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A Novel Synthesis of the C1-C17 Fragment of Carzinophilin

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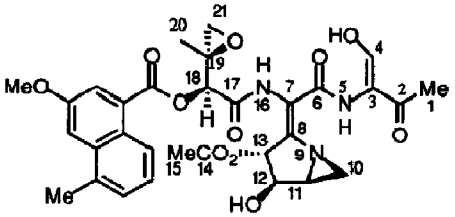
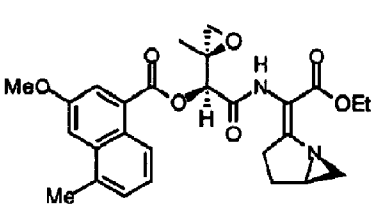
Abstract: *The title synthesis was achieved by featuring i) condensation of the 2-methylthio-Δ^1-pyrroline (C8-C13 moiety) with the Δ^2-oxazolin-5-one (C6,C7, N16, and C17 moiety), ii) activation of the Δ^2-oxazolin-5-one system toward nucleophilic reaction by introducing an allyloxycarbonyl group into the N9 position and subsequent ring opening with the 2-aminobutane (C1-N5 moiety), and iii) base-induced construction of the (E)-1-azabicyclo[3.1.0]hexane system from the 5-mesyloxymethyl-pyrrolidine as key steps.*

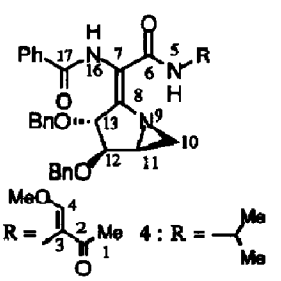
Carzinophilin (**1**) isolated from *Streptomyces sahachiroi* by Hata *et al.* in 1954,[1] is an prominent antitumor antibiotic which have been known as one of the interstrand cross-linking agents for DNA.[2] While the structure of **1** has been revised several times over 30 years,[3] Armstrong *et al.* reported in 1991 that ^{1}H- and ^{13}C-NMR spectra of **1** were superimposable on those of azinomycin B.[4,5] The latter compound is also an antitumor antibiotic having a characteristic 2-methylidene-1-azabicyclo[3.1.0]hexane system and exhibiting excellent cytotoxic activity. These unique history, novel structure, and excellent cytotoxicity delineated above make **1** and its related compounds as attractive targets for total synthesis.[6] Recently, Armstrong *et al.*[6b] and Coleman *et al.*[6c] reported the syntheses of bicyclic (*E*)- and (*Z*)-(pyrrolidin-2-ylidene)glycine esters and (Z)-(pyrrolidin-2-ylidene)glycine amide corresponding to the C6-C17 unit of **1**, respectively. We have also reported on the preparation of bicyclic (*E*)-(pyrrolidin-2-ylidene)glycine ester **2** involving the C6-C21 moiety of **1**.[7] However, the synthesis of bicyclic (*E*)-(pyrrolidin-2-ylidene)glycine amide skeleton has not hitherto been achieved.



