Synthesis of 1,3-Dioxin-4-ones and Their Use in Synthesis. XVII.[1,2] Chiral Spirocyclic 4-Oxo-1,3-dioxin-5-carboxylates: Asymmetric Synthesis of Carbocyclic *C*-Nucleoside Precursors

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Synthesis of 2-spirocyclic 1,3-dioxin-4-ones and their Diels–Alder reaction with cyclopentadiene are described. The study provides not only a new route to chiral carbocyclic *C*-nucleoside precursors, but also a new methodology for asymmetric Diels–Alder reactions.

Keywords asymmetric synthesis; chiral dienophile; 1,3-dioxin-4-one; carbocyclic *C*-nucleoside; diethylaluminum chloride; Diels–Alder reaction; diastereofacial selectivity

In Part XV of this series,[3] we reported that spiro dioxinone (A and B) having an *l*-menthone unit at the 2-position displayed remarkable diastereofacial selection in several reactions. For example, [2+2]photocycloaddition of A (R, R′=H) to cyclopentene gives the adduct formed by preferential attack of the alkene from the a-side [diastereomeric excess (d.e.), 71% by irradiation at room temperature], while methylation of the same dioxinone with lithium dimethylcuprate afforded the product formed by preferential attack of the reagent from the reverse side (b-side) again with high d.e. (85% by the reaction at −78 °C).

It is, therefore, of interest to synthesize new chiral spirocyclic dioxinones which can act as dienophiles in Diels–Alder reaction with suitable dienes and to examine their diastereoselectivity. If one can find high diastereofacial selectivity, it can provide not only a new type of diastereofacial selection in the Diels–Alder reaction, but also useful information for the clarification of the origin of the diastereofacial selectivity of these chiral spirocyclic dioxinones.

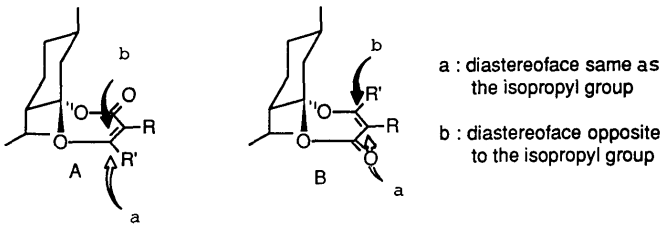

Fig. 1

Since compound **1** has already been synthesized from formyl Meldrum's acid (**3**) through the half ester (**4**) in our laboratories (Chart 1),[1] we have chosen this compound as the model dienophile for the following three reasons. 1) Though the 5,6-unsubstituted dioxinones and their alkyl derivatives could not react with cyclopentadiene under any condition (heat, use of a Lewis acid catalyst, or high pressure), introduction of the ester group at the 5-position is expected to enhance the activity of the dienophile for ordinary Diels–Alder reaction. 2) Successful use of a bicyclo[2.2.1]hept-5-en-2-ol and its derivatives (such as D and E) having two electron-withdrawing groups at the 3-position [readily obtainable from acetoxymethylenemalonates (C) and their analogues] in the synthesis of *C*-nucleosides and their carbocyclic analogues (Chart 2)[4,5] indicates that the adduct from **1** and cyclopentadiene, if obtained, would act like D and E (versatile precursors for the synthesis of carbocyclic *C*-nucleosides). 3) Replacement of the cyclohexanone unit in **1** with *l*-menthone would be easy and the derived chiral dioxinone (**2**) would serve as a novel chiral synthon for such nucleoside derivatives.

In this paper, we will report 1) successful use of **1** for stereospecific synthesis of carbocyclic *C*-nucleoside precursors (*e.g.* F: R=CH_3) and 2) the synthesis of the chiral

