Pergamon

Tetrahedron Vol. 50, No. 37, pp. 10839-10848, 1994

0040-4020/94 $7.00+0.00

0040-4020(94)00661-X

Diels-Alder Reaction of α-Substituted Acrylates and α-(Methylene)lactones: Conformation of Dienophiles and Endo/Exo Selectivity

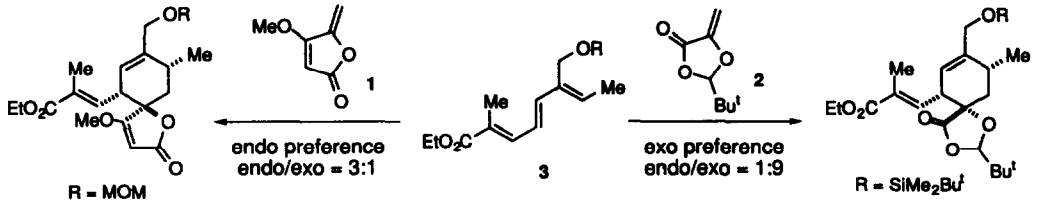
Kei Takeda,* Ikuhiro Imaoka, and Eiichi Yoshii*

Faculty of Pharmaceutical Sciences, Toyama Medical and Pharmaceutical University
2630 Sugitani, Toyama 930-01, Japan

Abstract: Diels-Alder reaction of 1,6-bis(trimethylsilyloxy)-2,4-hexadiene with α-substituted acrylates and 5 to 7- and 9 to 11-membered α-(methylene)lactones has been carried out to examine correlation of dienophile structure with endo/exo selectivity. While the conformationally flexible acrylates produced cycloadducts of endo/exo = 59:41 to 74:26, the 5 to 7-membered lactones with rigid s-cis conjugated system provided cycloadducts of endo/exo = 13:87 to 32:68 and the 9 to 11-membered lactones which can take both s-cis and s-trans conformation afforded endo/exo ratios of 37:63 to 57:43.

The usefulness of Diels-Alder (D-A) reaction in organic synthesis has been attributed to its high stereoselectivity based on endo cycloaddition, which is explained by the concept of secondary orbital overlap in the transition state.[1] Exo-mode addition, however, can predominate in some cases,[2-5] particularly in the combination of cyclopentadiene and methacrylic dienophiles,[2] but the factors that determine the abnormal addition mode have not been fully understood.[1d] In the course of our synthetic studies on spirotetronic acid containing natural products, we demonstrated that D-A reaction of γ-(methylene)tetronate **1** with triene **3** could be used for the direct construction of the subunit structure of kijanolide, though the reaction produced undesired endo adduct in excess (Scheme 1).[6] Some two years later, Roush and Brown disclosed that a highly exo-selective cycloaddition could be accomplished by the use of α-(methylene)dioxolanone **2** as a dienophile.[3b] This sharp contrast in the diastereoselectivities observed with **1** and **2** led us to investigate the D-A reactions of α-substituted acrylates and of α-(methylene)lactones of varying ring size in order to find a general correlation between dienophile structure and endo/exo ratio. As the diene in this study, we made a choice of the particular acyclic diene, 1,6-bis(trimethylsilyloxy)-2,4-hexadiene (**4**),[7] based on, for one thing, the ease in stereochemical assignment of cycloadducts (vide infra). We also considered an additional advantage in using the linear diene **4** over cyclopentadiene, although the latter has been extensively employed in the stereochemical studies of D-A reaction. Preferential exo selectivity in the cycloaddition of cyclopentadiene with methacrylic dienophiles has been believed partly due to a steric repulsion between the diene CH_2 and the α-CH_3 of the dienophiles in the endo transition state,[1d,8,9] the unfavorable steric factor that we wanted to eliminate in the present study.

Scheme 1



We first conducted the D-A reactions between α-substituted acrylates **5a-e** and **4** in *o*-dichlorobenzene (1 M for **5**, molar ratio of **4**/**5** = 3.0) at the temperature of 170 °C where each reaction proceeded at a reasonable rate. The ratios of endo products (**6a-e**) and exo products (**7a-e**) recorded in Table 1 were estimated by capillary GLC analysis after determination of their stereochemistries by conversion to bicyclic *cis*-lactones (**8a-e**) and dihydroxy ester (**9a-e**), respectively, by brief treatment with *p*-TsOH in CH_2Cl_2. All the acrylate (**5a-e**) showed endo preference (endo/exo = 59:41 to 74:26) in contrast to the exo selectivity reported for the reactions of cyclopentadiene with 2-(trimethylsilyloxy)acrylate (**5b**) (endo/exo = 29:71)[5c] and methacrylate (**5e**) (endo/exo = 32:68).[2a]

