Synthesis of Nucleosides and Related Compounds. XXXIV. 1) Synthesis of 5-Isotroso-1,3-dioxane-4,6-diones and Their Reactions

Nobuya Katagiri,* Hironori Nochi, Ayumu Kurimoto, Hiroshi Sato, and Chikara Kaneko

Pharmaceutical Institute, Tohoku University, Aobayama, Sendai 980, Japan.
Received January 19, 1994; accepted February 28, 1994

Synthesis of 5-isotroso-1,3-dioxane-4,6-dione (2: isotroso Meldrum’s acid) and related compounds and their reactions were described. Compound (2) reacted with various alcohols to give hydroxyiminoaico 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 heterodiencophile and underwent hetero Diels-Alder reaction with various dienes to form [4+2] adducts.

Keywords 1,3-dioxane-4,6-dione; hydroxyiminoaico 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 formylactic acid esters (D)3) and 1,3-dioxane-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-worker5) and Zavyalov6) reported independently the nitration of 1 to give 5-isotroso-2,2-dimethyl-1,3-dioxane-4,6-dione (F = 2, isotroso 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)7) 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-ene,8) we synthesized various 5-isotroso-1,3-dioxane-4,6-diones and studied their reactions, and these are the subjects of this paper.

Reaction of 5-Isotroso-2,2-dimethyl-1,3-dioxane-4,6-dione (Isotroso Meldrum’s Acid) with Alcohols Formyl Meldrum’s acid (B) reacts with alcohols in aprotic solvent under heating at 110°C to give formylactic acid esters...
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 acetoxymethyleneomalonate (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 carboxylic \(C\)-nucleosides.\(^10\)

We previously reported the reaction of dimethyl acetoxymimodalonate (K) with cyclopentadiene to give the 2-azabicyclo[2.2.1]hept-5-ene (L) and its successful transformation to the carboxylic nucleosides 9-(c-4, t-5-bishydroxymethyl-cyclopent-2-en-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 carboxylic 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 diene (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 hydroxyiminocacetate (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 1). Methyl, isopropyl, benzyl, and 2,2,2-trichloroethyll alcohols were found to react with 2 in the presence of \(p\)-toluenesulfonic acid under reflux to give the corresponding hydroxyminoacetates (5a–e) in 15–79% yields. Since hydroxyminoacetates are not easily prepared,\(^12\) this reaction would provide an efficient method for the synthesis of some of these compounds. Benzyl hydroxyminoacetate (5e) was then acetylated in the usual manner to give benzyl acetoxyminoacetate (7).

Compound 7 underwent [4+2] cycloaddition with cyclopentadiene in 5 M LiClO\(_4\)–Et\(_2\)O 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 carboxylic nucleosides because 2-sulfonyl-2-azabicyclo[2.2.1]hept-5-ene derivatives have already been transformed to carboxylic nucleosides.\(^14\)

Synthesis of 5-Acetoxyimino-1,3-dioxane-4,6-diones and Their Hetero Diels–Alder Reactions with Cyclopentadiene

As described above, dimethyl acetoxymimodalonate (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 LiClO₄-Et₂O and the yield of the adduct (L) was low. 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>
<thead>
<tr>
<th>Compound</th>
<th>R</th>
<th>Yield (%)</th>
<th>mp (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5a</td>
<td>Me</td>
<td>57</td>
<td>48–51</td>
</tr>
<tr>
<td>5b</td>
<td>iso-C₆H₁₃</td>
<td>51</td>
<td>57–58</td>
</tr>
<tr>
<td>5c</td>
<td>PhCH₂</td>
<td>79</td>
<td>73–74</td>
</tr>
<tr>
<td>5d</td>
<td>CCl₃CH₂</td>
<td>15</td>
<td>95–97</td>
</tr>
<tr>
<td>5e</td>
<td>l-Menthyl</td>
<td>45</td>
<td>Oil</td>
</tr>
</tbody>
</table>
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 heterodiels-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 cyclopenta-
diene 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 column chromatography.

