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An asymmetric synthesis of carboxylic acid derivatives, including lactic acid and α-amino acid derivatives, from optically active 1-chlorovinyl *p*-tolyl sulfoxides and ester lithium enolates with creation of chirality at the α-position

Masahiro Kido, Shimpei Sugiyama and Tsuyoshi Satoh*

Department of Chemistry, Faculty of Science, Tokyo University of Science, Ichigaya-Funagawara-Machi, Shinjuku-ku, Tokyo 162-0826, Japan

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Abstract—Treatment of optically active 1-chlorovinyl *p*-tolyl sulfoxides, which were synthesized from symmetrical ketones or methyl formate and (*R*)-(−)-chloromethyl *p*-tolyl sulfoxide in three steps, with lithium enolate of carboxylic acid *tert*-butyl esters gave optically active adducts having a substituent (alkyl, alkoxy, or dibenzylamino group) at the α-position with high 1,4-chiral induction from the sulfur chiral center. The adducts were converted to optically active esters, lactic acid, and α-amino acid derivatives having a chiral center at the α-position. When this addition reaction was carried out with an ester enolate generated from excess carboxylic acid *tert*-butyl ester with LDA in the presence of HMPA, the diastereomer of the adduct was obtained. By using the two reaction conditions for the generation of the ester enolate, a new method for asymmetric synthesis of both enantiomers of carboxylic acid derivatives having a substituent at the α-position from the one chiral source, (*R*)-(−)-chloromethyl *p*-tolyl sulfoxide, was achieved.

1. Introduction

Carboxylic acids,[1] including lactic acid and α-amino acid derivatives,[2] are one of the most important and fundamental compounds in organic, bioorganic, and synthetic organic chemistry. Innumerable studies on the chemistry and synthesis of carboxylic acids and their derivatives have already been reported; however in view of the importance of these compounds in organic chemistry, development of new and practical synthetic methods is still eagerly awaited. In addition, construction of a carbon stereogenic center at the α- or β-position of carboxylic acid derivatives is quite an important aspect of chemistry, because optically active compounds are most important in the science of drugs, biologically active compounds, and life. Control of the stereochemistry of the chiral carbon of carboxylic acids and esters at the α-position is now extensively studied. For example, the asymmetric aldol-type reactions[3] and Myers asymmetric alkylation[4] of the α-position of carbonyl compounds are well known.

In the previous studies, we have found that various lithium enolate of *tert*-butyl esters, such as *tert*-butyl propionate, reacted with 1-chlorovinyl *p*-tolyl sulfoxides, which were synthesized from symmetrical ketones, gave adducts of the esters having a carbon chiral center at the α-position in high yields.[5] The adducts have three chiral centers and in a theoretical sense, four diastereomers should be produced. However, in the above-mentioned reactions we obtained only single isomer of the adduct.

From this result, it was expected that, if α-substituted acetate and optically active 1-chlorovinyl *p*-tolyl sulfoxide having the same two substituents at the 2-position **3**, which was synthesized from symmetrical ketones **1** and (*R*)-(−)-chloromethyl *p*-tolyl sulfoxide **2**, were used in this reaction, various optically active adducts of ester **4** with 1,4-chiral induction from the sulfur chiral center could be synthesized. Furthermore, we anticipated that if α-alkoxy acetate and α-dialkylamino acetate were used as the nucleophiles, a new asymmetric synthesis of lactic acid derivatives **4**

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

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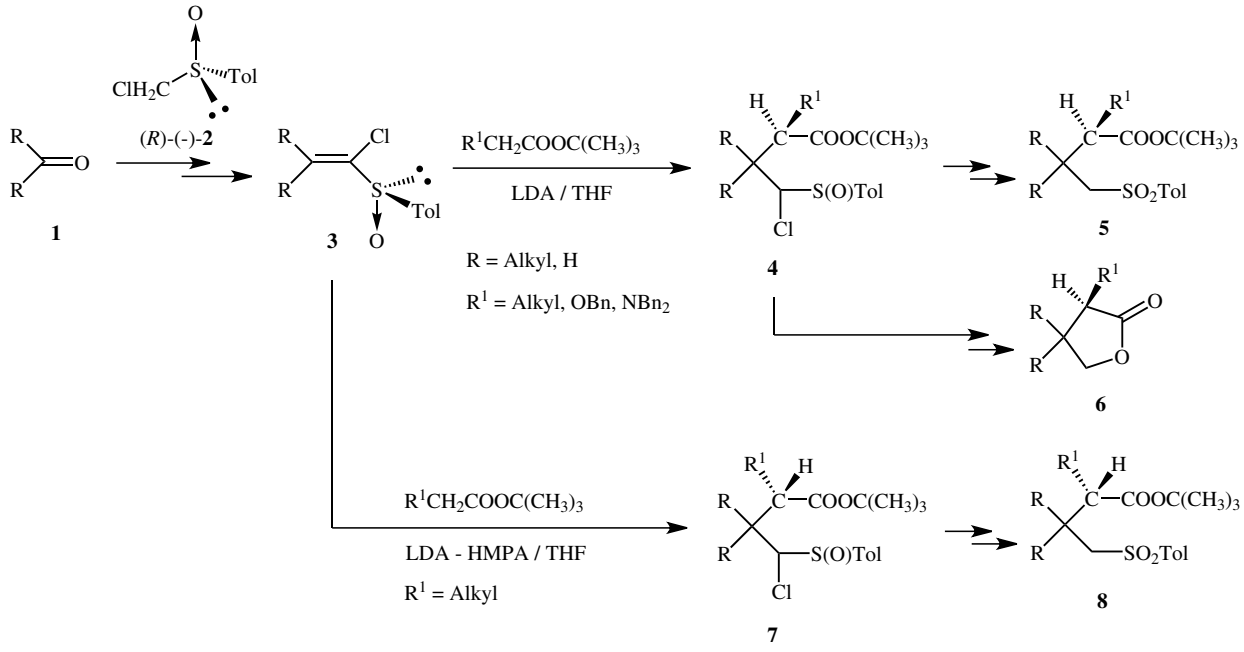


Scheme 1.

($R^1 = OH$) and α-amino acid derivatives **4** ($R^1 = NH_2$) could be achieved. Adducts **4** were expected to be converted to γ-sulfonyl esters **5** and lactones **6** (Scheme 1).

Some of these expected reactions have already been investigated, and we have previously communicated a novel asymmetric synthesis of both enantiomers of optically active adducts of esters **4** and **7** (R = alkyl) having a carbon chiral center at the α-position (Scheme 1).[6] We report herein, in detail, a study on the asymmetric synthesis of α-substituted carboxylic acid derivatives and, as an application of this method, the asymmetric synthesis of lactic acid derivatives and α-amino acid derivatives.

2. Results and discussion

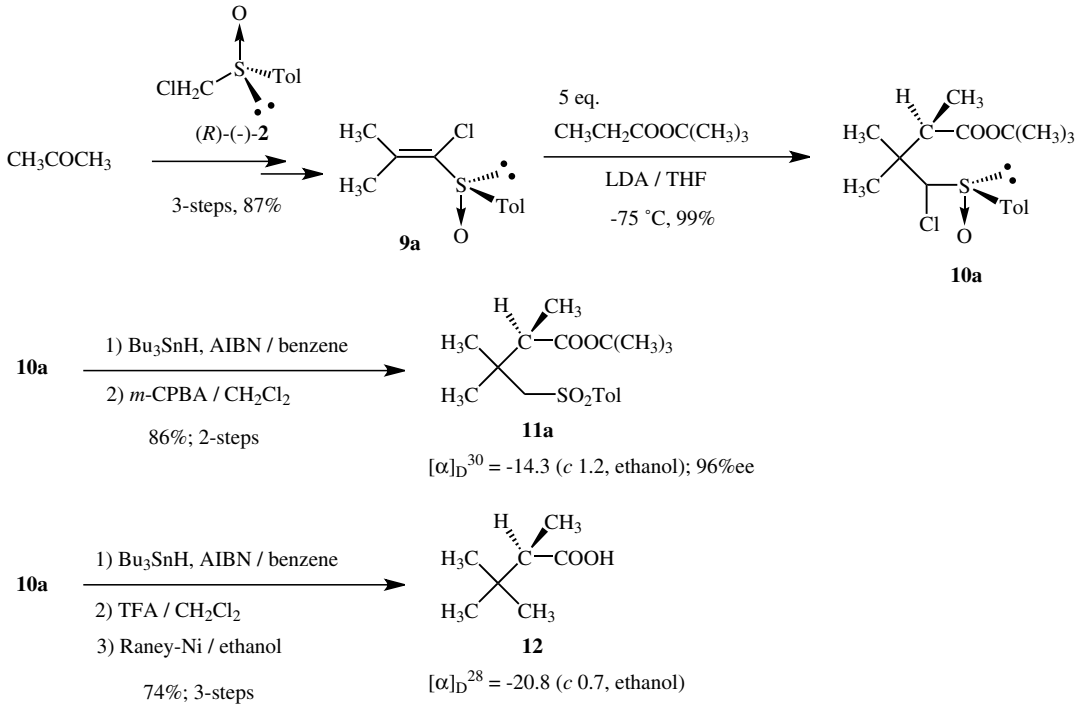
2.1. Synthesis of optically active 1-chlorovinyl *p*-tolyl sulfoxides from symmetrical ketones and reaction with the lithium enolate of α-alkylated *tert*-butyl acetate

A representative example is reported as follows (Scheme 2). First, 1-chlorovinyl *p*-tolyl sulfoxide **9a** was synthesized from acetone and (*R*)-(−)-chloromethyl *p*-tolyl sulfoxide **2**[7] in three steps in 87% overall yield. The lithium enolate of *tert*-butyl propionate (5 equiv) was generated from *tert*-butyl propionate with LDA in THF at −75 °C and to this reaction mixture was added a THF solution of 1-chlorovinyl *p*-tolyl sulfoxide **9a**. The addition reaction was found to be instantaneous and adduct **10a** was obtained within one minute in 99% yield. When less than 5 equiv of the lithium enolate of *tert*-butyl propionate was used, the reaction was not complete. Quite interestingly, although adduct **10a** has three stereogenic centers, only a single isomer was obtained according to its ^1H NMR spectrum. This result indicated that the stereochemistry of both the carbons bearing the chlorine and the methyl group was induced from the sulfur chiral center.

In order to eliminate two stereogenic centers (the carbon bearing a chlorine atom and the sulfinyl group), **10a** was first treated with Bu_3SnH under radical conditions (reduction of the chlorine atom). The sulfinyl group of the product was oxidized with *m*-chloroperbenzoic acid (*m*-CPBA) to give sulfone **11a** in high overall yield. The enantiomeric excess of sulfone **11a** was determined to be 96% by HPLC using Chiralpak AD (hexane–*i*-PrOH = 20:1) as a chiral stationary column.

