Diastereoselective Iodocarbocyclization Reaction of 2- or 3-Oxy-4-pentenylmalonate Derivatives

Tadashi Inoue, Osamu Kitagawa, Yoko Oda, and Takeo Taguchi*

Tokyo College of Pharmacy, 1432-1 Horinouchi, Hachioji, Tokyo 192-03, Japan

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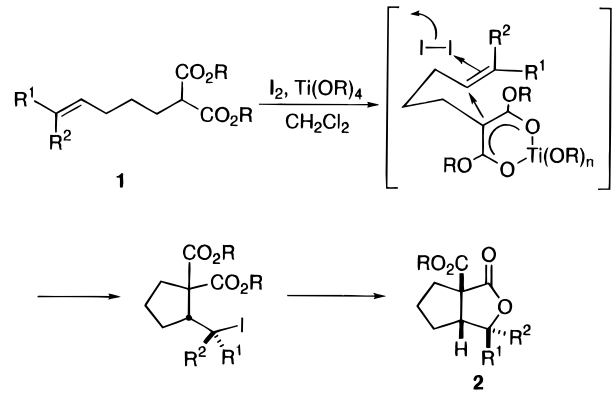
1,2- Or 1,3-asymmetric induction in the iodocarbocyclization reaction of 4-pentenylmalonate derivatives having a stereogenic center at an allylic or a homoallylic position has been investigated. The iodocarbocyclization reactions of 3-oxy-4-pentenylmalonate derivatives proceeded with high *cis*-selectivity through stereoelectronic control of the oxygenated substituent at an allylic position. In the reaction of (*S*)-2-siloxy-4-pentenylmalonate, an excellent diastereoselectivity was achieved through the utilization of double stereodifferentiation with a chiral titanium catalyst. Furthermore, as an application of the present reaction, the asymmetric syntheses of cyclosarkomycin and a synthetic intermediate of brefeldin A from optically pure 2- and 3-oxy-4-pentenylmalonate derivatives are also described.

Introduction

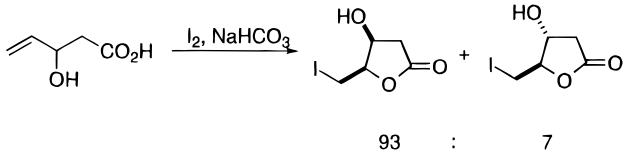
The stereoselective construction of functionalized or alkylated cyclopentane derivatives has attracted much attention in the field of synthetic organic chemistry because of the large number of cyclopentanoid natural products and their interesting biological activity.[1] As a new synthetic method for functionalized cyclopentane or cyclopropane derivatives, we recently found that the iodocarbocyclization reaction of 4-alkenyl- or allylmalonates proceeds in good yield by treatment with I_2 and $Ti(OR)_4$ (Scheme 1).[2,3] In this reaction, disubstituted (iodoalkyl)-cyclopentane derivatives or bicyclic lactones were obtained in a highly regio- and stereospecific manner through a 5-*exo* and *trans*-addition of a malonate anion (a titanium enolate) on a double bond activated by I_2.

For the synthesis of cyclopentanoid natural products, however, the stereoselective construction of more highly substituted cyclopentane skeletons is required. In line with this, the preparation of trisubstituted cyclopentanes through diastereoselective iodocarbocyclization reaction with substituted 4-pentenylmalonate derivatives was investigated. In this paper, we report the results of 1,2- or 1,3-asymmetric induction in the reaction of 4-pentenylmalonates having a stereogenic center at allylic or homoallylic position.[4] In the reaction of 2- or 3-oxy-4-pentenylmalonates, an excellent diastereoselectivity was achieved through investigation of the functionality on the oxygen atom or the utilization of double stereodifferentiation with a chiral titanium catalyst. Furthermore, as an application of the present reaction, the asymmetric syntheses of cyclosarkomycin and a synthetic intermediate of brefeldin A from optically pure 2- and 3-oxy-4-pentenylmalonate derivatives are also described.

Scheme 1



Scheme 2



Results and Discussion

1,2-Asymmetric Induction. It is known that halolactonization of 3-hydroxy-4-pentenoic acid under kinetic conditions proceeds with high *cis*-selectivity (Scheme 2).[5] The iodocarbocyclization of 3-oxy-4-pentenylmalonate which proceeds via a reaction mechanism similar to halolactonization may give a trisubstituted cyclopentane derivative having a *cis*-configuration with high stereoselectivity. At first, the iodocarbocyclization reaction of dimethyl 3-(benzyloxy)-4-pentenylmalonate (**1a**) was conducted for the optimization of the reaction conditions (Table 1). The introduction of an alkoxy substituent at an allylic position of 4-pentenylmalonate resulted in lowering the reactivity due to the decrease of electron density on the olefinic moiety; that is, the reaction of **1a**

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(1) (a) Trost, B. M. *Stereoselective Synthesis of Natural Product*; Bartmann, W., Winterfeldt, E., Eds.; Excerpta Medica: Amsterdam, 1979; Vol. 7, p 106. (b) Chan, D. M. T. *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, 1991; Vol. 5, p 271. (c) Taber, D. F.; You, K. K.; Rheingold, A. L. *J. Am. Chem. Soc.* **1996**, *118*, 547 and references cited therein.

(2) (a) Kitagawa, O.; Inoue, T.; Taguchi, T. *Tetrahedron Lett.* **1992**, *33*, 2167. (b) Kitagawa, O.; Inoue, T.; Hirano, K.; Taguchi, T. *J. Org. Chem.* **1993**, *58*, 3106. (c) Inoue, T.; Kitagawa, O.; Kurumizawa, S.; Ochiai, O.; Taguchi, T. *Tetrahedron Lett.* **1995**, *36*, 1479. (d) Inoue, T.; Kitagawa, O.; Ochiai, O.; Taguchi, T. *Tetrahedron: Asymmetry* **1995**, *6*, 691. (e) Inoue, T.; Kitagawa, O.; Ochiai, O.; Shiro, M.; Taguchi, T. *Tetrahedron Lett.* **1995**, *36*, 9333.

(3) Beckwith, A. L.; Zozer, M. J. *Tetrahedron Lett.* **1992**, *33*, 4975.

(4) Preliminary communication of this work: Kitagawa, O.; Inoue, T.; Taguchi, T. *Tetrahedron Lett.* **1994**, *35*, 1059.

(5) (a) Rollinson, S. W.; Amos, R. A.; Katzenellenbogen, J. A. *J. Am. Chem. Soc.* **1981**, *103*, 4114. (b) Chamberlin, A. R.; Dezube, M.; Dussault, P.; MacMills, M. C. *J. Am. Chem. Soc.* **1983**, *105*, 5819. (c) Tamaru, Y.; Kawamura, S.; Yoshida, Z. *Tetrahedron Lett.* **1985**, *26*, 2885. (d) Bartlett, P. A. In *Asymmetric Synthesis*: Morrison, J. D., Ed.; Academic Press: London, **1984**; Vol. 3, p 411. (e) Gardillo, G.; Orena, M. *Tetrahedron* **1990**, *46*, 3321.

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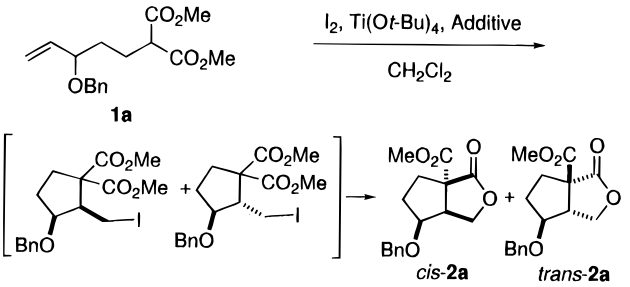
Table 1. Effect of Additive in Iodocarbocyclization[a]



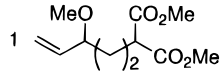
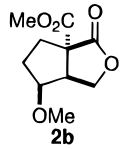
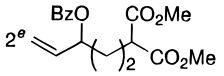
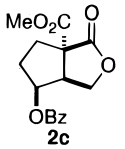
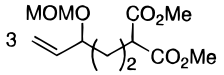
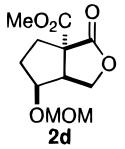
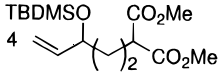
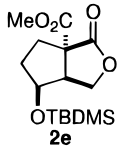
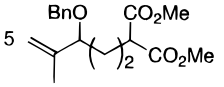
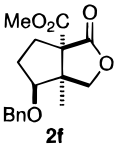
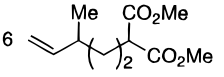
entry	I_2 (equiv)	additive	time (h)	**2a** yield (%)[b]	*cis*/*trans*[c]
1	1.2		51	28	10
2	2.0		12	58	7
3	4.0		10	82	12
4[d]	1.2	CuO	100	91	14
5	1.2	*n*-Bu_2SnO	40	63	17
6	1.2	*n*-Bu_4NI	24	0	

