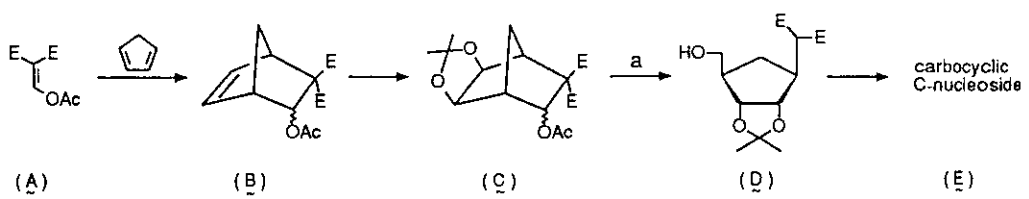
SYNTHESIS OF NUCLEOSIDES AND THEIR RELATED COMPOUNDS. 15[1] DIMETHYL rel-(1S,2S,3R,4R)-2-(2,3-EPOXY-4-HYDROXYMETHYLCYCLOPENT-1-YL)MALONATE AS A NOVEL BUILDING BLOCK FOR CARBOCYCLIC ARABINOSYL NUCLEOSIDES[2]

Nobuya Katagiri,* Masahiro Nomura, and Chikara Kaneko*
Pharmaceutical Institute, Tohoku University, Aobayama, Sendai 980, Japan

Abstract---Dimethyl 3-acetoxy-5,6-exo-epoxybicyclo[2.2.1]heptane-2,2-dicarboxylate (1) has been synthesized by epoxidation of the Diels-Alder adduct of dimethyl acetoxymethylenemalonate with cyclopentadiene and on reductive retrograde aldol reaction afforded dimethyl rel-(1S,2S,3R,4R)-2-(2,3-epoxy-4-hydroxymethylcyclopent-1-yl)malonate (2), which serves as the direct precursor of carbocyclic arabinosyl nucleosides. Synthesis of the related bicyclo-epoxides and their reactions are also described.

Previously, we have established a facile synthetic method of carbocyclic C-nucleosides (**E**) via the adduct (**B**) obtained by Diels-Alder reaction of dimethyl acetoxymethylenemalonate (**A**) with cyclopentadiene.[3] The adduct (**B**) was then converted to the acetonide (**C**), whose reductive retrograde aldol (RRA) C-C bond fission (a) gave the versatile synthetic building block (**D**) with complete stereoselection (Chart 1), as exemplified by its successful conversion to carbocyclic C-nucleosides by the manipulation of the malonate function into heterocycles.[3,4]



(A) (B) (C) (D) (E)

Chart 1. E=CO_2Me; a (RRA reaction): $NaBH_4$, K_2CO_3/MeOH

Recently, we have found that the use of di-l-menthyl acetoxymethylenemalonate (**A**: E=CO_2-l-menthyl) in the titanium tetrachloride catalyzed Diels-Alder reaction affords the corresponding adduct (chiral **B**) in high diastereomeric excess (d.e.≥90%) and hence, accomplished an efficient enantioselective synthesis of carbocyclic β-D-ribofuranosylmalonate (**D**).[5] In order to extend this methodology to stereoselective synthesis of carbocyclic C-nucleosides substituted unequally at the 2'- and 3'-positions, we have interested in synthesizing the epoxide of (**B**)

and examining its RRA reaction.

In this paper, we wish to report 1) the synthesis of the epoxide from the Diels-Alder adduct of dimethyl acetoxymethylenemalonate with cyclopentadiene and its RRA reaction, which have provided an novel synthetic route to carbocyclic arabinosyl nucleosides and 2) the synthesis of the epoxide of corresponding Diels-Alder adduct of methyl 3-acetoxy-2-cyanoacrylate and its RRA reaction, which have afforded methyl rel-(1S,2S,3R,5R)-6-cyano-2-hydroxy-3-hydroxymethylbicyclo-[3.1.0]hexane-6-carboxylate, expected as the synthon for carbocyclic 2'-deoxy-C-nucleosides.