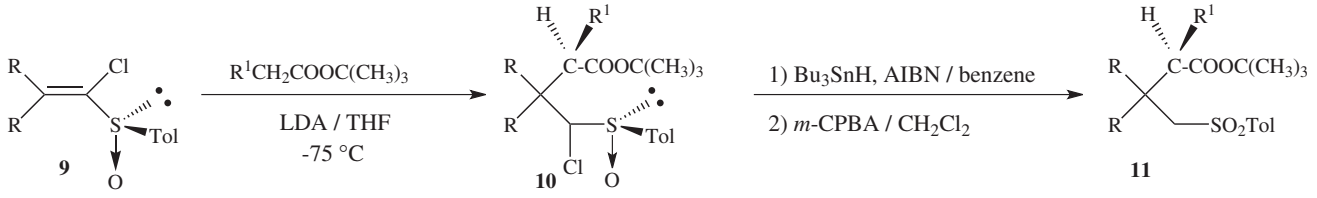
In order to determine the absolute configuration of the carbon bearing the methyl group, **10a** was converted to known carboxylic acid **12**. Thus, the chlorine atom in **10a** was reduced with Bu_3SnH and the *tert*-butyl ester was converted to a carboxylic acid with trifluoroacetic acid in dichloromethane. Finally, the sulfinyl group was reduced with Raney-Ni to give 2,3,3-trimethylbutyric acid **12**. As the sign of specific rotation of (*S*)-**12** was reported to be plus,[8] the absolute configuration of the synthesized **12**, which has a minus sign for the specific rotation, was determined to be (*R*).

Next, the generality of this reaction was examined and the results are summarized in Table 1. Acetone, cyclohexanone, and cyclopentadecanone were selected for the starting ketones and *tert*-butyl propionate, *tert*-butyl butyrate and *tert*-butyl hexanoate were selected as the esters. As shown in Table 1, the addition reaction of the lithium enolate (generated from the esters with LDA in THF at −75 °C) to the vinyl sulfoxides **9** gave adducts **10** in high yields, except in one case (entry 7). Reduction of the chlorine atom in **10** followed by oxidation of the sulfinyl group with *m*-CPBA afforded sulfone **11** in high overall yield. The enantiomeric excess of all sulfones **11** were determined to



Scheme 2.

Table 1. Asymmetric synthesis of carboxylic acid *tert*-butyl esters having an alkyl group at the α-position **11** from optically active 1-chlorovinyl *p*-tolyl sulfoxides **9**



Entry	Vinyl sulfoxide **9**		Adduct **10**[a]			Sulfone **11**			
	R	R		R^1	Yield (%)		Yield (%)	ee[b] (%)	$[\alpha]_D$[c]
1	**9b**	–$(CH_2)_5$–	**10b**	CH_3	99	**11b**	87	97	$[\alpha]_D^{26} = -5.3$ (*c* 1.8)
2	**9c**	–$(CH_2)_{14}$–	**10c**	CH_3	95	**11c**	82	97	$[\alpha]_D^{24} = -4.3$ (*c* 0.9)
3	**9a**	CH_3 CH_3	**10d**	CH_3CH_2	96	**11d**	91	93	$[\alpha]_D^{26} = -3.0$ (*c* 1.7)
4	**9b**	–$(CH_2)_5$–	**10e**	CH_3CH_2	96	**11e**	91	99	$[\alpha]_D^{26} = -4.9$ (*c* 1.8)
5	**9c**	–$(CH_2)_{14}$–	**10f**	CH_3CH_2	82	**11f**	81	97	$[\alpha]_D^{26} = -1.7$ (*c* 0.9)
6	**9a**	CH_3 CH_3	**10g**	n-C_4H_9	99	**11g**	81	96	$[\alpha]_D^{28} = -0.5$ (*c* 2.8)
7	**9c**	–$(CH_2)_{14}$–	**10h**	n-C_4H_9	71	**11h**	80	97	$[\alpha]_D^{27} = -1.9$ (*c* 0.9)

[a] All the adducts were observed as a single isomer determined from their ^{1}H NMR spectra.
[b] The enantiomeric excess was determined by HPLC using Chiralpak AD.
[c] The specific rotation was determined in ethanol.

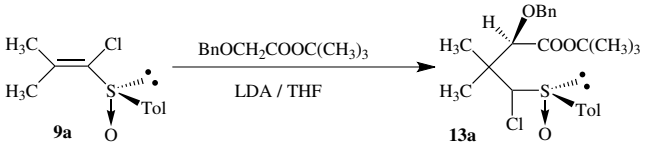
be 93–99% by using HPLC with Chiralpak AD (hexane–*i*-PrOH = 20:1). All of the signs of the specific rotation of sulfones **11** were minus and, at the same time, the generality of this reaction was verified.

2.2. Asymmetric synthesis of lactic acid derivatives using *tert*-butyl benzyloxyacetate

Next, an asymmetric synthesis of lactic acid derivatives was investigated on the basis of our method described above. We were interested in the addition reaction of 1-chlorovinyl *p*-tolyl sulfoxide with *tert*-butyl acetate having an oxygen atom at the α-position. At first, the addition reaction of *tert*-butyl benzyloxyacetate with 1-chlorovinyl *p*-tolyl sulfoxide **9a** was investigated and the results are summarized in Table 2.

First, the addition reaction was conducted in a similar way as described above (5 equiv of lithium enolate of *tert*-butyl benzyloxyacetate in THF at −78 °C for 15 min); however,

Table 2. Addition of lithium enolate of *tert*-butyl benzyloxyacetate to optically active 1-chlorovinyl *p*-tolyl sulfoxide **9a**



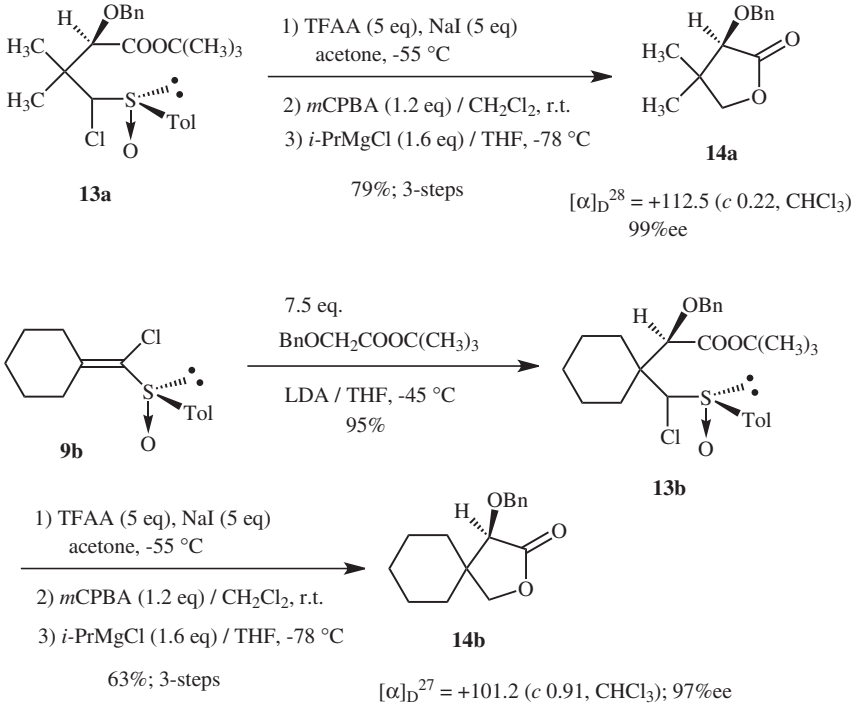
Entry	Solvent	Ester/equiv	Conditions	**13a**	
			Temp/°C (time/min)	Yield[a]/%	(Isomeric ratio)[b]
1	THF	5	−78 (15)	Trace	
2	THF	5	−78 (60)	11	(9:1)
3	THF	5	−45 to −40 (60)	55	(10:1)
4	THF	5	−78 to rt (10)	96	(12:1)
5	THF	7.5	−45 (60)	94[c]	
6	Toluene	5	−78 to rt (10)	58	(8:1)

[a] Isolated yield after silica gel column chromatography.
[b] The ratio of isolated two diastereomers (less polar product to more polar product on silica gel TLC).
[c] Trace of the more polar product was observed on TLC.

only a trace of the desired adduct **13a** was obtained (entry 1). Next, as shown in entry 2, the reaction time was prolonged to 60 min. In this reaction, the desired adduct **13a** was obtained in low yield as a mixture of two diastereomers. Although the yield was low, asymmetric induction from the sulfoxide chiral center was observed in this reaction. Next, the reaction was conducted at −45 °C and the temperature of the reaction mixture was slowly allowed to warm to −40 °C in 60 min. In these conditions, **13a** was obtained in moderate yield as a mixture of two diastereomers with similar asymmetric induction (entry 3).

Furthermore, the reaction was conducted at −78 °C and the cooling bath was removed immediately after **9a** was added to the reaction mixture (entry 4). Interestingly, this treatment gave almost a quantitative yield of adduct **13a**; however, although the ratio of the diastereomers was better, the product was still a mixture of two diastereomers. Finally, using 7.5 equiv of the lithium enolate of *tert*-butyl benzyloxyacetate at −45 °C for 60 min was found to be the conditions of choice (entry 5). In this case, interestingly, adduct **13a** was obtained in high yield and the product was almost a single isomer. In order to investigate the solvent effect, the reaction was conducted in toluene; however, no improvement of the yield was obtained (entry 6).

In order to determine the absolute configuration of the carbon bearing the benzyloxy group, adduct **13a** was converted to known lactone **14a** as follows (Scheme 3). Thus, to a mixture of **13a** and NaI in acetone at −55 °C was



Scheme 3.

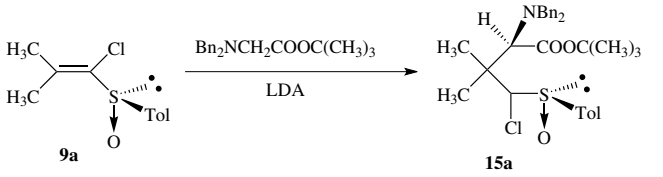
added TFAA to afford the desired γ-sulfanyl γ-lactone in high yield.[9] The sulfanyl group was oxidized with *m*-CPBA at room temperature to a sulfinyl group, and the resultant sulfinyl-lactone was treated with 1.6 equiv of *i*-PrMgCl to give lactone **14a** via a sulfoxide–magnesium exchange reaction[10] in 79% overall yield. The enantiomeric excess of **14a** was confirmed to be 99% by HPLC using Chiralpak AD (hexane–*i*-PrOH = 9:1). Comparing the sign of the specific rotation of the product with that of the reported optically active **14a** (the sign of the specific rotation of (*S*)-**14a** was reported to be minus[11]), the absolute configuration of the synthesized **14a**, which has a plus sign for the specific rotation, was determined to be (*R*). It is worth noting that the absolute configuration is the same as that of **11** (see Scheme 2 and Table 1), which implies that the principle for the chiral induction of the two reactions is the same.

In a similar way, the addition reaction of *tert*-butyl benzyloxyacetate with vinyl sulfoxide **9b**, which was derived from cyclohexanone and **2**, gave adduct **13b** in 95% yield as a single isomer. Adduct **13b** was converted to spiro γ-lactone **14b** in three steps in moderate overall yield. The enantiomeric excess of **14b** was confirmed to be 99% by HPLC using Chiralpak IA (hexane–*i*-PrOH = 9:1). The sign of the specific rotation of **14b** was plus, which indicated that the absolute configuration of **14b** must be (*R*).

