Communications to the Editor

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FACILE SYNTHESIS OF THE CARBOCYCLIC ANALOGUE OF β-RIBOFURANOSYL-MALONATE, NEW SYNTHON FOR CARBOCYCLIC C-NUCLEOSIDE FORMATION BY RETROGRADE ALDOL C-C BOND FISSION[1)]

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A new carbocyclic C-nucleoside precursor, the carbocyclic analogue of β-ribofuranosylmalonate, has been synthesized through Diels-Alder addition of cyclopentadiene to dimethyl acetoxymethylene-malonate, followed by retrograde C-C bond fission under reductive conditions.

KEYWORDS —— carbocyclic C-nucleoside; carbocyclic β-ribofurano-sylmalonate; Diels-Alder adduct; cyclopentadiene; dimethyl acetoxy-methylenemalonate; retrograde aldol reaction; sodium borohydride

In the synthesis of C-nucleosides starting from non-carbohydrate precursors, most methods have utilized [4+2] or [4+3] cycloadducts (A or B) between furan and an appropriate dienophile (either 3-substituted acrylate or oxyallyl species) as intermediates.[2)] From these bicycles to β-ribofuranosylacetates (G), the C-C bond originating from the dienophile must be cleaved by oxidation reactions either directly (D→F)[3)] or after regeneration of a double bond (E→G).[4)] In these methods, the carbon-carbon double bond in A and B (formed in the cycloaddition step) must be protected as a diol (C and D) before the above oxidation reactions are carried out.

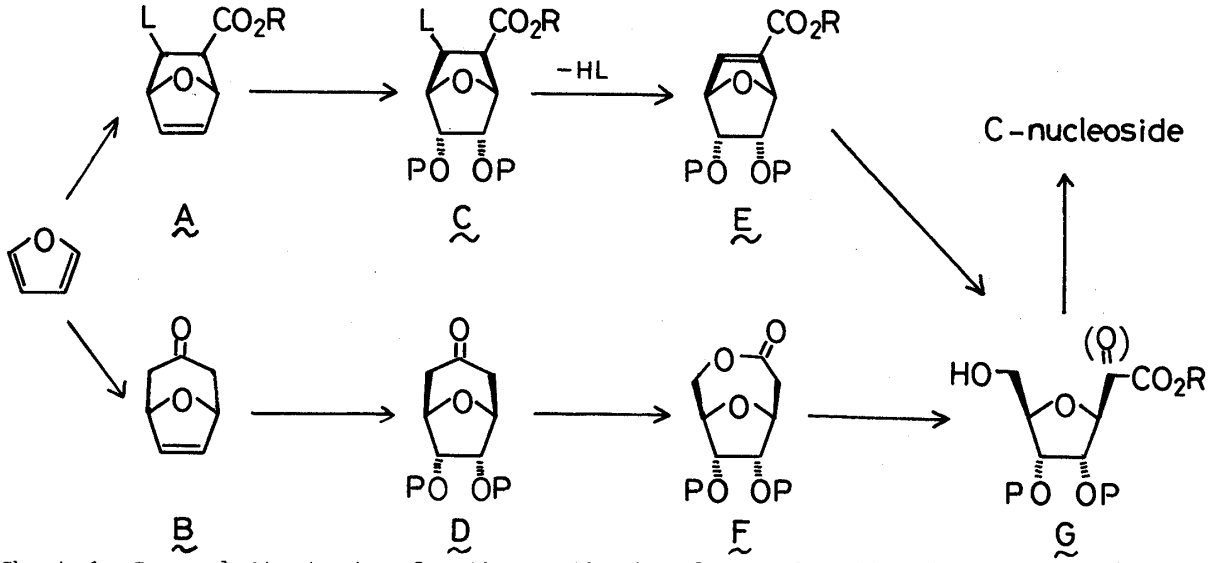

Chart 1. General Strategies for the Synthesis of C-Nucleosides from Furan (L and P Designate Appropriate Leaving and Protecting Groups, Respectively)

We now report a novel synthesis of carbocyclic analogue (1) of dimethyl β-ribofuranosylmalonate[5] by retrograde aldol C-C bond fission under reductive conditions which defines a simple and new route to introduce all required functions into cyclopentadiene in a stereospecific manner without using any oxidation reaction.[6]

