Studies on Synthesis of 10,11-Dihydro-5*H*-dibenzo[*a*,*d*]cycloheptene Derivatives. III.[1] Stereostructures of Isomeric 8,9-Dimethoxycarbonyldibenzo[2,3:5,6]bicyclo[5.2.0]nonan-4-ones Determined by ^{1}H–^{1}H and ^{13}C–{^{1}H} Nuclear Overhauser Effects in Nuclear Magnetic Resonance Spectroscopy

Yasuhiro FUJIWARA* and Masao OKAMOTO

Kyoto Pharmaceutical University, Misasagi-Nakauchi-cho 5, Yamashina-ku, Kyoto 607, Japan. *Received April 13, 1988*

Stereochemistry of 8,9-dimethoxycarbonyldibenzo[2,3:5,6]bicyclo[5.2.0]nonan-4-ones (2a, 3a, 4a, and 5a) and 8,9-dimethoxycarbonyl-4-hydroxydibenzo[2,3:5,6]tricyclo[5.2.0.0^{4,8}]nonanes (6a and 7a) was studied by chemical and spectrometrical means.

Intramolecular acid anhydride formation reactions of isomeric *cis*-dicarboxylic acids (3c, 5c, 6c, and 4c) afforded the anhydrides (3d, 5d, 6d, and 5d), respectively. Interconversion between 2a and 3a and between 4a and 5a at higher temperature by thermal reaction resulted in equilibria of 2a and 3a (3:2) and of 4a and 5a (20:1).

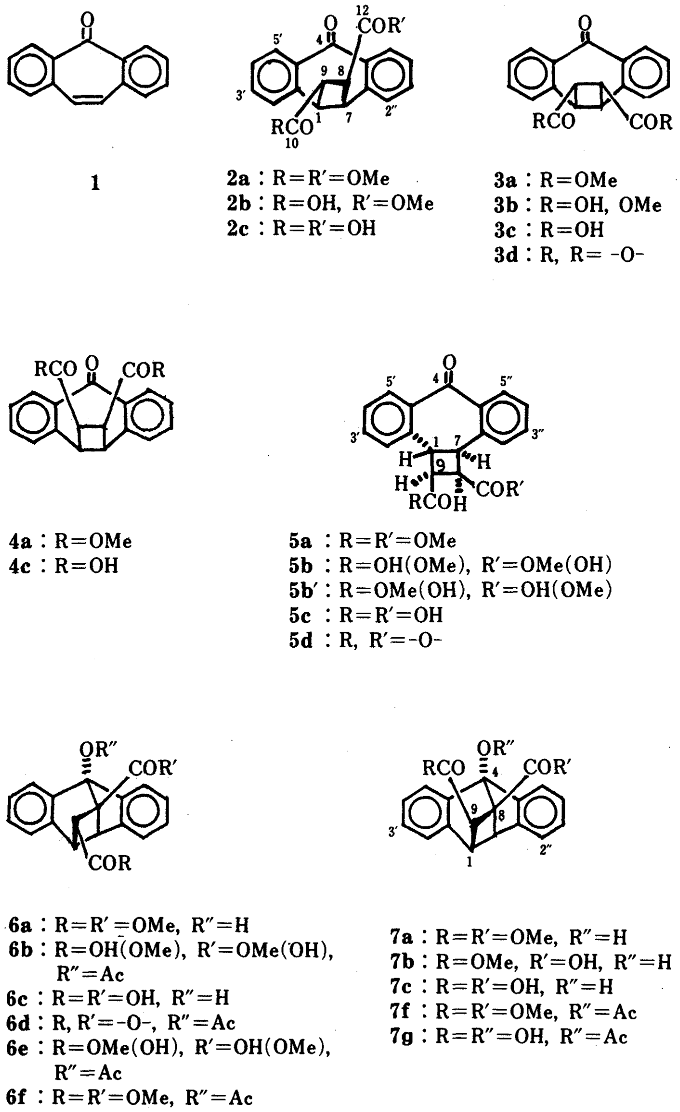
Detailed ^{13}C and ^{1}H assignments (3a, 4a, 5a, 6a, and 7a), and stereostructural assignments (3a, 4a, and 5a) were made by using nuclear magnetic resonance (NMR) techniques such as ^{1}H–{^{1}H} and ^{13}C–{^{1}H} NMR, ^{13}C/^{1}H chemical shift-correlated NMR, and ^{1}H–^{1}H and ^{13}C–{^{1}H} nuclear Overhauser effect (NOE) measurements. Moreover, a possible mechanism of interconversion between 4a and 5a is discussed.

Keywords dibenzo[*a*,*d*]cyclobutanocycloheptene derivative; dibenzo[2,3:5,6]tricyclo[5.2.0.0^{4,8}]nonane derivative; stereochemistry; thermodynamic stability; 2D NMR; ^{1}H–^{1}H NOE; ^{13}C–{^{1}H} NOE; saturation transfer effect

Previously,[1] in the course of our studies on the synthesis of dibenzo[*a*,*d*]cyclobutanocycloheptene derivatives, we have obtained four stereoisomers of 8,9-dimethoxycarbonyldibenzo[2,3:5,6]bicyclo[5.2.0]nonan-4-one (**2a**, **3a**, **4a** and **5a**) and two stereoisomeric 8,9-dimethoxycarbonyl-4-hydroxydibenzo[2,3:5,6]tricyclo[5.2.0.0^{4,8}]nonanes (**6a** and **7a**). Then, the stereostructures of **6a** and **7a** have been clarified by the existence of hydrogen-bonding. The structure of **2a**, including configuration and conformation, has been assigned on the basis of two-dimensional (2D) nuclear magnetic resonance (NMR) (2D INADEQUATE and ^{13}C/^{1}H chemical shift correlation (CH COSY)) and nuclear Overhauser effect (NOE) experiments, but this has not yet been done for **3a**, **4a**, and **5a**.

In the present paper, stereostructural analyses of **3a**, **4a**, and **5a**, and thermodynamic relationships among four stereoisomeric nonanones (**2a**, **3a**, **4a**, and **5a**) are described, together with chemical and NMR spectrometric data on **6a**, **7a**, and **2a**.

Chemical Methods First, intramolecular acid anhydride formation of the dicarboxylic acids[1] (**2c**, **3c**, **4c**, **5c**, **6c**, and **7c**) was investigated (Chart 1). Each of them was heated with acetic anhydride (Ac_2O) under reflux for 2 h. The dicarboxylic acids (**3c** and **5c**) readily reacted to give the anhydrides (**3d** and **5d**[2]), respectively. These products were identified by elementary analysis and infrared absorption (IR) spectroscopy. The anhydrides (**3d** and **5d**) were individually refluxed with methanol to give the monoesters (**3b** and **5b′**), and esterifications of **3b** and **5b′** with diazomethane (CH_2N_2) gave the starting diesters (**3a** and **5a**), respectively. Interestingly, when the dicarboxylic acid (**4c**) was treated with Ac_2O, followed by heating *in vacuo* at 200—240 °C for 1 h, the same anhydride (**5d**) was obtained as from **5c**. However, no intramolecular anhydride was obtained from **2c**. The dicarboxylic acid (**6c**) also reacted readily to give the acetylated anhydride (**6d**), but **7c** gave only the acetylated dicarboxylic acid (**7g**) as an amorphous mass. The anhydride (**6d**) was treated with methanol to give the monoester (**6e**), which was treated with CH_2N_2 to



