

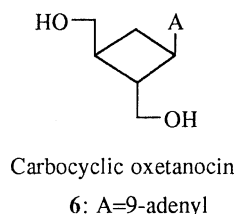
Synthesis of a Carbocyclic Oxetanocin Using Photocycloaddition

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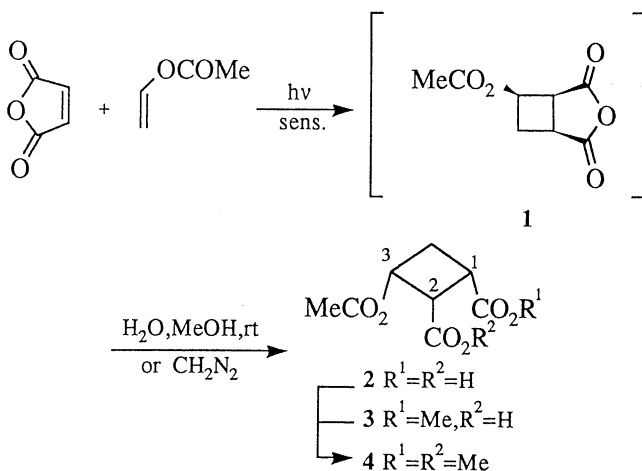
All-*cis*-3-acetoxycyclobutane-1,2-dicarboxylate **4** was provided from a photochemical endo-[2+2]cycloadduct between maleic anhydride and vinyl acetate, and **4** was coupled with adenine and reduced with LiAlH_4 to give a carbocyclic oxetanocin **6**.

Some carbocyclic oxetanocins exhibit very wide antiviral and potent anti-HIV activities.¹ Several synthetic methods for the oxetanocins have been reported.² Such studies are quite important as a scientific challenge against AIDS.³ Previously,



multi-step syntheses of a carbocyclic oxetanocin using photocycloaddition have been reported.^{2h} Here we wish to describe an improved and facile method to synthesize a similar oxetanocin analogue by way of a much shortened route employing the photocycloaddition of maleic anhydride with vinyl acetate as a key reaction.

Photoirradiation of maleic anhydride (72 mmol), vinyl acetate (312 mmol), and xanthone (14 mmol) in acetonitrile (500 ml) with a 400 W high-pressure mercury lamp through a Pyrex filter gave a methyl ester (**3**, 44% yield) of 1:1 cycloadduct **1** after treatment with methanol and column chromatography as shown in Scheme 1. Anhydride **1** was rather unstable and, when the reaction mixture was treated with water and washed with chloroform, the dicarboxylic acid **2** was obtained from the



Scheme 1.

aqueous layer as crystals (40%). The ester **3** was converted to **4** by the use of diazomethane (87%). The all-*cis* configuration of **4** was confirmed by the ^1H NMR data⁴ and NOE experiments. Thus, irradiation of 2'-H proton caused signal enhancements of 4.7, 6.2, and 2.2% for 1'-H, 3'-H, and one 4'-H, respectively. This is also in agreement with the endo-geometry in **1**, which was theoretically predicted from MO calculations (Figure 1).⁵ The orbital interactions by HSOMO-LUMO and LSOMO-HOMO π - π overlapping, including second-order interactions, and electrostatic interactions between maleic anhydride and vinyl acetate are apparently favorable for the formation of endo-adduct **1**.

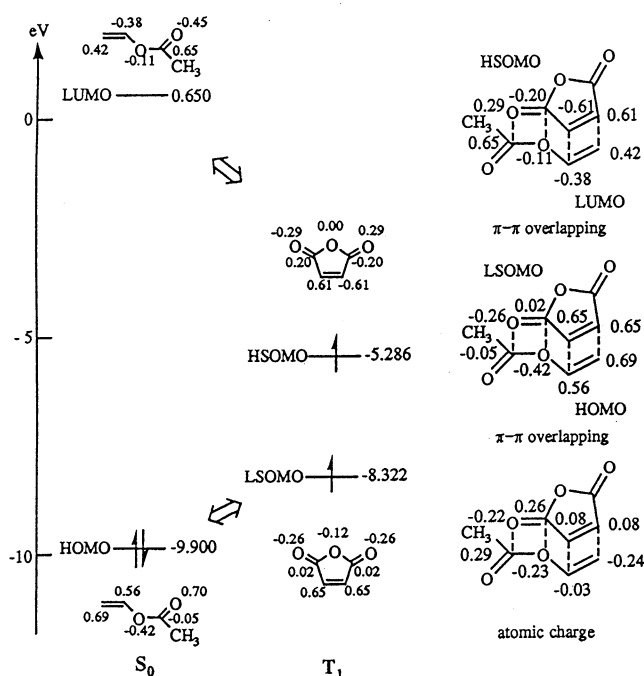
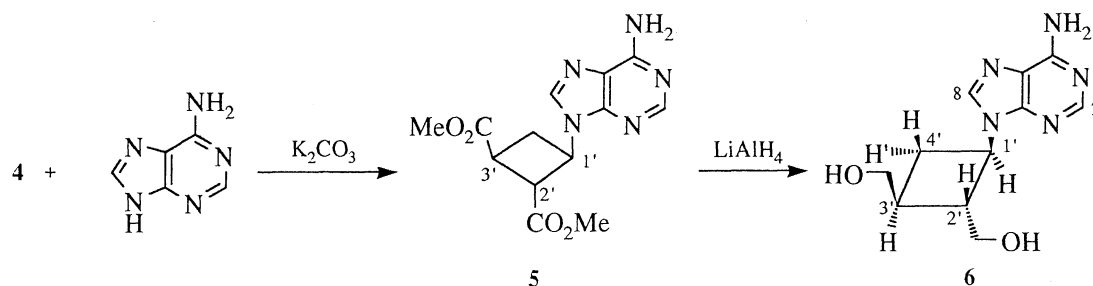


Figure 1. Estimated energies and coefficients of maleic anhydride and vinyl acetate and their interactions by PM3-CI method.

