A TOTAL SYNTHESIS OF CHICAMYCIN A* A NEW PYRROLO[1,4]BENZODIAZEPINE ANTITUMOR AGENT

Sir:

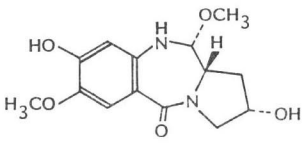
The chicamycins are a family of new antitumor antibiotics produced by a new strain of *Streptomyces* designated *Streptomyces albus,* No. J576-99 (ATCC 39143).[1,2] Depending on the method, two different forms, chicamycins A **(1)** and B **(2)**, can be isolated. Chicamycin belongs to a family of pyrrolo[1,4]benzodiazepine antibiotics[3] and is closely related to neothramycin.[4] It possesses marked antitumor activity against P388 leukemia as well as antibacterial activities against various Gram-positive and acid-fast bacteria.

We describe here the first total synthesis of chicamycin A based on our previously reported strategy.[5] The overall plan is to use the readily available intermediate **5**** and to carry out a selective reduction of the N10-C11 amide after inversion of the C2 center.

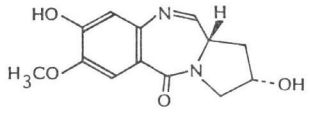
Our synthesis began with substituted benzoic acid **3** which was prepared by *p*-nitrobenzylation and nitration of vanilic acid.[7] Conversion to the acid chloride, followed by reaction with *trans*-4-hydroxyl-L-proline methyl ester at −20°C gave amide **4** in 84% yield. Catalytic reduction followed by refluxing in toluene gave the cyclized compound **5** (99%, mp 260~262°C, $[\alpha]_D^{25}$ +329° (*c* 0.25, CH_3OH)). Treatment with sodium hydride and benzoyl chloride gave the selectively protected intermediate **6** which was subsequently oxidized with JONES reagent to give the ketone **7** (83%, mp 224~226°C, $[\alpha]_D^{24}$ +388° (*c* 0.55, CH_3OH)). Reduction of the ketone with sodium borohydride afforded the epimeric alcohol **8** as the major product (62%, mp 250~251°C, $[\alpha]_D^{25}$ +265° (*c* 0.32, CH_3OH)). The inversion at C2 is detected by NMR (NMR (acetone-d_6+DMSO-d_6, δ) 2.38 (ddd, 1H, J=14, 9, 5 Hz), 2.74 (bd, 1H, J=14 Hz), 3.54 (bd, 1H, J=12 Hz), 3.84 (dd, 1H, J=12, 4 Hz), 3.91 (s, 3H), 4.35 (dd, 1H, J=9, 4 Hz), 4.46 (m, 1H), 7.18 (s, 1H), 7.52~7.82 (m, 4H), 8.22 (dd, 1H, J=8, 2 Hz)) and is consistent with hydride attack from the less hindered face of the molecule.

After acetylation **8** was treated with the LAWESSON reagent[8] to give the thioamide **9** (52% for two steps, mp 238~240°C, $[\alpha]_D^{24}$ +369° (*c* 0.29, CH_3OH)). Alkylation with methyl iodide followed by a mild hydrolysis of the acyl groups provided imino thioether **10** in quantitative yield. **10**: IR (KBr) 3410, 1585, 1496, 1450, 1430, 1275 cm^{-1}; NMR ($CDCl_3$+CD_3OD, δ) 2.24~2.82 (m, 5H), 3.54 (d, 1H, J=5 Hz), 3.66~4.20 (m, 6H), 4.30~4.58 (m, 1H), 6.57 (s, 1H), 7.40 (s, 1H); mass spectrum (70 ev) *m/z* (relative intensity), 306 (16) (M^+), 208 (100). This intermediate was treated with aluminum-amalgam*** for 18 hours, and then with 0.1 N methanolic $HgCl_2$ at 0°C. A silica gel chromatography at 5°C of the reaction mixture afforded chicamycin A (**1**) in 49% yield which was identical in all respects to the natural product (mp 162~164°C (ref.[1]) 161~163°C); $[\alpha]_D^{24}$ +335° (*c* 0.08, pyridine), (ref.[1]) $[\alpha]_D^{26}$ +350° (*c* 0.11, pyridine)); observed mass 262.0954 (calcd for $C_{14}H_{18}N_2O_5-CH_3OH$ 262.0952)). The over-reduction product **11** was isolated in 18% yield in addition to **1**. **11**: IR (KBr) 3380, 1630, 1595, 1565, 1510, 1440, 1265 cm^{-1}; NMR ($CDCl_3$+CD_3OD, δ) 1.84 (dt, 1H, J=14, 4 Hz), 2.23~2.58 (m, 1H), 3.50~4.12 (m, 8H), 4.30~4.60 (m, 1H), 6.17 (s, 1H), 7.46 (s, 1H); mass spectrum (70 ev) *m/z* 264 (100) (M^+). Since chicamycins A and B are interconvertible[1,2], we

Fig. 1.



