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Asymmetric Intramolecular Michael Addition of α-Sulfinyl Vinylic Carbanion to Enoates

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The first example of an asymmetric intramolecular Michael addition reaction with use of α-lithiated vinylic sulfoxide as a Michael donor is reported. Michael addition of the α-lithiated vinylic sulfoxide to (*Z*)-enoates proceeds with high diastereoselectivity to give the adducts with (*R*)-configuration at the *β*-position of the ester in the five-membered-ring formation. The selectivity was reversed in the six-membered-ring formation. The resulting ester enolates were reacted with alkyl halides or benzaldehyde with high diastereoselectivity.

Introduction

Asymmetric carbon−carbon bond formation is an attractive subject in organic chemistry. Vinylic sulfoxides have played an important role as a well-known chiral Michael acceptor.[1] In contrast, the application of vinylic sulfoxide as a "Michael donor" has remained unexplored for a long time, although generation of α-sulfinyl vinylic carbanions by α-deprotonation of vinylic sulfoxides was found more than two decades ago.[2] Attempts to employ the vinyl anion species for asymmetric reaction resulted in moderate to poor diastereoselectivity,[3] except for one example.[4] Recently, we have reported that an intramolecular Michael addition reaction of the α-lithiated vinylic sulfoxides to enoates proceeds with extremely high diastereoselectivity, giving functionalized cyclopentene and cyclohexene derivatives.[5]

In this paper, we describe full details of the asymmetric intramolecular Michael addition, especially the reactivity and generality of stereochemistry for various substrates. We also describe two or three asymmetric inductions in one pot utilizing reactions of the resulting enolates with electrophiles.

Result and Discussion

Asymmetric Intramolecular Michael Addition of α-Sulfinyl Vinylic Carbanion. We initially examined the intramolecular Michael addition of four geometric isomers of the vinylic sulfoxide **1a** (Table 1) and found that the diastereoselectivity of the Michael addition was significantly affected by the geometry of the *enoate* but not the *vinylic sulfoxide*. That is, upon treatment of the (*E*)-enoate (2*E*,6*E*)-**1a** with 1.5 equiv of LDA in THF at −78 °C, deprotonation of the α-sulfinyl proton and intramolecular Michael addition of the resulting carbanion to the enoate took place rapidly, giving the *γ*,*δ*-unsaturated esters (1′*R*)- and (1′*S*)-**2a** almost without selectivity (entry 1). In contrast, the intramolecular Michael addition of the corresponding (*Z*)-enoate (2*Z*,6*E*)-**1a** proceeded with very high diastereoselectivity to give the Michael adduct (1′*R*)-**2a** as a single isomer (entry 2). Products arising from deprotonation at the α-, *β*-, or *γ*-positions of the enoates were not detected at all.

Since α-sulfinyl carbanions generated from (*Z*)-*β*-monosubstituted vinylic sulfoxides are known to isomerize to the thermodynamically more stable (*E*)-isomer,[2,6] we expected that intramolecular Michael addition of (*Z*)-vinylic sulfoxides would proceed via (*Z*)- to (*E*)-isomerization. However, reaction of the (*Z*)-vinylic sulfoxides was sluggish, affording the cyclized products (1′*R*)- and (1′*S*)-**2a** in poor yield (entries 3 and 4). It should be noted that the (*Z*)-enoate (2*Z*,6*Z*)-**1a** showed higher selectivity than the corresponding (*E*)-isomer (2*E*,6*Z*)-**1a** even in the

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(1) For review, see: Carreño, M. C. *Chem. Rev.* **1995**, *95*, 1717−1760.
(2) Posner, G. H.; Tang, P.-W.; Mallamo, J. P. *Tetrahedron Lett.* **1978**, *42*, 3995−3998. Okamura, H.; Mitsuhira, Y.; Miura, M.; Takei, H. *Chem. Lett.* **1978**, 517−520.
(3) Fawcett, J.; House, S.; Jenkins, P. R.; Lawrence, N. J.; Russell, D. R. *J. Chem. Soc., Perkin Trans. 1* **1993**, 67−73 and references therein. Haynes, R. K.; Katsifis, A. G. *Aust. J. Chem.* **1989**, *42*, 1473−1483. Haynes, R. K.; Katsifis, A. G. *J. Chem. Soc., Chem. Commun.* **1987**, 340−342.
(4) Solladié, G.; Moine, G. *J. Am. Chem. Soc.* **1984**, *106*, 6097−6098.
(5) Maezaki, N.; Yuyama, S.; Sawamoto, H.; Suzuki, T.; Izumi, M.; Tanaka, T. *Org. Lett.* **2001**, *3*, 29−31.
(6) Maezaki, N.; Izumi, M.; Yuyama, S.; Sawamoto, H.; Iwata, C.; Tanaka, T. *Tetrahedron* **2000**, *56*, 7927−7945. Maezaki, N.; Izumi, M.; Yuyama, S.; Iwata, C.; Tanaka, T. *Chem. Commun.* **1999**, 1825−1826. Posner, G. H. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1983; Vol. 2A, pp 225−241. Schmidt, R. R.; Speer, H.; Schmid, B. *Tetrahedron Lett.* **1979**, 4277−7280.

