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Total Synthesis of (-)-Quinocarcin and (-)-10-Decarboxyquinocarcin

Tadashi Katoh, Masayuki Kirihara, Yuriko Nagata, Yuko Kobayashi, Katsuko Arai, Junko Minami, Shiro Terashima*

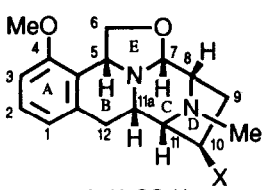
Sagami Chemical Research Center, Nishi-Ohnuma, Sagamihara, Kanagawa 229, Japan

Key words: total synthesis, quinocarcin, 10-decarboxyquinocarcin, antitumor antibiotic, aldol coupling, diastereoselective reduction, intermolecular aminal formation

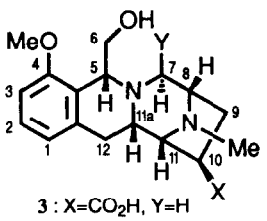
Abstract: The title total synthesis was accomplished by employing diastereoselective reduction of 1, 3-disubstituted isoquinolines as a key step. The cytotoxicity of 10-decarboxyquinocarcin and its 7-cyano congeners were found to be 10-1000 times more potent than those of quinocarcin and its 7-cyano congeners against P388 murine leukemia.

Quinocarcin(**1**), a natural secondary metabolite produced by *Streptomyces melanovinaceus* along with biologically inactive quinocarcinol(**3**), shows a notable antitumor activity[1]. Cyanation of **1** with sodium cyanide can produce the more stable 7-cyano congener, DX-52-1(**4**), which still retains significant antitumor activity. It is also reported that treatment of **4** with hidrochloric acid or silver nitrate can regenerate **1**[2].

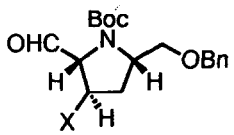
In the preceding paper we have succeeded in developing efficient synthetic routes to 5-substituted- and 3,5-disubstituted-2-formylpyrrolidine derivatives(**5** and **6**) corresponding to the D ring fragments of **1** and **2**, respectively[3]. We wish to report here the total synthesis of **1**[4, 5] and 10-decarboxyquinocarcin(**2**)(the ABCDE ring system of **1**)[6]. Our synthetic strategy involves the following 3 key steps: 1) aldol coupling of ketone **10** and **5** or **6**(**Scheme 1**); 2) highly diastereoselective reduction of 1,3-disubstituted isoquinolines **12** and **24**(**Scheme 1**); 3) intermolecular aminal formation of amino aldehydes **17** and **29**(**Scheme 2**).