Scheme 2

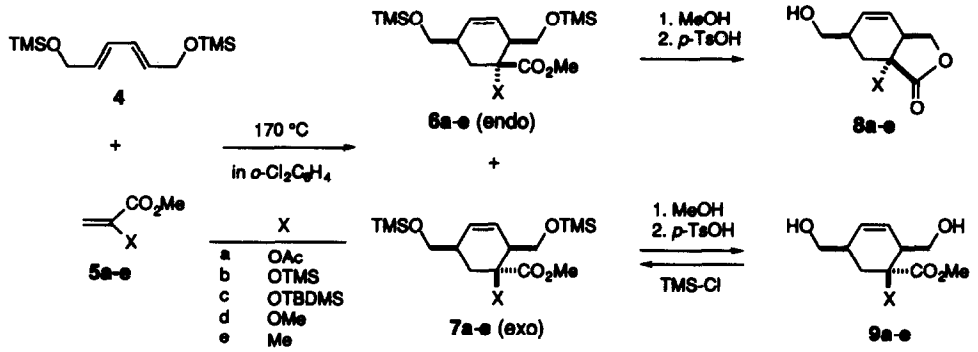


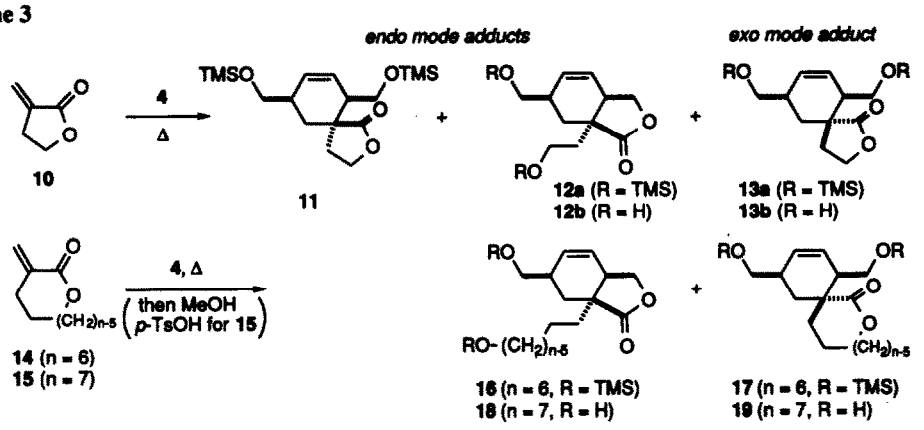
Table 1. D-A Reactions of 5a-e, 10, 14 and 15 with 4 in *o*-$Cl_2C_6H_4$ at 170 °C.

	time (h)	yield (%)[a]	endo : exo
5a (X = OAc)	70	65	74 : 26
5b (X = OTMS)	46	57	73 : 27
5c (X = OTBDMS)	70	49	64 : 36
5d (X = OMe)	70	31	59 : 41
5e (X = Me)	70	52	60 : 40
10 (n = 5)	22	41	29 : 71
14 (n = 6)	22	59	18 : 82
15 (n = 7)	22	57	21 : 79

a The yields are based on the consumed dienophiles.

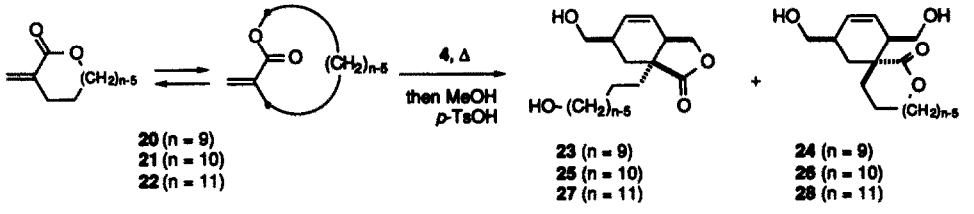
On the other hand, the reaction of α-methylene-γ-butyrolactone (**10**) with **4** at the same temperature resulted in preferential production of the exo adduct **13a** in ca. 2.5-fold excess (endo/exo = 29:71) (Table 1), but this exo preference is much less significant than that reported in the reaction of **10** with cyclopentadiene (endo/exo = 8:92 in refluxing toluene[4]). The *cis*-lactone **12a** isolated in a very small amount should be formed from the endo adduct **11** by an in situ lactonization-silyl transfer sequence.[10] This type of lactonization under the thermal conditions becomes exclusive in the reaction with α-methylene-δ-valerolactone (**14**), in which only γ-lactone **16** and α-spiro-δ-lactone **17**, endo and exo adducts respectively, were obtained in a ratio of 18:82. This exo selectivity higher than that with **10** was also observed with the 7-membered α-(methylene)lactone **15** (endo/exo = 21:79).[11]

Scheme 3



All of the cycloaddition reactions of the diene **4** with α-substituted acrylates (**5a-e**) as well as 5- to 7-membered α-(methylene)lactones (**10**, **14** and **15**) described above were proved to be kinetically controlled by the fact that when each endo/exo mixture was heated with a large excess of diene **4** under the same conditions there was no change in endo/exo ratio. Thus, the high exo selectivity with the 5- to 7-membered α-(methylene)lactones (71-82% exo), in contrast to the endo preference with conformationally flexible **5a-e** (26-41% exo), should be ascribed to their rigid s-cis conformation of the conjugated system. In order to know whether these preferential exo mode additions originate from the particular conformation of the dienophiles and/or some other intrinsic bias of the cyclic structure, we undertook D-A reactions of 9- to 11-membered α-(methylene)lactones (**20-22**) in which both s-cis and s-trans conformations are permitted (Scheme 4).[12] If s-cis conformation does correlate with exo selectivity, there should be an enhancement of endo selectivity as the ring size increases.

Scheme 4



Reactions between **20-22** and **4** were performed at 120 °C and also at 170 °C in *o*-dichlorobenzene (ε = 9.9),[13] as well as in nitrobenzene (ε = 34.8)[13] to see if solvent polarity can affect endo/exo ratios. The endo/exo ratios were determined by GLC analysis of the crude reaction mixture and/or by isolation of the cycloadducts after TsOH-catalyzed desilylation procedure. The results summarized in Table 2, in which the data obtained with 5- to 7-membered dienophiles (**10**, **14** and **15**) under the same conditions are included for comparison. The data indicate that in the medium-sized lactones (**20-22**) endo-mode cycloaddition becomes significant as expected regardless of the reaction temperature and the solvent employed, and the switching the solvent form *o*-dichlorobenzene to much polar nitrobenzene causes some enhancement of endo addition, the degrees of which depend on the ring size and are notable for the 7- and 10-membered lactones (**15** and **21**).

Table 2. The D-A Reaction of α-Methylenelactones 10, 14, 15 and 20-22 with 4.[a]

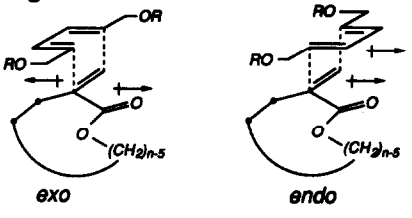
	o-dichlorobenzene				nitrobenzene					*o*-dichlorobenzene				nitrobenzene			
	temp (°C)	time (h)	yield[b] (%)	endo : exo	temp (°C)	time (h)	yield[b] (%)	endo : exo		temp (°C)	time (h)	yield[b] (%)	endo : exo	temp (°C)	time (h)	yield[b] (%)	endo : exo
10	120	22	38	26 : 74	120	22	63	29 : 71	**20**	120	22	27	52 : 48	120	22	24	56 : 44
	120	70	24	26 : 74	120	70	56	29 : 71		120	70	22	55 : 45	120	70	33	57 : 43
	170	22	41	29 : 71	170	22	73	32 : 68		170	22	40	55 : 45	170	22	57	55 : 45
14	120	22	40	13 : 87	120	22	64	19 : 81	**21**	120	22	57	38 : 62	120	22	19	46 : 54
	120	70	33	15 : 85	120	70	56	20 : 80		120	70	66	37 : 63	120	70	20	47 : 53
	170	22	59	18 : 82	170	22	64	27 : 73		170	22	77	42 : 58	170	22	21	47 : 53
15	120	22	*c*		120	22	*c*		**22**	120	22	37	49 : 51	120	22	53	50 : 50
	120	70	14	17 : 83	120	70	11	28 : 72		120	70	45	49 : 51	120	70	76	53 : 47
	170	22	57	21 : 79	170	22	51	28 : 72		170	22	75	48 : 52	170	22	73	49 : 51

