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STUDIES ON THE TOTAL SYNTHESIS OF OXETANOCIN; I. THE FIRST SYNTHESIS OF A NUCLEOSIDE HAVING OXETANOSYL-N-GLYCOSIDE[1]

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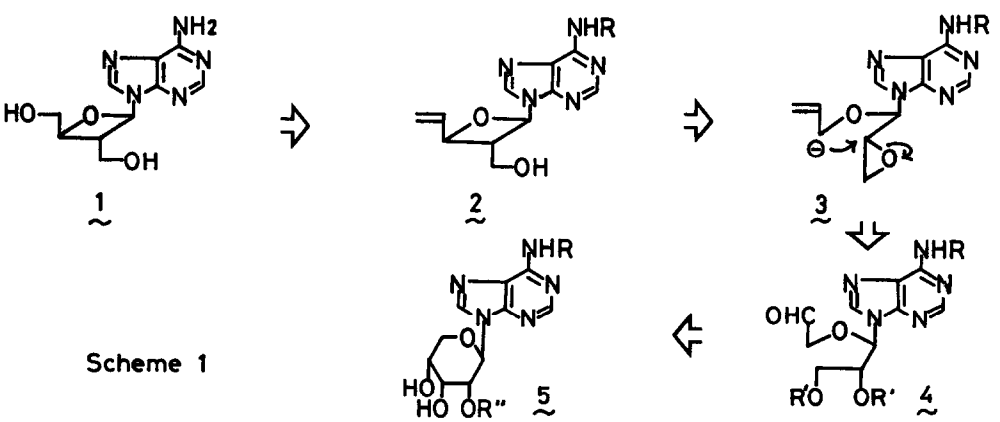
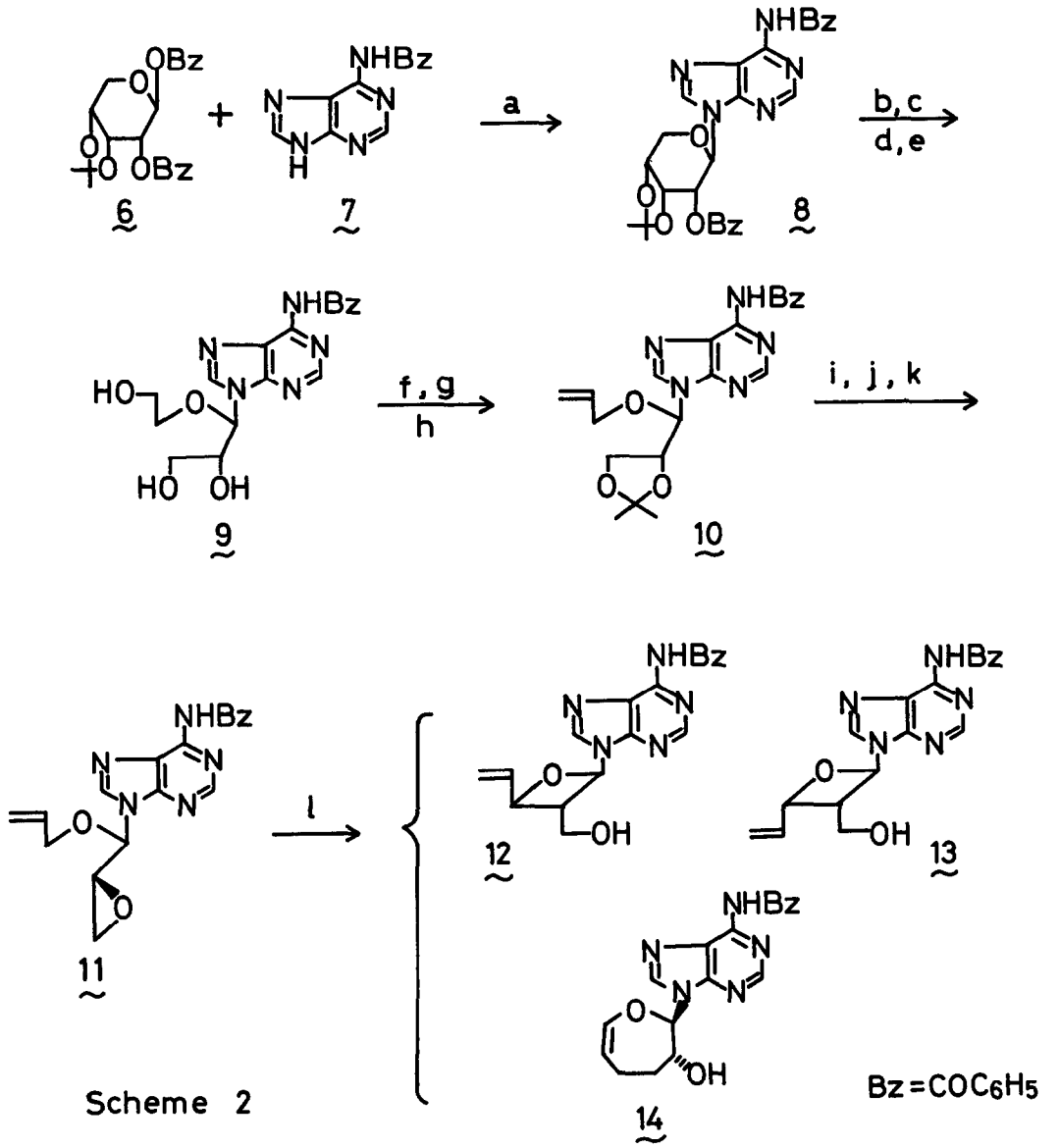
Abstract: The first synthesis of 9-(2-oxetanyl)adenine 12, a key intermediate for the synthesis of a novel nucleoside oxetanocin 1, has been achieved via cyclization between allyloxycarbanion and epoxy group.

