Synthesis of Nucleosides and Related Compounds. XXXIV.[1] Synthesis of 5-Isonitroso-1,3-dioxane-4,6-diones and Their Reactions

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Synthesis of 5-isonitroso-1,3-dioxane-4,6-dione (2: isonitroso Meldrum's acid) and related compounds and their reactions were described. Compound (2) reacted with various alcohols to give hydroxyiminoacetic acid esters in moderate yields. Compound 2 was acetylated in the usual manner to give 5-acetoxyimino-1,3-dioxane-4,6-dione (9) as a stable crystalline substance, which acted not as a heterodiene but as a heterodienophile and underwent hetero Diels–Alder reaction with various dienes to form [4+2] adducts.

Keywords 1,3-dioxane-4,6-dione; hydroxyiminoacetic acid; Diels–Alder reaction; asymmetric reaction; 2-azabicyclo[2.2.1]hept-5-ene; carbocyclic nucleoside

Meldrum's acid (**A** = **1**) is representative of 1,3-dioxane-4,6-diones and is a chemical equivalent of malonic acid diesters. Since **1** has shown the unique reactivity different from that of malonic acid diesters, compound **1** is an interesting reagent from the viewpoint of organic synthesis.[2] For example, formyl Meldrum's acid (**B**) derived from **1** by the usual formylation can be further transformed to formylacetic acid esters (**D**)[3] and 1,3-dioxine-4-ones (**E**)[4] *via* a ketene intermediate (**C**), both of which are versatile building blocks in organic synthesis.

In 1961, Eistert and his co-worker[5] and Zavyalov[6] reported independently the nitrosation of **1** to give 5-isonitroso-2,2-dimethyl-1,3-dioxane-4,6-dione (**F** = **2**, isonitroso Meldrum's acid). Since compound **2** corresponds to an isostere of **B**, it would be a potential reagent for organic synthesis. However, to the best of our knowledge, only two references are available concerning **2**: its catalytic reduction to the amine (**G**)[5] and the thermolysis of its *O*-alkylated derivatives (**H**).[7]

To develop a new methodology for the synthesis of carbocyclic nucleosides from 2-azabicyclo[2.2.1]hept-5-enes,[8] we synthesized various 5-isonitroso-1,3-dioxane-4,6-diones and studied their reactions, and these are the subjects of this paper.

Reaction of 5-Isonitroso-2,2-dimethyl-1,3-dioxane-4,6-dione (Isonitroso Meldrum's Acid) with Alcohols Formyl Meldrum's acid (**B**) reacts with alcohols in aprotic solvent under heating at 110°C to give formylacetic acid esters

