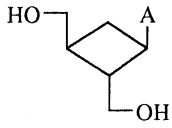
Synthesis of a Carbocyclic Oxetanocin Using Photocycloaddition

Kenichi Somekawa,* Ryosuke Hara, Kazushige Kinnami, Fumiko Muraoka, Takaaki Suishu, and Tetsuro Shimo
Department of Applied Chemistry and Chemical Engineering, Faculty of Engineering, Kagoshima University, Korimoto, Kagoshima 890

(Received December 12, 1994)

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 exibit 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,

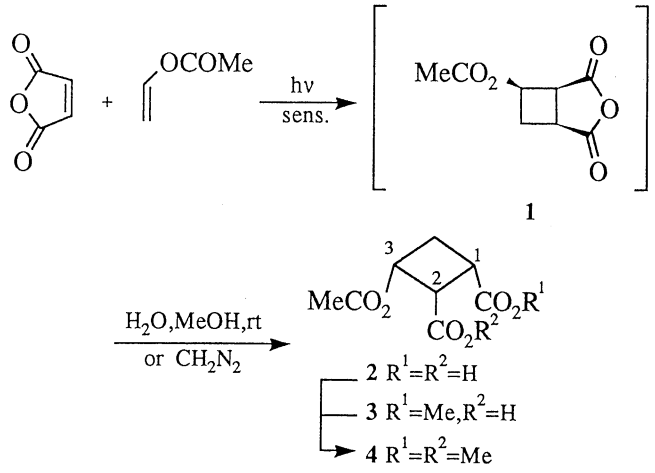


Carbocyclic oxetanocin

6: A=9-adenyl

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 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 data[4] 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**.



Scheme 1.

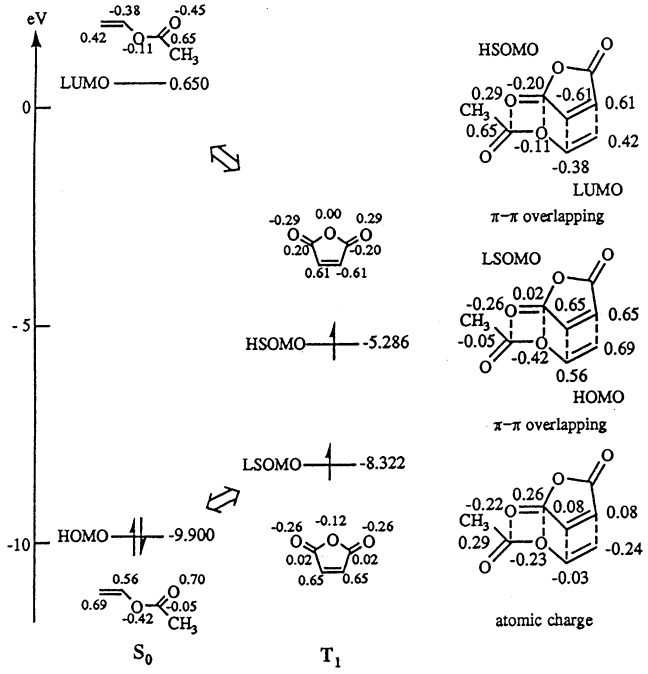
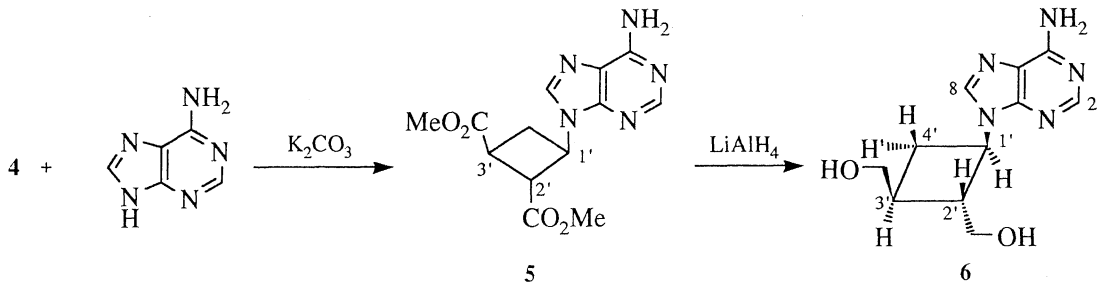


Figure 1. Estimated energies and cofficients of maleic anhydride and vinyl acetate and their interactions by PM3-CI method.

