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Benzofuran Derivatives. II. Synthesis of 2,3-Dihydrobenzofurans from Ethyl 2-Acylphenoxyacetates

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Ethyl 3-alkyl-3-hydroxy-5-nitro-2,3-dihydro-2-benzofurancarboxylates were obtained from the reaction of ethyl 2-acyl-4-nitrophenoxyacetates with potassium hydroxide in dry dioxane. The relative ratios of the *cis* and *trans* isomers with respect to C-2 and C-3 stereochemistry varied according to the structure of the acyl group. When the acyl group was acetyl, propionyl, or isobutyryl group, the *cis* isomers (2-alkoxycarbonyl groups and 3-hydroxyl groups are *cis*) were exclusively obtained in high yields. On the other hand, a nearly equimolecular amount of the *cis* and *trans* isomers was obtained from the reaction of 2-formyl derivatives under the same conditions.

A number of 2,3-dihydrobenzofuran derivatives have been synthesized from the reaction of salicylaldehydes with ethyl α-bromophenylacetates[1] or by its modified reactions.[2,3] The stereochemistry of the *cis* and *trans* isomers of 2,3-dihydrobenzofurans was determined by ^{1}H NMR spectra and chemical reactions.[2,4]

In the previous paper,[5] it was suggested that the *cis* and *trans* isomers of 3-alkyl-3-hydroxy-2,3-dihydro-2-benzofurancarboxylate ions were important intermediates for the production of benzofurans and 2-benzofurancarboxylic acids in the Rössing reaction of 4-substituted 2-acylphenoxyacetic acids.[6] However, such intermediates were not obtained at that time. In this paper, the author reports the syntheses and the stereochemistry of *cis*- and *trans*-2,3-dihydrobenzofurans obtained by the base-catalyzed intramolecular cyclization reaction of ethyl 2-acyl-4-nitrophenoxyacetates (the *cis* isomer is shown by an *cis* relationship between C-2 alkoxycarbonyl groups or carboxyl groups and C-3 hydroxyl groups).[7]

Results and Discussion

The syntheses of ethyl esters **1c** and **1d** were carried out according to the reported method.[5] Ethyl esters **1a** and **1b** were prepared by esterification of the corresponding carboxylic acids.

When esters **1a—d** were refluxed with three equivalents of potassium hydroxide in dry dioxane, 2,3-dihydrobenzofurans (**2a—d** and **3a,b**), ethyl 2-benzofurancarboxylates (**4a—d**), 2-benzofurancarboxylic acids (**5a—d**), and 2,3-dihydro-2-benzofurancarboxylic acids (**6b, d**) were obtained, respectively. The isolated yields of compounds **2—6** are summarized in Table 1. In the case of esters **1b—d**, 2,3-dihydrobenzofurans (**2b** and **3b**, **2c**, and **2d**) were obtained in high yields (65—70%), whereas ester **1a** afforded 2,3-dihydrobenzofurans (**2a** and **3a**) in a poor yield (8%). The spectral data of **2a,b** and **3a,b** are listed in Table 2.

A mixture of the two isomers **2a** and **3a** (3:2 mole ratio) was produced by the treatment of **1a** with base. The structural assignments of the two isomers are as follows. The ^{1}H NMR spectrum of the major component **2a** showed the C-2 methine proton signal at δ 5.26 (d, J=6.8 Hz) and that of the minor component **3a** gave the C-2 methine proton signal at δ 5.17 (d, J= 3.3 Hz). In general, the coupling constants due to C-2 and C-3 protons of 2,3-disubstituted 2,3-dihydrobenzofurans are $J_{cis} > J_{trans}$[8] as predicted by the Karplus equation.[9] The ^{1}H NMR signal of the C-2 proton of **3a** was located about δ 0.1 upfield from that of the C-2 proton of **2a** by the anisotropic effect of C-3 hydroxyl groups.[10] Additionally, a large nuclear Overhauser effect (15%) was observed between C$_2$–H and C$_3$–H in the major product **2a**, whereas a small effect (8%) in the minor product **3a** as shown in Table 3.[11,12] A large NOE is measured when the irradiation proton and the measured proton have *cis*-configura-

Table 1. The reaction of ethyl 2-acyl-4-nitrophenoxyacetates (**1a—d**) with potassium hydroxide in dry dioxane[a)]