Chicamycin A (**1**)



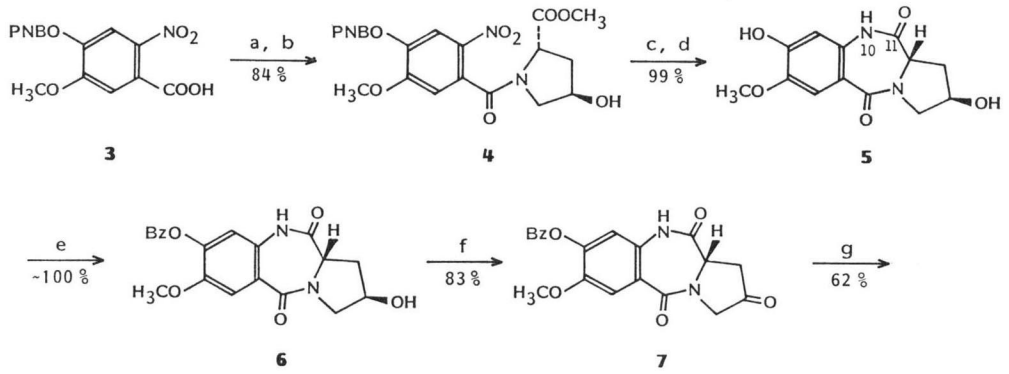
Chicamycin B (**2**)

* This antibiotic was originally called BBM-2040 A.

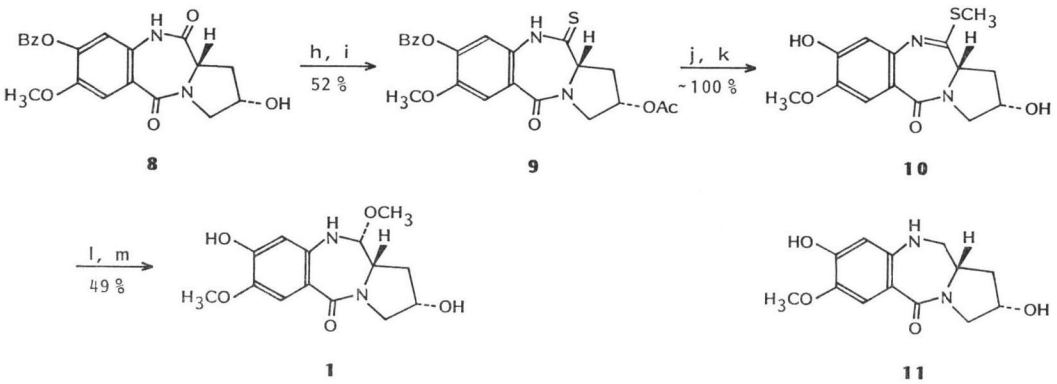
** The C8 ethyl ether of this compound was reported earlier.[6]

*** Aluminum amalgam was prepared according to the method of KECK *et al.*[9]

Scheme 1.



a. $SOCl_2$/THF
b. *trans*-4-Hydroxy-L-proline methyl ester/TEA/−20°C
c. H_2/Pd-C/EtOAc
d. Toluene/111°C
e. NaH/DMF/C_6H_5COCl
f. CrO_3/H_2SO_4/acetone
g. $NaBH_4/C_2H_5OH$



h. Ac_2O/pyridine
i. $(p\text{-}CH_3OC_6H_4PS_2)_2/C_6H_6$/80°C/1 hour
j. CH_3I/K_2CO_3/THF/14 hours
k. K_2CO_3/CH_3OH/0°C
l. Al-Hg/aq THF/0~5°C/18 hours
m. $HgCl_2/CH_3OH$/0°C

have achieved a 9-step synthesis of chicamycins with an overall yield of 10%. Recently, TOZUKA *et al.* reported synthesis of the C2 epimer of chicamycin by a different route.[10] The highlight of our synthesis is the newly developed, mild reduction of the secondary amide to the aldehyde oxidation level.

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