2.3. Asymmetric synthesis of α-amino acid derivatives using *N*,*N*-dibenzylglycine *tert*-butyl ester

We further extended the chemistry mentioned above to an asymmetric synthesis of α-amino acid derivatives. At first, the addition reaction of the lithium enolate of *N*,*N*-dibenzylglycine to 1-chlorovinyl *p*-tolyl sulfoxides followed by conversion of the adducts to α-amino acid derivatives was investigated as shown in Table 3, Schemes 4 and 5.

Table 3. Addition of lithium enolate of *N*,*N*-dibenzylglycine *tert*-butyl ester to optically active 1-chlorovinyl *p*-tolyl sulfoxide **9a**



Entry	Solvent	Ester/equiv	Conditions/°C (min)	Yield[a]/%
1	THF	5	−78 (15)	N.R.
2	THF	5	−45 (15)	24
3	THF	5	−45 (60)	72
4	THF	7.5	−45 (60)	99
5	Toluene	5	−45 (15)	15

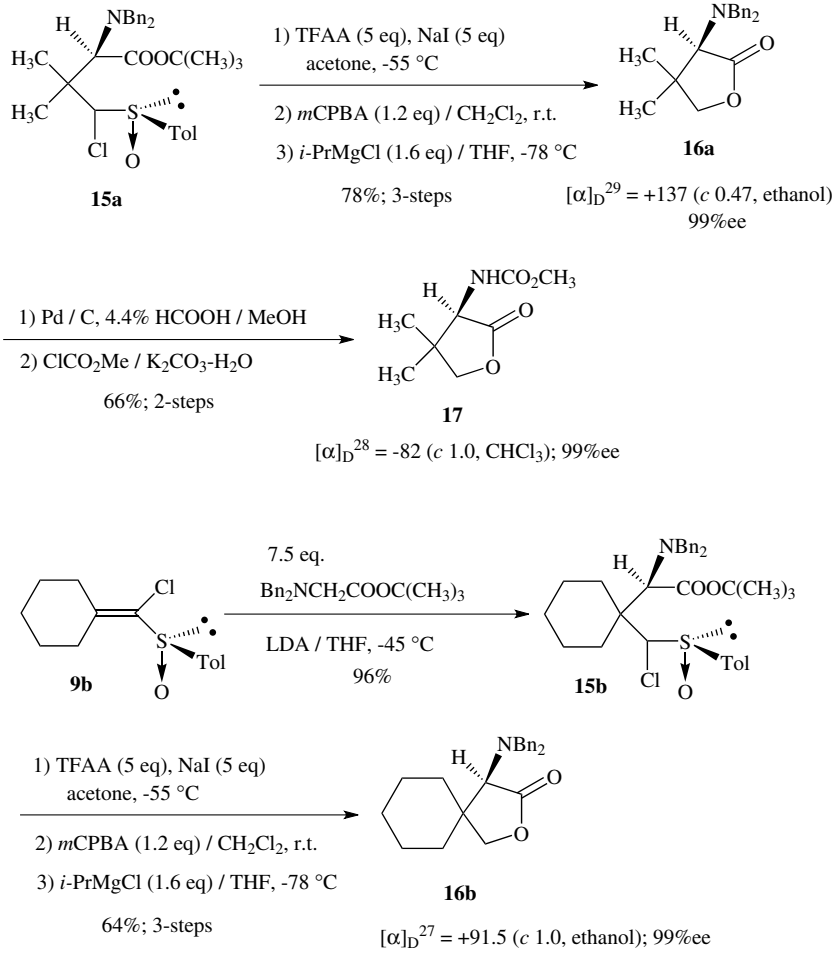
[a] The adduct was confirmed to be a single isomer from ^{1}H NMR.

Optically active 1-chlorovinyl *p*-tolyl sulfoxide **9a** was treated with 5 equiv of the lithium enolate of *N*,*N*-dibenzylglycine *tert*-butyl ester and the reaction mixture was stirred at −78 °C for 15 min (Table 3, entry 1); however, the reaction did not proceed. Raising the reaction temperature and prolonging the reaction time gave the desired adduct **15a** up to 72% (entries 2 and 3). Interestingly, although adduct **15a** has three chiral centers, only a single isomer was obtained. The best yield was obtained using 7.5 equiv of lithium enolate of *N*,*N*-dibenzylglycine *tert*-butyl ester (entry 4). Again, toluene was not a suitable solvent for this reaction (entry 5).

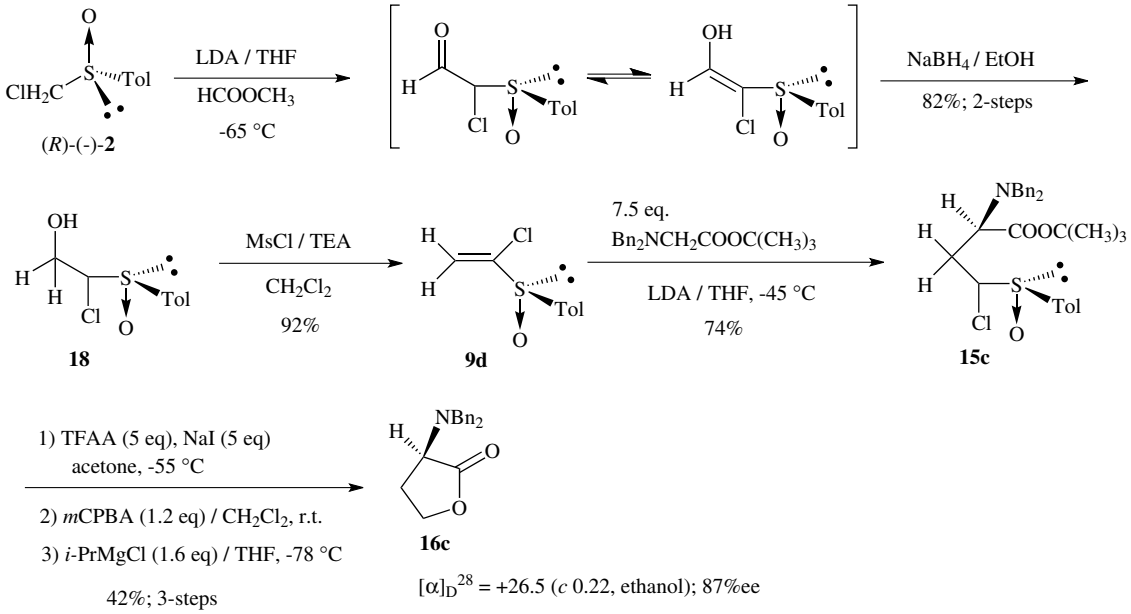
For determination of the absolute configuration of the α-position, adduct **15a** was converted to known cyclic α-amino acid derivative **17** again by using our method (see Scheme 4).[9,10] Thus, at first, **15a** was transformed to lactone **16a** in the same way as described in Scheme 3 in 78% overall yield. The enantiomeric excess of **16a** was confirmed to be 99% by HPLC using Chiralpak AD (hexane–*i*-PrOH = 9:1) as a chiral stationary column. Next, α-amino γ-lactone **16a** was converted to known **17**. Thus, **16a** was treated with Pd–C in the presence of formic acid in methanol to give debenzylated γ-lactone having a free amino group at the α-position.[12] The free amino group was treated with ethyl chloroformate to give *N*-methoxycarbonylated α-amino γ-lactone **17** in 66% overall yield from **16a**. Lactone **17** showed minus sign for the specific rotation. Versleijen et al. reported that (*R*)-carbomethoxyamino lactone **17** showed a minus sign for the specific rotation.[13] Thus, the absolute configuration at the α-carbon of our lactone **17** was determined to be (*R*). It is noteworthy that the absolute configuration of the synthesized **17** is the same as that of **11** (see Scheme 2 and Table 1) and **14** (see Scheme 3), which ascertains that the principle for chiral induction of the three reactions mentioned above is the same.

A spiro-cyclic α-amino γ-lactone having a quaternary carbon at the β-position was also synthesized starting from **9b** (Scheme 4). Thus, vinyl sulfoxide **9b** was treated with 7.5 equiv of lithium enolate of *N*,*N*-dibenzylglycine *tert*-butyl ester as described above to give an optically active adduct **15b** in a quantitative yield. Adduct **15b** was converted to optically active spiro α-amino γ-lactone **16b** in good overall yield by using the chemistry described above. Again, the enantiomeric excess was found to be 99% by using Chiralpak AD (hexane–*i*-PrOH = 9:1) as a chiral stationary column.

Furthermore, we tried to synthesize optically active α-amino γ-lactone without any substituents at the β-position (Scheme 5). First, the synthesis of optically active 1-chlorovinyl *p*-tolyl sulfoxide **9d** was investigated starting from methyl formate and (*R*)-(−)-**2**. Sulfoxide **2** was treated with LDA at −65 °C followed by the addition of methyl formate to give the desired aldehyde having a chlorine and a *p*-tolylsulfinyl group, which was observed as a mixture of keto and enol form by ^{1}H NMR and IR analyses. This mixture was reduced without further purification with $NaBH_4$ in ethanol to afford alcohol **18** in 82% overall yield. Alcohol **18** was treated with methanesulfonyl chloride in the presence of triethylamine (TEA) in CH_2Cl_2 at room temperature to give the desired enantiomerically pure vinylsulfoxide **9d** in high yield. In a similar way as described above, the addition reaction of **9d** with 7.5 equiv of the lithium enolate of *N*,*N*-dibenzylglycine *tert*-butyl ester was conducted; however, the yield and the asymmetric



Scheme 4.