Starting Materials **1** (R)	Recovery of **1**/%	Isolated Yields of Products/%				Total Yields/%
		2 and **3** (**2**:**3**[b)])	**4**	**5**[c)]	**6**[c)]	
1a (H)	62	8 (3:2)	1	0.5		71.5
1b (CH$_3$)	5	70 (16:1)	8	1	3	87
1c (CH$_2$CH$_3$)	2	67 (1:0)	10	2		81
1d (CH(CH$_3$)$_2$)	0	65 (1:0)	5	4	18	92

a) Esters **1a—d** were refluxed with potassium hydroxide in a 1:3 mole ratio in 30 ml of dry dioxane for 1 h. b) The ratios of the two isomers were determined by ^{1}H NMR analyses on the products **2** and **3** separated by silica-gel column chromatography. The isomerization of the two isomers was not recognized during chromatography. c) Acids **4** and **5** were analysed as the corresponding methyl esters.

Table 2. Physical data of 2,3-dihydrobenzofurans (**2a,b** and **3a,b**)

Compounds	R	^{1}H NMR$^{a,b)}$	
		C$_2$-H	C$_3$-R
2a	H	5.26 (d) ($J_{2H,3H}$=6.8 Hz)	5.62 (t)
3a	H	5.17 (d) ($J_{2H,3H}$=3.3 Hz)	5.56 (dd)
2b$^{c)}$	CH$_3$	4.99 (s)	1.88 (s)
3b$^{c)}$	CH$_3$	5.18 (s)	1.65 (s)

a) The chemical shifts in ppm down field from internal TMS in CDCl$_3$. b) Carefully argon degassed solution of **2a,b** and **3a,b** were used for the measurement. c) The structure of **2b** and **3b** were not assigned by IR measurements in CHCl$_3$ or CDCl$_3$.

Table 3. The NOE values (%) for 2,3-dihydrobenzofurans (**2a—d** and **3a,b**)

Compounds	Observed Signal [Irradiated Signal] NOE/%
2a	C$_2$-H [C$_3$-H] 15
3a	C$_2$-H [C$_3$-H] 8
2b	C$_2$-H [C$_3$-CH$_3$] 34
3b	C$_2$-H [C$_3$-CH$_3$] 15
2c	C$_2$-H [C$_3$-CH$_2$-] 8; C$_2$-H [C$_3$-C-CH$_3$] 17
2d	C$_2$-H [C$_3$-CH-] 5; C$_2$-H [C$_3$-C-CH$_3$$^{a)}$] 15; C$_2$-H [C$_3$-C-CH$_3$$^{b)}$] 12

The gas dissolved in solution was removed by bubbling with argon. a) The chemical shift of the methyl proton is δ 0.90. b) The chemical shift of the methyl proton is δ 1.08.

tions.[11] All these results suggest that the major product **2a** is *cis*, and the minor product **3a** is *trans*.

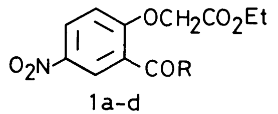
The ethyl ester **1b** afforded a mixture of the two isomers **2b** and **3b** in a 16:1 mole ratio. The chemical shift of the C-2 methine proton of **3b** is located about δ 0.2 downfield from that of the methine proton of **2b** by the anisotropic effect of C-3 methyl group.[8c,13] A large NOE (34%) was observed between C$_2$-H and C$_3$-Me in the product **2b**, whereas a small NOE (15%) was obtained in the product **3b**.[11,12] Thus, the major component **2b** was assigned to the *cis* isomer and the minor component **3b** to the *trans* isomer.

Ethyl esters **1c** and **1d** afforded the corresponding 2,3-dihydrobenzofurans **2c** and **2d** in high yields, respectively. Only one component of two isomers was detected with ^{1}H NMR measurement of the products. Similarly, the structure of **2c** and **2d** was concluded to be *cis* from the NOE measurement as described for the *cis* isomers **2a** and **2b**. An acid **6d** was assigned to *cis* stereochemistry by methylation followed by comparison with an authentic sample **8d** obtained from the reaction of methyl ester **7d** with potassium hydroxide.