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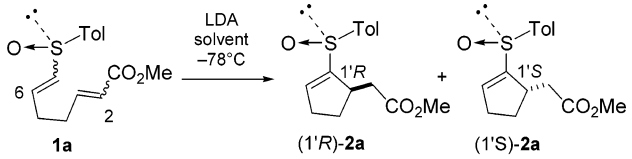
TABLE 1. Effects of Olefin Geometry on Intramolecular Michael Addition[a]



entry	substrate	enoate	vinylic sulfoxide	solvent	yield (%)[b] (1′*R*)-**2**	yield (%)[b] (1′*S*)-**2**	dr (1′*R*:1′*S*)
1	(2*E*,6*E*)-**1a**	E	E	THF	44	40	52:48
2	(2*Z*,6*E*)-**1a**	Z	E	THF	71	0	100:0
3	(2*E*,6*Z*)-**1a**	E	Z	THF	12	10	55:45
4	(2*Z*,6*Z*)-**1a**	Z	Z	THF	19	0	100: 0
5	(2*Z*,6*E*)-**1a**	Z	E	toluene	33	8	80:20
6	(2*Z*,6*E*)-**1a**	Z	E	ether	20	4	83:17
7	(2*Z*,6*E*)-**1a**	Z	E	DME[c]	37	8	82:18
8	(2*Z*,6*E*)-**1a**	Z	E	THF[c]	30	4	88:12
9	(2*Z*,6*E*)-**1a**	Z	E	THF[d]	0	0	

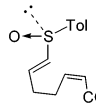
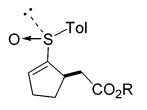
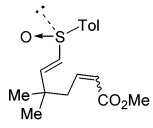
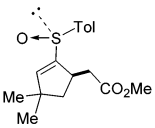
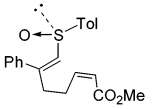
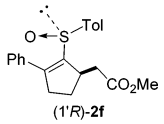
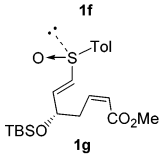
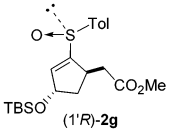
[a] All reactions were carried out with LDA (1.5 equiv) at −78 °C unless otherwise cited. [b] Isolated yield. [c] Reaction was carried out at −40 °C. [d] Reaction was carried out at 0 °C.

reaction of (*Z*)-vinylic sulfoxides. The reaction was considerably affected by the solvent. The best solvent was THF. Other solvents such as toluene, ether, and DME significantly reduced the yield (entries 5−7). The reaction should be carried out at low temperature, since the reaction at higher temperature (−40 °C) was sluggish, giving (1′*R*)- and (1′*S*)-**2a** in 30% and 4% yields, respectively (entry 8). At 0 °C, the reaction afforded a complex mixture (entry 9).

To examine the generality of this reaction, intramolecular Michael addition of several vinylic sulfoxides was investigated. The results are summarized in Table 2. The size of the ester moiety showed significant effects on the yield, but not the selectivity (entries 1−4), wherein the reactions proceeded with excellent diastereoselectivity, yielding five-membered-ring adducts with predominance of the (*R*)-isomer. However, the yield was decreased depending on the bulkiness of the ester moiety, in the order Me > Et > *i*-Pr ≫ *t*-Bu. Introduction of geminal methyl groups on the alkyl chain improved the yield presumably due to a geminal substituent effect.[7] Thus, the (*Z*)-enoate (2*Z*)-**1e** afforded (1′*R*)-**2e** in 89% yield with high diastereoselectivty (entry 5), but the corresponding (*E*)-enoate (2*E*)-**1e** provided (1′*R*)-**2e** in 49% yield with poor diastereoselectivity (entry 6). The selectivity was reduced in the reaction of *β*,*β*-disubstituted vinylic sulfoxide **1f** (entry 7). Asymmetric Michael addition was conducted on *γ*-oxygenated vinylic sulfoxide **1g**, which could undergo elimination of the oxygen. The cyclized product (1′*R*)-**2g** was obtained in 71% yield with excellent diastereoselectivity (entry 8).

In a six-membered ring formation, the stereochemistry of the enoate moiety affected the diastereoselectivity (Table 3). In contrast to the fact that the reaction with (*Z*)-enoate (2*Z*)-**1h** proceeded with very high selectivity (entry 1), the selectivity for the corresponding (*E*)-enoate (2*E*)-**1h** was very poor (entry 2). Interestingly, structural determination of the product revealed that the selectivity was completely reversed, giving the (1′*S*)-isomer predominately. Functionalized substrates **1i**−**k** also furnished the cyclized products with an (*S*)-carbon stereocenter with high diastereoselectivity (entries 3−5). An attempt for seven-membered ring formation failed, giving a complex mixture (entry 6).

