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SYNTHETIC APPROACH TO QUINOCARCIN

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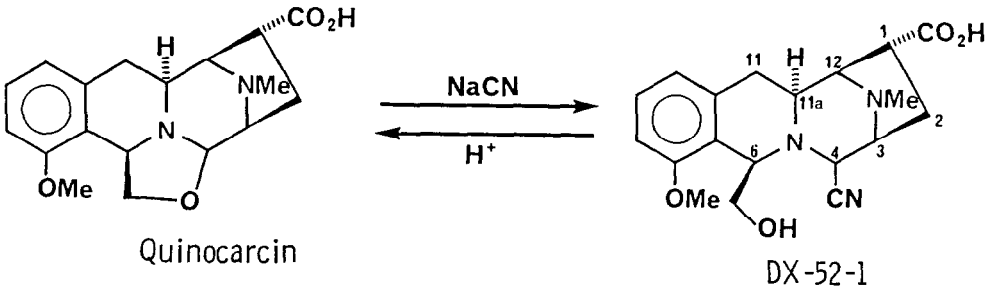
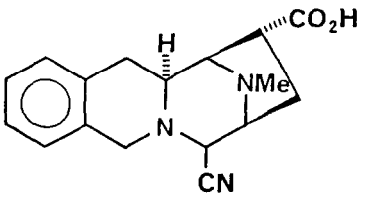
Abstract: A basic synthetic route to quinocarcin is elaborated. The optically active basic skeleton of quinocarcin, iminoazepinoisoquinoline 1 was efficiently synthesized starting from phenylalanine and glutamic acid derivative.

Quinocarcin is a novel antitumor antibiotic discovered in the culture broths of Streptomyces melanovinaceus[1]. The structure of quinocarcin and quinocarcinol (an inactive homologue) were elucidated by spectroscopic analysis[2] and X-ray crystallography[3]. Cyanation of quinocarcin gave DX-52-1, which is more stable than quinocarcin and retains significant antitumor activity. Upon treatment with mineral acid, DX-52-1 regenerated quinocarcin. In this report we describe the total synthesis of optically active demethoxydehydroxymethyl-DX-52-1 1, which has basic 3,12-iminoazepino[1,2-b]isoquinoline skeleton of quinocarcin. Recently the total synthesis of (±) quinocarcinol methyl ester was reported[4]. To establish the synthetic route of optically active quinocarcin, we chose L-phenylalanine and glutamic acid derivative as starting materials.

In three steps from L-phenylalanine (i) 37% HCHO / HCl 65% ii) HCl / EtOH 99% iii) $NaBH_4$ / MeOH-H_2O 69%) (3S)-3-hydroxymethyl-1,2,3,4-tetrahydroisoquinoline 2[5] ($[\alpha]_D$=-97.3°) was prepared. p-Nitrophenyl (L)-N-Cbz-γ-methyl-glutamate 3a[6] obtained from (L)-glutamic acid γ-methylester in two steps, was condensed with 2 in DMF to afford the amide 4a in 69% yield. Swern's oxidation of 4a proceeded smoothly to give tricyclic aminal 5a. (scheme 1) However,