1

2a : R=R′=OMe
2b : R=OH, R′=OMe
2c : R=R′=OH

3a : R=OMe
3b : R=OH, OMe
3c : R=OH
3d : R, R= -O-

4a : R=OMe
4c : R=OH

5a : R=R′=OMe
5b : R=OH(OMe), R′=OMe(OH)
5b′ : R=OMe(OH), R′=OH(OMe)
5c : R=R′=OH
5d : R, R′=-O-

6a : R=R′=OMe, R″=H
6b : R=OH(OMe), R′=OMe(OH), R″=Ac
6c : R=R′=OH, R″=H
6d : R, R′=-O-, R″=Ac
6e : R=OMe(OH), R′=OH(OMe), R″=Ac
6f : R=R′=OMe, R″=Ac

7a : R=R′=OMe, R″=H
7b : R=OMe, R′=OH, R″=H
7c : R=R′=OH, R″=H
7f : R=R′=OMe, R″=Ac
7g : R=R″=OH, R″=Ac

Chart 1

TABLE I. Physical and Spectral Data for Dibenzo[2,3:5,6]bicyclo-[5.2.0]nonan-4-one and 4-Hydroxydibenzo[2,3:5,6]tricyclo[5.2.0.0^{4,8}]-nonane Derivatives (3—7)

Compd. No.	Yield (%)	mp (°C) (Recrystn. solvent)	IR ν_{max}^{KBr} (cm^{-1}) ROCO	IR ν_{max}^{KBr} (cm^{-1}) CO	Formula	Analysis (%) Calcd (Found) C	Analysis (%) Calcd (Found) H
3b	Quant.	148—150 (AcOEt– *n*-hexane)	1715 1740	1665	$C_{20}H_{16}O_5$	71.42 (71.57	4.48 4.69)
3d	90	170—171	1780 1860	1660	$C_{19}H_{12}O_4$	74.99 (75.14	3.97 3.78)
5b′	Quant.	183—185 (Benzene)	1705 1735	1640	$C_{20}H_{16}O_5$	71.42 (71.36	4.80 5.19)
5d	88 75[a)]	284—286	1775 1865	1630	$C_{19}H_{12}O_4$	74.99 (75.25	3.97 3.62)
6d	57	208—211	1740 1780 1860		$C_{21}H_{14}O_5$	72.83 (72.83	4.09 3.88)
6e	71	267—269 (EtOH– Et_2O)	1700 1735 1755		$C_{22}H_{18}O_6$	69.83 (69.61	4.80 4.78)
6f	Quant. 74[b)]	157—159 (EtOH)	1735 1745 sh[e)]		$C_{23}H_{20}O_6$	70.40 (70.64	5.14 5.20)
7f	90[c)] 73[d)]	152—153 (Et_2O)	1735 1745		$C_{23}H_{20}O_6$	70.40 (70.48	5.14 5.18)

a) Yield from **4c**. *b)* From **6a**. *c)* From **7c** (2 steps). *d)* From **7a**. *e)* sh: shoulder.

afford the acetylated diester (**6f**) (identical with that obtained by treatment of **6a** with Ac_2O). The acetylated diester (**7f**) obtained by treatment of **7g** with CH_2N_2 was identical with the product obtained by heating of **7a** with Ac_2O. Physical data and IR data of these new compounds are listed in Table I.

Next, thermal interconversion reactions among the adducts (**2a**, **3a**, **4a**, and **5a**) were examined (Chart 2). Thus, the adducts were individually sealed *in vacuo* and heated at a definite temperature and for a fixed time. The reaction products were analyzed by high-performance liquid chromatography (HPLC). The diesters (**2a** and **3a**) were treated individually at 280 °C for 2 h. The reaction mixtures contained mainly **2a** and **3a** together with a small amount of a degradation product which might be compound **1** in both cases, and no peaks of **4a**, **5a**, **6a**, and **7a** were detected. The integral intensity ratio of **2a** to **3a** for the reaction mixture was 3 : 2 in both cases. Each of the diesters (**4a** and **5a**) was also heated at 320 °C in the same manner. The reaction mixtures contained only **4a** and **5a** and no other peaks of degradation products were detected by HPLC. The ratio of **4a** to **5a** was 20 : 1 in both cases. As a preliminary experiment, an equimolar mixture of 5*H*-dibenzo[*a*,*d*]-cycloheptatrien-5-one and dimethyl maleate was treated according to the same procedure, but no peak corresponding to these six isomers was detected by HPLC. These experimental data indicate that interconversion occurred between **2a** and **3a** and also between **4a** and **5a** and that **2a** and **4a** are thermodynamically more stable than **3a** and **5a**, respectively.

In the previous mass spectral data on these stereoisomers,[1)] the close similarity of the **2a** fragmentation pattern to that of **3a**, and of the **4a** fragmentation pattern to that of **5a**, are not in conflict with the results of the thermal reactions.

In order to determine the reactivity of the methine protons on the cyclobutane ring carbons under basic conditions, deuterium exchange reaction in the six isomers was investigated. Thus, methanol-d_1 (CH_3OD) solution containing one of the diesters (**2a**, **3a**, **4a**, **5a**, **6a**, and **7a**) and a small amount of potassium hydroxide (KOH) was heated under reflux for a few minutes and the solvent was evaporated off *in vacuo*. After several repetitions of the procedure, the reaction solution was neutralized with dilute deuteriochloric acid (DCl) and the solvent was evaporated off. The precipitate was recrystallized from CH_3OD or ethanol-d_1 (EtOD). Interestingly, when sodium carbonate (Na_2CO_3) was used as a base, **2a** was deuterated stereoselectively and was converted to monodeuterated **2a** (**2a**-d_1). Determination of the active position(s) of each isomer is described later.

NMR-Spectrometric Methods A steady-state NOE experiment in NMR spectroscopy is one of the most useful methods for elucidating stereochemistry of organic compounds in solution.[3)] Thus, NOE experiments were applied to stereochemical analysis in the present investigation. Assignments of proton and carbon resonances were undertaken by using NMR techniques such as selectively proton-decoupled ^1H and ^{13}C (^1H-{^1H} and ^{13}C-{^1H}) NMR, CH