TABLE 2. Five-Membered Ring Formation by Intramolecular Michael Addition[a]

entry	substrate (**1**)	major product (**2**)	yield (%)[b] major	yield (%)[b] minor	dr (1′*R*:1′*S*)
					
1	**1a** (R=Me)	(1′*R*)-**2a** (R=Me)	71	0	100 : 0
2	**1b** (R=Et)	(1′*R*)-**2b** (R=Et)	54	tr	>97 : 3
3	**1c** (R=*i*-Pr)	(1′*R*)-**2c** (R=*i*-Pr)	45	tr	>97 : 3
4	**1d** (R=*t*-Bu)	(1′*R*)-**2d** (R=*t*-Bu)	0	0	—
					
5	(2*Z*)-**1e**	(1′*R*)-**2e**	89	6	94 : 6[d]
6	(2*E*)-**1e**		49	30	62 : 38[d]
	 **1f**	 (1′*R*)-**2f**			
7			61	18	77 : 23
	 **1g**	 (1′*R*)-**2g**			
8			71[c]		94 : 6[d]

[a] All reactions were carried out with LDA (1.5 equiv) in THF at −78 °C. [b] Isolated yield unless otherwise stated. [c] Combined yield of (1′*R*)- and (1′*S*)-**2**. [d] Determined by ^{1}H NMR spectroscopic data on the basis of the signals due to the olefinc proton of vinylic sulfoxide.

The absolute configuration of the major products (1′*R*)-**2a** and (1′*S*)-**2h** was determined by the PGME (phenylglycine methyl ester) method[8] after conversion into the corresponding (*R*)- and (*S*)-PGME amides **3a**−**d** by hy-

(7) Review: Jung, M. E. *Synlett* **1999**, 843−846.

(8) (a) Yabuuchi, T.; Kusumi, T. *J. Org. Chem.* **2000**, *65*, 397−404. (b) For recent review, see: Seco, J. M.; Quiñoá, E.; Riguera, R. *Chem. Rev.* **2004**, *104*, 17−117.

TABLE 3. Six-membered Ring Formation by the Intramolecular Michael Addition Reaction[a]

entry	substrate	major product	yield (%)[b] major	yield (%)[b] minor	dr (*S* : *R*)
1	(2*Z*)-**1h**	(1′*S*)-**2h**	60	tr	97 : >3
2	(2*E*)-**1h**		40	38	51 : 49
3	**1i**	(4′*S*)-**2i**	47	7	87 : 13
4	**1j**	(1′*S*)-**2j**	54	tr	97 : >3
5[c]	**1k**	(1′*S*)-**2k**	86	8	91 : 9
6	**1l**	**2l**	0	0	—

[a] All reactions were carried out with LDA (2.5 equiv) in THF at −78 °C. [b] Isolated yield. [c] 1.5 equiv of LDA was used.

drolysis of the esters (LiOH in aqueous MeOH) followed by condensation with (*R*)- or (*S*)-PGME (PyBOP, HOBT, and *N*-methylmorpholine). The ^{1}H NMR spectroscopic data revealed that the amides **3a**−**d** are enantiomerically pure and no loss of optical purity was observed during the cyclization. The assignment was also confirmed by transformation of (1′*S*)-**2a** and (1′*S*)-**2h** into known acids **4a** and **4b** (Scheme 1).[9] The configuration of products **2e**, **2j**, and **2k** was assigned by the PGME method. Those of other products were assumed by comparison of ^{1}H NMR spectral data.

To clarify the reaction mechanism, the cyclized products (1′*R*)- and (1′*S*)-**2a** were treated with 1.5 equiv of LDA at −78 °C for 30 min, and then the reaction was quenched by regular workup. This operation resulted in complete recovery of the starting materials, wherein neither the retro-Michael reaction nor C2-epimerization via recyclization was observed. The results suggest that the intramolecular Michael addition is irreversible and kinetically controlled. We examined the effect of reagents affecting coordination of the sulfoxide on the intramolecular Michael addition. Addition of HMPA, which is known to solvate the metal cation and disrupt the weak chelation, caused a dose-dependent decrease of both yield and diastereoselectivity (Table 4, entries 1−4). Addition of TMEDA and LiI showed effects similar to those of HMPA on the yield and selectivity (entries 5 and 6). These results indicate that reagents disrupting the chelation cause remarkable decrease of the yield and selectivity. Although details of the reaction mechanism are not clear, chelation seems to play some important role for diastereoselectivity as well as reactivity.

