# A FACILE SYNTHESIS OF CHUANGXINMYCIN

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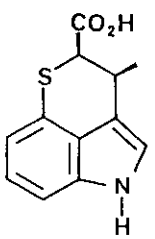
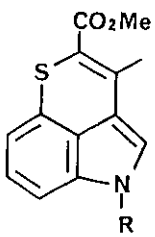
**Abstract** —— Chuangxinmycin was synthesized by means of intramolecular C-H bond insertion of carbene (carbenoid) generated by Bamford-Stevens type reaction.

Chuangxinmycin (1) is a unique antibiotic recently isolated from Actinoplanes tsinanensis n. sp. and found to be active against a variety of Gram-positive and Gram-negative bacteria.[1] Total synthesis of 1 was already reported by two research groups, who synthesized and used dehydrochuangxinmycin methyl ester (2) as a key intermediate.[2,3] The reduction of 2 into 1 was, however, yet remained as a troublesome problem because hydrogenation of $C_3$-$C_4$ double bond of 2 tended to accompany with rapid desulfurization. We attempted to synthesize 1 not through such the onerous reduction process.

Principle of our synthesis is based on direct $C_3$-$C_4$ single bond formation by means of intramolecular C-H bond insertion of carbene (carbenoid) 3. Starting material of our choice is 4-cyanomethylthioindole (4) which was easily prepared by the reaction of a xanthate 5 with chloroacetonitrile[4] and the successive deprotection of N-tosyl group.




**1** Chuangxinmycin




**2** (R = H or Ac)

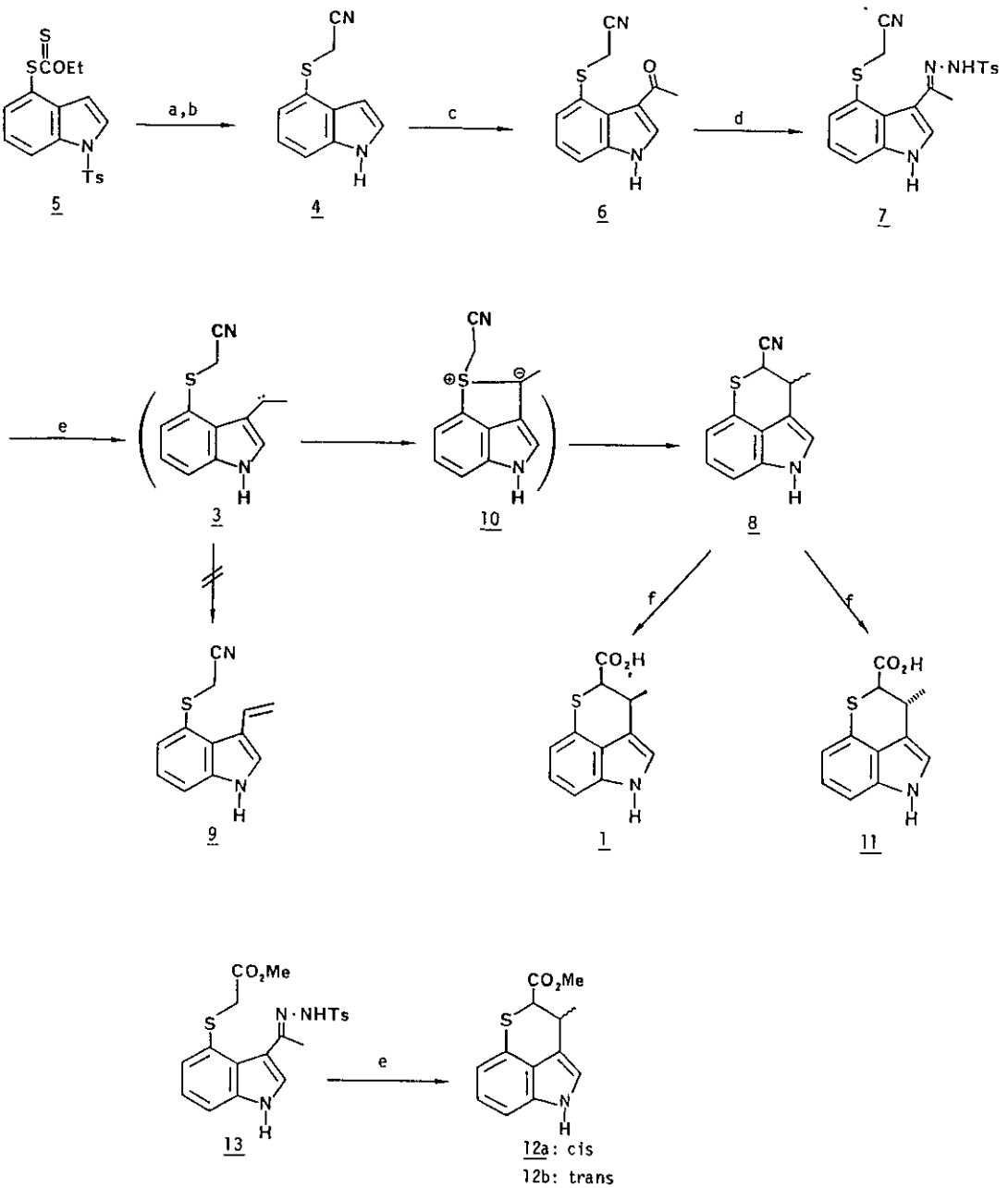
Acylation of the indole 4 leading to 6 was readily attained by $SnCl_4$-catalyzed Friedel-Crafts reaction with acetyl chloride (84% yield). Next, a tosylhydrazone 7 was synthesized as a stable precursor of the carbene 3. Treatment of 6 with tosyl hydrazide in acetic acid-ethanol at refluxing temperature gave the hydrazone 7.