The epoxide (1) was synthesized from the adduct obtained by $TiCl_4$ mediated Diels-Alder reaction of dimethyl acetoxymethylenemalonate with cyclopentadiene.[3,5] Thus, when the adduct (a mixture of endo- and exo-isomers, 2:3) was allowed to react with m-chloroperbenzoic acid (m-CPBA) in dichloromethane at room temperature for 1 day, the desired epoxide (1) was obtained in 77% yield, again as a mixture of two isomers. Since the approach of the oxidizing reagent is surely from the less hindered exo face, two isomers are the configurational isomers of the acetoxyl groups. Under the above conditions, the ratio of the endo- and exo-isomers was 1:1, showing that the formation of endo-(1) predominated over that of exo-(1). Since a single product (2) was expected irrespective of stereochemistry of the acetoxyl group, the epoxide (1) was subjected to RRA reaction without separation of the endo- and exo-isomers. The results are summarized in Table I. As expected, when the epoxide (1) was subjected to RRA reaction at -15 °C, the simple C-C bond fission product (2) was obtained in nearly quantitative yield. However, if the same reaction was carried out at room temperature, the lactone (3) was obtained in 53% yield together with 32% of (2). Since none of γ-lactone was obtained when (2) was treated with potassium carbonate in methanol at room temperature, it is evident that lactonization giving rise to (3) had occurred concertedly with the retrograde aldol C-C bond fission [c.f. formula (F)].

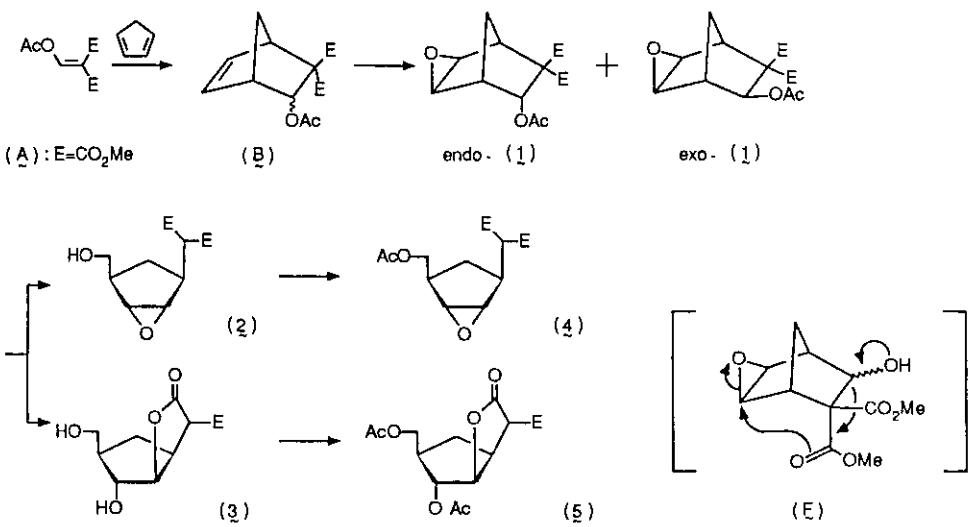


Chart 2

Table I. RRA Reaction of Epoxide (1)

Run	Solv.[a]	Base(equiv.)[b]	$NaBH_4$(equiv.)	Temp.(°C)	Time (h)	Yield(%) (2)	(3)
1	M	K(5)	5	r.t.	1	32	53
2	M-D(1:1)	K(3)	3	-15(r.t.)	1(1)	95	1
3	M	C(2)	2	0	1.5	84	5
4	M-D(1:1)	C(2)	5	r.t.	1.5	54	28

a: M=MeOH, D=dioxane. b: K=K_2CO_3, C=Cs_2CO_3.

The structures of both products (2) and (3) were determined by both nmr spectra[6] of their acetates (4) and (5) and their chemical reactions (vide infra). By treatment with p-toluenesulfonic acid in chloroform followed by acetylation (Ac_2O/pyridine), (2) was converted to (5) in 20% yield. $NaBH_4$ reduction of (5) afforded the alcohol (6) in 87% yield, which was identified as the tetra-acetate (7). The silylation of (3) with 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane (TIPDSC) in DMF in the presence of imidazole afforded the silylated product (8). When the epoxide (2) was treated with formamidine under basic conditions (NaOMe/MeOH), the cyclonucleoside (**11a**) was obtained together with several other products.[7] Since its separation from the other products was difficult at this stage, the whole products were converted to the corresponding acetates (Ac_2O/pyridine). Separation of the products by column chromatography gave (**9a**) in 30% yield as the sole isolable product. The use of acetoamidine led to the corresponding cyclonucleoside (**9b**) together with a small amount of the arabinosyl nucleoside (**10b**).