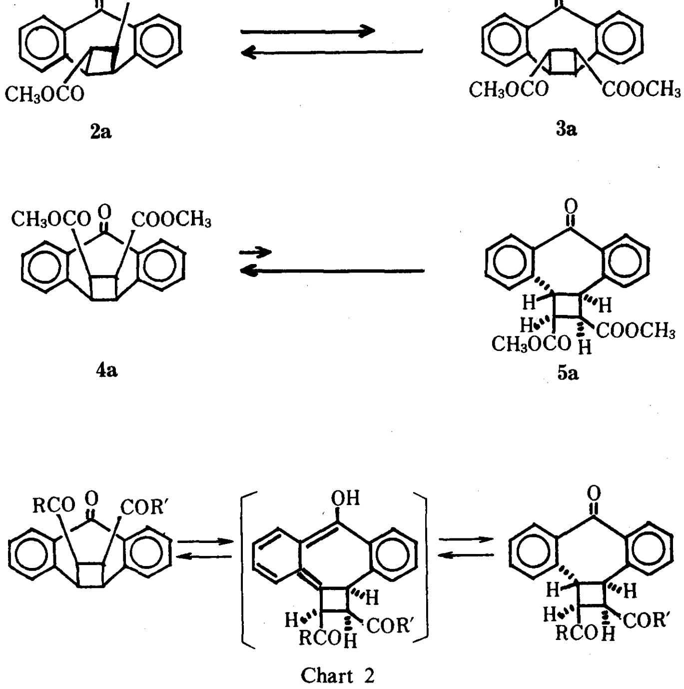
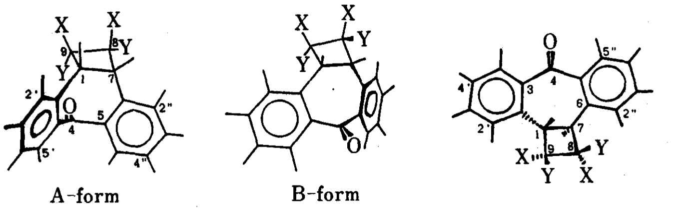


Chart 2



3a : X=COOCH₃, Y=H
4a : X=H, Y=COOCH₃

5a : X=H, Y=COOCH₃

Fig. 1. Possible Conformations of **3a** and **4a** Based on Stereomodels, and Plausible Conformation of **5a** Based on a Stereomodel and NOE Data

COSY,[4] and selectively proton-irradiated ^{13}C-^{1}H (^{13}C-{^{1}H}) NOE[1,3,5] experiments.

Assignments of Proton and Carbon Resonances of 3a and 4a The ^{1}H-NMR spectra of **2a**, **3a**, **4a**, and **5a** are shown in Fig. 2.

Assignments of proton and methine carbon resonances of **3a** were readily made based on the ^{1}H-{^{1}H} NMR and ordinary CH COSY (Table II). However, it was not easy to assign quaternary carbons in the benzene ring and/or to determine the connectivity of the carbons. Therefore, ^{13}C-{^{1}H} NOE experiments were employed to obtain information on the distances between protons and the quaternary carbons. Irradiation of H(5′) and H(5″) (H(5′,5″)) at δ 7.68 produced NOEs for carbon signals at δ 140.43 and at δ 200.55 (C(4)). On the other hand, irradiation at the resonances due to both H(1,7) and H(8,9) produced NOEs for the same carbon signal at δ 138.12 (Table III (**3a**)). These observations indicate that the quaternary carbon at δ 140.43 is closer to H(5′,5″) than that at δ 138.12. On the other hand, the carbon at δ 138.12 is closer to H(1,7) than that at δ 140.43. Therefore, quaternary carbons in the benzene rings and/or the connectivities should be assigned as shown in the last column of Table III. The assignments of carbonyl carbon (C(4)) and ester carbonyl carbons (C(10,12)) were obvious from the chemical shifts, and thus, all the ^{13}C and ^{1}H signals of **3a** have been assigned. We could assign most of the proton and carbon resonances of **4a** by similar means (Tables II and III). However, the C(1,7) and C(8,9) resonances (cyclobutane ring) could not be assigned, because the protons H(1,7) and H(8,9) had almost the same chemical shift values (δ 3.795). Accordingly, these carbon resonances were assigned by an ordinary ^{13}C-{^{1}H} NMR method, that is, low-power irradiation on the proton resonance at δ 7.42. Three-bond ^{13}C–^{1}H coupling of the carbon signal (doublet multiplet) at δ 45.76 was effectively decoupled; therefore, the signal at δ 45.76 was assigned to C(1,7).

In this way, we obtained assignments of all the carbons and protons of **3a** and **4a**. These results are listed in Table II together with the proton–proton spin-coupling constants.

Stereochemistry of 3a and 4a In **3a**, large NOE[1] between H(1,7) and H(2′,2″) was detected (15—16.5%) in the ^{1}H–^{1}H NOE experiment. Furthermore, small NOEs between H(8,9) and C(4) (7%), between H(8,9) and C(1″,1′) (C(6,2)) (11%), and also between H(8,9) and C(6″,6′) (C(5,3)) (8%) were observed in the ^{13}C–{^{1}H} NOE experiments (Tables III and IV). These results indicate that H(8) is located near to C(4), C(1″) and C(6″), and that H(9) is near to C(4), C(1′) and C(6′). Thus, the distances between the cyclobutane protons H(1) and H(7), and the benzene protons H(2′) and H(2″) can be considered to be very

TABLE II. Final Assignments of ^{13}C and ^{1}H Signals, and Proton–Proton Coupling Constants for **3a** and **4a** in $CDCl_3$

	3a		**4a**	
Carbon[a]	^{13}C Chemical shifts (δ)[b]	^{1}H Chemical shifts (δ)[b] and couplings (Hz)[c]	^{13}C Chemical shifts (δ)[b]	^{1}H Chemical shifts (δ)[b] and couplings (Hz)[c]
1,7	44.33	4.47 (m)	45.76[d]	3.795 (s)
2,6 (1′,1″)	138.12[e]		141.90	
3,5 (6′,6″)	140.43[e]		137.23[e]	
4	200.55		192.01	
8,9	47.89	3.45 (m)	43.54	3.795 (s)
10,12	172.03		172.18	
11,13	52.21	3.71 (s)	52.47	3.80 (s)
2′,2″	130.17	7.24 (ddd) (7.7, 1.3, 0.4)	124.44	7.42 (ddd) (7.9, 1.4, 0.5)
3′,3″	132.53	7.46 (ddd) (7.7, 7.5, 1.3)	132.95	7.54 (ddd) (7.9, 7.5, 1.4)
4′,4″	127.81	7.34 (ddd) (7.6, 7.5, 1.3)	127.19	7.38 (ddd) (7.6, 7.5, 1.4)
5′,5″	129.25	7.64 (ddd) (7.6, 1.3, 0.4)	132.24	8.19 (ddd) (7.6, 1.4, 0.5)

a) Labelling as shown in Chart 1. *b*) In ppm relative to internal $^{13}\underline{C}H_3Si(C\underline{H}_3)_3$, ± 0.001 ppm in ^{1}H and ± 0.015 ppm in ^{13}C. *c*) ± 0.12 Hz. *d*) Assignment was confirmed by a ^{13}C–{^{1}H} NMR method based on H(2′,2″). *e*) Assignments were confirmed by ^{13}C–{^{1}H} NOE experiments. Protonated carbon assignments were obtained from CH COSY spectra together with a consideration of ^{1}H–^{1}H coupling networks.

