Synthesis of Nucleosides and Their Related Compounds. XII.[1,2] Menthyl 2,4-Dioxo-1,3-oxazine-5-carboxylates: New Dienophiles for the Asymmetric Diels–Alder Reaction Directed towards Synthesis of Carbocyclic C-Nucleosides

Nobuya KATAGIRI,* Masatoshi HIROSE, Masayuki SATO and Chikara KANEKO*

Pharmaceutical Institute, Tohoku University, Aobayama, Sendai 980, Japan. *Received October 18, 1988*

2,4-Dioxo-1,3-oxazine-5-carboxylic acid esters prepared by thermal reaction of 4-oxo-1,3-dioxin-5-carboxylates with isocyanates were found to react with cyclopentadiene either in the presence or absence of suitable Lewis acid catalysts under quite mild conditions. Thus, reaction of methyl 3-substituted 2,4-dioxo-1,3-oxazine-5-carboxylates with cyclopentadiene either at room temperature or in the presence of a catalytic amount of titanium tetrachloride at −15 °C gave the corresponding adducts in almost quantitative yield. The 5-phenyl derivative was converted to a carbocyclic C-nucleoside precursor through reductive retrograde aldol reaction (RRA reaction) as a key step. This titanium tetrachloride-catalyzed Diels–Alder reaction, when applied to *l*-8-phenylmenthyl 2,4-dioxo-1,3-oxazine-5-carboxylate, afforded the corresponding adduct in high diastereomeric excess (95% for the major *endo* adduct).

Keywords asymmetric Diels–Alder reaction; chiral dienophile; 4-oxo-1,3-dioxin-5-carboxylate; 2,4-dioxo-1,3-oxazine-5-carboxylate; cyclopentadiene; titanium tetrachloride; 3-oxo-5-azatricyclo[6.2.1.$0^{2,7}$]undec-9-ene-7-carboxylate; reductive retrograde aldol reaction; carbocyclic C-nucleoside

A number of the nucleoside antibiotics contain a β-ribofuranosyl unit linked to a carbon atom in a heterocyclic ring and are termed C-nucleosides. After the discovery of pseudouridine in hydrolysates of ribonucleic acid (RNA) by Cohn,[3] a variety of C-nucleosides, such as showdomycin,[4] pyrazofurin,[5] oxazinomycin,[6] and formycin[7] have been found to exhibit interesting biological activities (antitumor and antiviral activities). Therefore, it is not surprising that much effort has been made to develop synthetic methods for C-nucleosides (natural ones as well as their analogues) in order to find new medicinal agents.[8]

In previous studies in this series, we have investigated the synthesis of C-nucleosides and their carbocyclic analogues either by using D-ribofuranose derivatives as the starting materials (line 1)[9–13] or through non-carbohydrate precursors (line 2).[14–19]

In the course of studies along line 2, we have found that 3-acetoxyacrylates (A) having an electron-withdrawing group at the 2-position readily cycloadd to cyclopentadiene to give the 4+2 adducts (B: $Z=CH_2$), and that these adducts on reductive retrograde aldol reaction (abbreviated hereafter as RRA reaction: $NaBH_4$–K_2CO_3/MeOH) are transformed *via* a short and effective synthetic route to carbocyclic analogues of C-nucleoside precursors (*e.g.* D: $Z=CH_2$), which can be further transformed to a variety of carbocyclic C-nucleosides.[14,20,21]

Later, the method has not only been extended to the enantioselective synthesis of the precursors themselves[16] but has also been applied to the corresponding C-nucleoside precursors (both racemic[17,18] and chiral[19]) utilizing dimethyl acetoxymethylenemalonate or its di-*l*-menthyl derivative (A: $W_1, W_2=CO_2Me$ or CO_2-*l*-menthyl) as the dienophile in a high-pressure Diels–Alder reaction with furan.

Our continuing efforts aiming at an extension of this methodology have led to menthyl 2,4-dioxo-1,3-oxazine-5-carboxylates (H: *e.g.* R = *l*-menthyl) as new chiral dienophiles, and here we wish to report these results in detail.

Diels–Alder Reaction of Methyl 2,4-Dioxo-1,3-oxazine-5-carboxylates with Cyclopentadiene and Use of Its Adducts in Synthesis of Carbocyclic C-Nucleoside Precursors Among a variety of heterocycles so far prepared from newly synthesized 4-oxo-1,3-dioxin-5-carboxylates (F),[22] we have focussed our attention on the corresponding oxazinediones (H). This is because of the following two observations (i and ii). These are: i) neither methoxymethylenemalonate (G) cycloaddition to cyclopentadiene,[14] nor C–C bond fission of the adduct actually formed from the diene and 3-acetoxyacrylate [one CO_2R group in I (A: $W_1, W_2=CO_2R$) is replaced with hydrogen] proceeds under the RRA reaction conditions,[21] and ii) unlike G, dialkyl acetoxymethylenemalonate (I) and its equivalents (A) cycloadd readily to the diene, and the adducts thus formed undergo the desired C–C bond fission on the RRA reaction.[14] It is therefore clear that the reactivity of F is much lower than that of H in the Diels–Alder reac-

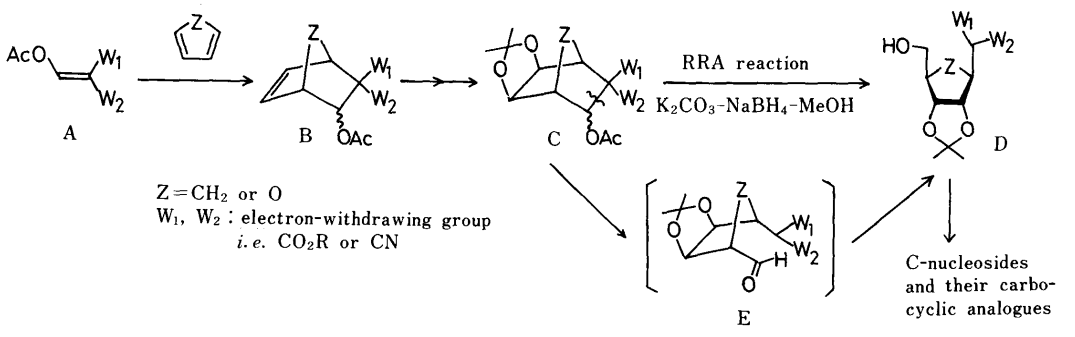

Chart 1

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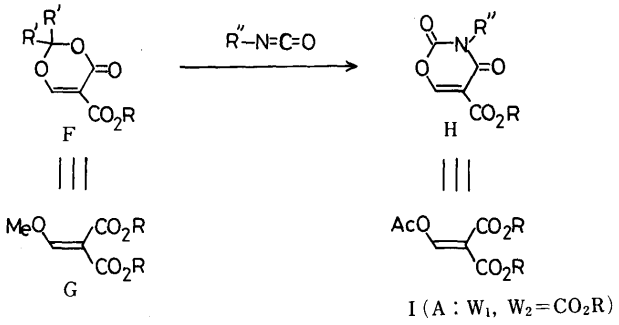