a The molar ratio of the dienophiles to 4 is 1:3.0. *b* The yields are based on the consumed dienophiles. *c* No reactions were observed.

The overall experimental results in the reactions of the acyclic diene **4** and α-(methylene)lactones (**10**, **14**, **15** and **20-22**) indicate that there exists a correlation between conformation of reacting dienophile and endo/exo selectivity, and it appears that the high exo selectivities with 5- to 7-membered lactones (**10**, **14** and **15**) are linked to their rigid s-cis conformations in the conjugated system. However, the level of the observed exo selectivity (71-87% in *o*-$Cl_2C_6H_4$) is lower than the 92% exo in the reaction of cyclopentadiene and α-methylene-γ-butyrolactone (**10**) reported by Buono and co-workers,[4] who summarized data for the highly exo selective D-A reactions of cyclopentadiene and **2** and α-methylenecyclohexanones. The remarkable exo selectivity in the reaction with cyclopentadiene may be to some extent due to a steric interaction between the methylene group of the diene and the β-methylene group of **10** that destabilizes the endo transition state. Recently Roush and Brown[3a] reasoned the very high exo selectivity of **2** (94% exo with cyclopentadiene) by applying Berson's dipole moment hypothesis.[14] Thus, the exo transition state is lower in energy than the endo transition state which has a greater net permanent dipole moment in such a way as translated to Fig 1 for our reaction with **4**. The dipolar effect model is consistent with some enhancement of endo/exo ratios on changing the *o*-$Cl_2C_6H_4$ solvent to much polar nitrobenzene.

In conclusion, we have demonstrated that in D-A reaction of α-(methylene)lactones and **4** the secondary orbital interactions are not significantly involved, rather much more important being the preferred conformation of the dienophile en-one system which is associated with a net dipole moment of the transition state. Our results are an indication that more attention should be paid to the correlation of dienophile conformation with stereochemistry of D-A reaction.

Fig 1



EXPERIMENTAL SECTION

General: IR spectra were recorded on a Perkin-Elmer FT1640 spectrometer. ^1H NMR spectra were taken on a Varian Unityplus-500 (500 MHz), Gemini-300 (300 MHz), or JEOL GX-270 (270 MHz) in $CDCl_3$ with reference to $CHCl_3$ (δ 7.26). ^{13}C NMR spectra were measured with Varian Unityplus-500 (125 MHz) or Gemini-300 (75 MHz) with reference to the $CDCl_3$ triplet (δ 77.2). Resonance patterns were described as s = singlet, d = doublet, t = triplet, m = multiplet, and br = broad. High-resolution mass spectra (HRMS) (EI-

MS) were obtained with a JEOL JMS-D-300 spectrometer combined with a JEOL JMA-2000 data processing system. Liquid chromatography under medium pressures (MPLC) was carried out with a Waters Model 6000A chromatograph by using prepacked columns (22 mm x 300 mm, 10 μ silica gel; 22 mm x 150 mm, 5 μ silica gel) (Kusano Kagakukikai Co.). For routine chromatography, the following adsorbents were used: Fuji-Davison silica gel BW-200 (150-325 mesh) for column chromatography; Merck precoated silica gel 60 F-254 plates for analytical thin-layer chromatography. GLC analyses were conducted on Shimazu GC-14AH with HiCAP column (0.2 mm x 25 m) combined with Shimazu C-R6A Chromatopac data processing system. All moisture sensitive reactions were performed under a positive pressure of nitrogen. Dry solvents and reagents were obtained by using standard procedures. Anhydrous $MgSO_4$ was used for drying all organic solvent extracts in workup, and removal of the solvents was performed with a rotary evaporator. Melting points were determined by using a Yanagimoto micro-melting point apparatus. All melting points are uncorrected. Elemental combustion analysis was performed at the Microanalysis Laboratory of this University.

The acrylates **5a,b,d** (X = OAc,[15] $OSiMe_3$,[5c] OMe[16]) and α-methylene-δ-valerolactone[17] were prepared according to the literature procedures. Acrylate **5c** was prepared according to the literature procedure for **5b**. α-Methylene-γ-butyrolactone (**10**) is commercially available.

Preparation of α-methylenelactone.

α-methylene-ε-caprolactone (15). This compound was prepared according to Paterson's procedure[17] for α-methylene-δ-valerolactone **14**. To a cooled (-80 °C) and stirred solution of LDA, prepared from *n*-BuLi (1.56 M in hexane, 59.5 mL, 92.8 mmol) and *i*-Pr_2NH (14.7 mL, 10.58 g, 92.8 mmol) in THF (200 mL), was added dropwise a solution of ε-caprolactone (10.0 g, 33.7 mmol) in THF (10 mL) over 15 min. After stirring at -80 °C for 1 h, TMSCl (18.9 mL, 16.2 g, 148.9 mmol) was added over 7 min. The reaction mixture was warmed to room temperature by removing the cooling bath, and then stirred for 1h. The solution was concentrated, and the residue was diluted with pentane (40 mL) before filtration. The filtrate was concentrated, and the residue was distilled to give enol silyl ether (10.4 g, 64%), 61-67 °C/3.5-4 mmHg.

To a solution of the enol silyl ether (10.4 g, 55.9 mmol) in CH_2Cl_2 (56 mL) was successively added α-chlorothioanisole (10.5 mL, 12.4 g, 78.2 mmol) and powdered $ZnBr_2$ (250 mg, 1.12 mmol) at room temperature. The reaction mixture was stirred for 28 h, then concentrated. The residue was subjected to column chromatography (silica gel, 500 g; hexane:AcOEt = 2:1) to give α-(phenylthiomethyl)-ε-caprolactone (12.5 g, 95%) as a pale yellow oil.