Scheme 5.

induction of the desired product **15c** were not satisfactory. Product **15c** was converted to a γ-lactone having an *N*,*N*-dibenzylamino group at the α-position **16c** in 42% overall yield. The enantiomeric excess of **16c** was found to be

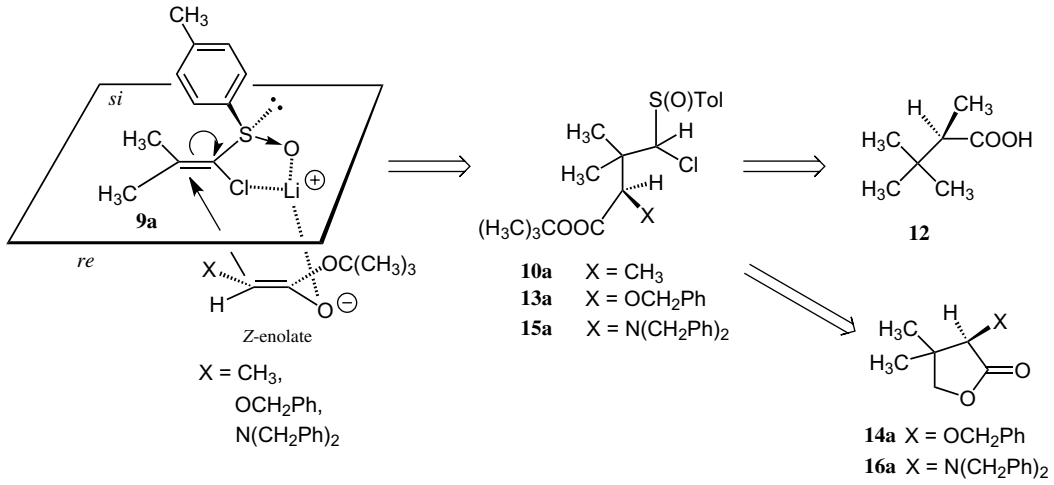
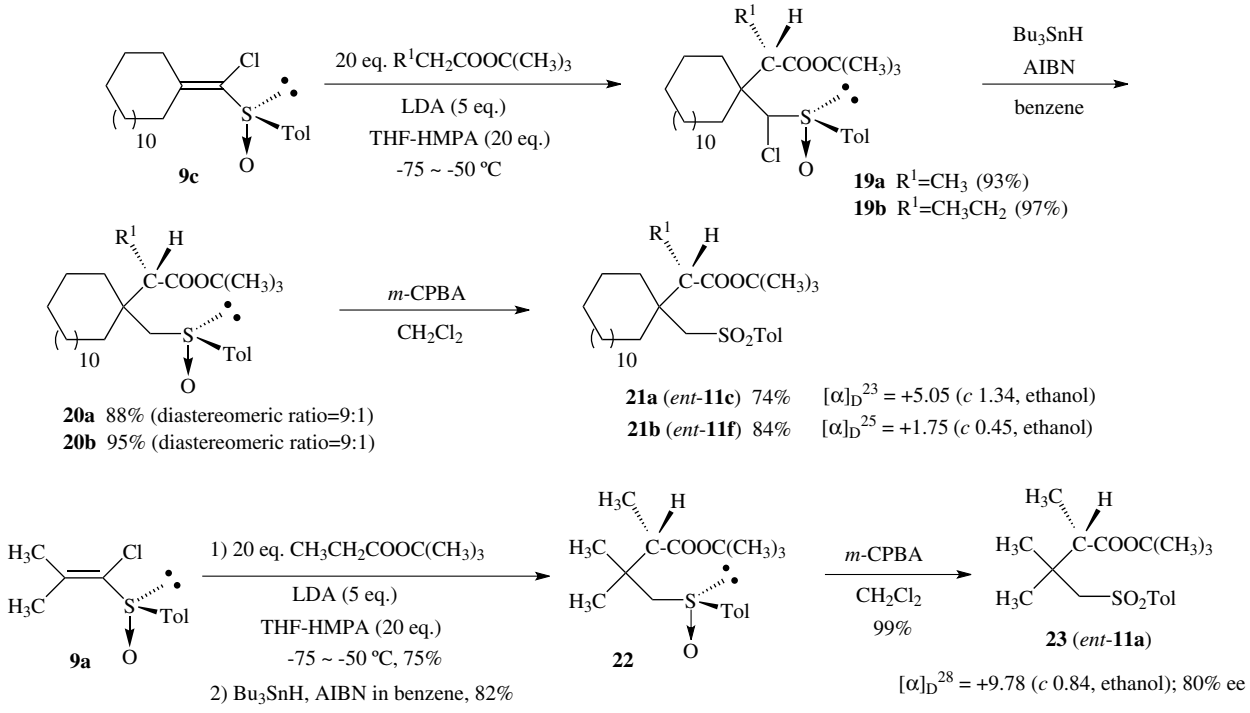


Figure 1.

87% by using Chiralpak AD (hexane–*i*-PrOH = 14:1) as a chiral stationary column. Comparing the results shown in Scheme 4 and Table 3 with those of in Scheme 5, it is ascertained that the two substituents on the β-position of the 1-chlorovinyl *p*-tolyl sulfoxides play an important role for the high 1,4-asymmetric induction.

A plausible mechanism for this 1,4-chiral induction from the sulfur chiral center is proposed as shown in Figure 1. Previously, we reported a plausible transition state model for the addition reaction of the lithium enolate of *tert*-butyl acetate to optically active 1-chlorovinyl *p*-tolyl sulfoxide **3**.[14] The lithium cation forms a five-membered chelate between the oxygen of the sulfoxide and the chlorine atom. In this event, the enolates were introduced to the vinyl sulfoxides from the less hindered *re*-face (Fig. 1). Treatment of carboxylic esters including *tert*-butyl propionate,[15a] *tert*-butyl benzyloxyacetate[15b] and *N*,*N*-dibenzylglycine *tert*-butyl ester[15c] with LDA in THF at low temperature was reported to give a *Z*-enolate. While the real reason is not clear at present, the *Z*-enolates would be placed as shown in Figure 1 by chelation with lithium and introduced from *re* face to afford adduct **10a**, **13a**, or **15a** with high 1,4-chiral induction from the sulfur chiral center.

Ireland et al.,[16a] Tanaka and Fuji,[16b] and Otera et al.[16c] reported that treatment of carboxylic acid ester with LDA in THF in the presence of HMPA gave the *E*-enolate predominantly. Moreover, Otera et al. reported that increasing the ester/LDA ratio, more *E*-enolates were produced.[16c] We



Scheme 6.

thought that if the reaction described above was conducted with LDA in the presence of HMPA and excess of esters, the enantiomer of α-substituted esters could be synthesized (Scheme 6).

Optically active 1-chlorovinyl *p*-tolyl sulfoxide **9c** was treated with 20 equiv of lithium enolates generated from *tert*-butyl propionate or *tert*-butyl butanoate with 5 equiv of LDA in the presence of 20 equiv of HMPA at −75 to −50 °C. These reactions gave **19a** and **19b** as an inseparable mixture of two diastereomers. Reduction of adducts **19a** and **19b** with Bu_3SnH gave **20a** and **20b**, respectively, in good yields. At this stage two diastereomers could be separated by silica gel column chromatography, and the diastereomeric ratios are shown in Scheme 6. Finally, the main products were oxidized with *m*-CPBA to afford **21a** and **21b**, respectively, in good yield. The sign of the specific rotation of **21a** was plus and all the other data indicated that **21a** is the enantiomer of **11c**. The enantiomeric excess was calculated to be over 99% using Chiralpak AD (hexane–*i*-PrOH = 9:1). In the same manner, **21b** was proved to be the enantiomer of **11f** and the enantiomeric excess found to be over 99%. The minor diastereomer (corresponding to **20a**) was oxidized to a sulfone and it was proved to be **11c**.

In order to confirm the generality of this reaction, **9a** was reacted with the *E*-enolate of *tert*-butyl propionate under the same conditions as above and the adduct was reduced with Bu_3SnH to afford **22** in good yield. Unfortunately, the product was found to be an inseparable mixture of two diastereomers. Sulfoxide **22** was oxidized with *m*-CPBA to give sulfone **23** in quantitative yield. As anticipated, product **23** was the enantiomer of **11a**; however, the enantiomeric excess was measured to be 80% by using HPLC with Chiralpak AD (hexane–*i*-PrOH = 20:1). Unfortunately, this technique was not useful for a synthesis of the enantiomers of the lactic acid and α-amino acid derivatives described above.

In conclusion, we have developed a new and efficient method for a synthesis of optically active carboxylic acid derivatives and lactones, including lactic acid and α-amino acid derivatives, having a chiral carbon center at the α-position from (*R*)-(−)-chloromethyl *p*-tolyl sulfoxide. Both enantiomers of the α-substituted carboxylic acid derivatives can be synthesized from one chiral source by choosing the conditions for the generation of the lithium ester enolates.

3. Experimental

All melting points were measured on Yanaco MP-S3 apparatus and are uncorrected. ^{1}H NMR spectra were measured in a $CDCl_3$ solution with JEOL JNMLA 500 and Burker XWIN-600 spectrometer. Electron-impact mass spectra (MS) were obtained at 70 eV by direct insertion by HITACHI M-80B mass spectrometer. IR spectra were recorded on a Perkin–Elmer Spectrum One FT-IR instrument. Silica gel 60N (KANTO CHEMICAL) containing 0.5% fluorescence reagent 254 and a quartz column were used for column chromatography and the products having UV absorption were detected by UV irradiation. In experiments requiring a dry reagent, and solvent, benzene, dichloromethane, *N*,*N*-diisopropylamine, triethylamine, and pyridine were distilled from CaH_2. THF was distilled from diphenylketyl and acetone was dried over $CaSO_4$ and distilled before use.

3.1. *tert*-Butyl 4-chloro-2,3,3-trimethyl-4-(*p*-tolylsulfinyl)-butanoate 10a

tert-Butyl propionate (0.15 mL; 1.13 mmol) was added to a solution of LDA (0.66 mmol) in 3 mL of dry THF at −78 °C with stirring. The solution was stirred for 10 min, and a solution of **9a** (30 mg; 0.131 mmol) in THF (0.5 mL) was added. The reaction mixture was stirred for 5 min, and the reaction was quenched by adding satd aq NH_4Cl. The whole was extracted with $CHCl_3$. The organic layer was dried over $MgSO_4$ and concentrated in vacuo. The product was purified by silica gel column chromatography to afford **10a** (46.5 mg; 99%) as a colorless oil; IR (neat) 2977, 1723 (CO), 1457, 1367, 1151, 1057 (SO) cm^{-1}; ^{1}H NMR δ 1.16 (3H, d, $J = 7.4$ Hz), 1.28 (3H, s), 1.42 (9H, s), 1.47 (3H, s), 2.43 (3H, s), 3.04 (1H, q, $J = 7.0$ Hz), 4.75 (1H, s), 7.31, 7.70 (each 2H, d, $J = 7.9$ Hz). MS *m*/*z* (%) 358 (M^+, trace), 342 (trace), 318 (trace), 285 (21), 271 (trace), 250 (trace), 229 (1), 212 (1), 196 (2), 163 (25), 140 (100), 139 (22), 127 (21), 91 (9). Calcd for $C_{18}H_{27}ClO_3S$: *M*, 358.1369. Found: *m*/*z* 358.1375.

3.2. *tert*-Butyl 2-{1-[chloro(*p*-tolylsulfinyl)methyl]cyclohexyl}-propionate 10b

Colorless oil; IR (neat) 2930, 1727 (CO), 1596, 1455, 1367, 1255, 1145, 1056 (SO), 849 cm^{-1}; ^{1}H NMR δ 1.34 (3H, d, $J = 7.1$ Hz), 1.47 (9H, s), 1.26–1.83 (10H, m), 2.44 (3H, s), 3.11 (1H, q, $J = 7.1$ Hz), 4.96 (1H, s), 7.33, 7.72 (each 2H, d, $J = 8.3$ Hz). MS *m*/*z* (%) 399 ($[M+H]^+$, trace), 381 (trace), 342 (1), 325 (15), 290 (2), 279 (3), 269 (2), 252 (1), 203 (27), 185 (4), 167 (64), 140 (100), 139 (20), 93 (20), 91 (12). Calcd for $C_{21}H_{32}ClO_3S$: *M*, 399.1761. Found: *m*/*z* 399.1750.