In our synthesis, which obeys the general strategy for the construction of A-type compound by using Diels-Alder addition of cyclopentadiene to acrylate derivatives, we chose dimethyl acetoxymethylenemalonate (2) as a dienophile. This is because not only would 2 be a suitable dienophile due to its high electron deficiency, but also the adduct thus formed cleaves the C-C bond by retrograde aldol reaction. 2 (bp 92-95°C/2 mmHg) was synthesized from readily available dimethyl methoxymethylenemalonate (3)[7] by basic hydrolysis followed by acetylation. The sequential reactions were the same as the synthesis of corresponding diethyl ester reported recently by Wolff et al.[8] Cycloaddition of cyclopentadiene to 2 proceeded smoothly (80°C, PhH, 72 h) to give the [4+2] adduct (4)[9] as a chromatographically separable mixture of endo and exo isomers (ca. 1:3 ratio) in 80% yield [4_{endo}: mp 92-94°C (ether-hexane); IR ($CHCl_3$) 1735 cm^{-1}; ^{1}H-NMR ($CDCl_3$)δ : 6.25 (1H, d, J=4 Hz, >CHOAc), and 4_{exo}: mp 113-114°C (ether-hexane); IR ($CHCl_3$) 1735 cm^{-1}; ^{1}H-NMR ($CDCl_3$)δ : 5.62 (1H, d, J=2 Hz,