(9) (a) Mislow, K.; Steinberg, I. V. *J. Am. Chem. Soc.* **1955**, *77*, 3807−3810. (b) Takano, S.; Yamada, O.; Iida, H.; Ogasawara, K. *Synthesis* **1994**, 592−596. In the case of compound **4a**, considerable loss of optical purity during derivatization was observed presumably as a result of strong alkaline conditions in the desulfurization reaction [**4a**: $[\alpha]_D^{26}$ +78.0 (lit.[10b] $[\alpha]_D^{30}$ +107.4); **4b**: $[\alpha]_D^{26}$ +81.9 (lit.[10b] $[\alpha]_D^{30}$ +84.4)].

SCHEME 1

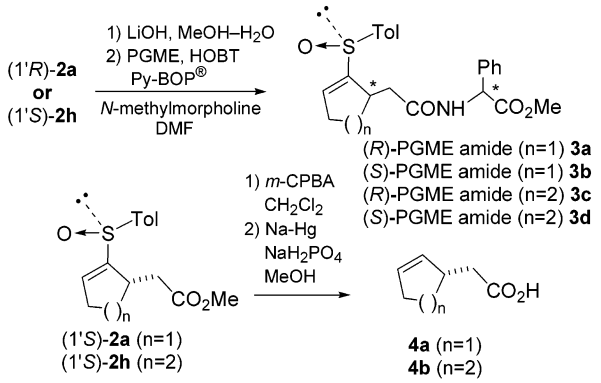


TABLE 4. Effects of Additives on Intramolecular Michael Addition of (2*Z*,6*E*)-1a[a]

entry	additive (equiv)	yield (%)[b] (1′*R*)-**2**	yield (%)[b] (1′*S*)-**2**	dr (1′*R*:1′*S*)
1	none	71	0	100: 0
2	HMPA (0.2)	52	8	87:13
3	HMPA (1)	33	7	83:17
4	HMPA (5)	21	11	66:34
5	TMEDA (1)	51	7	88:12
6	LiI (2)	45	16	74:26

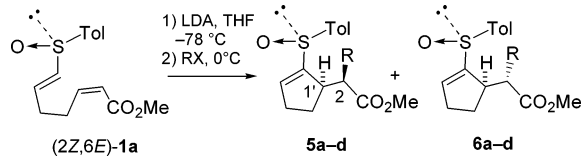
[a] All reactions were carried out with LDA (1.5 equiv) in THF at −78 °C. [b] Isolated yield.

One-Pot Two or Three Asymmetic Inductions by Intramolecular Michael Addition Followed by Trapping with Electrophiles. The intramolecular Michael addition of α-sulfinyl vinyl carbanion generates a new anion species, which is expected to react with electrophiles diastereoselectively, providing two stereocenters in a one-pot operation reaction.

After cyclization of vinylic sulfoxide (2*Z*,6*E*)-**1a**, the resulting enolate was trapped with MeI. Methylation proceeded in a stereoselective fashion, giving **5a** with (1′*R*,2*R*)-configuration predominantly along with a trace of its C2-epimer **6a** (Table 5, entry 1). In contrast to intramolecular Michael addition, the reaction was not influenced by the addition of a chelating agent (entry 2). The chelation seems not to play an important role in the alkylation, which proceeds at higher temperature than the intramolecular Michael addition. The same diastereoselectivity was observed with other alkyl halides (entries 3−5). However, secondary alkyl iodide did not react with the enolate (entry 6).

The absolute configuration of methylated product **5a** was unambiguously confirmed by X-ray single-crystal analysis. The assignment was consistent with the results of the PGME method.[8] The absolute configuration of the other products **5b**−**d** was determined by the PGME method.

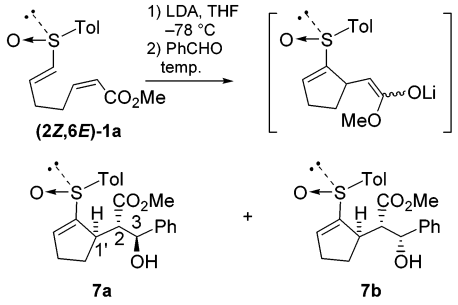
TABLE 5. Intramolecular Michael Addition Followed by Alkylation[a]



entry	RX	product	yield of **5** (%)[b]	dr (**5**:**6**)[c]
1	MeI	**5a**/**6a**	62	96:4
2	MeI, HMPA	**5a**/**6a**	48	95:5
3	BnBr	**5b**/**6b**	54	97:3
4	AllylBr	**5c**/**6c**	50	98:2
5	MOMCl	**5d**/**6d**	45	95:5
6	*i*-PrI		trace	

[a] All reactions were carried out with LDA (1.5 equiv) and RX (5 equiv) in THF at −78 °C. [b] Isolated yield. [c] Determined by ^{1}H NMR spectroscopic data on the basis of the signals due to the olefinc proton of vinylic sulfoxide.