3.3. *tert*-Butyl 2-{1-[chloro(*p*-tolylsulfinyl)methyl]cyclopentadecyl}propionate 10c

Colorless oil; IR (neat) 2929, 2875, 1727 (CO), 1459, 1369, 1241, 1150, 1059 (SO) cm^{-1}; ^{1}H NMR δ 1.37 (3H, d, $J = 7.1$ Hz), 1.2–1.4 (28H, m), 1.47 (9H, s), 2.43 (3H, s), 3.03 (1H, q, $J = 7.1$ Hz), 4.60 (1H, s), 7.35, 7.71 (each 2H, d, $J = 8.3$ Hz). MS *m*/*z* (%) 525 ($[M+H]^+$, trace), 451 (10), 329 (27), 293 (77), 275 (15), 219 (48), 140 (100), 95 (18), 57 (86). Calcd for $C_{30}H_{50}ClO_3S$: *M*, 525.3169. Found: *m*/*z* 525.3185.

3.4. *tert*-Butyl 4-chloro-2-ethyl-3,3-dimethyl-4-(*p*-tolylsulfinyl)butanoate 10d

Colorless oil; IR (neat) 2975, 2877, 1722 (CO), 1596, 1458, 1367, 1155, 1056 (SO), 948, 813 cm^{-1}; ^{1}H NMR δ 0.95 (3H, t, $J = 7.3$ Hz), 1.28 (3H, s), 1.42 (3H, s), 1.45 (9H, s),

2.43 (3H, s), 2.91 (1H, dd, $J = 11.6$, 3.4 Hz), 4.51 (1H, s), 7.31, 7.68 (each 2H, d, $J = 8.0$ Hz). MS m/z (%) 372 (M^+, trace), 356 (trace), 322 (trace), 299 (18), 264 (1), 263 (0.5), 229 (1), 196 (3), 177 (27), 159 (5), 140 (100), 139 (20), 91 (7). Calcd for $C_{19}H_{29}ClO_3S$: M, 372.1526. Found: m/z 372.1532.

3.5. *tert*-Butyl 2-{1-[chloro(*p*-tolylsulfinyl)methyl]cyclohexyl}butanoate 10e

Colorless oil; IR (neat) 2930, 2868, 1723 (CO), 1596, 1455, 1366, 1259, 1143, 1056 (SO), 811 cm^{-1}; ^1H NMR δ 0.98 (3H, t, $J = 7.0$ Hz), 1.49 (9H, s), 1.2–2.0 (12H, m), 2.44 (3H, s), 2.85 (1H, dd, $J = 12$, 3.1 Hz), 5.00 (1H, s), 7.33, 7.73 (each 2H, d, $J = 8.3$ Hz). MS m/z (%) 412 (M^+, trace), 395 (trace), 339 (16), 217 (33), 181 (90), 140 (100), 93 (24). Calcd for $C_{22}H_{33}ClO_3S$: M, 412.1839. Found: m/z 412.1837.

3.6. *tert*-Butyl 2-{1-[chloro(*p*-tolylsulfinyl)methyl]cyclopentadecyl}butanoate 10f

Colorless oil; IR (neat) 2929, 2851, 1727 (CO), 1569, 1455, 1367, 1256, 1149, 1059 (SO), 811 cm^{-1}; ^1H NMR δ 0.96 (3H, t, $J = 7.2$ Hz), 1.1–1.6 (28H, m), 1.49 (9H, s), 1.9–2.1 (2H, m), 2.43 (3H, s), 2.78 (1H, dd, $J = 12.0$, 3.0 Hz), 4.53 (1H, s), 7.31, 7.71 (each 2H, $J = 7.8$, 8.4 Hz). MS m/z (%) 539 ($[M+H]^+$, trace), 465 (10), 343 (33), 307 (100), 289 (14), 261 (13), 219 (40), 140 (68). Calcd for $C_{31}H_{52}ClO_3S$: M, 539.3325. Found: m/z 539.3323.

3.7. *tert*-Butyl 2-{1-[chloro(*p*-tolylsulfinyl)methyl]-1-methylethyl}hexanoate 10g

Colorless oil; IR (neat) 2973, 2921, 1723 (CO), 1494, 1464, 1367, 1146, 1057 (SO) cm^{-1}; ^1H NMR δ 0.90 (3H, t, $J = 8.0$ Hz), 1.28 (3H, s), 1.42 (3H, s), 1.44 (9H, s), 1.2–1.7 (6H, m), 2.43 (3H, s), 2.99 (1H, dd, $J = 11.6$, 2.5 Hz), 4.52 (1H, s), 7.31, 7.68 (each 2H, d, $J = 8.0$, 8.3 Hz). MS m/z (%) 400 (M^+, trace), 385 (trace), 373 (trace), 327 (16), 314 (2), 296 (3), 270 (17), 266 (6), 214 (11), 205 (35), 169 (17), 140 (100), 139 (17), 123 (10), 69 (8). Calcd for $C_{21}H_{33}ClO_3S$: M, 400.1839. Found: m/z 400.1855.

3.8. *tert*-Butyl 2-{1-[chloro(*p*-tolylsulfinyl)methyl]cyclopentadecyl}hexanoate 10h

Colorless oil; IR (neat) 2929, 2858, 1727 (CO), 1462, 1367, 1148, 1059 (SO) cm^{-1}; ^1H NMR δ 0.93 (3H, t, $J = 7.3$ Hz), 1.2–1.5 (28H, m), 1.48 (9H, s), 1 1.7–1.9 (6H, m), 2.43 (3H, s), 2.87 (1H, dd, $J = 11.3$, 4.0 Hz), (1H, s), 7.31, 7.71 (each 2H, d, $J = 8.0$ Hz). MS m/z (%) 567 ($[M+H]^+$, trace), 493 (21), 371 (69), 335 (100), 289 (45), 267 (19), 219 (100), 140 (100), 57 (100).

3.9. (2*R*)-(−)-*tert*-Butyl 2,3,3-trimethyl-4-(*p*-tolylsulfonyl)-butanoate 11a

AIBN (9.8 mg; 0.06 mmol) was added to a solution of **10a** (72.2 mg; 0.2 mmol) and Bu_3SnH (0.14 mL; 0.3 mmol) in 5 mL of benzene. The atmosphere in the flask was replaced with argon, and the reaction mixture was stirred and refluxed for 30 min. The solvent was removed in vacuo and the residue was purified by silica gel column chromatography to give dechlorinated sulfoxide (65 mg; 99%) as a colorless oil. *m*-CPBA (49.4 mg; 0.2 mmol) was added to a solution of the sulfoxide in 10 mL of CH_2Cl_2 at room temperature with stirring. The solution was stirred for 30 min, and the reaction was quenched by adding satd aq Na_2SO_3 and satd aq $NaHCO_3$. The whole was extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and concentrated in vacuo. The product was purified by silica gel column chromatography to afford **11a** (59.2 mg; 87%) as a colorless oil; IR (neat) 2977, 2932, 1722 (CO), 1462, 1368, 1147, 1087 (SO_2), 849, 817 cm^{-1}; ^1H NMR δ 1.09–1.10 (3H, m), 1.28–1.31 (6H, m), 1.41 (9H, s), 2.47 (3H, s), 2.52 (1H, q, $J = 7.1$ Hz), 3.07, 3.47 (each 1H, d, $J = 13.8$ Hz), 7.34, 7.80 (each 2H, d, $J = 8.1$ Hz). MS m/z (%) 340 (M^+, 0.2), 308 (trace), 284 (20), 267 (55), 266 (20), 238 (4), 211 (100), 182 (5), 157 (93), 139 (33), 129 (71), 111 (10), 91 (37). Calcd for $C_{18}H_{28}O_4S$: M, 340.1709. Found: m/z 340.1710. $[\alpha]_D^{30} = -14.3$ (c 1.2, ethanol). Compound **23**: $[\alpha]_D^{28} = +9.8$ (c 0.84, ethanol).

3.10. (2*R*)-(−)-*tert*-Butyl 2-{1-[(*p*-tolylsulfonyl)methyl]-cyclohexyl}propionate 11b

Colorless oil; IR (neat) 2928, 2870, 1716 (CO), 1597, 1455, 1367, 1147 (SO_2), 849, 817 cm^{-1}; ^1H NMR δ 1.05 (3H, d, $J = 7.0$ Hz), 1.43 (9H, s), 1.4–1.7 (10H, m), 2.44 (3H, s), 3.10, 3.58 (each 1H, d, $J = 14.7$ Hz), 3.17 (1H, q, $J = 7.3$ Hz), 7.33, 7.79 (each 2H, d, $J = 8.0$ Hz). MS m/z (%) 380 (M^+, trace), 350 (trace), 324 (16), 307 (28), 306 (8), 251 (100), 250 (2), 184 (1), 157 (70), 123 (26), 109 (5), 95 (87). Calcd for $C_{21}H_{32}O_4S$: M, 380.2021. Found: m/z 380.2012. $[\alpha]_D^{26} = -5.34$ (c 1.8, ethanol).

3.11. (2*R*)-(−)-*tert*-Butyl 2-{1-[(*p*-tolylsulfonyl)methyl]-cyclopentadecyl}propionate 11c

Colorless oil; IR (neat) 2928, 2856, 1719 (CO), 1597, 1458, 1367, 1319, 1146 (SO_2), 1087, 816 cm^{-1}; ^1H NMR δ 1.14 (3H, d, $J = 7.4$ Hz), 1.2–1.5 (28H, m), 1.43 (9H, s), 2.44 (3H, s), 2.86 (1H, q, $J = 7.4$ Hz), 3.22, 3.46 (each 1H, d, $J = 14.7$ Hz), 7.32, 7.79 (each 2H, d, $J = 8.25$ Hz). MS m/z (%) 506 (M^+, trace), 450 (3), 433 (7), 377 (35), 295 (15), 277 (30), 263 (100), 221 (84), 157 (40), 109 (42), 83 (79), 55 (96). Calcd for $C_{30}H_{50}O_4S$: M, 506.3430. Found: m/z 506.3431. $[\alpha]_D^{24} = -4.3$ (c 0.9, ethanol). Compound **21a**: $[\alpha]_D^{23} = +5.05$ (c 1.34, ethanol, 99% ee).

3.12. (2*R*)-(−)-*tert*-Butyl 2-ethyl-3,3-dimethyl-4-(*p*-tolylsulfonyl)butanoate 11d

Colorless oil; IR (neat) 2972, 2877, 1722 (CO), 1598, 1460, 1367, 1317, 1147 (SO_2), 1087, 949, 815 cm^{-1}; ^1H NMR δ 0.86 (3H, t, $J = 7.3$ Hz), 1.27 (3H, s), 1.31 (3H, s), 1.44 (9H, s), 1.5–1.6 (2H, m), 2.18 (1H, dd, $J = 10.1$, 4.9 Hz), 2.44 (3H, s), 3.04, 3.41 (each 1H, d, $J = 14.0$ Hz), 7.33, 7.78 (each 2H, d, $J = 8.3$ Hz). MS m/z (%) 354 (M^+, trace), 341 (trace), 322 (trace), 298 (18), 281 (52), 242 (8), 211 (100), 196 (6), 170 (3), 143 (62), 139 (26), 97 (33), 91 (28). Calcd for $C_{19}H_{30}O_4S$: M, 354.1864. Found: m/z 354.1862. $[\alpha]_D^{26} = -3.0$ (c 1.7, ethanol).