Oxetanocin 1, a novel nucleoside isolated from the culture filtrate of Bacillus megaterium NK84-0218, shows antiviral, antitumor and antibacterial activities[2]. The structure 1 was conclusively determined by X-ray crystallographic analysis[3]. Oxetanocin is the first natural product which has an oxetanosyl-N-glycoside[1]. Due to its intriguing structure and potential usefulness, we have embarked on the total synthesis of this challenging target. In this communication we would like to report on the first synthesis of 9-(2-oxetanyl)adenine 12, a key intermediate for the synthesis of oxetanocin.

The synthetic strategy for oxetanocin is illustrated in Scheme 1. The success of this synthesis depends upon the cyclization of epoxy allylic ether 3 to yield a strained oxetanoside 2.



Scheme 1



Scheme 2

a. bis(p-nitrophenyl)phosphate (0.1eq), sulfolane, 100mmHg, 130°, 45min; 37%. b. THF-CF_3CO_2H-H_2O (5:4:2), 30°, 21hr; 58%. c. $NaIO_4$ (1.2eq), H_2O-MeOH, r.t., 4.5hr. d. $NaBH_4$ (1.0eq), EtOH, -20°, 1hr. e. NaOH (2.0eq)-MeOH, 0°, 20min (51%, 3 steps). f. acetone, 2,2-dimethoxypropane, TsOH (2eq), r.t., 1hr 40min; 85%. g. DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2; 76%. h. $Ph_3P{=}CH_2$ (3eq), HMPA (2eq), THF-DMSO, -20°, 30mim; 33%. i. THF-CF_3CO_2H-H_2O (5:4:2), r.t., 15.5hr; 93%. j. MsCl (1eq), Et_3N, DMF-CH_2Cl_2, 0°, 40min; 47%. k. K_2CO_3-MeOH, r.t., 25min; 54%. l. t-BuLi (5eq), THF, -78°, 20min.

The epoxy allylic ether 11 was synthesized as follows. Condensation of 1,2-di-O-benzoyl-3,4-O-isopropylidene-β-D-ribopyranose 6[4,5] with N(6)-benzoyladenine in the presence of a catalytic amount of bis(p-nitrophenyl)phosphate gave 8[6] in 37% yield. Removal of the isopropylidene protecting group with trifluoroacetic acid followed by oxidation with sodium periodate yielded the dialdehyde. Then, the aldehyde groups were reduced with sodium borohydride. Removal of the O-benzoyl protecting group under alkaline conditions provided the acyclic triol 9[6] in 30% overall yield from 8. The vicinal hydroxy groups of 9 were protected as acetonide (85%), and the remaining primary hydroxy group was oxidized to aldehyde (76%). Wittig reaction of the aldehyde gave the allylic ether 10[6] in 33% yield. Hydrolysis of acetonide of the compound 10 followed by mesylation of the resulting primary alcohol gave the monomesylate. It was converted into epoxide 11[6] in 24% overall yield from 10.