TABLE 6. Intramolecular Michael Addition Followed by Aldol Reaction[a]



entry	temp (°C)	PhCHO (equiv)	yield (%)[b] **7a** + **7b**	dr (**7a**:**7b**)
1	−78	5	63	1:1.3[c]
2	0	5	60	13:1[d]
3	0	2	58	25:1[d]
4	0	5[e]	29	3.4:1[c]

[a] All reactions were carried out with LDA (1.5 equiv) in THF at −78 °C. [b] Combined yield of **7a** and **7b**. [c] Determined by ^{1}H NMR spectroscopic data on the basis of the signals due to the olefinc proton of vinylic sulfoxide. [d] Determined by HPLC. [e] 5 equiv of HMPA was added.

Then, we examined intramolecular Michael reaction followed by aldol reaction with benzaldehyde, wherein three stereocenters were constructed in a one-pot reaction.

Vinylic sulfoxide (2*Z*,6*E*)-**1a** was treated with LDA (1.5 equiv) and then the reaction was quenched with benzaldehyde at −78 °C (5 equiv) to give the adducts **7a** and **7b** as shown in Table 6. Interestingly, diastereoselectivity of the aldol reaction was remarkably improved at high temperature.

The relative stereochemistry at the C2 and C3 positions was confirmed as shown in Scheme 2. Since separation of the adducts **7a** and **7b** was difficult, a mixture of them was reduced to sulfides **8a** and **8b**. Reduction to diol followed by acetalization converted **8a** and **8b** into acetonides **9a** and **9b**, respectively. Comparison of coupling constants between C4 and C5 protons in the ^{1}H NMR spectral data for **9a** (J = 3.1 Hz) and **9b** (J = 11.6 Hz) revealed that the adducts, **7a** and **7b**, were assigned as anti and syn, respectively.[10] The absolute configuration of the C3 position was determined by the modified Mosher method,[11] and that of the C1′ position was assumed from the results of protonation and alkylation.

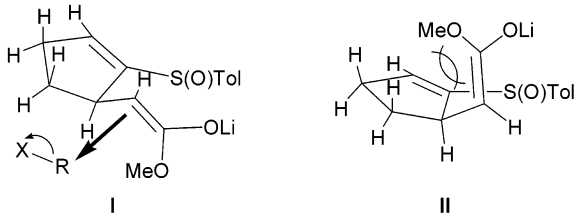
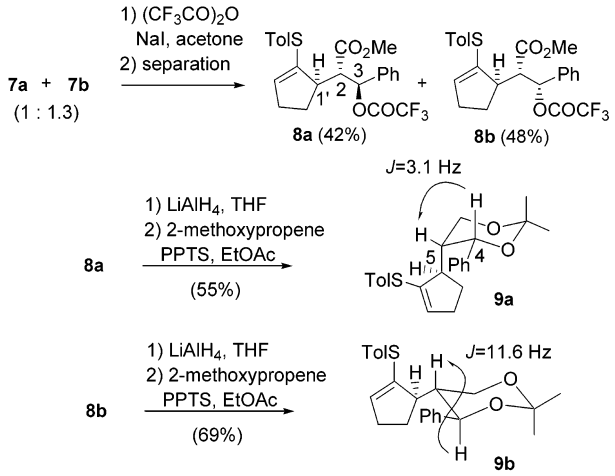


FIGURE 1. Plausible reaction mechanism for diastereoselective alkylation of enolate.

SCHEME 2



It was found that both products, **7a** and **7b**, have (1′*R*,2*S*) configuration. The ratio of C3-epimers was variable depending on the reaction temperature.

Diastereoselectivity of the alkylation can be explained as follows. The sterically less demanding enolate intermediate **I** would be more stable than intermediate **II** (Figure 1). The alkylation proceeded from the opposite side of the sulfinyl group in intermediate **I**, giving **5a**−**d** preferentially. Taking into account the fact that the chelating reagent had no effect on the selectivity, chelation would not always be necessary to rigidify the conformation at 0 °C.

Benzaldehyde also approaches from the same side of the enolate intermediate **II** to afford the aldols with (1′*R*,2*S*) configuration. High selectivity at high temperature presumably is attributed to isomerization from **7b** to the stable product **7a** via retro-aldol reaction.

Conclusion

We have found that the intramolecular Michael addition of the α-sulfinyl vinylic carbanion proceeds with excellent selectivity. (*Z*)-Configuration of the enoate was essential to achieve the high diastereoselectity. While five-membered ring formation afforded (1′*R*)-adducts, the reversed selectivity was observed in the six-membered

(10) The relation of the diastereomers **7a**,**b** and **8a**,**b** were confirmed by reduction of almost pure **7a** into **8a**.

(11) Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092−4096. For a recent review, see ref 8b.

ring formation. The resulting enolates were trapped diastereoselectivly with alkyl halide and benzaldehyde, giving two or three contiguous stereocenters in a one-pot reaction.