3.13. (2*R*)-(−)-*tert*-Butyl 2-{1-[(*p*-tolylsulfonyl)methyl]-cyclohexyl}butanoate 11e

Colorless oil; IR (neat) 2930, 2847, 1716 (CO), 1597, 1456, 1366, 1316, 1146 (SO_2), 1087, 815 cm^{-1}; ^1H NMR δ 0.88 (3H, t, $J = 7.4$ Hz), 1.44 (9H, s), 1.4–1.7 (8H, m), 2.0–2.1 (1H, m), 2.2–2.3 (1H, m), 2.44 (3H, s), 2.87 (1H, dd, $J = 10.1$, 4.9 Hz), 3.03, 3.63 (each 1H, d, $J = 14.6$ Hz), 7.33, 7.79 (each 2H, d, $J = 8.3$ Hz). MS *m*/*z* (%) 394 (M^+, trace), 362 (trace), 338 (17), 321 (24), 320 (14), 293 (2), 251 (100), 242 (4), 196 (3), 183 (22), 157 (75), 137 (23), 95 (95), 81 (17). Calcd for $C_{22}H_{34}O_4S$: *M*, 394.2178. Found: *m*/*z* 394.2182. $[\alpha]_D^{26} = -4.9$ (*c* 1.8, ethanol).

3.14. (2*R*)-(−)-*tert*-Butyl 2-{1-[(*p*-tolylsulfonyl)methyl]-cyclopentadecyl}butanoate 11f

Colorless oil; IR (neat) 2930, 2858, 1721 (CO), 1460, 1367, 1319, 1147 (SO_2), 1087 cm^{-1}; ^1H NMR δ 0.88 (3H, t, $J = 7.2$ Hz), 1.2–1.6 (28H, m), 1.6–1.7 (2H, m), 2.43 (3H, s), 2.52 (1H, dd, $J = 9.0$, 5.4 Hz), 3.24, 3.42 (each 1H, d, $J = 14.4$ Hz), 7.32, 7.79 (each 2H, $J = 8.4$ Hz). MS *m*/*z* (%) 520 (M^+, trace), 446 (18), 377 (75), 309 (33), 291 (28), 277 (10), 221 (100), 157 (23), 97 (12). Calcd for $C_{31}H_{52}O_4S$: *M*, 520.3587. Found: *m*/*z* 520.3593. $[\alpha]_D^{26} = -1.7$ (*c* 0.9, ethanol). Compound **21b**: $[\alpha]_D^{25} = +1.7$ (*c* 0.45, ethanol, 99% ee).

3.15. (2*R*)-(−)-*tert*-Butyl 2-[1,1-dimethyl-2-(*p*-tolylsulfonyl)-ethyl]hexanoate 11g

Colorless oil; IR (neat) 2960, 2872, 1718 (CO), 1598, 1466, 1392, 1367, 1317, 1147 (SO_2), 1087, 847 cm^{-1}; ^1H NMR δ 0.87 (3H, t, $J = 7.4$ Hz), 1.28 (3H, s), 1.31 (3H, s), 1.43 (9H, s), 1.2–1.5 (6H, m), 2.22 (1H, dd, $J = 12.0$, 3.1 Hz), 2.44 (3H, s), 3.03, 3.42 (each 1H, d, $J = 14.3$ Hz), 7.33, 7.79 (each 2H, d, $J = 8.0$ Hz). MS *m*/*z* (%) 382 (M^+, trace), 309 (45), 308 (28), 270 (16), 252 (5), 211 (100), 171 (66), 157 (47), 139 (25), 91 (27). Calcd for $C_{21}H_{34}O_4S$; *M*, 382.2178. Found: *m*/*z* 382.2188. $[\alpha]_D^{28} = -0.5$ (*c* 2.8, ethanol).

3.16. (2*R*)-(−)-*tert*-Butyl 2-{1-[(*p*-tolylsulfonyl)methyl]-cyclopentadecyl}hexanoate 11h

Colorless oil; IR (neat) 2929, 2871, 1715 (CO), 1597, 1462, 1367, 1316, 1148 (SO_2), 1087, 915, 817 cm^{-1}; ^1H NMR δ 0.88 (3H, t, $J = 7.4$ Hz), 1.2–1.5 (28H, m), 1.5–1.7 (4H, m), 1.9–2.0 (1H, m), 2.44 (3H, s), 2.56–2.58 (1H, m), 3.23, 3.46 (each 1H, d, $J = 14.4$ Hz), 7.33, 7.79 (each 2H, d, $J = 8.4$ Hz). MS *m*/*z* (%) 548 (M^+, trace), 474 (12), 377 (64), 337 (31), 319 (24), 221 (100), 157 (25), 139 (9), 97 (18), 57 (40). Calcd for $C_{33}H_{56}O_4S$; *M*, 548.3899. Found: *m*/*z* 548.3903. $[\alpha]_D^{27} = -1.9$ (*c* 0.9, ethanol).

3.17. (*R*)-(−)-2,3,3-Trimethylbutyric acid 12

AIBN (9.8 mg; 0.06 mmol) was added to a solution of **10a** (72.2 mg; 0.20 mmol) and Bu_3SnH (0.14 mL; 0.30 mmol) in 5 mL of benzene. The atmosphere in the flask was replaced with argon, and the reaction mixture was stirred and refluxed for 30 min. The solvent was removed in vacuo and the residue was purified by silica gel column chromatography to give dechlorinated product as colorless oil. To a solution of the product in 10 mL of CH_2Cl_2 was added trifluoroacetic acid (0.09 mL; 15 mmol). The solution was stirred overnight. The reaction was quenched by satd aq $NaHCO_3$. After the aqueous layer was acidified by 10% HCl, the whole was extracted with CH_2Cl_2 and the organic layer was evaporated to afford a carboxylic acid.

A solution of the carboxylic acid (40 mg; 0.15 mmol) and excess of Raney-Ni in EtOH was stirred and refluxed for 30 h. The Raney Ni was filtered off, and the filtrate was evaporated to give a residue, which was purified by silica gel column chromatography to afford **12** (19.8 mg; 82%) as a colorless oil; IR (neat) 2927, 1704 (CO), 1463, 1368, 1287, 1241, 1184, 945 cm^{-1}; ^1H NMR δ 1.00 (9H, s), 1.14 (3H, d, $J = 7.2$ Hz), 2.30 (1H, q, $J = 7.2$ Hz). $[\alpha]_D^{27} = -20.8$ (*c* 0.7, ethanol).

3.18. *tert*-Butyl 2-benzyloxy-4-chloro-3,3-dimethyl-4-(*p*-tolylsulfinyl)butanoate 13a

tert-Butyl benzyloxyacetate (142 mg; 0.65 mmol) was added to a solution of LDA (0.65 mmol) in 3 mL of dry THF at −45 °C with stirring. The solution was stirred for 15 min, then a solution of **9a** (20 mg; 0.087 mmol) in THF (0.5 mL) was added. The solution was stirred for 60 min at −45 °C and the reaction was quenched by adding satd aq NH_4Cl. The whole was extracted with $CHCl_3$. The organic layer was dried over $MgSO_4$ and concentrated in vacuo. The product was purified by silica gel column chromatography to afford **13a** (36 mg; 94%) as a colorless oil; IR (neat) 2978, 2936, 1732 (CO), 1455, 1393, 1370, 1258, 1220, 1159, 1121, 1054 (SO), 812 cm^{-1}; ^1H NMR δ 1.24 (3H, s), 1.44 (3H, s), 1.51 (9H, s), 2.39 (3H, s), 4.60 (1H, d, $J = 10.7$ Hz), 4.68 (1H, d, $J = 10.7$ Hz), 4.84 (1H, s), 4.92 (1H, s), 7.21, (2H, d, $J = 7.9$ Hz), 7.30–7.40 (5H, m). 7.58 (2H, d, $J = 8.25$ Hz). MS *m*/*z* (%) 451 (M^+, trace), 435 (trace), 349 (15), 303 (10), 255 (5), 230 (5), 196 (2), 140 (25), 91 (100), 57 (26). Calcd for $C_{24}H_{31}O_4ClS$: *M*, 450.1632. Found; *m*/*z* 450.1636.

Minor diastereomer: Colorless oil; IR (neat) 2979, 2934, 1739 (CO), 1463, 1393, 1369, 1159, 1112, 1055 (SO), 811 cm^{-1}; ^1H NMR δ 1.31 (3H, s), 1.51 (9H, s), 1.52 (3H, s), 2.43 (3H, s), 4.23 (1H, s), 4.36, 4.55 (each 1H, d, $J = 11.0$ Hz), 4.87 (1H, s), 7.26–7.37 (7H, m), 7.71 (2H, d, $J = 8.0$ Hz).

3.19. (*R*)-(+)-3-Benzyloxy-4,4-dimethyldihydrofuran-2-one 14a

A solution of NaI (56.5 mg; 0.375 mmol) in 5 mL of dry acetone was stirred for 15 min at −55 °C. TFAA (0.53 mL; 0.375 mmol) was added dropwise to the solution of NaI with stirring at −55 °C and the solution was stirred for 15 min. Adduct **13a** (33 mg; 0.075 mmol) in 1.5 mL of dry acetone was added dropwise to the suspension of NaI and TFAA at −55 °C with stirring and the reaction mixture was stirred for 10 min. The reaction was quenched by adding satd aq $NaHCO_3$ followed by satd aq Na_2SO_3. The whole was extracted with $CHCl_3$. The organic layer

was washed with satd aq $NaHCO_3$ and dried over $MgSO_4$. The solvent was removed in vacuo and the residue was purified by silica gel column chromatography to give γ-tolylsulfanyl γ-lactone as a mixture of two diastereomers. *m*-CPBA (49.4 mg; 0.2 mmol) was added to a solution of the γ-tolylsulfanyl γ-lactone in 10 mL of CH_2Cl_2 at 0 °C with stirring. The solution was stirred for 30 min, and the reaction was quenched by adding satd aq Na_2SO_3 and satd aq $NaHCO_3$. The whole was extracted with CH_2Cl_2. The organic layer was washed with satd aq $NaHCO_3$ and dried over $MgSO_4$. The product was purified by silica gel column chromatography to give γ-sulfinyl γ-lactone as a colorless oil. ^{i}PrMgCl (2.0 mol/L in THF; 0.06 mL, 0.12 mmol) was added to a solution of the γ-tolylsulfinyl γ-lactone at −78 °C with stirring under argon atmosphere. The solution was stirred for 15 min at −78 °C, and the reaction was quenched by adding satd aq NH_4Cl. The whole was extracted with $CHCl_3$. The product was purified by silica gel column chromatography to afford **14a** (18.9 mg; three steps 79%) as a colorless oil; IR (neat) 2967, 2916, 1788(CO), 1465, 1374, 1199, 1156, 1009, 749 cm^{-1}; ^{1}H NMR δ 1.10 (3H, s), 1.13 (3H, s), 3.73 (1H, s), 3.87 (1H, d, $J = 8.9$ Hz), 4.00 (1H, d, $J = 8.9$ Hz), 4.75, 5.04 (each 1H, d, $J = 12.2$ Hz), 7.29–7.40 (5H, m). MS *m*/*z* (%) 220 (M^+, 0.5), 114 (45), 99 (85), 91 (100). Calcd for $C_{13}H_{16}O_3$: *M*, 220.1100. Found; *m*/*z* 220.1101. $[\alpha]_D^{28} = +112.5$ (*c* 0.22, $CHCl_3$, 99% ee).