Examination of the 500 MHz 1H-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 the 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-toluoyldihymin-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
Meldrum's acid (2) reacts with various alcohols to give the corresponding hydroxyminoacetic acid esters whose O-acetates act as the dienophiles for hetero Diels–Alder reactions, and that acetoxyimino Meldrum's acid's dienes behave as the dienophiles. The dienophiles underwent [4+2] cycloadditions with cyclopentadiene to give 2-azabicyclo[2.2.1]hept-5-ene (15a) and 15b. 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 (1H-NMR) spectra at 60 and 500 MHz were recorded with JEOI JNM-PMX 60 and JEOI 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; bs, broad singlet. Low- and high-resolution mass spectra (MS) were obtained on JEOI JMS-DX303 303 JEOL JMS-AX500 mass spectrometers, respectively. Wako gel (C-200) and Merck Kiesel-gel 60F254 were employed 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-Isobutyl-2,2-dimethyl-1,3-dioxane-4,6-dione (2) with Methanol** A solution of 2 (1.73 g, 20 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 isobutylmalonate (3) (1.03 g, 70%) of mp 136-137°C (CHCl3-ether) and dimethyl isobutylmalonate (4) 111 (0.38 g, 24%), successively. Anal. Caled for C8H10O4: C, 47.7; H, 5.12; N, 9.52. Found: C, 46.3; H, 4.88; N, 9.44. 1H-NMR (CDCl3) δ: 3.79 (3H, s, Me), 5.10 (2H, br, CO₂H and OH).

**General Procedure for the Preparation of Alkyl Hydroxyminoacetates**

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, 1:1 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 1.

**Methyl Hydroxyminoacetate (5a):** Anal. Caled for C4H8NO2: C, 34.95; H, 4.89; N, 13.59. Found: C, 34.69; H, 4.81; N, 13.23. IR (CHCl3): 3334, 1746 cm⁻¹. 1H-NMR (CDCl3) δ: 3.89 (3H, s, Me), 7.64 (1H, s, imino-H), 9.35–9.9 (1H, br, OH).

**Isopropyl Hydroxyminoacetate (5b):** Anal. Caled for C6H12NO2: C, 45.79; H, 6.92; N, 10.68. Found: C, 45.71; H, 6.88; N, 10.23. IR (CHCl3): 3612, 1728 cm⁻¹. 1H-NMR (CDCl3) δ: 1.30 (6H, d, J = 7 Hz, 2X Me), 5.24 (1H, sept, J = 7 Hz, CH2Me2), 7.59 (1H, s, imino-H), 8.8–9.6 (1H, br, OH).

**Benzy1 Hydroxyminoacetate (5c):** Anal. Caled for C7H14NO2: C, 60.33; H, 5.06; N, 7.82. Found: C, 60.53; H, 5.27; N, 7.77. IR (CHCl3): 3661, 1736 cm⁻¹. 1H-NMR (CDCl3) δ: 3.50 (2H, s, CH2Ph), 7.37 (5H, s, Ph), 7.59 (1H, s, imino-H), 10.3–10.8 (1H, br, OH).

**2,2,2-Trichloroethyl Hydroxyminoacetate (5d):** Anal. Caled for C10H12Cl3NO2: 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 (CHCl3): 3648, 1752 cm⁻¹. 1H-NMR (CDCl3) δ: 3.87 (2H, s, CH2Cl2), 7.58 (1H, s, imino-H), 9.4–10.2 (1H, br, OH).

**l-Methyl Hydroxyminoacetate (5e):** Anal. Caled for C8H14NO2: C, 63.41; H, 9.31; N, 6.16. Found: C, 63.31; H, 9.41; N, 6.01. IR (CHCl3): 3620, 1728 cm⁻¹. 1H-NMR (CDCl3) δ: 0.6–2.2 (18H, m, methyl-H), 4.90 (1H, d, J = 4 Hz, 1H), 7.65 (1H, s, imino-H), 10.27 (1H, br, s, OH).