A solution of this material (12.4 g, 52.5 mmol) in MeOH (450 mL) was treated with $NaIO_4$ (11.2 g, 52.5 mmol) in H_2O (50 mL) at room temperature in the dark for 15 h. The reaction mixture was diluted with H_2O (500 mL) before extraction with CH_2Cl_2 (500 mL x 3). The combined organic phases were concentrated. The residue was dissolved in toluene (75 mL) and the solution was refluxed for 5 h. The solvent was removed under reduced pressure and the residue was purified by column chromatography (silica gel, 400 g; hexane:AcOEt = 2:1) before bulb-to-bulb distillation to give **6** (4.24 g, 64 %), a colorless oil, bp 90-105 °C (0.8 mmHg). R_f = 0.34 (hexane:AcOEt = 2:1). IR (film) 1725 cm^{-1}. ^1H NMR δ 1.65-1.92 (4H, m), 2.36 (2H, br t, J = 6.1 Hz, H-3), 4.16 (2H, br t, J = 4.9 Hz, H-6), 5.39 and 5.63 (each 1H, br s, $=CH_2$). ^{13}C NMR δ 27.6, 28.5 (C-4 and C-5), 31.8 (C-3), 69.2 (C-6), 122.6 ($=CH_2$), 143.0 (C-2), 173.1 (C-1). HRMS, *m/e* 126.0655 (calcd for $C_7H_{10}O_2$ (M^+), 126.0681).

By using the same procedure, the following α-(methylene)lactones were prepared.

α-methyleneoctan-8-olide (20). A colorless oil, bp 85-90 °C (0.15 mmHg). R_f = 0.46 (hexane:AcOEt = 9:1). IR (film) 1725 cm^{-1}. ^1H NMR δ 1.49-1.54 (6H, br m) 1.73-1.76 (2H, br m, H-7), 2.47-2.50 (2H, br m, H-3), 4.37 (2H, t, J = 6.6 Hz, H-8), 5.36 (1H, dd, J = 2.7, 1.6 Hz, $=CH_2$), 5.91 (1H, d, J = 1.6 Hz, $=CH_2$). ^{13}C NMR 23.9, 28.7, 29.0 (C4-C6), 28.1 (C-7), 33.0 (C-3), 64.5 (C-8), 123.5 (vinylic), 143.5 (C-2), 169.6 (C-1). HRMS, *m/e* 154.1004 (calcd for $C_9H_{14}O_2$ (M^+), 154.0993).

α-methylenenonan-9-olide (21).[18] A colorless oil, bp 90-100 °C (0.4 mmHg). R_f = 0.45 (hexane:AcOEt = 7:1). ^1H NMR δ 1.12-1.30 (2H, m) 1.35-1.70 (6H, m), 1.70-1.85 (2H, m), 2.47 (2H, br t, J

= 6.4 Hz, H-3), 4.34 (2H, br t, J = 5.4 Hz, H-9), 5.47 (1H, d, J = 0.7 Hz, $=CH_2$), 6.14 (1H, d, J = 1.7 Hz, $=CH_2$).

α-methylenedecan-10-olide (22).[18] A colorless oil, bp 95-105 °C (0.4 mmHg) (lit.[18] ~135 °C/0.05 mmHg). R_f = 0.55 (hexane:AcOEt = 9:1). ^{1}H NMR δ 1.20-1.60 (10H, m) 1.70-1.80 (2H, m), 2.36 (2H, br t, J = 6.4 Hz, H-3), 4.16 (2H, br t, J = 5.1 Hz, H-10), 5.44 (1H, s, $=CH_2$), 6.17 (1H, d, J = 1.5 Hz, $=CH_2$).

General procedure for the D-A reaction of acrylates 5a-e.

A solution of the acrylate (3 mmol), diene **4** (9 mmol) and 4,4'-thiobis(6-*tert*-butyl-*m*-cresol) (5 mg) in *o*-dichlorobenzene (3 mL) was placed in a pressure bottle and degassed.[19] The bottle was placed in a 170 °C oil bath and stirred for 70 h (46 h for **5b**). The mixture was cooled, and the solvent was removed under reduced pressure (100-150 °C/8 mmHg). The residue was subjected to bulb-to-bulb distillation to give the crude mixture (**6a-e** and **7a-e**) (~200 °C/0.04 mmHg) which was subjected to capillary GC analysis. The crude product was dissolved in MeOH (20 mL) and the solution was allowed to stand at room temperature overnight. The reaction mixture was concentrated, and a solution of the residue in CH_2Cl_2 (6 mL) was stirred for 15 min after addition of *p*-TsOH·H_2O (0.25 mmol). The solution was diluted with AcOEt (20 mL), then successively washed with saturated aqueous $NaHCO_3$ solution (10 mL) and water (10 mL x 3), and concentrated. The residue was purified by column chromatography and then MPLC to give **8a-e** and **9a-e**.

General procedure for the D-A reaction of α-(methylene)lactones (10 and 14).

A solution of **10** (200 mg, 2.03 mmol), diene **4** (1.57 g, 6.11 mmol) and 4,4'-thiobis(6-*tert*-butyl-*m*-cresol) (5 mg) in *o*-dichlorobenzene (2 mL) was placed in a pressure bottle and degassed. The bottle was placed in a 170 °C oil bath and stirred for 22 h. The reaction mixture was cooled and filtered through a short column of silica gel (20 g, AcOEt). The filtrate was concentrated, and the residue was subjected to GC analysis before column chromatography (silica gel 100 g, hexane:AcOEt = 5:1) and subsequent MPLC (hexane:AcOEt = 9:1) to give **12a** (9 mg, 1%), **13a** (205 mg, 29 %), and **11** (80 mg, 11%).

General procedure for the D-A reaction of α-(methylene)lactones (15 and 20-22).

