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Tetrahedron: *Asymmetry* 19 (2008) 401–406

An asymmetric synthesis of esters and γ-lactones with simultaneous construction of vicinal stereogenic carbons at the α- and β-position starting from optically active 1-chlorovinyl *p*-tolyl sulfoxides

Shimpei Sugiyama, Nobuhito Nakaya and Tsuyoshi Satoh*

Department of Chemistry, Faculty of Science, Tokyo University of Science, Ichigaya-funagawara-machi, Shinjuku-ku, Tokyo 162-0826, Japan

Received 8 January 2008; accepted 29 January 2008

Abstract—Treatment of optically active 1-chlorovinyl *p*-tolyl sulfoxides with two different substituents at the 2-position, which were synthesized from aldehydes or unsymmetrical ketones and (*R*)-(−)-chloromethyl *p*-tolyl sulfoxide in two or three steps, with the lithium enolate of carboxylic acid *tert*-butyl esters gave the adducts with substituents at the α- and β-position with high 1,3- and 1,4-chiral induction from the stereogenic sulfur center in high yields. The adducts were converted to optically active esters and γ-lactones having stereogenic centers at the α- and β-position in good to high yields. This procedure offers a new method for a synthesis of optically active carboxylic acid derivatives with stereogenic centers at the α- and β-position.

1. Introduction

Carboxylic acids and their derivatives are among the most important and fundamental compounds in organic and synthetic organic chemistry; innumerable studies with regard to the chemistry and synthesis of them have already been reported.[1] However, due to the importance of these compounds in organic chemistry, the development of new and practical synthetic methods is still eagerly sought.

The synthesis of optically active carboxylic acids and their derivatives is also one of the most important targets in synthetic organic chemistry.[2] Recently, highly enantio- and diastereoselective reactions for the construction of vicinal chiral carbon centers in one step have emerged as the most challenging topics. For example, asymmetric aldol-type reactions,[3] asymmetric Michael reactions,[4] and asymmetric Diels–Alder reactions[5] have been widely investigated. In addition, Uenishi et al.[6] reported a palladium-catalyzed asymmetric synthesis of esters or amino acid derivatives possessing vicinal stereogenic centers at the α- and β-position.

Recently, we reported a novel method for the asymmetric synthesis of esters and lactones with either a tertiary or a quaternary carbon at the β-position, from optically active 1-chlorovinyl *p*-tolyl sulfoxides, which were derived from aldehydes or unsymmetrical ketones in two or three steps,[7] and the lithium enolate of *tert*-butyl acetate.[8] We have also found that various lithium enolate of *tert*-butyl esters, such as *tert*-butyl propionate, reacted with the optically active 1-chlorovinyl *p*-tolyl sulfoxides, which were synthesized from symmetrical ketones, to afford various optically active adducts having a stereogenic center at the α-position in high enantiomeric excess (ee).[9]

Based on these results, it was expected that if the substituted *tert*-butyl acetate (R^3 = alkyl group; see Scheme 1) and optically active 1-chlorovinyl *p*-tolyl sulfoxides **3** having two different substituents at the 2-position, which were synthesized from aldehydes or unsymmetrical ketones **1** and optically active **2**, were used in this reaction, various optically active adducts **4** with 1,3- and 1,4-chiral induction from the stereogenic sulfur center could be synthesized. Furthermore, we anticipated that optically active adducts **4** could be converted to optically active γ-lactones **5** or esters **6** with vicinal stereogenic carbon centers at the α- and β-position (Scheme 1). Herein, we report the feasibility of this expectation as well as our results.