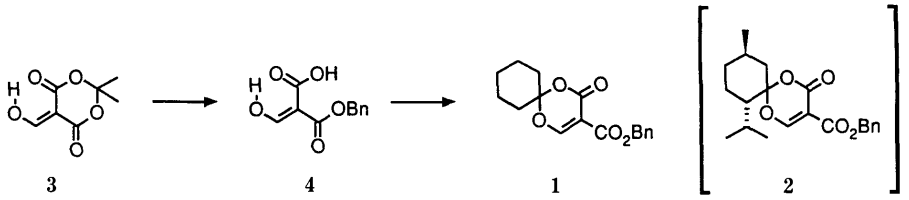

Chart 1

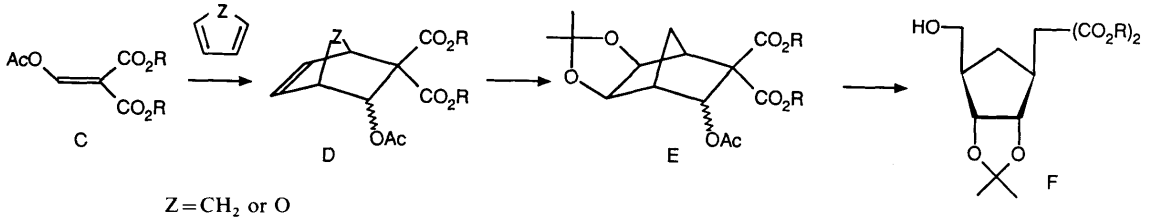

Chart 2

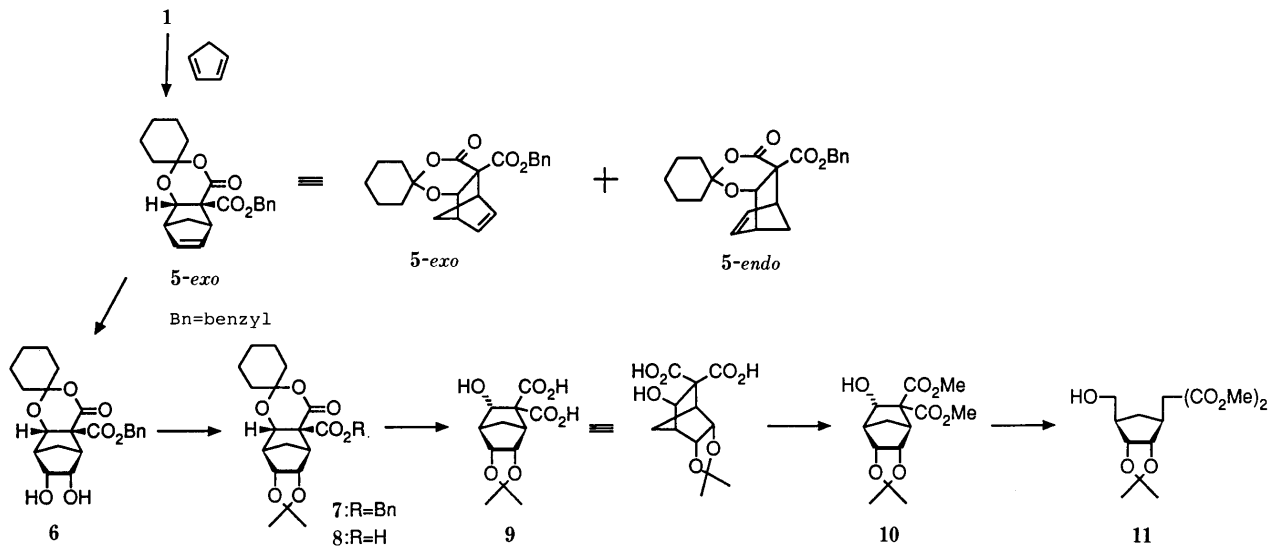

Chart 3

dioxinone (**2**) and its Diels–Alder reaction with cyclopentadiene under almost complete diastereofacial selection.

Diels–Alder Reaction of 1 with Cyclopentadiene: Stereoselective Synthesis of Carbocyclic *C*-Nucleoside Precursors (Racemic) In order to accomplish our aim, we first investigated Diels–Alder reaction of **1** with cyclopentadiene. Though **1** did not react with the diene on mere heating in an aprotic solvent, the reaction proceeded smoothly if diethylaluminum chloride was used as a catalyst. Thus, when a mixture of **1** and cyclopentadiene in toluene containing a small amount of the catalyst (throughout this paper, the amount of catalyst is *ca.* 1/5 eq to the dienophiles) was kept standing at *ca.* 0 °C, the desired adduct (**5**) was obtained as a mixture (*ca.* 10 : 1 ratio) of two diastereoisomers in 60% yield. The inspection of the proton nuclear magnetic resonance (^{1}H-NMR) spectrum revealed unequivocally that the *exo* adduct (**5**-*exo*) was formed predominantly.[6]

The usual dihydroxylation (osmium tetroxide, 4-methylmorpholine *N*-oxide in ether) of the major adduct (**5**-*exo*) to the *exo*-diol (**6**) followed by conversion to the acetonide (**7**) proceeded in 90% overall yield. Catalytic hydrogenation over palladium–charcoal in ethyl acetate then afforded the carboxylic acid (**8**), quantitatively. When the acid was warmed at around 50 °C in methanol, the dicarboxylic acid (**9**) was obtained in almost quantitative yield. The usual methylation of **9** by diazomethane gave the hydroxy dimethyl ester (**10**).

When **10** was treated with sodium borohydride and potassium carbonate in methanol[4,5] (the reaction has been termed the RRA reaction: reductive retrograde aldol reaction[5b]) under ice-cooling for 40 min, the expected C–C bond fission product (**11**) was obtained in 70% yield as the sole product. Compound **11** thus obtained was identical with the sample prepared previously in our laboratories through Diels–Alder adducts of dimethyl acetoxymethylenemalonate (C: R = CH_3) with cyclopentadiene (Chart 2), and its usefulness in the synthesis of a variety of carbocyclic *C*-nucleosides has been well documented already.[4]

The same reaction sequence was found to be applicable to the dihydro derivative of the adduct (**5**) as shown below.