Quinocarcin DX-52-1



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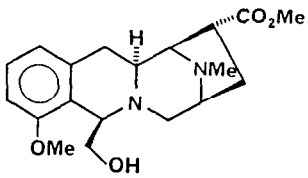
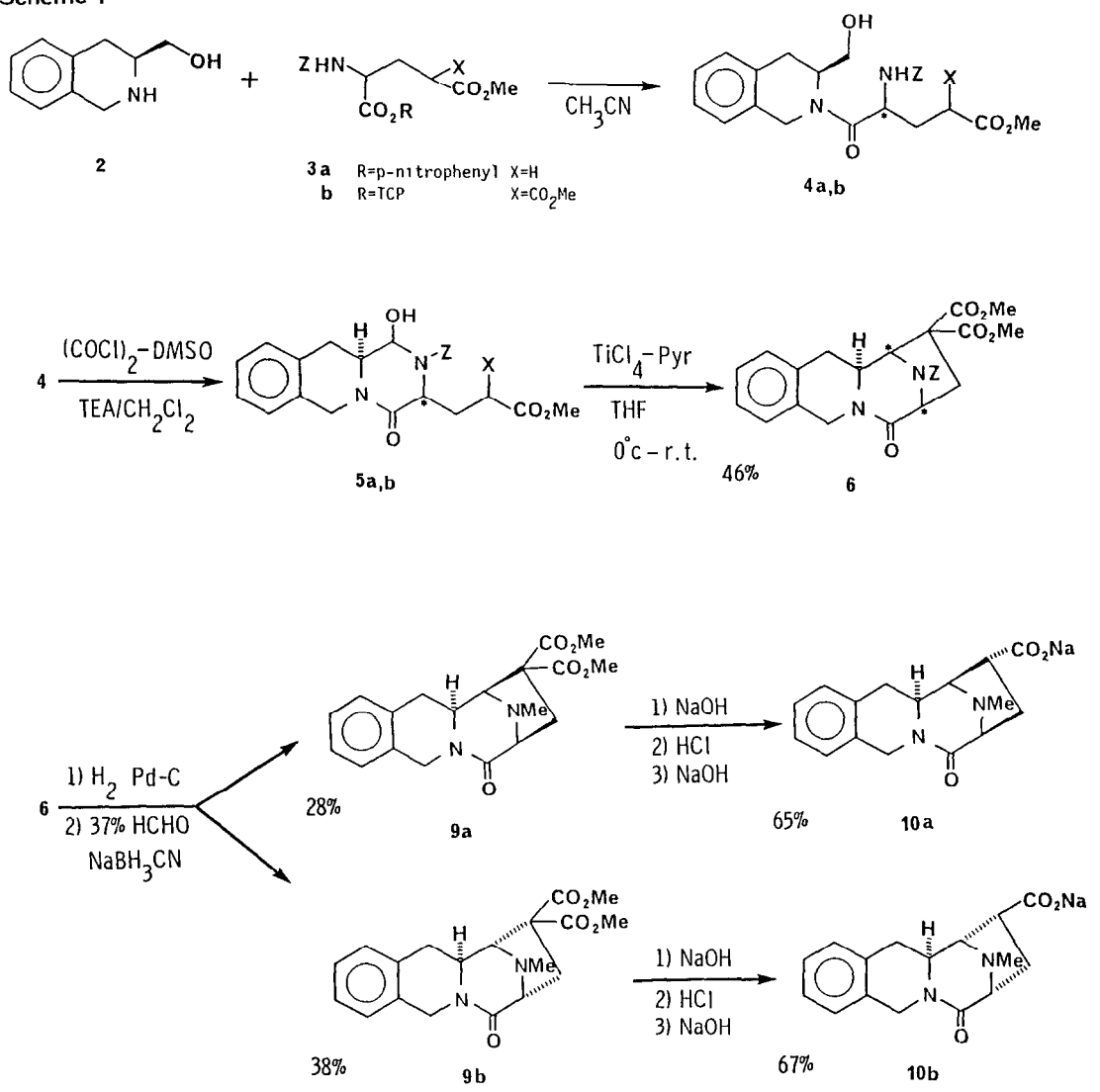


(±) Quinocarcinol Methyl Ester

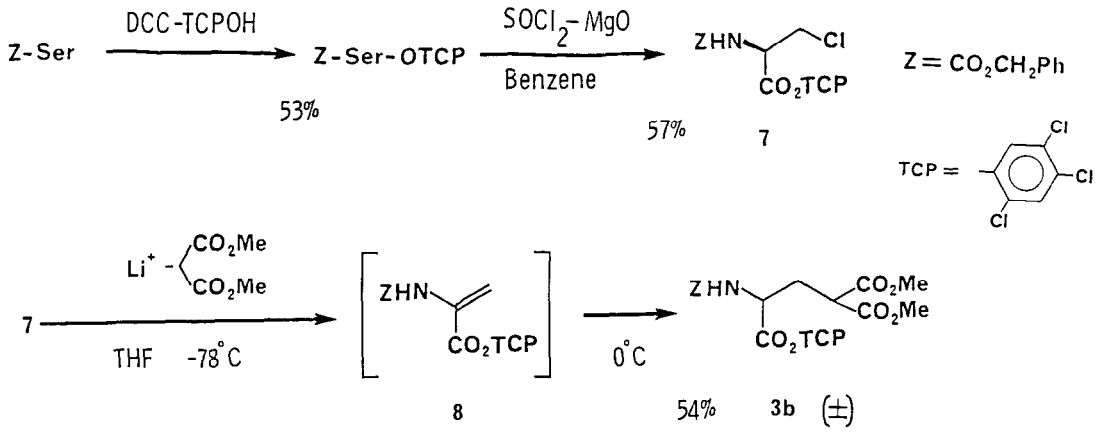
Scheme 1



subsequent cyclization, which is a key step in this synthetic route, was unsuccessful under several conditions employed. So we turned our attention to prepare 2,4,5-trichlorophenyl N-Cbz-γ-carboxy-γ,γ'-dimethyl glutamate 3b, which was expected to have an increased reactivity for cyclization. As outlined in scheme 2, γ-carboxy glutamate 3b was obtained in three steps from Cbz-L-serine. As expected[7], alkylation of N-Cbz-chloroalanine 2,4,5-trichlorophenylester 7 with dimethyl lithiomalonate proceeded via intermediate dehydroalanine 8 followed by Michael addition of malonate, so the desired γ-carboxy glutamate 3b was obtained as racemate.