* Corresponding author. Tel.: +81 3 5228 8272; fax: +81 3 5261 4631; e-mail: tsatoh@rs.kagu.trus.ac.jp

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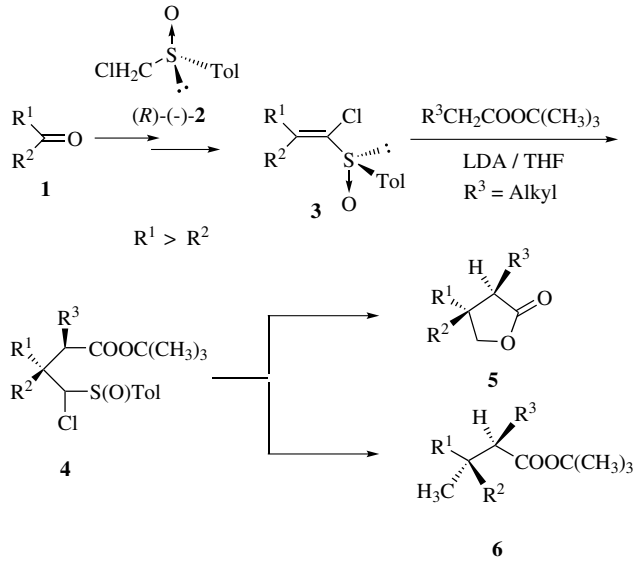
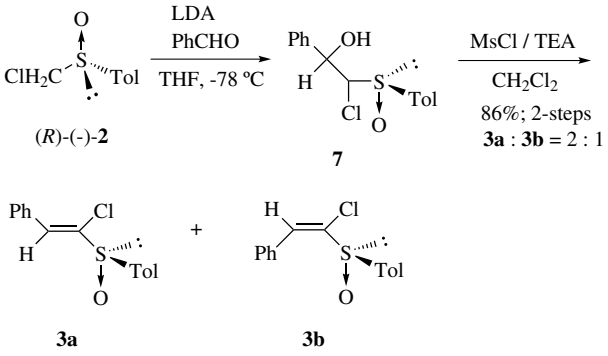
doi:10.1016/j.tetasy.2008.01.040



Scheme 1.

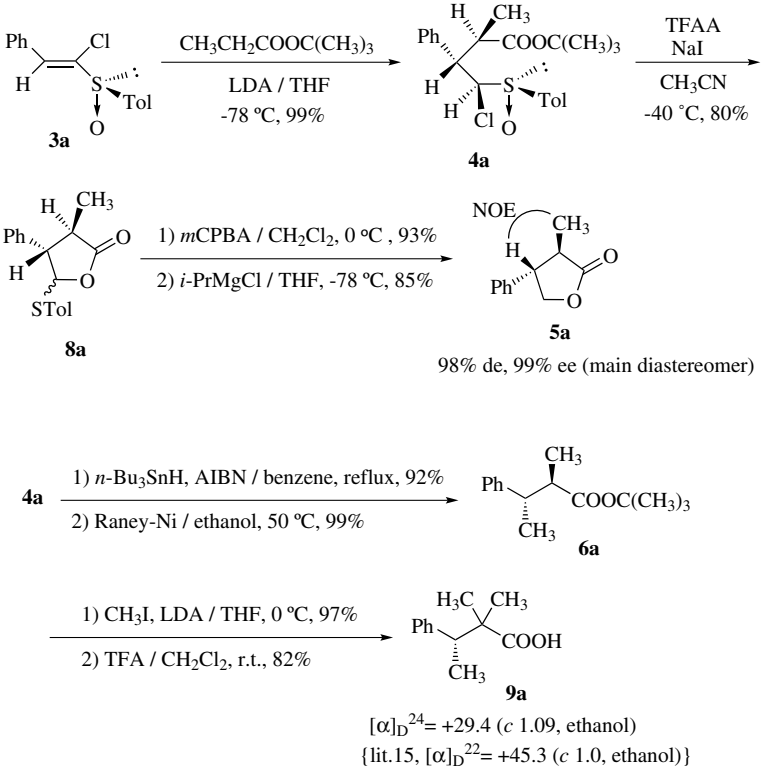
2. Results and discussion

For the substrates in this investigation, we synthesized optically active vinyl sulfoxides **3a** and **3b** from enantiomerically pure (*R*)-(−)-chloromethyl *p*-tolyl sulfoxide **2** and benzaldehyde.[10] Thus, **2** was treated with LDA in THF at −78 °C followed by benzaldehyde to give alcohol **7** as a mixture of two diastereomers in quantitative yield. Alcohol **7** was then treated with methanesulfonyl chloride with triethylamine (TEA) in CH_2Cl_2 at room temperature for 5 h to afford a 2:1 mixture of **3a** and **3b** in 86% overall yield from **2** (Scheme 2).