1 : X=CO_2H
2 : X=H



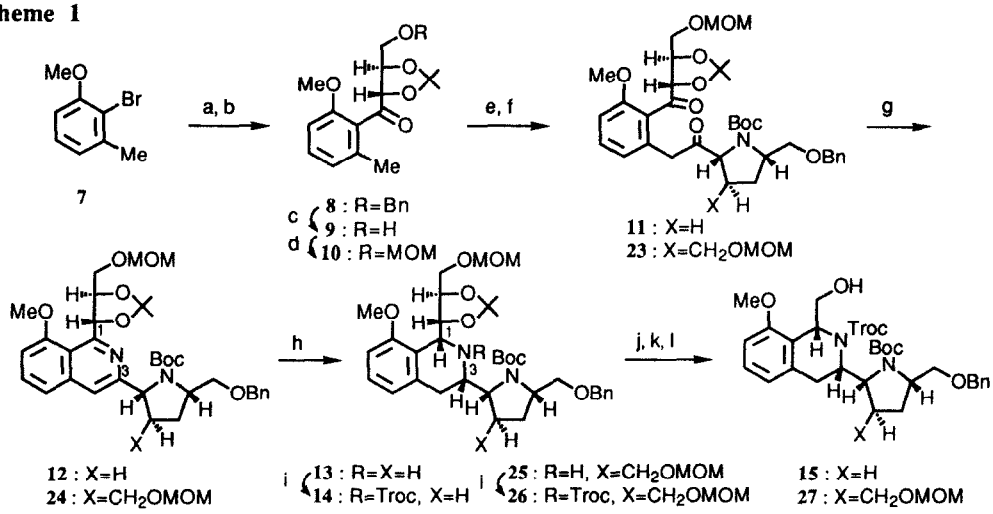
3 : X=CO_2H, Y=H
4 : X=CO_2H, Y=CN



5 : X=H
6 : X=CH_2OMOM

In the first series of experiments, the total synthesis of **2** was investigated as shown in **Scheme 1**. Thus, 2-bromo-3-methylanisole(**7**)[7] was converted into ketone **8**, $[\alpha]_D^{20}$+3.5°(c=1.03,$CHCl_3$), bearing a chiral auxiliary by coupling of the aryl lithium generated from **7** with 4-*O*-benzyl-2,3-isopropylidene-D-threose[8], followed by oxidation of an epimeric mixture of the secondary alcohol. Debenzylation of **8** and subsequent protection of resulting alcohol **9** gave methoxymethyl ether **10**, $[\alpha]_D^{20}$+6.1°(c=1.24,$CHCl_3$). The toluate anion[9] produced from **10** was allowed to react with **5**[3] in the presence of *N,N,N',N'*-tetramethylethylenediamine

Scheme 1



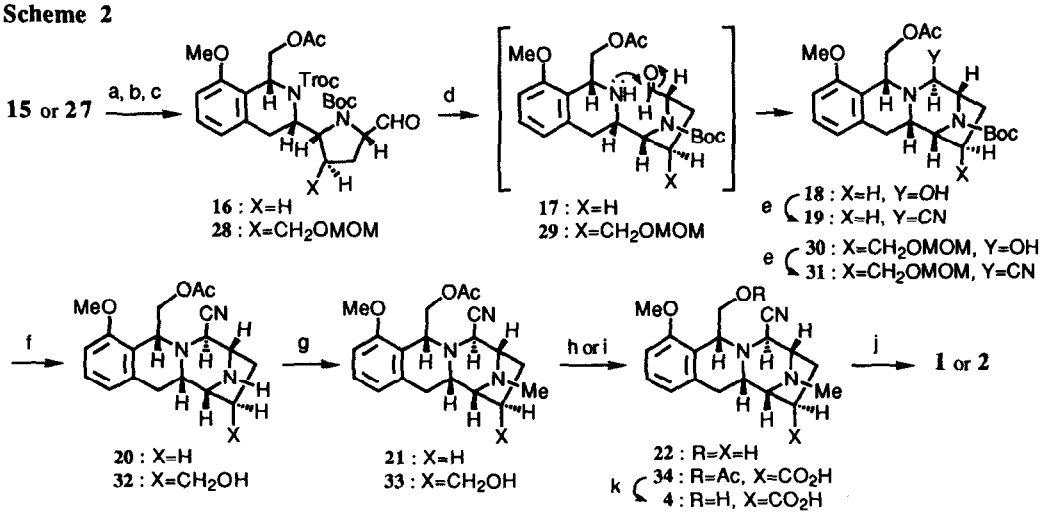
reagents and conditions: a) ^{n}BuLi, Et_2O, -78°C; 4-*O*-benzyl-2,3-isopropylidene-D-threose, -78°C b) Collins oxid., 97% (2 steps) c) H_2, $Pd(OH)_2$-C, MeOH, r.t. d) MOMCl, $^{i}Pr_2EtN$, CH_2Cl_2, r.t., 90% (2 steps) e) LDA, THF, -78°C; TMEDA; **5** or **6**, -78°C, 48% for **5**, 51% for **6** f) Jones oxid., 68% for **11**, 42% for **23** g) 14N NH_3, THF, r.t., 72% for **12**, 67% for **24** h) $NaBH_3CN$, 0.1N HCl-MeOH, 0°C, 98% for **13**, 93% for **25** i) TrocCl, Py.,r.t., 88% for **14**, 85% for **26** j) 12N HCl, MeOH, r.t. for **14**, $FeCl_3$-SiO_2, $CHCl_3$, r.t. for **26** k) $NaIO_4$, MeOH-H_2O, r.t. l) $NaBH_4$, MeOH-H_2O, r.t., 68% from **14**, 72% from **26**