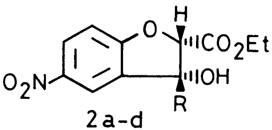
As shown in Table 1, the relative ratios of the two isomers were varied according to the structure of the acyl group. In the case of **1b—d**, the exclusive production of the *cis* isomers **2b—d** is explained by the steric repulsion of the ethoxycarbonyl group and the methyl, ethyl, or isopropyl group at the cyclization step. On the other hand, in the case of **1a**, compounds **2a** and **3a** were obtained in a nearly equimolecular ratio because the steric repulsion between the ethoxycarbonyl group and hydrogen atom is small.

2,3-Dihydrobenzofurans **2b** and **3b** were treated with potassium hydroxide in dry dioxane to elucidate the reaction mechanism, respectively. The results are listed in Table 4.

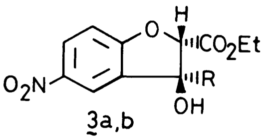
In the case of the *cis* isomer **2b**, products **4b**, **5b**, and **6b** were obtained in 9, 2, and 13% yields, respectively. A mixture of the two isomers **2b** and **3b** (70%; **2b**:**3b**=14:1) were recovered. On the other hand, in the case of the *trans* isomer **3b**, compounds **4b** and **5b** were produced in 71 and 15% yields, respectively. A mixture of compounds **2b** and **3b** (14%; **2b**:**3b**=2:1) was recovered. The structure of the acid **6b** was assigned to the *cis*-configuration by methylation followed by comparison with an authentic sample **8b**, prepared later, in which a NOE (33%) of C-2 methine proton was observed by the irradiation of C-3 methyl proton. These results showed that isomerization between the two isomers took place and the *cis* isomer



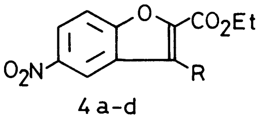
1a-d



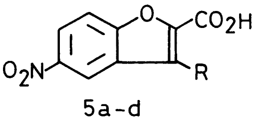
2a-d



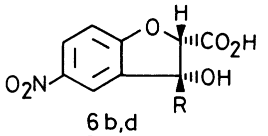
3a,b



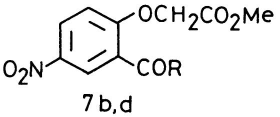
4a-d



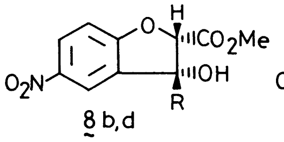
5a-d



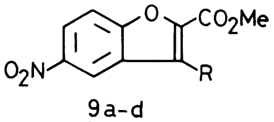
6b,d



7b,d



8b,d



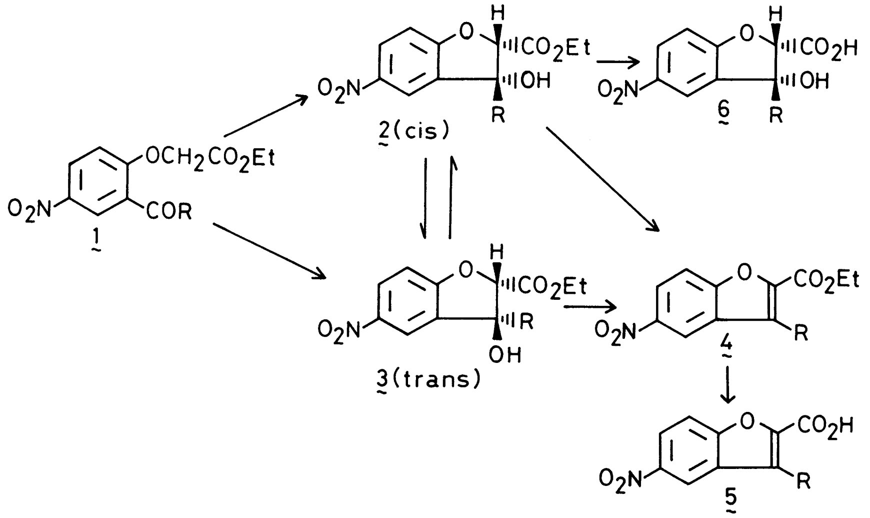
9a-d

a) R= H; b) R= CH$_3$; c) R=CH$_2$CH$_3$; d) R=CH(CH$_3$)$_2$

TABLE 4. THE REACTION OF 2,3-DIHYDROBENZOFURANS (**2b** AND **3b**) WITH POTASSIUM HYDROXIDE IN DRY DIOXANE

Starting Materials	Recovery of **2** and **3**/%(**2**:**3**[a])	Isolated Yields of Products/%			Total Yields/%
		4	**5**[b]	**6**[b]	
2b	70 (14:1)	9	2	13	94
3b	14 (2:1)	71	15		100

a) The ratios of the two isomers were determined by ^{1}H NMR measurement. b) Acids **4** and **5** were analysed as the corresponding methyl esters.