Scheme 2.

At first, 5 equiv of the lithium ester enolate of *tert*-butyl propionate was generated from *tert*-butyl propionate with LDA in THF at −78 °C (Scheme 3). To this solution was added 1-chlorovinyl *p*-tolyl sulfoxide (*Z*)-**3a**. The desired addition reaction took place within 5 min to afford adduct **4a** in a quantitative yield. Adduct **4a** has four stereogenic centers meaning that eight diastereomers could theoretically be produced. Interestingly, adduct **4a** was obtained as a single isomer. No other diastereomer was observed from a detailed inspection of the ^1H NMR spectra. This result implied that the addition reaction took place with high 1,2- 1,3-, and 1,4-asymmetric induction from the stereogenic sulfur center.



Scheme 3.

In order to determine the absolute stereochemistry of adduct **4a**, we first determined the relative stereochemistry of the two substituents at the α- and β-position (methyl and phenyl groups), as shown in Scheme 3. Thus, adduct **4a** was treated with trifluoroacetic anhydride (TFAA) in the presence of NaI in acetonitrile at −40 °C to give a mixture of two γ-lactones with a *p*-tolylsulfanyl group at the γ-position **8a** in 80% yield.[11] The sulfanyl group was oxidized, with *m*-chloroperbenzoic acid (*m*-CPBA) at 0 °C, to a sulfinyl group, and the sulfinylated lactone was treated with *i*-PrMgCl to give γ-lactone **5a** via a sulfoxide-magnesium exchange reaction[12] in 79% overall yield from **8a**.

The diastereomeric excess (de) of **5a** was confirmed to be 98% while the enantiomeric excess of the main diastereomer was measured to be 99% (ee) by using Chiralcel OD as a chiral stationary column. In order to determine the relative stereochemistry of the two substituents, the NOESY spectrum of **5a** was measured. From a detailed inspection of the spectra, we were able to determine that the relative stereochemistry of the two substituents was *trans*, as shown in Scheme 3.

Next, in order to determine the absolute configuration of the carbon bearing the phenyl group of **4a**, adduct **4a** was converted to the known carboxylic acid **9a** (see Scheme 3). Thus, the reduction of the chlorine atom in **4a** with Bu_3SnH[13] followed by reduction of the sulfinyl group with Raney-Ni[14] at 50 °C gave optically active ester **6a** in 91% overall yield from **4a**. The optically active ester **6a** was treated with excess LDA, followed by the addition of iodomethane in THF at 0 °C to give a dimethylated ester in quantitative yield. Finally, the dimethylated ester was treated with trifluoroacetic acid (TFA) in CH_2Cl_2 at room temperature to afford (3*R*)-2,2-dimethyl-3-phenylbutyric acid **9a** in good yield. Comparing the sign of the specific rotation of the product with that of the reported optically active **9a** [the sign of the specific rotation of (*R*)-**9a** was reported to be positive[15]], the absolute configuration of **9a** synthesized was unambiguously determined to be (*R*).

With regard to the absolute stereochemistry of the carbon bearing the chlorine atom of **4a**, we have already reported that an (*S*)-configuration is induced by the addition reaction of the lithium enolates of *tert*-butyl esters to 1-chlorovinyl *p*-tolyl sulfoxides having an (*R*)-sulfinyl group.[16] Based on the results mentioned above, adduct **4a** was determined to be (2*R*,3*R*,4*S*,S_R)-4-chloro-2-methyl-3-phenyl-4-(*p*-tolylsulfinyl)butylic acid *tert*-butyl ester, as shown in Scheme 3.