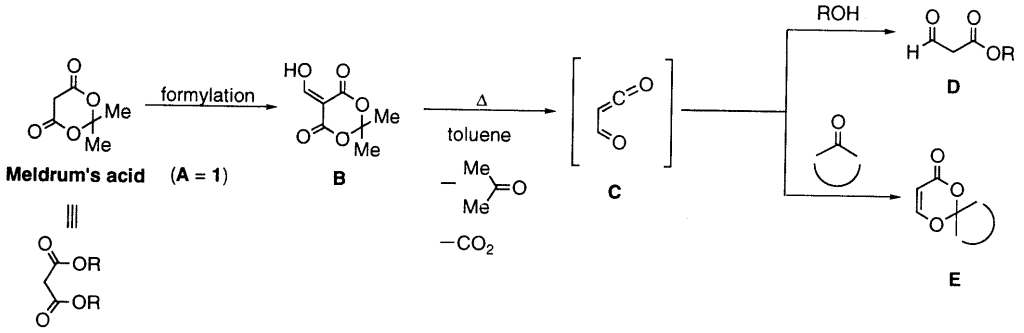


Chart 1

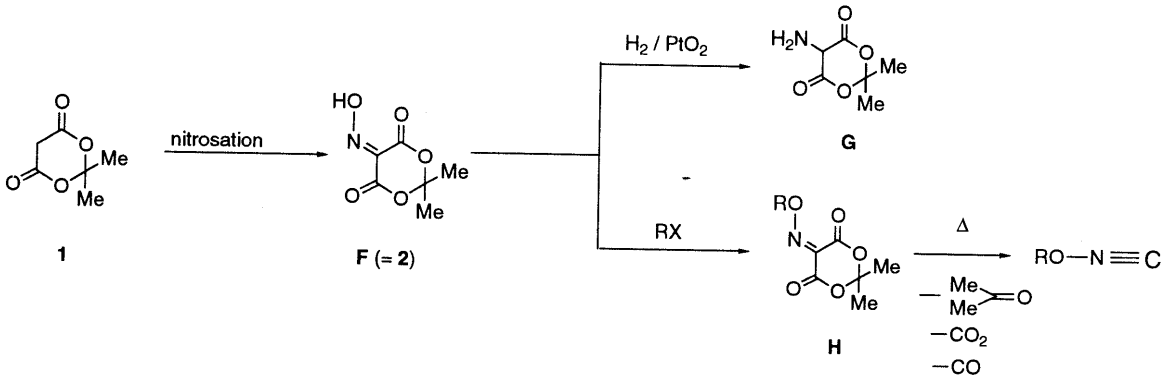


Chart 2

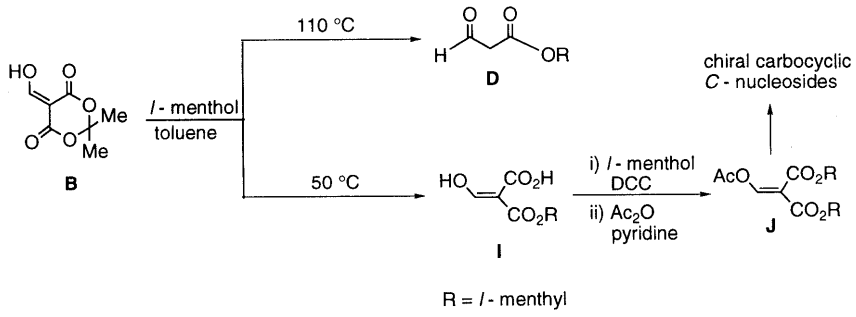


Chart 3

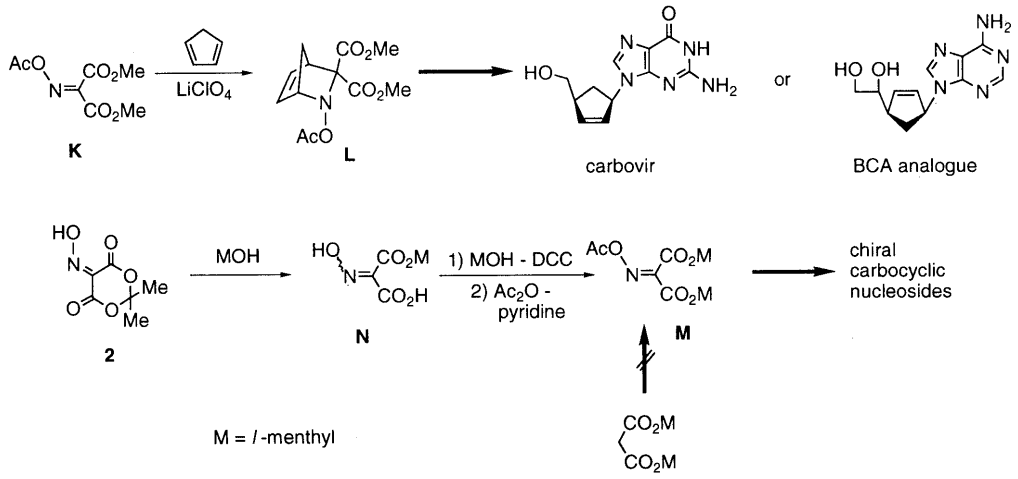


Chart 4

(**D**).[3] However, when the reaction was carried out at 50°C in toluene, the half esters (**I**) were obtained in quantitative yield.[9] Di-*l*-menthyl acetoxymethylenemalonate (**J**) derived from the half ester (**I**), was an excellent dienophile for the asymmetric Diels–Alder reaction, and was used for the synthesis of chiral carbocyclic *C*-nucleosides.[10]

We previously reported the reaction of dimethyl acetoxyiminomalonate (**K**) with cyclopentadiene to give the 2-azabicyclo[2.2.1]hept-5-ene (**L**) and its successful transformation to the carbocyclic nucleosides 9-(*c*-4,*t*-5-bishydroxymethyl-cyclopent-2-en-*r*-1-yl)-9*H*-adenine (BCA) and carbovir analogues having anti-human immunodeficiency virus (HIV) activity.[11] If we can create the corresponding di-*l*-menthyl ester (**M**), we could expect an enantioselective synthesis of carbocyclic nucleosides using the same procedure. After the direct nitrosation of di-*l*-menthyl malonate followed by acetylation had ended in failure, we planned the synthesis of the di-*l*-menthyl ester (**M**) from **2** *via* half ester (**N**) following the procedure for the synthesis of chiral dienophile (**J**). In order to obtain di-*l*-menthyl isonitrosomalonate, we investigated the reaction of **2** with various alcohols.

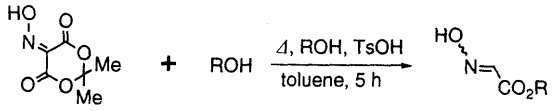
2 was found to react with methanol in the presence of *p*-toluenesulfonic acid at room temperature to give the half ester (**3**) in 70% yield as a crystalline substance. In this reaction, dimethyl isonitrosomalonate (**4**) was also formed as a by-product. However, the reaction of **2** with *l*-menthol to give **N** under the same conditions did not proceed and the starting material was recovered. This would be attributable to the steric hindrance of *l*-menthol. When the reaction was carried out under reflux in toluene, *l*-menthyl hydroxyiminoacetate (**5e**) was obtained in 45% yield, together with *l*-menthyl cyanoformate (**6**). We considered that the oxime (**5e**) thus obtained would be useful as a dienophile for the hetero Diels–Alder reaction. Accordingly, we investigated the reaction of **2** with various alcohols under reflux in toluene (Table I). Methyl, isopropyl, benzyl, and 2,2,2-trichloroethyl alcohols were found to react with **2** in the presence of *p*-toluenesulfonic acid under reflux to give the corresponding hydroxyiminoacetates (**5a—e**) in 15—79% yields. Since hydroxyiminoacetates are not easily prepared,[12] this reaction would provide an efficient method for the synthesis of these compounds. Benzyl hydroxyiminoacetate (**5c**) was then acetylated in the usual manner to give benzyl acetoxyiminoacetate (**7**). Compound **7** underwent [4+2] cycloaddition with cyclopentadiene in 5 M $LiClO_4$–Et_2O to give the 2-azabicyclo[2.2.1]hept-5-ene (**8**) as a sole product. Examination of the ^{1}H-NMR spectrum of compound **8** revealed that this compound is an *endo*-isomer ($J_{3,4}=4$ Hz).[13] The adduct (**8**) would be a versatile intermediate for the synthesis of carbocyclic nucleosides because 2-sulfonyl-2-azabicyclo[2.2.1]hept-5-ene derivatives have already been transformed to carbocyclic nucleosides.[14]

Synthesis of 5-Acetoxyimino-1,3-dioxane-4,6-diones and Their Hetero Diels–Alder Reactions with Cyclopentadiene As described above, dimethyl acetoxyiminomalonate (**K**) underwent hetero Diels–Alder reaction with cyclopentadiene to produce the 2-azabicyclo[2.2.1]hept-5-ene (**L**),

which served as an intermediate for the synthesis of the carbocyclic nucleosides BCA and carbovir analogues. However, compound **K** was found to react with cyclopentadiene only under high-pressure or in 5 M $LiClO_4$–Et_2O and the yield of the adduct (**L**) was low.[11] To more efficiently obtain a new 2-azabicyclo[2.2.1]hept-5-ene analogue chemically equivalent to **L**, we were interested in synthesizing 5-acetoxyimino-2,2-dimethyl-1,3-dioxane-4,6-diones and their hetero Diels–Alder reactions with cyclopentadiene. Usual acetylation of **2** gave 5-acetoxyimino-2,2-dimethyl-1,3-dioxane-4,6-dione (**9**) as a crystalline substance. Similarly, 3-acetoxyimino-2,4-dioxo-1,5-dioxaspiro[5.5]undecane (**12**) was prepared by nitrosation of the 1,3-dioxane-4,6-dione (**10**) followed by acetylation. The chiral dienophile (**15**) was also synthesized from the 1,3-dioxane-4,6-dione (**13**) which involved *l*-menthone at the acetal position. Compound **15** was purified by recrystallization from ether to give a single crystal of mp 134–135 °C. However, **15** was gradually isomerized to another diastereomer by allowing it to stand in chloroform at room temperature for a long period (*syn* and *anti* isomerization relative to C=N bond). The absolute structure of **15** is not yet determined.