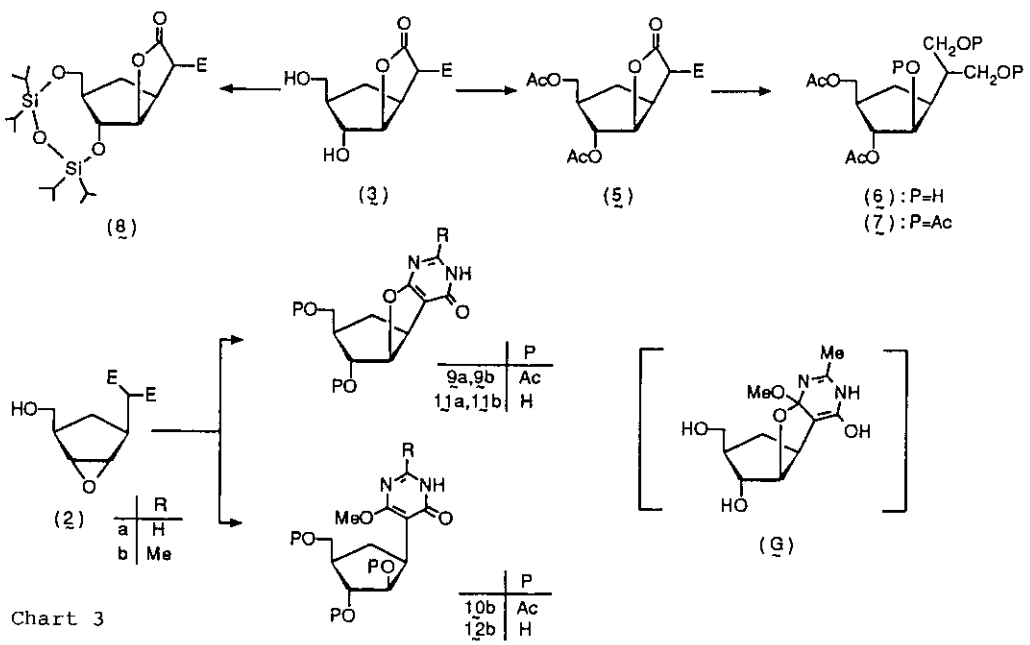
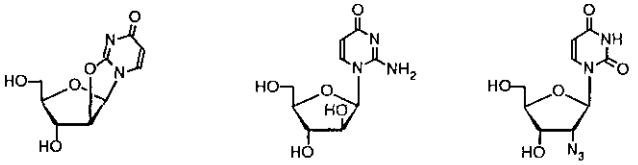


Chart 3

The fact that cyclonucleoside (**H**) derived from uridine was known to give either arabinoside (**I**) by ammonia[8] or 2'-azidonucleoside (**J**) by sodium azide[9] not only *indicates that (9) and (11) are useful synthons for the carbocyclic arabinosyl* C-nucleosides, but also suggests the intermediacy of (**G**) in the formation of (**10b**) from (**9b**). By saponification of these acetates (**9** and **10**) with ammonia in methanol, the corresponding alcohols (**11a,b**) and (**12b**) were obtained in pure forms, respectively.



(H) (I) (J)

Finally, the Diels-Alder adduct[4] (**13**) obtained from the cyanoacrylate and cyclopentadiene was epoxidized in the same manner. Though the yield of the epoxide (**14**) was high (ca. 80%), the reaction took longer (2 day) as compared with the case of the epoxidation of (**1**).

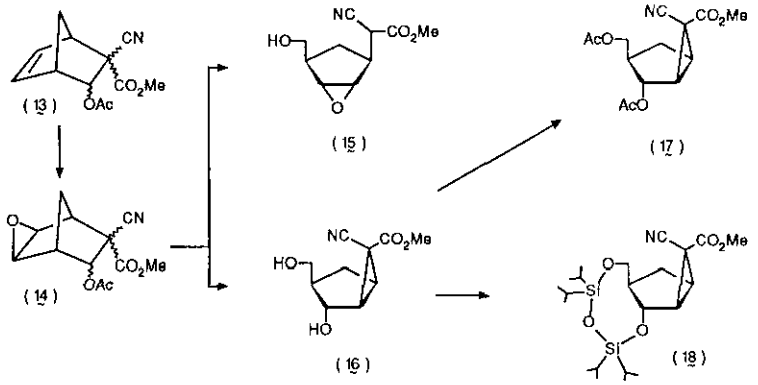
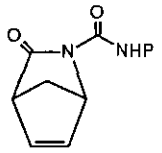
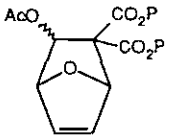


