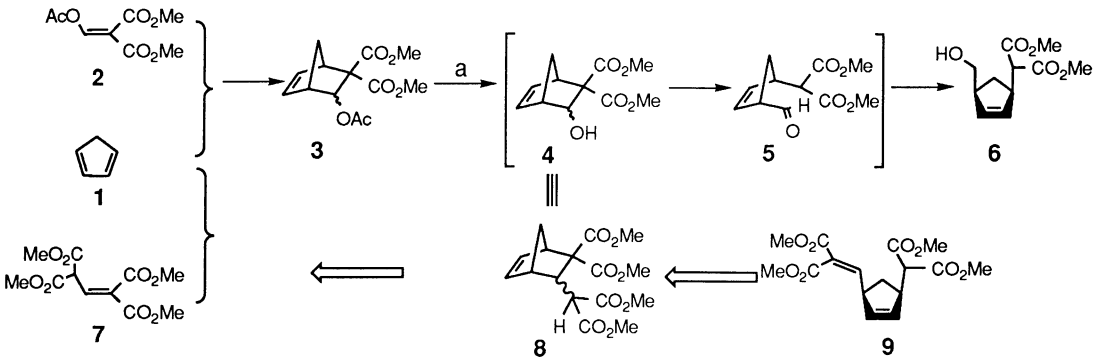
CHEMISTRY LETTERS, pp. 1285-1288, 1994.

Dimethyl 2-{3,3-Bis(methoxycarbonyl)bicyclo[2.2.1]hept-5-en-2-yl}malonate. Synthesis and Base-Catalyzed C-C Bond Cleavage Reaction

Kenji KITANO, Nobuya KATAGIRI,* and Chikara KANEKO*
Pharmaceutical Institute, Tohoku University, Aobayama, Sendai 980-77

The reaction of cyclopentadiene with 1,1,3,3-tetrakis(methoxycarbonyl)propene gives an *endo* and *exo* mixture of dimethyl 2-{3,3-bis(methoxycarbonyl)bicyclo-[2.2.1]hept-5-en-2-yl}malonate, which by base-mediated retro-Michael reaction gives stereoselectively the *cis*-isomer of dimethyl 2-{4-[2,2-bis(methoxycarbonyl)vinyl]cyclo-pent-2-en-1-yl}malonate.

Bicyclo[2.2.1]hept-2-ene derivatives which could be readily provided by Diels-Alder reaction of cyclopentadiene with an appropriate C-2 dienophile have been used for the synthesis of a variety of complex natural products.[1] In this methodology, the cleavage of C-C bond derived from the dienophile has provided a common access to *cis*-1,3-disubstituted cyclopentanes.[2] We have realized the cleavage of this bond by retrograde aldol reaction under the reductive conditions (a in Scheme 1: $NaBH_4$ in MeOH) and elaborated a shortest route to the precursor of carbocyclic C-nucleosides (Scheme 1, **1** → **6**).[3] Use of reductive conditions is the essential requisite for retention of *cis*-configuration in the newly formed 3,5-substituents in the cyclopentene ring. This method is superior to the previously reported oxidative C-C bond cleavage,[2] because in the latter case the C-C double bond derived from the diene in the bicycloheptenes had to be transformed into other functions which could survive the oxidative conditions.



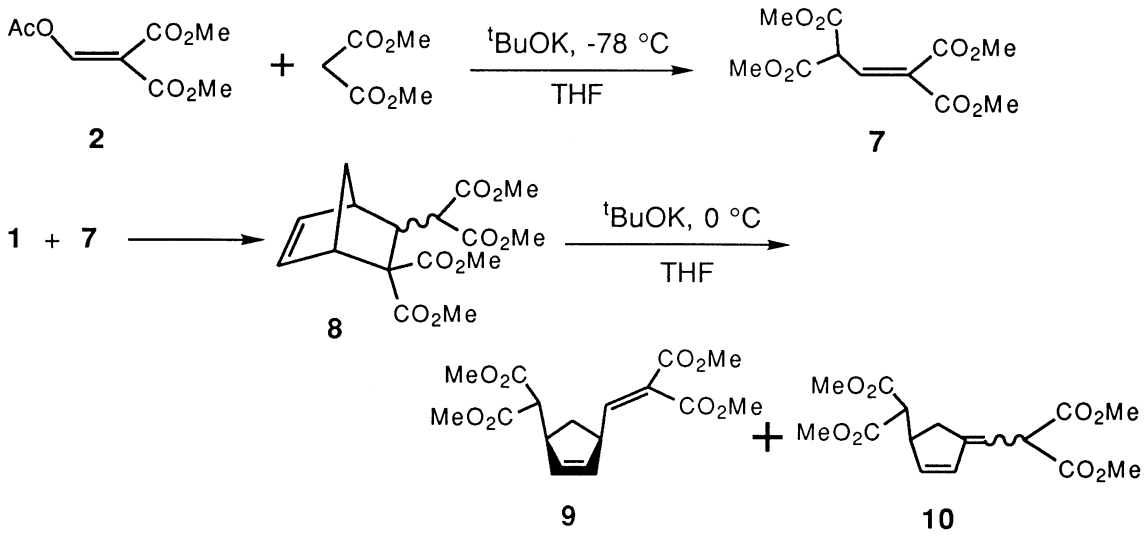
Scheme 1.