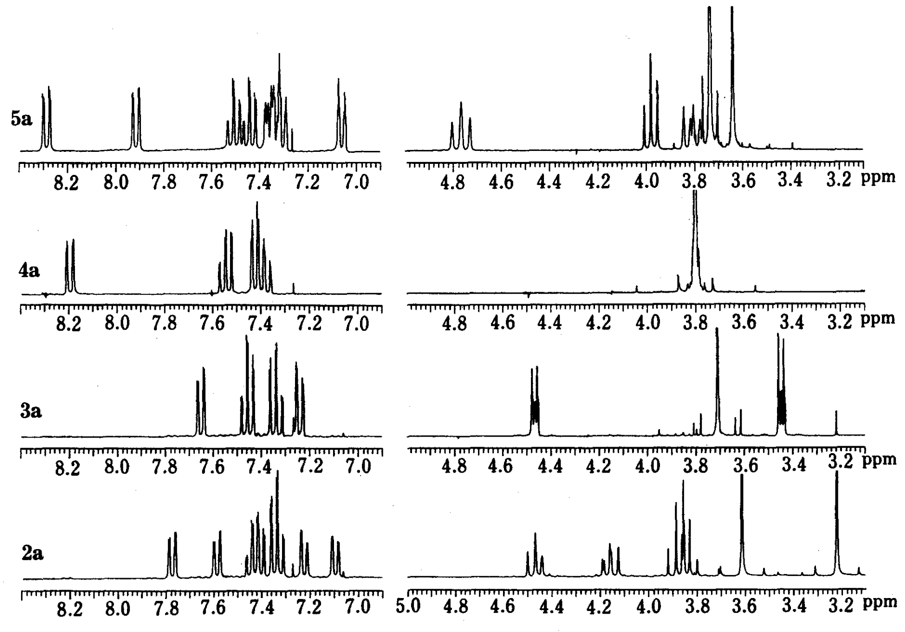


Fig. 2. ^{1}H-NMR Spectra of **2a**, **3a**, **4a**, and **5a** in $CDCl_3$

short. Therefore, **3a** should be an *exo–cis* adduct of the photocycloaddition reaction[1] and its conformation should be the A-form, of the two possible conformations (see Fig. 1). However, in the case of **4a** little information could be obtained from NOE measurements (Tables III and IV), because the chemical shifts of the cyclobutane methine protons were very close to each other. Measurements in several different solvents did not overcome the problem.

Since the characteristics of stereoisomers are generally reflected in their ^{13}C-NMR chemical shifts,[6] we attempted to compare the ^{13}C chemical shifts of the cyclobutane carbons in **4a** with those in **2a**.[1]

By comparing the chemical shifts of C(1,7) (δ 45.76) and C(8,9) (δ 43.54) in **4a** with those of **2a**,[1] we noticed that the order of the chemical shifts of these carbons in **4a** parallels that of the chemical shifts of C(7) (δ 46.79) and C(8) (δ 45.35) in **2a** but not that of the chemical shifts of C(1) and C(9) in **2a**. On the other hand, the order of the chemical shifts of C(1,7) (δ 44.33) and C(8,9) (δ 47.89) in **3a** parallels that of C(1) (δ 43.41) and C(9) (δ 47.23) in **2a**. These observations suggest that **4a** takes an *endo–cis* configuration.

Table III. ^{13}C–{^{1}H} NOE Values of **3a** and **4a** in CDCl$_3$

Observed carbon (δ)	Irradiated proton (δ) **3a** 7.65 (H(5′,5″))	4.47 H(1,7)	3.45 (H(8,9))	Assignment
138.12	1.04	1.30	1.11	C(2,6)(C(1′,1″))
140.43	1.45	1.00	1.08	C(3,5)(C(6′,6″))
172.03	0.97	1.20	1.59	C(10,12)
200.55	1.14	1.00	1.07	C(4)

Observed carbon (δ)	Irradiated proton (δ) **4a** 8.19 (H(5′,5″))	7.42 (H(2′,2″))	3.795 $(\mathrm{C\underline{H}_3}, >\mathrm{C\underline{H}})$	Assignment
137.23	1.47	1.00	1.18	C(3,5)(C(6′,6″))
141.90	1.01	1.27	1.46	C(2,6)(C(1′,1″))
172.18	1.00	1.00	2.15	C(10,12)
192.01	1.50	0.98	1.18	C(4)

The NOE values are given as the ratio of the signal intensity of on- to off-resonance decoupled spectra in the absolute intensity mode. Average error ±0.05. Decoupling power ($\gamma H_2/2\pi$): **3a**, 15 Hz; **4a**, 10 Hz.

Table IV. ^{1}H–^{1}H NOE Values of **3a** and **4a** in CDCl$_3$

Irradiated	Observed (%)[a] **3a** H(3′,3″)	H(2′,2″)	H(1,7)	H(8,9)
H(8,9)	0.0	3.0	3.5	—
H(1,7)	0.0	16.5	—	5.5
H(2′,2″)	15.0	—	15.0	4.0

Irradiated	Observed (%)[a] **4a** H(2′,2″)
H(1,7), H(8,9), C$\underline{H}_3$	19.5

a) Ratio of the intensity of a signal to that of the irradiated large-negative one in the difference spectra. Decoupling power ($\gamma H_2/2\pi$): **3a**, 3.4 Hz; **4a**, 2.8—3.4 Hz.

A large NOE was observed between the proton resonance at δ 3.795 and that from H(2′,2″). The bulk of the NOE enhancement should be ascribed to that between H(1,7) and H(2′,2″).[7]

Therefore, the stereostructure of **4a** should be an *endo–cis* type, having a similar ring conformation to that of **3a** (Fig. 1, A-form), which takes an *exo–cis* type of stereostructure.

Assignments of Proton and Carbon Resonances of 5a The ^{1}H-NMR spectrum of **5a** is shown in Fig. 2. Assignments of proton and proton-attached carbon resonances were determined similarly by means of ^{1}H-{^{1}H} NMR and CH COSY (Table V) experiments. The quaternary carbons and the connectivities among them were assigned by ^{13}C–{^{1}H} NOE (Fig. 3 and Table VI). As shown in Fig. 3c and Table VI, carbon signals at δ 136.48 and at δ 198.58 (C(4)) increased by 39 and 24%, respectively, when the H(5″) proton resonance at δ 8.29 was irradiated. Since larger magnitude of NOEs means shorter distance between irradiated and observed nuclei,[3] the carbon signal at δ 136.48 was assigned to C(5) (C(6″)). The carbon signals of C(3) (C(6′)), C(10) and C(12), except those of C(2) and C(6), were readily assigned in a similar manner. However, since the signals of C(2) (C(1′)) and C(6) (C(1′)) appeared at about δ 141.4 as a broad signal owing to complicated spin–spin couplings (Figs. 3b—e), a distinctly enhanced signal could not be obtained by on-resonance irradiation of H(1) or H(7). But, as shown in Fig. 3f, the difference spectrum between spectra (e) and (b) left an enhanced signal component at δ 141.47. Accordingly, we assigned the signal at δ 141.47 to C(2). Assignments of all the ^{13}C and ^{1}H signals of **5a** are listed in Table V together

Table V. Final Assignments of ^{13}C and ^{1}H Signals, and Proton–Proton Coupling Constants for **5a** in CDCl$_3$