Previously, we reported a plausible transition state model for the addition reaction of the lithium enolate of *tert*-butyl acetate or its homologues to optically active 1-chlorovinyl *p*-tolyl sulfoxides **3** with 1,3-[8] or 1,4-[9] chiral induction from the stereogenic sulfur center. A plausible mechanism for the simultaneous construction of the vicinal stereogenic carbons mentioned above is proposed as shown in Figure 1. Thus, the lithium cation forms a five-membered chelate between the oxygen atom of the sulfoxide and the chlorine atom. In this event, the enolates were introduced to vinyl sulfoxide **3a** from the less hindered *si* face (Fig. 1). Treatment of the carboxylic acid esters with LDA in THF at low temperature was reported to give the *Z*-enolate.[17] While the real reason remains unknown at present, the *Z*-enolate of *tert*-butyl propionate could be placed, as shown in Figure 1, by chelation with the lithium cation and is introduced from the *si* face to afford adduct **4a** with 1,2-, 1,3-, and 1,4-chiral induction from the stereogenic sulfur center.

In a similar way, the addition reaction of *tert*-butyl propionate with vinyl sulfoxide **3b** gave the adduct **4b** in a quantitative yield as an inseparable mixture of two diastereomers with a ratio of 95:5 as judged from their ^{1}H NMR spectra. Adduct **4b** was converted to γ-lactones **5b** in the same way as described above in moderate overall yield. Again, the diastereomeric excess and enantiomeric excess of **5b** were confirmed to be 89% (de), and 99% (ee) of the main diastereomer by using Chiralcel OD as a chiral stationary column. In order to determine the stereochemistry of the main product, the NOESY spectrum of **5b** was measured. From a detailed inspection of the spectrum, we were able to determine that the relative stereochemistry of the two substituents was *cis* to each other, as shown in Scheme 4. The minor isomer was expected to be the epimer with respect to the α-position.

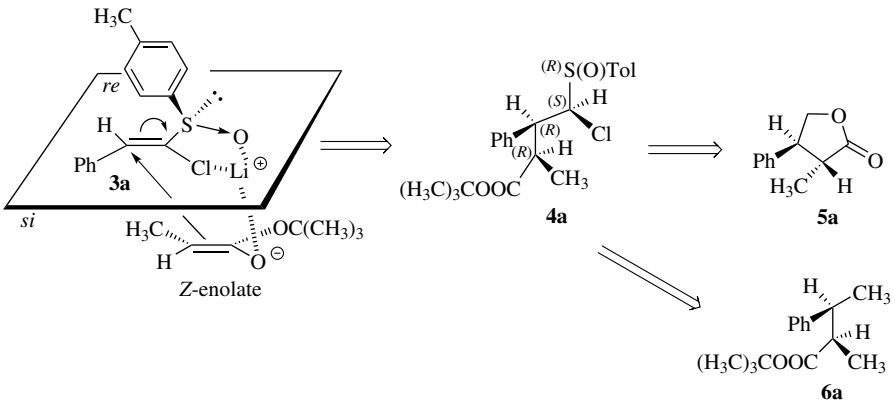
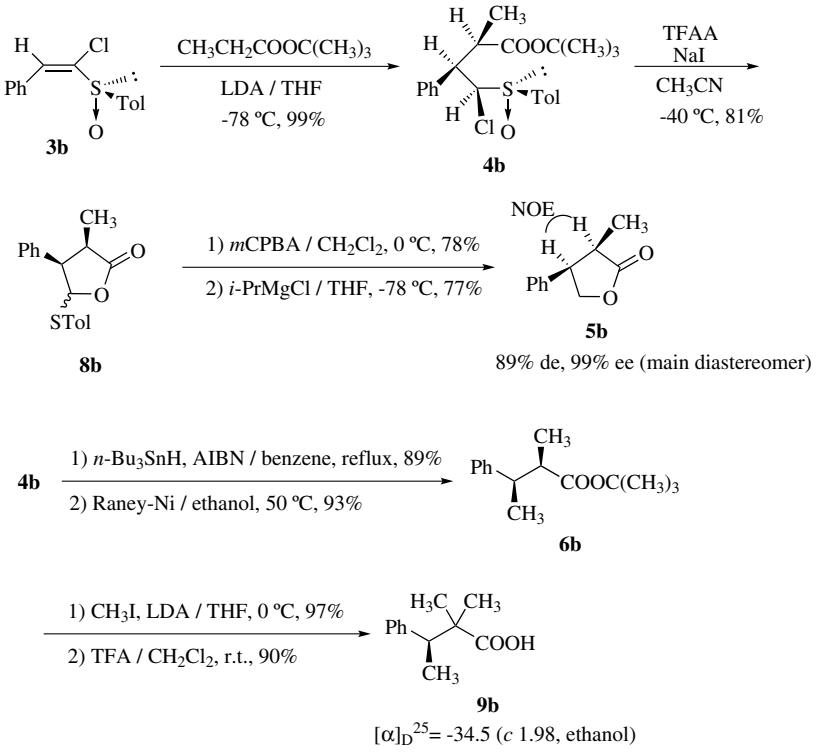
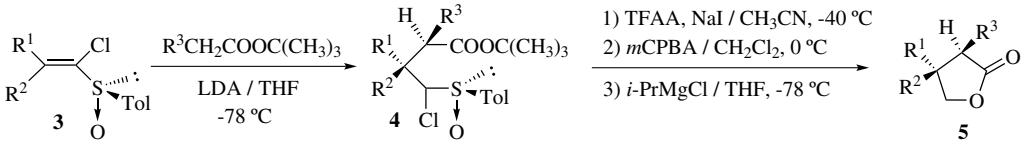


