THE NEW APPROACH TO ANTIBIOTIC CARBAZOMYCINS. THE FORMAL TOTAL SYNTHESIS OF CARBAZOMYCINS A AND B

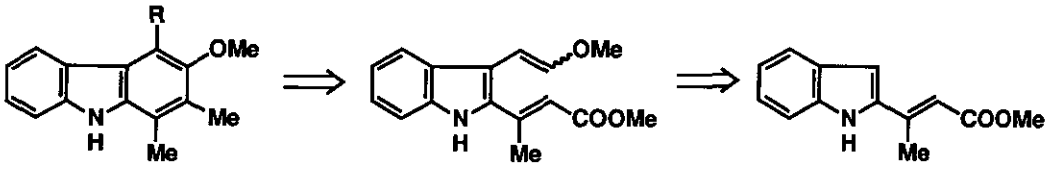
Satoshi Hibino,* Akiko Tonari, Tominari Choshi, and Eiichi Sugino

Faculty of Pharmacy & Pharmaceutical Sciences, Fukuyama University, Fukuyama, Hiroshima 729-02, Japan

Abstract——Deoxycarbazomycin B has been synthesized in a four step sequence. The key reaction has been the thermal electrocyclic reaction of 1,3,5-hexatriene system involving the indole 2,3-bond.

The electrocyclic reaction of 2,3-bisvinylindole has envisaged to be a synthetically efficient concept for the construction of selectively functionallized carbazole derivatives with dehydrogenation step. We have first realized this approach in the synthesis of hyellazole and 6-chlorohyellazole.[1]

We now describe here the synthesis of antibiotic carbazomycins A and B (**1**)[2] based on the thermal electrocyclic reaction of hexatriene system (**3**) involving indole 2,3-bond. For the synthesis of 2,3-bisvinylindole (**3**), we utilized methyl indolyl-2-butenoate (**4**)[3] as the starting material according to the retrosynthetic route. Vilsmeier reaction of **4** gave the aldehyde (**5**)[4] in quantitatively. Wittig reaction of **5** with methoxymethylenetriphenylphosphorane afforded the 2,3-bisvinylindole (**3**). Heating of the crude **3** in *o*-dichlorobenzene in the presence of



1a : R=OMe (carbazomycin A)
1b : R=OH (carbazomycin B)
2 : R=H (deoxycarbazomycin B)

3 **4**

dichlorodicyanoquinone (DDQ) gave the carbazole (**6**) and (**7**) in 32.5% and 38. 6% yields from **5**, respectively. Although the several conditions of this reaction listed in Table 1 were examined, the elimination of methanol at the final stage could not be avoided. With the high temperature, the total yield of **6** and **7** had a tendency to decrease. It seems that DDQ is much better than 10% Pd-C as the oxidizing agent in this case. The desired carbazole (**6**) was reduced with lithium aluminum hydride in dioxane at reflux temperature to give the deoxycarbazomycin B (**2**) in 87.8 % yield. The conversion of **2** into **1** has been already established.[4] Thus the formal total synthesis of carbazomycins A and B (**1**) has been completed by this strategy.

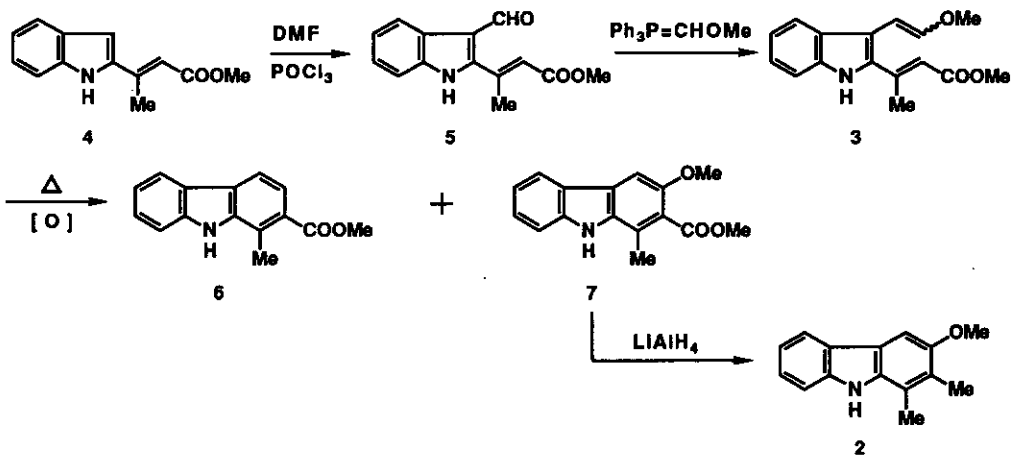


Table 1

Run	Solvent	Oxidizing agent	Time (h)	Yields (%)[a] from **5** **6** and **7**	
1	*o*-Dichlorobenzene	10% Pd-C	14	34.6	13.6
2	*o*-Dichlorobenzene	DDQ	1	38.6	32.5
3	Decalin	10% Pd-C	2	42.7	26.2
4	Decalin	DDQ	2	10.8	11.0
5	1,2,3,4-Tetramethylbenzene	10% Pd-C	14	26.4	13.0
6	1,2,3,4-Tetramethylbenzene	DDQ	2	22.4	12.6

[a] isolated yield

EXPERIMENTAL

Melting Points were measured by Yanagimoto micro melting point apparatus and were uncorrected. Ir spectra were recorded on a Shimadzu FTIR-8500 spectrometer. ^{1}H Nmr spectra were taken with JEOL PMX60Si and JEOL JNM-GX400 instruments with tetramethylsilane as an internal standerd. Ms spectra were recorded on a Shimadzu GC-MS 9020DF instrument. Silica gel (60-100 mesh, Merck Art 7734) was used for column chromatography.