(TMEDA), furnishing the desired coupling adduct as a diastereomeric mixture. This was subjected to Jones oxidation without separation to give diketone **11**, $[\alpha]_D^{20}$+37.2°(c=0.65,$CHCl_3$). Further treatment of **11** with aqueous ammonia provided key isoquinoline derivative **12**, $[\alpha]_D^{20}$+63.0°(c=0.77,$CHCl_3$).

Crucial reduction of **12** with sodium cyanoborohydride in acidic media proceeded in a completely diastereoselective manner, affording tetrahydroisoquinoline **13** as a sole product in an almost quantitative yield[10]. The stereochemistries at newly formed C1 and C3 positions in **13** were unambiguously confirmed based on the ^{1}H-NMR spectrum of oxazolidinone derivative derived from **13**[11]. Protection of the amino group of **13** gave 2,2,2-trichloroethyl carbamate **14**[12], $[\alpha]_D^{20}$+8.0°(c=0.50,$CHCl_3$). This was further converted to the alcohol **15**, $[\alpha]_D^{20}$+13.9°(c=0.72,$CHCl_3$), by sequential acidic hydrolysis of both the acetonide and the methoxymethyl groups, oxidative cleavage of the triol moiety, and reduction of the resulting aldehyde.

With the requisite absolute stereochemistries and carbon framework set up, our next efforts were devoted to formation of the ABCD ring system of **2**. Towards this end, the primary alcohol of **15** was protected in a form of acetate. Subsequent debenzylation produced the alcohol which was further subjected to Swern oxidation, giving rise to aldehyde **16**, $[\alpha]_D^{20}$+39.7°(c=0.94,$CHCl_3$)(**Scheme 2**). One of the critical steps in our synthetic scheme was anticipated to be the cyclization of amino aldehyde **17** *in situ* generated by removal of the Troc group of **16** to afford the requisite tetracyclic ring system. As expected, treatment of **16** with zinc powder in the presence of aqueous acetic acid cleanly produced desired tetracyclic aminal **18**. While **18** was fairly labile, immediate exposure of **18** to trimethylsilyl cyanide in the presence of zinc chloride[4] resulted in the formation of sturdy amino nitrile **19**, $[\alpha]_D^{20}$+21.7°(c=0.62,$CHCl_3$). To complete the projected synthesis, the Boc group in **19** was removed and the resulting amino group was reductively methylated[2a], giving rise to cyano derivative **21**, $[\alpha]_D^{20}$+16.4°(c=0.23, $CHCl_3$). Finally, saponification of **21** afforded 10-decarboxy-DX-52-1(**22**), $[\alpha]_D^{20}$

Scheme 2



reagents and conditions: a) Ac_2O, DMAP, Py., r.t. b) H_2, 10%Pd-C, EtOAc, r.t. c) $(COCl)_2$, DMSO, CH_2Cl_2, -78°C; Et_3N, 82% for **16** (3 steps), 74% for **28** (3 steps) d) Zn, THF-AcOH-H_2O, r.t. e)TMSCN, $ZnCl_2$, CH_2Cl_2, r.t., 56% for **19** (2 steps), 39% for **30** (2 steps) f) TFA, CH_2Cl_2, r.t., 91% for **20**, 82% for **32** g) 37% HCHO, $NaBH_3CN$, MeOH, r.t. for **20**, 72%, MeI, $^iPr_2EtN$, MeCN, 38°C for **32**, 68% h) 1N NaOH, MeOH, r.t. for **21**, 83% i) Jones oxid. for **33**, 79% j) $AgNO_3$, MeOH, r.t., 83% for **2**, 81% for **1** k) 1N NaOH, MeOH, r.t., 76%