3.20. *tert*-Butyl 2-benzyloxy-2-{1-[chloro(*p*-tolylsulfinyl)-methyl]cyclohexyl}acetate 13b

Colorless oil; IR (neat) 2978, 2931, 1739 (CO), 1495, 1456, 1394, 1368, 1159, 1083, 1060 (SO), 755 cm^{-1}; ^{1}H NMR δ 1.22–1.75 (10H, s), 1.40 (9H, s), 2.40 (3H, s), 4.26 (1H, s), 4.55, 4.67 (each 1H, d, $J = 11.4$ Hz), 4.94 (1H, s), 7.22–7.38 (5H, m), 7.44–7.49 (2H, m), 7.58–7.65 (2H, m). MS *m*/*z* (%) 490 (M^+, trace), 474 (0.2), 389 (30), 295 (27), 230 (31), 169 (33), 140 (100), 91 (100), 57 (88). Calcd for $C_{27}H_{35}O_4ClS$: *M*, 490.1944. Found: *m*/*z* 490.1949.

3.21. (*R*)-(+)-4-Benzyloxy-2-oxaspiro[4.5]decan-3-one 14b

Colorless oil; IR (neat) 2927, 2858, 1791 (CO), 1455, 1163, 1146, 736 cm^{-1}; ^{1}H NMR δ 1.23–1.76 (10H, m), 3.71 (1H, s), 3.87, 4.24 (each 1H, d, $J = 8.9$ Hz), 4.71, 5.02 (each 1H, d, $J = 11.8$ Hz), 7.28–7.42 (5H, m). MS *m*/*z* (%) 260 (M^+, 0.1), 154 (100), 111 (50), 91 (82), 81 (8). Calcd for $C_{16}H_{20}O_3$: *M*, 260.1413. Found *m*/*z* 260.1418. $[\alpha]_D^{27} = +101.2$ (*c* 0.91, $CHCl_3$).

3.22. *tert*-Butyl 2-dibenzylamino-4-chloro-3,3-dimethyl-4-(*p*-tolylsulfinyl)butanoate 15a

A solution of *N*,*N*-dibenzylglycine *tert*-butyl ester (204 mg; 0.656 mmol) in THF was added to a solution of LDA (0.656 mmol) in 4 mL of dry THF at −45 °C with stirring. The solution was stirred for 15 min, then a solution of **9a** (20 mg; 0.0874 mol) in THF (0.5 mL) was added. The solution was stirred for 1 h at −45 °C, and the reaction was quenched by adding satd aq NH_4Cl. The whole was extracted with $CHCl_3$. The organic layer was washed with satd aq NH_4Cl. The product was purified by silica gel column chromatography to afford **15a** (46.9 mg; 99%) as colorless crystals; mp 84–85 °C (hexane–AcOEt). IR (KBr) 2970, 2935, 2834, 1720 (CO), 1152, 1055, 738 cm^{-1}; ^{1}H NMR δ 1.00 (3H, s), 1.50 (9H, s), 1.59 (3H, s), 2.41 (3H, s), 3.67 (2H, d, $J = 13.7$ Hz), 3.75 (1H, s), 4.06 (2H, d, $J = 13.7$ Hz), 4.92 (1H, s), 7.25–7.29 (4H, m), 7.33, 7.36 (4H, m), 7.39–7.41 (2H, m), 7.64 (2H, d, $J = 8.1$ Hz). MS *m*/*z* (%) 540 (M^+, trace), 448 (5), 438 (5), 392 (2), 310 (22), 264 (18), 254 (65), 210 (8), 181 (5), 139 (5), 91 (100). Calcd for $C_{31}H_{39}ClNO_3S$: *M*, 540.2340. Found: *m*/*z* 540.2332. Anal. Calcd for $C_{31}H_{39}ClNO_3S$: C, 68.93; H, 7.09; Cl, 6.56; N, 2.59; S, 5.94. Found: C, 68.73; H, 7.22; Cl, 6.40; N, 2.30; S, 5.60.

3.23. *tert*-Butyl 2-dibenzylamino-2-{1-[chloro(*p*-tolylsulfinyl)methyl]cyclohexyl}acetate 15b

Colorless oil; IR (neat) 2929, 2867, 1723 (CO), 1455, 1367, 1143, 1052 (SO), 753 cm^{-1}; ^{1}H NMR δ 1.2–1.5 (10H, m), 1.52 (9H, s), 1.93 (1H, d, $J = 15.0$ Hz), 2.42 (3H, s), 2.83 (1H, m), 3.55 (2H, d, $J = 13.7$ Hz), 4.12 (1H, s), 4.92 (1H, s), 7.2–7.6 (14H, m).

3.24. (*R*)-(+)-3-Dibenzylamino-4,4-dimethyldihydrofuran-2-one 16a

A solution of NaI (96.8 mg; 0.630 mmol) in 4 mL of dry acetone was stirred for 15 min at −55 °C. TFAA (0.092 mL; 0.630 mmol) was added dropwise to a solution of NaI with stirring at −55 °C and the solution was stirred for 15 min. Adduct **15a** (68 mg; 0.126 mmol) in 1 mL of dry acetone was added dropwise to the solution of NaI and TFAA at −55 °C dropwise with stirring and the reaction mixture was stirred for 10 min. The reaction was quenched by adding satd aq $NaHCO_3$ followed by satd aq Na_2SO_3. The whole was extracted with $CHCl_3$. The organic layer was washed with satd aq $NaHCO_3$ and dried over $MgSO_4$. The solvent was evaporated and the residue was purified by silica gel column chromatography to give γ-tolylsulfanyl γ-lactone as a mixture of two diastereomers.

m-CPBA (32.8 mg; 0.138 mmol) was added to a solution of the γ-tolylsulfanyl γ-lactones in CH_2Cl_2 at 0°C with stirring. The solution was stirred for 30 min, and the reaction was quenched by adding satd aq Na_2SO_3 and satd aq $NaHCO_3$. The whole was extracted with CH_2Cl_2. The product was purified by silica gel column chromatography to afford a mixture of γ-tolylsulfinyl γ-lactones.

^{i}PrMgCl (2.0 mol/L, in THF; 0.41 mL) was added to a solution of the γ-tolylsulfinyl γ-lactones (60.6 mg; 0.135 mmol) at −78 °C with stirring under argon atmosphere. The solution was stirred for 15 min at −78 °C and the reaction was quenched by adding satd aq NH_4Cl. The whole was extracted with $CHCl_3$. The product was purified by silica gel column chromatography to afford **16a** (37.5 mg; 78%; three steps) as colorless crystals; mp 128–129 °C (hexane); IR (KBr) 2923, 1765 (CO), 1494, 1453, 1365, 1131, 1025, 1015 cm^{-1}; ^{1}H NMR δ 1.21 (3H, s), 1.84 (3H, s), 3.35 (1H, s), 3.78 (1H, d, $J = 9.0$ Hz),

3.86 (2H, d, $J = 14.1$ Hz), 3.92 (1H, d, $J = 9.0$ Hz), 3.98 (2H, d, $J = 14.1$ Hz), 7.26–7.29 (2H, m), 7.34–7.37 (4H, m), 7.45–7.47 (4H, m). Anal. Calcd for $C_{20}H_{23}NO_2$: C, 77.64; H, 7.49; N, 4.53. Found: C, 77.53; H, 7.35; N, 4.28. $[\alpha]_D^{29} = +137$ (*c* 0.47, ethanol).

3.25. (*R*)-(−)-(4,4-Dimethyl-2-oxotetrahydrofuran-3-yl)-carbamic acid methyl ester 17

10% Pd on carbon (83 mg) was added to a solution of **16a** (83 mg; 0.268 mmol) in 15 mL of 4.4% formic acid in methanol at room temperature. The solution was stirred for 2 h at 40 °C. The Pd on carbon was filtered off, and the filtrate was concentrated in vacuo to give a residue. Methyl chloroformate (0.024 mL; 0.32 mmol) was added to a solution of the residue in 4 mL of water and 0.3 mL of 1 M K_2CO_3 at 0 °C with stirring. The reaction mixture was stirred for 3 h at room temperature. The whole was extracted with diethyl ether. The product was purified by silica gel column chromatography to afford **17** (33.1 mg; 66%) as colorless crystals; mp 94–95 °C (hexane); IR (KBr) 3321 (NH), 2960, 2924, 1775 (CO), 1763 (CO), 1728 (CO), 1715 (CO), 1554, 1259, 1064 cm^{-1}; ^1H NMR δ 1.01 (3H, s), 1.26 (3H, s), 3.73 (3H, s), 4.04 (2H, m), 4.42 (1H, d, $J = 7.8$ Hz), 5.04 (1H, s). $[\alpha]_D^{28} = -82$ (*c* 1.0, $CHCl_3$).

3.26. (*R*)-(+)-4-Dibenzylamino-2-oxaspiro[4.5]decan-3-one 16b

Colorless crystals; mp 116–117 °C (hexane); IR (KBr) 3020, 2936, 1765 (CO), 1216, 757, 669 cm^{-1}; ^1H NMR δ 1.23–1.81 (10H, m), 3.27 (1H, s), 3.80 (2H, d, $J =$ 13.7 Hz), 3.84 (1H, d, $J = 9.3$ Hz), 3.87 (2H, d, $J =$ 13.7 Hz), 4.14 (1H, d, $J = 9.3$ Hz), 7.24–7.29 (2H, m), 7.32–7.38 (4H, m), 7.44–7.48 (4H, m). Anal. Calcd for $C_{23}H_{27}NO_2$: C, 79.05; H, 7.79; N, 4.01. Found: C, 79.00; H, 7.65; N, 3.77. $[\alpha]_D^{27} = +91.5$ (*c* 1.0, ethanol, 99% ee).

