Stereoselective Thio-Michael/Aldol Tandem Reaction to α,β-Unsaturated Esters

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A mixture of lithium thiophenolate, α,β-unsaturated ester, and aldehyde in CH_2Cl_2 afforded Michael/aldol tandem adducts, β-hydroxy-α-(1-phenylthioalkyl) esters, in moderate to good yields with a high syn-aldol selectivity. The reaction proceeded effectively when CH_2Cl_2 or ether was used as a solvent. The countercation of thiolate proved important; lithium cation provided the best results. The stereoselectivity and yield of the adducts greatly depended on the steric size of the ester group. Lithium selenolate, generated in situ by treatment of diphenyldiselenide with methyllithium, brought similar results, whereas alkoxide was too inert for the reaction. Application of the reaction to methacrylate provided a useful method to form a quaternary carbon center on a similar stereoselective level. In the reaction with crotonates, on the other hand, the anti-Michael selectivity dominated over the syn-aldol selectivity. The tandem adduct was useful for the stereoselective preparation of trisubstituted tetrahydrofuran via radical cyclization, whose configuration was found to be 2,3-trans-3,5-trans.

Introduction

The tandem or domino reaction has recently been of interest for organic synthesis because it offers a convenient and economical way to prepare desired organic molecules.[1] Additionally, combining more than one reaction in one pot usually provides a good solution, a solution that will give a better yield and a chance for reactive but not-easy-to-generate intermediates to be used in a synthetic sequence. The Michael addition is one of the most useful organic reactions to construct carbon skeletons.[2] Thiolate and its analogues are known as good nucleophiles for the reaction to give Michael adducts in good yields. The reaction begins with the nucleophilic attack of thiolate on the β-carbon of a Michael acceptor, generating an enolate intermediate. If the active enolate intermediate is captured with not a proton but an aldehyde, then a tandem Michael/aldol process is achieved.[3−5] The thio-functional group introduced here serves as a precursor of other functional groups and/or acts as a good activator for a further carbon−carbon bond-forming reaction.[6] When the present investigation was launched, the chemistry of the thio-tandem process with α,β-unsaturated esters, despite the few reports of the reaction with α,β-unsaturated ketones,[7] had remained unestablished: neither had the reaction conditions been opitimized nor had the stereochemical course of the reaction been known.[8] Recently, we have demonstrated that the tandem strategy successfully works for acrylates with the aldehydes in CH_2Cl_2 and that a high syn-aldol selectivity is achieved with *tert*-butyl acrylate.[9,10] This research reports in full detail our latest results on the tandem process, discussing a plausible pathway of the reaction and its stereochemical course. We will also demonstrate a stereoselective preparation of trisubstituted tetrahydrofuran derivatives from the tandem adduct as an extension of the methodology.

Results and Discussion

The Tandem Michael/Aldol Reaction to Acrylate Esters. The present reaction procedure is outlined in Scheme 1. First, methyl acrylate was chosen for the Michael acceptor. The results are summarized in Table 1.

To a heterogeneous mixture of lithium thiolate in CH_2Cl_2[11] were added methyl acrylate and benzaldehyde.

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(1) For review for tandem reaction, see: Posner, G. H. *Chem. Rev.* **1986**, *86*, 831. Tietze, L. F.; Beifuss, U. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 131. Bunce, R. A. *Tetrahedron* **1995**, *48*, 13103. Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115.

(2) Jung, M. E. In *Comprehensive Organic synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, 1991; Vol. 4, pp 1−67. Perlmutter, P. *Conjugate Addition Reactions in Organic Synthesis*; Pergamon Press: Oxford, 1992.

(3) Jansen, J. F. G. A.; Feringa, B. L. *Tetrahedron Lett.* **1991**, *32*, 3239.

(4) Davies, S. G.; Ichihara, O. *J. Synth. Org. Chem. Jpn.* **1997**, *55*, 26 and references therein. Davies, S. G.; Fenwick, D. R. *J. Chem. Soc., Chem. Commun.* **1997**, 565. Tsukada, N.; Shimada, T.; Gyoung, Y. S.; Asao, N.; Yamamoto, Y. *J. Org. Chem.* **1995**, *60*, 143. Yamamoto, Y.; Asao, N.; Yuehara, T. *J. Am. Chem. Soc.* **1992**, *114*, 5427. Hosomi, A.; Yanagi, T.; Hojo, M. *Tetrahedron Lett.* **1991**, *32*, 2371. Asao, N.; Uyehara, T.; Yamamoto, Y. *Tetrahedron* **1990**, *46*, 4563.

(5) Fleming, I.; Kilburn, J. D. *J. Chem. Soc., Chem. Commun.* **1986**, 305. 1198; Fleming, I.; Sarkar, A. K. *J. Chem. Soc., Chem. Commun.* **1986**, 1199.

(6) For example: Simpkins, N. S. *Sulphones in Organic Synthesis;* Pergamon Press: Oxford, 1993.

(7) (a) Barrett, A. G. M.; Kamimura, A. *J. Chem. Soc., Chem. Commun.* **1995**, 1755. (b) Yura, T.; Iwasawa N.; Mukaiyama, T. *Chem. Lett.* **1986**, 187. (c) Suzuki, M.; Kawagishi, T.; Noyori, R. *Tetrahedron Lett.* **1981**, *22*, 1809.

(8) Itoh, A.; Ozawa, S.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.* **1980**, *21*, 361; Levin, J. I. *Synth. Commun.* **1992**, 961.

(9) Preliminary communication on this work: Kamimura, A.; Mitsudera, H.; Asano, S.; Kakehi, A.; Noguchi, M. *Chem. Commun.* **1998**, 1095.

(10) Very recently, a related work has been published: Ono, M.; Nishimura, K.; Nagaoka, Y.; Tomioka, K. *Tetrahedron Lett.* **1999**, *40*, 1509.

(11) Lithium thiolate was generated by treatemnt of thiophenol in CH_2Cl_2 with BuLi at −78 °C, where no reaction between CH_2Cl_2 and BuLi was observed except a clean formation of lithium thiophenolate.

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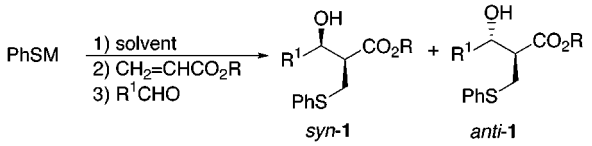
Scheme 1



The reaction mixture became homogeneous and was maintained at −78 °C for 1 h; desired tandem adduct **1a** was obtained in 31% yield along with the simple Michael adduct of the thiol and the acrylate (Table 1, entry 1). The reversed-phase HPLC analysis indicated that the diastereomeric ratio of **1a** was 71/29, with *syn*-**1a** found to be the major isomer. The two diastereomers of **1a** were separated by flash chromatography. Neither diastereomer of diastereomerically pure **1a** epimerized when they were each exposed to lithium thiolate in CH_2Cl_2. This initial result encouraged an attempt at optimizing the reaction conditions so as to improve the yield and the stereoselectivity. When the reaction conditions were set at −50 °C for 7 h, the yield of **1a** increased to 62% but the syn selectivity remained at a similar level (Table 1, entry 2). Cyclohexyl acrylate ensured the formation of **1c** with a slightly better syn selectivity (79/21) but with a moderate yield (Table 1, entry 4). Both the yield and the syn selectivity were dramatically improved when *tert*-butyl acrylate was used in the reaction; the desired tandem adduct **1d** was isolated in 80% yield with a 92/8 syn/anti ratio (Table 1, entry 5). This stereoselectivity is much higher than in the analogous aldol reaction of the ester enolate generated from *tert*-butyl propionate with LDA, the reported ratio being almost 1:1.[12] 2,6-Dimethylphenyl acrylate, an ester residue much more bulky than *tert*-butyl acrylate, underwent no formation of the tandem adduct (Table 1, entry 6). Consequently, we concluded that *tert*-butyl ester was the best choice for the ester part of the reaction.

Changes in the countercation varied the yields and the selectivities. Sodium thiolate, for example, afforded **1d** in a moderate yield (51%), but potassium thiolate was ineffective for the formation of **1d** (Table 1, entries 7 and 8). The presence of magnesium ions produced a mixture of **1d** in a low yield (Table 1, entry 9).[13] A variety of solvents were also examined for the reaction: ether was similar to CH_2Cl_2 in the results (Table 1, entries 5 and 11), while THF and C_2H_5CN were found useless (Table 1, entries 10 and 12). Thus, lithium ions in either CH_2Cl_2 or ether proved the best combination for a smooth reaction. These conditions were further applied to reactions of other aldehydes.