In order to develop a new method for the construction of *cis*-3,5-disubstituted cyclopentene from the bicyclic compounds, we have synthesized the bicyclo[2.2.1]hept-2-ene **8** which has a malonic acid unit instead of hydroxyl group in **4**, and examined its base-catalyzed C-C bond fission. In this paper, we will

report the successful result.

According to the retrosynthetic strategy for the synthesis of the bicyclic compound **8**, 1,1,3,3-tetrakis(methoxycarbonyl)propene (**7**) seems to be the suitable dienophile. Thus, the reaction of dimethyl acetoxymethylenemalonate (**2**)[4] with dimethyl malonate in THF containing ^{t}BuOK at -78 °C was examined and found to give the desired dienophile **7**[5,6] in 60% yield.

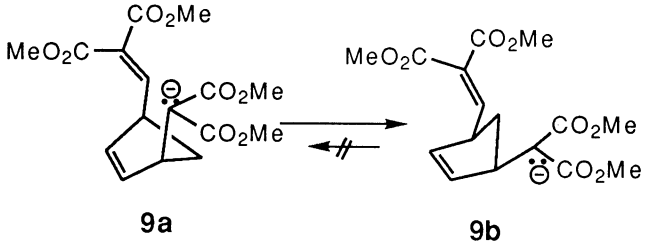
Diels-Alder reaction of **7** with cyclopentadiene in toluene was then examined. While this reaction proceeded at 60 °C in a satisfactory yield (76%, *endo*/*exo* = *ca.* 2.3)[7] to give the adduct (**8**),[8] the reaction was much accelerated either in the presence of $TiCl_4$ (0.1 equiv.) or under high-pressure. The best result (98%, *endo*/*exo* = *ca.* 2.0) was obtained when the reaction was carried out at room temperature under 10 kbar.



Scheme 2.

Next, we examined the C-C bond cleavage reaction of **8** under basic conditions. When the reaction was carried out at 0 °C in THF in the presence of ^{t}BuOK, the expected ring opened product (**9**) was obtained in 53% yield together with a minor amount (23%) of the double bond shifted product (**10**).[9] When the same reaction was carried out at room temperature, the yield of the latter compound (**10**) increased, while that of the former (**9**) decreased. If the same reaction was carried out at -78 °C, only 9 was obtained in only 4% and most of the starting material was recovered.These facts indicate clearly that the double bond shifted product (**10**) is formed from **9** under these conditions.

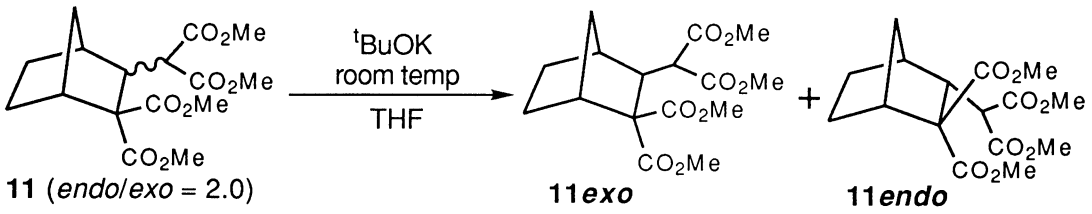
The complete lack of the intramolecular Michael cyclization reaction of **9** to the starting bicycloheptene (**8**) would probably be due to a very fast conformational change of the direct ring-opened conformer having



Scheme 3.

two *quasi*-diaxial substituents (**9a**) to the more stable conformer having *quasi*-diequatorial substituents (**9b**) as illustrated in Scheme 3.

