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CHIRAL SYNTHESIS OF THE ABC-RING SYSTEM OF QUINOCARCIN

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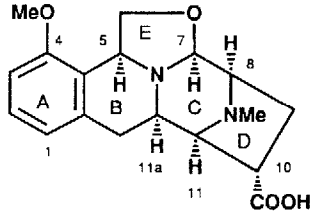
Abstracts: Stereoselective synthesis of an enantiomeric pair of the ABC-ring system of quinocarcin(**1**), a notable antitumor antibiotic, could be achieved in > 95%ee by utilizing each enantiomer of 4-*O*-benzyl-2,3-*O*-isopropylidene-threose as a chiral auxiliary and featuring novel diastereoselective reduction of the 1,3-disubstituted isoquinoline as a key step.

A novel antitumor antibiotic, quinocarcin (**1**), isolated from the culture broth of *Streptomyces melanovinaceus* along with quinocarcinol (**2**) which is the pharmacologically inactive dihydroderivative of **1**, shows a notable antitumor activity.[3,4] It has been also reported that the more stable semisynthetic derivative of **1**, DX-52-1 (**3**), retains significant antitumor activity of **1**.[5] The structures of **1-3** including their relative stereochemistries have been established as unique 3,12-iminoazepino[1,2-b]isoquinoline skeletons by X-ray crystallography, spectroscopic analysis, and chemical correlation.[5,6] However, their absolute configurations have not been established. Their remarkable antitumor activity and novel structures in addition to the lack of determination of their absolute stereochemistries distinguish these molecules as unusually attractive targets for total synthesis.[7,8,9]



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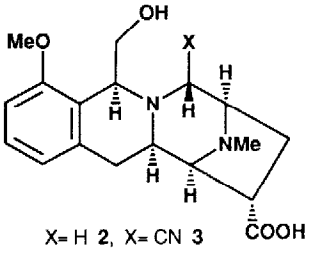
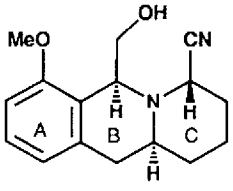


X= H **2**, X= CN **3**



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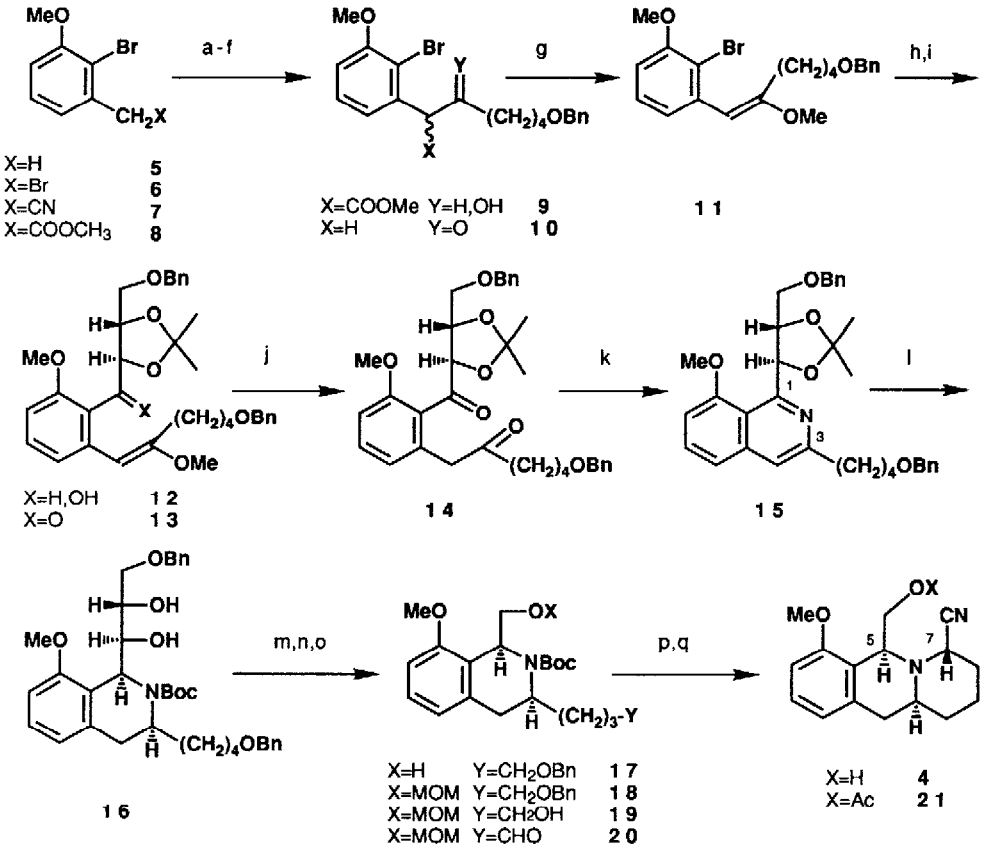
In conjunction with our ongoing project directed toward the total synthesis of **1** to establish the unknown absolute configuration of **1** and to elucidate its structure-activity relationship, we have already developed an efficient synthetic scheme for stereoselectively constructing the ABE-ring system of **1** with definite absolute configuration.[10] Based on the results accumulated in the model study, we embarked on stereoselective synthesis of an enantiomeric pair of the ABC-ring system of **1** (**4** and *ent*-**4**). In this report we wish to disclose that the stereocontrolled synthesis of both **4** and *ent*-**4** could be achieved in > 95 %ee without ambiguity in their absolute configurations by employing each enantiomer of 4-*O*-benzyl-2,3-*O*-isopropylidene-threose as a chiral auxiliary. The explored synthetic route features novel stereoselective reduction of the 1,3-disubstituted isoquinoline (**15**) (isoquinoline numbering) as a key step.