The reaction with aromatic and α,β-unsaturated aldehydes gave tandem adducts in good yields with a high syn selectivity (Table 1, entries 13−16). On the other hand, the yield of the tandem adducts with aliphatic aldehydes remained at a moderate level, and mixtures were isolated of the respective two diastereomers of **1j**−**l** in a ratio of ca. 3:1 (Table 1, entries 17−19). The α-branched aldehyde, such as isobutyraldehyde, was inert in the reaction (Table 1, entry 20). A competitive experiment between hexylaldehyde and benzaldehyde resulted in the selective formation of **1d** at a ratio of **1d**/**1k** = 90:10 (Scheme 2). This result thus indicates that in the reaction the aromatic aldehydes are more reactive than the aliphatic aldehydes.

We further applied the present procedure to selenolates or alkoxides since analogues of thiolates, selenolates for one, work as good nucleophiles in the Michael addition reaction (Scheme 3). The results are summarized in Table 2.

Our investigation needed lithium selenophenolate. Although it is usually generated through deprotonation of selenophenol,[14] it was instead generated directly from methyllithium and diphenyldiselenide.[15] To the lithium selenolate in ether, benzaldehyde first and then *tert*-butyl acrylate were added at −50 °C, and the mixture gave corresponding tandem adduct **2a** in 97% yield (Table 2, entry 1). The syn/anti ratio of **2a** turned out to be 87/13, almost equivalent to that of the thiolate reaction. Other aromatic aldehydes also underwent the smooth formation of **2** in good yields (Table 2, entries 2−5). The adduct of α,β-unsaturated aldehyde was isolated in a good yield but was a 1:1 mixture of the two diastereomers (Table 2, entry 6). The reaction with aliphatic aldehyde resulted in the formation of tandem adduct **2f** in a moderate yield (Table 2, entry 7). Phenoxide and benzyl alkoxide anion neither caused the Michael addition nor formed oxy-tandem adducts **3** under the present reaction conditions (Table 2, entries 8 and 9).

The Tandem Michael/Aldol Reaction to Methacrylate Esters. The present procedure was extended to methacryl esters providing a quaternary carbon center (Scheme 4 and Table 3).

The same sequence for methacrylate at −15 °C, for instance, afforded tandem adduct **4a** in 61% yield at a syn/anti ratio of 87/13 (Table 3, entry 1). The reaction under the conditions of −78 °C to room temperature slightly improved the yield but lowered the syn selectivity (Table 3, entry 2). The moderate reactivity of methacrylate ester toward the Michael addition required a higher reaction temperature for the smooth reaction progress. X-ray crystallographic analysis revealed the stereochemistry of the adduct to be 2*R**,3*S**, indicating that the reaction with methacrylate preferred to proceed through a stereochemical course similar to that of the reaction with acrylates (vide infra). This procedure proved compatible with other aromatic aldehydes, the reaction of which gave tandem adducts **4** in good yields in a syn-selective manner (Table 3, entries 3 and 4). Thus, the present method provides a useful preparation of quaternary carboncenters in a diastereoselective manner.[16] Selenium analogue **5** was also prepared in the reaction

(12) Heathcock, C. H.; Buse, C. T.; Kleschick, W. A.; Pirrung, M. C.; Sohn, J. E.; Lampe, J. *J. Org. Chem.* **1980**, *45*, 1066.

(13) Shono, T.; Matsumura, Y.; Kashimura, S.; Hatanaka, K. *J. Am. Chem. Soc.* **1979**, *101*, 4752.

(14) For generation of selenolate anion, see: Paulmier, C. *Selenium Reagents and Intermediates in Organic Synthesis*; Pergamon: Oxford, 1986; pp 25−27 and references therein. Liotta, D. *Acc. Chem. Res.* **1984**, *17*, 28. Clive, D. L. J. *Tetrahedron* **1978**, *34*, 1049. Reich, H. *Acc. Chem. Res.* **1979**, *12*, 22.

(15) Due to the high toxicity and terrible smell of selenophenol, we wished to avoid to use this substance and looked for a convenient alternative for our purpose. After several trials, we finally succeeded in finding a useful and safer method, in which lithium selenophenolate was generated by treatment of diphenyldiselenide with an equimolar amount of methyllithium in ether at the room temperature (see Experimental Section). Although half of the organoselenium source is wasted in forming methyl phenyl selenide, the most advantageous point of the method is that the generation of selenolate is achieved in one step from commercially available diphenyldiselenide, and this also minimizes unavoidable spread of the toxic selenium reagent during the experimental work.

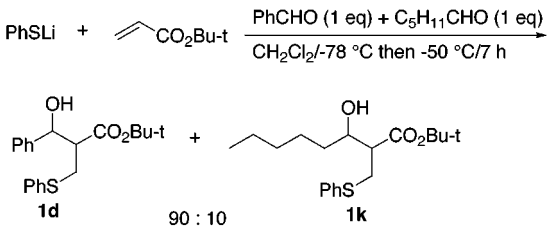
(16) For review for stereoselective construction of quaternary stereogenic center, see: Fuji, K. *Chem. Rev.* **1993**, *93*, 2037.

Table 1. Michael/Aldol Tandem Addition to Acrylates under Various Conditions

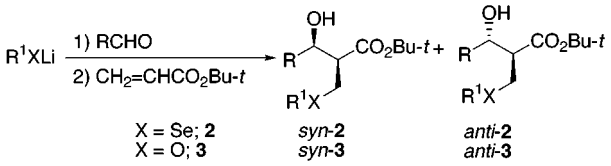
entry	R	R^1	M^+	solvent	*T* (°C)	time (h)	**1**; yield (%)[a]	syn/anti[b]
1	Me	Ph	Li	CH_2Cl_2	−78	1	**1a**; 31	71/29
2	Me	Ph	Li	CH_2Cl_2	−50	7	**1a**; 62	71/29
3	Et	Ph	Li	CH_2Cl_2	−50	7	**1b**; 64	66/34
4	*c*-Hex	Ph	Li	CH_2Cl_2	−50	7	**1c**; 62	79/21
5	*t*-Bu	Ph	Li	CH_2Cl_2	−50	7	**1d**; 80	92/8
6	2,6-DMP[c]	Ph	Li	CH_2Cl_2	−78 to rt	15	**1e**; 0	
7	*t*-Bu	Ph	Na	CH_2Cl_2	−50	15	**1d**; 51	86/14
8	*t*-Bu	Ph	K	CH_2Cl_2	−50	15	**1d**; 0	
9	*t*-Bu	Ph	MgBr	CH_2Cl_2	−50	15	**1d**; 27	63/37
10	*t*-Bu	Ph	Li	THF	−50	15	**1d**; 33	71/29
11	*t*-Bu	Ph	Li	ether	−50	15	**1d**; 86	87/13
12	*t*-Bu	Ph	Li	C_2H_5CN	−50	15	**1d**; 0	
13	*t*-Bu	1-Nap[d]	Li	CH_2Cl_2	−50	7	**1f**; 91	88/12
14	*t*-Bu	*p*-ClC_6H_4	Li	CH_2Cl_2	−50	7	**1g**; 71	88/12
15	*t*-Bu	PhCH=CH−[e]	Li	CH_2Cl_2	−50	7	**1h**; 52	81/19
16	*t*-Bu	C_3H_7CH=CH−[e]	Li	CH_2Cl_2	−50	7	**1i**; 66	85/15
17	*t*-Bu	Me	Li	CH_2Cl_2	−78 to rt	15	**1j**; 31	76/24
18	*t*-Bu	C_5H_{11}	Li	CH_2Cl_2	−50	7	**1k**; 65	72/28
19	*t*-Bu	C_9H_{19}	Li	CH_2Cl_2	−78 to rt	15	**1l**; 66	76/24
20	*t*-Bu	^{i}Pr	Li	CH_2Cl_2	−78 to rt	15	**1m**; 0	

[a] Isolated yield. [b] Determined by HPLC analyses. [c] 2,6-DMP = 2,6-dimethylphenyl. [d] 1-Nap = 1-naphthyl. [e] *E* isomer was used.

Scheme 2



Scheme 3



(Table 3, entry 6). In contrast, aliphatic aldehyde gave only a trace amount of tandem adduct **4d** (Table 3, entry 5).

The Tandem Michael/Aldol Reaction to Crotonate Esters. Examination was made on the extension of the reaction with crotonate esters (Scheme 5). The results are summarized in Table 4.