Figure 1.



Scheme 4.

Table 1. Asymmetric synthesis of γ-lactones having stereogenic centers at the α- and β-position of **5** from optically active 1-chlorovinyl *p*-tolyl sulfoxides **3**



Entry	Vinyl sulfoxide **3**			Adduct **4**			γ-Lactone **5**[a]			
		R^1	R^2		R^3	Yield (%)		Yield (%)	de (%)	ee[b] (%)
1	**3a**	Ph	H	**4c**	^{n}Bu	99	**5c**	70	99	99
2	**3b**	H	Ph	**4d**	^{n}Bu	99	**5d**	58	84	99
3	**3c**	$PhCH_2CH_2$	H	**4e**	CH_3	99	**5e**	67	61	99
4	**3d**	H	$PhCH_2CH_2$	**4f**	CH_3	99	**5f**	48	98	99
5	**3c**	$PhCH_2CH_2$	H	**4g**	^{n}Bu	99	**5g**	50	47	99
6	**3d**	H	$PhCH_2CH_2$	**4h**	^{n}Bu	99	**5h**	48	99	99
7	**3e**	$PhCH_2CH_2$	CH_3	**4i**	CH_3	90	**5i**	93	98	98
8	**3f**	CH_3	$PhCH_2CH_2$	**4j**	CH_3	93	**5j**	87	95	99
9	**3e**	$PhCH_2CH_2$	CH_3	**4k**	^{n}Bu	86	**5k**	65	97	99
10	**3f**	CH_3	$PhCH_2CH_2$	**4l**	^{n}Bu	83	**5l**	56	83	99

[a] Diastereomeric excess and enantiomeric excess were determined by HPLC using chiral stationary columns.
[b] Enantiomeric excess of the main diastereomer.

Furthermore, in order to determine the absolute configuration of the carbon bearing the phenyl group of γ-lactone **5b**, compound **4b** was converted to carboxylic acid **9b** in the same way as described above. As the sign of the specific rotation of the derived **9b** was negative, the absolute configuration of **9b** was unambiguously determined to be (*S*). Based on the results mentioned above, the absolute configuration of the adduct **4b** was determined to be (2*R*,3*S*,4*S*,S_R)-4-chloro-2-methyl-3-phenyl-4-(*p*-tolylsulfinyl)-butylic acid *tert*-butyl ester, as shown in Scheme 4.