[a] Iodocarbocyclization; **1a** (0.5 mmol), I_2 (see Table 1), Ti(O-*t*-Bu)$_4$ (0.5 mmol), Additive (1.2 equiv), CH_2Cl_2 (5 mL), rt. [b] Isolated yield. [c] Determined by ^{1}H-NMR (400 MHz). [d] The reaction was carried out at 0 °C.

under the conditions [Ti(O-*t*-Bu)$_4$ (1.0 equiv), I_2 (1.2 equiv), CH_2Cl_2, rt] reported previously[2a,b] gave the desired cyclized product **2a** in low yield (28%) along with recovery of the starting material **1a** (60%) (entry 1). By increasing the molar ratio of I_2 to 4 equiv, **2a** was obtained in 82% yield, favoring *cis*-selectivity (*cis*/*trans* = 12) as expected (entry 3). In addition, for this iodocarbocyclization, CuO or Bu_2SnO was found to be effective as an additive. As shown in entries 4 and 5, in the presence of 1.2 equiv of CuO or *n*-Bu_2SnO, **2a** was obtained in good yields (91%, 63%) even with 1.2 equiv of I_2, and similar high *cis*-selectivity (*cis*/*trans* = 14, 17) was observed. On the contrary, the addition of tertabutylammonium iodide, possibly a source of I^- in the reaction medium, completely prevented the reaction (entry 6). *n*-Bu_2SnO and CuO may accelerate the reaction through the trapping of HI formed as the reaction proceeds. Regarding the solvent effect, CH_2Cl_2 gave the best result, while, under the above conditions [CuO (1.2 equiv), Ti(O-*t*-Bu)$_4$ (1.0 equiv), I_2 (1.2 equiv), rt], other solvents such as CH_3CN (*cis*/*trans* = 5, 95% yield), toluene (complex mixture), *i*-PrOH (no reaction), and DMF (no reaction) led to lowered a chemical yield and diastereoselectivity.

Further investigation of the diastereoselectivity in the present reaction was performed with several substrates differing in the nature of their substituents (Table 2). All of the reactions in Table 2 were carried out in the presence of CuO, I_2, and Ti(O-*t*-Bu)$_4$ in CH_2Cl_2. With substrate **1b** having a methoxy substituent in place of the BnO substituent, similar high *cis*-selectivity and chemical yield (**2b**, *cis*/*trans* = 14, 93%) were observed (entry 1). The reaction of malonates **1c** or **1d** having benzoyloxy or methoxymethoxy substituents gave the cyclized product **2c**, **2d** in a slightly lower *cis*-selectivity, respectively (**2c**, *cis*/*trans* = 8; **2d**, *cis*/*trans* = 10, entries 2 and 3). Among the oxygenated substituents examined, the siloxy substituent gave the best result; that is, the reaction of **1e** proceeded with excellent diastereoselectivity (*cis*/*trans* = 100, entry 4) to give bicyclic lactone **2e**. With the 3-benzyloxy derivative **1f** having a methyl substituent at the 4-position, the lactone **2f** was obtained with similar high diastereoselectivity (*cis*/*trans* = 53, entry 5). Contrary to the 3-oxygenated substrates, the reaction of **1g** having a methyl (alkyl) substituent at an allylic position proceeded with very low diastereoselectivity (**2g**, *cis*/*trans* = 2, entry 6).[6]

Table 2. Iodocarbocyclization of 3-Substituted-4-pentenylmalonate[a]

Entry	Substrate **1**	Time (h)	Product **2**[b]	Yield (%)[c]	*cis* / *trans*[d]
1	 **1b**	20	 **2b**	93	14
2[e]	 **1c**	30	 **2c**	92	8
3	 **1d**	100	 **2d**	94	10
4	 **1e**	24	 **2e**	91	100
5	 **1f**	6	 **2f**	81	53
6	 **1g**	18	 **2g**	79	2

[a] Reaction conditions; **1** (0.5 mmol), Ti(O-*t*-Bu)$_4$ (0.5 mmol), I_2 (0.6 mmol), CuO (0.6 mmol), CH_2Cl_2 (5 mL), rt. [b] Structures of major isomers are shown. [c] Isolated yield. [d] Determined by ^{1}H-NMR (400 MHz). [e] To complete lactonization, the reaction mixture of the iodocarbocyclization was briefly heated at 140 °C.

It should be pointed out that the diastereoselectivity in the present reaction is similar to that of halolactonization under kinetic control. The high *cis*-selectivity observed in the reaction of **1a**−**f** can be explained on the basis of stereoelectronic effect of an oxygenated substituent at allylic position. That is, in the chairlike transition state A‡ and B‡ both having an olefinic moiety of pseudoequatorial orientation,[7] A‡ having an axial oxygenated substituent is generally more favorable than B‡ having an equatorial one due to destabilization of B‡ by the overlap between the π-orbital of the double bond activated by I_2 and the σ^*-orbital of the C−O bond (Figure 1). In the reaction of siloxy derivative **1e** with the lower lying σ^*_{C-O} than that of alkoxy derivative, higher diastereoselectivity may be observed because of further

(6) In the iodolactonization reaction of 3-methyl-4-pentenoic acid under kinetic conditions, similar low *cis*-selectivity is observed. (a) Bartlett, P. A. *Tetrahedron* **1980**, *36*, 2. (b) Günther, H. J.; Guntrum, E.; Jäger, V. *Annalen* **1984**, 15.

(7) Labelle, M.; Guindon, Y. *J. Am. Chem. Soc.* **1989**, *111*, 2204.

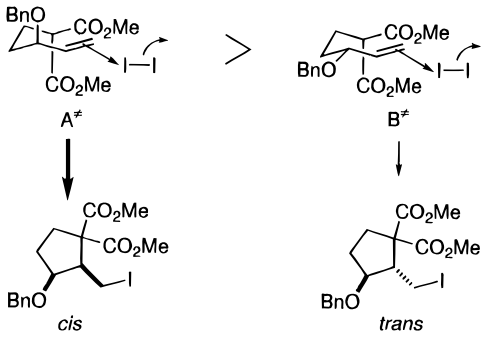
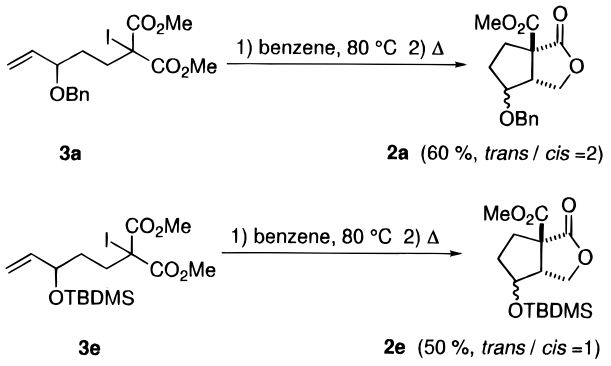


Figure 1. Transition state model in 1,2-asymmetric induction.

Scheme 3

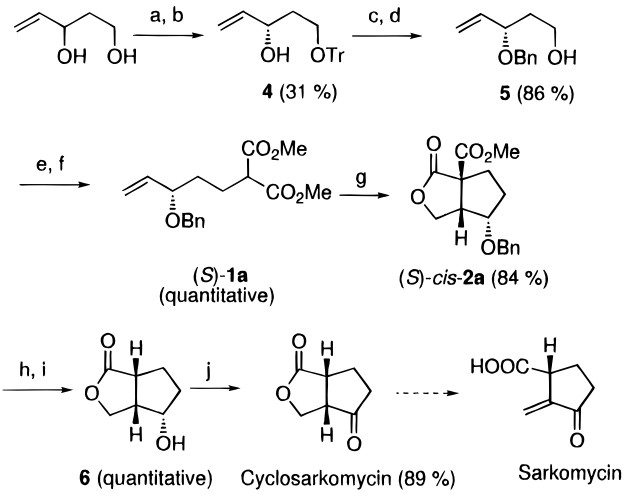


destabilization of transition state B‡ by strong $\pi-\sigma^*_{C-O}$ interaction,[8] while the reaction of methyl derivative **1g** having the higher lying σ^*_{C-C} should proceed with low diastereoselectivity.

For the preparation of similar cyclopentanoid compounds, Curran *et al.* have reported a radical iodine atom transfer cyclization of 4-pentenyl-α-iodomalonate.[9] To compare the diastereoselectivity in iodocarbocyclization with that in radical cyclization, the iodine atom transfer reaction of 3-oxy-4-pentenyl-α-iodomalonate derivatives **3a** and **3e** was examined. In contrast to the high *cis*-selectivity in the above iodocarbocyclization, the reaction of **3a** or **3e** under radical conditions gave a mixture of stereoisomers of the cyclized product **2a** or **2e** with low *trans*-selectivity or without selectivity (Scheme 3).

