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Diels-Alder Reaction of Dimethyl Acetoxymethylenemalonate with 3,4-Dialkoxyfurans and the Utility of Its Adducts in the Stereospecific Synthesis of Lyxopyranosyl C-Glycosides

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Dimethyl lyxopyranosylmalonates were synthesized in stereospecific manner from the adducts obtained from Diels-Alder reaction of 3,4-dialkoxyfurans and dimethyl acetoxymethylenemalonate, through retrograde aldol C-C bond fission under reductive condition as a key step.

In recent years a considerable number of highly modified C-glycosides have been isolated from natural sources. The interesting biological properties of these substances have made them interesting targets for chemical synthesis. The lyxopyranosyl C-glycoside constitutes the skeleton of pseudomonic acids which are a unique family of potent and promising antibiotics.[1] Numerous approaches to these materials from carbohydrate[2] or noncarbohydrate precursors[3] have been published.

In this communication, we would like to report a stereospecific synthesis of dimethyl lyxopyranosylmalonates from Diels-Alder adducts of 3,4-dialkoxyfurans with dimethyl acetoxymethylenemalonate through retrograde aldol C-C bond fission under reductive condition as a key step.

The 3,4-dialkoxyfurans 2 recently synthesized by Eugster et al.[4] are considerably active dienes in Diels-Alder reaction, compared with furan itself. However, only a few literatures are available concerning their Diels-Alder reaction[5] or the utility of their adducts in organic synthesis.

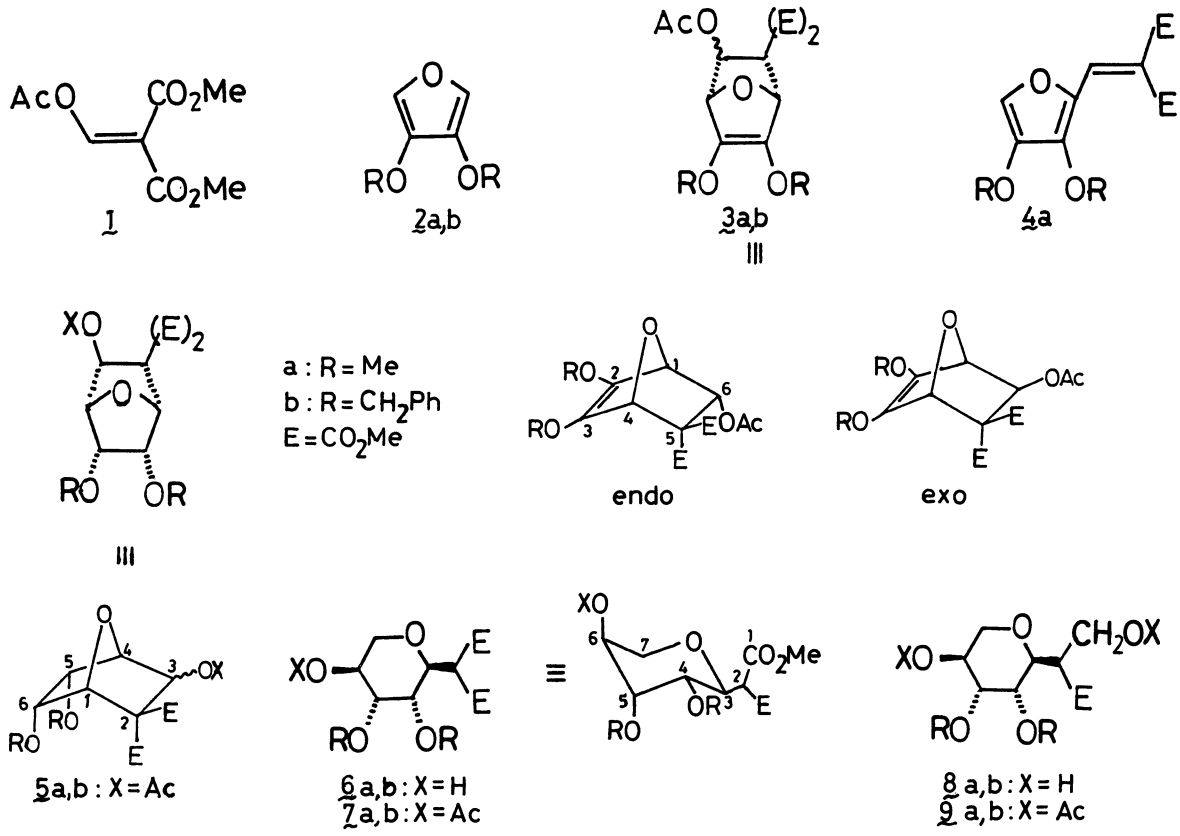
We chose dimethyl acetoxymethylenemalonate (1) as a dienophile, which has been recently developed by us,[6] and carried out Diels-Alder reaction with 2a and 2b. The results are shown in Table 1. Thus, when 3,4-dimethoxyfuran (2a) was allowed to react with 1 without solvent at room temperature for 9 d, the adduct 3a[7] [^{1}H NMR($CDCl_3$, 60 MHz) δ 5.87(1H, s, 3a-exo 6-H), 6.01(1H, d, J=4 Hz, 3a-endo 6-H)] was obtained as a mixture of endo and exo isomers (ca. 1:1) in quantitative yield. Separation by columm chromatography on silica gel gave only the exo isomer 3a-exo (mp 115-116 °C). None of the endo isomer was obtained because it reverted to the starting materials by retro Diels-Alder reaction in the column. In a higher temperature (40 °C), the reaction of 1 with 2a for 5 d gave 72% yield of the exo isomer 3a-exo as a sole product, whereas heating of a solution of 1 and 2a in benzene in a sealed tube at 90 °C for 3 d resulted in the formation of dimethyl 2-(3,4-dimethoxyfurfurylidene)malonate (4a: mp 108-109 °C) in 17% yield, together with a trace of 3a-exo.