+27.3°(c=0.13, $CHCl_3$), which was further treated with silver nitrate according to the reported method[2], furnished 10-decarboxyquinocarcin(**2**), $[\alpha]_D^{20}$-13.0°(c=0.23, MeOH).

Encouraged by the successful synthesis of **2**, we next undertook the total synthesis of **1** as follows. Thus, employing **6**[3] instead of **5**, amino alcohol **32** could be produced *via* **23**-**31**[**23**:$[\alpha]_D^{20}$-11.1°(c=0.83, $CHCl_3$), **24**:$[\alpha]_D^{20}$+15.1°(c=0.78, $CHCl_3$), **26**:$[\alpha]_D^{20}$-15.2°(c=1.25, $CHCl_3$), **27**:$[\alpha]_D^{20}$+1.10°(c=0.73, $CHCl_3$), **28**:$[\alpha]_D^{20}$-19.5°(c=0.41, $CHCl_3$), **30**:$[\alpha]_D^{20}$+28.8°(c=0.63, $CHCl_3$)] by the reaction sequence similar to that described for the preparation of **20** from **10** (**Scheme 1** and **Scheme 2**). It is noteworthy that the crucial reduction of **24** took place with complete diastereoselectivity similarly to that of **12** and that selective hydrolysis of the acetonide group of **26** was achieved by employing a combination of ferric chloride and silica gel developed by Kim *et al.*[13]. To complete the total synthesis of **1**, **32** was next subjected to selective *N*-methylation[4] to afford alcohol **33**, $[\alpha]_D^{20}$+28.8°(c=0.63, $CHCl_3$). This was oxidized with Jones reagent, yielding carboxylic acid **34**, $[\alpha]_D^{20}$+18.4°(c=0.38, $CHCl_3$). Saponification of **34** furnished **4**, $[\alpha]_D^{20}$+24.7°(c=0.32, MeOH). Further treatment of **4** with silver nitrate under the same conditions as reported[2], gave **1**, $[\alpha]_D^{25}$-30.6°(c=0.48, H_2O), which was identical with a natural sample of **1** in all respects(mp, $[\alpha]_D^{25}$, IR, ^{1}H-NMR, MS).

With completion of the total synthesis, **2** and its 7-cyano congeners(**21** and **22**) were subjected to *in vitro* cytotoxicity assay against P388 murine leukemia. Interestingly, it was found that these 10-decarboxy compounds were 10-1000 times more cytotoxic than the corresponding 10-carboxy compounds(**1**, **4**, and **34**)[IC_{50} (μg/mL); **2**: 3.9×10^{-3}, **21**: 2.0×10^{-4}, **22**: 8.2×10^{-4}, **1**: 3.6×10^{-2}, **4**: 3.3×10^{-2}, **34**: $>1.0\times10^{-1}$][14].

In summary, we have succeeded in completing the total synthesis of **1** and **2** and in finding out the 10-decarboxyquinocarcin derivatives(**2**, **21**, and **22**) which exhibit more increased cytotoxicity. Since the explored

synthetic scheme appears to be highly general and flexible to produce various structural types of quinocarcin congeners, these studies may open an opportunity for developing novel anticancer agents[14].