The existence of the β-methyl group spoiled the electrophilic reactivity of the crotonates. As a result, −50 °C was too low for the reaction (Table 4, entry 1). To enhance the reaction rate, the reaction mixture was allowed to warm to room temperature and the tandem adduct **6a** was obtained in 55% yield (Table 4, entry 2). The presence of three contiguous stereogenic centers in adduct **6a** gives rise to a possibility of the reaction forming a mixture of four diastereomers (**A**−**D**), two of which were obtained as major isomers (**A** and **C**) in a ratio of 53/1/45/1 (Table 4, entry 2). Selenolate also gave analogue **7** in 62% yield at a similar diastereomeric ratio (Table 4, entry 5). A better stereoselectivity was observed in the reaction of 1-naphthyl aldehyde (Table 4, entry 3). An aliphatic aldehyde was less reactive, forming only trace amounts of the adduct (Table 4, entry 4).

Determination of the configurations for these adducts was not easy. Fortunately, the major isomer (**7-A**) was isolated as a single crystal, and its X-ray analysis clearly revealed the stereochemistry of **7-A** to be 2*S**,3*R**,2α*S**.[17] Determination of the other diastereomers will be discussed in the following section.

Determination of Stereochemistry. The stereochemistry of the tandem adducts was determined by either X-ray crystallography, conversion of the adducts to known compounds, or comparison of HPLC and NMR patterns. A single crystal of the major isomer of **1a**, for example, was obtained by recrystallization, and its X-ray analysis unambiguously revealed the relative configuration of **1a** to be syn.[18] Configurations of other compound **1** were determined by comparison of ^{1}H NMR. For example, H3 signals for *syn*-**1** always appeared in the lower field than the corresponding signals for *anti*-**1**.

Seleno analogues **2a**, whose diastereomeric ratio was 81/19, were readily converted into known compound **9**. The ^{1}H NMR spectrum of the minor isomer of **9** was identical to the reported spectrum of *anti*-**9** (Scheme 6).[19] Thus, the configuration of major **2a** was assigned to be syn.

Despite our effort, the adducts from methacrylate never afforded any single crystal suitable for X-ray analysis. An attempt was made to convert it to acetal derivative **11** (Scheme 7).

Reduction of **4b** with $LiAlH_4$ gave diol **10**, which was then converted into acetal **11** by treatment with 2,2-dimethoxypropane. An NOE experiment on **11** suggested that the methyl group should be located in the cis position to the two axial protons (Scheme 7) because 4.3% of signal enhancement of the C2-methyl group was observed when H3 nucleus was irradiated. X-ray analysis of a single crystal of **11** proved this assignment to be true.[20]

The presence of an additional stereocenter in the adducts made determination of stereochemistry of **6** and **7** less simple. As we mentioned above, X-ray crystallographic analysis revealed the major isomer of **7** (**7-A**) to have a 2*S**,3*R**,2α*S** configuration. The second and third major isomers (**7-C** and **7-D**) were, however, extremely difficult to isolate in diastereomerically pure

(17) Crystallographic data for **7-A** have been deposited with the Cambridge Crystallographic Data Centre.

(18) Crystallographic data for *syn*-**1a** have been deposited with the Cambridge Crystallographic Data Centre (deposit no. 114923).

(19) Corey, E. J.; Kim, S. S. *J. Am. Chem. Soc.* **1990**, *112*, 4976.

(20) Crystallographic data for **11** have been deposited with the Cambridge Crystallographic Data Centre (deposit no. 114924).

Table 2. Michael/Aldol Tandem Addition to Acrylates with Selenolates or Alkoxides

entry	R^1X	R	solvent	*T* (°C)	time (h)	product	yield (%)[a]	syn/anti[b]
1	PhSe	Ph	ether	−50	7	**2a**	97	87/13
2	PhSe	*p*-ClC_6H_4	ether	−78 to rt	15	**2b**	78	78/22
3	PhSe	1-Nap[c]	ether	−78 to rt	15	**2c**	64	80/20
4	PhSe	1-Nap[c]	CH_2Cl_2	−50	7	**2c**	65	84/16
5	PhSe	2-Nap[c]	ether	−78 to rt	15	**2d**	64	84/16
6	PhSe	PhCH=CH−	ether	−50	7	**2e**	69	57/43
7	PhSe	C_5H_{11}	ether	−50	7	**2f**	46	58/42
8	PhO	Ph	CH_2Cl_2	−78 to rt	15	**3a**	0	
9	$PhCH_2O$	Ph	CH_2Cl_2	−78 to rt	15	**3b**	0	

[a] Isolated yield. [b] Determined by HPLC analyses. [c] 1-Nap = 1-naphthyl; 2-Nap = 2-naphthyl.

Scheme 4

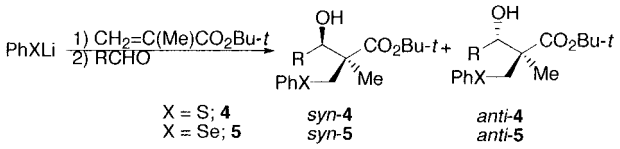


Table 3. Michael/Aldol Tandem Addition to *tert*-Butyl Methacrylates

entry	R	X	solvent	*T* (°C)	time (h)	product	yield (%)[a]	syn/anti[b]
1	Ph	S	CH_2Cl_2	−15	7	**4a**	61	87/13
2	Ph	S	CH_2Cl_2	−78 to rt	15	**4a**	67	83/17
3	*p*-ClC_6H_4	S	CH_2Cl_2	−78 to rt	15	**4b**	55	89/11
4	1-Nap[c]	S	CH_2Cl_2	−78 to rt	15	**4c**	39	80/20
5	C_5H_{11}	S	CH_2Cl_2	−78 to rt	15	**4d**	trace	-
6	Ph	Se	ether	−78 to rt	15	**5**	69	75/25

[a] Isolated yield. [b] Determined by HPLC analyses. [c] 1-Nap = 1-naphthyl.

Scheme 5

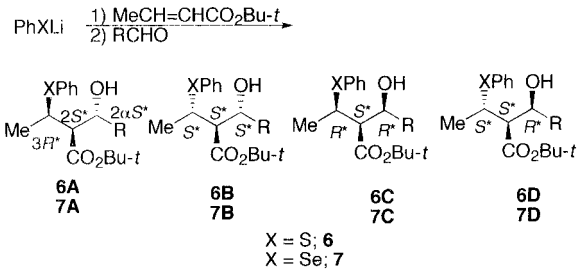


Table 4. Michael/Aldol Tandem Addition to *tert*-butyl Crotonates

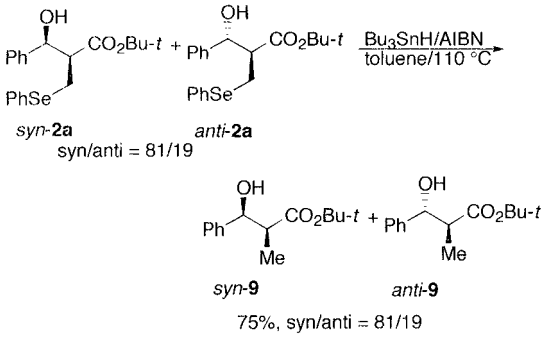
entry	R	X	solvent	*T* (°C)	time (h)	product	yield (%)[a]	A/B/C/D[b]
1	Ph	S	CH_2Cl_2	−50	7	**6a**	trace	
2	Ph	S	CH_2Cl_2	−78 to rt	15	**6a**	55	53/1/45/1
3	1-Nap[c]	S	CH_2Cl_2	−78 to rt	15	**6b**	60	75/1/15/9
4	C_5H_{11}	S	CH_2Cl_2	−78 to rt	15	**6c**	trace	
5	Ph	Se	ether	−78 to rt	15	**7**	62	56/1/42/1

[a] Isolated yield. [b] Determined by HPLC analyses. [c] 1-Nap = 1-naphthyl.

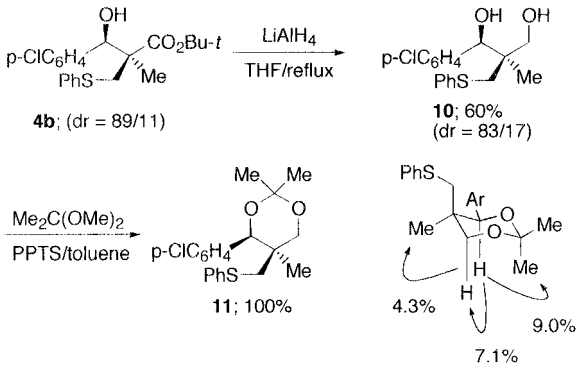
form. Only the HPLC method separated them in small amounts, not enough for this study to perform further transformation. Instead, we used a mixture of diastereomers of **6** or **7** for the following study.

