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3-Acetoxy-2-dimethylphosphonoacrylates. New Dienophiles and Their Use for the Synthesis of Carbocyclic C-Nucleoside Precursors by the Aid of RRA Reaction[1)]

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New dienophiles, 3-acetoxy-2-dimethylphosphonoacrylates, have been prepared and their Diels-Alder reactions with cyclopentadiene investigated. The [4 + 2] adducts thus formed were converted to carbocyclic C-nucleoside precursors by means of reductive retrograde aldol (RRA) reaction.

Recent reports of the antiviral activity of certain carbocyclic nucleosides have stimulated interests in elaboration of a new method permitting ready access of new analogues in this series of compounds.[2)] Though there are many reports concerned with Diels-Alder reaction using enoates as dienophiles, only a few studies on the reaction with the dienophiles activated by a phosphono group have been reported.[3)]

Previously, we have found that 3-acetoxyacrylates (**A**) having an electron-withdrawing group at the 2-position cycloadd either to furan under high pressure[4)] or to cyclopentadiene under ordinary conditions[5)] to give the [4 + 2] adducts (**B**) and reductive retrograde aldol reaction (RRA reaction: $NaBH_4$-K_2CO_3/MeOH) of these adducts provides a short and effective synthetic route to a series of synthetic precursors (e.g. **D**) for C-nucleosides or their carbocyclic analogues.

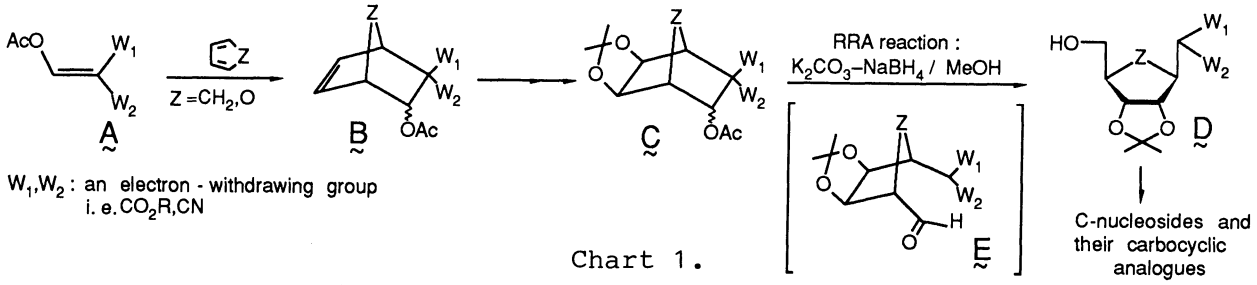

Chart 1.

Our continuing efforts aiming at an extension of this methodology have led to 3-acetoxy-2-dimethylphosphonoacrylates as new dienophiles, and here we wish to report the preliminary results.

When methyl dimethylphosphonoacetate (**1a**) was formylated by treatment with methyl formate under basic conditions, a sodium salt (**2a**: mp 198-200 °C) was obtained in quantitative yield. Acetylation of **2a** with acetyl chloride gave methyl 3-acetoxy-2-dimethylphosphonoacrylate [**3a**: bp 65-85 °C (0.1 mmHg)] in 91% yield as a mixture of E- and Z-isomers (E:Z=5:2), which were chromatographically inseparable. Determination of the E/Z ratio was made by ^{1}H-NMR spectroscopy by using the coupling constants between the olefinic proton and phosphorous atom as the criterion; i.e. the trans coupling constant ($J_{HC=CP}$=30-50 Hz) is larger than cis one (10-20 Hz).[6] Thus, in the spectrum of **3a**, the isomer having the olefinic proton signal at δ 8.66 with the coupling constant of 12 Hz was assigned as E-isomer, whereas one at δ 8.69 (J=34 Hz) as Z-isomer.

In the same manner, compound **3b** [bp 82-84 °C (0.01 mmHg)] was obtained solely as an E-isomer ($J_{HC=CP}$=10 Hz) in 85% yield from dimethylphosphonoacetonitrile (**1b**). In this case, none of the Z-isomer was detected in the product.

