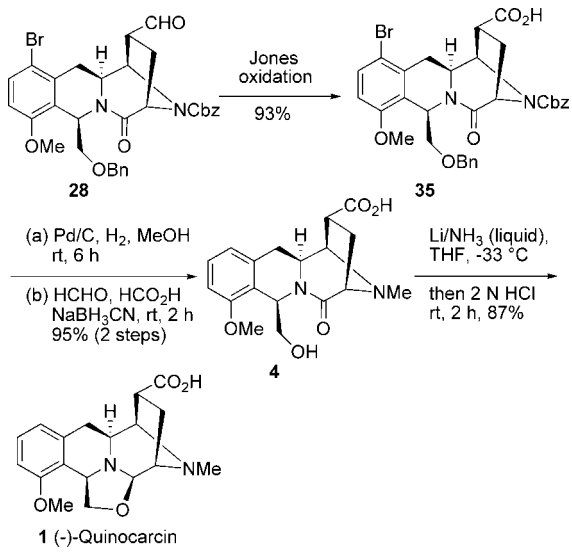
(28) Hiemstra and Speckamp have reported a stereospecific 5-exo-Trig cyclization; see ref 27a. In our case, only one diasteromer **28** with an exo-oriented aldehyde substituent was isolated from the cyclization of a mixture of *E*/*Z* isomers (8/1) of enol ether **27**.
(29) (a) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734–736. (b) Johnson, C. D. *Acc. Chem. Res.* **1993**, *26*, 476–482.
(30) Jia, Y.; Zhu, J. *J. Org. Chem.* **2006**, *71*, 7826–7834.

***Scheme 7.*** Total Synthesis of (−)-Quinocarcin (**1**)




lithium in liquid ammonia[31] followed by slow sequential addition of methanol and ammonium chloride, evaporation of ammonia, acidification, and neutralization afforded directly (−)-quinocarcin (**1**) in 87% yield after purification on C18 column. The physical, spectroscopic, and spectrometric data (UV, $^1$H NMR, $^{13}$C NMR, $[\alpha]_D$, and HRMS) of the synthetic material are identical to those of natural (−)-quinocarcin.[10]

(31) Evans, D. A.; Illig, C. R.; Saddler, J. C. *J. Am. Chem. Soc.* **1986**, *108*, 2478–2479.

## Conclusion

In conclusion, (−)-quinocarcin has been synthesized in a longest linear sequence of 22 steps from 3-hydroxybenzaldehyde with an overall yield of 16% (11 steps and 33% overall yield from the point of assembly). Our approach is highly convergent, modular, and easily amenable to multigram synthesis. It represented one of the most efficient syntheses to this natural product (Myers' synthesis: 16 steps, with 3.6% overall yield). We believe that the $Hf(OTf)_4$ catalyzed transformation of hemiaminal to amino thioether developed in the course of this study should find application to the synthesis of other related molecules.

**Acknowledgment.** Financial supports from CNRS and this institute (ICSN) are gratefully acknowledged. Y.C.W. thanks ICSN for a postdoctoral fellowship.

**Note Added after ASAP Publication.** Due to a production error, the images were incorrect for Figures 1 and 2 in the version published ASAP on May 3, 2008. The figures were corrected on May 7, 2008.

**Supporting Information Available:** Experimental procedures; characterization data; and copies of $^1$H and $^{13}$C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

JA800662Q