Chart 2

tion, because the former is isoelectronic with G, while the latter is with I. Actually, it was found that F did not react with cyclopentadiene[23] whereas the oxazinediones H derived from F, which could be synthesized from formyl Meldrum's acid (**1**) *via* the half ester **2**, afforded the desired 4+2 adducts on treatment with the diene in an aprotic solvent at room temperature (Chart 3). Thus, when methyl 3-substituted 2,4-dioxo-1,3-oxazine-5-carboxylates (**4**—**6**) were reacted with cyclopentadiene in toluene at room temperature, the expected 4+2 adducts **7**—**9** were obtained in almost quantitative yields as mixtures of *endo* and *exo* isomers. The results are summarized in Table I.

The ratio of *endo* and *exo* isomers was determined by proton nuclear magnetic resonance (^{1}H-NMR) spectroscopy using the signal patterns of the proton at the 2-position in these adducts **7**—**9** as the criterion. The signal due to the 2-proton of each *endo* isomer was observed as a doublet at lower field (δ 5.12—5.25), whereas that of the *exo* isomer was a singlet at a higher field (δ 4.63—4.73). Among the adducts obtained in the above reactions, the one **8** obtained from **5** was found to be separable by silica gel column chromatography. The *endo*/*exo* ratio decreases with increase of the bulkiness of substituent R_2; this is probably attributable to steric hindrance. The reaction proceeded much faster even at a lower temperature, if a suitable Lewis acid catalyst was added to the reaction mixture. Titanium tetrachloride was found to be more effective than diethylaluminum chloride and the reactions catalyzed by the former were completed within 1 h even at −15 °C (see Experimental). It is noteworthy that the relative amount of *endo* isomers increased appreciably when these catalysts were used.

Next, we investigated transformation of the adducts **7**—**9** to carbocyclic C-nucleoside precursors by means of the RRA reaction using **8***endo* as the substrate. When the adduct was subjected to RRA reaction at room temperature, a cyclopentene derivative **10** and a bicyclic compound **11** were obtained in yields of 55% and 45%, respectively. This fact shows that two types of the oxazine ring cleavage (a and b) operate in the RRA reaction of **8***endo*, namely through an initial nucleophilic attack of methanol at the 4-position or the 6-position. In path a, the O–CO bond is cleaved and the resultant bicyclic alcohol suffers usual C–C bond fission (retro aldol reaction) and reduction to give the 1,4-*cis*-2-cyclopentene derivative **10**. If the O–CO bond is

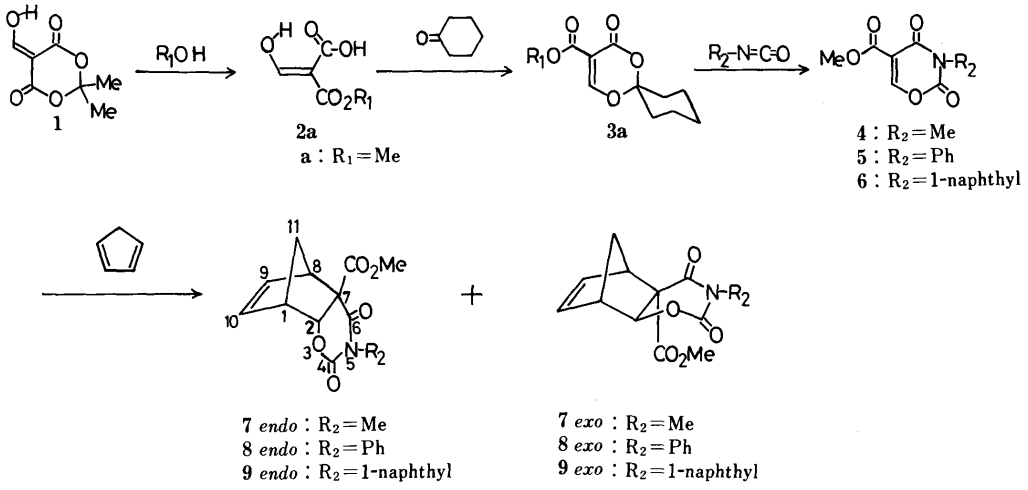

Chart 3

TABLE I. Diels–Alder Reaction of Cyclopentadiene with Methyl 3-Substituted 2,4-Dioxo-1,3-oxazine-5-carboxylates (**4**—**6**)

No.	R_2	Reaction temp. (°C)	Catalyst	Reaction time (h)	Adduct			
					No.	Yield (%)	*endo*/*exo*	mp (°C)
4	Me	Room temp.	None	24	**7**	91	2.6	Oil (mix.)[a]
		−15	Et_2AlCl	2		Quant.	3.5	
5	Ph	Room temp.	None	24	**8**	Quant.	1.3	156—157 (*endo*)
		−15	Et_2AlCl	2		60	2.0	146—148 (*exo*)
		−15	$TiCl_4$	1		87	2.0	
6	1-Naphthyl	Room temp.	None	72	**9**	Quant.	1.0	181—188 (mix.)[a]
		−15	$TiCl_4$	1		62	2.5	

a) A mixture of *endo* and *exo* isomers.