carzinophilin (**1**) = azinomycin B



2

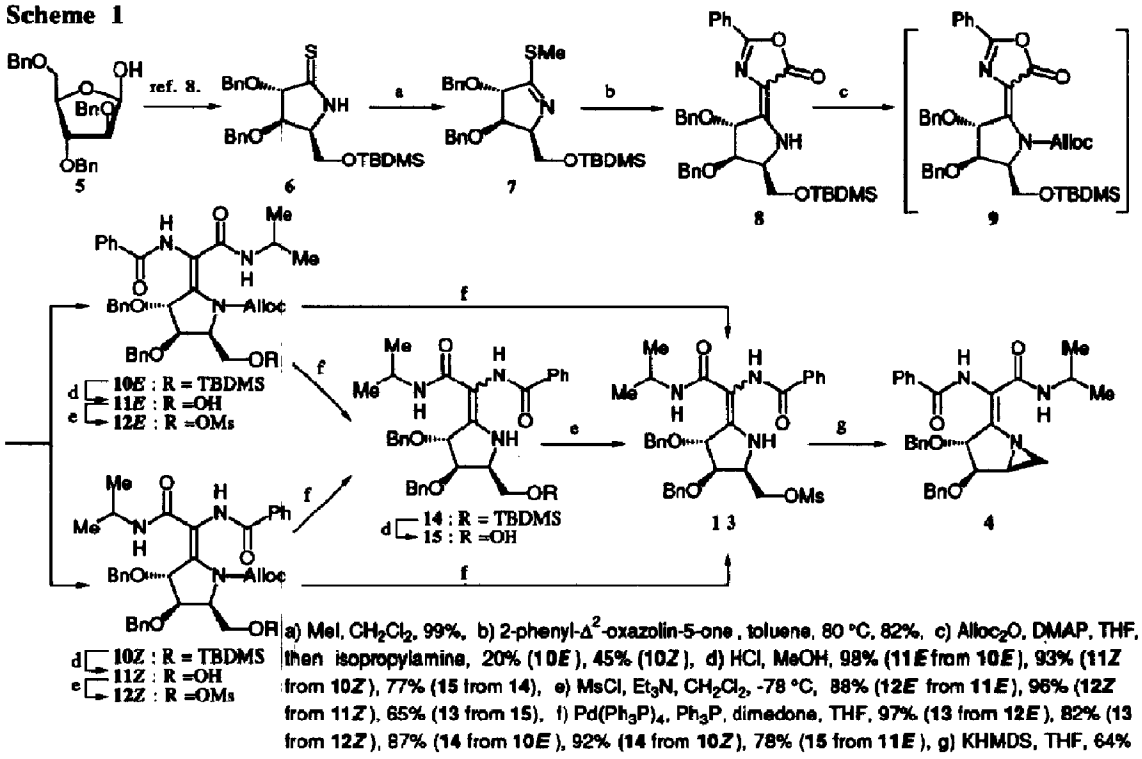


3 : R = **4** : R =

We wish to disclose here a novel synthesis of the C1-C17 fragment **3** of **1** with correct stereochemistry. Our synthetic strategy features i) condensation of the 2-methylthio-Δ^1-pyrroline (C8-C13 moiety) with the Δ^2-oxazolin-5-one (C6, C7, N16, and C17 moiety), ii) activation of the Δ^2-oxazolin-5-one system toward nucleophilic reaction by introducing an allyloxycarbonyl group into the N9 position and subsequent ring opening with the 2-aminobutane (C1-N5 moiety), and iii) base-induced construction of the (*E*)-1-azabicyclo[3.1.0]hexane system from the 5-mesyloxymethylpyrrolidine as key steps.

First, development of a novel synthetic route to **3** was studied by selecting the bicyclic (*E*)-(pyrrolidin-2-ylidene)glycine amide **4** carrying an isopropyl group as a model compound. The thiolactam **6** prepared from 2,3,5-tri-*O*-benzyl-β-D-arabinofuranose (**5**) following the procedure recently developed by us,[8] was transformed into the 2-methylthio-Δ^1-pyrroline **7** by the reaction with methyl iodide. Coupling of **7** with 2-phenyl-Δ^2-oxazolin-5-one was effected smoothly by heating at 80 °C in toluene, affording adduct **8** as an inseparable mixture of the (*E*)- and (*Z*)-isomers.[9] The isomeric ratio of **8***E* to **8***Z* was estimated as 6:4 by the ^{1}H-NMR in $CDCl_3$. The 4-methylene-Δ^2-oxazolin-5-one ring system of **8** appeared to be very stable since no reaction occurred even by heating with isopropylamine at 100 °C in a sealed tube. Simple desilylation was also observed by heating with highly reactive isopropylchloroalminum amide[10] in benzene. However, it was found that the Δ^2-oxazolin-5-one ring can be activated by acylation of the amino group of the pyrrolidine ring.