Carbon[a]	^{13}C Chemical shifts (δ)[b]	^{1}H Chemical shifts (δ)[b]	^{1}H–^{1}H Coupling constants (Hz)[c]
1	46.39	4.77 (dddd)	12.0, 10.5, 0.8, 1.1
2 (1′)	141.47[d]		
3 (6′)	139.30[d]		
4	193.58		
5 (6″)	136.48[d]		
6 (1″)	141.28[d]		
7	44.40	3.81 (ddd)	12.0, 8.1, 1.0
8	45.30	3.98 (ddd)	8.1, 8.1, 0.8
9	42.19	3.74 (dd)	10.5, 8.1
10	171.62[d]		
11	51.93	3.64 (s)	
12	171.99[d]		
13	52.17	3.74 (s)	
2′	123.11	7.31 (dddd)	7.5, 1.3, 0.4, 1.1
3′	132.40[e]	7.51 (ddd)	7.5, 7.5, 1.4
4′	126.92	7.325 (ddd)	7.8, 7.5, 1.3
5′	131.41	7.91 (ddd)	7.8, 1.4, 0.4
2″	124.91	7.06 (dddd)	7.5, 1.4, 0.4, 1.0
3″	132.69	7.44 (ddd)	7.5, 7.4, 1.5
4″	127.11	7.331 (ddd)	8.0, 7.5, 1.4
5″	132.37[e]	8.29 (ddd)	8.0, 1.5, 0.4

a) Labelling as shown in Chart 1. *b*) In ppm relative to internal $^{13}\underline{C}H_3Si(C\underline{H}_3)_3$, ±0.001 ppm in ^{1}H and ±0.015 ppm in ^{13}C. *c*) ±0.12 Hz in CDCl$_3$. *d*) Assignments were confirmed by ^{13}C–{^{1}H} NOE experiments. *e*) Assignments may be interchanged. Protonated carbon assignments were obtained from CH COSY spectra together with a consideration of ^{1}H–^{1}H coupling networks.

with the proton–proton spin-coupling constants.

Stereochemistry of 5a The relative configurations including conformation about C(1), C(7), C(8), and C(9) of **5a** were investigated on the basis of ^{1}H–^{1}H and ^{13}C–{^{1}H} NOE data. Observed ^{1}H–^{1}H NOE difference spectra in DMSO-d_6 and NOE values (%) are shown in Fig. 4 and Table VII.

As shown in Figs. 3 and 4, and Tables VI and VII, various magnitudes of NOEs were observed between following proton–proton and proton–carbon pairs: H(2′)–H(9) (15—17%), H(9)–H(7) (6—7.5%), H(2″)–H(7) (3—4.5%), H(2″)–H(8) (3.2—6.7%), H(1)–C(4) (12%), H(1)–C(10) (9%), and H(1)–C(12) (7%). These observations indicate that H(2′) is very close to H(9), and that H(7) takes a *cis* configuration with respect to H(9), which resides in a 1,3-relationship to H(7). H(2″) is located at similar distances from both H(7) and H(8). Furthermore, the NOE data also mean that H(1) is fairly close to the two methoxycarbonyl groups. Thus, H(1) and the methoxycarbonyl groups are in a *cis* configuration with respect to one another. In other words, the cyclopropane ring protons H(7), H(8), and H(9) take *cis* arrangements with respect to one another and H(1) takes a *trans* configuration with respect to these protons. In addition, the ring juncture between the four- and seven-membered ring is in *trans* relationship. Moreover, H(1) is spatially close to C(4). The stereostructure of **5a** thus determined is depicted in Fig. 1.

Additional Evidence for the Stereostructures of 6a and 7a The proton and carbon resonances of **6a** and **7a** were assigned similarly by ^{1}H–{^{1}H} NMR, CH COSY and ^{13}C–{^{1}H} NOE, as shown in Table VIII. The chemical structures and the configuration at C(9) have already been clarified by

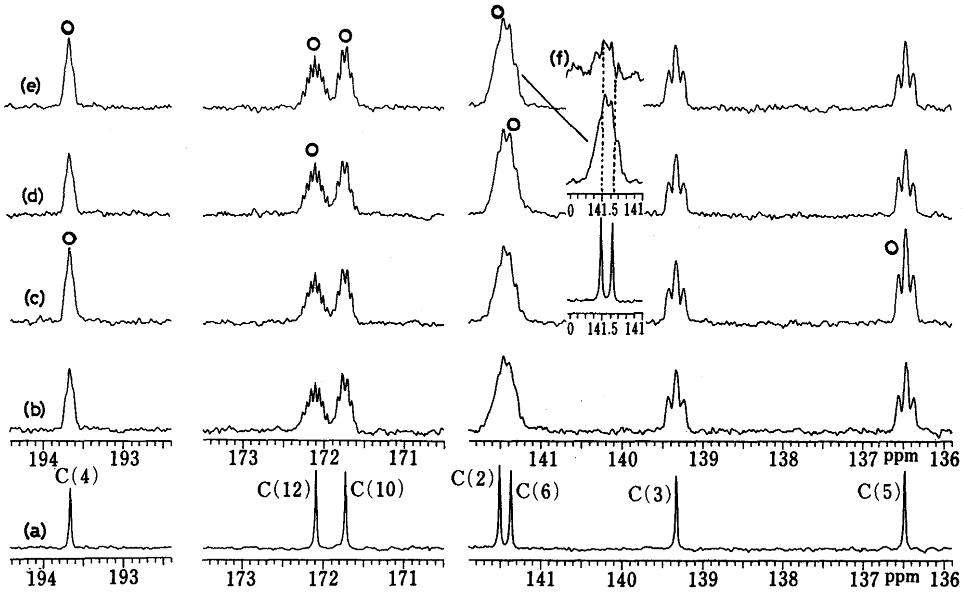


Fig. 3. ^{13}C–{^{1}H} NOE Spectra of **5a** in CDCl$_3$ at 25 °C

(a) Gated decoupling (^{1}H decoupling and no NOE); (b) as in (a), but off-resonance irradiated and no decoupling (control); (c) as in (b), but H(5″) irradiated; (d) as in (b), but H(2″) irradiated; (e) as in (b), but H(1) irradiated; (f) C(2) carbon signal in the difference spectrum between (e) and (b). Circles denote increased carbon signal owing to NOE. Saturation and acquisition times were 30 s (see reference 5*b*) and 1.2 s. Decoupling power ($\gamma H_2/2\pi$) was 11 Hz.

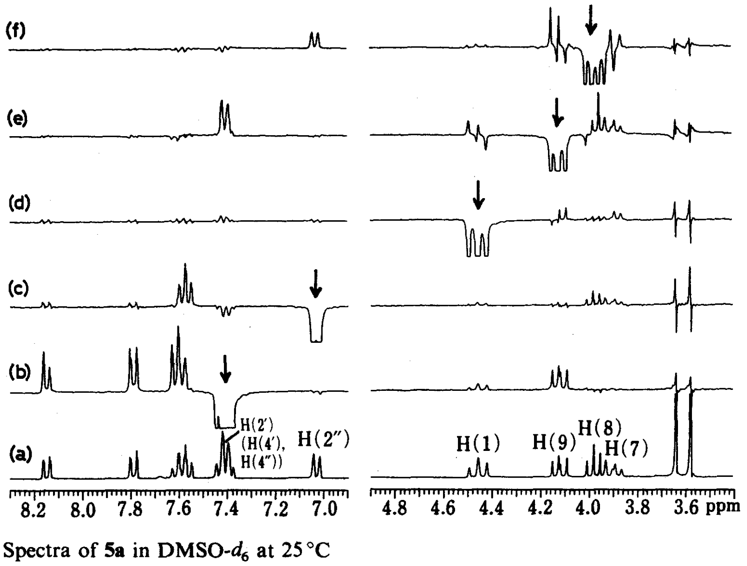


Fig. 4. ^{1}H–^{1}H NOE Difference Spectra of **5a** in DMSO-d_6 at 25 °C

(a) Off-resonance gated irradiation spectrum (control); (b), (c), (d), (e), (f) NOE difference spectra between on- (shown by arrow) and off-resonance saturated spectra. Saturation and acquisition times were 5 and 3 s. Decoupling power ($\gamma H_2/2\pi$) was 4.6 Hz.