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References and Notes

1. See the references 1 and 2 in the preceding paper.
2. a) Saito, H., Hirata, T., *Tetrahedron Lett.* **1987**, *28*, 4065. b) Saito, H., Kobayashi, S., Uosaki, Y., Sato, A., Fujimoto, K., Miyoshi, K., Morimoto, A., Hirata, T., *Chem. Pharm. Bull.*, **1990**, *38*, 1278.
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4. Total synthesis of (±)-**1**: Fukuyama, T., Nunes, J.J., *J. Am. Chem. Soc.*, **1988**, *110*, 5196.
5. Total synthesis of (-)-**1**: Garner, P., Ho, W. B., Shin, H., *J. Am. Chem. Soc.*, **1992**, *114*, 2767.
6. For our previous synthetic studies on optically active **1**, see a) Saito, S., Matsuda, F., Terashima, S., *Tetrahedron, Lett.*, **1988**, *29*, 6301. b) Saito, S., Tanaka, K., Nakatani, K., Matsuda, F., Terashima, S., *ibid.*, **1989**, *30*, 7423.
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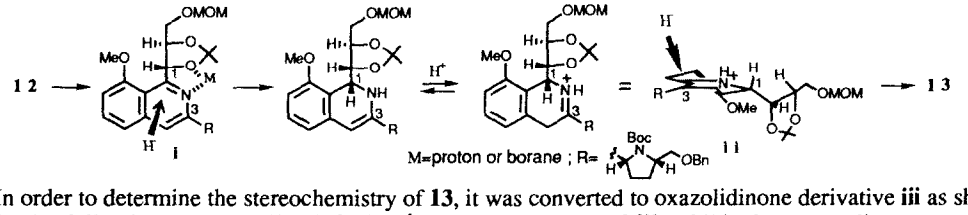
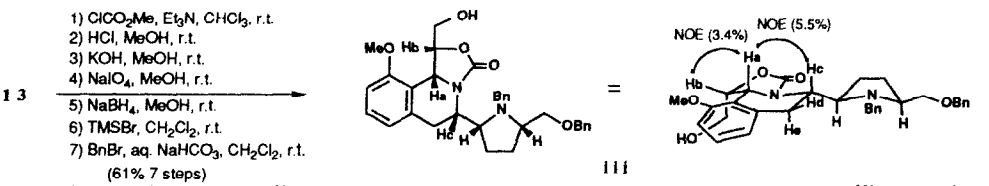
10. The highly diastereoselective reduction can be rationalized by 2-step asymmetric induction as shown below. Thus, the first hydride attack may proceed through the well-known Cram's cyclic model(see, **i**) and the second one may occur under an influence of the so-called stereoelectronic effect(see, **ii**).



11. In order to determine the stereochemistry of **13**, it was converted to oxazolidinone derivative **iii** as shown in the following scheme. The 400MHz ^{1}H-NMR spectrum of **iii** exhibited the coupling constant of 8.5Hz for Ha and Hb, establishing their *cis*-relationships[6]. NOEs were observed between the signals due to Ha and Hb, and those due to Ha and Hc. These results obviously revealed that the newly formed



tetrahydropyridine ring of **iii** takes a half-chair conformation and Ha, Hb, and Hc of **iii** are all in *cis*-relationships. Moreover, the coupling constant of 2.8Hz(axial-equatorial) was observed for Hc and Hd, and that of 11.6Hz(axial-axial) was recorded for Hc and He. Based on these spectral features, the stereostructure of **13** could be rigorously assigned as depicted.

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13. Kim, K. S., Song, Y. H., Lee, B. H., Hahn, C. S., *J. Org. Chem.*, **1986**, *51*, 404.
14. By employing the explored synthetic route, the synthesis of various congeners of **1** including *ent*-**1** and *ent*-**2** is presently being pursued in our laboratory. It is interesting to note that *ent*-**21** and *ent*-**22** preliminary prepared from *ent*-**5** and 4-*O*-benzyl-2,3-isopropylidene-L-threose were found to exhibit no significant cytotoxicity against P388 murine leukemia[IC_{50} (μg/mL); *ent*-**21**: >3.1, *ent*-**22**: >3.1]. The structure-activity relationships of the congeners of **1** will be reported in due course.

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