First of all, we attempted to remove the phenylseleno group at C3 position in **7**. This transformation reduced

Scheme 6



Scheme 7

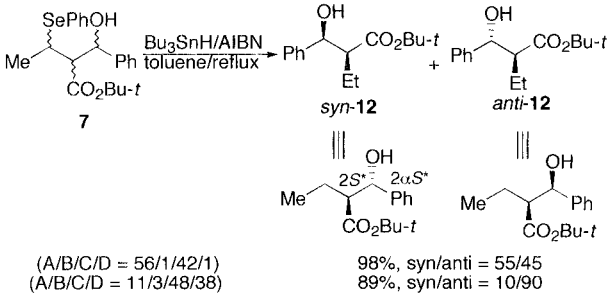


the number of diastereomers of **7** to two. We had in hand two kinds of mixtures of the four diastereoisomers of **7**, **A**/**B**/**C**/**D** = 56/1/42/1 for one and 11/3/48/38 for the other.[21] Treatment of the former mixture (**A**/**B**/**C**/**D** = 56/1/42/1) with Bu_3SnH gave a diastereomeric mixture of **12**, whose ratio was 55/45. The same transformation of the latter mixture (**A**/**B**/**C**/**D** = 11/3/48/38) afforded **12** in a ratio of 10/90 (Scheme 8). These results indicate that diastereomers **A** and **B** have identical configurations between C2 and C2α and so do **C** and **D**. Comparing the X-ray result of **7-A**, we concluded that diastereomers **A** and **B** are syn-aldols and diastereomers **C** and **D** anti-aldols.

We then tried to remove the stereogenic center of the hydroxyl carbon C2α of **7**. All the experiments to convert **7** into the corresponding ketone, however, failed due to the lability of the phenylseleno group under oxidative conditions. That each of the diastereoisomers of **6a** and **7** shared almost the same NMR patterns suggested the stereochemistry of **6a-A** and **7-A** to be identical. Instead, we used thio derivative **6a** for further transformation (Scheme 9). The results are summarized in Table 5.

(21) This mixture was prepared through the reaction with magnesium selenophenolate or thiophenolate which showed anti-aldol selectivity under the same reaction conditions. Details on this matter will be reported elsewhere.

Scheme 8



Scheme 9

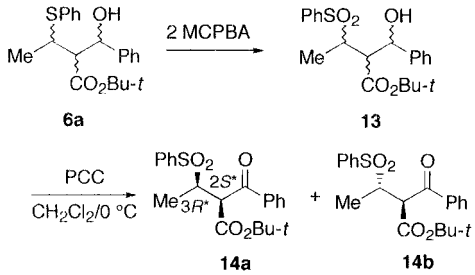


Table 5. Oxidation of 6a

entry	ratio of **6a** (A/B/C/D)[b]	**13**; yield[a] (%)	A/B/C/D[b]	**14**; yield[a] (%)	**14a**/**14b**[b]
1	53/1/45/1	96	50/1/48/1	75	96/4
2	5/1/32/62	68	3/1/32/64	100	34/66
3	100/0/0/0	100	100/0/0/0	94	100/0

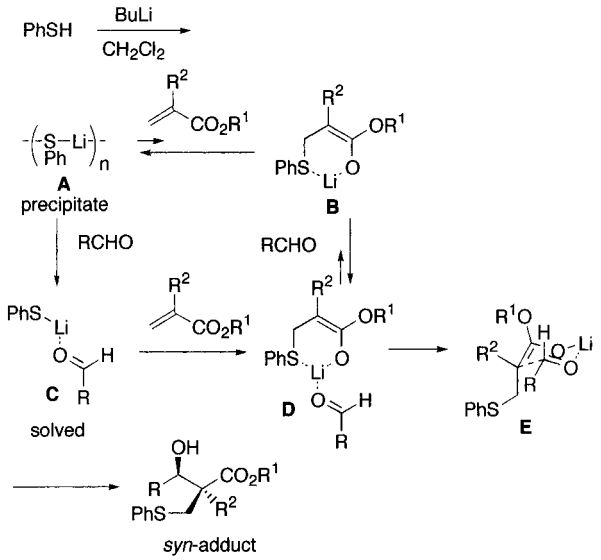
[a] Isolated yield. [b] Determined by HPLC analyses.

The oxidation started with two kinds of mixtures of four diastereoisomers of **6a**, their respective ratios **A**/**B**/**C**/**D** = 53/1/45/1 and 5/1/32/62.[21] The phenylthio group was first oxidized to sulfone **13**, and the subsequent PCC oxidation resulted in ketone **14** in good yields. The diastereomeric ratios of the mixtures were kept up within the experimental error during the oxidation (Table 5, entries 1 and 2). Diastereomerically pure **6a-A** was converted into pure **14a** in a quantitative yield (Table 5, entry 3).[22] The configuration of **14a** was thus determined to be 2*S**,3*R**. The former mixture afforded **14a** and **14b** at the ratio of 96/4, and the latter did **14** at the ratio of 34/66. These results suggest that **6a-C** has the same configuration at C2 and C3 as does **6a-A**, and that opposite to it is the configuration of **6a-B** and **6a-D**. Consequently, the configurations of all the four diastereomers of **6a** were determined to be 2*S**,3*R**,2α*S** for **A**, 2*S**,3*S**,2α*S** for **B**, 2*S**,3*R**,2α*R** for **C**, and 2*S**,3*S**,2α*R** for **D**.

Stereochemical Course of the Reaction. The tandem addition to acrylates and methacrylates provides syn-aldol adducts selectively, and the reaction mechanism is assumed to be the way as it follows (Scheme 10).

Thiophenol in CH_2Cl_2 is deprotonated with butyllithium. It gives lithium thiophenolate in a white precipitate, which should exist in polymeric form such as $(PhSLi)_n$ **A**. The concentration of the thiophenolate anion in the solution phase is very low. In the NMR spectrum of the heterogeneous mixture of PhSLi in CD_2Cl_2, almost no signals were observed in aromatic region. Addition of

Scheme 10



acrylate to the mixture seemingly solved a very small part of the precipitate but left most of PhSLi where it was. This was supported by the NMR experiments in which no significant peaks except those came from acrylate were detected in the NMR spectrum of the heterogeneous mixture of the acrylate and thiolate in CD_2Cl_2. Thus, active enolate intermediate **B** in the solution phase is very low of concentration. On the other hand, addition of aldehyde to the initial mixture of PhSLi gave a similar result; a small part of the precipitate seemed to be solved, but the mixture itself stayed as it was. No significant change in the chemical shift at the formyl proton was observed in the NMR spectrum of the mixture of PhSLi-aldehyde in CD_2Cl_2.

A dramatic change, however, occurred when both aldehyde and acrylate were added to the mixture: the whole precipitate rapidly solved (less than 5 min at −50 °C), and the reaction mixture turned into a homogeneous pale yellow solution. From this observation it is gathered that the two carbonyl groups cooperatively coordinate to the lithium cation so that they may form acrylate−thiolate−aldehyde complex **D** soluble in CH_2Cl_2. Complex **D** may be formed through a nucleophilic attack at acrylate by the sulfur atom in complex **C**, or through coordination of the aldehyde to complex **B**, but it is not clear that which pathway is favored.[23] Subsequent structural changes convert complex **D** to complex **E**, which affords the aldol adduct syn-selectively.