2-Bromo-3-methylanisole (**5**)[11] was derived to the benzyl cyanide (**7**) by sequential bromination of **5** and replacement of the resulting benzyl bromide (**6**) with cyanide anion. Alkaline hydrolysis followed by esterification gave the methyl ester (**8**). The lithium enolate generated from **8** was allowed to react with 5-benzyloxypentanal[12] in the presence of 1,4-diazabicyclo[2.2.2]octane (DABCO) or N,N,N',N'-tetramethylethylenedi-



a) Br2, light, CCl4, r.t. b) NaCN, DMSO, r.t., 56 % (2 steps) c) 1) KOH, MeOH, reflux 2) CH2N2, Ether, r.t.,90 % d) 1) LDA, THF, -78°C 2) DABCO or TMEDA, -78°C 3) BnO(CH2)4CHO, -78°C, 70% e) Jones oxd., 93 % f) NaCl, DMSO-H2O, 140°C, 90% g) (MeO)3CH, MeOH, CSA, reflux, 84% h) 1) nBuLi, Ether, -78°C 2) 4-*O*-Benzyl-2,3-*O*-isopropylidene-L-threose, -78°C → 0°C i) CrO3-2Py, MS3A,CH2Cl2, r.t. j) 1N HCl, THF, r.t. k) THF-14N NH3, r.t., 52%, (4 steps) l) 1) NaBH3CN, MeOH-0.1N HCl, 0°C 2) 12N HCl, MeOH, r.t. 3) (tBuOCO)2O, CHCl3-6N NaOH, reflux, 84% m) 1) NaIO4, MeOH-H2O, r.t. 2) NaBH4, 0°C, 94% n) MOMCl, (iPr)2NEt, THF, r.t. 93% o) 1) H2, Pd(OH)2-C, MeOH, 2) Swern oxd., 86% p) 1) TMSBr, CH2Cl2, r.t. 2) NaCN, MeOH, r.t., 75% q) Ac2O, Py, r.t., 88%

amine (TMEDA), yielding the alcohol (**9**) as a diasteromeric mixture. Jones oxidation of **9** and subsequent removal of the methoxycarbonyl group afforded the ketone (**10**).