Methyl 3-[2-(3-Formyl)indolyl]-2-butenoate (**5**). A solution of DMF (3ml) and $POCl_3$ (1.1ml, 11.85mmol) was stirred at room temperature for 30 min equipped with drying tube ($CaCl_2$). A solution of the indole (**4**) (0.85g, 3.95mmol) in DMF (8ml) was added to the solution of Vilsmeier reagent. After being stirred at room temperature for 2 h, the solution was poured into the ice-water. The mixture was neutralized by an aqueous 5% NaOH solution and then the preciptate was filtered. Recrystallization from methanol gave the aldehyde (**5**) (0.89g, 92.9%) as colorless prisms, mp 198-199.5℃. Ir(KBr): 1630cm^{-1}(C=O), 1710cm^{-1}(C=O); ^{1}H nmr $CDCl_3$): δ 2.68 (3H, s, CH_3), 3.77(3H, s, $COOCH_3$), 6.23(1H, s, vinyl proton), 7.19 -7.56 (4H, m, aromatic protons), 10.10(1H, s, CHO). Ms: *m/z* 243(M^+). *Anal.* Calcd for $C_{14}H_{13}NO_3$: C, 69.12; H, 5.39; N, 5.76. Found: C, 69.06; H, 5.42 ; N, 5.72.

2-Methoxycarbonyl-1-methylcarbazole (**6**) and 3-Methoxy-2-methoxycarbonyl-1-methylcarbazole (**7**). A solution of the aldehyde (**5**) (100mg, 0.411mmol) in anhyd. THF (3ml) was added to the stirred solution of methoxymethylenetriphenylphosphorane [prepared from methoxymethyltriphenylphosphonium chloride (0.42g, 1.23mmol) in anhyd. THF (3ml) and BuLi (0.79ml, 1.56M in hexane solution, 1.23mmol) under N_2 atmosphere] with cooling (ice). After being stirred at room temperature for 3 h, the mixture was quenched with an aqueous NH_4Cl solution and extracted with $CHCl_3$. The $CHCl_3$ layer was washed with brine, dried over Na_2SO_4 and concentrated. The residue was used for the next reaction. A mixture of the crude 2,3-bisvinylindole (**3**) in the presence of DDQ (94mg, 0.411 mmol) or 10% Pd-C (100mg) in an appropriate solvent (3ml) was heated at reflux temperature. The mixture was cooled to room temperature and filtered through celite. The filtrate was concentrated and the residue was purified by column chromatography (silica gel, 20g) to give the carbazoles (**6**) and (**7**). Reaction solvents and Yields were listed in Table 1.

The carbazole (**6**): colorless needles (elution with 5% EtOAc-hexane; recrystallized from $CHCl_3$-hexane), mp 139-140℃. Ir(KBr): 1712cm^{-1}(C=O); ^{1}H nmr($CDCl_3$): δ 2.81(3H, s, C_1-CH_3), 3.92(3H, s, $COOCH_3$), 7.22-8.23(7H, m, aromatic protons). Ms: *m/z* 239(M^+). *Anal.* Calcd for $C_{15}H_{13}NO_2$: C, 75.30; H, 5.48; N, 5.85. Found: C, 75.28; H, 5.51; N, 5.80.
The carbazole (**7**): pale yellow needles (elution with 10% EtOAc-hexane; recrystallized from $CHCl_3$-hexane), mp 116-117.5℃. Ir(KBr): 1714cm^{-1}(C=O); ^{1}H nmr($CDCl_3$): δ 2.46(3H, s, C_1-CH_3), 3.90(3H, s, OCH_3), 3.93(3H, s, $COOCH_3$), 6.97-8.11(6H, m, aromatic protons). Ms: *m/z* 269(M^+). *Anal.* Calcd for $C_{16}H_{15}NO_3$: C, 71.36; H, 5.61; N, 5.20. Found: C, 71.35; H, 5.70; N, 5.18.

1,2-Dimethyl-3-methoxycarbazole (deoxycarbazomycin B) (**2**). A solution of the carbazole (**7**) (30 mg, 0.11mmol) in anhyd. dioxane (3ml) was added dropwise to a stirred mixture of $LiAlH_4$ (100mg) in anhyd. dioxane under N_2 atmosphere. The mixture was refluxed at 120° for 14 h, which was quenched with EtOAc. The mixture was filtered through celite and the filtrate was concentrated. The residue was purified by column chromatography (silica gel, 10g) using 5% EtOAc-hexane as an eluent to give the carbazole (**2**) (22mg, 87.8%) as pale yellow needles, mp 129-131 ℃ (recrystallized from EtOAc-hexane) (lit.,[4] mp 129-131℃). ^{1}H Nmr spectra (400MHz) of **2** were in full agreement with those reported.[4] Ms: *m/z* 225(M^+). *Anal.* Calcd for $C_{15}H_{15}NO$: C, 79.97; H, 6.71; N, 6.22. Found: C, 79.91; H, 6.82 ; N, 6.20.

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