The above experiments indicate that, while the both adducts are unstable, 3a-endo is especially prone to retro Diels-Alder reaction and reverts to starting materials even in silica gel column. Similar reaction of 3,4-dibenzyloxyfuran (2b) with 1 at 40 °C gave again the adduct 3b-exo (mp 96-98 °C) in 57% yield.

Table 1. Diels-Alder Reaction of Dimethyl 2-Acetoxymethylenemalonate (1) with 3,4-Dimethoxyfuran (2a) under Various Conditions

Entry	Solvent	Temperature/°C	Yield/% of 3a	Ratio of endo and exo isomers
1	None	20	100	1:1
2	None	40	72(57)[a]	0:1(0:1)[a]
3	C_6H_6	90	Trace	0:1

a) The yield and ratio in parenthesis refer to those of adduct 3b.



Scheme 1.

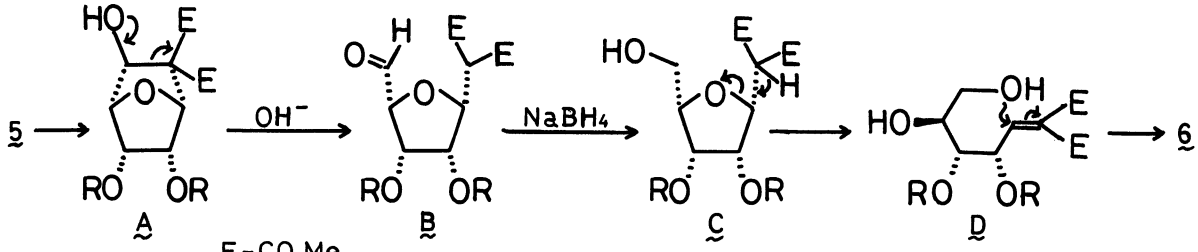
(All compounds are racemic, with the formulated enantiomer arbitrarily chosen.)

Catalytic reduction of 3a (a 1:1 mixture of endo and exo isomers) with 10% Pd-C in methanol gave two dihydro derivatives 5a-endo[8] [^{1}H NMR ($CDCl_3$, 60 MHz)

δ3.95(1H, dd, J=5.0 and 8.3 Hz, 5-H), 4.73(1H, t, J=5.0 Hz, 4-H), 5.32(1H, d, J=5.0 Hz, 1-H), 5.60(1H, d, J=5.0 Hz, 3-H)] and 5a-exo[9] [^{1}H NMR ($CDCl_3$, 60 MHz) δ3.83(1H, dd, J=5.5 and 9.0 Hz, 5-H), 4.63(1H, d, J=5.5 Hz, 4-H), 5.12(1H, d, J=4.7 Hz, 1-H), 6.17(1H, s, 3-H)] in quantitative yields, which were chromatographically separable. Thus, it is clear that the reduction occurs from the less hindered exo-side of 3a and the two methoxy groups of compounds 5a have the endo configurations. Similarly, the catalytic reduction of 3b-exo gave the dihydro derivative 5b-exo (mp 132-133 °C) in quantitative yield.

