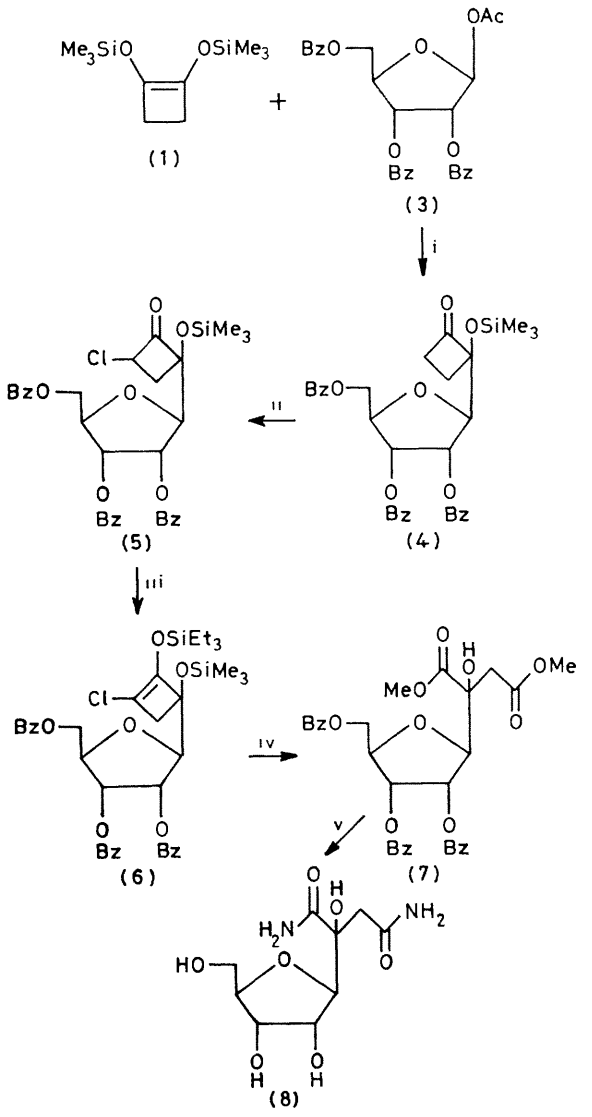
Highly Efficient Method for the Synthesis of Showdomycin

By TAN INOUE and ISAO KUWAJIMA*
(*Department of Chemistry, Tokyo Institute of Technology, Ookayama, Meguro-ku, Tokyo* 152, *Japan*)

Summary Showdomycin was prepared in excellent overall yield using 1,2-bis(trimethylsiloxy)cyclobut-1-ene for the construction of the maleimide unit of the molecule.

MUCH attention has been focused on synthetic approaches to nucleosides having carbon–glycosyl linkages because of their important antibiotic properties and potent anticancer and antiviral activities.[1] However, most of the synthetic methods reported so far have required multi-step procedures[2] and have not given very high overall yields.



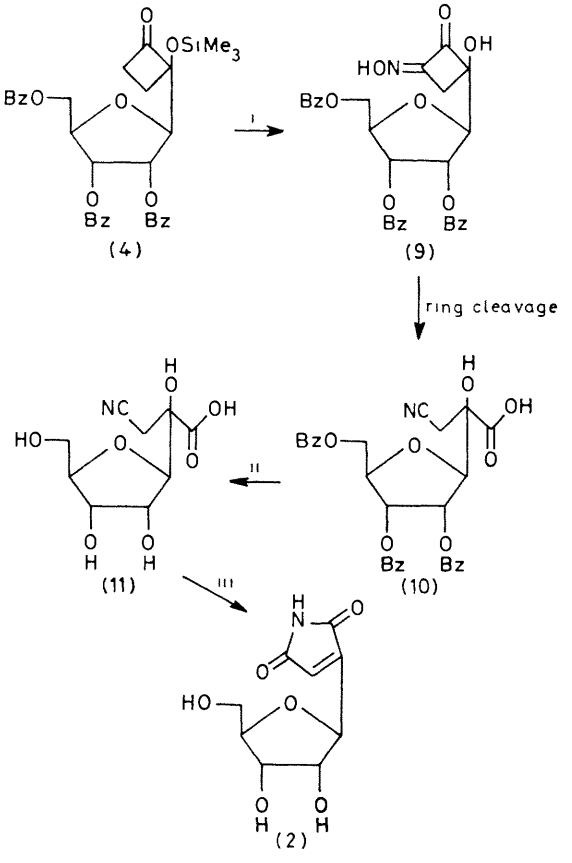
SCHEME 1. i, $SnCl_4$–CH_2Cl_2; ii, LHMDS–Me_3SiCl–tetrahydrofuran (THF) then Cl_2–CCl_4; iii, LHMDS–Et_3SiCl; iv, O_3, CH_2Cl_2–MeOH, then Me_2S, then CH_2N_2–Et_2O; v, NH_3–MeOH.

We have recently shown the synthetic utility of 1,2-bis(trimethylsiloxy)cyclobut-1-ene (**1**) in the preparation of cyclopentane-1,3-diones,[3] β-hydroxycyclopentanones,[4] γ-oxo-esters,[5] and 5-alkoxy-1,4-diketones.[6] We describe here a synthesis of showdomycin (**2**) which involves the cyclobutene (**1**) as an efficient source of the four-carbon unit required for construction of the maleimide unit of (**2**).

