

SYNTHESIS OF NUCLEOSIDES AND THEIR RELATED COMPOUNDS. 15¹
DIMETHYL *rel*-(1*S*,2*S*,3*R*,4*R*)-2-(2,3-EPOXY-4-HYDROXYMETHYLCYCLO-
PENT-1-YL)MALONATE AS A NOVEL BUILDING BLOCK FOR CARBOCYCLIC
ARABINOSYL NUCLEOSIDES²

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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 acetoxy methylenemalonate with cyclopentadiene and on reductive retrograde aldol reaction afforded dimethyl *rel*-(1*S*,2*S*,3*R*,4*R*)-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 acetoxy methylenemalonate (**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}

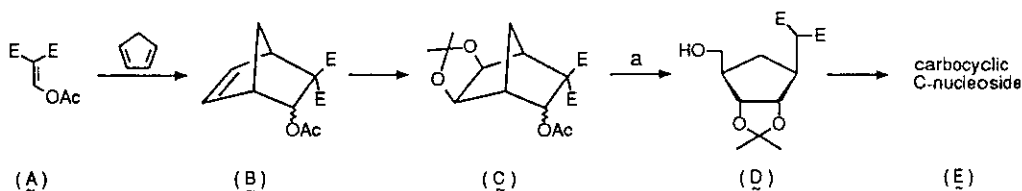


Chart 1. E=CO₂Me; a (RRA reaction): NaBH₄, K₂CO₃/MeOH

Recently, we have found that the use of di-1-menthyl acetoxy methylenemalonate (**A**: E=CO₂-1-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 acetoxy methylenemalonate with cyclopentadiene and its RRA reaction, which have provided a 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-(1*S*,2*S*,3*R*,5*R*)-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 acetoxy methylenemalonate 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 acetoxy 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 acetoxy 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)].