Experimental Section

Melting points are uncorrected. NMR spectra were recorded in $CDCl_3$ solution at 500 MHz (^1H) and 125, 75, or 67.8 MHz (^{13}C). IR absorption spectra (FT: diffuse reflectance spectroscopy) were recorded with KBr powder, and only noteworthy absorptions (cm^{-1}) are listed. Column chromatography was carried out with Merck silica gel 60 (70−230 mesh) or Kanto Chemical silica gel 60N (spherical, neutral, 63−210 μm). All air- or moisture-sensitive reactions were carried out in flame-dried glassware under an atmosphere of Ar or N_2. All solvents were dried and distilled according to standard procedures. All organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated with a rotary evaporator under reduced pressure. The general procedure of intramolecular Michael addition and characterization data of the vinyl sulfoxides (1′*R*)- and (1′*S*)-**2a**[12]−**c**, **2h**, and the PGME amides **3a**−**d** were given in the Supporting Information of ref 5.

General Procudure of Intramolecular Michael Addition Followed by Alkylation: Methyl (2*R*)-2-[(1*R*)-2-[(*R*)-(*p*-Tolylsulfinyl)]-2-cyclopentenyl]propanoate (5a). A solution of LDA (2.0 M in heptane/THF/ethylbenzene) (0.195 mL, 0.390 mmol) was added to a solution of the enoate (2*Z*,6*E*)-**1a** (72.4 mg, 0.260 mmol) in THF (4 mL). After 20 min, MeI (83 μL, 1.30 mmol) was added to the mixture and the whole was stirred at 0 °C for 30 min. The reaction was quenched with saturated NH_4Cl and the solvent was evaporated. The residue was dissolved with EtOAc and washed with brine prior to drying and solvent evaporation. The residue was chromatographed on silica gel with hexanes−EtOAc (2:1) to give **5a** (47.4 mg, 62%) as a colorless powder. Mp 67.0−68.5 °C (hexanes−EtOAc). $[\alpha]^{25}_D$ +63.1 (*c* 1.43, $CHCl_3$). ^1H NMR δ 1.09 (d, J = 7.3 Hz, 3H), 1.82 (dddd, J = 16.5, 8.5, 4.9, 3.7 Hz, 1H), 1.95 (ddt, J = 16.5, 9.8, 7.3 Hz, 1H), 2.35−2.56 (m, 2H), 2.42 (s, 3H), 3.22 (qd, J = 7.3, 3.1 Hz, 1H), 3.24−3.31 (m, 1H), 3.62 (s, 3H), 6.55 (m, 1H), 7.32 (d, J = 7.9 Hz, 2H), 7.49 (d, J = 7.9 Hz, 2H). ^{13}C NMR δ 10.2, 21.4, 25.7, 32.3, 41.0, 45.6, 51.6, 124.4, 129.8, 139.0, 141.0, 142.4, 147.2, 175.5. IR 1732, 1043. MS (EI) *m*/*z* (%) 292 (M^+, 1.1), 153 (100). HRMS (EI) calcd for $C_{16}H_{20}O_3S$ (M^+) 292.1133, found 292.1129. Anal. Calcd for $C_{16}H_{20}O_3S$: C, 65.72; H, 6.89; S, 10.97. Found: C, 65.70; H, 6.90; S, 10.90.

Methyl (2*S*,3*S*)-3-Hydroxy-3-phenyl-2-[(1*R*)-2-[(*R*)-(*p*-tolylsulfinyl)]-2-cyclopentenyl]propanoate (7a). A solution of LDA (2.0 M in heptane/THF/ethylbenzene) (54 μL, 0.11 mmol) was added to a solution of the enoate (2*Z*,6*E*)-**1a** (20.1 mg, 0.072 mmol) in THF (1 mL). After 20 min, PhCHO (37 μL, 0.36 mmol) was added to the mixture and the whole was stirred at 0 °C for 30 min. The reaction was quenched with saturated NH_4Cl and the solvent was evaporated. The residue was dissolved with EtOAc and washed with brine prior to drying and solvent evaporation. The residue was chromatographed on silica gel with hexanes−EtOAc (3:1) to give **7a** (16.7 mg, 60%, **7a**:**7b** = 13:1) as a yellow oil. $[\alpha]^{27}_D$ −107.5 (*c* 0.26, $CHCl_3$). ^1H NMR δ 2.06−2.13 (m, 1H), 2.37−2.48 (m, 2H), 2.41 (s, 3H), 2.59−2.70 (m, 1H), 3.11 (dddd, J = 11.0, 7.9, 4.9, 3.1 Hz, 1H), 3.29 (s, 3H), 3.51 (dd, J = 10.4, 3.1 Hz, 1H), 5.00 (t, J = 10.4 Hz, 1H), 5.06 (d, J = 10.4 Hz, 1H), 6.64 (dd, J = 5.2, 2.4 Hz, 1H), 7.24 (t, J = 7.3 Hz, 1H), 7.33 (t, J = 7.3 Hz, 2H), 7.35 (d, J = 8.5 Hz, 2H), 7.40 (d, J = 7.3 Hz, 2H), 7.53 (d, J = 8.5 Hz, 2H). ^{13}C NMR δ 21.2, 26.3, 31.7, 44.8, 51.2, 53.7, 72.2, 124.3, 126.5, 127.3, 128.1, 130.0, 137.0, 141.1, 143.4, 143.5, 146.8, 172.4. IR 3334, 1732, 1010. MS (FAB) *m*/*z* 385 (MH^+). HRMS (FAB) calcd for $C_{22}H_{25}O_4S$ 385.1474, found 385.1472.

