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A NEW METHOD FOR THE STEREOSELECTIVE SYNTHESIS OF NUCLEOSIDES FROM ACYCLIC EPOXY ALDEHYDES

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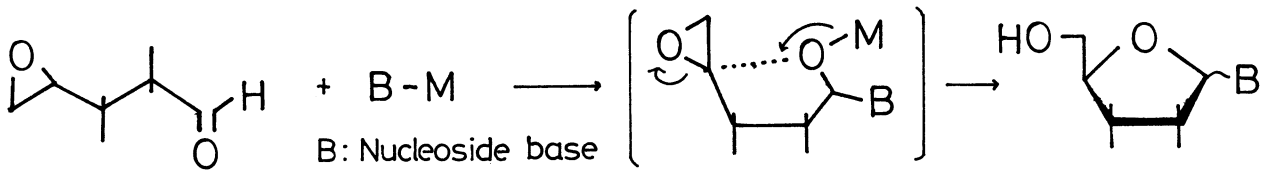
A new method for the stereoselective synthesis of nucleosides starting from acyclic epoxy aldehydes is developed. 2'-Deoxy-α-DL-ribonucleosides and α-L-lyxonucleosides are prepared by the reactions of the corresponding epoxy aldehydes with stannous salts of nucleoside bases utilizing stannous bromide as an activating reagent.

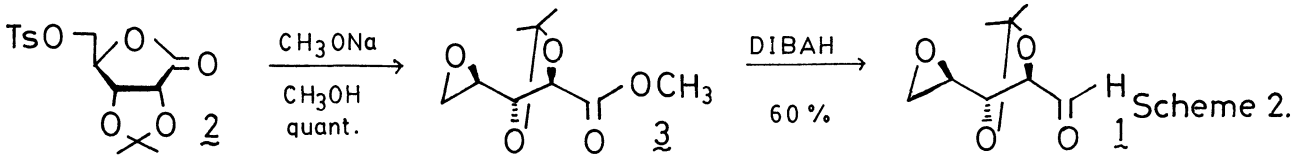
Various nucleosides are stereoselectively synthesized by the reaction between C-1 activated sugars (e.g. halosugars) and nucleoside bases.[1] However, in most cases, rather severe reaction conditions as high reaction temperature,[2] use of heavy metal compounds,[3] or use of strong Lewis acids[4] are required. Therefore, we have made an attempt to develop an alternative method in which the formation of nucleosides is carried out under milder conditions.

In this communication, we with to report a new method for the stereoselective synthesis of nucleosides from an epoxy aldehyde via an addition-cyclization process, which involves (1) initial addition of a metal salt of nucleoside base to a carbonyl part of the epoxy aldehyde and (2) a successive intramolecular cyclization of the adduct (Scheme 1).



Scheme 1.

As a model system for the examination of this approach, epoxy aldehyde 1 was chosen and prepared according to the following procedure (Scheme 2). Treatment of 2,3-O-isopropylidene-5-O-p-toluenesulfonyl-D-ribono-1,4-lactone (2)[5] with sodium methoxide in MeOH at 0 °C afforded an epoxy methyl ester 3[6] in quantitative yield. The epoxy methyl ester 3 was then reduced to the corresponding epoxy aldehyde 1[7] with diisobutylaluminum hydride (DIBAH) in toluene (60% yield).



Scheme 2.

Next, a nucleoside formation by the reaction of the epoxy aldehyde 1 with various metal salts of benzimidazole 4 was tried (Table 1, Entries 1-4). Of the metal salts screened, stannous salts were found to be the most effective to prevent the attack of benzimidazole to the epoxy ring (formation of 6) and to achieve the desired addition-cyclization process. Moreover, the increase of the yield of 5 is observed by an addition of a weak Lewis acid such as stannous chloride or stannous bromide (Entries 5,6).