Diels-Alder reactions of these dienophiles (**3a,b**) with cyclopentadiene were then examined under various conditions (Table 1). When the reaction of **3a** with cyclopentadiene was carried out under 1 atm (Entry 1), the adduct was obtained in 44% yield as a mixture of two isomers (**4** and **5**) in a ratio of ca. 7:8. Use of high pressure (Entry 2) not only increased the yield of the adduct (71%) but also affected the ratio of the isomers (ratio of **4**/**5**=5:4). Two isomers were separated readily by column chromatography.

^{1}H-NMR spectrum of each adduct revealed that **4** was an endo isomer relative to the acetoxyl group at the 3-position while **5** corresponded to the exo isomer,[7] and that configuration of the dimethylphosphono group in both compounds (**4** and **5**) is exo and that of methoxycarbonyl group is

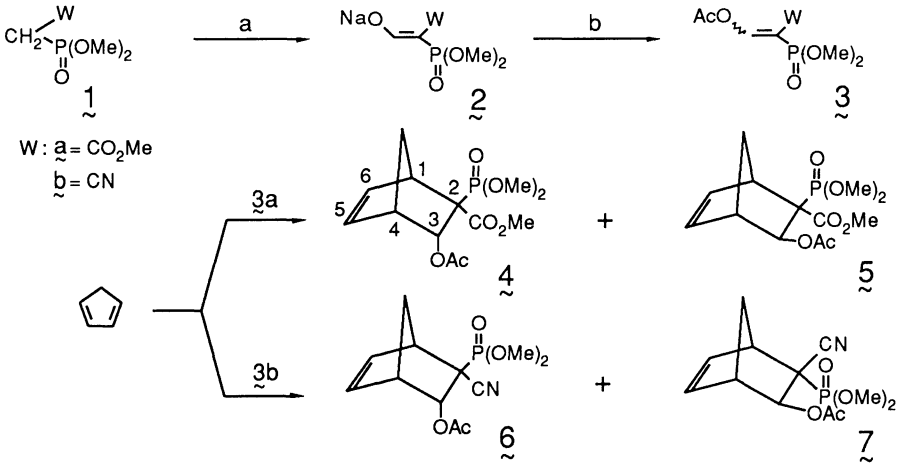

Chart 2. Reagents and conditions: a) HCO_2Me, NaOMe/MeOH, room temp ; b) AcCl, ether, room temp.

Table 1. Diels-Alder Reaction with **3a** and **3b** with Cyclopentadiene

Entry	Dienophiles	Reaction conditions	Yield/%	Ratio	
1	**3a**	80 °C (1 atm), 4 d, toluene	44	(**4**:**5**)	7:8
2	**3a**	room temp (11 kbar), 3 d, toluene	71		5:4
3	**3b**	room temp (1 atm), 3 d, neat	52	(**6**:**7**)	4.0:1
4	**3b**	65 °C (1 atm), 2 d, toluene	78		4.3:1
5	**3b**	room temp (11 kbar), 2 d, toluene	76		3.7:1

endo.[8] The fact that only two isomers (**4** and **5**) were obtained from **3a** (a mixture) implies that this cycloaddition is controlled by secondary orbital interaction of methoxycarbonyl group and the E/Z isomerization in **3a** has occurred under the reaction conditions. The dienophile (**3b**) was more active than **3a**, and reacted with cyclopentadiene even at room temperature under atmospheric pressure (Entry 3) to give two adducts (**6** and **7**, 4:1) in 52% yield. While heating (65 °C) or high pressure (11 kbar) improved the yield, the ratio of two isomers was not changed significantly (Entries 4 and 5). Again, the configurations of two isomers were determined by coupling constants between 3-proton and phosphorous atom as well as 3- and 4-protons.