Table VI. ^{13}C–{^{1}H} NOE Values of **5a** in $CDCl_3$

Observed carbon (δ)	Irradiated proton (δ)							Assignment
	8.29 (H(5″))	7.91 (H(5′))	7.06 (H(2″))	4.77 (H(1))	3.98 (H(8))	3.81 (H(7))	3.64 (H(11))	
136.48	1.39	1.03	0.97	1.02	0.96	1.01	0.97	C(5) (C(6″))
139.30	1.01	1.55	0.98	1.06	1.00	1.03	1.03	C(3) (C(6′))
141.28			(1.26)$^{b)}$			(1.34)$^{b)}$		C(6) (C(1″))
	1.00$^{a)}$	0.99$^{a)}$	1.13$^{a)}$	1.17$^{a)}$	1.02$^{a)}$	1.17$^{a)}$	0.99$^{a)}$	
141.47				(1.34)$^{b)}$				C(2) (C(1′))
171.62	1.01	1.00	1.03	1.09	1.02	1.32$^{c)}$	1.44	C(10)
171.99	1.00	1.01	1.06	1.07	1.39	1.03	1.16	C(12)
193.58	1.24	1.23	1.00	1.12	1.02	1.05	0.99	C(4)

NOE values are given as the ratio of the signal intensity of on- to off-resonance decoupled spectra in the absolute intensity mode. *a*) Average of the NOE values of C(6) and C(2) signals. *b*) The NOE value of the carbon signal which was assigned based on the NOE difference spectra. *c*) The enhanced intensity can be ascribed to the NOE between H(9) and C(10), since the irradiation was done near to the lower field peak of H(9) triplet (*ca.* 10 Hz). Average error ± 0.05. Decoupling power ($\gamma H_2/2\pi$): 11 Hz.

Table VII. ^{1}H–^{1}H NOE Values of **5a**

Solvent	Irradiated	Observed (%)$^{a)}$
$CDCl_3$	H(9), C$\underline{H}_3$(13)	H(2′) 15.0, H(1) 2.5, H(8) 9.5
	H(8)	H(2″) 6.7, H(7) 11.0, H(9) 14.0
	H(1)	H(2′) 2.5, H(7) 4.0
	H(2″)	H(8) 5.0, H(7) 4.5
	H(2′)	H(1) 4.0, H(9) 17.0
DMSO-d_6	H(7)	H(2″) 4.5, H(1) 4.5, H(9) 6.0
	H(8)	H(2″) 5.5
	H(9)	H(2′) 16.0, H(8) 4.1, H(7) 7.5
	H(1)	H(8) 2.5
	H(2″)	H(8) 3.2, H(7) 3.0

a) Ratio of the intensity of a signal to that of the irradiated large-negative one in the difference spectra. Decoupling power ($\gamma H_2/2\pi$): 2.8 Hz ($CDCl_3$), 2.8—4.6 Hz (DMSO-d_6). The proton assignments in DMSO-d_6 were performed by considering ^{1}H–^{1}H coupling networks from ^{1}H–{^{1}H} NMR and by comparing the spin-coupling constants with those in $CDCl_3$.

Table VIII. Final Assignments of ^{13}C and ^{1}H Signals, and Proton–Proton Coupling Constants for **6a** and **7a** in $CDCl_3$

Carbon$^{a)}$	**6a**		**7a**	
	^{13}C Chemical shifts (δ)$^{b)}$	^{1}H Chemical shifts (δ)$^{b)}$ and couplings (Hz)$^{c)}$	^{13}C Chemical shifts (δ)$^{b)}$	^{1}H Chemical shifts (δ)$^{b)}$ and couplings (Hz)$^{c)}$
1	44.64	3.82 (d) (6.0)	52.40	3.97 (dd) (6.5, 5.4)
2 (1′)	136.54$^{d)}$		132.17$^{d)}$	
3 (6′)	141.85$^{d)}$		143.26$^{d)}$	
4	86.92	4.46 (s, O$\underline{H}$)	84.85	4.21 (s, O$\underline{H}$)
5 (6″)	153.98		154.65	
6 (1″)	135.73$^{d)}$		134.52$^{d)}$	
7	53.05	4.90 (d) (6.0)	52.40	4.11 (d) (5.4)
8	64.14$^{d)}$		65.13$^{d)}$	
9	50.61	2.81 (s)	44.20	3.90 (d) (6.5)
10	173.05$^{d)}$		171.09$^{e)}$	
11	52.26	3.65 (s)	51.52	3.27 (s)
12	171.29$^{d)}$		171.44$^{d)}$	
13	52.26	3.79 (s)	52.14	3.67 (s)
2′	125.25	6.91 (ddd) (7.5, 1.3, 0.5)	124.80	6.90 (ddd) (7.5, 1.3, 0.5)
3′	127.57	7.06 (ddd) (7.5, 7.5, 1.3)	127.28	7.03 (ddd) (7.5, 7.5, 1.3)
4′	127.57	7.18 (ddd) (7.6, 7.5, 1.3)	127.84	7.135 (ddd) (7.6, 7.5, 1.3)
5′	121.62	7.62 (ddd) (7.6, 1.3, 0.5)	120.80	7.56 (ddd) (7.6, 1.3, 0.5)
2″	124.86	7.09 (m)	124.80	7.065 (m)
3″	127.83	7.09 (m)	127.49	7.07 (m)
4″	127.83	7.15 (dm) (7.2)	127.71	7.14 (dm) (7.3)
5″	119.72	7.33 (dm) (7.2)	119.82	7.38 (dm) (7.3)

a) Labelling as shown in Chart 1. *b*) In ppm relative to internal $^{13}\underline{C}H_3Si(C\underline{H}_3)_3$, ±0.001 ppm in ^{1}H and ±0.015 ppm in ^{13}C. *c*) ±0.12 Hz. *d*) Assignments were confirmed by ^{13}C–{^{1}H} NOE experiments. *e*) Assignments was confirmed by a ^{13}C–{^{1}H} NMR method based on C$\underline{H}_3$(11). Protonated carbon assignments were obtained from CH COSY spectra together with a consideration of ^{1}H–^{1}H coupling networks.

elementary analysis, IR, NMR and mass spectroscopy, and intramolecular hydrogen bonding determination.[1] We present here new experimental evidence clarifying the configuration at C(9) by using ^{1}H–^{1}H NOE and saturation transfer[8] experiments in ^{1}H-NMR (Table IX and Fig. 5). As shown in Table IX, NOE enhancement between H(7) and H(9), in a 1,3-relationship, was observed only for **7a** (12—15%) and not for **6a**. This indicates that H(7) and H(9) in **7a** are in *cis* configuration.