Scheme 1. The reaction pathways for the production of 2,3-dihydrobenzofurans (**2** and **3**) and related compounds (**4**, **5**, and **6**).

2b was more stable than the *trans* isomer **3b** as the steric repulsion between the ethoxycarbonyl group and the methyl group in **2b** was smaller than that in **3b**;[8a)] compound **3b** was more prone to dehydration than the *cis* isomer **2b** because the *trans* isomer **3b** was sterically less hindered to the approach of the base.

As shown in Scheme 1, the ester **4b** must be obtained mainly from the *cis* isomer **2b** in the reaction of the ester **1b** and base because the product composition of **4b** and **5b** from the ester **1b** was similar to that of products from **2b**, though the *trans* isomer **3b** afforded the ester **4b** in a high yield.

Experimental

All the melting points are uncorrected. The infrared absorption spectra (IR) were determined on a JASCO IRA-2 spectrometer. The nuclear magnetic resonance spectra (^{1}H) and nuclear Overhauser effects were determined at 90 MHz on a JEOL JNM-FX 90Q FT NMR spectrometer, using tetramethylsilane as an internal standard. Analytical and preparative HPLC were carried out with a YANACO Liquid Chromatograph L-4000 W apparatus equipped with a UV detector. A Yanapak ODS-T column (4 mm×25 cm) was used. The solvent system of 18—20% acetonitrile and 0.05 M (1 M=1 mol dm^{-3}) potassium dihydrogenphosphate buffer (pH=3.1) (vol/vol) was used as eluent. Wakogel C-200 (Wako) was used for column chromatography. Dry dioxane was prepared by the method of Fieser.[14)] Unless otherwise stated, anhydrous sodium sulfate was employed as the drying agent.

A General Procedure for the Reaction of Ethyl 2-Acyl-4-nitrophenoxyacetates (1a—d) with Potassium Hydroxide in a 1:3 Mole Ratio. A typical procedure will be described for the reaction of **1b**. A mixture of **1b** (300 mg, 1.12 mmol), potassium hydroxide powder (191 mg, 3.40 mmol), and dry dioxane (30 ml) was refluxed for 1 h. After cooling, insoluble materials in the reaction mixture were removed by filtration. The residue obtained upon evaporation of the dioxane was dissolved in benzene and insoluble materials were filtered. After evaporation of the benzene, the residue (254 mg) was chromatographed on silica gel (30 g). The first fraction eluted with benzene gave 23 mg (8%) of **4b** as crystals. The second fraction eluted with benzene–ether (30:1) gave 15 mg (5%) of **1b** as crystals. The third fraction eluted with benzene–ether (20:3) gave 210 mg (70%) of a mixture of **2b** and **3b** as crystals. The relative ratio of **2b** and **3b** (16:1) was determined by ^{1}H NMR spectroscopy.

The insoluble materials obtained above were combined and dissolved in water and acidified with 6 M hydrochloric acid. The resulting acids were extracted with ether and methylated with diazomethane. The residue (40 mg) obtained upon evaporation of the ether was chromatographed on silica gel (15 g). The first fraction eluted with benzene gave the methyl ester of **5b** (3 mg, 1%) as colorless crystals, which were identified by comparison with an authentic sample of **9b** obtained later. The second fraction eluted with benzene–ether (20:3) gave the methyl ester of **6b** (9 mg, 3%) as crystals. This was identified by comparison with an authentic sample **8b** obtained from the reaction of **7b** with potassium hydroxide.

The results of the reaction of esters **1a**, **1c**, and **1d** with potassium hydroxide in dry dioxane are listed in Table 1. Methyl esters of **5a**, **5c**, **5d**, and **6d** were identified by comparison with authentic samples **9a**, **9c**, **9d**, and **8d** obtained later.