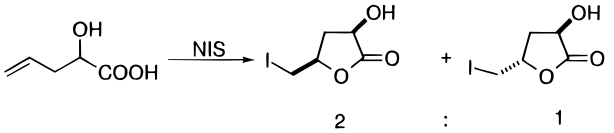
Synthesis of (−)-Cyclosarkomycin. Sarkomycin, a compound isolated from a strain of the soil microorganism *Streptomyces erythrochromegenes*, exhibits weak antibacterial activity and strong activity against the ascites type of tumor.[10] However, because of the chemical lability, the target of most synthetic efforts has been commonly directed to stable cyclosarkomycin which can be converted to sarkomycin by treatment with acid.[11] In spite of this interesting biological activity, the synthesis of optically active cyclosarkomycin has been reported by only two groups.[12] As an application of the present reaction, we have attempted the asymmetric synthesis

Scheme 4[a]



[a] (a) TrCl, pyridine; (b) Ti(O-*i*-Pr)$_4$, L-(+)-dicyclohexyl tartrate, *t*-BuOOH; (c) NaH, BnBr; (d) TsOH, MeOH; (e) MsCl, Et$_3$N; (f) NaH, dimethyl malonate; (g) Ti(O-*t*-Bu)$_4$, I$_2$, CuO and then separation of *trans*-isomer by MPLC; (h) KOH(aq) and then heating (140 °C); (i) H$_2$, Pd(OH)$_2$; (j) Swern oxidation.

Scheme 5



of cyclosarkomycin through the iodocarbocyclization of optically active 3-(benzyloxy)-4-pentenylmalonate (*S*)-**1a**.

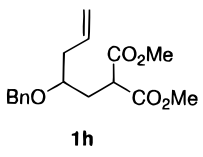
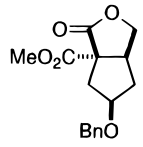
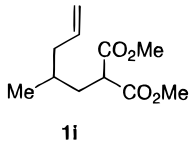
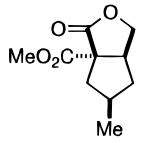
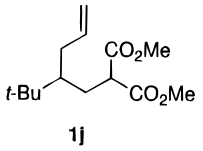
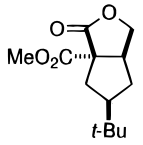
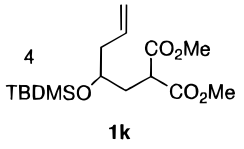
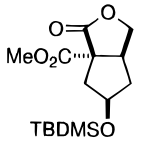
Optically active substrate (*S*)-**1a** was prepared with an optically purity of 99% from 4-pentene-1,3-diol via Sharpless's kinetic resolution[13] as a key step (Scheme 4). Similar to racemate **1a**, the iodocarbocyclization reaction of (*S*)-**1a** proceeded with high *cis*-selectivity (*cis*/*trans* = 14) to give the optically active (*S*)-**2a** in good yield. After separation of the *trans*-isomer from (*S*)-**2a** by MPLC, hydrolysis of the methyl ester group, decarboxylation, debenzylation, and Swern oxidation gave optically active cyclosarkomycin in 20% overall yield from 4-pentene-1,3-diol {$[\alpha]_D$ −384 (*c* = 1.67, CH_2Cl_2); lit. $[\alpha]_D$ −397 (*c* = 2.00, CH_2Cl_2)[12a]}.

1,3-Asymmetric Induction. In contrast to 3-hydroxy-4-pentenoic acid derivatives, it was reported that halolactonization of 2-hydroxy-4-pentenoic acid having an oxygenated substituent at a homoallylic position under kinetic conditions proceeds with low *cis*-selectivity (*cis*/*trans* = 2, Scheme 5).[14]

We have investigated the diastereoselectivity of the iodocarbocyclization reaction with several 4-pentenylmalonates having substituents at a homoallylic position under the conditions described above (Table 3, condition A). The iodocarbocyclization of 2-(benzyloxy)-4-pentenylmalonate **1h** proceeded with moderate *cis*-selectivity (*cis*/*trans* = 6.5) to give bicyclic lactone **2h** in good yield (entry 1). With malonates **1i** and **1j** having an alkyl substituent such as a methyl or *tert*-butyl group at the homoallylic position, *cis*-bicyclic lactones **2i** and **2j** were preferentially obtained with moderate diastereoselectivity similar to that of **2h**, respectively (entries 2 and 3).

(8) Keek, G. E.; Boden, E. P. *Tetrahedron Lett.* **1984**, *25*, 265.
(9) Curran, D. P.; Chang, C.-T. *J. Org. Chem.* **1989**, *54*, 3140.
(10) (a) Umezawa, H.; Takeuchi, T.; Nitta, K. *J. Antibiot. Ser. A* **1953**, *6*, 101. A synthesis of sarkomycin: (b) Helmchen, G.; Ihrig, K.; Schindler, H. *Tetrahedron Lett.* **1987**, *39*, 183 and references cited therein.
(11) (a) Marx, J. N.; Minaskanian, G. *Tetrahedron Lett.* **1979**, *43*, 4175. (b) Marx, J. N.; Minaskanian, G. *J. Org. Chem.* **1982**, *47*, 3306. (c) Wexler, B. A.; Toder, B. H.; Minaskanian, G.; Smith, A. B., III. *J. Org. Chem.* **1982**, *47*, 3333.
(12) (a) Linz, G.; Weetman, J.; Hady, A. F. A.; Helmchen, G. *Tetrahedron Lett.* **1989**, *30*, 5599. (b) Ikeda, I.; Kanematsu, K. *J. Chem. Soc., Chem. Commun.* **1995**, 453.
(13) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765.
(14) (a) Kitagawa, O.; Sato, T.; Taguchi, T. *Chem. Lett.* **1991**, 177. (b) Ohfune, Y.; Hori, K.; Sakaitani, M. *Tetrahedron Lett.* **1986**, *27*, 6079.

Table 3. Iodocarbocyclization of 2-Substituted-4-pentenylmalonate[a]

Entry	Substrate **1**	Conditions	Product **2**[b]	Yield (%)[c]	*cis* / *trans*[d]
1	 **1h**	A	 **2h**	83	6.5
2	 **1i**	A	 **2i**	88	6.3
3	 **1j**	A	 **2j**	72	7
4	 **1k**	B	 **2k**	83	12
5	**1j**	C	**2j**	91	8

[a] Reaction conditions; **1** (0.5 mmol), Ti(O-*t*-Bu)$_4$ (0.5 mmol), CH_2Cl_2 (5 mL), A; I_2 (0.6 mmol), CuO (0.6 mmol), rt. B; I_2 (2 mmol), dimethoxypyridine (1 mmol), −78 °C. C; I_2 (2 mmol), dimethoxypyridine (1 mmol), −35 °C. [b] Structure of major isomer is shown. [c] Isolated yield. [d] Determined by ^{1}H-NMR (400 MHz).

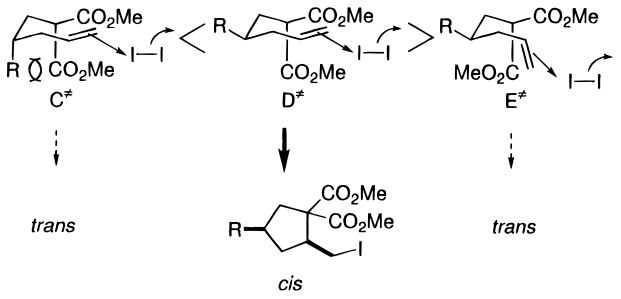
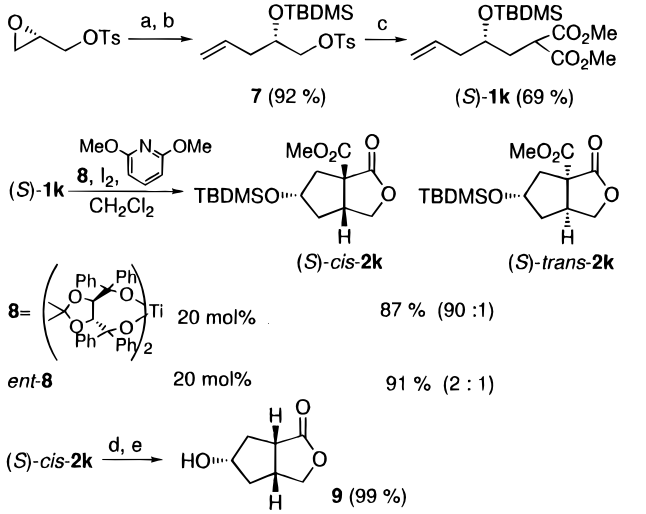


Figure 2. Transition state model in 1,3-asymmetric induction.