**Benzy1 Acetoxycarbonyl (7) to a solution of 5e (358 mg, 2 mmol) in acetic anhydride (2 ml) was added pyridine (0.1 ml) with ice-cooling. After 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: Calc. for C11H18O3 (M⁺ - AcOH): 161.0476. Found: 161.0517. IR (CHCl3): 1738, 1791 cm⁻¹. 1H-NMR (CDCl3) δ: 2.23 (3H, s, Ac), 5.36 (2H, s, CH2Ph), 6.03-7.1 (5H, s, Ph), 7.82 (1H, s, imino-H).

**Benzy1 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 ml LiClO4-Et2O (40 ml)
was added cyclopotentadiene (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) colorless chromatography. Elution with hexane-ethyl acetate (7:1) gave a colorless oil. High-resolution mass spectrometry (HRMS): Calculated for C<sub>10</sub>H<sub>18</sub>N<sub>2</sub>O<sub>2</sub>(M<sup>+</sup>): 287.1297. Found: 287.1292. IR (CHCl<sub>3</sub>): 1715 cm<sup>-1</sup>. N<sup>11</sup>-NMR (CDCl<sub>3</sub>): 1.81 (1H, dd, J = 3, 10 Hz, C<sub>2</sub>-H), 2.10 (3H, s, Ac), 2.13 (1H, dd, J = 3, 10 Hz, C<sub>1</sub>-H), 3.41 (1H, brs, C<sub>2</sub>-H), 3.82 (1H, d, J = 4 Hz, C<sub>5</sub>-H), 4.36 (1H, brs, C<sub>3</sub>-H), 5.18 (2H, s, PhH), 6.27 (2H, m, C<sub>3</sub>-H and C<sub>9</sub>-H), 7.09 (1H, d, J = 8 Hz, C<sub>6</sub>-H).

5-Actecynino-2,2-dimethyl-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. Calc. For C<sub>10</sub>H<sub>12</sub>N<sub>2</sub>O<sub>4</sub>; C: 54.6; H: 5.2; N: 7.25. Found: C: 54.6; H: 5.2; N: 7.2.

2) A solution of 9 (1.08 g, 5 mmol) in dry benzene (10 ml) and cyclopotentadiene (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 (1.65 g, 58%). The mother liquor was condensed in vacuo to give 1.65 g of white powder, recrystallized from 2-propanol (1:5) to give colorless prisms. Anal. Calc. For C<sub>25</sub>H<sub>28</sub>N<sub>2</sub>O<sub>4</sub>; C: 61.6; H: 4.9; N: 5.4. Found: C: 61.6; H: 4.9; N: 5.4.

Conversion of 11 to 17 A solution of 16 (100 mg, 0.18 mmol) in dry benzene (5 ml) was refluxed for 11 h. Evaporation of the solvent gave a mixture of 17 (76%) and 18 (17%) as a crystalline solid. Due to the instability in the column chromatography, the two compounds were inseparable from each other. Therefore, these yields were determined by NMR.

7-Acetyl-3,3,9,10-tetramethyl-1,5-dioxo-7-aza-2,4-dioxaspiro[5.5]undecene (18) A mixture of 17 (216 mg, 1 mmol) and 2,3-dimethybutadiene (98 mg, 1.2 mmol) in dry toluene (3 ml) with a teflon stopper, and the tube was filled with dry nitrogen. It was then placed in a high-pressure reactor and pressurized to 80 bar 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. Calc. For C<sub>33</sub>H<sub>38</sub>N<sub>2</sub>O<sub>4</sub>; C: 76.5; H: 6.4; N: 4.71. Found: C: 76.5; H: 6.4; N: 4.71.