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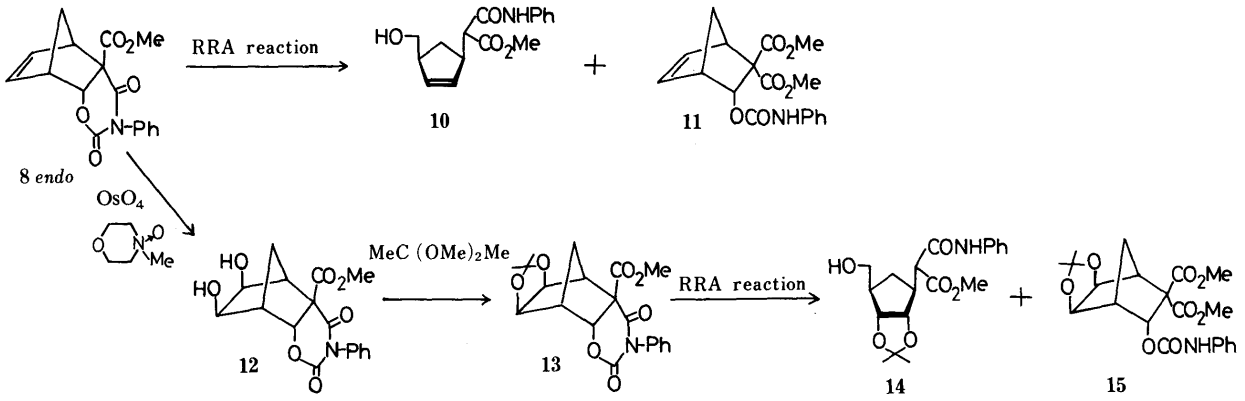


Chart 4

retained and the N–CO bond is cleaved in this step (path b), however, the final product is the bicyclic compound **11**.

Oxidation of **8***endo* with osmium tetroxide–4-methylmorpholine N-oxide gave the *cis* diol **12**, whose hydroxyl groups were protected with an isopropylidene group in a usual manner to give the acetonide **13**. When the acetonide was subjected to RRA reaction, the desired C-nucleoside precursor **14** was again obtained as the major product, together with a bicyclic compound **15**.

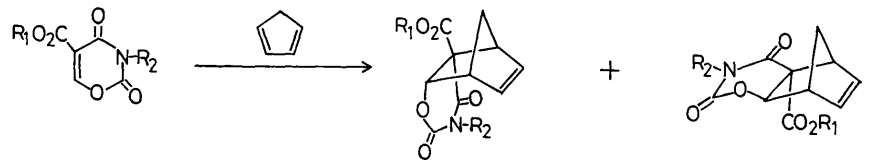
***l*-Menthyl 2,4-Dioxo-1,3-oxazine-3-carboxylates as Chiral Dienophiles** As mentioned in the previous section, the two-step reaction, namely Diels–Alder reaction of methyl 2,4-dioxo-1,3-oxazine-3-carboxylates with cyclopentadiene and the RRA reaction of the adducts thus obtained, has provided a stereospecific route to carbocyclic C-nucleoside precursors as racemic compounds. It should be possible to extend this approach to asymmetric synthesis, if one can create chiral dienophiles which afford the adducts with a high diastereomeric excess (de) in the Diels–Alder reaction with cyclopentadiene. Next, we describe the synthesis of some chiral oxazinediones as dienophiles, as well as their successful use in the asymmetric Diels–Alder reaction.

According to the method previously reported in the racemic series,[22] chiral dienophiles **16**—**18** were synthesized from formyl Meldrum's acid (**1**). Thus, when **1** was allowed to react with *l*-menthol in benzene at 50—60 °C, the half ester **2b** was obtained in 84% yield. Use of a higher temperature (*e.g.* reflux in benzene) resulted in almost exclusive formation of *l*-menthyl formylacetate. Similar reaction of **1** with *l*-8-phenylmenthol at around 50—60 °C gave the half ester **2c** as a crystalline compound in 78% yield. These half esters reacted readily with cyclohexanone, when both were treated with acetic anhydride at room temperature in the presence of *p*-toluenesulfonic acid, to give the corresponding dioxines **3b**, **c** in satisfactory yields.

Table II. Menthyl 2,4-Dioxo-1,3-oxazine-5-carboxylates (**16**—**18**)

No.	R_1	R_2	Reaction time (h)	Yield (%)	mp (°C)	$[\alpha]_D$ (°)	IR ($CHCl_3$) cm^{-1}					^{1}H-NMR ($CDCl_3$) δ
							C=O				C=C	6-H
16	*l*-Menthyl	Me	5	35	117—119	−67.1	1788	1754	1727	1700	1631	8.20
17	*l*-Menthyl	Ph	9	12	186—188	−58.1	1792	1746 (sh)	1735	1700	1635	8.30
18	*l*-8-Phenylmenthyl	Me	7	69	120—122	−73.8	1788	1746	1731 (sh)	1697	1631	6.63

Table III. Asymmetric Diels–Alder Reaction of Cyclopentadiene with Menthyl 2,4-Dioxo-1,3-oxazine-5-carboxylates (**16**—**18**)



16—**18** **19** *endo*—**21** *endo* **19** *exo*—**21** *exo*

No.	R_1	R_2	Reaction temp. (°C)	Catalyst[a]	Reaction time (h)	Adduct				
						No.	Yield (%)	*endo*/*exo*	de (%)[b]	mp (°C)
16	*l*-Menthyl	Me	−78	$TiCl_4$	1	**19**	78	5.0	44	Oil (mix.)[c]
17	*l*-Menthyl	Ph	Room temp.	None	72	**20**	Quant.	3.3	22	142—147 (mix.)[c]
			−78	$TiCl_4$	1		Quant.	3.3	60	
18	*l*-8-Phenylmenthyl	Me	Room temp.	None	48	**21**	43	5.0	20	156—158 (*endo*)
			−78	$TiCl_4$	1		53	8.0	≥95	

a) A catalytic amount of titanium tetrachloride was used. *b*) The de corresponds to that of the *endo* adduct. *c*) A mixture of *endo* and *exo* isomers.