Contrary to the stereoelectronic effect observed in the above 1,2-asymmetric induction, the 1,3-asymmetric induction may be controlled by steric effect. That is, in the chairlike transition state C‡ and D‡ both with an equatorial olefinic group (Figure 2),[15] the reaction may proceed through sterically favorable D‡ having substituent R of equatorial orientation to avoid 1,3-diaxial repulsion between the R group and the ester group in C‡. As the transition state which gives rise to the minor *trans*-isomer, the contribution of E‡ with an axial olefinic group and equatorial R group may be also considerable because, in the reaction of **1j** having a sterically hindered *tert*-butyl group which cannot situate to axial position in the transition state, a *trans*-cyclized product is obtained with diastereoselectivity similar to that in the case of malonate derivative **1i** having a methyl substituent.

(15) Labelle, M.; Morton, H. E.; Guindon, Y.; Springler, J. P. *J. Am. Chem. Soc.* **1988**, *110*, 4533.

Scheme 6



a; MgBr, $LiCuCl_4$,. b; NaH, TBDMSCl. c; NaH, $CH_2(CO_2Me)_2$, 1,4-Dioxane. d; LiCl, H_2O, DMSO. e; TsOH, THF-H_2O

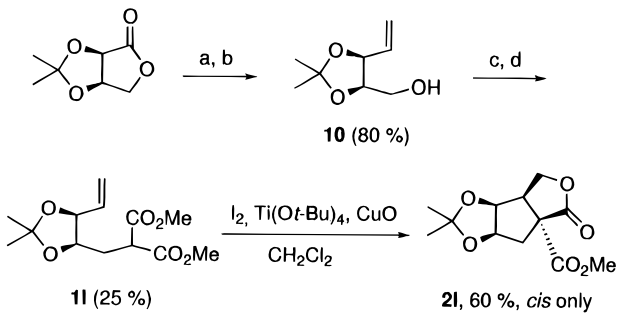
By using 2,6-dimethoxypyridine in place of CuO, the reaction can proceed at low temperature; the siloxy derivative **1k** provided the cyclized product **2k** with relatively high *cis*-selectivity (*cis*/*trans* = 12, entry 4).

Double Stereodifferentiation. Recently, we have succeeded in the development of a catalytic asymmetric iodocarbocyclization reaction which proceeds with high enantioselectivity by using a chiral titanium catalyst.[2d,e] This result prompted us to attempt a double stereodifferentiation by the use of the chiral titanium catalyst to get high 1,3-asymmetric induction in the reaction of 4-pentenylmalonate with a homoallylic substituent. That is, high 1,3-asymmetric induction may be achieved through the co-operative effects of inherent 1,3-asymmetric induction and enantiofacial selectivity of olefin by the chiral titanium catalyst. For the investigation of this double stereodifferentiation, an optically pure 4-pentenylmalonate with a homoallylic substituent is required. Optically pure 2-siloxy-4-pentenylmalonate (*S*)-**1k** was easily prepared in 63% overall yield from commercially available (*S*)-(+)-glycidyl tosylate (Scheme 6).[16] In the presence of 20 mol % of titanium alkoxide **8** prepared from (*R*,*R*)-1,4-diol (TADDOL),[17] the reaction of (*S*)-**1k** proceeded with excellent diastereoselectivity (*cis*/*trans* = 90) to give the product *cis*-(*S*)-**2k** in good yield (matched pair). On the other hand, the reaction of (*S*)-**1k** using titanium alkoxide *ent*-**8** from (*S*,*S*)-1,4-diol under the same conditions resulted in considerable decrease in diastereoselectivity (*cis*/*trans* = 2, mismatched pair). The bicyclic lactone *cis*-**2k** can be easily converted to a synthetic intermediate **9** of brefeldin A as reported by Gais *et al.*[18]

Complete diatereoselective reaction based on the double 1,2- and 1,3-*cis*-selectivity was also achieved. (2*R*,3*S*)-2,3-Dihydroxy-4-pentenylmalonate 2,3-acetonide (**11**) could be easily prepared from commercially available (−)-2,3-*O*-isopropylidene-D-erythronolactone in short steps

(16) (*S*)-(+)-Glycidyl tosylate was purchased from Azmax Co. Ltd.
(17) (a) Dahinden, R.; Beck, A. K. Seebach, D. *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed.; Wiley: Chichester, 1994; Vol. 3, p 2167. (b) Narasaka, K.; Iwasawa, N. *Organic Synthesis: Theory and Applications*; Hudlicky, T., Ed.; JAI Press Inc.: London, 1993; p 93. (c) Narasaka, K. *Synthesis* **1991**, 1.
(18) Gais, H. J.; Lied, T. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 145.

Scheme 7[a]



[a] (a) DIBALH; (b) Ph_3PCH_3Br, *n*-BuLi; (c) MsCl, Et_3N; (d) NaH, $CH_2(CO_2Me)_2$.

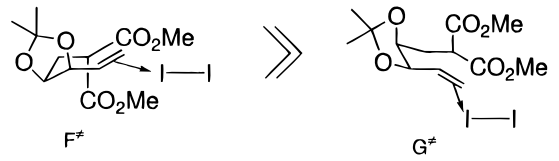


Figure 3. Transition state model in the reaction of **1l**.

(Scheme 7). The iodocarbocyclization of **11** smoothly proceeded to give the tetrasubstituted cyclopentanoid **21** as a single stereoisomer. This excellent stereoselectivity can be rationally explained on the basis of the cooperative effect of allylic and homoallylic chiral induction; that is, in the chairlike transition state $F^{\ddagger}$ and $G^{\ddagger}$ (Figure 3), $F^{\ddagger}$ having an axial and equatorial oxygenated substituent at an allylic and a homoallylic position should be favored from the viewpoint of stereoelectronic and steric effects, respectively (see also Figures 1 and 2).

In conclusion, we have succeeded in the development of diastereoselective iodocarbocyclization of 4-pentenylmalonate with an oxygenated substituent at allylic or homoallylic position which proceeds with high *cis*-selectivity through an inherent stereoelectronic effect and double stereodifferentiation. The present reaction should be widely applicable to the synthesis of cyclopentanoid natural products.

Experimental Section

Melting points were determined on a micro melting point apparatus and are uncorrected. ^{1}H- and ^{13}C-NMR spectra were recorded on 400 MHz spectrometer. In ^{1}H- and ^{13}C-NMR, chemical shifts were expressed in δ (ppm) down field from $CHCl_3$ (7.26 ppm) and $CDCl_3$ (77.0 ppm) as the internal standard, respectively. The mass spectra were recorded by electron impact. Column chromatography was performed on silica gel, Wakogel C-200 (75−150 μm). Medium-pressure liquid chromatography (MPLC) was performed on a 30 × 4 cm i.d. prepacked column (silica gel, 50 μm).

Starting Materials. The spectral data and the preparations of **1a**−**c,k** are given below.

3-(Benzyloxy)-4-pentenylpropanedioic Acid Dimethyl Ester (1a). To a solution of 3-(benzyloxy)-4-penten-1-ol[19] (2.05 g, 11 mmol) in CH_2Cl_2 were added Et_3N (1.9 mL, 14 mmol) and methanesulfonyl chloride (0.9 mL, 12 mmol) at 0 °C. After being stirred for 10 min at room temperature, the mixture was poured into 10% HCl and extracted with ether. The ether extracts were evaporated to dryness. To a solution of NaH (60% in oil, 0.5 g, 13 mmol) and dimethyl malonate (1.5 mL, 13 mmol) in THF (25 mL) was added the residue, and then the reaction mixture was stirred at 140 °C for 3 days. The mixture was poured into 10% HCl and extracted with ether. The ether extracts were dried over $MgSO_4$ and evaporated to dryness. The residue was purified by column chromatography (hexane/AcOEt = 9) to give **1a** (2.94 g, 90%). **1a**: colorless oil; IR (neat) 2953, 1733 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 7.32 (5H, m), 5.72 (1H, ddd, J = 7.7, 10.6, 17.0 Hz), 5.21−5.27 (2H, m), 4.58 (1H, d, J = 11.8 Hz), 4.34 (1H, d, J = 11.8 Hz), 3.76 (1H, m), 3.72 (6H, s), 3.36 (1H, t, J = 7.5 Hz), 1.91−2.09 (2H, m), 1.50−1.70 (2H, m); ^{13}C-NMR ($CDCl_3$) δ 169.7, 138.6, 138.4, 128.3, 127.7, 127.4, 117.5, 79.9, 70.1, 52.3, 51.5, 33.0, 24.8; MS *m*/*z* 307 ($M^+ + H^+$), 199 ($M^+ - OBn$). Anal. Calcd for $C_{17}H_{22}O_5$: C, 66.65; H, 7.24. Found: C, 66.61; H, 7.34.