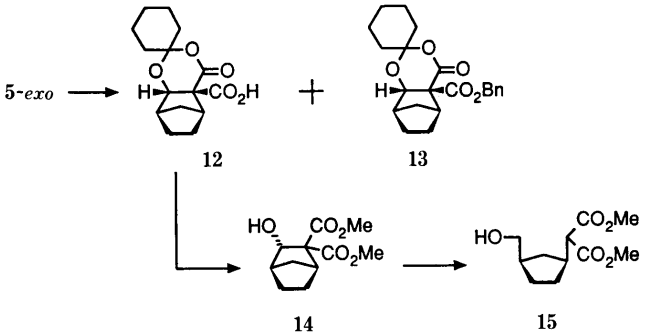

Chart 4

When **5**-*exo* was hydrogenated over palladium–charcoal in ethyl acetate, the corresponding dihydro derivative was obtained in quantitative yield as a mixture (*ca.* 1 : 1) of the acid (**12**) and the ester (**13**). Use of a mixture of ethyl acetate and methanol as the solvent, however, gave **12** as the sole product in nearly quantitative yield. Hydrolysis (10% HCl in ether, 8 h at room temperature) followed by treatment with diazomethane gave the dimethyl ester (**14**) in 89% yield. The RRA reaction of **14** afforded the cyclopentylmalonate derivative (**15**)[4a] almost quantitatively.

Synthesis of Chiral Spirocyclic Dioxinones (2) and Their Diels–Alder Reaction with Cyclopentadiene It has been found from the above study that **1** can cycloadd to cyclopentadiene and the adducts thus obtained can be transformed stereoselectively to a carbocyclic *C*-nucleoside precursor (**11**). Therefore, it is clear that if one succeeds in obtaining the corresponding adducts in an optically pure form, one can create a new synthetic method for enantiomerically pure carbocyclic *C*-nucleosides.

The half benzyl ester (**4**)[1] previously used for the synthesis of **1** was used again as the starting material. Thus, the ester **4** and *l*-menthone were condensed in the presence of acetic anhydride to give the dioxinone (**2**) as a mixture of diastereomers (*ca.* 1 : 1 ratio) in the yield of 90%. Though these compounds were unstable to silica gel chromatography under ordinary conditions, it was found that if the chromatography was carried out at below −20 °C, the

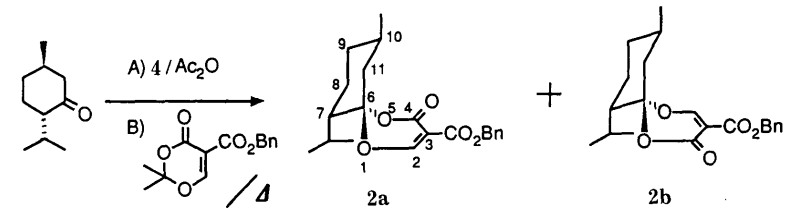

Chart 5

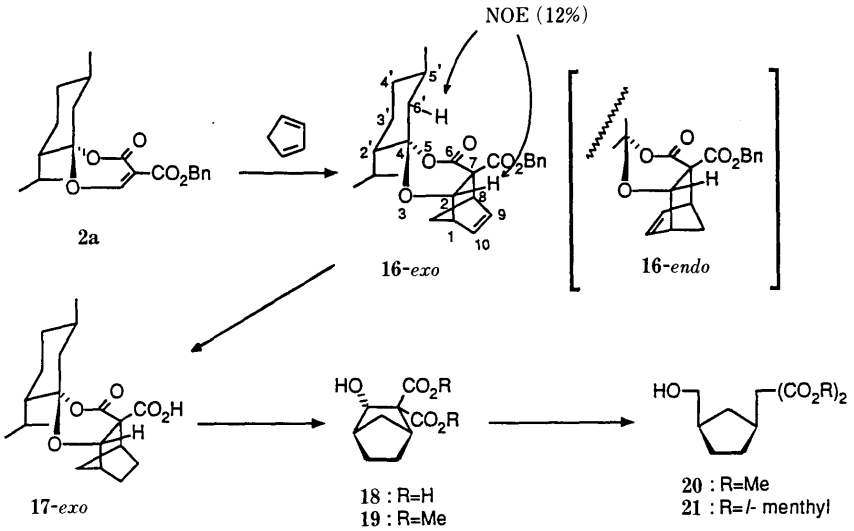

Chart 6

separation of the adducts into the less polar (**2a**) and the more polar (**2b**) isomers could be achieved without any significant decomposition. As described in the experimental section, the dienophile **2** can also be prepared by an alternative method which utilizes [4+2]cycloaddition of *l*-menthone to benzyloxycarbonylformylketene thermally generated from the 2,2-dimethyl derivative of **1**.[7]

Structure determination of the less and the more polar dienophiles (**2a** and **2b**) was done by ^{1}H-NMR spectroscopic study. Previously, pairs of 2,3-unsubstituted and 2-methyl analogues [A(6*S*) and B(6*R*): R=H, R′=H and Me)] were synthesized and their structures were determined by X-ray crystallographic analysis.[3,8] The ^{1}H-NMR spectra of the 6*S* and 6*R* isomers in each case are very similar except that the methine proton of the isopropyl group and the axial proton at C-11 of the 6*R* isomers appeared at lower field (*ca.* 0.1 ppm) than those of the corresponding 6*S* isomers. As detailed in the experimental section, this characteristic feature was also observed in the spectra of **2a** and **2b**. Thus, the less polar isomer was assigned as the 6*S* isomer. It should be noted that mobility on silica gel also supports this assignment. Thus, the 6*S* isomer (**2a**) is, just like the 2,3-unsubstituted and 2-methyl analogues,[9] less polar on silica gel than the 6*R* isomer (**2b**).

