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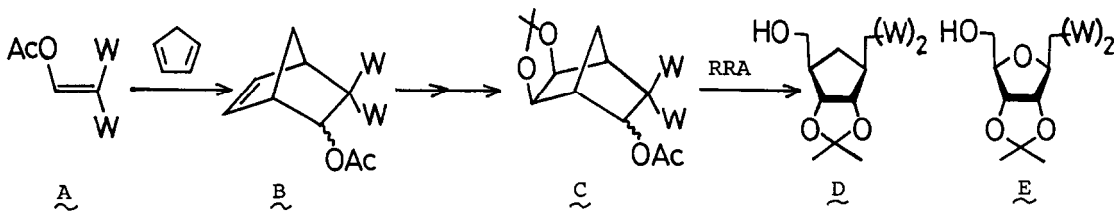
HIGH-PRESSURE MEDIATED DIELS-ALDER REACTION OF DI-ℓ-MENTHYL ACETOXYMETHYLENEMALONATE WITH FURAN: ENANTIOSELECTIVE SYNTHESIS OF β-D-RIBOFURANOSYLMALONATE, A PROSPECTIVE SYNTHON FOR C-NUCLEOSIDE

Nobuya Katagiri[a*], Hidenori Akatsuka[a], Chikara Kaneko[a*], and Akira Sera[b]

[a] Pharmaceutical Institute, Tohoku University, Aobayama, Sendai 980, Japan; [b] Department of Chemistry, Faculty of Science, Kobe University, Kobe 657, Japan

Abstract: β-D-Ribofuranosylmalonate [D]-**4** has been synthesized through high-pressure Diels-Alder reaction of furan with di-ℓ-menthyl acetoxymethylenemalonate (**1b**), followed by reductive retrograde aldol C-C bond fission. A mechanism accounting for the observed diastereoselectivity in the Diels-Alder reaction is proposed.

Previously, we have established a facile synthetic method of carbocyclic analogues of β-ribofuranosylmalonate **D** (W=CO_2R) from cyclopentadiene and demonstrated their usefulness by their conversion to a variety of carbocyclic C-nucleosides. Novelty of the method is the use of 3-acetoxyacrylate derivatives **A** having a strong electron-withdrawing substituent at 2-position, which permits stereoselective cleavage of the C-C bond of the acetonide **C** derived from the Diels-Alder adduct **B** by reductive retrograde aldol reaction (termed as RRA)[1,2] (Scheme 1).



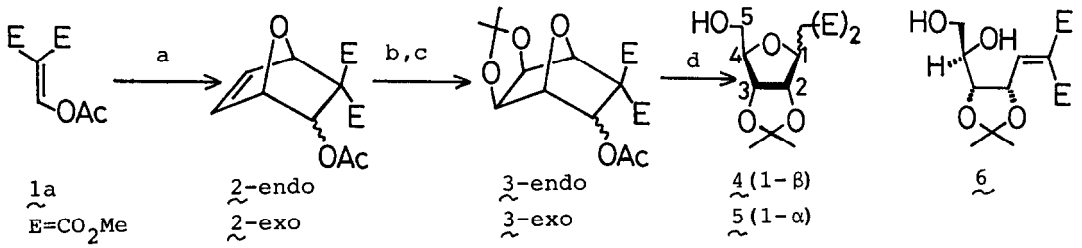
Scheme 1 W=CO_2R, CN, etc. RRA: K_2CO_3/$NaBH_4$/MeOH, ambient temperature

Recently, we have found that the use of di-ℓ-menthyl acetoxymethylenemalonate (**1b**) in titanium tetrachloride-catalyzed Diels-Alder reaction with cyclopentadiene affords the adduct **B** in ≥90% d.e. and hence accomplished an enantioselective synthesis of carbocyclic β-D-ribofuranosylmalonate (chiral **D**).[3]

Here, we report an efficient and highly stereoselective synthesis of β-ribofuranosylmalonate **E** (both racemic and chiral) from furan, by essentially the same methodology.

Though furan itself did not react with dimethyl acetoxymethylenemalonate (**1a**) at ambient temperature under ordinary conditions, the efforts in our laboratories have recently revealed that the Diels-Alder reaction of **1a** with furan proceeds smoothly under high-pressure (11 kbar).[4] In order to realize our aim, the adduct **2** (a mixture of **2**-endo and **2**-exo adducts) was converted without separation[5] to the corresponding acetonides **3** by the usual manner. If the RRA reaction of **3**[6] was carried out under carefully controlled conditions (0 °C, 15 min.), one could obtain an almost pure cis-malonate **4** quantitatively. Inspection of 500 MHz NMR spectrum of the product showed that a very small amount (less than 3%) of the α-anomer **5** was also formed under the condition.[7]

Knowing that all of the method so-far reported for the introduction of malonyl group into D-ribose or its derivative afforded always the undesired α-anomer as the major products,[8,9] it is evident that the method if extensible to EPC (enantiomerically pure compounds) synthesis would provide a very short and highly stereoselective synthesis of C-nucleoside precursor [D]-**4a**.