Next, the generality of this reaction was examined and the results are summarized in Table 1. Benzaldehyde, 3-phenylpropanal, and 4-phenyl-2-butanone were selected as the starting aldehyde or ketone, and *tert*-butyl propionate and *tert*-butyl hexanoate were selected as the esters. As shown in Table 1, the conjugate addition reaction of the lithium enolate (generated from the ester with LDA in THF at −78 °C) to vinyl sulfoxides **3** gave adducts of esters **4** in high to quantitative yields. Adducts **4d**, **4e**, **4g**, and **4l** were obtained as an inseparable mixture of two diastereomers.

Adducts **4** were converted to γ-lactones **5** in the same manner as described above in moderate to good overall yields. The diastereomeric excess of all the γ-lactones **5** was determined to be 83–99% by using HPLC with Chiralcel OD, except for **5e** and **5g**. At present, the low diastereoselectivities of **5e** and **5g** are still unexplained. However, all of the enantiomeric excess of the γ-lactones **5** from both the main diastereomers and minor diastereomers was found to be excellent. From these results, it can be concluded that in these reactions, the facial selection of the 1-chlorovinyl *p*-tolyl sulfoxides is perfect; however, facial selection of the enolate of the esters is not good in some cases. It is also worthwhile noting (as shown in the entries 7–10) that the vicinal quaternary and tertiary carbon centers were constructed with high diastereo- and enantioselectivity by this method.[18]

3. Conclusion

In conclusion, we have reported an asymmetric synthesis of optically active carboxylic acid derivatives with simultaneous construction of vicinal stereogenic centers at the α- and β-position from (*R*)-(−)-chloromethyl *p*-tolyl sulfoxide as a source of chirality. Unfortunately, in some cases (**5e** and **5g**), the diastereoselectivity was not satisfactory; however, the method described above contributes to the synthesis of optically active esters having tertiary and/or quaternary carbon stereogenic centers at the α- and β-position.

Acknowledgment

This work was supported by a Grant-in-Aid for Scientific Research No. 19590018 from the Ministry of Education, Culture, Sports, Science and Technology, Japan, which is gratefully acknowledged.

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18. The synthesis of **5i** is reported as a representative example for this method. *tert*-Butyl 3-[chloro(*p*-tolylsulfinyl)methyl]-2,3-dimethyl-5-phenylpentanoate **4i**: *tert*-Butyl propionate (0.12 mL; 0.80 mmol) was added to a solution of LDA (0.80 mmol) in 2.5 mL of dry THF at −78 °C with stirring under an argon atmosphere. The solution was stirred for 10 min, and a solution of **3e**[8] (50 mg; 0.16 mmol) in THF (0.6 mL) was added. The reaction mixture was stirred for 10 min, and the reaction was quenched by adding saturated aq NH_4Cl. The whole was extracted with $CHCl_3$ and the organic layer was dried over $MgSO_4$. The solvent was