Scheme 1

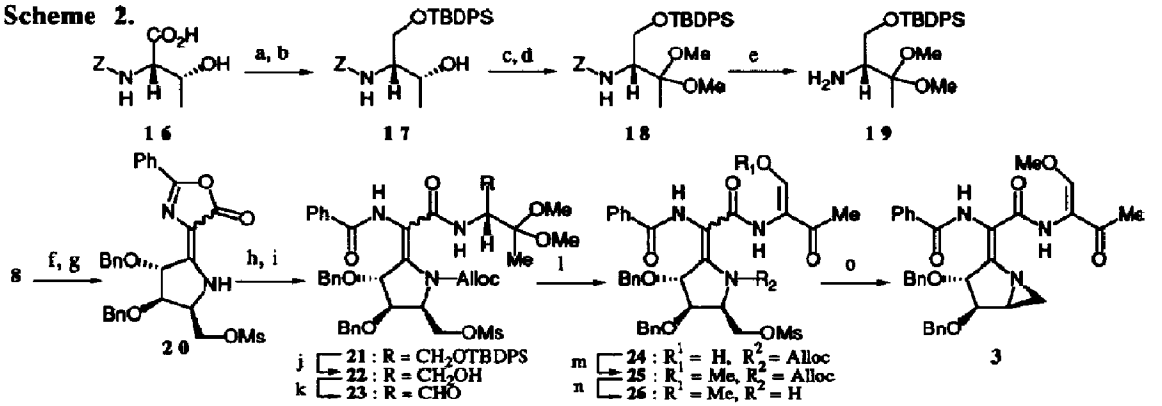


a) MeI, CH_2Cl_2, 99%, b) 2-phenyl-Δ^2-oxazolin-5-one, toluene, 80 °C, 82%, c) $Alloc_2O$, DMAP, THF, then isopropylamine, 20% (**10***E*), 45% (**10***Z*), d) HCl, MeOH, 98% (**11***E* from **10***E*), 93% (**11***Z* from **10***Z*), 77% (**15** from **14**), e) MsCl, Et_3N, CH_2Cl_2, -78 °C, 88% (**12***E* from **11***E*), 96% (**12***Z* from **11***Z*), 65% (**13** from **15**), f) $Pd(Ph_3P)_4$, Ph_3P, dimedone, THF, 97% (**13** from **12***E*), 82% (**13** from **12***Z*), 87% (**14** from **10***E*), 92% (**14** from **10***Z*), 78% (**15** from **11***E*), g) KHMDS, THF, 64%

Thus, the *N*-allyloxycarbonyl (*N*-Alloc) derivative **9** was prepared by treating **8** with $Alloc_2O$ in the presence of DMAP. Treatment of **9** with isopropylamine at room temperature cleanly underwent the ring opening to give the (pyrrolidin-2-ylidene)glycine amide **10***E* and **10***Z* in 20 and 45% yields, respectively, after separation by column chromatography.[11] As detailed in **Scheme 1**, both **10***E* and **10***Z* were readily transformed into mesylate **13** by a combination of desilylation, mesylation, and removal of the *N*-Alloc group. It is worth noting that removals of the *N*-Alloc groups of **10**, **11**, and **12** accompanied isomerizations of the (pyrrolidin-2-ylidene)glycine amide parts by way of the imine-enamine equilibria, resulting in the formations of **14** (from **10***E* or **10***Z*), **15** (from **11***E*)[12], and **13** (from **12***E* or **12***Z*) as inseparable tautomeric mixtures. Finally, construction of the aziridine ring was achieved by treating **13** with potassium hexamethyldisilazide in THF to furnish **4**[13] as a single isomer (*vide infra*).

As described above, we have succeeded in developing a novel synthetic route to construct the 1-azabicyclo[3.1.0]hexane system carrying (*E*)-(pyrrolidin-2-ylidene)glycine amide moiety. Based on these results, the synthesis of C1-C17 fragment **3** of **1** was next attempted. As shown in **Scheme 2**, *N*-benzyloxycarbonyl L-threonine (**16**) was converted to the 2-aminobutane **19** corresponding to C1-N5 moiety in five steps. Taking into account the later synthetic steps, **8** was transformed into mesylate **20**. Right after purification by column chromatography on silica gel, **20** was obtained as a mixture of (*E*)- and (*Z*)-isomers (6:4 isomeric ratio). Interestingly, recrystallization of **20** from AcOEt-hexane took place an isomerization, giving the pure (*Z*)-isomer of **20** (**20*Z***) (>90% recovery), mp. 126-129 °C. After *N*-allyloxycarbonylation of **20*Z***, the formed *N*-Alloc derivative was treated with **19** in a high concentration at 50 °C to yield adduct **21*E*** (68%) and **21*Z*** (23%) after separation by column chromatography. Isomerization of the olefin moiety was observed during these two operations. Both isomers of **21** (**21*E*** and **21*Z***) were elaborated to **25** (**25*E*** and **25*Z***), respectively. Thus, selective deprotection of the TBDPS group of **21*E*** was achieved employing HF-pyridine complex in pyridine, and subsequent oxidation of the generated hydroxyl function of **22*E*** afforded (*E*)-aldehyde **23*E***. Acidic hydrolysis of the dimethyl acetal in **23*E*** gave rise to (*E*)-β-ketoaldehyde **24*E*** in its enol form, which was immediately methylated with diazomethane to give enol ether **25*E***. The (*Z*)-isomer **25*Z*** was similarly prepared from **21*Z***. Removals of the *N*-Alloc group from **25*E*** and **25*Z***[14] afforded (*E*)-2-methylidenepyrrolidine **26*E*** as a single product. The unprotected (*Z*)-2-methylidenepyrrolidine **26*Z*** was also isolated when the reaction employing **25*Z*** was worked up after short period of time. Isomerization of **26*Z*** into **26*E*** completed within 6 h by standing a solution of **26*Z*** in $CDCl_3$ at room temperature. Finally, a combined use of tetrabutylammonium fluoride and molecular sieves 4A was found to effect the aziridine ring formation of **26*E***, giving rise to **3**[13] as a single isomer (*vide infra*).