2c: Colorless crystals from benzene, mp 108—110 °C. IR(KBr): ν_{max} 3420 (OH) and 1735 cm^{-1} (CO_2). Found: C, 55.29; H, 5.35%. Calcd for $C_{13}H_{15}NO_6$: C, 55.51; H, 5.38%.

2d: Colorless plates from hexane–benzene, mp 106—107 °C. IR(KBr): ν_{max} 3432 (OH) and 1739 cm^{-1} (CO_2). Found: C, 56.80; H, 5.72%. Calcd for $C_{14}H_{17}NO_6$: C, 56.95; H, 5.80%.

4a: Colorless prisms from benzene, mp 152—153 °C. IR(KBr): ν_{max} 1729 cm^{-1}(CO_2). Found: C, 56.21; H, 3.86%. Calcd for $C_{11}H_9NO_5$: C, 56.17; H, 3.85%.

4b: Colorless short needles from hexane–benzene, mp 146.0—147.5 °C. IR(KBr): ν_{max} 1700 cm^{-1} (CO_2). Found: C, 57.87; H, 4.53%. Calcd for $C_{12}H_{11}NO_5$: C, 57.83; H, 4.44%.

4c: Colorless short needles from benzene, mp 110.5—111.0 °C. IR(KBr): ν_{max} 1722 cm^{-1} (CO_2). Found: C, 59.61; H, 5.07%. Calcd for $C_{13}H_{13}NO_5$: C, 59.31; H, 4.98%.

4d: Colorless short needles from benzene–hexane, mp 103.5—106.0 °C. IR (KBr): ν_{max} 1719 and 1707 cm^{-1} (CO_2). Found; C, 60.38; H, 5.36; N, 5.20%. Calcd for $C_{14}H_{15}NO_5$: C, 60.65; H, 5.45; N, 5.05%.

Separation and Identification of cis- *and* trans-*2,3-Dihydrobenzofurans (2a, b and 3a, b).*

Ethyl Esters 2a and 3a. The *cis* isomer **2a** was obtained by fractional crystallization of the mixture of **2a** and **3a** (5:2 mole ratio) from benzene–ether followed by ether. The *trans* isomer **3a** was separated from the mixture of two isomers by using an HPLC and purified by recrystallization of the crude compound **3a**.

2a: Colorless plates from benzene–hexane, mp 134—135 °C.[15] IR(KBr): ν_{max} 3540 (OH) and 1727 cm^{-1} (CO_2). Found: C, 52.07; H, 4.33; N, 5.38%. Calcd for $C_{11}H_{11}NO_6$: C, 52.17; H, 4.38; N, 5.53%.

3a: Colorless short needles from benzene–hexane, mp 96—97 °C.[15] IR(KBr): ν_{max} 3440 (OH) and 1728 cm^{-1} (CO_2). Found: C, 52.33; H, 4.38; N, 5.35%. Calcd for $C_{11}H_{11}NO_6$: C, 52.17; H, 4.38; N, 5.53%.

Ethyl Esters 2b and 3b. The *cis* isomer **2b** was obtained by fractional crystallization of the mixture of **2b** and **3b** (14:1 mole ratio) from benzene. The *trans* isomer **3b** was obtained by column chromatography of the residue obtained by concentration of the mother liquor on silica gel and eluted with benzene–ether (30:1).

2b: Colorless plates, mp 156.0—157.5 °C. IR(KBr): ν_{max} 3440 (OH) and 1740 cm^{-1} (CO_2). Found: C, 53.67; H, 4.85%. Calcd for $C_{12}H_{13}NO_6$: C, 53.93; H, 4.90%.

3b: Crystals, mp 52.5—54.0 °C. IR(KBr): ν_{max} 3430 (OH) and 1725 cm^{-1} (CO_2). Found: C, 54.00; H, 5.02; N, 5.21%. Calcd for $C_{12}H_{13}NO_6$: C, 53.93; H, 4.90; N, 5.24%.