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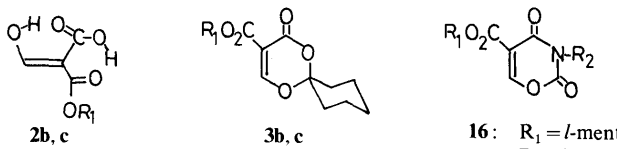


2b, c **3b, c**

b: R_1 = *l*-menthyl
c: R_1 = *l*-8-phenylmenthyl

16: R_1 = *l*-menthyl, R_2 = Me
17: R_1 = *l*-menthyl, R_2 = Ph
18: R_1 = *l*-8-phenylmenthyl, R_2 = Me

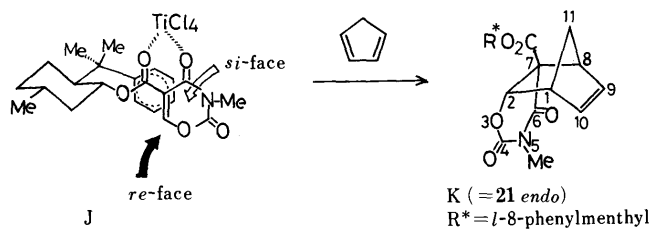
Chart 5

Heating of the latter compounds with various isocyanates in toluene under reflux gave the desired chiral 1,3-oxazine-2,4-diones **16**—**18** (Chart 5). The results are summarized in Table II.

In the infrared (IR) spectra of these compounds, four carbonyl absorption bands are observed at around 1700—1790 cm^{-1}. The nuclear magnetic resonance (NMR) spectrum of **18** showed the signal due to the olefinic proton at extremely high field (δ 6.63), owing to the ring current effect of the benzene ring.

On the basis of the Diels–Alder reaction mentioned in the previous section using achiral dienophiles, we then investigated asymmetric Diels–Alder reaction of the chiral dienophiles (**16**—**18**) with cyclopentadiene. The results are summarized in Table III.

The dienophiles **17** and **18** reacted with cyclopentadiene even without any catalyst at room temperature to give the corresponding adducts **20** and **21** as mixtures of *endo* and *exo* isomers. Though these isomers could not be separated chromatographically, their ratios (*endo*/*exo*) were determined from their ^{1}H-NMR spectra to be 3.3 and 5.0, respectively. While the de's of *exo*-isomers could not be determined, those of *endo* isomers were determined readily from the ^{1}H-NMR spectra to be 22% for **20***endo* and 20% for **21***endo*. Much higher de was obtained, however, if a Lewis acid catalyst was used in the Diels–Alder reaction. Since we knew already that titanium tetrachloride was more effective than diethylaluminum chloride, titanium tetrachloride was used throughout in the asymmetric Diels–Alder reaction. When the dienophile **16** was allowed to react with cyclopentadiene in dichloromethane containing a catalytic amount of titanium tetrachloride, the reaction proceeded smoothly even at −78 °C and was completed within 1 h. The adduct **19** was obtained in 78% yield and the *endo*/*exo* ratio and the de of the *endo* isomer were determined to be 5.0% and 44%, respectively. Similar reaction of **17** with cyclopentadiene gave the adduct (**20**, *endo*/*exo* = 3.3, de 60% for the *endo* isomer) in quantitative yield. On the other hand, the dienophile **18** having a *l*-8-phenylmenthyl group as a chiral auxiliary reacted with cyclopentadiene under the same conditions to give the adduct **21** (*endo*/*exo* = 8.0) in 53% yield with de 95% (for the major *endo* isomer). The *endo* isomer **21***endo* was purified by recrystallization from ether to give a single isomer (mp 156—158 °C).



J K (=**21** *endo*) R* = *l*-8-phenylmenthyl

Fig. 1

By analogy to the concept proposed by Oppolzer for Diels–Alder reaction of *l*-8-phenylmenthyl acrylate with cyclopentadiene under similar conditions,[24] we propose the mechanism shown in Fig. 1. Titanium tetrachloride chelates with two carbonyl groups of the dienophile **18** to form the chelated species (J), whose *re*-face is less hindered than the other face (*si*-face). Cyclopentadiene thus approaches J from the less hindered face preferentially to give the adduct K (**21**), and hence **21** should have (2*S*,7*S*)-configuration. Stacking effect between the phenyl and oxazine rings in J might be involved in the high diastereoselectivity observed in the above Diels–Alder reaction.

In conclusion, we have elaborated several menthyl 1,3-oxazine-2,4-diones as new dienophiles, which are potential reagents for the synthesis of C-nucleoside precursors. Presently, we are investigating the absolute structure of the adduct **21** in order to confirm the proposed mechanism (Fig. 1). At the same time, extensive investigations on the reaction of these dienophiles with furan aiming at the synthesis of C-nucleosides are in progress.

Experimental

All melting points were determined on a Yanaco model MP instrument, and are uncorrected. Optical rotations were measured with a JASCO DIP-340 digital polarimeter. Infrared (IR) spectra were measured on a JASCO A-102 spectrometer. ^{1}H-NMR spectra at 60 and 100 MHz were recorded with JEOL JNM-PMX 60 si and JEOL JNM-FX100 spectrometers using tetramethylsilane (TMS) as an internal standard, respectively. The abbreviations of signal patterns are as follows: s, singlet; d, doublet; m, multiplet; dd, doublet of doublets; dt, doublet of triplets; br, broad; br s, broad singlet. Low-resolution mass spectra (MS) were obtained on a Hitachi M-52G instrument. Wakogel (C-200) and Merck Kieselgel 60 F254 were employed for silica gel column and preparative thin layer chromatography (TLC), respectively. The ratio of solvent mixtures for chromatography is shown as volume/volume.

Genral Procedure for Diels–Alder Reaction of Cyclopentadiene with Methyl 3-Substituted 2,4-Dioxo-1,3-oxazine-5-carboxylates (4—6) Method a: A solution of an oxazine (**4**—**6**)[22] (2 mmol) and cyclopentadiene (2 ml) in anhydrous dichloromethane (5 ml) was allowed to stand at room temperature for 24 h. The reaction mixture was concentrated *in vacuo*, and the residue was subjected to silica gel (10 g) column chromatography. Elution with hexane–ethyl acetate gave the corresponding adduct (**7**—**9**). The results are given in Table I.