Next, we carried out the hetero Diels–Alder reaction of 5-acetoxyimino-1,3-dioxane-4,6-diones (**9**) with cyclo-

TABLE I. Synthesis of Hydroxyiminoacetates from 5-Isonitroso-2,2-dimethyl-1,3-dioxane-4,6-dione



5a—e

Compound	R	Yield (%)	mp (°C)
5a	Me	57	48—51
5b	iso-C_3H_7	51	57—58
5c	$PhCH_2$	79	73—74
5d	CCl_3CH_2	15	95—97
5e	*l*-Menthyl	45	Oil

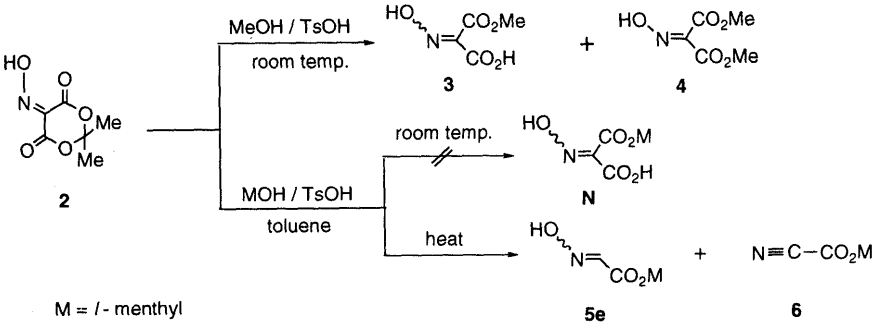


Chart 5

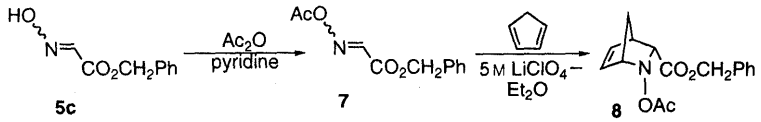


Chart 6

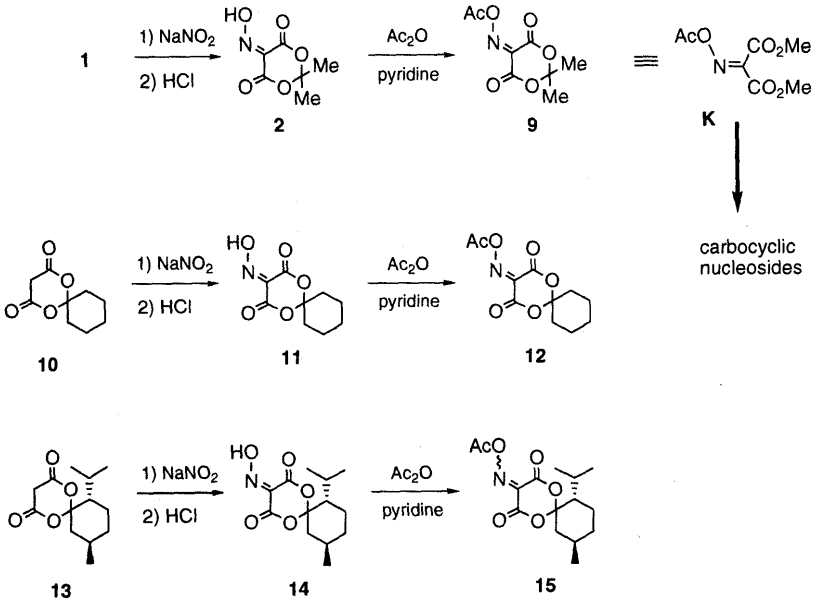


Chart 7

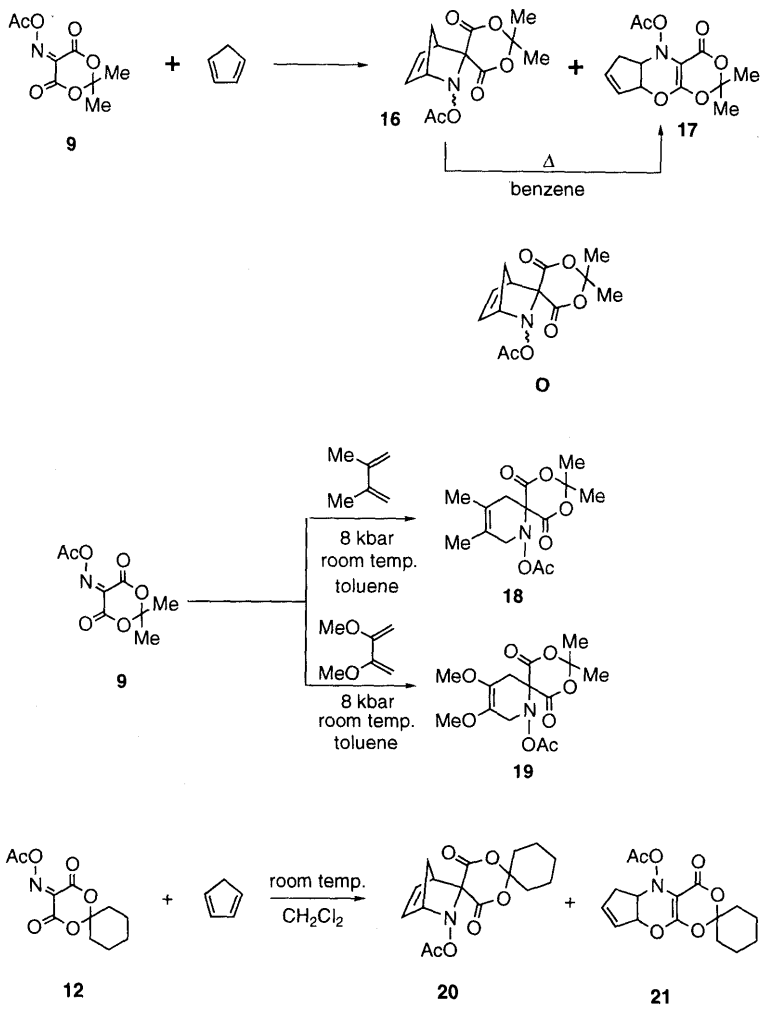


Chart 8

pentadiene under various conditions. When **9** was allowed to react with cyclopentadiene without solvent, the adduct (**16**) was obtained in a quantitative yield. When the same reaction was carried out in benzene at room temperature, 10% of the tricyclic product (**17**) was obtained as a by-product together with 58% of the [4+2] adduct (**16**). This tricyclic product (**17**) became the sole product when the reaction was carried out at 80°C. Compound **17** was also obtained by heating of **16** in benzene. Thus, it is obvious that the tricyclic compound (**17**) was not formed directly by hetero Diels–Alder reaction of cyclopentadiene with **9** as a heterodiene, but obtained indirectly by ring transformation (**O** in Chart 8) from **16**, which was formed by Diels–Alder reaction utilizing **9** as a dienophile. It would be further proof of this mechanism that **9** does not react with electron-rich dienophiles such as 2,3-dihydrofuran or ethyl vinyl ether.

Acyclic dienes such as 2,3-dimethyl-1,3-butadiene and 2,3-dimethoxy-1,3-butadiene reacted with **9** under high-pressure in toluene to give the corresponding [4+2] adducts (**18** and **19**) in moderate yields. Reaction of the spiro dienophile (**12**) with cyclopentadiene in dichloromethane afforded the [4+2] adduct (**20**) and the tricyclic product (**21**) in 72% and 18% yield, respectively.