Scheme 2.

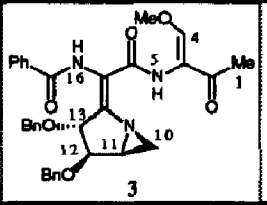
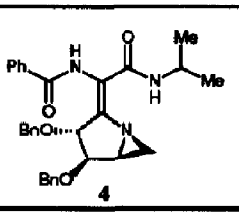
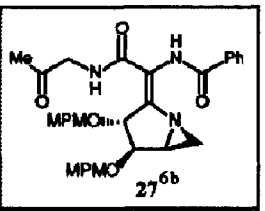


With **3** and **4** in hand, assignment of their stereochemistries was next attempted. Thus, the stereochemistries of C3-C4 double bond and pyrrolidine moiety involved in **3** and **4** could be rigorously established by observing NOEs between the signals due to H-1 and H-4, H-4 and C4-OCH_3, H_α-10 and H-11, H-11 and H-12, and H-13 and H_β-10 (carzinophilin numbering) in their ^{1}H-NMR spectra. However, no information was obtained using an NOE technique as to their (pyrrolidin-2-ylidene)glycine amide parts. Incidentally, an NOE between the amide proton (H-5 or H-16) and the proton on the pyrrolidine ring (H-13)

was not described by Yokoi *et al.* in their report concerning the structure determination of azinomycins.[5] However, as shown in **Table 1**, the signal patterns of the ^{1}H-NMR spectra recorded on **3** and **4** were found to show a marked resemblance to that reported for 4-*O*-methyl azinomycin B [carzinophilin (**1**) 4-*O*-methyl ether] by Yokoi *et al.*[5] and to be clearly different from that described for the bicyclic (*Z*)-(pyrrolidin-2-ylidene)glycine amide **27** by Armstrong *et al.*[6b] Accordingly, the (pyrrolidin-2-ylidene)glycine amide parts of **3** and **4** were tentatively assigned to have the same (*E*)-configurations as that of **1**.

Based on the results accumulated in these studies, the total synthesis of **1** is in progress in our laboratory.

Table 1. Chemical shifts and coupling constants in the ^{1}H-NMR spectra of 3, 4 and 27 ($CDCl_3$).

protons	4-*O*-methyl azinomycin B[5] [carzinophilin (1) 4-*O*-methyl ether]	 3	 4	 27[6b]
1	2.24, s	2.23, s		
4	7.19, s	7.16, s		
4-OCH_3	3.90, s	3.89, s		
5	10.89, s	11.03, bs	9.47, bd, 7.5	6.95, dd, 4.8, 4.8
10a	2.25, d, 3.9	2.30, d, 4.1	2.23, d, 4.1	2.18, d, 3.6
10b	2.51, d, 5.4	2.44, d, 4.8	2.35, d, 5.4	2.40, dd, 1, 5.3
11	3.22, ddd, 5.8, 5.4, 3.9	3.10, ddd, 4.1, 4.1, 4.8	3.06, ddd, 4.1, 5.4, 5.4	3.03, ddd, 3.6, 4.9, 5.3
12	4.63, dd, 5.8, 3.9	4.59, dd, 4.1, 4.7	4.55, dd, 4.1, 5.4	4.42, dd, 1, 4.9
13	5.55, d, 3.9	5.01, dd, 1.0, 4.1	5.01, dd, 0.9, 4.1	5.12, dd, 1, 1
16	8.50, s	8.28, bs	8.43, bs	7.89, b

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12. Deallyloxycarbonylation of **11Z** was not examined.
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