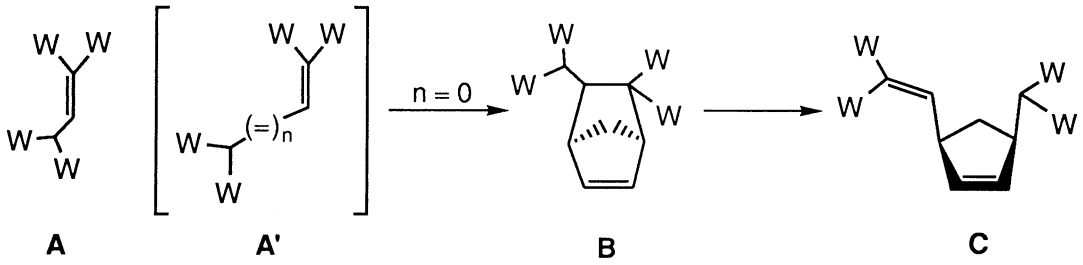
In support for the above conclusion, the result of base treatment of the dihydro derivative (**11**) derived from **8** by catalytic hydrogenation (H_2 / 5% Pd-C in MeOH, room temp) seems to be worthy of comment. Thus, when **11** (*endo*/*exo*= *ca.* 2.0) was treated by ^{t}BuOK in THF for 1 d, none of the ring opened product was obtained and the bicyclic compound was composed of 91% *exo*- (**11*exo***) and 9% *endo*-isomers (**11*endo***). This fact shows that the Michael reaction is reversible and the more thermodynamically stable *exo* isomer (**11*exo***) was formed predominatingly over the less stable *endo*-isomer (**11*endo***).



Scheme 4.

In conclusion, the construction of the bicyclo[2.2.1]hept-2-ene (**8**) and its base-mediated retro-Michael reaction to *cis*-3,5-disubstituted cyclopentene (**9**) are novel in the points that neither oxidation nor reduction is required and yet the reaction proceeds in complete retention of stereochemistry.

The entire conversion (**7** → **8** → **9**) demonstrated in this paper would promise that the same reactions proceed in the case of the isoelectronic compounds, if suitable strain is involved in the bicyclic compounds (cf. **A** → **B** → **C**). Variation of **A** to the higher vinylogous compounds (cf. **A'**: n ≥ 1), alteration of the ring size of cycloalkadienes, and use of photo[2+2]cycloaddition for construction of the bicyclic compounds (e.g. cyclopentene and its higher methylene homologues) are the prospective future projects.



Scheme 5. W: an electron-withdrawing group.

References

1) G. Desimoni, G. Tacconi, A. Barco, and G. P. Pollini, "Natural Products Synthesis through Pericyclic Reactions," American Chemical Society, Washington, D. C. (1983), pp. 119-254.

2) G. Just, T. J. Liak, M.-I. Lim, P. Pavin, and Y. S. Tsantrizos, *Can. J. Chem.*, **58**, 2024 (1980); R. Noyori, T. Sato, and Y. Hayakawa, *J. Am. Chem. Soc.*, **100**, 2561 (1978); P. Kozikowski and A. Ames, *ibid.*, **103**, 3923 (1981).

3) C. Kaneko, N. Katagiri, M. Nomura, and H. Sato, *Israel J. Chem.*, **31**, 247 (1991) and references cited therein.

4) N. Katagiri, H. Akatsuka, T. Haneda, C. Kaneko, and A. Sera, *J. Org. Chem.*, **53**, 5464 (1988). See also, I. A. Wolf, D. W. Olds, and G. E. Hilvest, *Synthesis*, **1984**, 732.

5) ^{1}H-NMR ($CDCl_3$) δ 3.79 (6H, s, 2 x OMe), 3.83 and 3.85 (each 3H, s, 2 x OMe), 4.74 (1H, d, J = 10 Hz, 3-H), 7.25 (1H, d, J = 10 Hz, 2-H).

6) Synthesis of sodium salt of the corresponding tetraethyl ester by condensation of chloroform with diethyl sodiomalonate was reported, N. G. Galakotos, J. E. H. Hancock, O. M. Morgan, M. R. Robert, and J. K. Wallace, *Synthesis*, **1978**, 472. See also, C. K. Ingold and E. A. Perren, *J. Chem. Soc.*, **119**, 1591 (1921). Though synthesis of **7** was reported quite recently, its ^{1}H-NMR data are quite different from ours. R. A. S. Demir and C. Tanyeli, *Synth. Commun.*, **21**, 1433 (1991).