The chiral dienophile (**15**) also reacted with cyclopentadiene without solvent at room temperature to give two kinds of [4+2] products (**22** and **23**, tentatively assigned), which could not be isolated by column chromatography due to its instability. Therefore, the mixture was subjected to catalytic hydrogenation using Pd–C to give the dihydro derivatives (**24** and **25**), which were isolated as a mixture of diastereomers (**24**:**25**=1:1) by colunn chromatography.

Examination of the 500 MHz ^{1}H-NMR spectrum of the mixture has revealed that there are two separate products. This means that cyclopentadiene approaches from the less hindered convex face of **15** (**15a** or **15b**) to form only two products (*exo* and *endo* adducts relative to two carbonyl groups). A similar phenomenon was observed in the cyclopropanation of chiral 5-arylidene-1,3-dioxane-4,6-dioxines with diazomethane previously carried out in our laboratory.[15]

In order to improve the diastereoselectivity, we then synthesized *p*-toluoyloxyimino-1,3-dioxane-4,6-dione (**15′**) as a chiral dienophile. As expected, the asymmetric Diels–Alder reaction of **15′** with cyclopentadiene gave a mixture of diastereoisomers (**22′** and **23′**) which on catalytic hydrogenation resulted in the formation of **24′** and **25′** with the ratio of 5:3.

In conclusion, we have clarified that isonitroso

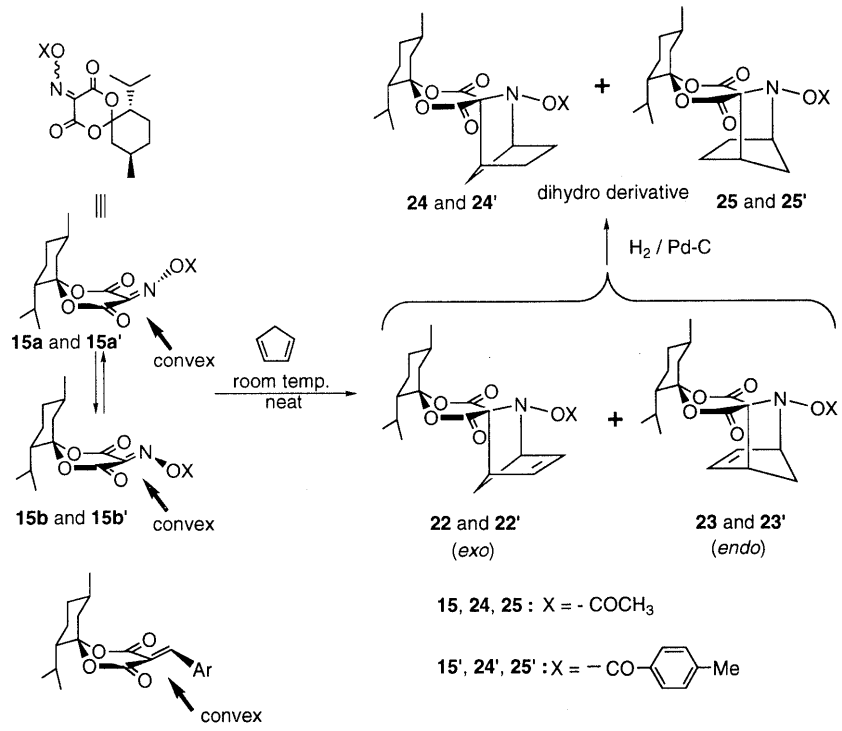


Chart 9

Meldrum's acid (**2**) reacts with various alcohols to give the corresponding hydroxyiminoacetic acid esters whose *O*-acetates act as the dienophiles for hetero Diels–Alder reactions, and that acetoxyimino Meldrum's acids behave as the dienophiles. The dienophiles underwent [4+2] cycloadditions with cyclopentadiene to give 2-azabicyclo[2.2.1]hept-5-enes. The potential utility of these bicyclic compounds in carbocyclic nucleosides synthesis is clear, and further work on the synthesis of carbocyclic nucleosides from these adducts is underway.