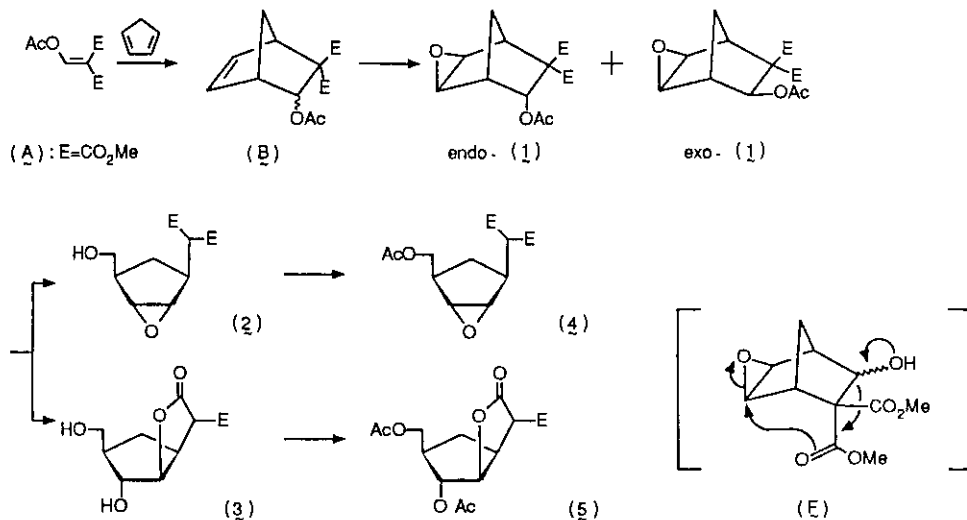


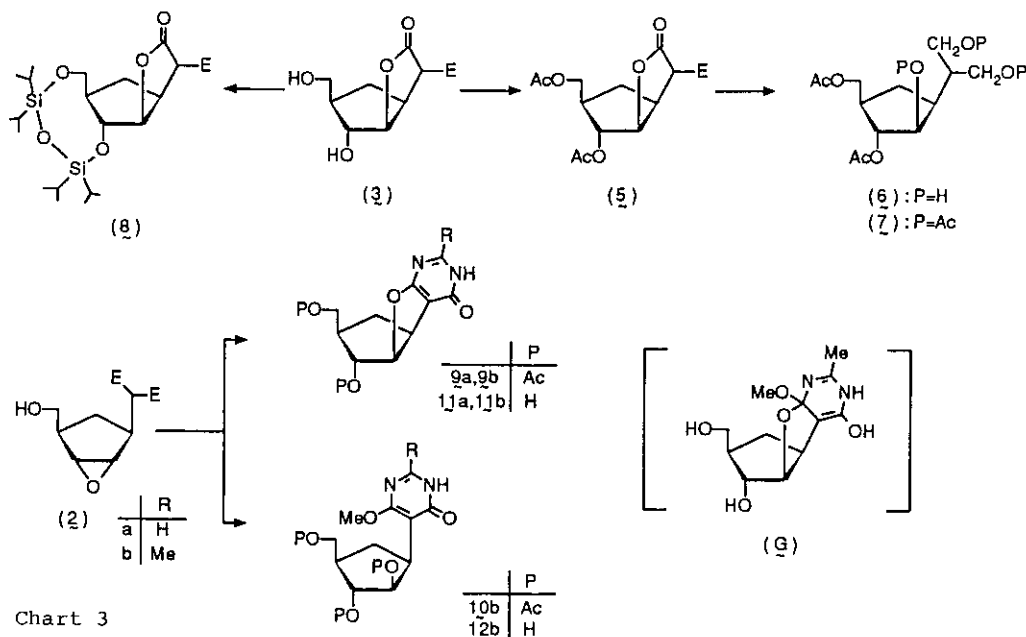
Chart 2

Table I. RRA Reaction of Epoxide (1)

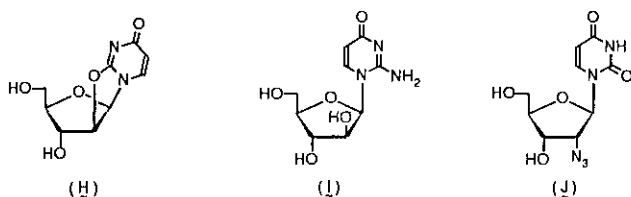
Run	Solv. ^a	Base(equiv.) ^b	NaBH ₄ (equiv.)	Temp.(°C)	Time (h)	Yield(%)	
						(2)	(3)
1	M	K(5)	5	r.t.	1	32	53
2	M-D(1:1)	K(3)	3	-15(r.t.)	1(1)	95	1
3	M	C(2)	2	0	1.5	84	5
4	M-D(1:1)	C(2)	5	r.t.	1.5	54	28

a: M=MeOH, D=dioxane. b: K=K₂CO₃, C=Cs₂CO₃.

The structures of both products (2) and (3) were determined by both nmr spectra⁶ of their acetates (4) and (5) and their chemical reactions (vide infra). By treatment with p-toluenesulfonic acid in chloroform followed by acetylation (Ac₂O/pyridine), (2) was converted to (5) in 20% yield. NaBH₄ 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-tetraisopropylidisiloxane (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 (Ac₂O/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).



The fact that cyclonucleoside (H) derived from uridine was known to give either arabinoside (I) by ammonia⁸ or 2'-azidonucleoside (J) by sodium azide⁹ 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.



Finally, the Diels-Alder adduct⁴ (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).

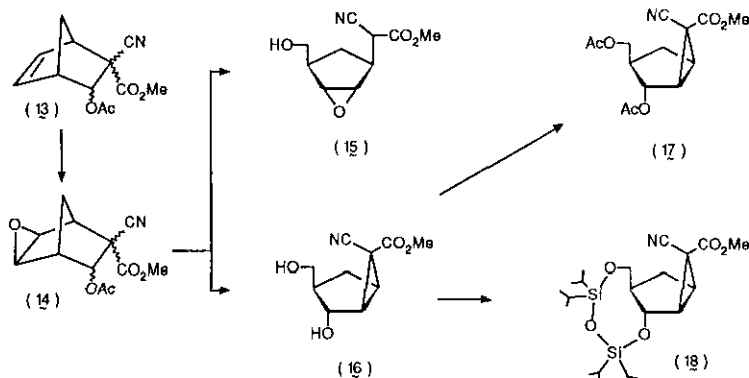
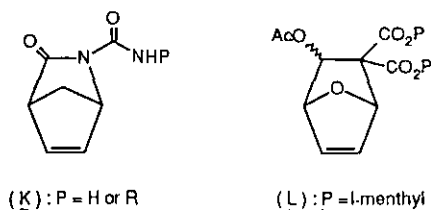


Chart 4

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 C₃-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) (racemic¹² and chiral¹³) 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.



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