Method b: Diethylaluminum chloride (0.1 mmol) or titanium tetrachloride (one drop) was added to a solution of an oxazine (**4**—**6**) (1 mmol) and cyclopentadiene (0.33 g, 5 mmol) in anhydrous dichloromethane (5 ml) with stirring under ice-salt cooling. After being stirred under ice-salt cooling for 1 h, the reaction mixture was diluted with dichloromethane (10 ml). The solution was washed with water, dried over anhydrous sodium sulfate, and concentrated *in vacuo*. The residue was subjected to silica gel (5 g) column chromatography. Elution with hexane–ethyl acetate gave the corresponding adduct (**7**—**9**). The results are given in Table I.

Methyl *endo*- and *exo*-5-Methyl-4,6-dioxo-3-oxa-5-azatricyclo-[6.2.1.$0^{2,7}$]undec-9-ene-7-carboxylate (**7**, *endo*:*exo* = 13:5): Eluent, hexane–ethyl acetate (3:1); pale yellow oil. *Anal.* Calcd for $C_{12}H_{13}NO_5$: C, 57.37; H, 5.22; N, 5.58. Found: C, 57.09; H, 5.31; N, 5.45. IR ($CHCl_3$): 1742, 1688, 1623 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.67 (2H, m, 11-H), 3.17 (3H × 13/18, s, N-Me, *endo*), 3.30 (3H × 5/18, s, N-Me, *exo*), 3.73 (3H × 5/18, s, CO_2Me, *exo*), 3.80 (3H × 13/18, s, CO_2Me, *endo*), 4.63 (1H × 5/18, s, 2-H, *exo*), 5.12 (1H × 13/18, d, J = 4 Hz, 2-H, *endo*), 6.27 (2H, m, olefinic H). MS *m/z*: 236 (M^+ − Me).

Methyl *exo*-4,6-Dioxo-5-phenyl-3-oxa-5-azatricyclo[6.2.1.$0^{2,7}$]undec-9-ene-7-carboxylate (**8***exo*): Eluent, hexane–ethyl acetate (3:1); mp 146—

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148 °C, colorless plates (ethyl acetate). *Anal.* Calcd for $C_{17}H_{15}NO_5$: C, 65.17; H, 4.82; N, 4.47. Found: C, 65.22; H, 4.77; N, 4.33. IR ($CHCl_3$): 1749, 1700, 1600 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.87 (2H, br s, 11-H), 3.33 (1H, m, 1-H), 3.67 (1H, m, 8-H), 3.80 (3H, s, CO_2Me), 4.73 (1H, s, 2-H), 6.20 (1H, dd, J=3, 6 Hz, olefinic H), 6.50 (1H, dd, J=3, 6 Hz, olefinic H), 7.30 (5H, m, phenyl H).

Methyl *endo*-4,6-Dioxo-5-phenyl-3-oxa-5-azatricyclo[6.2.1.0^{2,7}]undec-9-ene-7-carboxylate (**8***endo*): Eluent, hexane–ethyl acetate (3 : 1); mp 156—158 °C, colorless plates (ethyl acetate). *Anal.* Calcd for $C_{17}H_{15}NO_5$: C, 65.17; H, 4.82; N, 4.47. Found: C, 65.12; H, 4.78; N, 4.39. IR ($CHCl_3$): 1750, 1700, 1600 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.76 (2H, m, 11-H), 3.47 (1H, m, 1-H), 3.80 (1H, m, 8-H), 3.87 (3H, s, CO_2Me), 5.25 (1H, d, J= 5 Hz, 2-H), 6.00 (2H, m, olefinic H), 7.36 (5H, m, phenyl H).

Methyl *endo*- and *exo*-5-(1-Naphthyl)-4,6-dioxo-3-oxa-5-azatricyclo-[6.2.1.0^{2,7}]undec-9-ene-7-carboxylate (**9**): Eluent, hexane–ethyl acetate (2 : 1); mp 184—186 °C (*endo* : *exo* = 1 : 1). *Anal.* Calcd for $C_{21}H_{17}NO_5$: C, 69.41; H, 4.72; N, 3.86. Found: C, 69.41; H, 4.72; N, 3.66. IR ($CHCl_3$): 1750, 1704, 1631, 1600 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.70 (2H, m, 11-H), 3.70 (3H × 1/2, s, CO_2Me, *exo*), 3.80 (3H × 1/2, s, CO_2Me, *endo*), 4.73 (1H × 1/2, s, 2-H, *exo*), 5.20 (1H × 1/2, d, J=4 Hz, 2-H, *endo*), 6.37 (2H, m, olefinic H), 7.40 (7H, m, naphthyl H).

Methyl 2-(4β-Hydroxymethyl-2-cyclopenten-1β-yl)-2-(*N*-phenylcarbamoyl)acetate (10) and Dimethyl 2-*endo*-(*N*-Phenylcarbamoyloxy)bicyclo[2.2.1]hept-5-ene-3,3-dicarboxylate (11) K_2CO_3 (66 mg, 0.478 mmol) and $NaBH_4$ (36 mg, 0.958 mmol) were added to a solution of **8***endo* (75 mg, 0.239 mmol) in absolute MeOH (5 ml)–anhydrous 1,2-dimethoxyethane (3 ml) with stirring under ice-cooling. After being stirred at room temperature for 1 h, the mixture was neutralized with AcOH (0.5 ml), and concentrated *in vacuo*. The residue was subjected to silica gel (5 g) column chromatography. Elution with hexane–ethyl acetate (3 : 1) gave **11** (mp 162—164 °C) as colorless prisms (ether). Yield, 37 mg (45%). *Anal.* Calcd for $C_{18}H_{19}NO_6$: C, 62.60; H, 5.55; N, 4.06. Found: C, 62.62; H, 5.45; N, 4.02. IR ($CHCl_3$): 1758, 1619 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.57 (3H, s, CO_2Me), 3.78 (3H, s, CO_2Me), 6.13 (1H, dd, J=3, 6 Hz, olefinic H), 6.33 (1H, d, J=4 Hz, 2-H), 6.50 (1H, s, NH), 6.67 (1H, dd, J=3, 6 Hz, olefinic H), 7.23 (5H, m, phenyl H). MS *m/z*: 345 (M^+). Further elution with hexane–ethyl acetate (1 : 1) gave **10** as a colorless oil. Yield, 35 mg (55%). *Anal.* Calcd for $C_{16}H_{19}NO_4$: C, 66.42; H, 6.62; N, 4.84. Found: C, 66.31; H, 6.59; N, 4.59. IR ($CHCl_3$): 1746, 1719, 1681, 1619 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.52 (1H, s, $CH_2O\underline{H}$), 3.40 (2H, d, J=5 Hz, $C\underline{H}_2OH$), 3.73 (3H, s, CO_2Me), 5.73 (2H, m, olefinic H), 7.32 (5H, m, phenyl H). MS *m/z*: 289 (M^+).