Since the less polar dienophile (**2a**) was much easier to purify and hence is readily available in quantity, we then used **2a** as the dienophile in the Diels–Alder reaction with cyclopentadiene. When this reaction was carried out again in the presence of diethylaluminum chloride as the catalyst and the reaction mixture was separated just as in the racemic series, a single adduct (**16**-*exo*) was obtained in 60% yield as the sole isolable product.[10] The configuration of the product was determined unequivocally as depicted by the formula **16**-*exo*, by the ^{1}H-NMR method. Thus, the coupling constant (*ca.* 0 Hz)[4,5] between H-1 and H-2 clearly shows the *exo*-configuration at the newly formed bicyclo[2.2.1]heptene system and a significant nuclear Overhauser effect (NOE), 12%, between H-2 and H-6′ (equatorial) indicates a proximate relationship of these protons in space.

In order to determine the absolute configuration of **16**-*exo*, the following transformation was carried out. Thus, hydrogenation of **16**-*exo* to the dihydro derivative (**17**-*exo*), its hydrolysis to the dicarboxylic acid (**18**-*exo*), methylation to the diester (**19**-*exo*) by diazomethane, followed by the RRA reaction (sodium borohydride and potassium carbonate in methanol, room temperature) led to **20**. The absolute configuration of **20** was confirmed by comparison of the specific rotation value ($[\alpha]_D^{26}$ −6.17°) with that of an authentic sample ($[\alpha]_D$ −4.1°) derived from the di-*l*-menthyl ester (**21**: d.e. 67%)[4c] previously prepared in our laboratory. The enantiomeric excess of **20** prepared from **16**-*exo* was determined to be 95% by 500 MHz ^{1}H-NMR analysis of its (*R*)-methoxy-α-trifluoromethylphenylacetate (Mosher's method[11]).

Discussion

It has now become clear that the high diastereofacial selectivity of chiral spirocyclic dioxinones found in our previous study[3] also holds in the Diels–Alder reaction. It is noteworthy, however, that the preferred face for the attack is the a-side (*cis* to the isopropyl group) which is the reverse of that found in catalytic hydrogenation and methylation by lithium dimethylcuprate and is the same as that in the

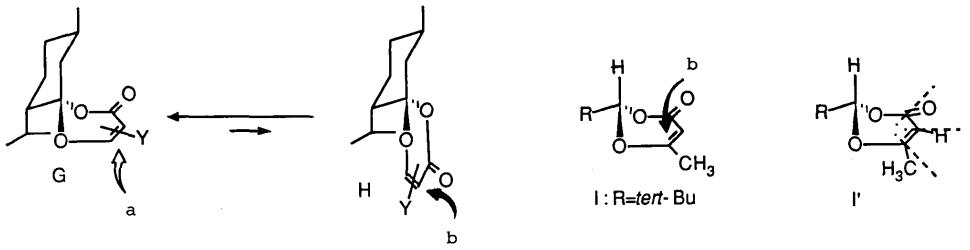

Chart 7

photo[2+2]cycloaddition to cyclopentene. In a previous paper,[3] we explained the diastereoselectivity by assuming that the spirocyclic dioxinones exist in an equilibrium between two sofa conformers (G and H) and the major conformer (G) takes the major role when the attacking reagents are relatively small so as to accept them from the more exposed a-side, while when the reagents are bulky they only attack the least hindered b-face of the minor conformer (H).

So long as we assume that cyclopentadiene in the above Diels–Alder reaction is a small reagent, the same argument can still hold for the present case. Quite recently, Seebach and his collaborators published an interesting paper[12] concerning diastereoselection found in some thermal reactions of chiral 2-*tert*-butyl-1,3-dioxin-4-one (I) and related compounds including our spicocyclic dioxinones. By assuming that the stable conformer (*e.g.* G) is the only species present, they have proposed a novel idea for the higher reactivity of the diastereotopic face (b-side of I and/or G) which appears to be more hindered than the a-side by the presence of the axial hydrogen atom on the acetal center. In their proposal, the trigonal centers of the dioxinones (*e.g.* I) are pyramidalized in the same direction from which the reaction occurs (see formula I'). Though we can not deny that Seebach's proposal could be extended to some reactions of our spirocyclic dioxinones (*e.g.* methylation with lithium dimethycuprate and catalytic hydrogenation, both of which occur through the b-side attack of conformer G with the same pyramidalization as I'),[3] the preponderance of a-side attack in the Diels–Alder reaction of spirocyclic dioxinones found in the present study has revealed that there exists another mechanism. It is tempting to propose that the a-side attack is due solely to the preferential attack of the diene from the less-hindered face of G, and not due to the pyramidalization as proposed by Seebach. In other words, Seebach's proposal for the preferential b-side attack rests entirely on the conformation (I') of the unperturbed substrates (I and/or G) and hence corresponds to the assumption that the transition states are much more closely related to the starting materials than the products. Our proposal for the a-side attack corresponds to the assumption that the transition states are much closer to the products than the substrates.