A carbon–glycosyl linkage was initially formed as follows. The cyclobutene (**1**) was treated with the fully protected β-D-ribose derivative (**3**) in the presence of tin(IV) chloride (1 equiv.) in methylene chloride at room temperature for 2 h. The resulting adduct (**4**) (i.r. 1775 cm^{-1}) was isolated in 92% yield, exclusively as the desired β-anomer probably owing to the neighbouring group participation of the benzoyl group attached to C-2.[7]

To transform the cyclobutanone ring of (**4**) into a maleimide group, we initially examined the synthetic route shown in Scheme 1. The monochlorinated ketone (**5**) (i.r. 1780 cm^{-1}) was prepared *via* the trimethylsilyl enol ether of (**4**), and was converted into its triethylsilyl enol ether (**6**) (i.r. 1670 cm^{-1}) with lithium hexamethyldisilazide (LHMDS)† and chlorotriethylsilane. Ozonolysis of crude (**6**) followed by treatment with diazomethane afforded the diester (**7**) in 64% yield from (**4**). Treatment of the diester (**7**) with a saturated methanolic solution of ammonia at room temperature for 2 days led to the formation of the corresponding diamide (**8**) (i.r. 1650 cm^{-1}) in 84% yield, accompanied by simultaneous removal of the protecting groups. We failed to convert the amide (**8**) into showdomycin (**2**) in satisfactory yields, although various procedures were examined.

We next examined another method for ring cleavage of the cyclobutanone (Scheme 2). Treatment of the trimethylsilyl enol ether of (**4**) with nitrosyl chloride (1 equiv.)[8]



SCHEME 2. i, LHMDS–Me_3SiCl–THF then NOCl–CH_2Cl_2; ii, NH_3–MeOH; iii, $(CF_3CO)_2O$–benzene.

† Employment of lithium di-isopropylamide usually resulted in partial removal of the protecting benzoyl groups and conversion into the silyl enol ether was not so effective.

in methylene chloride at −40 °C gave the corresponding α-oximino-cyclobutanone (**9**) (i.r. 1760 cm^{-1}) cleanly. When crude (**9**) was stood in methylene chloride at room temperature for 2 days, ring cleavage took place efficiently to afford the desired cyano-carboxylic acid (**10**) (i.r. 3610—2510, 2225 cm^{-1}) in 99% yield from the adduct (**4**). To remove its protecting groups,‡ (**10**) was treated with methanolic ammonia and the de-benzoylated product (**11**) was obtained almost quantitatively. Cyclization of the cyano-carboxylic acid (**11**) followed by dehydration was effected by treatment with trifluoroacetic anhydride in benzene at 35 °C for 6 h, and showdomycin (**2**) was isolated in 77% yield. The product (**2**) was spectroscopically and chromatographically identical with authentic natural showdomycin. Its overall yield was 70% based on the starting β-D-ribose derivative (**3**).

In addition to the extremely short synthetic procedure and high efficacy achieved, little purification of the intermediates involved is required in this method, which compares well with the methods[9,10] reported so far. We are currently studying the synthesis of other *C*-glycosides such as pyrazomycin and formycin B using a similar synthetic strategy.

We thank the Ministry of Education the Japanese Government for a Grant-in-Aid, and the Kurata Foundation for partial support, and Dr. Hideo Otsuka of Shionogi Research Laboratory for a generous gift of natural showdomycin.

(*Received*, 31*st December* 1979; *Com.* 1335.)

‡ After cyclization into the maleimide ring, removal of the protecting groups was very difficult because of a side reaction (see ref. 9)

[1] R. J. Suhadolnik, 'Nucleoside Antibiotics,' Wiley-Interscience, New York, 1970, pp. 354–404; G. D. Davies, Jr. and C. C. Cheng *Prog. Med. Chem.*, 1976, **13**, 303.
[2] S. Hanessian and A. G. Pernet, *Adv. Carbohydr. Chem. Biochem.*, 1976, **33**, 111.
[3] E. Nakamura and I. Kuwajima, *J. Am. Chem. Soc.*, 1977, **99**, 961.
[4] I. Kuwajima and I. Azegami, *Tetrahedron Lett.*, 1979, 2369.
[5] E. Nakamura, K. Hashimoto, and I. Kuwajima, *J. Org. Chem.*, 1977, **42**, 4166.
[6] I. Kuwajima, I. Azegami, and E. Nakamura, *Chem. Lett.*, 1978, 1431.
[7] T. Ogawa, A. G. Pernet, and S. Hanessian, *Tetrahedron Lett.*, 1973, 3543.
[8] J. K. Rasmussen and A. Hassner, *J. Org. Chem.*, 1974, **39**, 2558.
[9] J. G. Buchanan, A. E. Edgar, M. J. Power, and C. T. Shanks, *J. Chem. Soc., Perkin Trans.* 1, 1979, 225.
[10] L. Kalvoda, J. Farkaš, and F. Šorm, *Tetrahedron Lett.*, 1970, 2297; G. Trummlitz and J. G. Moffat, *J. Org. Chem.*, 1973, **38**, 1841; L. Kalvoda, *J. Carbohydr. Nucleosides, Nucleotides*, 1976, **3**, 47; L. Kalvoda, *Collect. Czech. Chem. Commun.*, 1972, **37**, 4046; 1976, **41**, 2034; R. E. Harmon, G. Wellman, and S. K. Gupta, *Carbohydr. Res.*, 1969, **11**, 574; 1970, **14**, 123; R. Noyori, T. Sato, and Y. Hayakawa, *J. Am. Chem. Soc.*, 1978, **100**, 2561.