In order to elucidate hydrogen bonding indirectly, saturation transfer experiments on intermolecular exchange between alcoholic and water protons were undertaken with **6a** and **7a**. They were conducted on the alcoholic compounds dissolved in $CDCl_3$ containing a trace of water. In the solution, water protons undergo slow and reversible exchange with the alcoholic protons. As the water resonance is well separated from the resonances due to the alcoholic protons (4.46 ppm for **6a** and 4.21 ppm for **7a**), it was easy to irradiate the water resonance and to observe the saturation transfer effect onto the alcoholic proton resonance. As shown in Fig. 5, saturation of the water resonance results in complete saturation of the alcoholic proton resonance at δ 4.46 of **6a**. In **7a** the decrease in intensity of the alcoholic peak at δ 4.21 was 65% when the water resonance was saturated. This observation can be interpreted as follows: the internal hydrogen bonding slowed the exchange of protons to such an extent that the relaxation of saturated protons in each site becomes more rapid than the exchange rate between the sites.[9] In other words, the exchange between water and alcoholic protons is more depressed, due to hydrogen bonding, in **7a** than in **6a**.

Consequently, total ^{13}C and ^{1}H assignments and the stereochemistry for all isomers of 8,9-di(methoxycarbonyl)dibenzo[2,3:5,6]bicyclo[5.2.0]nonan-4-one (**2a**, **3a**, **4a**, and **5a**) and 8,9-dimethoxycarbonyl-4-hydroxydibenzo-[2,3:5,6]tricyclo[5.2.0.$0^{4,8}$]nonane (**6a** and **7a**) were confirmed by using several techniques of NMR spectroscopy.

In order to determine the deuterium (D) substitution position(s) of the deuterio compounds obtained by D-displacement reaction of these six stereoisomers (**2a**—**7a**) with base as mentioned above, we measured the ^1H- and ^{13}C-NMR of the D-compounds. The reactions of **2a** with Na_2CO_3–CH_3OD and KOH–CH_3OD readily proceeded, and the D-displacement took place only at C(8) in the former case and at C(8) and C(9) in the latter as judged from the ^1H- and ^{13}C-NMR spectra. In the reactions of **3a** and **4a** with KOH–CH_3OD, D-displacement reactions mainly took place at C(8) and C(9) in **3a** as determined by ^1H-NMR, and also at C(8) and C(9) in **4a** as determined by ^{13}C-NMR. Interestingly, in the case of the reaction of **5a** with KOH–CH_3OD, the D-displacement occurred at all the carbons in the cyclobutane ring in the displacement order of C(9) (thoroughly) $\gg$ C(7) $>$ C(1) $\geq$ C(8) by analysis of the ^1H- and ^{13}C-NMR spectra. The ^1H-NMR of the reaction products of **6a** and **7a** with KOH–CH_3OD led us to conclude that the displacement took place more easily at C(9) of **7a** but not at C(9) of **6a**.

Table IX. ^1H–^1H NOE Values of **6a** and **7a** in $CDCl_3$

Irradiated	Observed (%)[a)	
	6a	**7a**
H(9)	H(7) 1.2, H(1) 4.5	H(2′) 2.0, H(7) 15.0
H(1)	H(2′) 14.0, H(7) 16.0, H(9) 8.3	H(2′) 16.5, H(7) 12.0
H(7)	H(2″) 6.5, H(1) 14.0, H(9) 3.2	H(2″) 7.5, H(1) 9.5, H(9) 12.0
H(2′)	H(1) 14.5, H(9) 3.7	H(1) 12.0
OH	H(5′) 3.7, H(5″) 4.0, H(9) 3.8	H(5′) 7.5, H(5″) 4.0

a) Ratio of the intensity of a signal to that of the irradiated large-negative one in the difference spectra. Decoupling power ($\gamma H_2/2\pi$): **6a**, 4.0 Hz; **7a**, 3.4 Hz.

On the basis of the chemical and the spectrometrical results, the interconversions between the isomers are discussed below.

From the thermal reaction of **4a** and **5a**, and the stereochemistry of **4a**, **5a**, and **5d**, it seemed reasonable to assume that a reversible reaction route involving an intermediate as shown in Chart 2 exists between compounds **4** and **5** at elevated temperatures. Therefore, the inversion reaction of **5a** to **4a** at elevated temperature would proceed *via* the route in Chart 2 to give mainly the thermodynamically stable **4a**. The inversion of **4c** to **5d** (intramolecular anhydride formation reaction) would also proceed *via* the route to produce mainly thermodynamically stable **5d**, because of the existence of the sterically restricted interaction between CO (4) and anhydride ether oxygen of the anhydride expected to be formed from **4c**.

The reversible reaction between **4** and **5** seems to be supported by the result on the D-displacement reaction of the less stable **5a**; the reaction takes place rather easily at C(7) in **5a**.

In D-displacement reactions at active positions on the cyclobutane carbons, the displacement at C(8) and/or C(9) in the diesters, **2a**, **3a**, **4a**, **6a**, and **7a**, occurred at the *exo*-projecting hydrogen(s) somewhat more easily than at the *endo* one(s), while the displacement at C(1) and/or C(7) in these diesters did not occur so much. It is considered that the former fact is due to sterical factors, while the latter is due to electronic factors.

In conclusion, the ^{13}C and ^1H signals for the five compounds (**3a**, **4a**, **5a**, **6a**, and **7a**) were precisely assigned by using NMR techniques such as ^1H-{^1H} and ^{13}C-{^1H} NMR, CH COSY, and ^{13}C-{^1H} NOE. The stereochemical correlations including relative configuration and conformation were also clarified by chemical means and NOE. Interestingly, on the basis of the interconversion reaction of **4** and **5**, *cis*- and *trans*-isomers at the ring juncture between the four- and seven-membered rings, the diester **4a** is

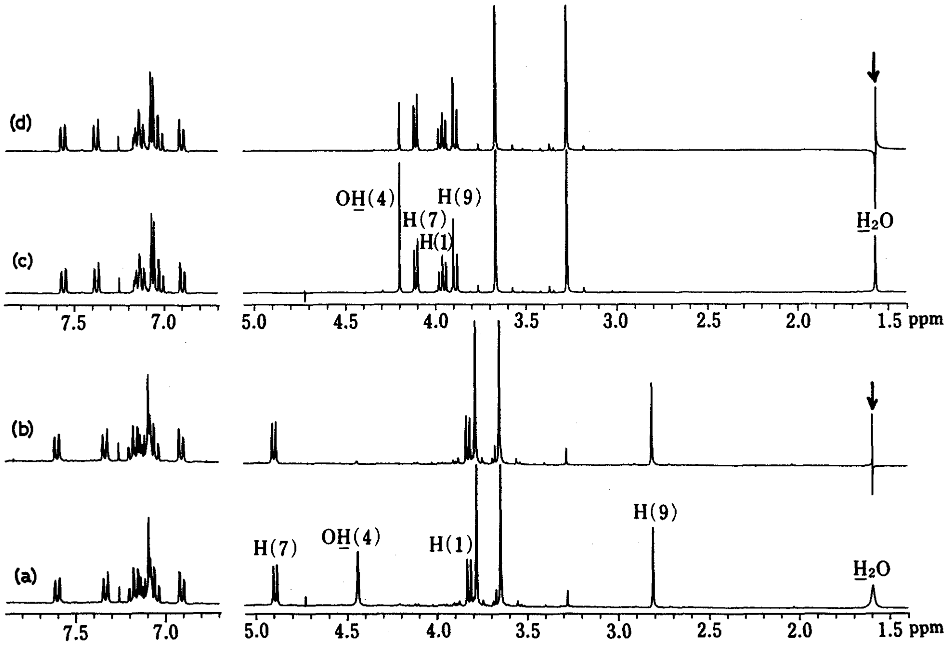


Fig. 5. ^1H-NMR Spectra of **6a** and **7a** for Saturation Transfer Determination

(a), (c) Off-resonance decoupling spectra of **6a** and **7a**, respectively. (b) and (d) as in (a) and (c), respectively, but H_2O signal decoupled (shown by arrow).

thermodynamically more stable than **5a**. However, the acid anhydride (**5d**) is the only stable product which is obtained from heating of **5c** and of **4c** with Ac_2O.