3.27. 2-Chloro-2-(*p*-tolylsulfinyl)ethanol 18

A solution of (*R*)-(−)-**2** (100 mg; 0.53 mmol) in 1 mL of dry THF was added dropwise to a solution of LDA (0.74 mmol) in 4 mL of THF at −65 °C. The solution was stirred at −65 °C for 10 min, and then methyl formate (0.164 mL; 2.65 mmol) was added. The reaction mixture was stirred for 10 min and the reaction was quenched with satd aq NH_4Cl. The whole was extracted with CH_2Cl_2 and the organic layer was washed with satd aq NH_4Cl and dried over $MgSO_4$. The solvent was evaporated to give a solid residue. A solution of $NaBH_4$ (19.4 mg) in 2 mL of ethanol was added dropwise to a solution of the solid residue in 3 mL of ethanol at room temperature for 20 min, then the reaction was quenched by adding NH_4Cl. The solvent was evaporated and the residue was extracted with $CHCl_3$. The organic layer was washed with satd aq NH_4Cl and dried over $MgSO_4$. The solvent was evaporated and the residue was purified by silica gel column chromatography to give **18** (116 mg; two steps 82%; about 4:1 diastereomeric mixture) as a colorless oil; IR (neat) 3391 (OH), 2924, 1651, 1596, 1494, 1455, 1086 (SO), 1039, 813 cm^{-1}; ^1H NMR δ 2.43 (0.6H, s), 2.44 (2.4H, s), 3.75–3.78 (1H, m), 4.16–4.22 (1H, m), 4.29–4.36 (1H, m), 4.50 (0.8H, dd, $J = 5.3$, 3.7 Hz), 4.65 (0.2H, dd, $J = 7.7$, 5.3 Hz), 7.36 (2H, d, $J = 8.0$ Hz), 7.55 (0.4H, d, $J = 8.3$ Hz), 7.68 (1.6H, d, $J = 8.3$ Hz). MS *m*/*z* (%) 218 (M^+, 6), 171 (4), 166 (4), 140 (100), 139 (70), 123 (8), 111 (7), 92 (63), 91 (42). Calcd for $C_9H_{11}ClO_2S$: *M*, 218.0168. Found *m*/*z* 218.0167.

3.28. (*R*)-1-Chloroethenyl *p*-tolyl sulfoxide 9d

To a solution of **18** (100 mg; 0.46 mmol) in 5 mL of dry CH_2Cl_2 was added triethylamine (0.46 mL; 3.45 mmol) followed by methanesulfonyl chloride (0.09 mL; 1.15 mmol) with stirring at 0 °C. The reaction mixture was stirred at 0 °C for 10 min and at room temperature for 6 h. The reaction was quenched with water, and the whole was extracted with CH_2Cl_2. The organic layer was washed successively with 10% HCl and satd $NaHCO_3$. The organic layer was dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by silica gel column chromatography to afford **9d** (84 mg; 92%) as a colorless oil; IR (neat) 3100, 3008, 2925, 1606 (C=C), 1492, 1454, 1399, 1092, 1063 (SO), 906 cm^{-1}; ^1H NMR δ 2.42 (3H, s), 5.96 (1H, d, $J = 3.0$ Hz), 6.44 (1H, d, $J = 3.0$ Hz), 7.32, 7.60 (each 2H, d, $J = 8.1$ Hz). MS *m*/*z* (%) 200 (M^+, 20), 152 (48), 139 (100), 123 (23), 117 (17), 91 (38). Calcd for C_9H_9ClOS: *M*, 200.0053. Found *m*/*z* 200.0063.

3.29. *tert*-Butyl 2-dibenzylamino-4-chloro-4-(*p*-tolylsulfinyl)-butanoate 15c

Colorless oil; IR (neat) 2977, 2930, 1722 (CO), 1494, 1455, 1368, 1150, 1086, 1057 (SO), 751 cm^{-1}; ^1H NMR δ 1.52 (9H, s), 2.1–2.2 (1H, m), 2.42 (3H, s), 2.6–2.7 (1H, m), 3.53 (1H, dd, $J = 8.0$, 6.1 Hz), 3.62, 3.80 (each 2H, d, $J = 13.6$ Hz), 4.57 (1H, dd, $J = 10.7$, 6.0 Hz), 7.21–7.37 (12H, m), 7.43–7.47 (2H, m). MS *m*/*z* (%) 511 (M^+, 0.1), 494 (10), 422 (27), 420 (70), 358 (30), 272 (100), 254 (42), 236 (35), 180 (25), 139 (25), 91 (100). Calcd for $C_{29}H_{34}ClNO_3S$: *M*, 511.1948. Found; *m*/*z* 511.1941.

3.30. (*R*)-(+)-3-Dibenzylaminodihydrofuran-2-one 16c

Colorless oil; IR (neat) 2919, 1770 (CO), 1494, 1455, 1373, 1180, 1150, 1022, 750 cm^{-1}; ^1H NMR δ 2.2–2.3 (2H, m), 3.68, 3.92 (2H, d, $J = 13.7$ Hz), 3.76 (1H, t, $J = 9.5$ Hz), 4.08–4.12 (1H, m), 4.30–4.36 (1H, m), 7.24–7.27 (2H, m), 7.29–7.34 (4H, m), 7.40–7.44 (4H, m). MS *m*/*z* (%) 281 (M^+, 5), 196 (20), 190 (10), 146 (88), 132 (25), 91 (100). Calcd for $C_{18}H_{19}NO_2$: *M*, 281.1416. Found: *m*/*z* 281.1412. $[\alpha]_D^{28} = +26.5$ (*c* 0.22, ethanol).

3.31. *tert*-Butyl 2-{1-[chloro(*p*-tolylsulfinyl)methyl]cyclopentadecyl}propionate 19a

tert-Butyl propionate (0.36 mL; 2.4 mmol) was added to a solution of LDA (0.6 mmol) in the presence of HMPA (0.4 mL; 2.4 mmol) in 5 mL of dry THF at −78 °C with stirring. The solution was stirred for 10 min, then a solution of **9c** (47.4 mg; 0.12 mmol) in THF (0.5 mL) was added. The reaction mixture was stirred at −78 °C for 5 min and the reaction temperature was allowed to warm

to −50 °C, and was stirred for 2 h. The reaction was quenched by adding satd aq NH_4Cl. The whole was extracted with $CHCl_3$. The organic layer was washed with satd aq NH_4Cl and dried over $MgSO_4$. The product was purified by silica gel column chromatography to afford **19a** (58.6 mg; 93%) as colorless oil (ca. 9:1 diastereomeric mixture); IR (neat) 2928, 2857, 1728 (CO),1715 (CO), 1597, 1456, 1368, 1256, 1153, 1057 (SO) cm^{-1}; ^1H NMR δ 1.29 (3H, d, $J = 7.2$ Hz), 1.2–1.5 (28H, m), 1.46 (9H, s), 2.42 (0.3H, s), 2.43 (2.7H, s), 2.87 (0.1H, q, $J = 7.2$ Hz), 3.04 (0.1H, q, $J = 7.2$ Hz), 3.21 (0.9H, q, $J = 7.2$ Hz), 3.42 (0.9H, q, $J = 7.2$ Hz), 4.60 (0.1H, s), 5.05 (0.9H, s), 7.31 (1.8H, d, $J = 8.4$ Hz), 7.71 (0.2H, d, $J = 7.8$ Hz), 7.74 (1.8H, d, $J = 8.4$ Hz). MS m/z (%) 524 (M^+, trace), 507 (trace), 451 (10), 329 (30), 293 (100), 275 (13), 236 (8), 219 (38), 140 (80), 95 (14). Calcd for $C_{30}H_{49}ClO_3S$: M, 524.3091. Found: m/z 524.3088.

3.32. *tert*-Butyl 2-{1-[chloro(*p*-tolylsulfinyl)methyl]cyclopentadecyl}butanoate 19b

Colorless oil (ca. 9:1 diastereomeric mixture); IR (neat) 2929, 2857, 1723 (CO), 1459, 1367, 1148, 1083, 1057 (SO), 810 cm^{-1}; ^1H NMR (the main product is reported) δ 0.88 (3H, t, $J = 7.2$ Hz), 1.2–1.5 (30H, m), 1.50 (9H, s), 2.43 (3H, s), 2.76 (1H, dd, $J = 9.6$, 4.8 Hz), 4.90 (1H, s), 7.31, 7.72 (each 2H, d, $J = 8.4$ Hz). MS m/z (%) 538 (M^+, trace), 465 (8), 343 (43), 307 (100), 289 (15), 261 (11), 219 (32), 140 (57), 139 (18). Calcd for $C_{31}H_{51}ClO_3S$: M, 538.3248. Found: m/z 538.3248.

3.33. *tert*-Butyl {1-[(*p*-tolylsulfinyl)methyl]cyclopentacecyl}-propionate 20a

Colorless oil; IR (neat) 2929, 2857, 1717 (CO), 1457, 1367, 1249, 1147, 1084, 1048 (SO), 850, 810 cm^{-1}; ^1H NMR δ 1.30 (3H, d, $J = 7.8$ Hz), 1.2–1.5 (28H, m), 1.43 (9H, s), 2.41 (3H, s), 2.65 (1H, q, $J = 7.8$ Hz), 2.90, 3.05 (each 1H, d, $J = 14.4$ Hz), 7.31, 7.59 (each 2H, d, $J = 7.8$ Hz). MS m/z (%) 490 (M^+, trace), 474 (12), 417 (10), 344 (12), 296 (22), 295 (100), 277 (15), 140 (25), 83 (70). Calcd for $C_{30}H_{50}O_3S$: M, 490.3480. Found: m/z 490.3480.

3.34. *tert*-Butyl {1-[(*p*-tolylsulfinyl)methyl]cyclopentadecyl}-butanoate 20b

Colorless oil; IR (neat) 2391, 2857, 1715 (CO), 1460, 1366, 1257, 1147, 1084, 1044 (SO), 811 cm^{-1}; ^1H NMR δ 0.93 (3H, t, $J = 7.2$ Hz), 1.2–1.5 (28H, m), 1.44 (9H, s), 1.6–1.9 (2H, m), 2.37–2.40 (1H, m), 2.40 (3H, s), 2.85, 3.09 (each 1H, d, $J = 14.4$ Hz), 7.31, 7.59 (each 2H, d, $J = 7.8$ Hz). MS m/z (%) 504 (M^+, trace), 488 (10), 431 (12), 344 (13), 309 (100), 291 (23), 140 (23), 97 (11). Calcd for $C_{31}H_{52}O_3S$: M, 504.3637. Found: m/z 504.3632.

3.35. *tert*-Butyl 2,3,3-trimethyl-4-(*p*-tolylsulfinyl)butanoate 22

Colorless oil (ca. 4:1 diastereomeric mixture); IR (neat) 2973, 2874, 1721 (CO), 1459, 1367, 1254, 1223, 1146, 1085 (SO), 1043, 849, 811 cm^{-1}; ^1H NMR δ 1.10 (2.4H, d, $J = 7.2$ Hz), 1.12 (0.6H, d, $J = 7.2$ Hz), 1.25 (0.6H, s), 1.26 (2.4H, s), 1.31 (0.6H, s), 1.32 (2.4H, s), 1.47 (9H, s), 2.41 (3H, s), 2.43 (0.8H, q, $J = 7.2$ Hz), 2.55 (0.2H, q, $J = 7.2$ Hz), 2.66 (0.8H, d, $J = 13.8$ Hz), 2.82 (0.2H, d, $J = 14.4$ Hz), 2.89 (0.2H, d, $J = 14.4$ Hz), 2.97 (0.8H, d, $J = 13.8$ Hz), 7.32 (2H, d, $J = 7.8$ Hz), 7.51 (1.6H, d, $J = 7.8$ Hz), 7.52 (0.4H, d, $J = 7.8$ Hz). MS m/z (%) 324 (M^+, trace), 308 (5), 269 (100), 267 (70), 251 (23), 213 (19), 177 (18), 155 (16), 140 (38), 129 (77). Calcd for $C_{18}H_{28}O_3S$: M, 324.1759. Found: m/z 324.1768.

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