Methyl (2*S*,3*S*)-3-Phenyl-2-[(1*R*)-2-(*p*-tolylthio)-2-cyclopentenyl]-3-(2,2,2-trifluoroacetoxy)propanoate (8a) and Methyl (2*S*,3*R*)-3-Phenyl-2-[(1*R*)-2-(*p*-tolylthio)-2-cyclopentenyl]-3-(2,2,2-trifluoroacetoxy)propanoate (8b). $(CF_3CO)_2O$ (0.160 mL, 1.14 mmol) was added to a mixture of the sulfoxides **7a** and **7b** (112 mg, 0.292 mmol, **7a**:**7b** = 1:1.3) and NaI (127 mg, 1.02 mmol) in acetone (2 mL) with stirring at 0 °C and the stirring was continued at the same temperature for 5 min. The reaction was quenched with saturated $NaHCO_3$ and the mixture was extracted with Et_2O. The extract was washed with saturated $Na_2S_2O_3$, saturated $NaHCO_3$, and brine prior to drying and solvent evaporation. The residue was chromatographed on silica gel with hexanes−EtOAc (40:1) to give **8a** (57.1 mg, 42%) as a colorless powder and **8b** (64.3 mg, 48%) as a yellow oil. **8a**: Mp 79.3−81.0 °C (MeOH). $[\alpha]^{26}_D$ −73.0 (*c* 1.82, $CHCl_3$). ^1H NMR δ 2.14−2.22 (m, 1H), 2.15−2.39 (m, 3H), 2.32 (s, 3H), 3.26−3.32 (m, 1H), 3.42 (s, 3H), 3.49 (dd, J = 11.0, 3.1 Hz, 1H), 5.74−5.78 (m, 1H), 6.47 (d, J = 11.0 Hz, 1H), 7.12 (d, J = 7.9 Hz, 2H), 7.26 (d, J = 7.9 Hz, 2H), 7.29−7.36 (m, 3H), 7.40 (dd, J = 7.9, 1.8 Hz, 2H). ^{13}C NMR δ 21.0, 28.1, 31.2, 46.1, 51.7, 54.0, 78.6, 114.2 (q, $J_{C,F}$ = 284 Hz), 127.5, 128.6, 129.2, 129.9, 129.9, 131.1, 134.8, 136.8, 137.2, 137.3, 156.0 (q, $J_{C,F}$ = 42 Hz), 170.8. IR 1786, 1149. MS (EI) *m*/*z* (%) 464 (M^+, 71.8), 167 (100). HRMS (EI) calcd for $C_{24}H_{23}F_3O_4S$ (M^+) 464.1269, found 464.1268. **8b**: $[\alpha]^{26}_D$ −36.4 (*c* 1.43, $CHCl_3$). ^1H NMR δ 2.04 (dddd, J = 13.4, 8.5, 3.7, 3.1 Hz, 1H), 2.12 (dtd, J = 13.4, 9.2, 8.9 Hz, 1H), 2.18−2.32 (m, 2H), 2.34 (s, 3H), 2.79−2.85 (m, 1H), 3.69 (s, 3H), 3.37 (dd, J = 9.8, 3.1 Hz, 1H), 5.53−5.56 (m, 1H), 6.57 (d, J = 9.8 Hz, 1H), 7.12 (d, J = 7.9 Hz, 2H), 7.23 (d, J = 7.9 Hz, 2H), 7.27−7.36 (m, 5H). ^{13}C NMR δ 21.1, 29.5, 31.2, 45.7, 51.9, 54.6, 78.9, 114.4 (q, $J_{C,F}$ = 284 Hz), 127.9, 128.6, 129.2, 130.0, 130.1, 131.4, 134.6, 135.7, 136.6, 137.4, 155.9 (q, $J_{C,F}$ = 41 Hz), 171.3. IR 1790, 1740. MS (EI) *m*/*z* (%) 464 (M^+, 71.8), 464 (100). HRMS (EI) calcd for $C_{24}H_{23}F_3O_4S$ (M^+) 464.1269, found 464.1261.