Experimental

All melting points were determined on a micro-hot stage (Yanagimoto) and are uncorrected. Infrared (IR) spectra were measured on a JASCO A-102 spectrometer. Proton-nuclear magnetic resonance (^{1}H-NMR) spectra at 60 and 500 MHz were recorded with JEOL JNM-PMX 60 and JEOL JNM-FX 500 spectrometers using tetramethylsilane (TMS) as an internal standard, respectively. The abbreviations of signals patterns are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; dd, doublet of doublets; br, broad; br s, broad singlet. Low- and high-resolution mass spectra (MS) were obtained on JEOL JMS-DX303 303 JEOL JMS-AX500 mass spectrometers, respectively. Wako gel (C-200) and Merck Kiesel-gel 60F_{254} were empolyed for silica gel column and thin layer chromatography (TLC), respectively. The ratios of mixtures of solvents for chromatography are shown as volume/volume. High-pressure reactions were carried out using a piston-cylinder apparatus equipped with a PK. 15. B pump (Hikari Koatsu Kiki Co., Ltd.).

Reaction of 5-Isonitroso-2,2-dimethyl-1,3-dioxane-4,6-dione (2) with Methanol A solution of **2**[5] (1.73 g, 10 mmol), methanol (0.64 g, 20 mmol), and *p*-toluenesulfonic acid (0.17 g, 1 mmol) in dry toluene (30 ml) was allowed to stand at room temperature for 12 h. After evaporation of the solvent *in vacuo*, the residue was submitted to silica gel (100 g) column chromatography. Elution with hexane–ethyl acetate (3 : 1) gave hydrogen methyl isonitrosomalonate (**3**) (1.03 g, 70%) of mp 136–137 °C ($CHCl_3$–ether) and dimethyl isonitrosomalonate (**4**)[11] (0.38 g, 24%), successively. *Anal.* Calcd for $C_4H_5NO_5$ (**3**): C, 32.66; H, 3.43; N, 9.52. Found: C, 32.31; H, 3.48; N, 9.44. ^{1}H-NMR ($CDCl_3$) δ: 3.79 (3H, s, Me), 5.10 (2H, br, CO_2H and OH).

General Procedure for the Preparation of Alkyl Hydroxyiminoacetates (5a—e) A solution of **2** (10 mmol), alcohols (20 mmol), and *p*-toluenesulfonic acid (1 mmol) in dry toluene (30 ml) was refluxed for 5 h. After evaporation of the solvent, the residue was purified by silica gel (50 g) column chromatography using hexane–ethyl acetate (3 : 1 for **5a**, 2 : 1 for **5b**, 4 : 1 for **5c**, 5 : 1 for **5d**, 10 : 1 for **5e**) as an eluent to give **5a—e**. The results are shown in Table I.

Methyl Hydroxyiminoacetate (**5a**): *Anal.* Calcd for $C_3H_5NO_3$: C, 34.95; H, 4.89; N, 13.59. Found: C, 34.69; H, 4.81; N, 13.23. IR ($CHCl_3$): 3334, 1746 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.89 (3H, s, Me), 7.64 (1H, s, imino-H), 9.3—9.9 (1H, br, OH).

Isopropyl Hydroxyiminoacetate (**5b**): *Anal.* Calcd for $C_5H_9NO_3$: C, 45.79; H, 6.92; N, 10.68. Found: C, 45.71; H, 6.88; N, 10.23. IR ($CHCl_3$): 3612, 1728 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.30 (6H, d, J=7 Hz, 2 × Me), 5.24 (1H, septet, J=7 Hz, C$\underline{H}$Me$_2$), 7.59 (1H, s, imino-H), 8.8—9.6 (1H, br, OH).

Benzyl Hydroxyiminoacetate (**5c**): *Anal.* Calcd for $C_9H_9NO_3$: C, 60.33; H, 5.06; N, 7.82. Found: C, 60.53; H, 5.27; N, 7.77. IR ($CHCl_3$): 3661, 1736 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 5.30 (2H, s, C$\underline{H}_2$Ph), 7.37 (5H, s, Ph), 7.59 (1H, s, imino-H), 10.3—10.8 (1H, br, OH).

2,2,2-Trichloroethyl Hydroxyiminoacetate (**5d**): *Anal.* Calcd for $C_4H_4Cl_3NO_3$: C, 21.79; H, 1.83; Cl, 48.25; N, 6.35. Found: C, 21.84; H, 1.88; Cl, 48.17; N, 6.40. IR ($CHCl_3$): 3648, 1752 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.87 (2H, s, CH_2CCl_3), 7.58 (1H, s, imino-H), 9.4—10.2 (1H, br, OH).

l-Menthyl Hydroxyiminoacetate (**5e**): *Anal.* Calcd for $C_{12}H_{21}NO_3$: C, 63.41; H, 9.31; N, 6.16. Found: C, 63.31; H, 9.41; N, 6.01. IR ($CHCl_3$): 3620, 1728 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.6—2.2 (18H, m, menthyl-H), 4.90 (1H, dt, J=4, 10 Hz), 7.65 (1H, s, imino-H), 10.27 (1H, br s, OH).

Benzyl Acetoxyiminoacetate (7) To a solution of **5c** (358 mg, 2 mmol) in acetic anhydride (2 ml) was added pyridine (0.1 ml) with ice-cooling. After being being kept for 3 h at room temperature, the mixture was condensed *in vacuo* to give an oily substance, which was purified by silica gel (20 g) column chromatography using hexane–ethyl acetate (3 : 1) as an eluent to give **7** (225 mg, 51%) as a colorless oil. High-resolution MS *m/z*: Calcd for $C_9H_7NO_2$ (M^+ – AcOH): 161.0476. Found: 161.0517. IR ($CHCl_3$): 1738, 1791 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.23 (3H, s, Ac), 5.36 (2H, s, C$\underline{H}_2$Ph), 7.43 (5H, s, Ph), 7.82 (1H, s, imino-H).