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** (4.48mmol), $LiAlH_4$ (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 data[4] 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 D_2O 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'-CH_2, and 4'-H, respectively.

This work was financially supported by a Grant-in-Aid for Scientific Research (C) from the Ministry of Education, Science and Culture (No. 06651012), and Shorai Foundation for Science and Technology (1994). We thank professor C. Kaneko of Tohoku University for the useful suggestion at 1994 Symposium of Japan Photochemistry.

References and Notes

1 a) Y. Nishiyama, N. Yamamoto, Y. Yamada, Y. Ichikawa, and K. Takahashi, *J. Antibiot.*, **42**, 1854 (1989) ; b) T. Maruyama, Y. Hanai, Y. Sato, R. Snoeck, G. Andrei, M. Hosoya, J. Balzalini, and E. D. Clercq, *Chem. Pharm. Bull.* **41**, 516 (1993), and references cited therein.

2 a) M. Honjo, T. Maruyama, Y. Sato, and T. Horii, *Chem. Pharm. Bull.*, **37**, 1413 (1989); b) Y. Ichikawa, A. Narita, A. Shiozawa, Y. Hayashi, and K. Narasaka, *J. Chem. Soc., Chem. Commun.*, **1989**, 1919; c) G. S. Bisacchi, A. Braitman, C. W. Cianci, J. M. Clark, A. K. Field, M. E. Hagen, D. R. Hockstein, M. F. Malley, T. Mitt, W. A. Slusarchyk, J. E. Sundeen, B. J. Terry, A. W. Tuomari, E. R. Weaver, M. G. Young, and R. Zahler , *J. Med. Chem.*, **34**, 1415 (1991); d) I. C. Cotterill and S. M. Roberts, *J. Chem. Soc., Perkin Trans* 1, 2585 (1992). e) P.Pecquet, F. Huet, M. Legraverend, and E. Bisagni, *Heterocycles*, **34**, 739 (1992); f) X. Chen, S. M. Siddiqi, and S. W. Schneller, *Tetrahedron Lett.*, **33**, 2249 (1992); g) H. Ito, T. Taguchi, and Y. Hanzawa, *Tetrahedron Lett.*, **34**, 7639 (1993); h)M. E. Jung and A. W. Sledeski, *J. Chem. Soc., Chem. Commun.*, **1993**, 589 ; i) N.Katagiri, *Yakugaku Zasshi*, **113**, 285 (1993).

3 H. Ito, Y. Hanzawa, and T. Taguchi, *J. Synth. Org. Chem., Jpn.*, **52**, 217 (1994).

4 All the new compounds gave the correct analytical and MS data. Selected NMR data are given below: **2**, ^1H NMR (400 MHz, D_2O, 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 ($CDCl_3$): 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 ($CDCl_3$): 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). ^{13}C NMR (100 MHz): 20.7, 31.1, 32.1, 48.6, 52.1, 63.1, 170.0, 172.1; **5**, ^1H NMR ($CDCl_3$): 2.86 (1H, q, J=9.2Hz), 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-d_6): 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'-CH_2), 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, NH_2), 8.12 (1H, s, 2-H), 8.22 (1H, s, 8-H). ^{13}C NMR (DMSO-d_6): 29.08 (3'-C), 32.47 (4'-C), 47.43, 47.71 (CH_2OH), 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).

5 T. Sakai, Y. Kimura, K. Kitasaka, T. Tsuboi, M. Utaka, and K. Somekawa, *Chem. Express*, **8**, 49 (1993).

6 C. R. Johnson and R. L. De Jong, *J. Org. Chem.*, **57**, 594 (1992).