Methyl *endo*-9,10-*exo*-Dihydroxy-4,6-dioxo-5-phenyl-3-oxa-5-azatricyclo[6.2.1.0^{2,7}]undecane-7-carboxylate (12) A 60% aqueous 4-methylmorpholine N-oxide solution (1 ml) and OsO_4–*tert*-BuOH solution (0.5 ml) [prepared from *tert*-BuOH (200 ml), OsO_4 (1 g), and 30% aqueous H_2O_2 (3 drops)] were added to a solution of **8***endo* (313 mg, 1 mmol) in acetone (2 ml) with stirring. After being stirred at room temperature for 1 h, the reaction mixture was poured into ice water, and extracted with $CHCl_3$. The organic layer was dried over anhydrous sodium sulfate, and concentrated *in vacuo*, then the residue was subjected to silica gel (7 g) column chromatography. Elution with hexane–ethyl acetate (1 : 2) gave **12** (mp 195—197 °C) as colorless needles (hexane–ethyl acetate). Yield, 260 mg (75%). *Anal.* Calcd for $C_{17}H_{17}NO_7$: C, 58.79; H, 4.93; N, 4.03. Found: C, 58.75; H, 4.89; N, 3.84. IR ($CHCl_3$): 3323, 1758, 1704 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.55 (1H, d, J=15 Hz, 11-H), 2.17 (1H, d, J=15 Hz, 11-H), 2.67 (1H, m, 1-H), 3.00 (1H, m, 8-H), 3.87 (3H, s, CO_2Me), 3.93 (1H, dd, J=2 Hz, J=6 Hz, 10-H), 4.18 (1H, dd, J=2 Hz, J=6 Hz, 9-H), 5.15 (1H, d, J=5 Hz, 2-H), 7.65 (5H, m, phenyl H).

Methyl *endo*-9,10-*exo*-Dihydroxy-di-*O*-isopropylidene-4,6-dioxo-5-phenyl-3-oxa-5-azatricyclo[6.2.1.0^{2,7}]undecane-7-carboxylate (13) 2,2-Dimethoxypropane (1.2 ml) and *p*-TsOH · H_2O (21 mg) were added to a solution of **12** (217 mg, 0.62 mmol) in acetone (2 ml) with stirring. After being stirred at room temperature for 4 h, the reaction mixture was neutralized with pyridine (10 mg), and concentrated *in vacuo*. The crystalline substance was recrystallized from hexane–ethyl acetate to give **13** (mp 224—226 °C) as colorless needles. Yield, 220 mg (92%). *Anal.* Calcd for $C_{20}H_{21}NO_7$: C, 62.01; H, 5.46; N, 3.62. Found: C, 61.86; H, 5.39; N, 3.66. IR ($CHCl_3$): 1753, 1708 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.37, 1.50 (6H, s × 2, isopropylidene-Me), 2.92 (1H, m, 1-H), 3.33 (1H, m, 8-H), 3.88 (3H, s, CO_2Me), 4.30 (1H, d, J=6 Hz, 10-H), 4.43 (1H, d, J=6 Hz, 9-H), 5.08 (1H, d, J=5 Hz, 2-H), 7.38 (5H, m, phenyl H).

Methyl 2-(4β-Hydroxymethyl-2α-,3α-isopropylidenedioxycyclopent-1β-yl)-2-(*N*-phenylcarbamoyl)acetate (14) and Dimethyl *exo*-5,6-Isopropylidenedioxy-2-*endo*-(*N*-phenylcarbamoyloxy)bicyclo[2.2.1]heptane-3,3-dicarboxylate (15) K_2CO_3 (116 mg, 0.48 mmol) and $NaBH_4$ (63 mg, 2.10 mmol) were added to a solution of **13** (161 mg, 0.42 mmol) in absolute MeOH (20 ml) with stirring under ice cooling. After being stirred at room temperature for 36 h, the reaction mixture was neutralized with AcOH, and concentrated *in vacuo*. The residue was subjected to silica gel (4 g) column chromatography. Elution with hexane–ethyl acetate (2 : 1) gave **15** (mp 176—178 °C) as colorless needles (hexane–ethyl acetate). Yield, 87 mg (49%). *Anal.* Calcd for $C_{21}H_{25}NO_8$: C, 60.13; H, 6.01; N, 3.34. Found: C, 59.94; H, 6.22; N, 3.26. IR ($CHCl_3$): 3446, 1738, 1604, 1527 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.33, 1.45 (6H, s × 2, isopropylidene-Me), 3.62 (3H, s, CO_2Me), 3.77 (3H, s, CO_2Me), 4.58 (1H, d, J=6 Hz, 6-H), 5.23 (1H, d, J=6 Hz, 5-H), 6.10 (1H, d, J=5 Hz, 2-H), 6.73 (1H, br s, NH), 7.20 (5H, m, phenyl H). Further elution with hexane–ethyl acetate (3 : 7) gave **14** as a colorless oil. Yield, 43 mg (29%). *Anal.* Calcd for $C_{19}H_{25}NO_6$: C, 62.79; H, 6.93; N, 3.85. Found: C, 63.05; H, 6.80; N, 3.68. IR ($CHCl_3$): 3354, 1723, 1677, 1600, 1546 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.30, 1.48 (6H, s × 2, isopropylidene-Me), 3.67 (2H, d, J=5 Hz, $C\underline{H}_2OH$), 3.78 (3H, s, CO_2Me), 4.48 (2H, m, cyclopentyl 2- and 3-H), 7.37 (5H, m, phenyl H), 8.87 (1H, br s, NH). MS *m/z*: 348 (M^+ − Me).