The next step is bonding between **4** and adenine (Scheme 2). A mixture of **4** (23.5 mmol), adenine (27.5 mmol), potassium carbonate (27.5 mmol) and dry DMF (200 ml) was stirred at 90 °C for 12 h. After evaporation of the solvent, extraction with chloroform and recrystallization from dichloromethane-ethanol afforded pure **5** (mp 195-196 °C, 31%). The all-*trans* configuration of **5** was mainly inferred by the ^1H NMR data following NOE experiments.⁴ Irradiation of 2'-H gave no enhancements on 3'-H. That of 1'-H gave 3.2 and 3.0% enhancements on 3'-H and one of 4'-H, respectively, but small (0.8%) enhancement on 2'-H signal. The detailed mechanism for



Scheme 2.

the addition of adenine leading to the stable all-*trans* compound is not clear at present. Since 2-H of **4** should be highly acidic due to methoxycarbonyl groups, the reaction would have proceeded by way of elimination-addition process via cyclobutene intermediate. A mixture of **4**, potassium carbonate and dry DMF, however did not show elimination for the cyclobutene intermediate at 90 °C. Added adenine might have catalyzed the elimination and proceeded following Michael-addition. Another possibility is a direct S_N2 type reaction at C-3, but this seems less likely. The alkaline conditions employed in the present reaction could cause the *cis-trans* epimerization at C-3, as has been reported for a similar dimethylcyclobutene derivative.⁶

The mixture of **5** (4.48 mmol), LiAlH₄ (27.4 mmol) and dry THF (90 ml) was stirred at room temperature and refluxed for 5 h, and treated with water. The white precipitate was filtered and washed with methanol. The filtrate was evaporated and the residue gave a white solid (**6**) (mp 187-189 °C, 77%), after Soxhlet extraction with diethyl ether. The ¹H NMR data⁴ was identical to that of carbocyclic oxetanocin A in the literature.^{2a} The all-*trans* configuration in the cyclobutane ring was confirmed by NOE data in the D₂O solution. Thus, irradiation of 1'-H proton caused signal enhancements of 5.1, 7.4, 7.2, and 0.0% for 4'-H, 3'-H, 2'-CH₂, and 4'-H, respectively.

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- All the new compounds gave the correct analytical and MS data. Selected NMR data are given below: **2**, ¹H NMR (400 MHz, D₂O, δ ppm): 2.05 (3H, s), 2.65 (2H, m), 3.21 (1H, m), 3.91 (1H, td), 5.19 (1H, q); **3**, ¹H NMR (CDCl₃): 2.05 (3H, s), 2.63 (1H, m), 2.87 (1H, td), 2.99 (1H, td), 3.69 (3H, s), 3.85 (1H, m), 5.21 (1H, q, J=8.0 Hz), 8.1 (1H, br); **4**, ¹H NMR (CDCl₃): 2.01 (3H, s), 2.62 (1H, m), 2.87 (1H, m), 2.96 (1H, m), 3.70 (3H, s), 3.71 (3H, s), 3.82 (1H, td, J=8.1, 3.4 Hz), 5.61 (1H, m). ¹³C NMR (100 MHz): 20.7, 31.1, 32.1, 48.6, 52.1, 63.1, 170.0, 172.1; **5**, ¹H NMR (CDCl₃): 2.86 (1H, q, J=9.2 Hz), 2.99 (1H, m), 3.27 (1H, q, J=9.2 Hz), 3.72 (3H, s), 3.80 (3H, s), 4.16 (1H, t, J=9.2 Hz), 5.07 (1H, m), 5.62 (2H, bs), 7.93 (1H, s), 8.35 (1H, s); **6**, ¹H NMR (DMSO-d₆): 2.10 (1H, m, 3'-H), 2.23 (1H, m, 4'-H), 2.44 (1H, m, 4'-H'), 2.78 (1H, m, 2'-H), 3.52 (4H, m, 2', 3'-CH₂), 4.61 (1H, t, J=5.1 Hz, OH), 4.63 (1H, m, 1'-H), 4.75 (1H, t, J=5.0 Hz, OH), 7.18 (2H, s, NH₂), 8.12 (1H, s, 2-H), 8.22 (1H, s, 8-H). ¹³C NMR (DMSO-d₆): 29.08 (3'-C), 32.47 (4'-C), 47.43, 47.71 (CH₂OH), 61.61 (2'-C), 63.58 (1'-C), 119.10 (5-C), 139.51 (6-C), 149.38 (4-C), 152.12 (8-C), 155.96 (2-C).
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