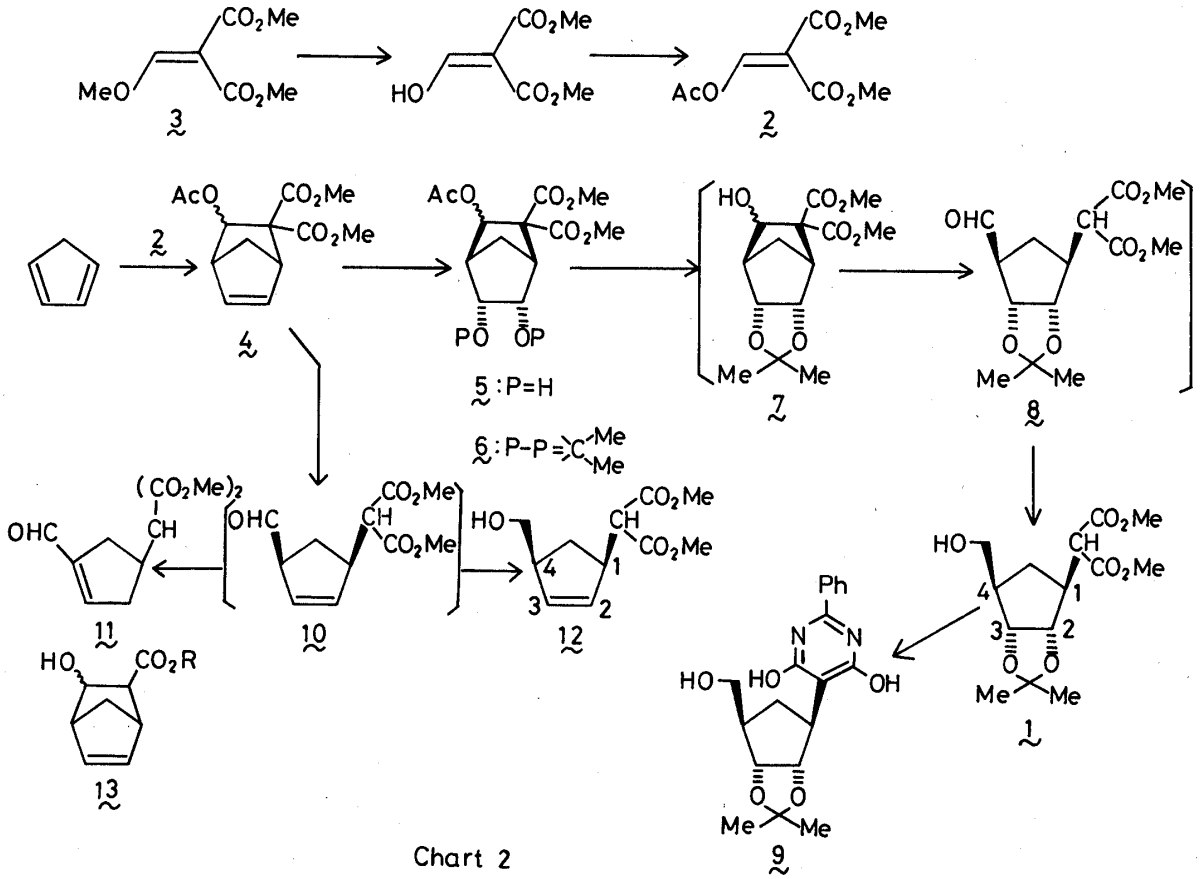

Chart 2

>CHOAc)].[10] The adduct (4) was hydroxylated (OsO_4, 60% aqueous 4-methylmorpholine N-oxide, acetone, 2 h, room temperature) to give quantitatively the exo diol (5) and the diol was protected as its acetonide (6) (acetone, $Me_2C(OMe)_2$, TsOH, 2 h, room temperature, quantitative yield). When 6 was treated with methanol containing K_2CO_3 and $NaBH_4$ for 1 h at room temperature, the desired compound [1: IR ($CHCl_3$) 3500, 1750 (sh), 1730 cm^{-1}; ^{1}H-NMR ($CDCl_3$)δ : 1.30 (3H, s, isopropylidene-Me), 1.50 (3H, s, isopropylidene-Me), 3.50 (1H, d, J=8 Hz, -CH($CO_2Me)_2$), 4.3-4.6 (2H, m, -CH-O x 2)] was obtained in quantitative yield. Obviously, the alcohol (7) primarily formed undergoes a facile C-C bond fission (retrograde aldol reaction) and the aldehyde (8) thus formed is reduced to the final product (1). As an example illustrating the construction of a heterocyclic subunit from this product, 1 was treated with benzamidine in the presence of sodium methoxide in methanol at 40°C for 48 h to give a pyrimidine carbocyclic C-nucleoside [9: mp 248-250°C ($CHCl_3$)].[11,12]

Facile C-C bond scission by retrograde aldol reaction also occurred, when the adduct (4) was directly subjected to basic hydrolysis. Thus, treatment of 4 in methanol containing K_2CO_3 at room temperature (1 h) afforded the aldehyde [11: IR ($CHCl_3$) 1750, 1730, 1675 cm^{-1}; ^{1}H-NMR ($CDCl_3$)δ : 2.0-3.7 (6H, m), 3.72 (6H, s, CO_2Me x 2), 6.70 (1H, m, =C-H), 9.70 (1H, s, -CHO)]. The same reaction of 4 in the presence of sodium borohydride gave the alcohol [12: IR ($CHCl_3$) 3500, 1750 (sh), 1730 cm^{-1}; ^{1}H-NMR ($CDCl_3$)δ : 3.56 (2H, d, J=5 Hz, 5-H), 3.75 (6H, s, CO_2Me x 2), 5.74 (2H, s, 2- and 3-H)] in quantitative yield. These experiments tell clearly that the configuration of C-4 in both 1 and 12 is retained under these reductive conditions ($NaBH_4/K_2CO_3$/methanol).

It was revealed that such retrograde aldol reaction did not occur in the adduct (13).[14] Therefore, the presence of two electron-withdrawing groups as neighbors of the hydroxyl group seems to be essential for this retrograde aldol reaction. The present method seems not only to provide a new route for the synthesis of C-nucleoside precursors but also to be applicable for the introduction of formyl and acetic acid appendages at the 1- and 4-positions of a 1,3-diene system. Further work is now in progress to extend our scheme to the synthesis of C-nucleosides by treating furan with 2 and its analogues.

REFERENCES AND NOTES

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9) All new compounds herein reported were supported either by elemental analyses or by high-resolution mass spectra and showed acceptable spectral data.

10) 4_{endo}: ^{1}H-NMR ($CDCl_3$)δ : 1.50 (2H, m), 1.93 (3H, s), 3.18 (1H, br s), 3.33 (1H, br s), 3.65 (3H, s), 3.77 (3H, s), 6.08 (1H, dd, J=3, 6 Hz), 6.65 (1H, dd, J=3, 6 Hz). 4_{exo}: ^{1}H-NMR ($CDCl_3$)δ : 1.7-2.4 (2H, m), 2.02 (3H, s), 2.92 (1H, br s), 3.40 (1H, br s), 3.70 (3H, s), 3.75 (3H, s), 6.0-6.4 (2H, m).

11) In the ^{13}C-NMR spectrum ($CDCl_3$-CD_3OD) of 9, there are signals due to two methyl carbons of the isopropylidene group at δ 25.48 and 27.83, indicating the β-configuration at the 1-position.[5b,13]

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