The Reaction of 2,3-Dihydrobenzofurans (2b and 3b) with Potassium Hydroxide. A typical procedure will be described for the reaction of **2b**. A mixture of **2b** (100 mg, 0.37 mmol), potassium hydroxide powder (63 mg, 1.12 mmol), and dry dioxane (10 ml) was refluxed for 1 h. The reaction mixture was worked up as described for the reaction of **1b** with potassium hydroxide. From the residue obtained upon evaporation of benzene, ethyl ester **4b** (8 mg) was obtained in 9% yield. Seventy percent of a mixture of **2b** and **3b** (70 mg, 14:1 mole ratio) was recovered. Methyl esters of **5b** (2 mg) and **6b** (12 mg) were obtained by methylation in 2 and 13% yields, respectively. The result of the reaction of **3b** with potassium hydroxide in dry dioxane is listed in Table 4.

Preparation of Materials (1a—d, 7b, 7d, 8b, 8d, and 9a—d). Compounds **1c** and **1d** were prepared according to the reported method.[5] Ethyl ester **1a** was prepared from 2-formyl-4-nitrophenoxyacetic acid[5] by heating with ethanol and sulfuric acid. Similarly, ethyl ester **1b** was prepared from 2-acetyl-4-nitrophenoxyacetic acid[5] obtained by nitration[16] of 2-acetylphenoxyacetic acid.[17] Compound **1b** was identified by comparison with an authentic sample obtained by the reported method.[5] Methyl esters **7b** and **7d** were obtained from the corresponding phenoxyacetic acids[5] by methylation with diazomethane, respectively. In the same manner as has been described for **2b**, 2,3-dihydrobenzofurans **8b** and **8d** were obtained from the corresponding methyl esters **7b** and **7d**, respectively. Methyl esters **9a—d** were prepared by methylation of acids **5a**[18] and **5b—d**[5] with diazomethane, respectively.

1a: Colorless short needles from ethanol, mp 91—93 °C. Found: C, 52.40; H, 4.38%. Calcd for $C_{11}H_{11}NO_6$; C, 52.17; H, 4.38%.

7b: Colorless short needles from methanol, mp 105.0—106.5 °C. Found: C, 52.16; H, 4.29%. Calcd for $C_{11}H_{11}NO_6$: C, 52.17; H, 4.38%.

7d: Yellow crystals from hexane–ether, mp 57.0—57.8 °C. Found: C, 55.32; H, 5.35; N, 4.89%. Calcd for $C_{13}H_{15}NO_6$: C, 55.51; H, 5.38; N, 4.98%.

8b: Colorless short needles from benzene, mp 133.0—134.0 °C. IR (KBr): ν_{max} 3415 (OH) and 1750 cm^{-1} (CO_2). Found: C, 52.09; H, 4.38; N, 5.40%. Calcd for $C_{11}H_{11}NO_6$: C, 52.17; H, 4.38; N, 5.53%.

8d: Pale yellow prisms from ether–hexane, mp 96.0—97.5 °C(bp 156 °C at 2 Torr; 1 Torr=133.322 Pa). IR(KBr): ν_{max} 3420 (OH) and 1748 cm^{-1}(CO_2). Found: C, 55.54; H, 5.32%. Calcd for $C_{13}H_{15}NO_6$: C, 55.51; H, 5.38%.

9a: Colorless short needles from benzene, mp 163.5—164.5 °C. Found: C, 54.32; H, 3.14%. Calcd for $C_{10}H_7NO_5$: C, 54.32; H, 3.19%.

9b: Colorless short needles from methanol, mp 147.0—148.5 °C. Found: C, 56.29; H, 3.98%. Calcd for $C_{11}H_9NO_5$: C, 56.17; H, 3.85%.

9c: Colorless plates from benzene–hexane, mp 120—121 °C. Found: C, 58.06; H, 4.52%. Calcd for $C_{12}H_{11}NO_5$: C, 57.83; H, 4.44%.

9d: Colorless short needles from benzene–hexane, mp 110 °C. Found: C, 59.19: H, 4.96%. Calcd for $C_{13}H_{13}NO_5$: C, 59.31; H, 4.98%.

The Nuclear Overhauser Effect Measurement. The solution (calcd 5% wt/vol) was filtered and carefully degassed by argon. A small amount of tetramethylsilane was used as an internal standard. The irradiation power of the second radio frequency field was checked by using a standard sample of 4% 3-hydroxy-4-methoxybenzaldehyde-[$^2H_1$]chloroform solution (wt/vol) as the NOE (20%) of C-5 hydrogen atom was observed by the irradiation of C-4 methoxyl group. The homogated decoupling technique was employed in the measurement (at least three measurements were made).

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