For introducing the side chain bearing a chiral auxiliary, **10** was converted into a mixture of the *E*- and *Z*-enol ether (**11**) (*E*-**11**:*Z*-**11** = 3:1).[13] This could be readily separated by column chromatography on silica gel. Reaction of the aryl lithium generated from the major *E*-enol ether (**11**) with 4-*O*-benzyl-2,3-*O*-isopropylidene-L-threose[14] underwent smoothly, giving the alcohol (**12**) as a diastereomeric mixture.[15] After Collins oxidation of **12**, acidic hydrolysis of the enol ether moiety of the ketone (**13**) and subsequent treatment of the resulting diketone (**14**) with aqueous ammonia produced the isoquinoline (**15**), caramel, $[\alpha]_D^{20}$ -60.3 °(c 1.01, $CHCl_3$).

Crucial reduction of **15** turned out to be effected with complete diastereoselectivity by employing sodium cyanoborohydride in acidic medium. Thus, after successive acidic hydrolysis of the acetonide group and protection of the amino group, the reduction product could be isolated in a form of the diol carbamate (**16**), caramel, $[\alpha]_D^{20}$ +19.4 °(c 1.00, $CHCl_3$). This compound(**16**) was found to consist of a single isomer among four possible diastereomers. The stereostructure of **16** was unambiguously established as shown on the basis of the 400 MHz ^1H NMR spectrum of the 2-oxazolidone derivative derived from **16**.[16]

This remarkable stereoselectivity may be rationalized by the following two-step asymmetric transformation. It is well known that reduction of an isoquinolinium salt with hydride reagents occurs preferentially at the C_1,N_2-double bond and the 1,4-dihydroisoquinolinium salt produced by bond migration can be further reduced to afford a 1,2,3,4-tetrahydroisoquinoline.[17] Accordingly, the usual chelation model interacting with the alkoxy group adjacent to C_1,N_2-double bond can nicely explain high stereoselectivity in the first reduction of **15** in a similar manner to that previously reported for the reduction of 3,4-dihydroisoquinoline derivative.[10] High stereoselectivity achieved in the second stereoselective reduction under an influence of the newly formed C_1-chiral center may be accounted for by the stereoelectronic control proposed for stereoselective reduction of a tetrahydropyridinium salt with hydride reagents.[18]

The produced diol carbamate (**16**) was converted to the methoxymethyl ether (**18**), caramel, $[\alpha]_D^{20}$ +8.79 °(c 1.02, $CHCl_3$), by way of the alcohol (**17**), caramel, $[\alpha]_D^{20}$ -10.5 °(c, 1.06, $CHCl_3$), by sequential oxidative cleavage of the 1,2-glycol part of **16**, reduction of the resulting aldehyde, and protection of the primary alcohol of **17** as a methoxymethyl ether. Debenzylation of **18** followed by Swern oxidation of the alcohol (**19**) yielded the aldehyde (**20**). Exposure of **20** to trimethylsilyl bromide resulted in simultaneous removal of the methoxymethyl and *tert*-buthoxycarbonyl groups, furnishing the unstable aminal, which without isolation was treated with sodium cyanide to give the stable cyano derivative (**4**),[19] caramel, $[\alpha]_D^{20}$ +17.4°(c 1.34, $CHCl_3$). The 400 MHz ^1H NMR spectrum of the acetate (**21**), caramel, $[\alpha]_D^{20}$ -16.5 °(c 0.79, MeOH), prepared from **4**, cleanly disclosed the stereostructure of **21** as pictured.[20]

By employing 4-*O*-benzyl-2,3-*O*-isopropylidene-D-threose instead of the L-isomer, the enantiomeric cyano derivative (*ent*-**4**), caramel, $[\alpha]_D^{20}$ -17.7 °(c 1.39, $CHCl_3$), and the acetate (*ent*-**21**), caramel, $[\alpha]_D^{20}$ +16.3 °(c 0.59, MeOH), were prepared in the same manner as described above.[21] Two sorts of the alcohols (**4** and *ent*-**4**) so obtained were converted to the corresponding MTPA esters. Comparison of their 400 MHz ^1H NMR spectra confirmed that the optical purity of **4** and *ent*-**4** was more than 95 %ee.

As mentioned above, the efficient synthetic scheme to synthesize an enantiomeric pair of the ABC-ring system of **1** with definite absolute configuration could be successfully explored by featuring novel diastereoselective reduction of 1,3-disubstituted isoquinoline derivative as a key step. Employing this synthetic methodology, the total synthesis of **1** is being pursued in our laboratory.

