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Enantioselective Synthesis of 5-Substituted- and 3,5-Disubstituted-2-formylpyrrolidine Derivatives, the Key D-Ring Fragments of (-)-Quinocarcin and (-)-10-Decarboxyquinocarcin

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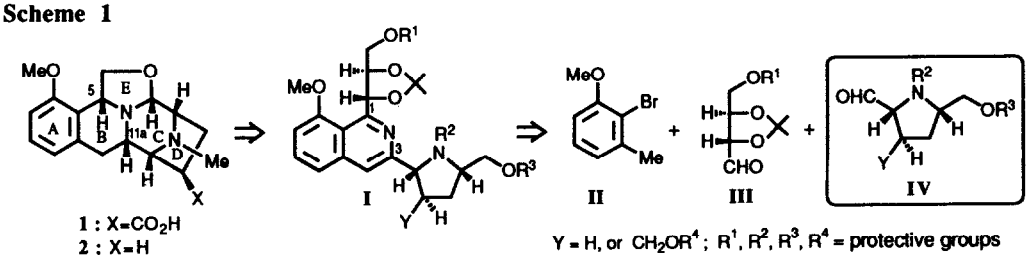
Key words: quinocarcin, 10-decarboxyquinocarcin, D-ring fragment, 5-substituted-2-formylpyrrolidine, 3,5-disubstituted-2-formylpyrrolidine

Abstract: *The title synthesis was achieved starting from (S)-glutamic acid and (S)-pyroglutamic acid by featuring formation of an N-protected aminal, substitution of the methoxy group with cyanide anion, and reduction of the cyanide to an aldehyde as common key steps.*

Quinocarcin(**1**), a novel antitumor antibiotic isolated from *Streptomyces melanovinaceus*, exhibits promising antitumor activity against several lines of solid mammalian carcinomas[1,2]. The stereostructure of **1** except absolute configuration was revealed by X-ray diffraction and spectral studies to have a novel 8,11-iminoazepino[1,2-b]isoquinoline skeleton with six asymmetric centers[3]. The absolute configuration of **1** shown below was suggested by Remers *et al.* in 1988 on the basis of the computer simulation of binding of **1** to DNA[4]. In 1992, Garner *et al.* completed the total synthesis of (-)-**1**, leading to confirmation of its absolute configuration[5]. Its remarkable antitumor activity and unique structural feature make **1** exceptionally intriguing and timely target for total synthesis and manifold synthetic studies on **1** have hitherto been reported[5,6,7,8].

In the course of our continuing efforts on the total synthesis of **1** with an aim to elucidate its structure-activity relationships, we have already succeeded in developing the efficient synthetic schemes to enantiomeric pairs of the ABE and ABC ring systems of **1**[9]. On the basis of the results accumulated in these model studies, we embarked on the total synthesis of **1** and unnatural 10-decarboxyquinocarcin(**2**)(the ABCDE ring system of **1**) in optically active forms. The retrosynthetic plan for **1** and **2** was outlined in **Scheme 1**. The key step in our synthetic strategy was envisioned to be the diastereoselective reduction of **I** accessible from **II**, **III**, and **IV**

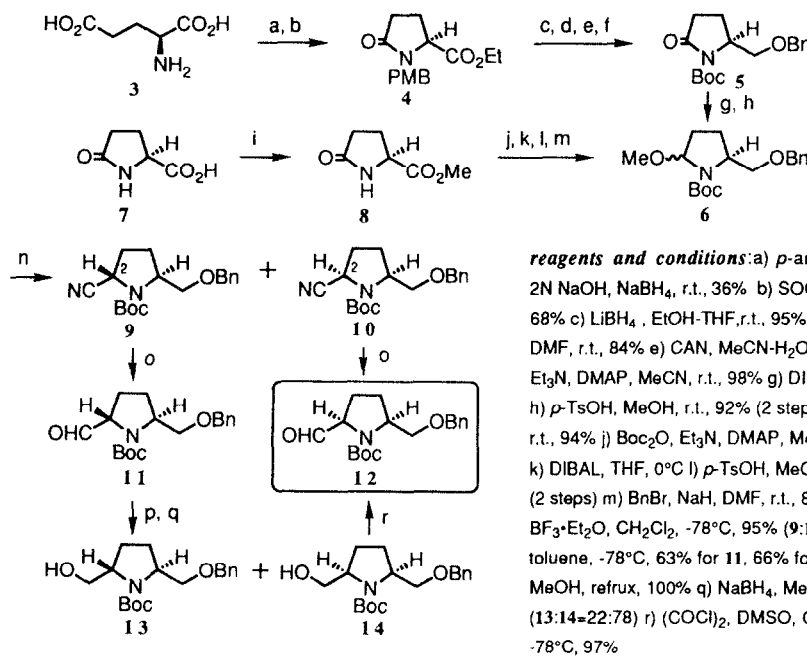
Scheme 1



to control the stereochemistries at C5 and C11a positions in **1** and **2** simultaneously in one step. To implement this synthetic scheme, we focused our attention on developing an efficient synthetic route to **IV** since the preparation methods of **II**[10] and **III**[11] have already been established[9]. In this communication, we wish to report a facile and enantioselective synthesis of **IV**, the key D ring fragments required for the total synthesis of **1** and **2**. The accompanying paper details the total synthesis of **1** and **2** accomplished by featuring the diastereoselective reduction of **I**[12].