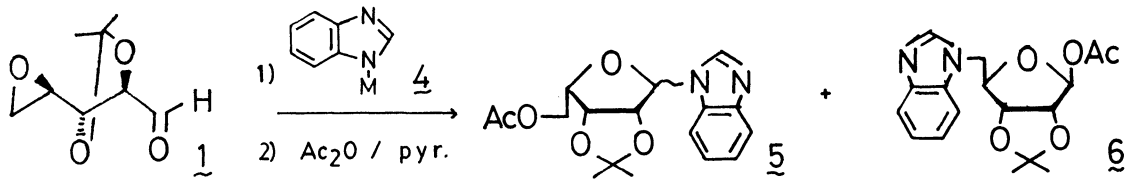
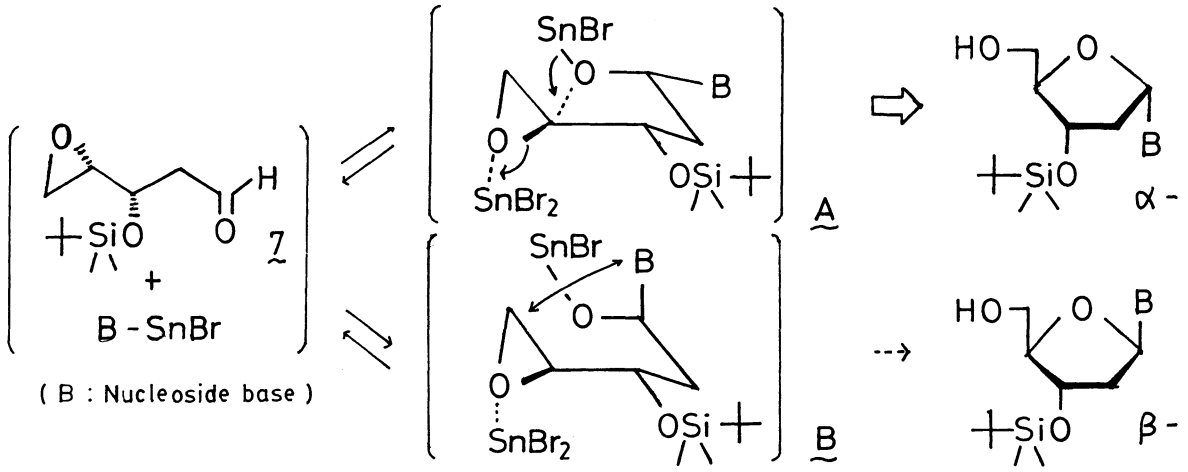


Table 1.

Entry	M of 4	Solvent	Yield of 5/%	(α/β)	Yield of 6/%
1	$-Al^iBu_2$	CH_2Cl_2	10	——	35
2	$-Ti(O^iPr)_3$	toluene-DMF	0	——	18
3	$-SnMe_3$	toluene-DMF	45	(80/20)	0
4	-SnCl	THF	40	(80/20)	0
5	$-SnCl+SnCl_2$	THF	54	(80/20)	0
6	$-SnBr+SnBr_2$	THF	60	(80/20)	0

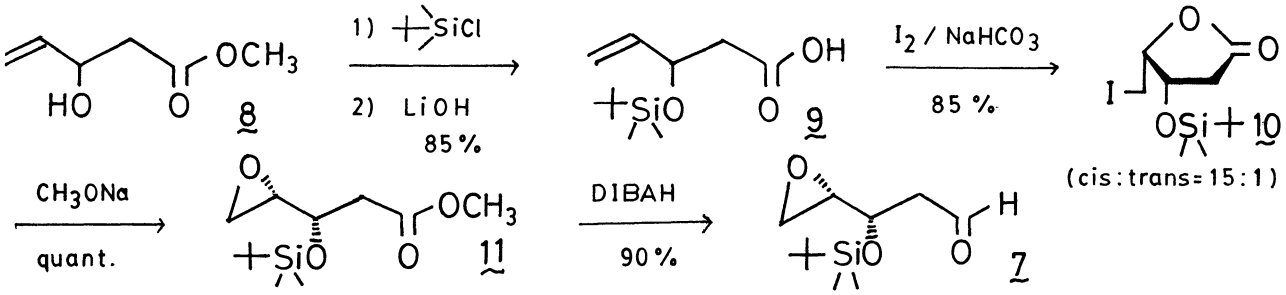
These results indicate that the application of this addition-cyclization process to an epoxy aldehyde 7 might afford 2'-deoxy-α-ribonucleosides selectively based on the following assumption (Scheme 3).



Scheme 3.

Of the two adducts ([A] and [B]) existing in equilibrium with the starting materials, the epoxy aldehyde 7 and a nucleoside base, the cyclization to form the α-anomer from [A] should proceed preferentially because the other isomer causes

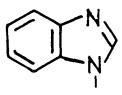
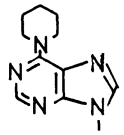
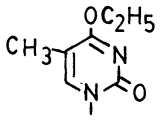
much steric interaction in the transition state of cyclization.



Scheme 4.