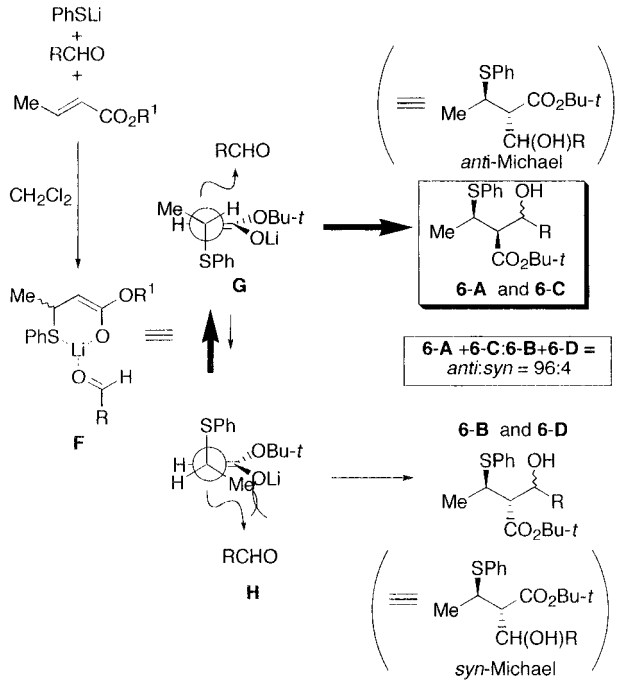
When the same reaction is carried out in THF, a more coordinative solvent, formation of complex **D** is impossible because a large amount of THF molecules predominantly coordinate to the lithium cation, which loses its Lewis acidity, and in fact, the yield and the selectivity became poor (see Table 1, entry 10). Consequently, we can conclude that the Lewis acidity of naked lithium cation is the key driving force to let the reaction proceed successfully.[24] For this reason, it requires lithium cation

(22) No epimerization were observed during the transformation to **14**; no trace amount of **14b** was observed in the ^1H NMR spectrum of the crude reaction mixture starting from diastereomerically pure **6a-A** (Table 6, entry 3).

(23) Reversed order of the addition, i.e., the aldehyde first then the acrylate, sometimes gave better yields of the tandem adducts, but the stereoselectivity was almost identical.

(24) Grieco, P. A.; Kaufman, M. D.; Daeuble, J. F.; Saito, N. *J. Am. Chem. Soc.* **1996**, *118*, 2095. Grieco, P. A.; Beck, J. P.; Handy, S. T.; Saito, N.; Daeuble, J. F. *Tetrahedron Lett.* **1994**, *35*, 6783. Grieco, P. A.; Nunes, J. J.; Gaul, M. D. *J. Am. Chem. Soc.* **1990**, *112*, 4595 and references therein.

Scheme 11



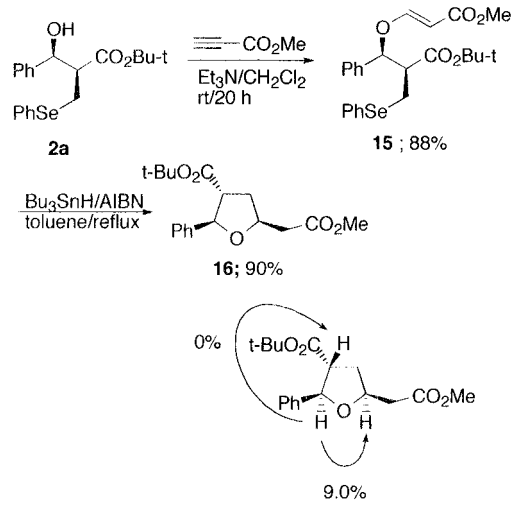
as the countercation and CH_2Cl_2 as the solvent for the present tandem reaction to be successfully performed.

In regard to the reaction with crotonates, on the other hand, the syn-aldol selectivity disappeared and the anti-Michael selectivity dominated instead. Although the reason this switching of selectivity is not yet made clear, this anti-Michael selectivity is plausibly explained as Scheme 11 shows. The first stage of the reaction is the formation of three-component complex **F**, which is achieved in a similar way that forms complex **D** in Scheme 10. Complex **F** further changes into two conformational isomers **G** and **H**. As with conformer **G**, due to the steric bias brought by the phenylthio group, the aldehyde preferentially attacks the top face of the enolate giving an anti-Michael adduct. As with conformer **H**, the aldehyde comes from the bottom face to give a syn-Michael adduct. Conformer **G** should be a more favorable conformation than conformer **H** in that the latter causes a steric repulsion to arise between the methyl group and the oxygen atom in the enolate unit. As a result, the aldol reaction proceeds through the attack of the aldehyde at the top face of conformer **G**, giving an anti-Michael product selectively. Similar observations have been reported in the Michael addition of thiolate anion to acrylate esters and nitroolefins.[25,26]

Stereoselective Preparation of Tetrahydrofuran. To see the applicability of the present method, stereoselective preparation of trisubstituted tetrahydrofuran was examined (Scheme 12).[27]

Seleno-tandem adduct **2a** was O-alkenylated with methyl propiolate and gave **15** in a good yield.[28] Compound **15** was then put under the standard radical cyclization conditions (Bu_3SnH/AIBN at 110 °C) and yielded tetrahydrofuran **16** as the sole isomer. The cyclization took place with a high stereoselectivity as had been reported in the previous literature.[29−31] The stereochemistry of **16** was determined by the NOE experiment in which the 2,3-trans-3,5-trans configuration was elucidated because H5 and H3 signals were enhanced by 9.0% and 0.0%, respectively, when the H2 nucleus was irradiated. This application proves the utility of the tandem reaction in organic synthesis.

Scheme 12



Conclusion

We have presented a new method of the Michael/aldol tandem reaction among lithium thiolate (or selenolate), acrylate, and aldehyde, all of which were condensed in one pot, giving good yields of β-hydroxy-α-phenylthio- or β-hydroxy-α-phenylselenoalkyl esters with a high stereoselectivity. The reaction progress and selectivity largely depend on the choice of solvents, countercations, and the ester parts of acrylate. Since the present reaction procedure readily creates multifunctional molecules besides a new carbon−carbon bond, this will open up a new method in organic synthesis. Further application and mechanistic investigation on the reaction is now underway in our laboratory.

Experimental Section

General. All ^1H and ^{13}C NMR spectra were measured in $CDCl_3$ and recorded on JEOL EX-270 (270 MHz for ^1H and 67.5 MHz for ^{13}C) spectrometer. All the reactions in this paper were performed under nitrogen atmosphere. Solvents used in the reaction described here were dried over appropriate drying agents (K for THF, Na for ether and toluene, and CaH_2 for all other solvents) and distilled under nitrogen before use. Aldehydes were purified by distillation. Methyl and ethyl acrylate,

(25) Miyata, O.; Shinada, T.; Ninomiya, I.; Naito, T.; Date, T.; Okamura, K.; Inagaki, S. *J. Org. Chem.* **1991**, *56*, 6556.

(26) Kamimura, A.; Ono, N. *J. Chem. Soc., Chem. Commun.* **1988**, 1278. Kamimura, A.; Ono, N. *Tetrahedron Lett.* **1989**, *30*, 731. Kamimura, A.; Sasatani, H.; Hashimoto, T.; Kawai, T.; Hori, K.; Ono, N. *J. Org. Chem.* **1990**, *55*, 2437. Hori, K.; Higuchi, S.; Kamimura, A. *J. Org. Chem.* **1990**, *55*, 5900.

(27) Reviews for tetrahydrofuran synthesis: Harmange, J.-C.; Figadère, B. *Tetrahedron: Asymmetry* **1993**, *4*, 1711. Postema, M. H. D. *Tetrahedron* **1992**, *48*, 8545. Boivin, T. L. B. *Tetrahedron* **1987**, *43*, 3309.

(28) Winterfeldt, E.; Preuss, H. *Chem. Ber.* **1966**, *99*, 450.

(29) Curran, D. P.; Porter, N. A.; Giese, B. *Stereochemistry of Radical Reactions*; VCH: Weinheim, 1996.

(30) Frauenrath, H.; Runsink, J. *J. Org. Chem.* **1987**, *52*, 2707. Lindermann, R. J.; Godfrey, A. *J. Am. Chem. Soc.* **1988**, *110*, 6249. Hoppe, D.; Krämer, T.; Erdbrügger, C. F.; Egert, E. *Tetrahedron Lett.* **1989**, *30*, 1233. Hopkins, M. H.; Overman, L. E.; Rishton, G. M. *J. Am. Chem. Soc.* **1991**, *113*, 5354; Brown, M. J.; Harrison, T.; Herrinton, P. M.; Hopkins, M. H.; Hutchinson, K. D.; Mishra, P.; Overman, L. E. *Ibid.* **1991**, *113*, 5365. Brown, M. J.; Harrison, T.; Overman, L. E. *Ibid.* **1991**, *113*, 5378.

(31) Lee, E.; Park, C. M. *J. Chem. Soc., Chem. Commun.* **1994**, 293.

which were purchased from Nakalai Tesque, *tert*-butyl acrylate, Bu_3SnH, thiophenol, and diphenyldiselenide, which were from Aldrich, were used without further purification. Other α,β-unsaturated esters were prepared from corresponding acyl chloride and alcohols or acid and isobutene.