Next, dihydro compounds 5a,b were submitted to retrograde aldol C-C bond fission under reductive condition, which was recently elaborated by us.[6,10] Thus, 5a-exo was treated with K_2CO_3-$NaBH_4$ in methanol at room temperature for 4 h to give the lyxopyranosyl C-glycoside 6a[11] and the hydroxymethyl derivative 8a (a 1:1 mixture of diastereomers) in 85% and 15% yields, respectively. The signal at δ4.21(3-H) in the ^{1}H NMR spectrum of 6a indicates that compound 6a is a lyxopyranosyl derivative and the configuration of the malonyl residue is equatorial (cf. Scheme 1). Compound 6a was also obtained in 52% yield from 5a-endo by similar treatment. In order to clarify further their structures, both compounds 6a and 8a were acetylated in the usual manner (Ac_2O-pyridine) to give the monoacetylated 7a[12] [^{1}H NMR($CDCl_3$, 500 MHz)δ3.57(1H, dd, J=3.0 and 10.0 Hz, 4-H), 3.72(1H, d, J=6.0 Hz, 2-H), 3.75(1H, dd, 5-H), 3.80(1H, d, J=13.5 Hz, 7-H axial), 3.88(1H, dd, J=2 and 13.5 Hz, 7-H equatorial), 4.29(1H, dd, J=6.0 and 10.0 Hz, 3-H), 4.97(1H, dd, 6-H)] and the diacetylated products 9a, respectively. The same treatment of 5b-exo afforded the lyxopyranosyl C-glycoside 6b in 90% yield, together with the hydroxymethyl derivative 8b (4%) corresponding to 8a. Again, acetylation of 6b and 8b gave the corresponding acetylated products 7b and 9b.

Formation of lyxopyranosyl C-glycosides 6 from the bicyclo compounds 5 can



Scheme 2.

be explained by the route shown in Scheme 2. Thus, the alcohol A initially formed by simple methanolysis undergoes the C-C bond fission through retrograde aldol reaction to give the aldehyde B. Reduction of the formyl group of B with $NaBH_4$ results in the formation of dimethyl lyxofuranosylmalonate C,[13] whose cleavage to D by retro Michael reaction and recyclization leads to the final product 6.

In summary, we have synthesized dimethyl lyxopyranosylmalonates in stereospecific manner from 3,4-dialkoxyfurans in three steps. The enantioselective synthesis of 6 using chiral dienophile (e.g., dimenthyl ester of 1) and application of 6 to the synthesis of ribofuranosyl C-nucleoside are now under investigation.

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7) 3a-exo: IR($CHCl_3$) 1755, 1738, and 1691 cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) selected peaks, δ 2.07(3H, s, OAc), 3.68(3H, s, OMe), 3.74(6H, s, OMeX2), 3.79(3H, s, OMe), 4.65(1H, d, J=2 Hz, 1-H), 5.16(1H, d, J=2 Hz, 4-H).

8) 5a-endo : mp 85-86 °C; IR($CHCl_3$) 1743cm^{-1}.

9) 5a-exo: mp 111-113 °C; IR($CHCl_3$) 1744cm^{-1}.

10) C. Kaneko, N. Katagiri, M, Sato, M. Muto, T. Sakamoto, S. Saikawa, T. Naito, and A. Saito, J. Chem. Soc., Perkin Trans.1, 1986, 1283; N. Katagiri, M. Tomura, T. Haneda, and C. Kaneko, J. Chem. Soc., Chem. Commun., in press.

11) 6a: IR($CHCl_3$) 3480, 1754, and 1733 cm^{-1}; ^1H NMR($CDCl_3$, 500 MHz)δ inter alia 1.95(1H, brs, OH), 3.38(3H, s, OMe), 3.50(3H, s, OMe), 3.72(3H, s, CO_2Me), 3.73(3H, s, CO_2Me), 4.21(1H, dd, J=5.5 and 10.0 Hz, 3-H).

12) 7a: IR($CHCl_3$) 1742 and 1734cm^{-1}.

13) Diethyl 2-(2,3-O-isopropylidene-α,β-lyxofuranosyl)malonate has been prepared from D-mannose by Hanessian and Pernet. S. Hanessian and A. G. Pernet, Can. J. Chem., 52, 1266(1974).

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