The hydrazone 7 (0.63 mmol) was treated with NaH (0.65 mmol) in diethyleneglycol dimethyl ether (diglyme) (5.5 ml) at room temperature for 20 min and was heated for 10 min at refluxing temperature. The mixture obtained after usual workup was chromatographed ($SiO_2/CH_2Cl_2$) to afford the desired cyclization product 8 as a stereoisomeric mixture (8a/8b = 43/57) in 76% yield.[5] Major isomer 8b was isolated in pure form as crystals, and it was tentatively assigned as trans isomer (vide infra). Base-catalyzed epimerization of 8b occurred easily to give the mixture with the ratio 8a/8b = 4/6. Thus, the mixture 8 formed from 7 may be an equilibrium one under the reaction conditions. Furthermore, it is worth to point out that the decomposition of 7 scarcely gave normal product 9 of Bamford-Stevens reaction. The fact was probably due to participation of sulfur which stabilized intermediary carbene (carbenoid) 3 as a sulfur ylide 10.[6]

The stereoisomeric mixture 8 was hydrolyzed with NaOH in refluxing ethanol (28 h) to give a mixture of chuangxinmycin 1 and its trans isomer 11 in 94% yield (1/11 = 4/6). The isomer 8b gave also similar result. Hydrolysis of 8 into 1 and 11 proceeded consequently with no steric control. Such epimerization of the isomer observed for 8a and 8b has also been reported in alkaline hydrolysis of chuangxinmycin methyl ester (12a).[3] Isolation of 1 was, however, easily attained by fractional crystallization of the mixture from $CH_2Cl_2$-ether giving pure (±)-chuangxinmycin melted at 190 - 191 °C [Lit.[1] (-)-1; 192-192.5 °C, (±)-1; 181-184[2] or 145-145.5[3] °C].

Similarly to the case of 7, a hydrazone 11 was synthesized and its Na salt was pyrolyzed to afford chuangxinmycin methyl ester (12a)and its trans isomer 12b in 45% yield. The isomeric ratio 12a/12b was 40/60, so that, in the formation of 8, major isomer 8b might be trans one.

Intramolecular C-H bond insertion of carbene (carbenoid) generated by Bamford-Stevens type reaction was shown here to be useful for a facile synthesis of




a: $ClCH_2CN/H_2NCH_2CH_2NH_2$, b: $C_6H_{11}ONa$, c: $CH_3COCl/SnCl_4$, d: $TsNHNH_2/CH_3CO_2H/C_2H_5OH$,
e: NaH/Diglyme, f: $NaOH/C_2H_5OH$

chuangxinmycin. Further application of the intramolecular C-H bond insertion of carbene (carbenoid) is now progress.

**REFERENCES AND NOTES**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(5) 8b: colorless granules melted at 203.5-205.5 °C (from ethyl acetate). Nmr(400MHz, acetone-$d_6$) δ1.62(d, J=6.8Hz, 3H), 3.57(qdd, J=6.8, 4.0, and 1.5Hz, 1H), 4.53(d, J=4.0Hz, 1H), 6.93(dd, J=7.3 and 0.5Hz, 1H), 7.12(dd, J=8.2 and 7.3Hz, 1H), 7.26(dd, J=8.2 and 0.5Hz, 1H), 7.30-7.33(m, 1H), 10.26-10.42(m, 1H)ppm. Ir(KBr) 3390 and 2240 $cm^{-1}$. Mass(m/z, %) 214($M^+$, 100), 199(55), and 174(73). Anal. Calcd. for $C_{12}H_{10}N_2S$ : C,67.26; H,4.70; N,13.07; S,14.96. Found: C,67.21; H,4.64; N,13.02; S,14.75.
Nmr spectrum of the mixture 8a and 8b (400MHz, acetone-$d_6$) δ1.41(d, J=6.8Hz, 1.29H), 1.60(d, J=6.8Hz, 1.71H), 3.54(qdd, J=6.8, 4.0, and 1.5Hz, 0.57H), 3.72(qdd, J=6.8, 4.4, and 0.7Hz, 0.43H), 4.31(d, J=4.4Hz, 0.43H), 4.47(d, J=4.0Hz, 0.57H), 6.90-6.95(m, 1H), 7.08-7.15(m, 1H), 7.23-7.33(m, 2H), 10.23-10.43(m, 1H)ppm.

(6) For reviews, see a) M. P. Doyle, Acc. Chem. Res., 1986, 19, 348. b) A. Oku and T. Harada, J. Syn. Org. Chem. Japan, 1986, 44, 736 and refs. cited therein.


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