As was the case of 5a, tricyclic aminal 5b was obtained in 78% overall yield from 3b as a diastereomeric mixture. In consequence of several attempts with various conditions, 5b underwent cyclization upon treatment with $TiCl_4$-pyridine in THF, to afford desired 6 as a diastereomeric mixture, which has an iminoazepinoisoquinoline ring system. Hydrogenolysis and subsequent reductive alkylation of 6 gave rise to stereoisomers 9a and 9b in the ratio of ca

Scheme 2



1:1.4, which were separated easily by silicagel column chromatography. Ester hydrolysis followed by decarboxylation of 9a and 9b afforded 10a, 10b in 65%, 67% yield respectively[8]. (scheme 1) Reduction of lactam 10a to cyclic aminal proceeded upon careful treatment with $LiAlH_4$ at 0°C-r.t. Cyanation of unisolated aminal 11 afforded desired product 1. (scheme 3) Similarly stereoisomer 12 was obtained from 10b along with hydroxymethyl analog 13.

The structure of 1[9] was confirmed by ^1H and ^{13}C-NMR spectroscopic analysis by comparison with DX-52-1. As shown in Table 1, NMR data of 1 were almost identical with those of DX-52-1 except for aromatic ring and 6-carbon and proton , while those of isomer diverges notably from those of DX-52-1. Although a few steps need to be optimized this elaborated route should provide an efficient route to quinocarcin and its analog which is hardly derived by chemical modification of natural product quinocarcin.

The compound 1 exhibits antimicrobial activity against B. subtilis.

Scheme 3

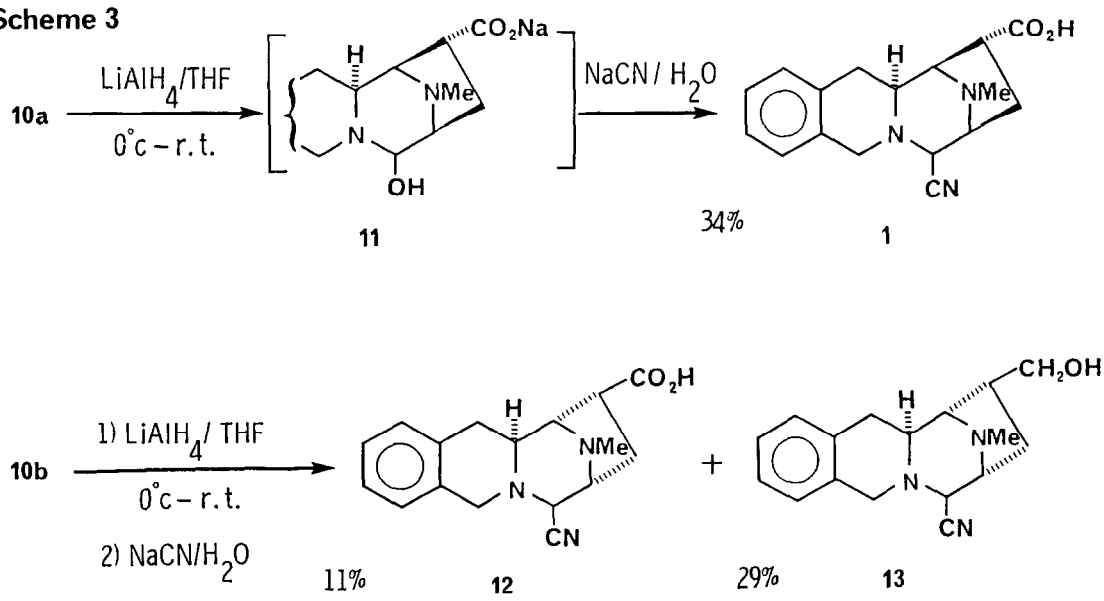


Table 1 ^{13}C and ^{1}H NMR data of DX-52-1, 1 and 12

	^{13}C NMR (D_2O) ppm		
	DX-52-1	**1**	**12**
1	45.1	45.2	50.3
2	33.0	31.1	28.7
3	65.2	65.0	65.7
4	58.3	59.1	58.9
11	30.0	29.4	27.5
11a	58.7	59.4	55.8
12	70.8	69.8	69.9
N-Me	41.8	41.7	42.5
CO_2H	183.7	183.6	184.2
CN	119.4	117.9	122.5

	^{1}H NMR ppm	
	DX-52-1 (D_2O)	**1** ($CDCl_3$)
1	3.09 (dd J=10.1, 5.5Hz)	3.22 (dd J=9.5, 6.0Hz)
2α	2.50 (dt J=13.2, 6.0Hz)	2.67 (dt J=13.4, 6.0Hz)
2β	2.03 (dd J=13.2, 10.0Hz)	2.01 (dd J=13.4, 9.5Hz)
3	3.57 (dd J=5.8, 3.0Hz)	3.57 (dd J=6.0, 2.6Hz)
4	4.23 (d J=3.0Hz)	3.78 (d J=2.6Hz)
12	3.49 (bs)	3.50 (bs)
N-Me	2.20 (s)	2.42 (s)

References and Notes

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8. $[\alpha]_D^{22}$ (EtOH, c=0.5) of 10a, 10b is -107.3° and -66.4° respectively
9. MS of 1 (Me ester) m/z=311 (M^+)

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