Michael/Aldol Tandem Reaction to α,β-Unsaturated Esters with Thiolate Anion. Preparation of *tert*-Butyl 3-Hydroxy-3-phenyl-2-(phenylthiomethyl)propionate (*syn*-1d). General Procedure. To a solution of thiophenol (0.242 g, 2.20 mmol) in CH_2Cl_2 (2 mL) was added butyllithium in hexanes (1.1 M, 2 mL, 2.2 mmol) at −78 °C, and lithium thiophenolate precipitated as white solid. To the heterogeneous mixture were added *tert*-butyl acrylate (0.256 g, 2.00 mmol) and benzaldehyde (0.212 g, 2.00 mmol) at −78 °C; the reaction mixture turned to a pale yellow solution, which was maintained at −50 °C for 7 h. Aqueous HCl (1M, 5 mL) was added, and the mixture was extracted with ethyl acetate (3 × 30 mL). The organic phase was washed with brine (10 mL) and dried over Na_2SO_4. After filtration and removal of the solvent in vacuo, crude product was purified with flash chromatography (silica gel/hexanes−ether 20:1 then 3:1 v/v) and the desired tandem product **1d** was obtained in 80% yield (0.548 g, 1.59 mmol) as pale yellow oil. HPLC analysis indicated disatereomeric ratio was 92/8: ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.14−7.33 (m, 10 H), 4.97 (d, 1 H, J = 5.6 Hz), 3.21 (d, 1 H, J = 5.6 Hz), 3.20 (d, 1 H, J = 8.3 Hz), 2.86 (td, 1 H, J = 5.6, 7.6 Hz), 2.83−2.93 (br, 1 H), 1.33 (s, 9 H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 172.4, 140.8, 135.8, 129.2, 128.8, 128.3, 127.9, 126.3, 126.0, 81.8, 74.2, 53.2, 31.2, 27.9; IR 3100−3700, 1720 cm^{-1}. Anal. Calcd for $C_{20}H_{24}O_3S$: C, 69.74; H, 7.02. Found: C, 69.35; H, 7.08.

The two diastereomers of **1a** and **1b** were separated by careful flash column chromatography (hexanes−ether 5:1 v/v).

Methyl 3-hydroxy-3-phenyl-2-(phenylthiomethyl)propionate (*syn*-1a): mp 59 °C (from hexane−CH_2Cl_2); ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.11−7.37 (m, 10 H), 5.04 (dd, 1 H, J = 2.6, 5.0 Hz), 3.57 (s, 3 H), 3.26 (dd, 1 H, J = 9.2, 13.9 Hz), 3.20 (dd, 1 H, J = 4.6, 13.9 Hz), 2.97 (td, 1 H, J = 5.0, 9.3 Hz), 2.78 (d, 1 H, J = 3.0 Hz); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 173.4, 140.7, 135.3, 129.3, 128.9, 128.4, 128.0, 126.2, 125.9, 74.0, 53.0, 51.9, 30.7; IR 3200−3700, 1730 cm^{-1}. Anal. Calcd for $C_{17}H_{18}O_3S$: C, 67.52; H, 6.00. Found: C, 67.24; H, 6.01.

Methyl 3-hydroxy-3-phenyl-2-(phenylthiomethyl)propionate (*anti*-1a): colorless oil; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.18−7.37 (m, 10 H), 4.96 (t, 1 H, J = 5.6 Hz), 3.63 (s, 3H), 3.05 (dd, 1 H, J = 3.6, 10.2 Hz), 3.00 (1H, dd, J = 6.6, 10.2 Hz), 2.94−3.03 (m, 1 H), 2.95 (d, 1 H, J = 5.6 Hz); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 173.8, 141.0, 134.9, 130.1, 128.9, 128.6, 128.2, 126.6, 126.0, 74.2, 52.6, 52.0, 33.2; IR 3200−3700, 1730 cm^{-1}. Anal. Calcd for $C_{17}H_{18}O_3S$: C, 67.52; H, 6.00. Found: C, 67.22; H, 5.98.

***tert*-Butyl 3-hydroxy-2-methyl-3-phenyl-2-(phenylthiomethyl)propionate (*syn*-4a):** colorless oil; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.14−7.38 (m, 10 H), 4.96 (s, 1 H), 3.45 (d, 1 H, J = 12.2 Hz), 3.27 (br, 1 H), 3.08 (d, 1 H, J = 12.5 Hz), 1.43 (s, 9 H), 1.18 (s, 3 H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 174.1, 139.6, 137.9, 129.2, 128.8, 127.9, 127.8, 127.6, 125.9, 82.1, 52.9, 41.6, 39.8, 27.9, 18.6; IR 3100−3700, 1720 cm^{-1}. Anal. Calcd for $C_{21}H_{26}O_3S$: C, 70.36; H, 7.31. Found: C, 70.94; H, 7.04.

***tert*-Butyl (2*S**,3*R**)-2-((*S**)-hydroxyphenylmethyl)-3-phenylthiobutanoate (6a-A):** mp 101−102 °C; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.22−7.60 (m, 10 H), 5.20 (dd, 1 H, J = 3.6, 8.9 Hz), 3.79 (dq, 1 H, J = 4.6, 7.3 Hz), 2.95 (dd, 1 H, J = 4.3, 8.9 Hz), 2.63 (d, 1 H, J = 3.6 Hz), 1.43 (d, 3 H, J = 7.3 Hz), 1.23 (s, 9 H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 170.2, 141.8, 136.0, 131.6, 128.9, 128.3, 128.1, 127.1, 126.8, 81.4, 73.4, 59.0, 43.6, 27.7, 21.0; IR 3300−3600, 1720 cm^{-1}. Anal. Calcd for $C_{21}H_{26}O_3S$: C, 70.36; H, 7.31. Found: C, 70.37; H, 7.51.

***tert*-Butyl (2*S**,3*R**)-2-((*R**)-hydroxyphenylmethyl)-3-phenylthiobutanoate (6a-C):** colorless oil; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.20−7.60 (m, 10 H), 5.03 (d, 1 H, J = 5.0 Hz), 3.43 (qd, 1 H, J = 6.9, 8.9 Hz), 2.76 (dd, 1 H, J = 5.0, 8.9 Hz), 1.43 (d, 3 H, J = 7.3 Hz), 1.30 (s, 9 H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 172.8, 141.8, 134.0, 133.0, 128.8, 128.2, 127.5, 126.8, 125.8, 82.2, 72.2, 58.0, 43.5, 27.8, 20.0; IR 3300−3600, 1720 cm^{-1}. Anal. Calcd for $C_{21}H_{26}O_3S$: C, 70.36; H, 7.31. Found: C, 70.13; H, 7.53.

Michael/Aldol Tandem Reaction to α,β-Unsaturated Esters with Selenolate Anion. Preparation of *tert*-Butyl 3-Hydroxy-3-phenyl-2-(phenylselenomethyl)-propionate (*syn*-2a). General procedure. Methyllithium in ether (1.1 M, 3.0 mL, 3.3 mmol) was added to a solution of diphenyldiselenide (1.03 g, 3.30 mmol) in ether (6 mL) at room temperature until the yellow color of the diselenide disappeared. The colorless solution was maintained at the same temperature for 30 min and then cooled to −50 °C. Benzaldehyde (0.350 g, 3.30 mmol) was added to the mixture, and the resulting mixture was allowed to stir for 10 min. The reaction mixture turned to homogeneous pale yellow solution. To the solution was added *tert*-butyl acrylate (0.385 g, 3.00 mmol), and the reaction mixture was allowed to stir at −50 °C for 7 h. Aqueous HCl (1 M, 10 mL) was added, and the resulting mixture was extracted with ethyl acetate (3 × 30 mL). The organic phases were combined and dried over Na_2SO_4. After filtration and removal of the solvent in vacuo, crude product was purified with flash chromatography (silica gel/hexanes−ether 20:1 then 3:1 v/v) to give desired tandem product **2a** in 97% yield (1.126 g, 2.88 mmol) as a pale yellow oil. HPLC analysis indicated disatereomeric ratio was 87/13: ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.19−7.36 (m, 10 H), 4.98 (d, 1 H, J = 5.6 Hz), 3.14 (d, 1 H, J = 6.3 Hz), 3.14 (d, 1 H, J = 7.6 Hz), 2.96 (dt, 1 H, J = 5.6, 7.6 Hz), 2.8−3.0 (br, 1 H), 1.35 (s, 9 H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 172.6, 140.8, 132.3, 129.0, 128.4, 128.3, 127.9, 126.8, 126.3, 81.9, 74.6, 54.0, 27.9, 24.4; IR 3620−3100, 1725 cm^{-1}. Anal. Calcd for $C_{20}H_{24}O_3Se$: C, 61.38; H, 6.18. Found: C, 61.26; H, 6.13.