References and notes

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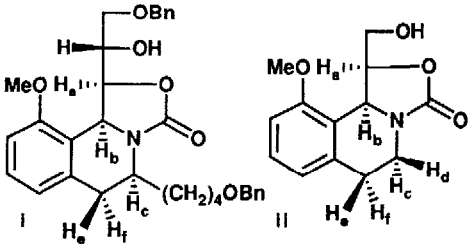
12) H. Nagaoka, T. Miyakoshi, J. Kasuga, and Y. Yamada, *Tetrahedron Lett.*, **26**, 5053 (1985).
13) The configurations of enol ether moieties of *E*- and *Z*-**11** were determined by using NOE techniques. Thus, NOEs were observed between the signals due to olefinic proton and methoxy group in the 400 MHz ^{1}H NMR NMR spectrum of *E*-**11**. On the other hand, in the 400 MHz ^{1}H NMR spectrum of *Z*-**11**, NOE was observed for the signals of allylic methylene when the signal due to olefinic proton was irradiated.
14) T. Mukaiyama, K. Suzuki, and T. Yamada, *Chem. Lett.*,929 (1978).
15) Interestingly, the reaction of the aryl lithium generated from *Z*-**11** or the dimethyl acetal derivative of **10** with 4-*O*-benzyl-2,3-*O*-isopropylidene-L-threose was found to afford no addition product under the same conditions. This may be due to the chelation between lithium cation and oxygen atom of the Z-enol ether or the dimethyl acetal which lowers reactivity of the corresponding lithium anion.
16) For determining the stereochemistry of **16**, the 2-oxazolidone derivative (**i**) was prepared from **16** (NaH, THF, r.t., 72 %). In the 400 MHz ^{1}H NMR spectrum of **i**, the coupling constant of 8.5 Hz for Ha and Hb established their *cis*-relationships.[10] NOEs were observed between the signals due to Hb and Hc, revealing that the newly formed tetrahydropyridine ring of **i** takes a chair-like conformation and the C1- and C3-side chains (isoquinoline numbering) of **i** are in a *cis*-configuration. The coupling pattern and chemical shift for Hc of **i** could be compared well with those for Hc of **ii** rather than those for Hd of **ii** (**i**; JHcHe=11.4 Hz, JHcHf=2.3 Hz, δHc 3.25 : **ii**; JHcHe=12.5 Hz, JHcHf=3.4 Hz, JHdHe=5.6 Hz, JHdHf=1.3 Hz, δHc 3.20, δHd 4.15).[10] Based on these spectral features, the stereochemistry of **16** could be rigorously assigned as pictured.



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18) a) Y. Nakagawa and R. V. Stevens, *J. Org. Chem.*, **53**, 1871 (1988) and references cited there. b) Similar asymmetric induction has been reported for the reduction of 1,3-disubstitued-3,4-dihydroisoquinolines with sodium borohydride; A. Ishida, H. Fujii, T. Nakamura, T. Ohishi, E. Aoe, Y. Nishibata, and A. Kinumaki, *Chem. Pharm. Bull.*, **34**, 1994 (1986).
19) All attempts to cyclize the amino acetal ring (E ring of **1**) from **4** according to the reported methods[5] turned out to be fruitless.
20) The signals due to the C5- and C7-protons (quinocarcin numbering) overlapped incidentally in the 400 MHz ^{1}H NMR spectrum of **4**. However, the 400 MHz ^{1}H NMR spectrum of **21** exihibited the signal due to the C7-proton as a separated broad triplet (J=3.5 Hz) at δ 4.24.
21) Those compounds (**4**, *ent*-**4**, **21** and *ent*-**21**) showed the following IC50 (μg/ml) values when subjected to P388 murine leukemia *in vitro* cytotoxicicity assay; **4**: 8.4, *ent*-**4**: 13, **21**: 6.0, *ent*-**21**: 1.1. We are indebted to Dr. K. Sakai and Miss K. Yamada, Sagami Chemical Research Center, for carrying out *in vitro* cytotoxicity assay.

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