Reaction of 12 with Cyclopotentadiene A solution of 12 (1.28 g, 5 mmol) in cyclopotentadiene (1.65 g, 25 mmol) in dichloromethane (10 ml) was allowed to stand at room temperature for 18 h. The reaction mixture was concentrated in vacuo. The resulting crystalline substance was purified by recrystallization from ether to give 1-azacyclo[3.2.1]oct-2-ene-3-carboxylic acid (20) (116 g, 72%) of mp 124–126°C. The mother liquor contained 8-azacycotox-4a,7a-dihydro-7H(8H)-cyclopenten-2,3-diol (1.0 g, 98%) of mp 156–160°C (ethanol) as colorless prisms. Anal. Calc. For C<sub>21</sub>H<sub>24</sub>N<sub>2</sub>O<sub>4</sub>; C: 55.8; H: 5.8; N: 4.98. Found: C: 55.8; H: 5.8; N: 4.98.

20) A solution of 9 (1.08 g, 5 mmol) in dry benzene (10 ml) and cyclopotentadiene (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 (1.65 g, 58%). The mother liquor was condensed in vacuo to give 1.65 g of white residue, recrystallized from 2-propanol (1:5) to give colorless prisms. Anal. Calc. For C<sub>25</sub>H<sub>28</sub>N<sub>2</sub>O<sub>4</sub>; C: 61.6; H: 4.9; N: 5.4. Found: C: 61.6; H: 4.9; N: 5.4.

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 17 (76%) and 18 (17%) as a crystalline solid. Due to the instability in the column chromatography, the two compounds were inseparable from each other. Therefore, these yields were determined by NMR.

7-Acetyl-3,3,9,10-tetramethyl-1,5-dioxo-7-aza-2,4-dioxaspiro[5.5]undecene-9-ene (19) A compound of 204 mg, 62% was obtained from the reaction of 9 (216 mg, 1 mmol) with 2,3-dimethybutadiene (137 mg, 1.2 mmol) in the same manner as described above for the preparation of 18. mp 83–85°C (ether). Anal. Calc. For C<sub>33</sub>H<sub>38</sub>N<sub>2</sub>O<sub>4</sub>; C: 76.5; H: 6.4; N: 4.71. Found: C: 76.5; H: 6.4; N: 4.71.
atmosphere in ethyl acetate (29 ml) at room temperature for 2 h. The catalyst 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_{16}H_{22}NO_2: 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, brs, C_2-H), 2.804 (1/2 × 1H, brs, C_2-H), 2.55 (1H, m, C_14,C_15-H), 1.36—2.34 (14H, m, C_24—C_28-H, —CH_2—, methyl-H), 4.017 (1H, brs, C_2-H).

(7S,10R,10S)-7-Isopropyl-10-methyl-3-p-tolylazoiminooxymino-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_{24}NO_2: 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, methyl-Me), 2.296 (1H, quintet C_13equatorial-H), 1.598—2.059 (8H, m, methyl-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).

(10S,13R,10S)-10-Isopropyl-2,5-methano-13-methyl-1-p-tolylazoxy-7,16-dioxo-1-aza,8,15-dioxaspiro[5.2.5]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 chromatography 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_{24}H_{24}NO_2 (M^{+}): 453.2151. Found: 453.2164. ^{1}H-NMR (CDCl_3) δ: 1.200—2.380 (14H, m, C_{24—28}-H, —CH_2—, methyl-H), 2.401 (3H, s, ring-Me), 2.680 (1H, br.d, J = 10 Hz, C_{14equatorial}-H), 2.829 (1H × 5/8, br s, C_2-H), 2.857 (1H × 3/8, br s, C_2-H), 4.135 (1H × 5/8, br s, C_2-H), 4.157 (1H × 3/8, brs, C_2-H), 7.222 (2H, d, J = 8.1 Hz), 7.842 (2H, d, J = 8.1 Hz).

Acknowledgement This work was supported in part by a Grant-in-Aid for Scientific Research on Priority Areas (No. 04226103) from the Ministry of Education, Science and Culture, Japan.

References