Next, we investigated transformation of the adducts to carbocyclic C-nucleoside precursors by means of the RRA reaction using **4** and **6** as the substrates. When these adducts were subjected to RRA reaction under ice-salt cooling, the corresponding 1,4-cis-disubstituted cyclopent-2-ene derivatives (**8**) were obtained in quantitative yields. Similarly, the dihydro derivative (**9a**) derived from **4** by catalytic hydrogenation was transformed by RRA reaction to a 1,3-cis-cyclopentane derivative (**10a**) in

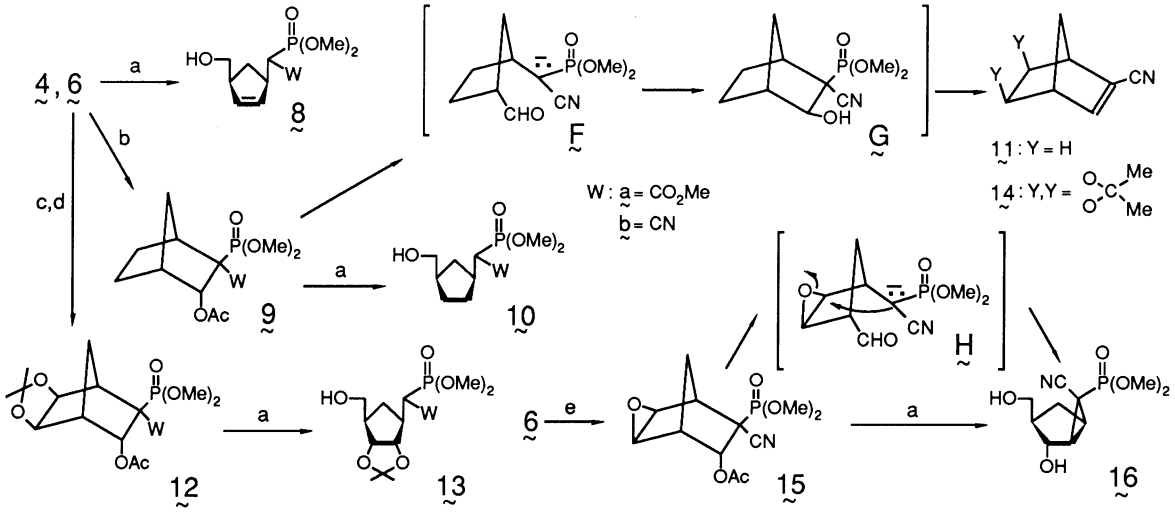

Chart 3. Reagents and conditions: a) RRA reaction (K_2CO_3-$NaBH_4$, MeOH), icesalt cooling; b) H_2/Pd-C, MeOH-AcOEt (6:1), room temp; c) OsO_4-4-methyl-morpholine N-oxide, AcOEt; d) $MeC(OMe)_2Me$-TsOH, acetone; e) mCPBA, CH_2Cl_2.

quantitative yield. However, the same reaction of the dihydro derivative (**9b**) gave, in addition to **10b**, 2-cyanonorbornene (**11**) (quant.; **10b**:**11**=13:10). It is obvious that **11** is formed by intramolecular Horner-Emmons reaction[9] (cf. **F**→**G**). According to the usual manner, **4** and **6** were transformed to the corresponding acetonides (**12**). Compound **12a** was again subjected to RRA reaction to give the desired C-nucleoside precursor (**13a**). The same reaction of **12b**, however, gave **14** as a major product (73%) with a trace amount (4%) of **13b**. Finally, the RRA reaction of the epoxide (**15**) derived from **6** was found to give a bicyclo[3.1.0]hexane (**16**) as a sole product (75%).[10] It is obvious that a change of the substituents at C_5- and C_6-positions in the bicyclic system causes a marked change in the conformation (and hence, reactivity) of the initially formed cyclopentane intermediates (**F**-**H**).

Our efforts are now paid for the preparation of new analogues of carbocyclic C-nucleosides from **8**, **10**, and **13**, all of which have a side chain at 1-position suitable for further elaboration by Horner-Emmons strategy.[9]

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8) Coupling constant (14 Hz) between 2-phosphorous atom and 3-proton in cis relationship is larger than that (6 Hz) in trans.
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