Benzyl 2-Acetoxy-2-azabicyclo[2.2.1]hept-5-ene-3-*endo*-carboxylate (8) To a solution of **7** (1.67 g, 7.5 mmol) in 5 M $LiClO_4$–Et_2O (40 ml)

was added cyclopentadiene (2.49 g, 38 mmol) at room temperature. After standing for 2 h, the mixture was poured into water. The organic layer was separated, and then dried over anhydrous sodium sulfate. After removal of the solvent, the residue was subjected to silica gel (100 g) column chromatography. Elution with hexane–ethyl acetate (7 : 1) gave **8** (0.81 g, 38%) as a colorless oil. High-resolution MS *m/z*: Calcd for $C_{16}H_{17}NO_4$ (M^+): 287.1157. Found: 287.1192. IR ($CHCl_3$): 1751 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.81 (1H, dd, J=3, 10 Hz, C_7-H), 2.10 (3H, s, Ac), 2.13 (1H, dd, J=3, 10 Hz, C_7-H), 3.41 (1H, br s, C_4-H), 3.82 (1H, d, J=4 Hz, C_3-H), 4.36 (1H, br s, C_1-H), 5.18 (2H, s, CH_2Ph), 6.27 (2H, m, C_5 and C_6-H), 7.37 (5H, s, CH_2Ph).

5-Acetoxyimino-2,2-dmethyl-1,3-dioxane-4,6-dione (9) To a solution of **2** (1.73 g, 10 mmol) in acetic anhydride (6 ml) was added pyridine (0.3 ml) with ice-cooling. The mixture was kept at room temperature for 2 h, and then condensed *in vacuo* to give **9** (1.38 g, 64%) of mp 71—73°C (ether) as colorless prisms. *Anal.* Calcd for $C_8H_9NO_6$: C, 44.66; H, 4.22; N, 6.51. Found: C, 44.78; H, 4.23; N, 6.55. IR ($CHCl_3$): 1821, 1790, 1660 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.86 (6H, s, 2 × Me), 2.40 (3H, s, Ac).

3-Isonitroso-2,4-dioxo-1,5-dioxaspiro[5.5]undecane (11) To a suspension of 2,4-dioxo-1,5-dioxaspiro[5.5]undecane[4] (**10**) (7.73 g, 42 mmol) in methanol (60 ml) was added a solution of $NaNO_2$ (2.90 g, 42 mmol) in water (10 ml) with stirring at room temperature. After being stirred for 2 h, the reaction mixture was condensed *in vacuo*. The residue was neutralized with 10% HCl, and then extracted with ethyl acetate (50 ml). The organic layer was washed with brine (50 ml × 3), and dried over anhydrous sodium sulfate. Evaporation of the solvent *in vacuo* gave **11** (6.43 g, 69%) of mp 102—104°C (ether–hexane) as colorless needles. *Anal.* Calcd for $C_9H_{11}NO_5 \cdot 1/2H_2O$: C, 48.64; H, 5.40; N, 6.30. Found: C, 48.49; H, 5.16; N, 6.58. IR ($CHCl_3$): 1779, 1754 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.1—2.2 (10H, m, cyclohexane-H), 10.31 (1H, br s, OH).

3-Acetoxyimino-2,4-dioxo-1,5-dioxaspiro[5.5]undecane (12) To a solution of **11** (2.13 g, 10 mmol) in acetic anhydride (10 ml) was added pyridine (0.5 ml) with ice-cooling. After being kept at room temperature for 3 h, the reaction mixture was condensed *in vacuo* to give **12** (2.09 g, 82%) of mp 162—163 °C (ethyl acetate) as colorless needles. *Anal.* Calcd for $C_{11}H_{13}NO_6$: C, 51.76; H, 5.32; N, 5.49. Found: C, 51.50; H, 5.08; N, 5.34. IR ($CHCl_3$): 1824, 1795, 1773 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.2—2.3 (10H, m, cyclohexane-H), 2.37 (3H, s, Ac).

(7*S*,10*R*)-7-Isopropyl-10-methyl-3-isonitroso-2,4-dioxo-1,5-dioxaspiro[5.5]undecane (14) To a suspension of (7*S*,10*R*)-7-isopropyl-10-methyl-2,4-dioxo-1,5-oxaspiro[5.5]undecane (**13**)[14] (1.00 g, 4.2 mmol) in methanol (6 ml) was added a solution of $NaNO_2$ (0.29 g, 4.2 mmol) in water (1 ml) with stirring at room temperature. After being stirred for 2 h, the reaction mixture was neutralized with 10% HCl, and then extracted with ethyl acetate (10 ml). The organic layer was washed with brine (10 ml × 3), and dried over anhydrous sodium sulfate. Evaporation of the solvent *in vacuo* gave **14** (0.46 g, 41%) of mp 142—143 °C (ether–hexane) as colorless needles. *Anal.* Calcd for $C_{13}H_{19}NO_5$: C, 57.98; H, 7.11; N, 5.20. Found: C, 57.97; H, 7.19; N, 5.12. IR ($CHCl_3$): 1776, 1751 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.921 (3H, d, J=6 Hz, isopropyl-Me), 0.936 (3H, d, J=6 Hz, isopropyl-Me), 0.992 (3H, d, J=7 Hz, Me), 1.40–2.30 (9H, m, menthyl-H, C<u>H</u>Me_2), 8.8—9.8 (1H, br, OH).

(7*S*,10*R*)-3-Acetoxy-7-Isopropyl-10-methyl-2,4-dioxo-1,5-dioxaspiro[5.5]undecane (15) To a solution of **14** (269 mg, 1 mmol) in acetic anhydride (1 ml) was added pyridine (0.1 ml) under stirring with ice-cooling. After being kept at room temperature for 2 h, the reaction was condensed *in vacuo* to give **15** (131 mg, 42%) of mp 134—135 °C (ether) as colorless needles. *Anal.* Calcd for $C_{15}H_{21}NO_6$: C, 57.86; H, 6.80; N, 4.50. Found: C, 58.00; H, 7.03; N, 4.40. IR ($CHCl_3$): 1821, 1789, 1763 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.921, 0.932 (each 3H, d, J=6 Hz, isopropyl-Me), 0.990 (3H, d, J=7 Hz, Me), 1.5—2.0 (8H, m, $C_{7-9,11}$-H, C<u>H</u>Me_2), 2.260 (1H, quint. J=7 Hz, C_{10}-H), 2.402 (3H, s, Ac).