3-Methoxy-4-pentenylpropanedioic Acid Dimethyl Ester (1b). **1b** was prepared from 3-methoxy-4-penten-1-ol[20] in accordance with a procedure similar to that for **1a**. **1b**: colorless oil; IR (neat) 2981, 1738 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 5.63 (1H, ddd, J = 7.7, 10.6, 17.0 Hz), 5.21−5.27 (2H, m), 3.73 (6H, s), 3.52 (1H, q, J = 7.5 Hz), 3.36 (1H, t, J = 7.5 Hz), 3.25 (3H, s), 1.87−2.09 (2H, m), 1.42−1.65 (2H, m); ^{13}C-NMR ($CDCl_3$) δ 169.8, 138.1, 117.6, 82.4, 56.2, 52.5, 51.5, 32.9, 24.9; MS *m*/*z* 199 ($M^+ - OMe$). Anal. Calcd for $C_{11}H_{18}O_5$: C, 57.38; H, 7.88. Found: C, 57.14; H, 7.98.

3-(Benzoyloxy)-4-pentenylpropanedioic Acid Dimethyl Ester (1c). **1c** was prepared from 3-(benzoyloxy)-4-penten-1-ol[21] in accordance with a procedure similar to that for **1a**. **1c**: colorless oil; IR (neat) 2954, 1740, 1736 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 8.06 (2H, dd, J = 1.5, 1.8 Hz), 7.57 (1H, tt, J = 1.8, 7.4 Hz), 7.45 (2H, tt, J = 1.5, 7.4 Hz), 5.88 (1H, ddd, J = 6.2, 10.6, 17.2 Hz), 5.52 (1H, tq, J = 1.2, 6.2 Hz), 5.35 (1H, td, J = 1.2, 17.2 Hz), 5.24 (1H, td, J = 1.2, 10.6 Hz), 3.74 (3H, s), 3.73 (3H, s), 3.42 (1H, t, J = 7.4 Hz), 1.97−2.11 (2H, m), 1.75−1.89 (2H, m); ^{13}C-NMR ($CDCl_3$) δ 169.5, 165.7, 135.8, 133.0, 130.4, 129.7, 128.4, 117.3, 74.4, 52.5, 51.3, 31.8, 24.4; MS *m*/*z* 320 (M^+). Anal. Calcd for $C_{17}H_{20}O_6$: C, 63.74; H, 6.29. Found: C, 63.74; H, 6.29.

2-(*tert*-Butyldimethylsiloxy)-4-pentenylpropanedioic Acid Dimethyl Ester (1k). To a solution of 1-(tosyloxy)-4-penten-2-ol[22] (5.1 g, 20 mmol) in DMF (100 mL) was added imidazole (1.6 g, 24 mmol) and *tert*-butyldimethylsilyl chloride (3.6 g, 24 mmol) at 0 °C. After being stirred for 1.5 h at room temperature, the mixture was poured into aqueous NH_4Cl solution, and the products were extracted with ether. The ether extracts were evaporated to dryness. The residue was purified by column chromatography (hexane/AcOEt = 50) to give 1-(tosyloxy)-2-(*tert*-butyldimethylsiloxy)-4-pentene (6.1 g, 83%). **1k** was prepared from 1-(tosyloxy)-2-(*tert*-butyldimethylsiloxy)-4-pentene (404 mg, 1.1 mmol) in accordance with a procedure similar to that for **1a**. Purification by column chromatography (hexane/AcOEt = 19) gave **1k** (273 mg, 75%). **1k**: colorless oil; IR (neat) 2858, 1757, 1740 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 5.77 (1H, ddd, J = 6.0, 10.4, 17.1 Hz), 5.16 (1H, td, J = 1.5, 17.1 Hz), 5.05 (1H, td, J = 1.5, 10.4 Hz), 4.13 (H, m), 3.73 (6H, s), 3.37 (1H, t, J = 7.9 Hz), 1.87−2.02 (2H, m), 1.47−1.58 (2H, m), 0.89 (9H, s), 0.05 (3H, s), 0.03 (3H, s); ^{13}C-NMR ($CDCl_3$) δ 169.8, 140.9, 114.3, 73.1, 52.4, 51.6, 35.3, 25.8, 24.5, 18.2, −4.4, −4.9; MS *m*/*z* 331 ($M^+ + H^+$), 315 ($M^+ - Me$), 299 ($M^+ - OMe$). Anal. Calcd for $C_{16}H_{30}O_5Si$: C, 58.14; H, 9.15. Found: C, 58.09; H, 9.15.

General Procedure for Iodocarbocyclization Reactions. To a solution of the malonate (0.5 mmol) in dry CH_2Cl_2 (5 mL) was added Ti(O-*t*-Bu)$_4$ (0.2 mL, 0.5 mmol). After the mixture was stirred for 10 min, I_2 (152 mg, 0.6 mmol) and CuO (48 mg, 0.6 mmol) were successively added, and then the reaction mixture was stirred at room temperature for the indicated period (see Tables 2 and 3). The mixture was poured into 10% HCl, and the products were extracted with ether. The ether extracts were washed with aqueous $Na_2S_2O_3$ solution, dried over $MgSO_4$, and evaporated to dryness. The residue was purified by column chromatography and then

(19) Reitz, A. B.; Nortey, S. O.; Maryanoff, B. E. *J. Org. Chem.* **1987**, *52*, 4191.

(20) Coates, R. M.; Rogers, B. D.; Hobbs, S. J.; Peck, D. R.; Curran, D. P. *J. Am. Chem. Soc.* **1987**, *109*, 1160.

(21) Larock, R. C.; Stolz-Dunn, S. K. *Tetrahedron Lett.* **1989**, *30*, 3487.

(22) Klunder, J. M.; Onami, T.; Sharpless, K. B. *J. Org. Chem.* **1989**, *54*, 1295.

MPLC to give the cyclic product as a diastereomeric mixture. The stereochemistries of diastereomers were determined on the basis of NOE experiments.

6-(Benzyloxy)-3-oxotetrahydro-1*H*-cyclopenta[*c*]furan-3a(3*H*)-carboxylic Acid Methyl Ester (2a). Compound **2a** was prepared from **1a** (153 mg, 0.5 mmol). Purification by column chromatography (hexane/AcOEt = 3) and then MPLC (hexane/AcOEt = 3) gave *trans*-**2a** (less polar, 9 mg, 6%) and *cis*-**2a** (more polar, 122 mg, 84%). *cis*-**2a**: colorless oil; IR (neat) 2957, 2360, 1771, 1750 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 7.28−7.38 (5H, m), 4.64 (1H, dd, J = 2.5, 9.3 Hz), 4.60 (1H, d, J = 12.0 Hz), 4.44 (1H, d, J = 12.0 Hz), 4.33 (1H, dd, J = 8.1, 9.3 Hz), 4.08 (1H, dt, J = 5.0, 7.0 Hz), 3.78 (3H, s), 3.19 (1H, dt, J = 2.5, 7.6 Hz), 2.36 (1H, ddd, J = 5.4, 7.0, 13.6 Hz), 2.34 (1H, ddd, J = 7.2, 9.0, 13.6 Hz), 1.98 (1H, dddd, J = 5.0, 5.4, 7.2, 13.0 Hz), 1.79 (1H, tdd, J = 7.0, 9.0, 13.0 Hz); ^{13}C-NMR ($CDCl_3$) δ 176.0, 170.3, 137.7, 128.5, 127.9, 127.4, 80.2, 71.6, 66.1, 59.9, 53.2, 48.0, 30.8, 30.4; MS m/z 290 (M^+), 259 (M^+ − OMe). Anal. Calcd for $C_{16}H_{18}O_5$: C, 66.19; H, 6.25. Found: C, 66.04; H, 6.23. *trans*-**2a**: colorless oil; IR (neat) 2956, 1775, 1750 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 7.27−7.38 (5H, m), 4.57 (1H, dd, J = 8.5, 9.5 Hz), 4.55 (1H, d, J = 11.9 Hz), 4.47 (1H, d, J = 11.9 Hz), 4.10 (1H, dd, J = 2.7, 9.5 Hz), 3.87 (1H, ddd, J = 3.3, 4.8, 8.0 Hz), 3.78 (3H, s), 3.20 (1H, ddd, J = 2.7, 8.0, 8.5 Hz), 2.69 (1H, ddd, J = 7.2, 10.5, 13.5 Hz), 2.26 (1H, ddd, J = 4.1, 7.1, 13.5 Hz), 2.04 (1H, dddd, J = 3.3, 4.1, 7.2, 13.6 Hz), 1.74 (1H, dddd, J = 4.8, 7.1, 10.5, 13.6 Hz); ^{13}C-NMR ($CDCl_3$) δ 175.9, 169.6, 137.8, 128.5, 127.9, 127.6, 85.6, 71.0, 70.3, 60.0, 53.2, 51.7, 31.5, 30.9, 30.4; MS m/z 259 (M^+ − OMe). Anal. Calcd for $C_{16}H_{18}O_5$: C, 66.19; H, 6.25. Found: C, 66.24; H, 6.24.