evaporated and the residue was purified by silica gel column chromatography (hexane/AcOEt = 3:1) to give adduct **4i** (63.5 mg; 90%) as a colorless oil; IR (neat) 2979, 1728 (CO), 1598, 1495, 1456, 1368, 1256, 1217, 1160, 1058 (SO) cm^{-1}; ^1H NMR δ 1.29 (3H, d, $J = 7.2$ Hz), 1.43 (9H, s), 1.53 (3H, s), 1.96–2.07 (1H, m), 2.17–2.28 (1H, m), 2.44 (3H, s), 2.85 (2H, double quintet, $J = 13.1$, 5.0 Hz), 3.16 (1H, q, $J = 7.2$ Hz), 4.91 (1H, s), 7.19–7.35 (7H, m), 7.75 (2H, d, $J = 8.3$ Hz). MS *m/z* (%) 448 (M^+, trace), 431 (6), 375 (17), 255 (3), 253 (11), 217 (23), 199 (8), 171 (13), 143 (57), 140 (100), 139 (24), 91 (91). Calcd for $C_{25}H_{33}O_3ClS$: M, 448.1839. Found; *m/z* 448.1825. $[\alpha]_D^{27} = -50.9$ (*c* 1.77, EtOH). 3,4-Dimethyl-4-(2-phenylethyl)tetrahydrofuran-2-one **5i**: A suspension of NaI (137.4 mg; 0.92 mmol) in 3.2 mL of acetonitrile was stirred for 10 min at −40 °C. TFAA (0.13 mL; 0.92 mmol) was added dropwise to the suspension of NaI with stirring at −40 °C and the suspension was stirred for 10 min. Adduct **4i** (82.3 mg; 0.18 mmol) in 0.5 mL of acetonitrile was added dropwise to the suspension of NaI and TFAA at −40 °C with stirring for 10 min. The reaction was quenched by adding saturated aq $NaHCO_3$ followed by saturated aq Na_2SO_3. The whole was extracted with $CHCl_3$. The organic layer was washed with saturated aq $NaHCO_3$ and dried over $MgSO_4$. The solvent was removed in vacuo and the residue was purified by silica gel column chromatography (hexane/AcOEt = 3:1) to give γ-tolylsulfanyl γ-lactone as a colorless oil; IR (neat) 3026, 2978, 2923, 1771 (CO), 1602, 1495, 1455, 1388, 1334, 1254, 1184, 1165, 1117, 964 cm^{-1}. *m*-CPBA (49.5 mg; 0.22 mmol) was added to a solution of the sulfanyl-lactone in 3.6 mL of CH_2Cl_2 at 0 °C with stirring. The solution was stirred for 20 min, and the reaction was quenched by adding saturated aq Na_2SO_3 and saturated aq $NaHCO_3$. The whole was extracted with CH_2Cl_2. The organic layer was washed with saturated aq $NaHCO_3$ and dried over $MgSO_4$. The solvent was evaporated and the residue was purified by silica gel column chromatography (hexane/AcOEt = 2:1) to give a γ-tolylsulfinyl γ-lactone as a colorless oil; IR (neat) 2927, 1791 (CO), 1598, 1495, 1455, 1390, 1330, 1152, 1084, 1041 (SO), 1015 cm^{-1}. ^iPrMgCl (2.0 mol/L in THF; 0.27 mL, 0.54 mmol) was added dropwise to a solution of the resultant sulfinyl-lactone in 3.6 mL of dry THF at −78 °C with stirring under an argon atmosphere. The solution was stirred for 15 min at −78 °C, and the reaction was quenched by adding saturated aq NH_4Cl. The whole was extracted with $CHCl_3$. The solvent was removed in vacuo and the residue was purified by silica gel column chromatography (hexane/AcOEt = 3:1) to afford **5i** (37.3 mg; 93% in three steps) as a colorless oil; IR (neat) 3062, 3027, 2977, 1773 (CO), 1603, 1497, 1455, 1390, 1368, 1289, 1124, 1096, 1042, 1009 cm^{-1}; ^1H NMR δ 1.09 (3H, s), 1.14 (3H, d, $J = 7.3$ Hz), 1.67–1.78 (1H, m), 1.83–1.93 (1H, m), 2.40 (1H, q, $J = 7.2$ Hz), 2.48–2.58 (1H, m), 2.65–2.75 (1H, m), 3.95 (2H, s), 7.16–7.33 (5H, m). MS *m/z* (%) 218 (M^+, 72) 187 (31), 171 (7), 157 (7), 143 (7), 131 (9), 113 (47), 104 (55), 91 (100). Calcd for $C_{14}H_{18}O_2$: M, 218.1306. Found; *m/z* 218.1309. $[\alpha]_D^{26} = -11.0$ (*c* 0.93, EtOH).