Reaction of 5-Acetoxyimino-2,2-dimethyl-1,3-dioxane-4,6-dione (9) with Cyclopentadiene 1) A solution of **9** (1.08 g, 5 mmol) in cyclopentadiene (1.65 g, 25 mmol) was allowed to stand at room temperature for 24 h. The reaction mixture was condensed *in vacuo* to give 1-acetoxy-9,9-dimethyl-7,11-dioxo-2,5-methano-1-aza-8,10-dioxaspiro[5.5]undec-3-ene (**16**) (1.39 g, 99%) of mp 114—116 °C (ether). *Anal.* Calcd for $C_{13}H_{15}NO_6$: C, 55.51; H, 5.38; N, 4.98. Found: C, 55.43; H, 5.32; N, 4.93. IR ($CHCl_3$): 1791, 1751 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.66 (1H, m, CH<u>H</u>′), 1.79 (6H, s, 2 × Me), 2.00 (3H, s, Ac), 2.57 (1H, m, C<u>H</u>H′), 3.57 (1H, m, C_5-H), 4.67 (1H, m, C_2-H), 6.44 (1H, dd, J=10, 6 Hz, C_4-H), 6.63 (1H, dd, J=10, 6 Hz, C_3-H).

2) A solution of **9** (1.08 g, 5 mmol) in dry benzene (10 ml) and cyclopentadiene (1.65 g, 25 mmol) was allowed to stand at room temperature for 5 d. The reaction mixture was condensed *in vacuo* to give a crystalline substance, which was purified by recrystallization from ether to give **16** (1.63 g, 58%). The mother liquor was condensed *in vacuo* to give a crystalline substance, recrystallization of which afforded 8-acetoxy-4a,7a-dihydro-2,2-dimethyl-7*H*,9*H*-cyclopent[*b*][1,4-oxazino[2,3-*d*][1,3]dioxin-9-one (**17**) (0.28 g, 10%) of mp 156—160 °C (ethyl acetate) as colorless prisms. *Anal.* Calcd for $C_{13}H_{15}NO_6$: C, 55.51; H, 5.38; N, 4.98. Found: C, 55.29; H, 5.49; N, 4.99. IR ($CHCl_3$): 1785, 1764 cm^{-1}. ^{1}H-NMR ($CDCl_3$) ($CDCl_3$) δ: 1.646, 1.663 (each 3H, s, Me), 2.117 (3H, s, Ac), 2.690, 3.143 (each 1H, ddd, J=4, 2, 2 Hz, C_7-H), 4.436 (1H, m, C_{7a}-H), 5.257 (1H, m, C_{4a}-H), 5.802 (1H, ddd, J=4, 3, 2 Hz, C_6-H), 6.068 (1H, m, C_5-H).

3) A solution of **9** (1.08 g, 5 mmol) and cyclopentadiene (1.65 g, 25 mmol) in dry benzene (10 ml) was refluxed for 5 h. After evaporation of the solvent, the crystalline residue was recrystallized from ethyl acetate to give **17** (0.59 g, 21%).

Conversion of 16 to 17 A solution of **16** (50 mg, 0.18 mmol) in dry benzene (5 ml) was refluxed for 11 h. Evaporation of the solvent gave a mixture of **9** (76%) and **17** (17%) as a crystalline solid. Due to the instability of **9** in the column chromatography, the two compounds were inseparable from each other. Therefore, these yields were determined by ^{1}H-NMR spectrum of the mixture.

7-Acetyl-3,3,9,10-tetramethyl-1,5-dioxo-7-aza-2,4-dioxaspiro[5.5]undec-9-ene (18) A mixture of **9** (216 mg, 1 mmol) and 2,3-dimethylbutadiene (98 mg, 1.2 mmol) in dry toluene was placed in a Teflon tube (4 ml) with a teflon stopper, and the tube was filled with dry toluene. It was then placed in a high-pressure reactor and pressurized to 8 kbar at room temperature for 18 h. The pressure was released and the reaction mixture was concentrated *in vacuo*. The resulting crystalline substance was purified by recrystallization from ether to give **18** (202 mg, 68%) of mp 132—134 °C. *Anal.* Calcd for $C_{14}H_{19}NO_6$: C, 56.56; H, 6.44; N, 4.71. Found: C, 56.54; H, 6.31; N, 4.48. IR ($CHCl_3$): 1791, 1771, 1756 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.67 (6H, s, 2 × Me), 2.79, 2.86 (each 3H, s, C_9-, C_{10}-Me), 2.50 (3H, s, Ac), 2.71 (2H, m, 2 × C_{11}-H), 3.91 (2H, m, 2 × C_8-H).

7-Acetyl-9,10-dimethoxy-3,3-dimethyl-1,5-dioxo-7-aza-2,4-dioxaspiro[5.5]undec-9-ene (19) This compound (204 mg, 62%) was obtained from the reaction of **9** (216 mg, 1 mmol) with 2,3-dimethoxybutadiene (137 mg, 1.2 mmol) in the same manner as described above for the preparation of **18**, mp 83—85 °C (ether). *Anal.* Calcd for $C_{14}H_{19}NO_8$: C, 51.06; H, 5.82; N, 4.25. Found: C, 50.90; H, 5.71; N, 4.22. IR ($CHCl_3$): 1788, 1750, 1716 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.80, 1.96 (each 3H, s, C_3-Me), 2.01 (3H, s, Ac), 2.88 (2H, m, 2 × C_{11}-H), 3.68 (6H, s, OMe), 3.99 (2H, m, 2 × C_8-H).

Reaction of 12 with Cyclopentadiene A solution of **12** (1.28 g, 5 mmol) with cyclopentadiene (1.65 g, 25 mmol) in dichloromethane (10 ml) was allowed to stand at room temperature for 18 h. The mixture was concentrated *in vacuo*. The resulting crystalline substance was purified by recrystallization from ethyl acetate to give 1-acetyl-2,5-methano-7,16-dioxo-1-aza-8,15-dioxadispiro[2.2.5.2]pentaundecan-9-one (**20**) (1.16 g, 72%) of mp 124—126 °C. The mother liquor contained 8-acetoxy-4a,7a-dihydro-7*H*,9*H*-cyclopent[*b*][1,4]oxazino[2,3-*d*][1,3]dioxin-9-one-2-spiro-1′-cyclohexane (**21**) and a trace of **20**. However, compound **21** was not isolated by silica gel column chromatography. Therefore, the yield of **21** (18%) was determined by its ^{1}H-NMR spectrum. **20**: *Anal.* Calcd for $C_{16}H_{19}NO_6$: C, 59.80; H, 5.96; N, 4.36. Found: C, 59.90; H, 6.02; N, 4.34. IR ($CHCl_3$): 1776, 1751 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.4—2.8 (12H, m, cyclohexane-H, CH_2), 1.97 (3H, s, Ac), 3.54 (1H, m, C_5-H), 4.64 (1H, m, C_2-H), 6.29 (1H, dd, J=6, 4 Hz, C_4-H), 4.64 (1H, m, C_2-H), 6.29 (1H, dd, J=6, 4 Hz, C_4-H), 6.59 (1H, dd, J=6, 4 Hz, C_3-H). **21**: ^{1}H-NMR ($CDCl_3$) δ: 1.3—2.3 (11H, m, C_7-H, cyclohexane-H), 2.113 (3H, s, Ac), 3.117 (1H, m, C_7-H), 4.419 (1H, m, C_{7a}-H), 5.257 (1H, m, C_{4a}-H), 5.780 (1H, ddd, J=3, 2, 2 Hz, C_6-H), 6.048 (1H, ddd, J=3, 2, 2 Hz, C_5-H).