6-Methoxy-3-oxotetrahydro-1*H*-cyclopenta[*c*]furan-3a-(3*H*)-carboxylic Acid Methyl Ester (2b). Compound **2b** was prepared from **1b** (115 mg, 0.5 mmol). Purification by column chromatography (hexane/AcOEt = 3) and then MPLC (hexane/AcOEt = 3) gave *trans*-**2b** (less polar, 6 mg, 6%) and *cis*-**2b** (more polar, 90 mg, 84%). *cis*-**2b**: colorless oil; IR (neat) 2958, 2832, 1772, 1741 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 4.56 (1H, dd, J = 2.5, 9.2 Hz), 4.34 (1H, dd, J = 8.1, 9.2 Hz), 3.87 (1H, dt, J = 5.0, 6.9 Hz), 3.77 (3H, s), 3.30 (3H, s), 3.19 (1H, dt, J = 2.5, 7.7 Hz), 2.36 (1H, ddd, J = 7.3, 8.8, 13.6 Hz), 2.26 (1H, ddd, J = 5.6, 6.9, 13.6 Hz), 1.96 (1H, tdd, J = 5.1, 7.4, 13.1 Hz), 1.72 (1H, tdd, J = 7.0, 8.8, 13.1 Hz); ^{13}C-NMR ($CDCl_3$) δ 176.1, 170.3, 82.1, 65.9, 59.8, 57.1, 53.2, 47.9, 30.2; MS m/z 183 (M^+ − OMe). Anal. Calcd for $C_{10}H_{14}O_5$: C, 56.07; H, 6.59. Found: C, 56.02; H, 6.57. *trans*-**2b**: colorless oil; IR (neat) 2957, 1773, 1743 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 4.59 (1H, dd, J = 8.4, 9.6 Hz), 4.13 (1H, dd, J = 2.8, 9.6 Hz), 3.78 (3H, s), 3.64 (1H, dt, J = 2.9, 4.7 Hz), 3.30 (3H, s), 3.11 (1H, m), 2.58 (1H, ddd, J = 7.1, 11.0, 13.4 Hz), 2.23 (1H, ddd, J = 3.7, 7.0, 13.4 Hz), 1.98 (1H, dtdd, J = 1.3, 3.5, 7.0, 13.7 Hz), 1.67 (1H, dddd, J = 4.8, 7.1, 11.0, 13.7 Hz); ^{13}C-NMR ($CDCl_3$) δ 175.9, 169.6, 87.9, 70.3, 60.1, 56.6, 53.2, 51.4, 31.5, 30.3; MS m/z 183 (M^+ − OMe). Anal. Calcd for $C_{10}H_{14}O_5$: C, 56.07; H, 6.59. Found: C, 56.14; H, 6.59.

6-(Benzoyloxy)-3-oxotetrahydro-1*H*-cyclopenta[*c*]furan-3a(3*H*)-carboxylic Acid Methyl Ester (2c). Compound **2c** was prepared from **1c** (160 mg, 0.5 mmol). After the reaction mixture of the iodocarbocyclization was heated at 140 °C for 5 min, the crude mixture was purified by column chromatography (hexane/AcOEt = 3) and then MPLC (hexane/AcOEt = 3) to give *trans*-**2c** (less polar, 16 mg, 11%) and *cis*-**2c** (more polar, 124 mg, 82%). *cis*-**2c**: colorless oil; IR (neat) 2967, 2957, 1778, 1740, 1723 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 8.00 (2H, td, J = 1.2, 7.6 Hz), 7.59 (1H, tt, J = 1.2, 7.6 Hz), 7.46 (2H, tt, J = 1.5, 7.6 Hz), 5.54 (1H, dt, J = 4.9, 6.2 Hz), 4.47 (1H, dd, J = 7.1, 9.8 Hz), 4.42 (1H, dd, J = 2.1, 9.8 Hz), 3.83 (3H, s), 3.42 (1H, dt, J = 2.1, 6.7 Hz), 2.60 (1H, ddd, J = 6.1, 8.0, 14.0 Hz), 2.42 (1H, td, J = 7.2, 14.0 Hz), 2.18 (1H, m), 2.04 (1H, m); ^{13}C-NMR ($CDCl_3$) δ 175.5, 169.7, 133.5, 129.6, 129.2, 128.6, 76.6, 66.2, 60.2, 53.3, 49.1, 32.4, 30.4; MS m/z 304 (M^+), 273 (M^+ − OMe). Anal. Calcd for $C_{16}H_{16}O_6$: C, 63.15; H, 5.30. Found: C, 63.08; H, 5.29. *trans*-**2c**: white solid; mp 80 °C; IR (neat) 2958, 2919, 1779, 1745, 1718 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 8.00 (2H, m), 7.59 (1H, tt, J = 1.3, 7.5 Hz), 7.46 (2H, m), 5.27 (1H, m), 4.67 (1H, dd, J = 8.6, 9.9 Hz), 4.37 (1H, dd, J = 2.9, 9.9 Hz), 3.79 (3H, s), 3.27 (1H, m), 2.76 (1H, ddd, J = 7.0, 12.2, 13.1 Hz), 2.42 (1H, ddd, J = 2.6, 7.0, 13.1 Hz), 2.19 (1H, m), 1.95 (1H, dddd, J = 5.2, 7.0, 12.2, 14.4 Hz); ^{13}C-NMR ($CDCl_3$) δ 175.3, 169.4, 166.0, 133.4, 129.6, 128.5, 81.7, 70.2, 60.5, 53.3, 52.3, 32.3, 31.6; MS m/z 304 (M^+), 273 (M^+ − OMe). Anal. Calcd for $C_{16}H_{16}O_6$: C, 63.15; H, 5.30. Found: C, 62.76; H, 5.31.

5-(*tert*-Butyldimethylsiloxy)-3-oxotetrahydro-1*H*-cyclopenta[*c*]furan-3a(3*H*)-carboxylic Acid Methyl Ester (2k). To a solution of **1k** (165 mg, 0.5 mmol) in dry CH_2Cl_2 (5 mL) were added Ti(O-*t*-Bu)$_4$ (0.2 mL, 0.5 mmol) and 2,6-dimethoxypyridine (0.14 mL, 1 mmol) under argon atmosphere at −78 °C. After the mixture was stirred for 30 min, I_2 (508 mg, 2 mmol) was added at the same temperature, and then the reaction mixture was gradually warmed up from −78 °C to room temperature during 24 h. The mixture was poured into 10% HCl and extracted with ether. The ether extracts were washed with aqueous $Na_2S_2O_3$ solution, dried over $MgSO_4$, and evaporated to dryness. The residue was heated at 140 °C for 10 min and then purified by column chromatography (hexane/AcOEt = 9) to give the cyclic product as a diastereomeric mixture (*cis*/*trans* = 12). Further purification by MPLC (hexane/AcOEt = 9) gave *trans*-**2k** (less polar, 10 mg, 6%) and *cis*-**2k** (more polar, 120 mg, 76%). *cis*-**2k**: white solid; mp 107 °C; IR ($CHCl_3$) 2927, 1766, 1742 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 4.59 (1H, t, J = 8.9 Hz), 4.39 (1H, m), 4.17 (1H, dd, J = 3.3, 8.9 Hz), 3.77 (3H, s), 3.18 (1H, ddt, J = 1.5, 3.2, 9.3 Hz), 2.39 (1H, td, J = 1.6, 13.7 Hz), 2.35 (1H, dd, J = 3.3, 13.7 Hz), 2.09 (1H, ddd, J = 3.7, 9.4, 13.8 Hz), 1.78 (1H, dd, J = 1.5, 13.8 Hz), 0.85 (9H, s), 0.04 (6H, s); ^{13}C-NMR ($CDCl_3$) δ 175.8, 170.9, 73.9, 73.6, 60.3, 53.1, 43.8, 43.2, 25.5, 17.8, −5.2; MS m/z 315 (M^+ + H^+), 299 (M^+ − Me), 283 (M^+ − OMe). Anal. Calcd for $C_{15}H_{26}O_5Si$: C, 57.31; H, 8.34. Found: C, 57.19; H, 8.31. *trans*-**2k**: white solid; mp 60−62 °C; IR (neat) 2949, 2927, 1768, 1730 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 4.58 (1H, dd, J = 7.0, 9.2 Hz), 4.31 (1H, quint, J = 4.4 Hz), 4.11 (1H, dd, J = 1.7, 9.2 Hz), 3.77 (3H, s), 3.37 (1H, dq, J = 1.7, 8.4 Hz), 2.54 (1H, ddd, J = 1.9, 4.1, 14.0 Hz), 2.31 (1H, dd, J = 4.8, 14.0 Hz), 2.09 (1H, dddd, J = 2.0, 4.2, 8.4, 13.1 Hz), 1.68 (1H, ddd, J = 4.5, 8.0, 13.1 Hz), 0.85 (9H, s), 0.06 (3H, s), 0.04 (3H, s); ^{13}C-NMR ($CDCl_3$) δ 176.2, 169.7, 73.2, 72.1, 59.7, 53.1, 43.9, 42.9, 42.4, 30.9, 25.6, 17.9, −4.9; MS m/z 315 (M^+ + H^+), 299 (M^+ − Me), 283 (M^+ − OMe). Anal. Calcd for $C_{15}H_{26}O_5Si$: C, 57.31; H, 8.34. Found: C, 57.44; H, 8.32.