A solution of **15** (200 mg, 1.58 mmol), diene **4** (1.22 g, 4.76 mmol) and 4,4'-thiobis(6-*tert*-butyl-*m*-cresol) (5 mg) in *o*-dichlorobenzene (1.6 mL) was placed in a pressure bottle and degassed. The bottle was placed in a 170 °C oil bath and stirred for 22 h. The reaction mixture was cooled and filtered through a short column of silica gel (20 g, AcOEt). The filtrate was concentrated and the residue was subjected to capillary gas chromatography analysis. The crude product was dissolved in MeOH (20 mL) and the solution was allowed to stand at room temperature overnight. The reaction mixture was concentrated, and the residue was subjected to column chromatography (silica gel, 100 g; hexane-AcOEt = 2:1 to AcOEt) to give a mixture (180 mg) of **18** and **19**, and the starting material **15** (44 mg, 22%). The mixture was subjected to MPLC (AcOEt) to give **18** (42 mg, 14%) and **19** (128 mg, 43%).

Table 3. GLC Retention Times of Diels-Alder Adducts.

compd	R_t[a]	conditions[b]	compd	R_t[a]	conditions[b]	compd[c]	R_t[a]	conditions[b]
6a	5.83	A	**7d**	8.89	B	**18**	14.70	B
6b	5.13	A	**7e**	7.86	B	**19**	14.75	B
6c	7.59	A	**11**	6.69	A	**23**	15.80	B
6d	9.27	B	**12a**	6.77	A	**24**	15.96	B
6e	7.97	B	**13a**	7.38	A	**25**[d]	16.91	B
7a	5.94	A	**16**	8.68	A	**26**[d]	16.91	B
7b	5.33	A	**17**	9.57	A	**27**	16.97	A
7c	7.72	A				**28**	13.36	A

a R_t in minutes. *b* A: 230 °C (5 min), then programmed to 280 °C (5 °C/min); B: 200 °C (8 min), then programmed to 280 °C (10 °C/min). *c* TMS ether. The TMS ethers were obtained by treatment with 3 equivs of TMS-Cl and *i*-Pr_2NEt in CH_2Cl_2 in the presence of 0.1 equiv of DMAP. *e* **25** and **26** were inseparable.

Table 4. Characterization Data for the Cycloadducts from Acrylates.[a]

compd[b]	TLC, R_f (solvent)	IR (neat), cm^{-1}	HRMS, calcd (found)	
8c	0.53 (hexane-AcOEt = 1:2)	3420, 1780	$C_{15}H_{27}O_4Si$ (M^++1):	299.1676 (299.1675)
8d	0.48 (AcOEt)	3425, 1780	$C_{10}H_{14}O_4$:	198.0891 (198.0867)
8e	0.51 (AcOEt)	3420, 1770	$C_{10}H_{14}O_3$:	182.0942 (182.0923)
9c	0.37 (hexane-AcOEt = 1:2)	3380, 1740	$C_{16}H_{31}O_5Si$ (M^++1):	331.1938 (331.1921)
9d	0.31 (AcOEt)	3385, 1735	$C_{11}H_{19}O_5$ (M^++1):	231.1231 (231.1214)
9e	0.38 (AcOEt)	3355, 1730	$C_{11}H_{18}O_4$:	214.1204 (214.1201)

a All compounds were obtained as colorless oils. *b* For **8a,b** and **9a,b** see ref. 3c and 7.

Table 5. Characterization Data for the Cycloadducts from α-(Methylene)lactones.

compd	TLC R_f(solvent)[a]	mp, °C (solvent)[a]	IR cm^{-1}	HRMS (M^+) or C/H Combustion analysis calcd (found)	
11	0.45 (H-A = 4:1)	oil	1770[b]	$C_{17}H_{32}O_4Si_2$:	356.1837 (356.1823)
12a	0.50 (H-A = 4:1)	oil	1775[b]	$C_{17}H_{32}O_4Si_2$:	356.1837 (356.1845)
13a	0.44 (H-A = 4:1)	53-54 (H-A)	1770[c]	$C_{17}H_{32}O_4Si_2$:	C, 57.26 (57.37); H, 9.04 (9.03)
16	0.50 (H-A = 4:1)	oil	1775[b]	$C_{18}H_{34}O_4Si_2$:	370.1993 (370.2011)
17	0.38 (H-A = 4:1)	28-30 (H)	1730[c]	$C_{18}H_{34}O_4Si_2$:	C, 58.33 (58.34); H, 9.25 (9.27)
18	0.27 (H-P = 99:1)	oil	3385, 1755[b]	$C_{13}H_{20}O_4$:	240.1360 (240.1337)
19	0.26 (H-P = 99:1)	oil	3385, 1720[b]	$C_{13}H_{20}O_4$:	240.1360 (240.1353)
23	0.31 (A)	oil	3385, 1755[b]	$C_{15}H_{24}O_4$:	268.1673 (268.1655)
24	0.38 (A)	124-125 (H-A)	3320, 1720[c]	$C_{15}H_{24}O_4$:	C, 67.14 (66.93); H, 9.01 (8.99)
25	0.38 (A)	oil	3404, 1755[b]	$C_{16}H_{26}O_4$:	282.1829 (282.1850)
26	0.41 (A)	110-112 (H-A)	3375, 1720[c]	$C_{16}H_{26}O_4$:	C, 68.06 (67.95); H, 9.28 (9.28)
27	0.41 (A)	oil	3385, 1760[b]	$C_{17}H_{28}O_4$:	296.1986 (296.1946)
28	0.43 (A)	117-118 (H-A)	3335, 1725[c]	$C_{17}H_{28}O_4$:	C, 68.89 (68.76); H, 9.52 (9.73)

a H = hexane, A = AcOEt, P = 2-propanol. *b* neat. *c* KBr.