***tert*-Butyl 3-hydroxy-2-methyl-3-phenyl-2-(phenylselenomethyl)propionate (*syn*-5):** colorless oil; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.20−7.48 (m, 10 H), 4.98 (s, 1 H), 3.40 (d, 1 H, J = 12.2 Hz), 2.93 (d, 1 H, J = 12.5 Hz), 1.45 (s, 9 H), 1.18 (s, 3 H). ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 174.8, 139.7, 132.5, 129.3, 129.2, 128.2, 128.1, 127.9, 126.9, 82.5, 78.8, 53.2, 33.7, 28.2, 20.6; IR 3100−3650, 1720 cm^{-1}. Anal. Calcd for $C_{21}H_{26}O_3Se$: C, 62.22; H, 6.46. Found: C, 62.35; H, 6.51.

***tert*-Butyl (2*S**,3*R**)-2-((*S**)-hydroxyphenylmethyl)-3-phenylselenobutanoate (7-A):** mp 111 °C; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.27−7.64 (m, 10 H), 5.21 (dd, 1 H, J = 4.0, 9.2 Hz), 3.75 (dq, 1 H, J = 4.0, 7.3 Hz), 2.89 (dd, 1 H, J = 4.0, 9.2 Hz), 2.43 (1 H, d, J = 4.0 Hz), 1.58 (d, 3 H, J = 7.3 Hz), 1.23 (s, 9 H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 170.4, 141.8, 134.1, 129.0, 128.4, 128.2, 128.1, 127.3, 127.1, 81.6, 74.4, 59.9, 39.9, 27.8, 22.5; IR 3300−3600, 1720 cm^{-1}. Anal. Calcd for $C_{21}H_{26}O_3Se$: C, 62.22; H, 6.46. Found: C, 62.05; H, 6.39.

***tert*-Butyl (2*S**,3*R**)-2-((*R**)-hydroxyphenylmethyl)-3-phenylseleno-butanoate (7-C):** pale yellow oil; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.23−7.64 (m, 10 H), 5.06 (d, 1 H, J = 5.6 Hz), 3.6−3.8 (br, 1 H), 3.30 (dq, 1 H, J = 6.9, 7.3 Hz), 2.80 (dd, 1 H, J = 5.9, 7.9 Hz), 1.55 (d, 3 H, J = 6.9 Hz), 1.35 (s, 9 H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 172.7, 141.7, 135.1, 128.9, 128.7, 128.2, 127.6, 127.5, 126.0, 82.3, 73.0, 58.9, 38.4, 27.9, 21.5; IR 3300−3600, 1720 cm^{-1}. Anal. Calcd for $C_{21}H_{26}O_3Se$: C, 62.22; H, 6.46. Found: C, 62.23; H, 6.67.

***tert*-Butyl (2*S**,3*S**)-2-((*S**)-hydroxyphenylmethyl)-3-phenylseleno-butanoate (7-D):.** pale yellow oil; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.47−7.51 (m, 2 H), 7.15−7.27 (m, 8 H), 5.24 (d, 1 H, J = 4.3 Hz), 3.6−3.7 (br, 1 H), 3.45 (dq, 1 H, J = 6.9, 7.3 Hz), 2.72 (dd, 1 H, J = 5.0, 8.6 Hz), 1.40 (d, 3 H, J = 6.9 Hz), 1.19 (s, 9 H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 172.8, 141.9, 135.5, 129.0, 128.4, 128.2, 127.9, 127.4, 125.7, 82.2, 73.1, 58.2, 37.9, 27.8, 20.4; IR 3300−3600, 1720 cm^{-1}.

Reductive Removal of Phenylseleno Group from Tandem Adduct 2a. Preparation of *tert*-Butyl 3-Hydroxy-2-methyl-3-phenylpropionate 9. A solution of **2a** (0.232 g, 0.5 mmol, 81/19 mixture of *syn*-**2a** and *anti*-**2a**), Bu_3SnH (0.291 g, 1.00 mmol), and AIBN (0.016 g, 0.10 mmol) in toluene (2 mL) was heated at 110 °C for 2.5 h. The resulting mixture was subjected to flash chromatography (silica gel/hexane ether 10:1 then 3:1 v/v) to give **9**[12,19] as a colorless oil in 75% yield (0.116 g, 0.380 mmol). RP HPLC analysis showed diastereo-

meric ratio of **9** was 81/19. Anal. Calcd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53. Found: C, 70.71; H, 8.61.

For *syn*-**9** (major isomer): ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.26−7.35 (m, 5 H), 5.03 (d, 1 H, J = 4.3 Hz), 3.13 (br, 1 H), 2.69 (dq, 1 H, J = 4.3, 7.3 Hz), 1.40 (s, 9 H), 1.11 (d, 3 H, J = 7.3 Hz); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 175.3, 141.5, 128.1, 127.4, 126.1, 81.1, 73.8, 47.0, 27.9, 11.0.

For *anti*-**9** (minor isomer): ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.26−7.35 (m, 5 H), 4.70 (d, 1 H, J = 7.9 Hz), 3.22 (br, 1 H), 2.71 (quint, 1 H, J = 7.3 Hz), 1.44 (s, 9 H), 1.01 (d, 3 H, J = 7.3 Hz); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 175.3, 141.8, 128.3, 127.8, 126.6, 81.2, 73.8, 47.7, 27.9, 14.9.

Conversion of **7** to **12** was carried out in the same way.

***tert*-Butyl 2-(hydroxyphenylmethyl)butanonate (*syn*-12):** colorless oil; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.16−8.06 (m, 5 H), 4.81 (d, 1 H, J = 6.9 Hz), 2.47 (ddd, 1 H, J = 1.3, 2.0, 7.3 Hz), 1.40−1.69 (m, 2 H), 1.47 (s, 9 H), 0.83 (dt, 1 H, J = 2.0, 7.3 Hz); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 174.2, 141.8, 128.1, 127.5, 126.4, 80.9, 74.4, 55.2, 27.9, 23.6, 11.9. Anal. Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 71.86; H, 9.25.

***tert*-Butyl 2-(hydroxyphenylmethyl)butanonate (*anti*-12):** colorless oil; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.24−7.65 (m, 5 H), 4.76 (t, 1 H, J = 6.6 Hz), 3.12 (d, 1 H, J = 6.3 Hz), 2.58 (ddd, 1 H, J = 5.3, 7.3, 9.3 Hz), 1.40−1.69 (m, 2 H), 1.40 (s, 9 H), 0.91 (t, 3 H, J = 7.3 Hz); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 174.6, 142.3, 128.2, 127.5, 126.3, 81.0, 74.9, 55.1, 27.9, 22.8, 11.4. Anal. Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 71.51; H, 9.18.

Reduction of 4b. To a suspension of $LiAlH_4$ (0.284 g, 7.48 mmol) in THF (10 mL) was added **4b** (0.733 g, 1.87 mmol) at room temperature over 30 min, and the resulting mixture was heated at refluxing temperature for 1 h. Diluted HCl (1 M, 10 mL) was slowly added to the ice-cooled reaction mixture, and THF in the biphasic mixture was removed with a rotary evaporator. The water phase was then extracted with EtOAc (3 × 30 mL), and the organic phase was combined and dried over Na_2SO_4. After removal of Na_2SO_4 and solvent, crude product **10** was purified by flash chromatography (silica gel/hexanes−ethyl acetate 10:1 then 5:1 v/v): pale yellow oil; 60% yield (0.323 g, 1.12 mmol); ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.11−7.31 (m, 5 H), 4.81 (s, 1 H), 3.73 (d, 1 H, J = 11.5 Hz), 3.45 (d, 1 H, J = 10.9 Hz), 3.32 (d, 1 H, J = 12.2 Hz), 2.78 (d, 1 H, J = 12.5 Hz), 1.50−1.60 (br, 2 H), 0.80 (s, 3 H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 138.9, 133.5, 129.4, 129.0, 128.9, 128.1, 126.2, 77.5, 68.8, 43.5, 37.6, 18.5; IR 3300−3700 cm^{-1}. Anal. Calcd for $C_{17}H_{19}ClO_2S$: C, 63.25; H, 5.93. Found: C, 63.11; H, 6.30.