Knowing the preponderance of a-side attack of the spirocyclic dioxinones in photo[2+2]cycloaddition reactions,[3,8] it seems clear that more thorough experiments are needed for complete clarification of the diastereofacial selectivity of these chiral dioxinones (G and I).

Experimental

All melting points were determined on a micro-hot stage (Yanagimoto) and are uncorrected. Infrared (IR) spectra were recorded on a JASCO A-102 spectrometer and ^{1}H-NMR spectra on a JNM-PMX60SI or JEOL JNM-FX500 spectrometer (with tetramethylsilane as an internal standard). Mass spectra (MS) were taken either with a Hitachi M-52 spectrometer or with a JEOL JMS-01SG-2 spectrometer. Silica gel used for column chromatography was Wakogel C-200. Preparative thin-layer chromatography (PLC) was performed on Merck Kieselgel 60 F254. High pressure liquid chromatography (HPLC) was performed with a Waters μ-PORASIL column (30 cm).

Benzyl 6-Oxo-3,5-dioxatricyclo[6.2.1.0^{2,7}]undec-9-ene-4-spirocyclohexane-7-carboxylate (5-*exo* and 5-*endo*) A toluene solution of diethylaluminum chloride (0.44 ml of 1.8 M solution, 0.8 mmol) was added to a solution of compound **1**[11] (1.21 g, 4 mmol) and cyclopentadiene (2.64 g, 40 mmol) in dry toluene (30 ml) under ice-salt cooling, and the whole was stirred for 9 h at *ca.* 0 °C. The reaction mixture was poured into water and extracted with CH_2Cl_2, and the extract was dried over $MgSO_4$. The residue obtained after evaporation of the solvent was subjected to silica gel column chromatography. Elution with hexane–ethyl acetate (15 : 1) afforded 755 mg (51%) of **5**-*exo*. Further elution with the same solvent then afforded 86.5 mg (6%) of **5**-*endo*.

5-*exo*: mp 93—95 °C (prisms from ether–pentane). High-resolution (HR)-MS *m/z*: M^+ Calcd for $C_{22}H_{24}O_5$: 368.1622. Found: 368.1588. IR ($CHCl_3$): 1720 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.7—2.7 (12H, m, $-(CH_2)_5-$, C_{11}-H), 3.00 (1H, m, C_1-H), 3.73 (1H, m, C_8-H), 4.50 (1H, s, C_2-H), 5.15 (2H, dd, J=11, 12 Hz, $-CH_2Ph$), 6.03 (2H, m, olefinic protons), 7.33 (5H, s, –Ph).

5-*endo*: mp 128—129 °C (prisms from ether–pentane). HR-MS *m/z*: M^+ Calcd for $C_{22}H_{24}O_5$: 368.1622. Found: 368.1663. IR ($CHCl_3$): 1723 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.1—1.2 (12H, m, $-(CH_2)_5-$, C_{11}-H), 3.20 (1H, m, C_1-H), 3.55 (1H, m, C_8-H), 5.07 (1H, d, J=4 Hz, C_2-H), 5.25 (2H, s, $-CH_2Ph$), 6.29 (2H, m, olefinic protons), 7.36 (5H, s, –Ph).

Benzyl 9,10-*exo*-Dihydroxy-3,5-dioxa-6-oxotricyclo[6.2.1.0^{2,7}]undecane-4-spirocyclohexane-7-carboxylate (6) Osmium tetroxide (0.5 ml of 1.3% *tert*-butanol solution) and aqueous *N*-methylmorpholine *N*-oxide (0.8 ml of 60% solution) were added to a solution of the adduct (**5**-*exo*, 111 mg, 0.3 mmol) in ether (1 ml), and the whole was stirred at room temperature for 15 min. After the addition of water, the product was taken up in ether and dried over $MgSO_4$. The residue obtained after evaporation of the solvent was chromatographed over silica gel (10 g). Elution with hexane–ether (1 : 1) afforded quantitatively the diol (**6**, 123 mg) as an oil. HR-MS *m/z*: M^+ Calcd for $C_{22}H_{26}O_7$: 402.1677. Found: 402.1712. IR ($CHCl_3$): 3650—3150 (OH), 1725 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.8—2.2 (12H, m, $-(CH_2)_5-$, C_{11}-H), 2.35 (1H, m, C_1-H), 3.10 (1H, m, C_8-H), 3.30 (2H, s, 2 OH), 3.75 (2H, dd, J=6, 11 Hz, C_9-H, C_{10}-H), 4.57 (1H, s, C_2-H), 5.20 (2H, s, $-CH_2Ph$), 7.30 (5H, s, Ph).