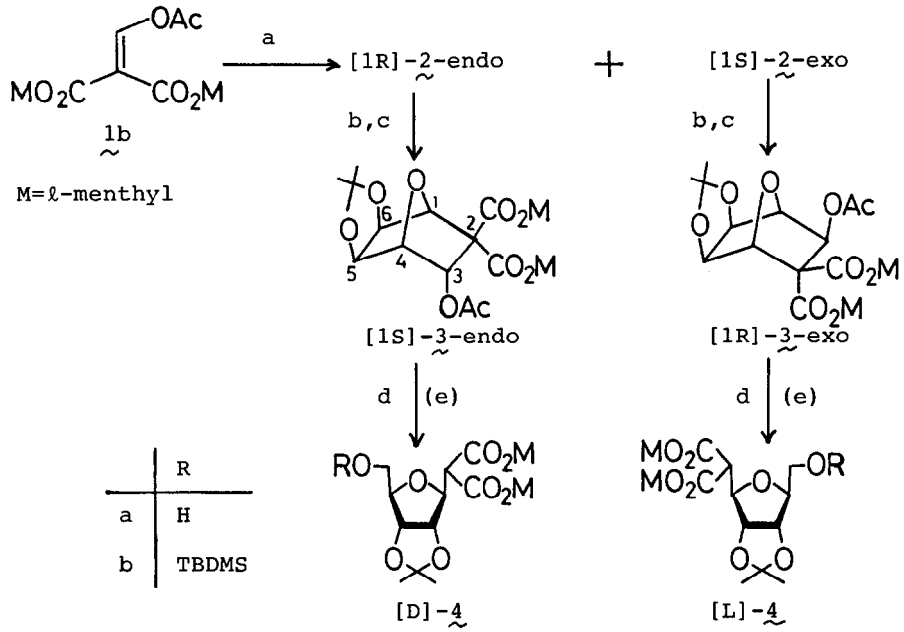


1a (E=CO_2Me) — 2-endo, 2-exo — 3-endo, 3-exo — 4(1-β), 5(1-α) — 6

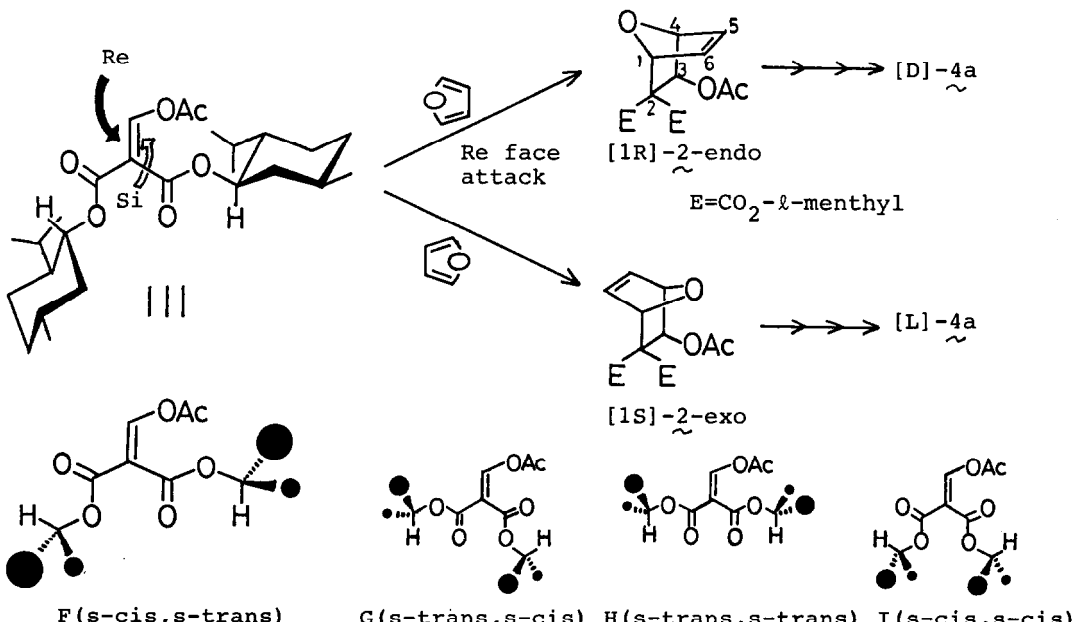
a: furan (3 mol equiv. to **1a**), 11 kbar, room temperature, 3 days
b: OsO_4, 4-methylmorpholine N-oxide, AcOEt/acetone
Scheme 2 c: p-TsOH, $Me_2C(OMe)_2$, acetone
d: K_2CO_3, $NaBH_4$ (each 5 mol equiv. to **3**), MeOH, 0 °C, 15 min.