The starting material, the epoxy aldehyde 7, was prepared in high yield from the readily available olefinic ester 8 according to the route outlined in Scheme 4.[8] The epoxy aldehyde 7 thus prepared was treated with a variety of stannous salts of nucleoside bases in the presence of stannous bromide. And the results are summarized in Table 2. Typical procedure of the reaction is as follows: A hexane (0.65 ml) solution of BuLi (1 mmol) and THF (4 ml) solution of $SnBr_2$ (557 mg, 2 mmole) were added successively to a THF (1.5 ml) solution of 2-hydroxypyridine (95 mg, 1 mmol) under an argon atmosphere at 0 °C. To this mixture was added a THF (1.5 ml) solution of 7 (115 mg, 0.5 mmol) at -15 °C. The resulting mixture was stirred overnight to attain to room temperature and was quenched with 5% Na_2CO_3 solution (5 ml). The resulting precipitate was filtered off through a Celite pad, and the filtrate was extracted with $CHCl_3$. The organic layer was dried over anhydrous Na_2SO_4. After evaporation of the extract, the residue was purified by silica gel thin layer chromatography to afford 1-[3-O-t-butyldimethylsilyl-2-deoxy-α-DL-ribofuranosyl]-2-pyridone (128 mg) and the β-anomer (5 mg) (79% total yield, α/β=96/4).[9]

Table 2.

Nucleoside base (B)	Yield of nucleosides/%	α/β ratio
	81	80/20
	95	64/36
	79	96/4
	91	>95/5

As shown in Table 2, it is noted that 2'-deoxy-α-ribonucleosides are prepared in good yields with expected high α-selectivity.[10] As it is still difficult to obtain 2'-deoxy-ribonucleosides in a stereoselective manner from C-1 activated sugars because of the absence of a neighboring group at C-2,[11] the present methodology based on the addition-cyclization process[12] will give a new and effective answer for the problem. Further work in this area is currently underway in our laboratory.

References

1) R. T. Walker, "Comprehensive Organic Chemistry," ed by E. Haslam, Pergamon, Oxford (1979), Vol. 5, p.53.
2) T. Sato, T. Shimadate, and Y. Ishido, Nippon Kagaku Zasshi, 81, 1440 (1960).
3) N. Yamaoka, K. Aso, and K. Matsuda, J. Org. Chem., 30, 149 (1965).
4) H. Vorbrüggen, K. Krolikiewcz, and B. Bennua, Chem. Ber., 114, 1234 (1981).
5) L. Hough, J. K. N. Jones, and D. L. Mitchell, Can. J. Chem., 36, 1720 (1958).
6) 6: ^{1}H-NMR ($CDCl_3$) δ 1.33 (3H, s) 1.60 (3H, s) 2.50-3.10 (3H, m) 3.73 (3H, s) 4.05 (1H, t, J = 7 Hz) 4.73 (1H, d, J = 7 Hz); IR 1755 cm^{-1}.
7) 1: ^{1}H-NMR ($CDCl_3$) δ 1.40 (3H, s) 1.57 (3H, s) 2.57-3.17 (3H, m) 4.15 (1H, dd, J = 8 Hz, 6 Hz) 4.50 (1H, dd, J = 8 Hz, 2 Hz) 9.73 (1H, d, J = 2 Hz); IR 1730 cm^{-1}.
8) 10 was prepared according to the reported method; A. R. Chamberlin, M. Dezube, P. Dussault, and M. C. McMills, J. Am. Chem. Soc., 105, 5819 (1983).
7: ^{1}H-NMR ($CDCl_3$) δ 0.07 (3H, s) 0.13 (3H, s) 0.87 (9H, s) 2.50-3.10 (5H, m) 3.88 (1H, q, J = 6 Hz) 9.67 (1H, t, J = 2 Hz); IR 1730 cm^{-1}.
9) U. Séquin and C. Tamm, Helv. Chim. Acta, 55, 1196 (1972).
10) The configuration of C-1' was determined by NMR spectroscopy; M. J. Robins and R. K. Robins, J. Am. Chem. Soc., 87, 4934 (1965); Ref. 9.
11) W. Wierenga and H. I. Skulnick, Carbohydr. Res., 90, 41 (1981).
12) In the present method, the possibility of the cyclization via the initial opening of the epoxy ring followed by the formation of the oxocarbenium ion intermediate may not be took into account, because the oxocarbenium ion intermediates of 2-deoxy-ribose derivatives usually give a mixture of almost equal amount of α- and β-nucleosides; U. Niedballa and H. Vorbrüggen, J. Org. Chem., 39, 3654 (1974).

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