7) The same reaction using dimethyl acetoxymethylenemalonate (**2**) as the dienophile proceeded in a much slower rate than that of **7**. Since **2** could react with furan under high pressure conditions,[a] it seems possible that **7** serves as the dienophile in Diels-Alder reaction with furan. a) A. Sera, T. Kubo, K. Itoh, H. Yamada, Y. Mikata, C. Kaneko, and N. Katagiri, *J. Org. Chem.*, **53**, 5460 (1988).

8) **8**: mp 103-110 °C (AcOEt-hexane). The *endo*/*exo* ratio (*ca.* 2:1) was determined by ^{1}H-NMR analysis. ^{1}H NMR ($CDCl_3$) δ *endo* isomer: 1.43 (1H, J = 9 Hz, 7-H), 1.91 (1H, d, 9 Hz, 7-H'), 2.75 (1H, br s, 1-H), 3.24 (1H, d, J = 11 Hz, 2'-H), 3.36 (1H, br s, 4-H), 3.71 (1H, dd, J =11 and 3 Hz, 2-H), 3.61, 3.70, 3.77, 3.78 (each 3H, s, 4 x Me), 6.25 (1H, dd, J = 5, 2.5 Hz, 5- or 6-H), 6.29 (1H, dd, J = 5, 2.5 Hz, 5- or 6-H); *exo* isomer: 1.55 (1H, dd, J = 9.5, 2 Hz, 7-H), 2.02 (1H, d, J = 9.5 Hz, 7-H'), 2.65 (1H, br s, 1-H), 3.28 (1H, dd, J = 11, 2 Hz, 2-H), 3.36 (1H, br s, 4-H), 3.48 (1H, d, J = 11 Hz, 2'-H), 3.67, 3.68, 3.70, 3.76 (each 3H, s, 4 x Me), 5.99 (1H, dd, J = 5, 2.5 Hz, 5- or 6-H), 6.37 (1H, dd, J = 5, 3.3 Hz, 5- or 6-H).

9) **9** and **10**: oil (**9**/**10** = 2.4 and ***E*-10**/***Z*-10**= 2.2). ^{1}H NMR ($CDCl_3$) δ **9**: 1.44 (1H, dt, J = 13.5, 7.5 Hz, 5-H), 2.48 (1H, dt, J = 13.5, 8 Hz, 5-H'), 5.58-5.65 (1H, m, 2- or 3-H), 5.80-5.85 (1H, m, 2- or 3-H), 6.78 (1H, d, J = 10 Hz, -CH=); **10**: *E*-isomer: 2.33 (1H, dt, J = 17.5, 3 Hz, 5-H), 2.84 (1H, ddd, J = 17.5, 8, 2 Hz, 5-H'), 4.14 (1H, d, J = 10 Hz, $CH(CO_2Me)_2$), 5.62 (1H, dm, J = 10 Hz, =CH-), 6.07 (1H, dd, J = 5.5, 2.5 Hz, 2- or 3-H), 6.24 (1H, dd, J = 5.5, 2 Hz, 2- or 3-H); *Z*-isomer: 4.31 (1H, d, J = 10 Hz, $CH(CO_2Me)_2$), 5.45 (1H, d, J = 10 Hz, =CH-), 6.24 (1H, dd, J = 5.5, 2 Hz, 2- or 3-H), 6.44 (1H, d, J = 5.5 Hz, 2- or 3-H).

10) ^{1}H-NMR ($CDCl_3$) δ **11*exo***; 1.90 (1H, d, J = 10.5 Hz, 7-H), 2.05 (1H, br s, 1-H), 2.83 (1H, br s, 4-H), 3.32 (1H, d, J = 10 Hz, $CH(CO_2Me)_2$), 3.47 (1H, dd, J = 10, 1.8 Hz, 2-H), 3.61, 3.71, 3.73, 3.75 (each 3H, s, 4 x Me); **11*endo***; 1.99 (1H, d, J = 10.5 Hz, 7-H), 2.20 (1H, br s, 1-H), 2.83 (1H, br s, 4-H), 3.09 (1H, ddd, J = 12, 3.5, 1.2 Hz, 2-H), 3.67, 3.70, 3.75, 3.73 (each 3H, s, 4 x Me), 4.24 (1H, d, J = 10 Hz, $CH(CO_2Me)_2$).

(Received April 18, 1994)