The Synthesis of Cyclosarkomycin. (*S*)-3-Hydroxy-4-pentenyl Triphenylmethyl Ether (4). To a solution of racemic trityl ether **4** (13.76 g, 40 mmol) in CH_2Cl_2 (100 mL) was added successively molecular sieves (MS 4A, 1.5 g), Ti(O-*i*-Pr)$_4$ (6 mL, 40 mmol), and (−)-(*S*,*S*)-dicyclohexyl tartrate (7.8 g, 48 mmol) at −23 °C under an argon atmosphere. After the mixture was stirred for 30 min, 3.33 M *t*-BuOOH in toluene (5.41 mL, 24 mmol) was added, and then the reaction mixture was allowed to stand for 1 month at −23 °C. Workup by the reported procedure[13] and then purification of the residue by column chromatography (hexane/AcOEt = 9) gave **4** (4.27 g, 31%). **4**: colorless oil; $[\alpha]^{26}_D$ +17.3 (*c* 0.78, $CHCl_3$); IR (neat) 3419, 2878 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 7.34−7.42 (6H, m), 7.15−7.28 (9H, m), 5.76 (1H, ddd, J = 5.6, 10.5, 17.2 Hz), 5.17 (1H, d, J = 17.2 Hz), 5.00 (1H, d, J = 10.5 Hz), 4.27 (1H, m), 3.31 (1H, td, J = 5.5, 9.4 Hz), 3.19 (1H, td, J = 6.0, 9.4 Hz), 2.74 (1H, d, J = 3.8 Hz), 1.79 (2H, m); ^{13}C-NMR ($CDCl_3$) δ 143.8, 140.7, 128.6, 127.9, 127.1, 114.3, 71.8, 61.8, 36.7; MS m/z 344 (M^+); HRMS calcd for $C_{24}H_{24}O_2$ m/z 344.1776 (M^+), found 344.1798.

(*S*)-3-(Benzyloxy)-4-penten-1-ol (5). To a suspension of NaH (60% in oil, 0.6 g, 15 mmol) in THF (15 mL) was added a solution of **4** (4.27 g, 12.4 mmol) in THF (10 mL) at 0 °C. After the mixture was stirred for 30 min, BnBr (1.9 mL, 16.1 mmol) was added, and then the reaction mixture was refluxed for 1 h. The mixture was poured into 10% HCl and extracted with ether. The ether extracts were dried over $MgSO_4$ and evaporated to dryness. The residue was dissolved in MeOH (12 mL), and a catalytic amount of TsOH was added. After being stirred for 12 h at room temperature, the mixture was poured into 5% aqueous $NaHCO_3$ solution and extracted with ether. The ether extracts were dried over $MgSO_4$ and evapo-

rated to dryness. The residue was purified by column chromatography (hexane/AcOEt = 5) to give **5** (2.06 g, 86%). **5**: colorless oil; $[\alpha]^{28}_D$ −64.0 (*c* = 1.00, $CHCl_3$); IR (neat) 3382, 2872 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 7.27−7.38 (5H, m), 5.80 (1H, ddd, *J* = 7.6, 10.0, 17.6 Hz), 5.24−5.31 (2H, m), 4.63 (1H, d, *J* = 11.8 Hz), 4.36 (1H, d, *J* = 11.8 Hz), 4.02 (1H, dt, *J* = 4.6, 7.9 Hz), 3.69−3.85 (2H, m), 2.41 (1H, dd, *J* = 4.8, 6.3 Hz), 1.74−1.95 (2H, m); ^{13}C-NMR ($CDCl_3$) δ 180.2, 138.1, 128.5, 127.8, 127.7, 117.6, 79.9, 70.3, 60.6, 37.7; MS *m*/*z* 175 (M^+ − OH). Anal. Calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 74.64; H, 8.38.

(*S*)-3-(Benzyloxy)-4-pentenylpropanedioic Acid Dimethyl Ester [(*S*)-1a]. (*S*)-**1a** was prepared from **5** (1.9 g, 10 mmol) in accordance with a procedure similar to that for racemic **1a**. Purification by column chromatography (hexane/AcOEt = 9) gave (*S*)-**1a** (3.06 g, quantitative). ^{1}H and ^{13}C-NMR data of (*S*)-**1a** coincided with those of racemic **1a**. (*S*)-**1a**: $[\alpha]^{26}_D$ −66.7 (*c* = 1.03, $CHCl_3$).

(*S*)-Tetrahydro-6-(benzyloxy)-3-oxo-1*H*-cyclopenta[*c*]-furan-3a(3*H*)-carboxylic Acid Methyl Ester [(*S*)-2a]. (*S*)-**2a** was prepared from (*S*)-**1a** in accordance with typical procedure of iodocarbocyclization reaction. (*S*)-*cis*-**2a**: $[\alpha]^{27}_D$ −46.2 (*c* = 1.05, $CHCl_3$).

Bicyclic Lactone (6). A solution of (*S*)-*cis*-**2a** (1.45 g, 5 mmol) in 1 N KOH (80 mL) was stirred for 12 h at room temperature. The mixture was poured into 10% HCl and extracted with AcOEt. The AcOEt extracts were dried over $MgSO_4$ and evaporated to dryness. The residue was dissolved in xylene (15 mL) and refluxed for 12 h. After evaporation of xylene, MeOH (1 mL) and $Pd(OH)_2$ were added to the residue, and then the reaction mixture was stirred under H_2 atmosphere for 2 h. After removal of the catalyst by filtration and evaporation of MeOH, purification of the residue by column chromatography (hexane/AcOEt = 3) gave **6** (710 mg, quantitative). **6**: white solid; mp 54 °C; $[\alpha]^{25}_D$ −69.9° (*c* = 0.98, $CHCl_3$); IR (neat) 3472, 2965, 1743 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 4.60 (1H, dd, *J* = 2.9, 9.7 Hz), 4.36 (1H, q, *J* = 6.2 Hz), 4.30 (1H, dd, *J* = 8.1, 9.7 Hz), 3.05 (1H, dt, *J* = 3.2. 9.6 Hz), 2.94 (1H, m), 2.13 (1H, m), 2.01 (1H, tdd, *J* = 7.7, 9.5, 13.4 Hz), 1.91 (1H, m), 1.53−1.72 (2H, m); ^{13}C-NMR ($CDCl_3$) δ 180.7, 74.1, 66.6, 43.5, 43.0, 34.5, 26.3; MS *m*/*z* 143 ($M^+ + H^+$), 124 ($M^+ - H_2O$). Anal. Calcd for $C_7H_{10}O_3$: C, 59.14; H, 7.09. Found: C, 59.25; H, 7.07.

(*S*)-Cyclosarkomycin. To a mixture of $(COCl)_2$ (0.48 mL, 5.5 mmol) and DMSO (0.85 mL, 12 mmol) in CH_2Cl_2 (15 mL) at −78 °C was added a solution of **6** (355 mg, 2.5 mmol) in CH_2Cl_2 (5 mL). After the mixture was stirred for 1 h at −10 °C, $(i\text{-Pr})_2$NEt (2.2 mL, 12.5 mmol) was added at −78 °C, and then the reaction mixture was stirred for 30 min. The mixture was poured into H_2O and extracted with CH_2Cl_2. The CH_2Cl_2 extracts were dried over $MgSO_4$ and evaporated to dryness. The residue was purified by column chromatography (hexane/AcOEt = 1) to give (*S*)-cyclosarkomycin (312 mg, 89%). (*S*)-Cyclosarkomycin: $[\alpha]^{27}_D$ −384.0 (*c* = 1.67, CH_2Cl_2); ^{1}H and ^{13}C-NMR data coincided with those reported in the literature.[12a]

Double Stereodifferentiation. (*S*)-4-(*tert*-Butyldimethylsiloxy)-5-(*p*-tosyloxy)-1-pentene (7). Compound **7** was prepared from (*S*)-glycidyl tosylate in accordance with the reported procedure.[22] **7**: colorless oil; $[\alpha]^{27}_D$ +6.80 (*c* = 1.03, $CHCl_3$); IR (neat) 2928, 2856, 1730 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 7.79 (2H, d, *J* = 8.3 Hz), 7.43 (2H, d, *J* = 8.0 Hz), 5.71 (1 H, ddd, *J* = 7.2, 10.7, 16.5 Hz), 4.98−5.06 (2H, m), 3.82−3.93 (3H, m), 2.45 (3H, s), 2.10−2.30 (2H, m), 0.84 (9H, s), 0.03 (3H, s), 0.01 (3H, s); ^{13}C-NMR ($CDCl_3$) δ 144.8, 133.2, 133.1, 129.8, 128.0, 72.6, 69.6, 38.7, 25.7, 21.6, 18.0, −4.7; MS *m*/*z* 329 ($M^+ - CH_2{=}CHCH_2$). Anal. Calcd for $C_{18}H_{30}O_4SSi$: C, 58.35; H, 8.17. Found: C, 58.58; H, 8.45.