First, the synthesis of 5-substituted-2-formylpyrrolidine **12** corresponding to **IV**(Y=H) was examined as shown in **Scheme 2**. Commercially available (S)-glutamic acid(**3**) was converted to ethyl ester **4**, $[\alpha]_D^{20}$+35.1°(c=1.00, $CHCl_3$), by protection of the amino group followed by simultaneous lactam and ester formations. After reduction of **4**, sequential benzylation of the resulting alcohol and exchange of the *N*-protecting group afforded carbamate **5**, $[\alpha]_D^{20}$-77.0°(c=1.00, $CHCl_3$). Reduction of **5** with diisobutylaluminium hydride(DIBAL) followed by formation of an *N*-protected aminal with acidic methanol furnished 2-methoxypyrrolidine **6** as an epimeric mixture[13]. After experimentation, it was found that **6** could be prepared more readily starting with (S)-pyroglutamic acid(**7**). Thus, after protection of methyl ester **8** derived from **7** according to the reported method[15], sequential reduction with DIBAL, formation of an *N*-protected aminal, and benzylation successfully produced **6**.

Scheme 2



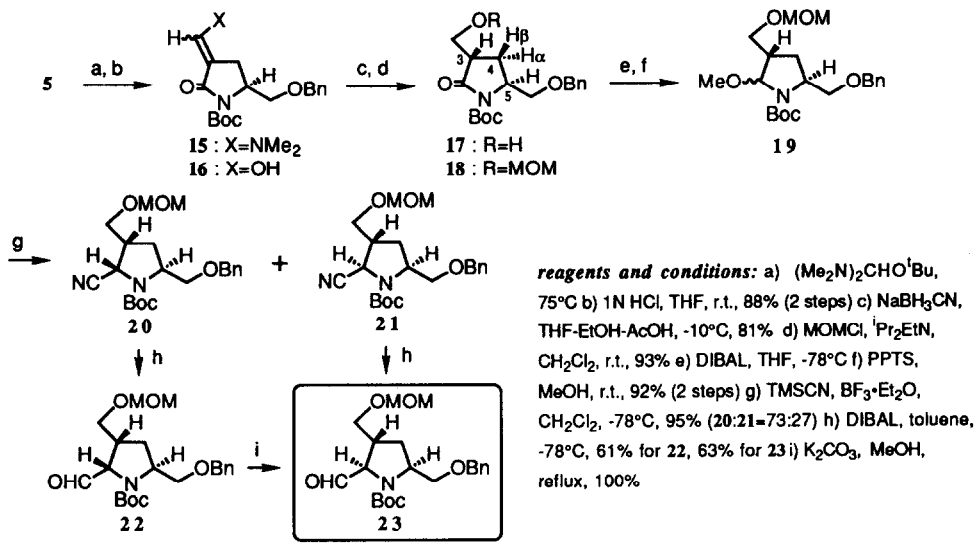
reagents and conditions:a) *p*-anisaldehyde, 2N NaOH, $NaBH_4$, r.t., 36% b) $SOCl_2$, EtOH, refrlux, 68% c) $LiBH_4$, EtOH-THF,r.t., 95% d) BnBr, NaH, DMF, r.t., 84% e) CAN, MeCN-H_2O, r.t., 83% f) Boc_2O, Et_3N, DMAP, MeCN, r.t., 98% g) DIBAL, THF, -78°C h) *p*-TsOH, MeOH, r.t., 92% (2 steps) i) $SOCl_2$, MeOH, r.t., 94% j) Boc_2O, Et_3N, DMAP, MeCN, r.t., 100% k) DIBAL, THF, 0°C l) *p*-TsOH, MeOH, r.t., 76% (2 steps) m) BnBr, NaH, DMF, r.t., 84% n) TMSCN, BF_3•Et_2O, CH_2Cl_2, -78°C, 95% (**9**:**10**=69:31) o) DIBAL, toluene, -78°C, 63% for **11**, 66% for **12** p) K_2CO_3, MeOH, refrux, 100% q) $NaBH_4$, MeOH, r.t, 97% (**13**:**14**=22:78) r) $(COCl)_2$, DMSO, CH_2Cl_2; Et_3N, -78°C, 97%