(10*S*,13*R*)-1-Acetoxy-10-isopropyl-2,5-methano-13-methyl-7,16-dioxo-1-aza-8,15-dioxaspiro[5.2.5.2]pentadecane (24 and 25) A mixture of **15** (311 mg, 1 mmol) and cyclopentadiene (990 mg, 15 mmol) was allowed to stand at room temperature for 1 d. The mixture was concentrated *in vacuo* to give an oily residue (540 mg), which contained (10*S*,13*R*)-1-acetoxy-10-isopropyl-2,5-methano-13-methyl-7,16-dioxo-1-aza-8,15-dioxaspiro[5.2.5.2]pentadec-3-ene (**22** and **23**). The residue was submitted to catalytic reduction using Pd–C (54 mg) under hydrogen

atmosphere in ethyl acetate (29 ml) at room temperature for 2 h. The catalyst was filtered off, and the filtrate was concentrated *in vacuo*. The resulting residue was purified by silica gel column chromatography using hexane–ethyl acetate (3 : 1) to give a mixture of **24** and **25** (87 mg, 23% from **15**), mp 119—125 °C (ether–hexane) as colorless prisms. *Anal.* Calcd for $C_{20}H_{29}NO_6$: C, 63.30; H, 7.70; N, 3.69. Found: C, 63.21; H, 7.63; N, 3.63. IR ($CHCl_3$): 1783, 1762, 1748 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.884 (3H, d, J=3 Hz, isopropyl-Me), 0.914 (3H, d, J=3 Hz, isopropyl-Me), 0.970 (3H, d, J=3 Hz, Me), 2.037 (3H, s, Ac), 2.753 (1/2 × 1H, br s, C_5-H), 2.804 (1/2 × 1H, br s, C_5-H), 2.55 (1H, m, $C_{14\ equatorial}$-H), 1.36—2.34 (14H, m, $C_{3,4}$-H, $-CH_2-$, menthyl-H), 4.017 (1H, br s, C_2-H).

(7*S*,10*R*)-7-Isopropyl-10-methyl-3-*p*-toluoyloxyimino-2,4-dioxo-1,5-dioxaspiro[5.5]undecane (15′) To a solution of **14** (2.43 g, 9 mmol) and pyridine (1 ml) in dry dichloromethane (30 ml) was added *p*-toluoyl chloride (1.39 g, 9 mmol) under stirring with ice-cooling. After being stirred overnight at room temperature, the reaction mixture was condensed *in vacuo*. The resulting residue was coevaporated with dry toluene three times to give a crystalline substance, which, after washing with pentane, was recrystallized from ether–hexane to afford **15′** (1.74 g, 50%) of mp 146—149 °C as colorless needles. *Anal.* Calcd for $C_{21}H_{25}NO_6$: C, 65.10; H, 6.50; N, 3.62. Found: C, 65.01; H, 6.52; N, 3.40. IR ($CHCl_3$): 1795, 1780, 1760 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.922 (3H, d, J=6.3 Hz, isopropyl-Me), 0.956 (3H, d, J=6.6 Hz, isopropyl-Me), 1.010 (3H, d, J=7.2 Hz, menthyl-Me), 2.296 (1H, quintet $C_{11\ equatorial}$-H), 1.598—2.059 (8H, m, menthyl-H), 2.464 (3H, s, ring-Me), 7.344 (2H, d, J=8.4 Hz, ring-H), 8.151 (2H, d, J=8.1 Hz, ring-H).

(10*S*,13*R*)-10-Isopropyl-2,5-methano-13-menthyl-1-*p*-toluoyloxy-7,16-dioxo-1-aza-8,15-dioxaspiro[5.2.5.2]pentadecane (24′ and 25′) A solution of **15′** (97 mg, 0.25 mmol) and cyclopentadiene (83 mg, 1.25 mmol) in toluene (2 ml) was stirred at room temperature for 1 d Cyclopentadiene (83 mg, 1.25 mmol) was added and the reaction mixture was stirred again overnight at room temperature. After evaporation of the solvent, the residue without purification was submitted to catalytic hydrogenation under atmospheric pressure at room temperature using 5% Pd–C (50 mg) in ethyl acetate (10 ml). After being shaken for 12 h, the catalyst was filtered off using celite. The filtrate was purified by silica gel column chromtography using hexane–ethyl acetate (5 : 1) as an eluent to give a mixture of **24′** and **25′** (5 : 3, 40 mg, 35% from **15′**) as a colorless oil. High-resolution MS *m/z*: Calcd for $C_{26}H_{31}NO_6$ (M^+): 453.2151. Found: 453.2164. ^{1}H-NMR ($CDCl_3$) δ: 1.200—2.380 (14H, m, $C_{3,4}$-H, $-CH_2-$, menthyl-H), 2.401 (3H, s, ring-Me), 2.680 (1H, br d, J=10 Hz, $C_{14\ equatorial}$-H), 2.829 (1H × 5/8, br s, C_5-H), 2.857 (1H × 3/8, br s, C_5-H), 4.135 (1H × 5/8, br s, C_2-H), 4.157 (1H × 3/8, br s, C_2-H), 7.222 (2H, d, J=8.1 Hz), 7.842 (2H, d, J=8.1 Hz).

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