Benzyl 9,10-*exo*-Isopropylidenedioxy-6-oxo-3,5-dioxatricyclo[6.2.1.0^{2,7}]-undecane-4-spirocyclohexane-7-carboxylate (7) Pyridinium *p*-toluenesulfonate (15.7 mg) was added to a solution of the diol (**6**, 367 mg, 0.9 mmol) in dimethoxypropane (3 ml), and the whole was stirred at room temperature for 3.5 h. The residue obtained after evaporation of the solvent was chromatographed on silica gel (20 g). Elution with hexane–ethyl acetate (10 : 1) afforded 360 mg (89%) of the acetonide (**7**) as prisms of mp 146—147 °C (CH_2Cl_2–ethyl acetate). *Anal.* Calcd for $C_{25}H_{30}O_7$: C, 67.85; H, 6.83. Found: C, 67.89; H, 6.97. IR ($CHCl_3$): 1725 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.9—2.1 (12H, m, $-(CH_2)_5-$, C_{11}-H), 1.17, 1.42 (each 3H, s, isopropylidene-Me), 2.45 (1H, m, C_1-H), 3.25 (1H, m, C_8-H), 3.97 (2H, dd, J=5, 14 Hz, C_9-H, C_{10}-H), 4.56 (1H, s, C_2-H), 5.24 (2H, s, $-CH_2Ph$), 7.35 (5H, s, Ph). MS *m/z*: 442 (M^+).

Dimethyl 3-*exo*-Hydroxy-5,6-*exo*-isopropylidenedioxybicyclo[2.2.1]heptane-2,2-dicarboxylate (10) The benzyl ester (**7**, 108 mg, 0.24 mmol) was hydrogenated over 10% palladium–charcoal (30 mg) in a mixture (7 ml) of methanol and ethyl acetate (1 : 9) under atmospheric pressure. The catalyst was filtered off, and methanol was evaporated off *in vacuo*. The crude acid

(**8**) thus obtained was dissolved in methanol (5 ml) and the whole was warmed at 50 °C for 2 h. The residue [the dicarboxylic acid (**9**)] obtained after evaporation of the solvent was methylated with diazomethane in a usual manner. The product obtained was chromatographed over silica gel (5 g). Elution with hexane–ethyl acetate (2 : 1) afforded 46.5 mg (64%) of the dimethyl ester **10** as an oil. IR ($CHCl_3$): 3620 (OH), 1733 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.24, 1.43 (each 3H, s, isopropylidene-Me), 2.00 (2H, m, C_7-H), 2.32 (1H, m, C_4-H), 2.54 (1H, br s, OH), 2.89 (1H, m, C_1-H), 3.71 (6H, s, 2 × ester-Me), 4.11 (2H, br d, J=2 Hz, C_5-H, C_6-H), 4.50 (1H, br s, C_3-H).

Racemic Dimethyl (4-Hydroxymethyl-2,3-isopropylidenedioxycyclopent-1-yl)malonate (11) Potassium carbonate (120 mg, 0.87 mmol) and sodium borohydride (32.9 mg, 0.87 mmol) were added to the dimethyl ester **10** (52.4 mg, 0.17 mmol) in methanol (5 ml) under ice-cooling, and the whole was stirred at 0 °C for 40 min. After addition of acetic acid to make the mixture acidic, the solvent was evaporated off *in vacuo*. The product was taken up in ether, and the ether layer was washed with water and dried over $MgSO_4$. The residue obtained after evaporation of the solvent was chromatographed over silica gel (5 g). Elution with hexane–ethyl acetate (1 : 1) afforded 34.5 mg (67%) of **11** as an oil. The spectra (^{1}H-NMR and IR) as well as *Rf* value on thin layer chromatography (TLC) were identical with those of an authentic sample.[4a]

6-Oxo-3,5-dioxatricyclo[6.2.1.0^{2,7}]undecane-4-spirocyclohexane-7-carboxylate (12) The adduct (**5**-*exo*, 184 mg, 0.5 mmol) was hydrogenated over 10% palladium–charcoal (20 mg) in methanol–ethyl acetate (1 : 9, 4.5 ml) at 1 atm to give 134 mg (96%) of the debenzylated dihydro derivative (**12**) of mp 122—124 °C (prisms from ether–pentane). HR-MS m/z: M^+ Calcd for $C_{15}H_{20}O_5$: 280.1310. Found: 280.1296. IR ($CHCl_3$): 3450—2800, 1765, 1725, 1700 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.5—3.0 (16H, m, $-(CH_2)_5-$, C_9-H, C_{10}-H, C_{11}-H), 2.43 (1H, m, C_1-H), 3.15 (1H, m, C_8-H), 4.64 (1H, s, C_2-H), 9.97 (1H, s, $-CO_2\underline{H}$).

When the above hydrogenation reaction was carried out in ethyl acetate alone, the dihydro benzyl ester (**13**) was obtained together with **12**. The ratio of **12** and **13** was *ca.* 1 : 1.

13: oil. HR-MS m/z: M^+ Calcd for $C_{22}H_{26}O_5$: 370.1779. Found: 370.1759. IR ($CHCl_3$): 1720 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.6—2.3 (16H, m, $-(CH_2)_5-$, C_9-H, C_{10}-H, C_{11}-H), 2.37 (1H, br s, C_1-H), 3.21 (1H, br s, C_8-H) 4.62 (1H, br s, C_2-H), 5.21 (2H, s, $C\underline{H}_2$Ph), 7.37 (5H, s, Ph).