Nucleophilic addition of cyanide anion to the reactive *N*-acyliminium ion generated from **6** was effected by employing trimethylsilyl cyanide in the presence of boron trifluoride etherate, giving rise to *trans*-2-cyanopyrrolidine **9**, $[\alpha]_D^{20}$+19.8°(c=1.05, $CHCl_3$), and its *cis*-isomer **10**, mp 77.0-78.0°C, $[\alpha]_D^{20}$ -124°(c=0.81, $CHCl_3$), in a ratio of 69:31[13]. Combination of single crystal X-ray analysis of **9**[14] and

spectroscopic properties of **9** and **10** established the stereochemistries at C2 positions of the both isomers. Finally, **10** was reduced with DIBAL to provide desired **12**, $[\alpha]_D^{20}$-5.5°(c=1.02, $CHCl_3$). On the other hand, **9** was similarly reduced with DIBAL to yield *trans*-2-formylpyrrolidine **11**, $[\alpha]_D^{20}$-91.8°(c=1.58, $CHCl_3$). This could be transformed to thermodynamically more stable isomer **12**, by 4-step sequence involving epimerization, reduction of inseparable aldehydes **11** and **12**, separation of diastereomeric alcohol **13** and **14** and Swern oxidation of *cis*-alcohol **14**.

Next, we addressed on the synthesis of 3,5-disubstituted-2-formylpyrrolidine **23** corresponding to **IV**(Y=CH_2OR^4) which is necessary for the total synthesis of **1** as shown in **Scheme 3**. In order to introduce a hydroxymethyl group into C3 position of **5**, it was first treated with Bredereck's reagent[16] leading to enamine **15**. This was subjected to acidic hydrolysis to afford enol **16**[6k]. Selective reduction of **16** with sodium cyanoborohydride[6k] furnished an inseparable mixture of desired *trans*-alcohol **17**[17] and its *cis*-isomer[17]. This mixture could be readily separated by column chromatography on silica gel after protection with a methoxymethyl group[6k], affording *trans*-methoxymethyl ether **18**, $[\alpha]_D^{20}$-42.4°(c=0.93, $CHCl_3$), and its *cis*-isomer, $[\alpha]_D^{20}$-45.9°(c=1.02, $CHCl_3$), in a ratio of 88:12.

Scheme 3



By employing the reaction sequence similar to that described for the preparation of **9** and **10**, **18** was derived to 2,5-*trans*-3-substituted-2-cyanopyrrolidine **20**[18], $[\alpha]_D^{20}$-70.1°(c=1.07, $CHCl_3$), and its 2,5-*cis*-isomer **21**[18], $[\alpha]_D^{20}$+2.01°(c=2.08, $CHCl_3$), in a ratio of 73:27 *via* 3-substituted-2-methoxypyrrolidine **19**. Finally, **21** was reduced with DIBAL, furnishing desired **23**, $[\alpha]_D^{20}$-16.1°(c=1.43, $CHCl_3$). On the other hand, **20** was similarly reduced to give 2,5-*trans*-3,5-disubstituted-2-formylpyrrolidine **22**, $[\alpha]_D^{20}$ -24.8°(c=0.79, $CHCl_3$), which converged to **23** by base-catalyzed epimerization.

As described above, we have succeeded in establishing efficient and enantioselective routes to the key D ring fragments(**12** and **23**) of **1** and **2** employing (S)-glutamic acid and (S)-pyroglutamic acid as chiral starting

materials. Successful total synthesis of **1** and **2** utilizing **23** and **12** as the key D-ring fragments is the subject of the accompanying paper[12].

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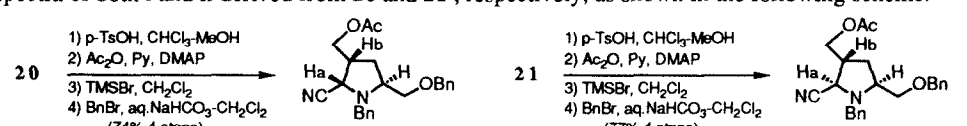
17. The stereochemistry of **17** was proven by NOE measurement of **18** derived from **17**. Thus, NOEs were observed between the signals due to C3-H and C4-Hβ, and those due to C5-H and C4-Hα in the 400MHz ^{1}H-NMR spectrum of **18**. On the other hand, the 400MHz ^{1}H-NMR spectrum of the *cis*-isomer of **18** showed NOEs between the signals due to C3-H and C4-Hα, and those due to C5-H and C4-Hα. Accordingly, C3-H and C5-H in **17** were assigned to have *trans* configuration.
18. The stereochemistries of **20** and **21** were confirmed by NOE measurements in the 400MHz ^{1}H-NMR spectra of both **i** and **ii** derived from **20** and **21** , respectively, as shown in the following scheme.



NOE between Ha and Hb in **i** and that between Ha and Hb in **ii** were found to be 6.8% and 0.6%, respectively. Based on these results, the stereostructures of both **20** and **21** were rigorously assigned as depicted.

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