***l*-Menthyl Hydrogen Hydroxymethylenemalonate (2b)** A solution of formyl Meldrum's acid[25] (**1**) (17.2 g, 0.1 mol) and *l*-menthol (15.6 g, 0.1 mol) in benzene (100 ml) was heated at 50—55 °C for 2 h. The solvent was evaporated off *in vacuo*, and the residue (22.8 g, 84%) was used for the preparation of compound **3b** without further purification due to its instability. $[\alpha]_D^{26}$ −59.0° (*c*=3.7, $CHCl_3$). IR ($CHCl_3$): 1708, 1627, 1604 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 4.93 (1H, dt, J=4, 11 Hz, menthyl 1-H), 7.30 (1H, s, olefinic H), 12.43 (2H, br s, CO_2H and enolic OH). MS *m/z*: 270 (M^+).

***l*-8-Phenylmenthyl Hydrogen Hydroxymethylenemalonate (2c)** A solution of **1** (1.4 g, 8.16 mmol) and *l*-8-phenylmenthol (1.9 g, 8.16 mmol) in benzene (13 ml) was heated at 50 °C for 4 h. The solvent was evaporated off *in vacuo*, and the crystalline substance was recrystallized from *n*-pentane to give **2c** of mp 93—95 °C, pale yellow plates, 2.2 g (78%). $[\alpha]_D^{24}$ −122° (*c*= 1.5, $CHCl_3$). *Anal.* Calcd for $C_{20}H_{26}O_5$: C, 69.37; H, 7.57. Found: C, 69.17; H, 7.33. IR ($CHCl_3$): 1707, 1623, 1604 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 5.10 (1H, dt, J=4, 11 Hz, menthyl 1-H), 6.82 (1H, s, olefinic H), 7.17 (5H, s, phenyl H), 12.38 (1H, s, OH), 14.33 (1H, br s, OH).

***l*-Menthyl 4-Oxo-1,3-dioxin-2-spirocyclohexane-5-carboxylate (3b)** *p*-TsOH · H_2O (1.6 g, 8.3 mmol) was added to a mixture of **2b** (22.4 g, 83 mmol), cyclohexanone (16.3 g, 166 mmol), and acetic anhydride (16.9 g, 166 mmol) with stirring under ice cooling. After being stirred at room temperature for 6 h, the reaction mixture was poured into water and extracted with hexane. The organic layer was washed with water three times, dried over anhydrous sodium sulfate, and concentrated *in vacuo*. The residue (21.4 g, 74%) was used for the preparation of compounds **16** and **17** without further purification. $[\alpha]_D^{25}$ −56.2° (*c*=3.2, $CHCl_3$). IR ($CHCl_3$): 1769, 1708, 1600 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 4.87 (1H, dt, J=4, 11 Hz, menthyl 1-H), 8.17 (1H, s, olefinic H). MS *m/z*: 351 (M^+).

***l*-8-Phenylmenthyl 4-Oxo-1,3-dioxin-2-spirocyclohexane-5-carboxylate (3c)** *p*-TsOH · H_2O (70 mg, 0.37 mmol) was added to a mixture of **2c** (1.28 g, 3.7 mmol), cyclohexanone (0.73 g, 7.4 mmol), and acetic anhydride (0.76 g, 7.4 mmol) with stirring at room temperature. After being stirred at room temperature for 4 h, the mixture was poured into water, and extracted with $CHCl_3$. The organic layer was washed with water, dried over anhydrous sodium sulfate, and concentrated *in vacuo*. The crystalline substance was recrystallized from ether–hexane to give **3c** of mp 123—125 °C, colorless plates, 1.3 g (83%). $[\alpha]_D^{24}$ −59.5° (*c*=1.2, $CHCl_3$). *Anal.* Calcd for $C_{26}H_{34}O_5$: C, 73.21; H, 8.04. Found: C, 72.93; H, 7.78. IR ($CHCl_3$): 1773, 1692, 1600 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 5.00 (1H, dt, J=4, 11 Hz, menthyl 1-H), 6.63 (1H, s, olefinic H).

***l*-Menthyl 2,4-Dioxo-3-methyl-1,3-oxazine-5-carboxylate (16)** A solution of **3b** (3.5 g, 10 mmol) and methyl isocyanate (1.1 g, 20 mmol) in toluene (20 ml) was heated under reflux for 5 h. After removal of the solvent, the crystalline substance was recrystallized from hexane–ether to give **1b** as colorless needles, 1.1 g (35%). *Anal.* Calcd for $C_{16}H_{23}NO_5$: C, 62.12; H, 7.49; N, 4.53. Found: C, 62.00; H, 7.56; N, 4.52.

***l*-Menthyl 2,4-Dioxo-3-phenyl-1,3-oxazine-5-carboxylate (17)** A solution of **3b** (3.5 g, 10 mmol) and phenyl isocyanate (1.19 g, 10 mmol) in toluene (20 ml) was heated under reflux for 6 h. After removal of the solvent, the crystalline substance was recrystallized from ether to give **17** as colorless needles, 0.43 g (12%). *Anal.* Calcd for $C_{21}H_{25}NO_5$: C, 67.90; H, 6.78; N, 3.77. Found: C, 67.92; H, 6.93; N, 3.89.

***l*-8-Phenylmenthyl 2,4-Dioxo-3-methyl-1,3-oxazine-5-carboxylate (18)** A solution of **3c** (426 mg, 1 mmol) and methyl isocyanate (171 mg, 3 mmol) in toluene (2 ml) was heated under reflux for 5 h. After removal of the

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solvent, the crystalline substance was recrystallized from hexane–ether to give **18** as colorless needles, 226 mg (69%). *Anal.* Calcd for $C_{22}H_{27}NO_5$: C, 68.55; H, 7.06; N, 3.63. Found: C, 68.34; H, 6.78; N, 3.61.