Table 6. ^{13}C- and ^1H-NMR Spectral Data for 8c-e.

position	8c (X = OTBDMS)		8d (X = OMe)		8e (X = Me)	
	δC	δH[a]	δC	δH[a]	δC	δH[a]
1	123.3	5.66 (ddd; 10.0, 4.4, 2.7)	123.2	5.68 (ddd; 10.4, 4.1, 2.5)	124.8	5.63 (ddd; 10.0, 4.1, 2.5)
2	131.6	5.90 (br dm; 10.0)	131.7	5.92 (br d; 10.4)	130.4	5.85 (br dm; 10.0)
3	34.7	2.57-2.63 (m)	34.6	2.57-2.63 (br m)	35.0	2.38-2.44 (br m)
4	30.8	1.56 (dd;13.2, 10.4) 1.88 (dd; 13.2, 4.9)	27.5	1.76 (dd; 13.7, 9.3) 2.05 (dd; 13.7, 5.5)	29.2	1.60 (dd; 13.2, 9.3) 1.65 (dd; 13.2, 6.0)
4a	74.4	-	77.4	-	40.3	-
5	178.1	-	176.6	-	182.2	-
7	70.3	3.75 (dd; 8.8, 8.8) 4.47 (dd; 8.8, 8.8)	70.2	3.83 (dd; 8.8, 8.8) 4.52 (dd; 8.8, 8.8)	70.8	3.84 (dd; 8.8, 8.8) 4.44 (dd; 8.8, 8.8)
7a	44.0	2.85-2.94 (m)	38.3	3.11-3.16 (br m)	42.5	2.69-2.72 (br m)
3-CH_2	65.8	3.57 (dd; 11.0, 6.0) 3.65 (dd; 11.0, 6.0)	65.5	3.60 (dd; 10.7, 5.8) 3.65 (dd; 10.7, 6.3)	65.9	3.56 (d; 6.6)
OH	-	2.06 (br s)	-	1.63 (br s)	-	2.23 (br s)
X	25.8,18.4 -2.9, -3.5	0.06 (s), 0.19 (s) 0.83 (s)	51.8	3.42 (s)	21.2	1.23 (s)

a Multiplicity and *J* in Hz are recorded in parenthesis.

Table 7. ^{13}C- and ^{1}H-NMR Spectral Data for 9c-e.

position	9c (X = OTBDMS)		9d (X = OMe)		9e (X = Me)	
	δC	δH[a]	δC	δH[a]	δC	δH[a]
1	79.6	-	82.8	-	44.6	-
2	44.7	2.96-3.00 (m)	42.8	3.03-3.06 (br m)	42.0	2.78-2.81 (br m)
3	130.4	5.60-5.70 (m)	130.0	5.60-5.70 (br m)	131.3	5.77-5.78 (m)
4	126.8	overlapped with H-3	126.4	overlapped with H-3	129.3	overlapped with H-3
5	38.9	2.61-2.67 (br m)	38.2	2.54-2.59 (br m)	36.8	2.43-2.49 (br m)
6	31.9	1.87 (dd; 12.6, 10.4) 2.26 (ddd; 12.6, 6.8, 1.6)	27.0	1.73 (dd; 12.9, 9.6) 2.42 (ddd; 12.9, 6.6, 1.6)	32.1	1.70 (dd; 13.5, 10.4) 2.03 (dd; 13.5, 6.3)
2-CH_2	63.3	3.71-3.78 (m)	63.5	3.54-3.72 (m)	62.4	3.68 (dd; 11.5, 4.4) 3.76 (dd; 11.5, 4.4)
5-CH_2	66.0	3.54 (dd; 10.4, 4.9) 3.62 (dd; 10.4, 4.9)	65.9	overlapped with 2-CH_2	65.9	3.53 (dd; 12.4, 4.4) 3.62 (dd; 12.4, 4.4)
CO	52.2		52.4	-	52.2	-
OMe	173.2	3.70 (s)	172.1	3.74 (s)	178.1	3.65 (s)
OH	-	2.15 (br s)	-	2.75 (br s)		2.16 (br s)
X	25.9, 18.4 -2.5, -3.7	0.07 (s), 0.13 (s) 0.88 (s)	52.1	3.29 (s)	24.1	1.27 (s)

a Multiplicity and *J* in Hz are recorded in parenthesis.

Fig 2.

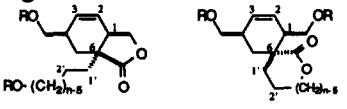


Table 8. ^{1}H-NMR Spectral Data for Bicyclic γ-Lactones.[a]

position	12a (n = 5)	16 (n = 6)	18 (n = 7)	23 (n = 9)	25 (n = 10)	27 (n = 11)
1	3.07-3.08 (br m)	2.83-2.87 (br m)	2.85-2.92 (br m)	2.83-2.92 (m)	2.84-2.88 (br m)	2.81-2.89 (br m)
2	5.66 (ddd; 10.0, 5.0, 2.5)	5.64 (ddd; 10.0,4.5,2.5)	5.70 (ddd; 9.9, 4.4, 2.2)	5.70 (ddd; 10.4, 4.4, 2.2)	5.68 (ddd; 10.2, 4.4, 2.2)	5.66 (ddd; 10.3, 4.4, 2.2)
3	5.81 (br d; 10.0)	5.75 (br d; 10.0)	5.84 (br d; 9.9)	5.85 (ddd; 10.4, 2.2, 2.2)	5.83 (ddd; 10.2,1.9, 1.9)	5.82 (ddd; 10.3, 1.6, 1.6)
4	2.39-2.43 (br m)	2.35-2.39 (br m)	2.40-2.46 (br m)	2.37-2.50 (m)	2.38-2.43 (br m)	2.36-2.42 (br m)
5	1.41 (dd; 13.5, 11.3) 1.71 (dd; 13.5, 5.0)	1.43 (dd; 13.5, 11.0) 1.71 (dd; 13.5, 5.0)	1.50-1.77 (m)	1.64-1.75 (m)	1.62-1.70 (m)	1.18-1.70 (m)
1-CH_2	3.77 (dd; 10.2, 8.7) 4.41 (dd; 8.7, 8.7)	3.76 (dd; 10.0, 8.5) 4.39 (dd; 8.5, 8.5)	3.86 (dd; 8.8, 8.8) 4.44 (dd; 8.8, 8.8)	3.85 (dd; 8.8, 8.8) 4.44 (dd; 8.8, 8.8)	3.83 (dd; 8.8, 8.8) 4.42, (dd; 8.8, 8.8)	3.82 (dd; 8.8, 8.8) 4.41 (dd; 8.8, 8.8)
4-CH_2	3.46, 3.49 (each dd; 9.7, 6.5)	3.42-3.53 (br m)	3.52, 3.57 (each dd; 11.0, 6.0)	3.50-3.60 (m)	3.50, 3.52 (each dd; 13.0, 10.5)	3.48-3.52 (2H, m)
1'-(n-4)'	1.78 (dt; 14.0, 6.3) 1.93 (dt; 14.0, 7.0)	1.46-1.56 (m) 1.58-1.68 (m)	1.50-1.77 (m)	1.20-1.65 (m)	1.20-1.59 (m)	1.18-1.70 (m)
(n-3)'	3.68-3.76 (br m)	3.42-3.58 (m)	3.63 (t; 6.3)	3.61 (t; 6.0)	3.58 (t; 6.3)	3.56 (t; 6.6)
R	0.07 (s) 0.08 (s)	0.05 (s) 0.06 (s)	2.08 (br s)	1.88 (br s)	2.21 (br s)	2.49 (br s)

a The numberings shown in Fig. 2 were used for convenience.