(+)-2-(*tert*-Butyldimethylsilyloxy)-4-pentenylpropanedioic Acid Dimethyl Ester [(*S*)-1k]. (*S*)-**1k** was prepared from **7** in accordance with the similar procedure for **1a**. ^{1}H- and ^{13}C-NMR data of (*S*)-**1k** coincided with those of racemic **1k**. (*S*)-**1k**: $[\alpha]^{26}_D$ +25.72 (*c* = 2.22, $CHCl_3$).

5-(*tert*-Butyldimethylsiloxy)tetrahydro-3-oxo-1*H*-cyclopenta[*c*]furan-3a(3*H*)-carboxylic Acid Methyl Ester (2k). To a toluene (3 mL) solution of (*R*,*R*)-TADDOL (93 mg, 0.2 mmol), under an argon atmosphere, was added 0.228 M Ti(O-*i*-Pr)$_4$ in toluene (0.44 mL, 0.1 mmol) at room temperature. After the mixture was stirred at this temperature for 1 h, toluene and 2-propanol were removed under reduced pressure. The solid residue was cooled to −78 °C, and then to this was added a CH_2Cl_2 solution (5 mL) of malonate (*S*)-**1k** (165 mg, 0.5 mmol) and 2,6-dimethoxypyridine (0.13 mL, 1 mmol). After the mixture was stirred at this temperature for 1 h, I_2 (0.5 g, 2 mmol) was added, and the mixture was stirred for 8 h at −78 to −50 °C. The mixture was poured into 10% HCl and extracted with ether. The ether extracts were washed with aqueous $Na_2S_2O_3$ solution, dried over $MgSO_4$, and evaporated to dryness. The residue was heated for 30 min at 140 °C, and then purification by column chromatography (hexane/AcOEt = 9) gave the cyclic product (*S*)-**2k** (136 mg, 87%) in the ratio of *cis*/*trans* = 90. ^{1}H- and ^{13}C-NMR data of (*S*)-**2k** coincided with those of racemic **2k**. (*S*)-*cis*-**2k**: $[\alpha]^{28}_D$ +45.20 (*c* = 1.29, $CHCl_3$).

(3a*R*)-(3aα,5*β*,6aα)-Hexahydro-5-hydroxy-1*H*-cyclopenta[*c*]furan-1-one (9). To a solution of (*S*)-*cis*-**2k** (157 mg, 0.5 mmol) in DMSO (5 mL) were added LiCl (79 mg, 2 mmol) and H_2O (27 mg, 1.5 mmol), and then the reaction mixture was heated at 140 °C for 12 h. The mixture was poured into 10% HCl and extracted with ether. The ether extracts were dried over $MgSO_4$ and evaporated to dryness. The residue was dissolved in THF−H_2O (5:1, 5 mL), and a catalytic amount of TsOH was added. After being stirred for 12 h at room temperature, the mixture was poured into 5% aqueous $NaHCO_3$ solution and extracted with ether. The ether extracts were dried over $MgSO_4$ and evaporated to dryness. The residue was purified by column chromatography (hexane/AcOEt = 1/2) to give **9** (70 mg, 99%). **9**: $[\alpha]^{26}_D$ +68.96 (*c* = 0.87, CH_2Cl_2) [lit. $[\alpha]^{20}_D$ +61.2 (*c* = 2.64, CH_2Cl_2)]; ^{1}H and ^{13}C NMR data coincided with those reported in the literature.[18]

(+)-(2*R*,3*S*)-2,3-*O*-Isopropylidene-4-pentenylpropanedioic Acid Dimethyl Ester (11). To a solution of (−)-2,3-*O*-isopropylidene-D-erythronolactone (316 mg, 2 mmol) in CH_2Cl_2 (15 mL) at −78 °C was added dropwise DIBALH (1 M hexane solution, 2 mL, 2 mmol) under an argon atmosphere. After being stirred for 1 h at the same temperature, the reaction mixture was treated with 1 N NaOH (5 mL), $MgSO_4$, and Na_2SO_4. Insoluble materials were removed by filtration with a Celite pad, and the filtrate was evaporated under reduced pressure. The residue was added to a solution of $Ph_3P{=}CH_2$, which was prepared from the phosphonium bromide (1.43 g, 4 mmol) and LDA (4 mmol) in 1,4-dioxane. After being refluxed for 24 h, the mixture was poured into H_2O and extracted with Et_2O. The Et_2O extracts were dried over $MgSO_4$ and evaporated to dryness. Purification of the residue by column chromatography (hexane/AcOEt = 3) gave **10** (253 mg, 80%). To a solution of **10** (158 mg, 1 mmol) in CH_2Cl_2 (20 mL) at 0 °C were added Et_3N (0.3 mL, 2.2 mmol) and MsCl (0.16 mL, 2.1 mmol). After being stirred for 30 min, the mixture was poured into H_2O and extracted with Et_2O. The ether extracts were dried over $MgSO_4$ and evaporated to dryness. To a solution of NaH (60% in oil, 190 mg, 4.8 mmol) and dimethyl malonate (0.55 mL, 4.8 mmol) in 1,4-dioxane (20 mL) was added the residue, and then the reaction mixture was refluxed for 3 days at 140 °C. The mixture was poured into H_2O and extracted with Et_2O. The ether extracts were dried over $MgSO_4$ and evaporated to dryness. Purification of the residue by column chromatography (hexane/AcOEt = 3) gave **11** (69 mg, 25%). **11**: colorless oil; $[\alpha]^{24}_D$ +27.57 (*c* = 0.50, $CHCl_3$); IR (neat) 2988, 2955, 1738 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 5.82 (1H, ddd, *J* = 7.4, 10.4, 17.1 Hz), 5.37 (1H, d, *J* = 17.1 Hz), 5.29 (1H, d, *J* = 10.4 Hz), 4.58 (1H, dd, *J* = 6.3, 7.4 Hz), 4.15 (1H, ddd, *J* = 4.4, 6.3, 9.6 Hz), 3.75 (3H, s), 3.73 (3H, s), 3.63 (1H, dd, *J* = 5.7, 8.9 Hz), 2.00 (1H, dd, *J* = 4.4, 8.9 Hz), 1.98 (1H, dd, *J* = 5.7, 9.6 Hz), 1.46 (3H, s), 1.34 (3H, s); ^{13}C-NMR ($CDCl_3$) δ 169.9, 196.4, 133.1, 119.0, 108.7, 79.2, 75.5, 52.6, 52.5, 48.4, 30.3, 28.0, 25.6; MS *m*/*z* 257 (M^+ − Me). Anal. Calcd for $C_{13}H_{20}O_6$: C, 57.34; H, 7.40. Found: C, 57.26; H, 7.36.

Tricyclic Lactone 2l. Compound **2l** was prepared from **1l** (136 mg, 0.5 mmol) in accordance with general procedure

of iodocarbocyclization reaction. Purification by column chromatography (hexane/AcOEt = 5) gave **2l** (77 mg, 60%) as a single diastereomer (*cis* only). *cis*-**2l**: white solid; mp 145 °C; $[\alpha]^{24}_{D}$ +18.25 (*c* = 0.75, $CHCl_3$); IR ($CHCl_3$) 2987, 1772, 1742 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 4.79 (1H, t, *J* = 5.0 Hz), 4.67 (1H, dd, *J* = 5.3, 8.0 Hz), 4.64 (1H, d, *J* = 8.8 Hz), 4.34 (1H, dd, *J* = 6.5, 8.8 Hz), 3.78 (3H, s), 3.03 (1H, t, *J* = 7.3 Hz), 2.73 (1H, d, *J* = 15.1 Hz), 2.4 (1H, dd, *J* = 4.9, 15.0 Hz), 1.44 (3H, s), 1.30 (3H, s); ^{13}C-NMR ($CDCl_3$) δ 174.5, 169.5, 111.7, 81.3, 80.2, 65.4, 60.8, 53.3, 49.0, 35.9, 25.3, 24.3; MS *m*/*z* 241 (M^+ − Me), 225 (M^+ − OMe). Anal. Calcd for $C_{12}H_{16}O_6$: C, 56.24; H, 6.29. Found: C, 56.01; H, 6.28.

Supporting Information Available: Characterization data and experimental procedures of **1a,d**−**j** and **2d**−**j** (8 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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