Chart 4

When the epoxide (**14**) (again as a mixture of two isomers) was subjected to the RRA reaction, two products (**15**) and (**16**) were obtained whose ratio depended upon the conditions employed. Thus, at -15 °C the simple C-C bond fission product (**15**) was obtained as the major product, while at room temperature the cyclopropane (**16**) as the sole one. *The structure of (16) was verified from nmr spectrum of the corresponding* diacetate (**17**) and by its silylation to the expected product (**18**). Knowing that electrophilic cyclopropanes suffer ready C-C bond cleavage either by appropriate reducing reagent or nucleophile,[10] (**16**) seems to be a nice precursor for the carbocyclic 2'-deoxy- and 2'(cis to the C_3'-OH group)-substituted nucleosides. In summary, we have elaborated (**1**) as the new synthon for carbocyclic arabinosyl and/or the corresponding cyclonucleosides, as exemplified by the synthesis of (**12**) and (**11**). Since the highly selective syntheses of (**K**)[11] as well as (**L**) (racemic[12] and chiral[13]) have already been attained, we are currently investigating the extension of this methodology either to the synthesis of the carbocyclic arabinosyl nucleosides or to the enantiomerically pure arabinosyl C-nucleosides.



(K) : P = H or R



(L) : P = l-menthyl

REFERENCES AND NOTES

1. Part 14: N. Katagiri, H. Watanabe, and C. Kaneko, Chem. Pharm. Bull., in press.
2. This paper also forms part 44 of "Cycloadditions in Syntheses." Part 43: M. Sato, K. Takayama, T. Furuya, N. Inukai, and C. Kaneko, Chem. Pharm. Bull., in press.
3. N. Katagiri, T. Haneda, and C. Kaneko, Chem. Pharm. Bull., 1986, **34**, 4875 ; N. Katagiri, T. Haneda, S. Tomizawa, and C. Kaneko, Nucleic Acids Res. Symposium Ser., 1986, **17**, 1 .
4. N. Katagiri, M. Tomura, T. Haneda, and C. Kaneko, J. Chem. Soc., Chem. Commun., 1987, 1422.
5. N. Katagiri, T. Haneda, N. Watanabe, E. Hayasaka, and C. Kaneko, Chem. Pharm. Bull., 1988, **36**, 3867 ; N. Katagiri, T. Haneda, E. Hayasaka, N. Watanabe, and C. Kaneko, J. Org. Chem., 1988, **53**, 226 .
6. All new compounds were identified either by elemental analysis or by high-resolution mass spectrum and the structures were supported by acceptable spectral data.
7. Optimization for the cyclonucleoside formation has not yet been done, and isolation as well as structure determination of other products are in progress.
8. D. M. Brown, D. B. Parihar, A. R. Todd, and S. Varadarajan, J. Chem. Soc., 1958, 3028.
9. J. P. H. Verheyden, D. Wagner, and J. G. Moffatt, J. Org. Chem., 1971, **36**, 250.
10. Cyclopropane derivatives activated by two electron-withdrawing substituents such as COOR, COR, and CN at geminal position were found to be useful intermediates in organic synthesis: S. J. Danishefsky, Acc. Chem. Res., 1979, **12**, 66.
11. S. Daluge and R. Vince, J. Org. Chem., 1978, **43**, 2311; J. R. Malpass and N. J. Tweddle, J. Chem. Soc., Perkin Trans. I, 1977, 874; N. Katagiri, M. Muto, and C. Kaneko, Tetrahedron Lett., 1989, **30**, 1645.
12. N. Katagiri, H. Akatsuka, T. Haneda, C. Kaneko, and A. Sera, J. Org. Chem., 1988, **53**, 5464. See also, A. Sera, M. Ohara, T. Kubo, K. Itoh, H. Yamada, Y. Mikita, C. Kaneko, and N. Katagiri, ibid., 1988, **53**, 5460.
13. N. Katagiri, H. Akatsuka, C. Kaneko, and A. Sera, Tetrahedron Lett., 1988, **29**, 5397.

Received, 8th June, 1989