Table 9. ^{13}C-NMR Spectral Data for Bicyclic γ-Lactones.[a]

position	12a (n = 5)	16 (n = 6)	18 (n = 7)	23 (n = 9)	25 (n = 10)	27 (n = 11)
1	38.9	39.0	39.2	39.1	39.1	39.0
2	124.2	124.0	125.1	125.0	125.2	125.0
3	130.8	130.9	130.5	130.5	130.5	130.4
4	35.1	34.9	35.2	35.1	35.2	35.1
5	29.8	29.8	28.9	29.0	29.0	29.0
6	42.7	43.7	44.1	44.0	44.1	44.0
1-CH_2	70.8	70.7	71.0	70.9	70.9	70.9
4-CH_2	66.3	66.1	66.0	65.8	65.9	65.8
C=O	181.0	180.9	181.7	181.7	181.6	181.7
1'-(n-4)'	35.1	27.2, 29.4	20.3, 32.9, 33.8	23.9, 25.5, 29.7 32.6, 34.0	23.9, 25.7, 29.2 30.0, 32.8, 34.2	24.0, 25.7, 29.3, 29.4 29.9, 32.7, 34.1
(n-3)'	58.5	62.6	62.4	62.7	63.0	62.9
R	-0.4, -0.5	-0.4, -0.5	-	-	-	-

a The numberings shown in Fig. 2 were used for convenience.

Table 10. ^{1}H-NMR Spectral Data for Spirolactones.[a]

position	11 (n = 5)	13a (n = 5)	17 (n = 6)	19 (n = 7)	24 (n = 9)	26 (n = 10)	28 (n = 11)
1	2.24-2.28 (m)	2.38-2.48 (m)	2.92-2.95 (br m)	2.83-2.88 (br m)	2.89-2.94 (br m)	2.75-2.76 (br m)	2.71-2.72 (br m)
2	5.72 (dddd; 10.5, 4.5 2.0, 2.0)	5.57 (br ddd; 10.4, 3.3, 2.2)	5.45 (ddd; 10.5, 3.0, 3.0)	5.77-5.87 (m)	5.79 (br d; 10.1)	5.79 (br ddd; 10.0, 1.0, 1.0)	5.75 (br d; 10.8)
3	5.77 (br d; 10.5)	5.72 (br ddd; 10.4, 2.2, 2.2)	5.70 (ddd; 10.5, 3.0, 3.0)	overlapped with H-2	5.85 (ddd; 10.1, 4.6, 1.6)	5.84 (dddd; 10.0 5.1, 2.2, 2.2)	5.84 (ddd; 10.8, 4.9, 2.0)
4	2.34-2.35 (m)	2.38-2.48 (m)	2.41-2.44 (br m)	2.63-2.70 (br m)	2.54-2.60 (br m)	2.46-2.50 (br m)	2.42-2.44 (br m)
5	1.53 (dd; 13.5, 5.5)	1.64 (dd; 14.3, 5.5)	1.86 (dd; 14.0, 4.5)	1.75 (dd; 13.7, 9.9)	NA[b]	1.65-1.71 (m)	1.21-1.85 (m)
1-CH_2	1.68 (dd; 13.5, 11.5)	1.93 (dd; 14.3, 7.1)	2.01 (dd; 14.0, 8.0)	2.12 (dd; 13.7, 7.1)	2.10 (dd; 13.2, 6.6)	2.02 (dd; 13.1, 6.5)	1.98 (dd; 13.2, 6.6)
4-CH_2	3.67 (dd; 10.0, 6.5) 3.48 (dd; 10.0, 6.5)	3.36 (dd; 12.9, 7.7) 3.50 (dd; 12.9, 10.1)	3.41 (dd; 10.5, 8.0) 3.47 (dd; 10.5, 8.5)	3.58 (dd; 10.4, 4.4) 3.64 (dd; 10.4, 4.9)	3.56 (dd; 10.4, 4.4) 3.65 (dd; 10.4, 4.9)	3.55 (dd; 10.2, 4.2) 3.63 (dd; 10.2, 4.7)	3.70 (dd; 11.5, 3.8) 3.78 (dd; 11.5, 4.4)
1'-(n-4)'	2.09-2.12 (m)	1.98 (dd; 12.9, 6.0) 2.38-2.48 (m)	1.72-1.83 (m) 1.92-2.00 (m)	1.62-1.85 (m)	1.25-1.79 (m)	1.42-1.52 (m) 1.74-1.81 (m)	1.21-1.85 (m)
(n-3)'	4.27-4.32 (m)	4.23 (dd; 8.2, 6.0)	4.24 (ddd; 10.5, 4.0)	4.19-4.33 (m)	4.20 (ddd; 10.7, 6.24.4)	4.16 (dddd; 11.1, 8.0, 4.0)	4.09 (ddd 11.1, 7.1, 1.6)
R	0.08 (s) 0.10 (s)	0.05 (s) 0.06 (s)	0.07 (s) 0.08 (s)	2.09-2.16 (br s)	1.25-1.79 (br s)	1.90 (br s)	1.21-1.85 (br s)

a The numberings shown in Fig. 2 were used for convenience. *b* not assigned.