Fortunately, the same methodology has been found to be applicable to the enantioselective synthesis. Thus, under 11 kbar for 5 days, di-ℓ-menthyl acetoxymethylenemalonate (**1b**) reacted with furan to give both endo- and exo-adducts with significant d.e.s, respectively. Thus, after conversion of the adducts **2** obtained by the high-pressure Diels-Alder reaction to the corresponding acetonides **3**, the products were separated into each endo- and exo-isomers (40% and 20% yields, respectively) and d.e. was determined as 54% for the endo-addition and 61% for the exo-addition reactions by 500 MHz NMR spectra.[10,11] The structures of the major diastereomers in each adduct was determined after their conversion to **4b**, followed by comparison of 500 MHz NMR spectra with that of authentic β-D-ribofuranosylmalonate derivative [D]-**4b**[12]. As a result, the major adduct for the endo addition was determined as the D-form (natural configuration), while that for the exo addition was the L-form (non-natural configuration) (Scheme 3: only the formulae corresponding to the major diastereoisomers of each type of addition are shown).

In order to account for the diastereoselectivity observed, we consider the following explanation as the most reasonable (Scheme 4). Among four low-energy conformations **F-I**, no asymmetric induction is expected in the case of **H** and **I** whose both sides are the same sterically. Thus, predominancy of **F** (Re face is



Scheme 3 a,b,c,d: the same in Scheme 2
e: $^{t}BuMe_2SiCl$ (TBDMSCl), imidazole, DMF



Scheme 4

the less crowded) over **G** (Si face is the less crowded) under high-pressure condition only seems to account for the observed selectivity.

While complete clarification of the reason for this novel asymmetric induction should await further experiments, the method seems to be practicable because the final product having the desired stereochemistry ([D]-**4b**) can be obtained as a crystalline form (mp 85-86 °C).

REFERENCES AND NOTES

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5 The separation of each adduct (**2**-endo: oil and **2**-exo: mp 80-81 °C) by silica gel chromatography, though possible, resulted in partial cycloreversion to the original components.

6 Though the corresponding acetonides **3** can be separated without any decomposition chromatographically into **3**-endo and **3**-exo isomers (52 and 18% yields, respectively), such separation is unneccessary to synthesize **4**.

7 The fact that the amount of α-anomer **5** increased gradually by using longer period and/or an elevated temperature shows that isomerization of **4** to **5** via **6** occurs under these conditions.

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9 F. Cermain, Y. Chapleur, and B. Castro, Synthesis, 1983, 119.

10 In his pioneering work, Jurczak reacted di-ℓ-menthyl fumarate with butadiene under 6.9 kbar and obtained the adduct with 12.8% d.e. So far, the highest d.e. in Diels-Alder reactions leading to carbocycles is 50% reported by Dauben, who reacted 8-phenylmenthyl 2,4-pentadienoate with p-benzoquinone under 15 kbar: J. Jurczak, Bull. Chem. Soc. Jpn., 52, 3438 (1979); M. G. Dauben and R. A. Bunce, Tetrahedron Lett., 23, 4875 (1982).

11 High d.e. (60-100%) was reported for Diels-Alder reactions of 1-methoxy-buta-1,3-diene to sugar aldehydes under a comparable condition: J. Jurczak, T. Bauer, and S. Jarosz, Tetrahedron, 42, 6477 (1986).

12 The authentic silylated derivative [D]-**4b** was synthesized from D-ribose by acetonide formation, the silylation, and subsequent reaction with di-ℓ-menthyl malonate under strongly basic conditions. It should be noted that the yields of the malonylated products were less than 5% with ca. 5:1 ratio for α-/ β-anomer (hence the yield of [D]-**4b** is ca. 1% from D-ribose). The method employed is the same with that reported for synthesis of the corresponding 5-O-trityl derivative [D]-**4** (R=trityl): see reference 9.

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