Dimethyl 3-*exo*-Hydroxybicyclo[2.2.1]heptane-2,2-dicarboxylate (14) The dihydro acid (**12**, 240 mg, 0.86 mmol) was stirred in ether (10 ml) containing 10% HCl (10 ml) for 8 h at room temperature. After evaporation of the solvent *in vacuo*, the residue was dissolved in ether. To this solution, diazomethane (prepared in ether) was added dropwise until the yellow color of diazomethane persisted. The residue obtained after evaporation of the solvent was purified by silica gel column chromatography. Elution with hexane–ethyl acetate (5 : 1) gave 203 mg (89%) of **14** as prisms, mp 78—80 °C (ether–pentane). *Anal.* Calcd for $C_{11}H_{16}O_5$: C, 57.88; H, 7.07. Found: C, 57.87; H, 7.04. IR ($CHCl_3$): 3610, 1732 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.7—1.8 (6H, m, C_5-H, C_6-H, C_7-H). 2.00 (1H, br, O$\underline{H}$), 2.30 (1H, m, C_4-H), 2.90 (1H, m, C_1-H), 3.73 (6H, s, 2 × $CO_2\underline{Me}$), 4.58 (1H, d, J=2 Hz, C_3-H). MS m/z: 229 (M^+ + 1).

Dimethyl *cis*-(3-Hydroxymethylcyclopent-1-yl)malonate (15) Potassium carbonate (691 mg, 5 mmol) and sodium borohydride (189 mg, 5 mmol) were added to the bicycloalcohol (**14**, 229 mg, 1 mmol) in methanol (5 ml) under ice-cooling, and the whole was stirred at 0 °C for 25 min. The crude product, obtained by the procedure given for **11**, was chromatographed over silica gel (20 g). Elution with hexane–ether (2 : 1) afforded 225 mg (98%) of **15** as an oil. The spectral data (IR and ^{1}H-NMR) were identical with those of an authentic sample.[4a]

Benzyl (6*S*,7*S*,10*R*)- and (6*R*,7*S*,10*R*)-7-Isopropyl-10-methyl-4-oxo-1,5-dioxaspiro[5.5]undec-2-ene-3-carboxylate (2a and 2b) a) *p*-Toluenesulfonic acid (190 mg, 1 mmol) was added to a solution of the half benzyl ester **4**[1] (2.22 g, 10 mmol) and *l*-menthone (4.62 g, 30 mmol) in acetic anhydride (3.06 g, 30 mmol) under ice-salt cooling, and the whole was kept standing at 0 °C in a refrigerator for 5 d. The reaction mixture was directly applied to a silica gel (80 g) column cooled at −30 °C. Elution with hexane–ethyl acetate (5 : 1) afforded a mixture of **2a** and **2b** (the separation should be carried out at below −20 °C to avoid decomposition of the dioxinone). The ratio of the two diastereomers was determined as *ca.* 1 : 1 by HPLC analysis.

b) Methyl 2,2-dimethyl-4-oxo-1,3-dioxin-5-carboxylate[1] (131 mg, 0.5 mmol) and *l*-menthone (231 mg) were refluxed in dry benzene (3 ml) for 30 min. Low temperature silica gel column chromatography over silica gel (12 g) as in a) then afforded a *ca.* 1 : 1 mixture of **2a** and **2b** in a combined yield of 70% (126 mg). The mixture thus obtained was separated on a Merck Lobar column (10401) cooled at *ca.* −25 °C using hexane–ether (10 : 1) as an eluent. **2a** (60 mg) and then **2b** (60 mg) were eluted in that order.

2a: Oil. 500 MHz ^{1}H-NMR ($CDCl_3$) δ: 0.90 (3H, d, J=6.5 Hz, C_{10}-Me), 0.91 (3H, d, J=6.5 Hz, isopropyl-Me), 0.96 (3H, d, J=6.5 Hz, isopropyl-Me), 1.15 (1H, t, J=13.0 Hz, axial-C_{11}-H), 2.14 (1H, m, C$\underline{H}$Me$_2$), 2.52 (1H, ddd, J=13.0, 3.6, 2.4 Hz, equatorial-C_{11}-H), 5.29 (2H, s, C$\underline{H}_2$Ph), 7.3—7.5 (5H, m, Ph), 8.20 (1H, s, C_2-H).

2b: Oil. 500 MHz ^{1}H-NMR ($CDCl_3$) δ: 0.85 (3H, d, J=7.2 Hz, isopropyl-Me), 0.89 (3H, d, J=6.8 Hz, C_{10}-Me), 0.95 (3H, d, J=7.2 Hz, isopropyl-Me), 1.22 (1H, t, J=14.0 Hz, axial-C_{11}-H), 2.30 (1H, m, C$\underline{H}$Me$_2$), 2.52 (1H, ddd, J=14.0, 4.2, 2.2 Hz, equatorial-C_{11}-H), 5.29 (2H, s, C$\underline{H}_2$Ph), 7.3—7.5 (5H, m, Ph), 8.19 (1H, s, C_2-H).