Table 11. ^{13}C-NMR Spectral Data for Spirolactones.[a]

position	11 (n = 5)	13a (n = 5)	17 (n = 6)	19 (n = 7)	24 (n = 9)	26 (n = 10)	28 (n = 11)
1	36.2	36.2	37.0	37.0	36.7	36.5	36.8
2	126.9	126.9	126.8	128.8	129.4	129.4	129.4
3	129.6	129.2	128.0	131.5	131.9	131.3	131.2
4	42.7	42.4	42.7	40.9	40.6	40.8	40.6
5	30.4	30.6	32.7	30.8	30.5	31.7	31.9
6	43.1	42.9	43.6	50.0	48.8	47.8	49.4
1-CH_2	66.5	63.4	62.7	62.4	62.5	62.4	62.7
4-CH_2	63.6	66.0	66.1	65.8	66.2	66.0	66.2
C=O	180.2	180.8	176.5	178.7	177.2	176.7	176.3
1'-(n-4)'	35.7	32.1	20.1, 26.1	23.3, 28.7, 34.2	19.2, 22.2, 27.2 29.8, 36.5	21.2, 24.1, 25.0 25.2, 26.0, 33.4	19.8, 21.7, 23.3, 25.0 26.6, 26.7, 33.3
(n-3)'	65.1	65.3	69.8	68.7	64.8	66.0	64.9
R	-0.3, -0.4	-0.4, -0.5	-0.3, -0.5	-	-	-	-

a The numberings shown in Fig. 2 were used for convenience.

Acknowledgments. The author (KT) wishes to thank The Tamura Foundation for the Promotion of Science and Technology for support of this work.

REFERENCES AND NOTES

1. For reviews on Diels-Alder reaction, see: (a) Oppolzer, W.; in *Comprehensive Organic Synthesis*; Trost, B. M., Freming, I. Eds.; Pergamon: Oxford, 1991; Vol. 5, pp 315-399. (b) Carruthers, W. *Cycloaddition Reactions in Organic Synthesis*; Pergamon: Oxford, 1990. (c) Fringuelli, F.; Taticchi, A. *Dienes in the Diels-Alder Reaction*; John Wiley & Sons, Inc.: New York, 1990. (d) Sauer, J.; Sustmann, R. *Angew. Chem. Int. Ed. Engl.* **1980**, *19*, 779-806.
2. (a) Kobuke, Y.; Fueno, T.; Furukawa, J. *J. Am. Chem. Soc.* **1970**, *92*, 6548-6553. (b) Kobuke, Y.; Sugimoto, T.; Furukawa, J.; Fueno, T. *J. Am. Chem. Soc.* **1972**, *94*, 3633-3635.
3. (a) Roush, W. R.; Brown, B. B. *J. Org. Chem.* **1992**, *57*, 3380-3387. (b) Roush, W. R. Brown, B. B. *Tetrahedron Lett.* **1989**, *30*, 7309-7312. (c) Roush, W. R.; Essenfeld, A. P.; Warmus, J. S.; Brown, B. B. *Tetrahedron Lett.* **1989**, *30*, 7305-7308.
4. Fotiadu, F.; Michel, F.; Buono, G. *Tetrahedron Lett.* **1990**, *31*, 4863-4866.
5. For some examples of exo-selective Diels-Alder reaction, see: (a) Sustmann, R.; Sicking, W.; Lamy-Schelkens, H.; Ghosez, L. *Tetrahedron Lett.* **1991**, *32*, 1401-1404 and references cited therein. (b) Adam, W.; Albert, R.; Hasemann, L.; Nava Salgado, V. O.; Nestler, B.; Peters, E.-M.; Peters, K.; Prechtl, F.; von Schnering, H. G. *J. Org. Chem.* **1991**, *56*, 5782-5785. (c) Creary, X.; Inocencio, P. A.; Underiner, T. L.; Kostromin, R. *J. Org. Chem.* **1985**, *50*, 1932-1938.
6. (a) Takeda, K.; Yano, S.; Sato, M.; Yoshii, E. *J. Org. Chem.* **1987**, *52*, 4135-4137.
   For intramolecular reaction, see: (b) Takeda, K.; Igarashi, Y.; Okazaki, K.; Yoshii, E.; Yamaguchi, K. *J. Org. Chem.* **1990**, *55*, 3431-3434.
7. Takeda, K.; Shibata, Y.; Sagawa, Y.; Urahata, M.; Funaki, K.; Hori, K.; Sasahara, H.; Yoshii, E. *J. Org. Chem.* **1985**, *50*, 4673.
8. Houk, K. N.; Lusku, L. J. J. *Am. Chem. Soc.* **1971**, *93*, 4606-4607.
9. Konovalov, A. I.; Kamasheva, G. I.; Loskutow, M. P. *Zh. Org. Khim.* **1973**, *9*, 2048-2050.
10. Treatment of **11** with MeOH followed by treatment of the desilylation product with *p*-TsOH in CH_2Cl_2 afforded **12b**. This compound was also obtained by treatment of **12a** with MeOH. On the other hand, treatment of **13a** with MeOH followed by *p*-TsOH in CH_2Cl_2 gave **13b**.
11. The initial D-A adducts were separable on capillary GLC, but could not be separated on MPLC.
12. Examination of molecular models showed that they can adopt both s-cis and s-trans conformations and their interconversion can be possible. For conformations of the parent medium ring lactones, see: (a) Wiberg, K. B.; Waldron, R. F. *J. Am. Chem. Soc.* **1991**, *113*, 7697-7705. (b) Huisgen, R.; Ott, T. *Tetrahedron* **1959**, *6*, 253-267.
13. Dean, J. A. *Lange's Handbook of Chemistry*, 12th ed.; McGraw-Hill: New York, NY, 1979.
14. Berson, J. A.; Hamlet, Z.; Mueller, W. A. *J. Am. Chem. Soc.* **1962**, *84*, 297-304.
15. Wolinsky, J.; Novak, R.; Vasileff, R. *J. Org. Chem.* **1964**, *29*, 3596-3598.
16. Ogata, N.; Nozakura, S.; Murahashi, S. *Bull. Chem. Soc. Jap.* **1970**, *43*, 2987-2988.
17. Paterson, I. *Tetrahedron* **1988**, *44*, 4207-4219.
18. Baldwin, J. E.; Adlington, R. M.; Mitchell, M. B.; Robertson, J. *Tetrahedron* **1991**, *47*, 5901-5918.
19. For the degassing procedure, see: Ciganek, E. *Org. React.*, **1984**, *32*, 97.

(*Received in Japan* 6 *July* 1994; *accepted* 25 *July* 1994)