***l*-Menthyl *endo*- and *exo*-5-Methyl-4,6-dioxo-3-oxa-5-azatricyclo-[6.2.1.0^{2,7}]undec-9-ene-7-carboxylate (19)** Titanium tetrachloride (1 drop) was added to a solution of **16** (309 mg, 1 mmol) and cyclopentadiene (331 mg, 5 mmol) in anhydrous dichloromethane (5 ml) with stirring at −78 °C. After being stirred at −78 °C for 1 h, the reaction mixture was diluted with dichloromethane. The solution was washed with water, dried over anhydrous sodium sulfate, and concentrated *in vacuo*. The residue was subjected to silica gel (5 g) column chromatography. Elution with hexane–ethyl acetate (10 : 1) gave **19** (*endo* : *exo* = 5 : 1, de 44.3% for the *endo* isomer[26]) as a pale yellow oil. Yield, 293 mg (78%). *Anal.* Calcd for $C_{21}H_{29}NO_5$: C, 67.18; H, 7.79; N, 3.73. Found: C, 67.01; H, 7.82; N, 3.65. IR ($CHCl_3$): 1742, 1692 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.17 (3H, s, N-Me), 3.38 (1H, m, 1-H), 3.82 (1H, m, 8-H), 4.56 (1H × 1/6, s, 2-H, *exo*), 4.67 (1H, m, menthyl 1-H), 5.08 (1H × 5/6, d, J = 4 Hz, 2-H, *endo*), 6.40 (2H, m, olefinic H). MS *m/z*: 376 ($M^+ + 1$).

***l*-Menthyl *endo*- and *exo*-4,6-Dioxo-5-phenyl-3-oxa-5-azatricyclo-[6.2.1.0^{2,7}]undec-9-ene-7-carboxylate (20)** Method a: A solution of **17** (181 mg, 0.487 mmol) and cyclopentadiene (5 ml) in anhydrous dichloromethane (5 ml) was allowed to stand at room temperature for 3 d. The reaction mixture was concentrated *in vacuo*, then the residue was subjected to silica gel (4 g) column chromatography. Elution with hexane–ethyl acetate (5 : 1) gave **20** (*endo* : *exo* = 10 : 3, de 21.8% for the *endo* isomer) as a crystalline substance (mp 142—147 °C). Yield, 213 mg (100%). *Anal.* Calcd for $C_{26}H_{31}NO_5$: C, 71.37; H, 7.14; N, 3.20. Found: C, 71.36; H, 7.22; N, 3.23. IR ($CHCl_3$): 1743, 1700, 1600 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.41 (1H, m, 1-H), 3.82 (1H, m, 8-H), 4.63 (1H × 3/13, s, 2-H, *exo*), 4.73 (1H, m, menthyl 1-H), 5.15 (1H × 10/13, d, J = 4 Hz, 2-H, *endo*), 6.43 (2H, m, olefinic H), 7.22 (5H, m, phenyl H).

Method b: Titanium tetrachloride (1 drop) was added to a solution of **17** (230 mg, 0.619 mmol) and cyclopentadiene (205 mg, 3.095 mmol) in anhydrous dichloromethane (5 ml) with stirring at −78 °C. After being stirred at −78 °C for 1 h, the reaction mixture was diluted with dichloromethane. The solution was washed with water, dried over anhydrous sodium sulfate, and concentrated *in vacuo*. The residue was subjected to silica gel (5 g) column chromatography. Elution with hexane–ethyl acetate (5 : 1) gave **20** (*endo* : *exo* = 10 : 3, de 60.0% for *endo* isomer). Yield, 264 mg (98%).

***l*-8-Phenylmenthyl *endo*- and *exo*-5-Methyl-4,6-dioxo-3-oxa-5-azatricyclo[6.2.1.0^{2,7}]undec-9-ene-7-carboxylate (21)** Method a: A solution of **18** (20 mg, 0.051 mmol) and cyclopentadiene (5 ml) in anhydrous dichloromethane (1 ml) was allowed to stand at room temperature for 48 h. The reaction mixture was concentrated *in vacuo*, then the residue was subjected to silica gel (1 g) column chromatography. Elution with hexane–ethyl acetate (8 : 1) gave **21** (*endo* : *exo* = 5 : 1, de 20% for *endo* isomer) as a crystalline substance. Yield, 10 mg (43.4%). ^{1}H-NMR ($CDCl_3$) δ: 3.13 (3H × 5/6, s, N-Me, *endo*), 3.27 (3H × 1/6, s, N-Me, *exo*), 3.92 (1H × 5/6 × 3/5, d, J = 5 Hz, 2-H, *endo*), 4.83 (1H, m, menthyl 1-H), 5.05 (1H × 5/6 × 2/5, d, J = 5 Hz, 2-H, *endo*), 6.23 (2H, m, olefinic H), 7.25 (5H, s, phenyl H).

Method b: Titanium tetrachloride (1 drop) was added to a solution of **18** (226 mg, 0.586 mmol) and cyclopentadiene (193 mg, 2.932 mmol) in anhydrous dichloromethane (5 ml) with stirring at −78 °C. After being stirred at −78 °C for 1 h, the reaction mixture was diluted with dichloromethane. The solution was washed with water, dried over anhydrous sodium sulfate, and concentrated *in vacuo*. The residue was subjected to silica gel (5 g) column chromatography. Elution with hexane–ethyl acetate (8 : 1) gave **21** (*endo* : *exo* = 8 : 1, de 95% for *endo* isomer). Yield, 140 mg, (53%). Recrystallization of the adduct from ether gave **21** *endo* (mp 156—158 °C) as colorless plates. *Anal.* Calcd for $C_{27}H_{33}NO_5$: C, 71.21; H, 7.37; N, 3.10. Found: C, 71.24; H, 7.01; N, 2.96. IR ($CHCl_3$): 1731, 1685, 1600 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.17 (3H, s, N-Me), 3.40 (1H, m, 1-H), 3.80 (1H, m, 7-H), 4.88 (1H, m, menthyl 1-H), 5.03 (1H, d, J = 4 Hz, 2-H), 6.32 (2H, m, olefinic H), 7.28 (5H, s, phenyl H).

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References and Notes

1) The following papers are included in this series: Part I, reference 9; Part II, reference 10; Part III, reference 11; Part IV, reference 12; Part V, reference 13; Part VI, reference 14; Part VII, reference 15; Part VIII, reference 16; Part IX, reference 17; Part X, reference 18; Part XI, reference 19.
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