Benzyl (1*S*,2*S*,2′*S*,4*S*,5′*R*,7*R*,8*R*)-6-Oxo-3,5-dioxatricyclo[6.2.1.0^{2,7}]undec-9-ene-4-spiro(2′-isopropyl-5′-methyl)cyclohexane-7-carboxylate (16-*exo*) A solution of diethylaluminum chloride in toluene (44.4 μl of 1.8 M solution, 0.08 mmol) was added to a solution of **2a** (141 mg, 0.39 mmol) and cyclopentadiene (280 mg, 4.2 mmol) in dry toluene (1 ml) under ice-salt cooling, and the whole was kept standing at 0 °C for 15 h. The reaction mixture was poured into ice-water and the product was taken up in dichloromethane and dried over $MgSO_4$. The residue obtained after evaporation of the solvent was chromatographed over silica gel (15 g). Elution with hexane–ethyl acetate (40 : 1) gave 90.8 mg (55%) of **16**-*exo* as an oil. HR-MS m/z: M^+ Calcd for $C_{26}H_{32}O_5$: 424.2248. Found: 424.2275. IR ($CHCl_3$): 1725 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.3—2.8 (20H, m), 3.01 (1H, m, C_1-H), 3.73 (1H, m, C_8-H), 4.58 (1H, br s, C_2-H), 5.14 (2H, s, C$\underline{H}_2$Ph), 6.06 (2H, m, C_9-H, C_{10}-H), 7.35 (5H, s, Ph).

Dimethyl (1*S*,3*S*,4*S*)-3-Hydroxybicyclo[2.2.1]heptane-2,2-dicarboxylate (19) The adduct (**16**-*exo*, 83.6 mg, 0.19 mmol) was hydrogenated in methanol (5 ml) over 10% palladium–charcoal (30 mg) at room temperature. The crude reaction product (**17**-*exo*) thus obtained was dissolved in 5 ml of ether and, after addition of 10% HCl (2 ml), the whole was stirred at room temperature for 25 h. After evaporation of the solvent *in vacuo*, the residue was suspended in ether and methylated with diazomethane in a usual manner. The product was chromatographed over silica gel (5 g). Elution with hexane–ethyl acetate (5 : 1) afforded 25.2 mg (58%) of **19** as an oil. The IR and ^{1}H-NMR spectra were identical with those of **14**.

Dimethyl (1′*S*,3′*R*)-(3-Hydroxymethylcyclopent-1-yl)malonate (20) a) The bicyclo compound (**19**, 25.2 mg, 0.11 mmol) was dissolved in methanol (2 ml) and, after addition of potassium carbonate (76.0 mg, 0.55 mmol) and sodium borohydride (20.8 mg, 0.55 mmol) under ice-cooling, the whole was stirred for 25 min at 0 °C. After acidification with acetic acid and evaporation *in vacuo*, the residue was partitioned into water and ether. The organic layer was dried over $MgSO_4$. After evaporation of the solvent, the residue was subjected to column chromatography on silica gel (5 g). Elution with hexane–ethyl acetate (2 : 1) gave 24.3 mg (96%) of **20** as an oil. The spectral data (^{1}H-NMR and IR) as well as the sign of the specific rotation value ($[\alpha]_D^{26}$ −6.17° (c=0.49, $CHCl_3$)) were identical with those of an authentic sample prepared by method b.

b) Di-*l*-menthyl (1′*S*,3′*R*)-(3-acetoxymethylcyclopent-1-yl)malonate (**21**, diastereomeric excess, 67%[4c]; 74.2 mg, 0.15 mmol) was refluxed for 9 h in sodium methoxide solution prepared from sodium (124 mg) and absolute methanol (10 ml). Most of the solvent was evaporated off *in vacuo*. The residue was acidified with 10% hydrochloric acid and the solution was extracted with ether. The ether extract was treated with diazomethane in a usual manner and purified as in a) to give **20** as an oil. Yield, 20 mg (58%). $[\alpha]_D^{25}$ −4.1° (c=0.40, $CHCl_3$).

Acknowledgement A part of the cost of this work was defrayed by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science and Culture, Japan. The authors are grateful to Mr. K. Kawamura and Miss. M. Inada for measurement of mass spectra, to Miss. K. Mushiake for measurement of ^{1}H-NMR spectra, and to Mrs. A. Sato for elemental analyses.

References and Notes

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4) Synthesis of carbocyclic *C*-nucleosides through Diels–Alder adducts

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6) The terms *exo* and *endo* refer to the newly formed double bond to the dioxinone ring.

7) 1,3-Dioxin-4-ones, when heated at an appropriate temperature, generate formyl- or acyl-ketene, which react *in situ* either with polarized unsaturated functions (1,2-dipoles) in a [4+2] manner to give six-membered heterocycles or with nucleophiles to give formyl- or acyl-acetylated products. See, M. Sato, *Yuki Gosei Kagaku Kyokai Shi*, **46**, 596 (1988) and *idem*, *Yakugaku Zasshi*, **108**, 805 (1988) and references cited therein.

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9) We have already synthesized more than a dozen pairs of spirocyclic dioxinones (6*S*- and 6*R*-isomers) of this type having a variety of substituents at the 2- and/or 3-positions. The characteristic differences of the ^{1}H-NMR spectra as well as the differences of mobility on silica gel were found in all pairs of the 6*S*- and 6*R*-isomers. The details of this work will be published soon.

10) When the mixture of **2a** and **2b** was used in the same Diels–Alder reaction, the corresponding cycloadducts (**16**-*exo* and the *exo*-adduct of **2b**) were obtained in 61% yield. The two diastereomers were readily separated by silica gel column chromatography.

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