Finally, cyclization of 11 was carried out according to a similar procedure reported by Still, who synthesized vinyl oxetanes via allyloxycarbanion cyclization[7]. Treatment of the epoxy allylic ether 11 with t-butyllithium (THF, -78°, 20min) afforded vinyl oxetanes 12[6] (5%) and 13[6] (5%) (unoptimized) concomitant with the seven-membered ring product 14[6] (10%).

The vinyl oxetane structures 12 and 13 were assigned from their 400 MHz ^{1}H-NMR spectral data (Table 1).

Table 1. ^{1}H-NMR Data ($CDCl_3$) of 12 and 13

	Chemical Shifts (ppm)*								Coupling Constants (Hz)	
	2-H	3-H	4-H	olefin H			CH_2O		$J_{2,3}$	$J_{3,4}$
12	6.57	3.51	5.07	6.28	5.47	5.38	4.07	3.98	5.6	6.7
13	6.50	3.88	5.69	6.22	5.60	5.47	4.10	3.93	4.5	8.0

* Numbering as of oxetane ring.

In order to confirm these structures unequivocally, 12 was derived from oxetanocin 1 by 7 steps[8]. The vinyl oxetane 12 synthesized from 11 was completely identical with that derived from 1 by 400 MHz ^{1}H-NMR spectrometry.

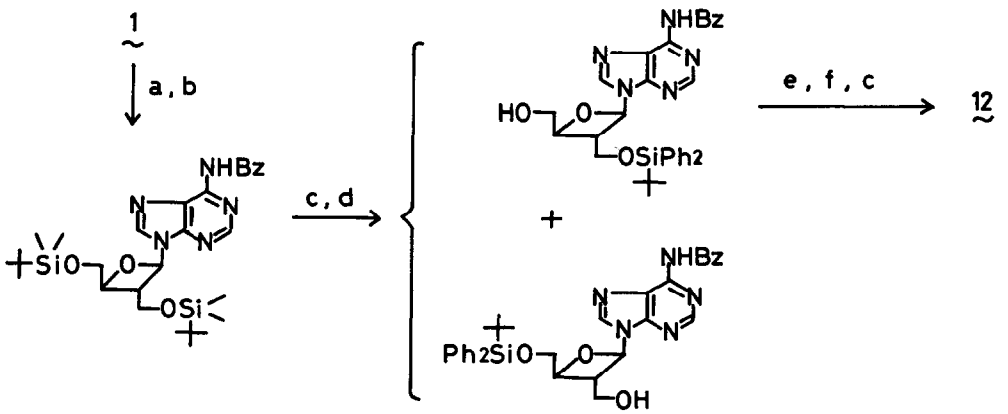
To the best of our knowledge, this is the first synthesis of oxetanosyl-N-glycoside.

Final conversion from 12 to 1 is now ongoing.

Acknowledgement. We are grateful to Professor Shosuke Yamamura, University of Keio, for his valuable advice. We also thank to Mr. Masaya Sato for NMR spectral measurement.

REFERENCES AND NOTES

1. We would like to propose "oxetanoside" for the glycoside having oxetane ring, like as furanoside for furan ring and pyranoside for pyran ring.
2. N. Shimada, S. Hasegawa, T. Harada, T. Tomisawa, A. Fujii and T. Takita, J. Antibiot., 39, 1623 (1986).
3. H. Nakamura, S. Hasegawa, N. Shimada, A. Fujii, T. Takita and Y. Iitaka, J. Antibiot., 39, 1629 (1986).
4. Compound 6 was synthesized from D-ribose in a similar manner to the preparation of the corresponding diacetate[5].
5. J, Gelas and D. Horton, Carbohyd. Res., 45, 181 (1975).
6. Satisfactory analytical data were obtained for all new compounds.
7. W. C. Still, Tetrahedron Lett., 2115 (1976).
8. The transformation of 1 to 12 was carried out as follows. The details will be reported elswhere.



a. t-Bu(Me)$_2$SiCl (2eq), pyridine. b. PhCOCl, pyridine. c. n-Bu$_4$NF, THF.
d. t-Bu(Ph)$_2$SiCl, pyridine. e. Swern Ox. f. Ph$_3$P=CH$_2$, THF-DMSO.

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