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Reduction of carboxylic esters to ethers with triethyl silane in the combined use of titanium tetrachloride and trimethylsilyl trifluoromethanesulfonate

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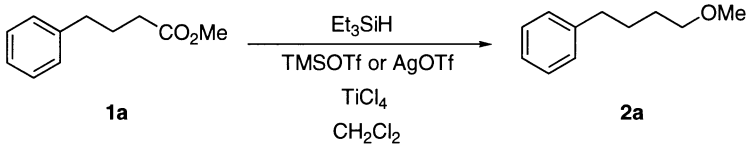
Abstract—Aliphatic acyclic and cyclic ethers are prepared on treatment of their corresponding carboxylic esters and lactones with triethylsilane in the presence of titanium tetrachloride and trimethylsilyl trifluoromethanesulfonate.

1. Introduction

The reduction of carboxylic esters to the corresponding alcohols, for example, with lithium aluminium hydride ($LiAlH_4$), has been a widely used synthetic method, however there are a few reports on the reduction of carboxylic esters to ethers. Pettit and his co-workers have reported the reduction of carboxylic esters to ethers with boron trifluoride etherate and metal hydride, sodium borohydride ($NaBH_4$), in diglyme—tetrahydrofuran being the most satisfactory.[1] The yields of ethers are greatly correlated with the bulkiness of the ester alcohol groups in such reductions. While reduction of the methyl ester of 5β-cholanic acid gave the corresponding methyl ether in only 7% yield, reduction of the secondary and tertiary butyl esters gave ethers in 41 and 76% yields, respectively. Tsurugi et al. also achieved the conversion of carboxylic esters to ethers with trichlorosilane (Cl_3SiH) under γ-irradiation.[2] Only alkyl aliphatic carboxylates could be reduced to the corresponding ethers in good yields. Recent work of Cutler and his co-workers have established the process of manganese acetyl complexes catalyzed hydrosilylation of carboxylic esters, however, only esters of straight-chain carboxylic acids have cleanly yielded their corresponding ethers.[3] In previous papers, we have already reported that cyclic ethers are prepared from lactones on treatment with silyl

Table 1. Reduction of **1a** with Et_3SiH in the presence of $TiCl_4$ and TMSOTf or AgOTf



1a **2a**

Entry	Et_3SiH (mol)	$TiCl_4$ (mol)	TMSOTf (mol)	AgOTf (mol)	TMSCI (mol)	Yield (%)	
						2a	**1a**
1	5.0	3.0	–	–	–	27	61
2	5.0	1.5	0.5	–	–	35	54
3	5.0	1.5	1.5	–	–	65	14
4	5.0	1.5	3.0	–	–	81	–
5	3.0	1.5	3.0	–	–	58	–
6	5.0	–	3.0	–	–	–	88
7	5.0	1.5	–	3.0	–	63	–
8	5.0	1.5	–	3.0	3.0	76	–

Keywords: triethylsilane; titanium tetrachloride; trimethylsilyl trifluoromethanesulfonate.
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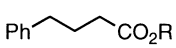
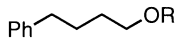
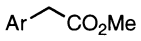
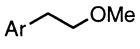
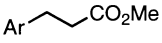
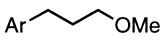
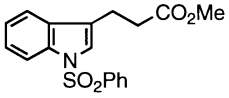
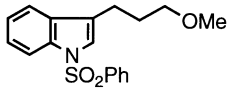
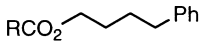
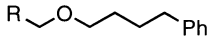
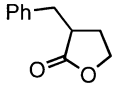
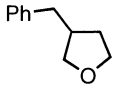
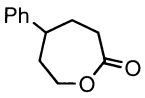
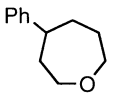
Table 2. Reduction of esters with Et_3SiH in the presence of $TiCl_4$ and TMSOTf

entry	Ester		Ether	yield (%)
				
1	R = Me	**(1a)**		81
2	= Et	**(1b)**		78
3	= nBu	**(1c)**		79
4	= iPr	**(1d)**		(39)[a]
5	= cHex	**(1e)**		(34)[b]
6	= Ph	**(1f)**		(67)[c]
				
7	Ar = Ph	**(1g)**		40
8	=4-Br-C_6H_4-	**(1h)**		80
9	= 4-O_2N-C_6H_4-	**(1i)**		72
				
10	Ar = Ph	**(1j)**		75
11	= 4-MeO-C_6H_4-	**(1k)**		89
12		**(1l)**		43
				
13	R = iPr	**(1m)**		72
14	R = tBu	**(1n)**		65
15		**(1o)**		67
16		**(1p)**		40[d]

[a]The product was 4-phenylbutanol (**3**). **1d** was recovered in 41% yield.
[b]The product was 4-phenylbutanol (**3**). **1e** was recovered in 51% yield.
[c]The product was 4-phenylbutanol (**3**).
[d]**1p** was recovered in 13% yield.