(4*S*,5*R*)-2,2-Dimethyl-4-phenyl-5-[(1*R*)-2-(*p*-tolylthio)-2-cyclopentenyl]-1,3-dioxane (9a). The sulfide **8a** (33.7 mg, 0.0726 mmol) was added to a suspension of $LiAlH_4$ (13.8 mg, 0.36 mmol) in THF (0.5 mL) with stirring at 0 °C and the stirring was continued at the same temperature for 5 min. The reaction was quenched with saturated NH_4Cl and the mixture was extracted with EtOAc. The extract was washed with water and brine prior to drying and solvent evaporation. The residue (27.7 mg) was dissolved with EtOAc (2 mL) and PPTS (0.4 mg, 2 μmol) and 2-methoxypropene (9 μL, 0.09 mmol) and the whole was stirred at room temperature for 2 h. The reaction was quenched with saturated $NaHCO_3$ and the mixture was extracted with EtOAc. The extract was washed with water and brine prior to drying and solvent evaporation. The residue was chromatographed on silica gel with hexanes−EtOAc (40:1) to give **9a** (15.1 mg, 55% in two steps) as a colorless oil. $[\alpha]^{27}_D$ −85.5 (*c* 0.72, $CHCl_3$). ^1H NMR δ 1.53 (s, 6H), 1.41−1.49 (m, 1H), 1.65−1.74 (m, 1H), 1.89−1.96 (m, 2H), 2.02 (dtd, J = 5.5, 3.1, 1.8 Hz, 1H), 2.32 (s, 3H), 2.96−3.02 (m, 1H), 4.02 (dd, J = 12.2, 1.8 Hz, 1H), 4.19 (dd, J = 12.2, 3.1 Hz, 1H), 5.15−5.18 (m, 1H), 5.26 (d, J = 3.1 Hz, 1H), 7.09 (d, J = 7.9 Hz, 2H), 7.15−7.31 (m, 5H), 7.38 (d, J = 7.9 Hz, 2H). ^{13}C NMR δ 19.2, 21.1, 29.5, 30.2, 30.6, 40.8, 45.9, 65.4, 73.5, 99.2, 125.9, 126.9, 127.8, 129.7, 130.5, 130.8, 132.4, 137.2, 140.7, 140.8. IR 1724. MS (EI) *m*/*z* (%) 380 (M^+, 65.8), 216 (100). HRMS (EI) calcd for $C_{24}H_{28}O_2S$ (M^+) 380.1810, found 380.1810.

X-ray Analysis. Crystal data for **5a**: $C_{16}H_{20}O_3S$, M = 292.38, monoclinic, space group P*21*, a = 7.941(4) Å, b = 7.367(4) Å, c = 13.372(6) Å, α = 90.0°, β = 97.40°(4), γ = 90.0°, volume = 775.8(7) Å^3, Z = 2, D_c = 1.252 Mg m^{-3}, μ = 1.891 mm^{-1}, crystal dimensions 0.4 × 0.1 × 0.02 mm^3, F(000) = 312, T = 293(2) K, θ = 3.33−67.54°. 1868 reflections measured, unique reflections 1485 [R_{int} = 0.1380], min and max. Absorption correction factor 0.615 and 1.000, R1 = 0.0734, *w*R2 =

(12) The HRMS of **3a** reported in the Supporting Information of ref 5 is incorrect, and should be revised as follows: HRMS (FAB) calcd for $C_{23}H_{26}NO_4S$ (MH^+) 412.1583, found 412.1577.

0.2116 for 1479 reflections with $I > 2\sigma(I)$ and R1 = 0.1187, wR2 = 0.2501 for all reflections and 84 refined parameters. Final electron density 0.489 and −0.491 eÅ^{-3}, S = 1.490, absolute Flack structure parameter −0.02(8).

The data set was collected on a Rigaku AFC5R diffractometer with Cu·Kα radiation (λ = 1.5418 Å). The structure was solved by direct methods with SHELX-97[13] and refined by full-matrix least squares on F^2 by SHELXL-97.[14] Non-hydrogen atoms were refined by the anisotropic temperature factor and hydrogens were isotropic. The hydrogens were placed by the riding method. The molecular views were realized by ORTEP−III.[15]

Supporting Information Available: Experimental procedure and characterization data for compounds **1a**−**1l**, **2e**−**2g**, **2i**−**2k**, **4a**, **4b**, **5b**−**5d**, and **9b**. General procedure for preparation of PGME amide. ORTEP drawing and CIF file for **5a**. ^{1}H NMR spectral data of compounds (1′*R*)-**2e**−**2g**, (4′*S*)-**2i**, (1′*S*)-**2j**−**k**, **5a**−**5d**, and **7a**. This material is available free of charge via the Internet at http://pubs.acs.org. Crystal and data collection parameters have been deposited with the Cambridge Crystallographic Data Center (CCDC-231930, email: deposit@ccdc.cam.ac.uk).

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