Acetalization of 10. A solution of **10** (0.131 g, 4.80 mmol), 2,2-dimethoxypropane (0.50 g, 4.8 mmol), and PPTS (0.025 g, 0.10 mmol) in toluene (2 mL) was heated under refluxing conditions for 1 h. The reaction mixture was then concentrated in vacuo, and the crude product was subjected to flash chromatography (silica gel/hexanes−ethyl acetate 10:1 v/v) to give **11** as a white solid in 100% yield (0.152 g, 4.80 mmol): mp 96−97 °C; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.10−7.35 (m, 9 H), 4.81 (s, 1 H), 4.04 (d, 1 H, J = 12.2 Hz), 3.66 (dd, 1 H, J = 1.7, 12.2 Hz), 3.58 (d, 1 H, J = 12.5 Hz), 2.50 (dd, 1 H, J = 1.7, 12.9 Hz), 1.53 (s, 6 H), 0.82 (s, 3 H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 136.5, 129.7, 129.6, 129.5, 129.4, 128.7, 128.6, 126.4, 100.0, 80.2, 67.4, 38.5, 36.5, 30.4, 19.7, 19.4. Anal. Calcd for $C_{20}H_{23}ClO_2S$: C, 66.19; H, 6.39. Found: C, 66.47; H, 6.69.

Oxidation of 6a. A solution of **6a** (**A**:**B**:**C**:**D** = 53:1:45:1, 0.257 g, 0.710 mmol) and *m*-CPBA (80%, 0.270 g, 1.56 mmol) in chloroform (10 mL) was heated to refluxing temperature for 5 h. The reaction mixture was condensed under reduced pressure, and the crude solution in chloroform was subjected into flash chromatography (silica gel/hexanes−ethyl acetate 5:1 then 3:1 v/v) to give **13** in 96% yield (0.266 g, 0.680 mmol). The diastereomertic ratio of **13** was 50:1:48:1. Oxidation carried out with diastereomerically pure **6a-A** gave a single isomer of **13** as viscous oil.

***tert*-Butyl (2*S**,3*R**)-2-((*S**)-hydroxyphenylmethyl)-3-benzenesulfonylbutanoate (13a):** ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.27−7.96 (m, 10 H), 5.04 (dd, 1 H, J = 3.0, 8.6 Hz), 3.73 (td, 1 H, J = 4.6, 7.3 Hz), 3.32 (dd, 1 H, J = 4.6, 8.6 Hz), (d, 1 H, J = 7.3 Hz), 1.18 (s, 9 H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 169.8, 141.1, 137.5, 133.9, 129.1, 128.9, 128.2, 128.0, 127.1, 81.8, 72.2, 60.4, 52.7, 27.4, 12.2; IR 3150−3700, 1730 cm^{-1}. Anal. Calcd for $C_{21}H_{26}O_5S$: C, 64.59; H, 6.71. Found: C, 64.50; H, 6.93.

***tert*-Butyl (2*S**,3*R**)-3-Benzenesulfonyl-2-benzoylbutanoate 14a.** To a solution of **13** (diastereomeric ratio = 50:1:48:1, 0.21 g, 0.54 mmol) in CH_2Cl_2 was added PCC (0.182 g, 0.80 mmol), and the resulting suspension was allowed to stir for 4 h at ambient temperature. The supernatant of the reaction mixture was subjected to column chromatography (silica gel−hexane ether 10:1 then 1:1 v/v) to give **14** in 75% yield (0.158 g, 0.410 mmol): white crystal; diastereomertic ratio of **14** was 96:4; mp 76−77 °C; ^{1}H NMR (270 MHz, $CDCl_3$) δ 8.06 (d, 2 H, J = 7.3 Hz), 7.94 (d, 2 H, J = 7.3 Hz), 7.48−7.70 (m, 6 H), 4.93 (d, 1 H, J = 8.9 Hz), 4.20 (td, 1 H, J = 7.3, 8.9 Hz), 1.37 (s, 9 H), 1.22 (d, 3 H, J = 7.3 Hz); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 192.9, 165.8, 137.2, 136.3, 133.9, 129.1, 129.0, 128.9, 128.7, 128.6, 82.9, 59.4, 52.7, 27.5, 12.3; IR 1740, 1730 cm^{-1}. Anal. Calcd for $C_{21}H_{24}O_5S$: C, 64.93; H, 6.23. Found: C, 64.67; H, 6.34.

***tert*-Butyl (2*S**,3*S**)-3-benzenesulfonyl-2-benzoylbutanoate (14b):** mp 100−101 °C; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.45−8.01 (m, 10 H), 4.90 (d, 1 H, J = 8.3 Hz), 4.32 (td, 1 H, J = 7.9, 7.3 Hz), 1.44 (d, 3 H, J = 7.3 Hz), 1.34 (s, 9H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 191.3, 165.4, 137.6, 135.7, 133.9, 133.7, 129.1, 129.0, 128.9, 128.6, 83.4, 58.4, 54.0, 27.6, 11.7; IR 1740, 1680 cm^{-1}.

Conjugate Addition of 2a to Methyl Propiolate. To a solution of **2a** (0.587 g, 1.50 mmol) in CH_2Cl_2 (10 mL) were added Et_3N (0.22 mL, 1.6 mmol) and methyl propiolate (0.504 g, 6.00 mmol), and the reaction mixture was allowed to stand at room temperature for 12 h. After removal of solvent, the residue was subjected to flash chromatography (silica gel/hexanes−ether 20:1 v/v) to give **15** as colorless oil in 88% yield (0.630 g): ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.41 (1 H, d, J = 12.2 Hz), 7.16−7.38 (m, 10 H), 5.22 (d, 1 H, J = 12.5 Hz), 5.06 (d, 1 H, J = 7.6 Hz), 3.63 (s, 3 H), 3.25 (d, 1 H, J = 4.0, 12.2 Hz), 3.17 (dd, 1 H, J = 9.9, 11.9 Hz), 3.06 (ddd, 1 H, J = 4.0, 7.6, 9.6 Hz), 1.25 (s, 9 H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 169.8, 167.7, 160.7, 136.8, 132.7, 132.4, 129.0, 128.8, 128.6, 126.9, 126.9, 98.9, 84.7, 81.8, 54.2, 51.0, 27.7, 24.9; IR 2980, 1730, 1540 cm^{-1}. Anal. Calcd for $C_{24}H_{28}O_5Se$: C, 60.63; H, 5.94. Found:C, 60.62; H, 5.96.

Preparation of 2,3-*trans*-3,5-*trans*-3-(*tert*-Butoxycarbonyl)-5-(methoxycarbonylmethyl)-2-phenyltetrahydrofuran (16). A mixture of **14** (0.452 g, 0.950 mmol), Bu_3SnH (0.395 g, 1.20 mmol), and AIBN (0.035 g, 0.20 mmol) in toluene (10 mL) was heated under refluxing conditions for 3 h. After the mixture was cooled, solvent was removed and the residue was subjected into flash chromatography (silica gel/hexanes−ethyl acetate 10:1 v/v) to give **16** as colorless oil in 90% yield (0.229 g, 0.900 mmol): ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.28−7.37 (m, 5 H), 5.00 (d, 1 H, 7.6 Hz), 4.54 (quint, 1 H, J = 6.9 Hz), 3.72 (s, 3 H), 2.89 (ddd, 1 H, J = 6.3, 7.6, 13.5 Hz), 2.80 (dd, 1 H, J = 6.9, 15.2 Hz), 2.64 (dd, 1 H, J = 6.3, 15.5 Hz), 2.49 (quint, 1 H, J = 6.6 Hz), 2.00 (ddd, 1 H, J = 7.6, 9.6, 12.9 Hz), 1.43 (s, 9 H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 172.1, 171.1, 140.9, 128.9, 127.6, 125.8, 83.7, 75.2, 53.0, 51.6, 40.1, 35.5, 27.9, 27.3; IR 2950, 1710 cm^{-1}. Anal. Calcd for $C_{18}H_{24}O_5$: C, 67.48; H, 7.55. Found: C, 67.24; H, 7.79.

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Supporting Information Available: Physical data for compounds **1b**,**c**,**f** −**l**, **4b**,**c**, **6b**, and **2b**−**f**, spectroscopic charts for compounds **2f**, **4a**, and **14b**, and ORTEP drawings for structures *syn*-**1a**, **7-A**, and **11**. This material is available free of charge via the Internet at http://pubs.acs.org.

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