In consequence of the stereochemical studies of these stereoisomers, it is clear that a photocycloaddition reaction of 5*H*-dibenzo[*a*,*d*]cycloheptatrien-5-one (**1**) with dimethyl maleate or fumarate in dioxane takes place easily to give *cis* adducts (**2a** and **3a**) in high yield, whereas the reaction with maleic anhydride gives the *trans* adduct (**5d**) in poor yield.[2]

Experimental

All melting points were measured with a Yanagimoto micromelting point apparatus and are uncorrected. IR spectra were recorded on a Shimadzu IR-420 spectrophotometer. Mass spectra (MS) were obtained on a Hitachi M-80 mass spectrometer with a direct inlet system operating at an ionization energy of 20 eV. HPLC was performed on a Shimadzu LC-3A chromatograph equipped with an ultraviolet (UV) detector (254 nm) at a flow rate of 1.2 ml/min of 70% methanol–water, using Shim-pack CLC-ODS column (3 × 150 mm).

All the ^{13}C-(75.4 MHz) and ^1H-(300.0 MHz) NMR spectra, and ^1H–^1H and ^{13}C–{^1H} NOE spectra were obtained on a Varian XL-300 spectrometer using a 5 mm broad-band probe and operating in a pulse Fourier-transform mode with quadrature detection. The software used to obtain the CH COSY[1,4] spectra (not shown) was from Varian Instruments, version 6.1D. All spectra except the spectra for saturation transfer determination were recorded for $CDCl_3$ and DMSO-d_6 solutions which contained 20—70 mg of samples in 0.6 ml of solvents, including tetramethylsilane (TMS) as an internal reference. The spectra of **6a** and **7a** for saturation transfer determination were recorded for 10.0 mg of samples in 0.6 ml of $CDCl_3$ solution. ^1H–^1H and ^{13}C–{^1H} NOE experiments were performed by the procedure described in the previous paper.[1]

Chemical shifts were determined in ppm from TMS as an internal standard. The abbreviations used are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad.

Intramolecular Acid Anhydride Formation Reaction of 2c—7c with Ac_2O (General Procedure) A mixture of dicarboxylic acid (1 mmol) and Ac_2O (8 ml) was heated under reflux for 2 h. The excess of Ac_2O and formed AcOH were evaporated off *in vacuo*. The residual mass was sublimed *in vacuo* at 200—240 °C and washed with a small amount of anhydrous ether. The physical data, IR data, and yield of the anhydrides are listed in Table I.

Methanolysis of Anhydride (General Procedure) A mixture of an anhydride (1 mmol) and methanol (10 ml) was heated under reflux for 0.2—1 h. After removal of the solvent by evaporation, the residual solid was recrystallized from the solvent shown in Table I. The physical data, IR data, and yield of the monomethyl esters are listed in Table I.

***O*-Acetylation of Alcohols (6a and 7a)** A mixture of alcohol (1 mmol) and acetic anhydride (12 ml) was heated under reflux for 8 h (**6a**) or 25 h (**7a**). After removal of excess Ac_2O by evaporation *in vacuo*, the residual solid was crystallized from EtOH (**6f**) or ether (**7f**). The physical data, IR data, and yield of the *O*-acetates are listed in Table I.

Deuterium Displacement Reaction (General Procedure) A mixture of a diester (50 mg) and CH_3OD (3—8 ml) including *ca.* 0.5% by weight of KOH or 5% by weight of Na_2CO_3 was heated under reflux for 5—10 min. After removal of solvents by evaporation *in vacuo*, the residual mass was added to 3—8 ml of CH_3OD and the solution was heated for 5—10 min. After 3—5 repetitions of the procedure, the solution was neutralized by addition of diluted DCl and the solvent was evaporated off. The residual mass was recrystallized from CH_3OD or ethanol-d_1.

Acknowledgment The authors wish to express their gratitude to Dr. Yoshihiro Kuroda of Kyoto University for discussions regarding the NMR aspects of this work, to Dr. Yoshio Sumida of Kyoto Pharmaceutical University for measurement of the mass spectra and also to the members of the Elemental Analysis Room of Nippon Shin-yaku Co., Ltd. Thanks are also due to Mr. Motoshige Sumino, Miss Chiduru Maeda and Mr. Takashi Kawashima for technical assistance.

References and Notes

1) Part II: M. Okamoto, Y. Fujiwara, T. Oka and Y. Uemura, *Chem. Pharm. Bull.*, **36**, 521 (1988).
2) Syntex Corp., Brit. Patent, 1428481 (Cl. CO7CD, A61K) [(*Chem. Abstr.*, **85**, 46267*a* (1976)]. The photocycloaddition of 5*H*-dibenzo[*a*,*d*]cyclohepten-5-one (**1**) with maleic anhydride in benzene by external irradiation with a 100 W high-pressure mercury lamp gave the anhydride (**5d**) in poor yield (10%).
3) J. H. Noggle and R. E. Schirmer, "The Nuclear Overhauser Effect, Chemical Applications," Academic Press, New York, 1971, Chapter 3.
4) A. Bax, "Two-Dimensional NMR in Liquids," D. Reidel Publishing Co., Dordrecht, Holland, 1982, Chapters 1 and 2.
5) *a*) N. Niccolai, C. Rossi, V. Brizzi and W. A. Gibbons, *J. Am. Chem. Soc.*, **106**, 5232 (1984); *b*) M. A. Khaled and C. L. Watkins, *ibid.*, **105**, 3363 (1983); *c*) H. Seto, T. Sasaki, H. Yonehara and J. Uzawa, *Tetrahedron Lett.*, **1978**, 928.
6) W. R. Woolfenden and D. M. Grant, *J. Am. Chem. Soc.*, **88**, 1496 (1966); D. M. Grant and B. V. Cheney, *ibid.*, **89**, 5315 (1967).
7) In the NOE experiments on the di-(monomethyl)amide of the acid (**4c**) in DMSO-d_6, large NOEs between H(1,7)(δ 3.48)–H(8,9)(δ 3.66) (16%) and between H(1,7)–H(2′,2″)(δ 7.27) (10%) were observed, when H(1,7) resonance was irradiated.
8) S. Forsén and R. A. Hoffman, *J. Chem. Phys.*, **39**, 2892 (1963); J. H. Noggle and R. E. Schirmer, "The Nuclear Overhauser Effect, Chemical Applications," Academic Press, New York, 1971, Chapter 7.
9) J. Feeney and A. Heinrich, *J. Chem. Soc., Chem. Commun.*, **1966**, 295.