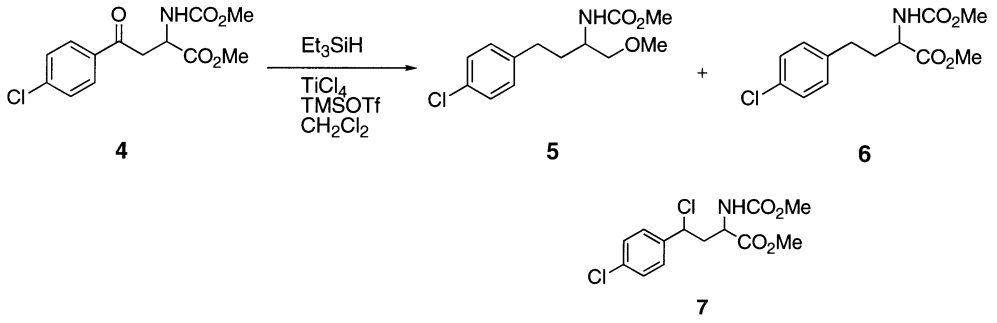
nucleophiles by promotion of trityl salt such as triphenylmethylium hexachloroantimonate ($TrSbCl_6$), or by the catalyst system of antimony pentachloride ($SbCl_5$) with chlorotrimethylsilane (TMSCl) and tin(II) iodide (SnI_2).[4] In the case of acyclic esters, however, these catalysts are unable to promote such reduction effectively.

In this paper, we would like to report a convenient synthesis of several acyclic and cyclic ethers from the corresponding carboxylic esters, with triethylsilane (Et_3SiH) in the presence of titanium tetrachloride ($TiCl_4$) and trimethylsilyl trifluoromethanesulfonate (TMSOTf).

2. Results and discussion

To begin with the reduction of methyl 4-phenylbutylate (**1a**) using 5.0 mol equiv. of Et_3SiH and 3.0 mol equiv. of $TiCl_4$ in dichloromethane was carried out. Reaction gave desired methyl ether (**2a**) in only 27% yield, along with

Table 3. Synthesis of β-amino ether (**5**) by the reduction of aromatic ketone (**4**) with Et_3SiH in the presence of $TiCl_4$ and TMSOTf



Entry	Substrate	Et_3SiH (mol)	$TiCl_4$ (mol)	TMSOTf (mol)	Yield (%)		
					5	**6**	**7**
1	(*R*)-**4**	5.0	3.0	6.0	71	–	–
2	(*S*)-**4**	5.0	3.0	6.0	75	–	–
3	(*R*)-**4**	3.0	1.5	3.0	–	87	–
4	(*S*)-**4**	3.0	1.5	3.0	–	84	–
5	rac-**4**	3.0	3.0	–	–	25	38

recovery of **1a** in 61% yield (Table 1, entry 1). We then examined the reduction of **1a** using Et_3SiH in the presence of $TiCl_4$ and TMSOTf or AgOTf, in expectation of in situ formation of titanium triflate species, under several conditions. Results were summarized in Table 1.

The reaction has been accelerated by the combined use of $TiCl_4$ and TMSOTf (entries 2–4). When the reduction was carried out using 1.5 mol equiv. of $TiCl_4$ and 3.0 mol equiv. of TMSOTf, the reaction has proceeded smoothly and the yield of **2a** has been improved to 81% (entry 4). In the reaction using small excess amounts of Et_3SiH (3.0 mol equiv.), the yield of **2a** has been reduced to 58% (entry 5). Moreover, TMSOTf alone did not promote this reaction at all (entry 6).

In the reaction using $TiCl_4$ and AgOTf (2 equiv. with respect to $TiCl_4$), which has been reported to generate dichlorobis(trifluoromethanesulfonato)titanium ($TiCl_2(OTf)_2$) in situ,[5] the yield of **2a** was a 63% (entry 7). When TMSCl (2 equiv. with respect to $TiCl_4$) was added to the combination of $TiCl_4$ and AgOTf, the yield of **2a** has been improved to 76% (entry 8). These results suggested the titanium species generated in situ from $TiCl_4$ and AgOTf were identical with those generated from $TiCl_4$ and TMSOTf, and TMSCl played important role in the reduction of carboxylic esters to ethers. Study for details in the reaction mechanism is now under way.

Next, we examined the reduction of various carboxylic esters under the condition shown in entry 4 in Table 1. These results were summarized in Table 2. Reduction of carboxylic esters derived from primary alcohols (**1a–c**) gave corresponding ethers in good yields (entries 1–3), however, in the case of carboxylic esters derived from branched alcohols (**1d** and **e**) and phenyl ester (**1f**), reaction product was 4-phenylbutanol (**3**) instead of desired ethers. Substituents such as bromo (**1h**), nitro (**1i**) and methoxy (**1k**) group were inert for this hydrosilylation (entries 8, 9 and 11). In the case of the substrate which contains indole ring, this reaction gave corresponding ether in moderate yield, which was accompanied by 2,3-dihydrogenated product in 30% yield (entry 12). Although Cutler's method, using manganese acetyl complexes, gave satisfactory results only for straight-chain esters, our reduction using $TiCl_4$ and TMSOTf gave good results in the case of carboxylic esters derived from branched carboxylic acids (**1m** and **n**, entries 13 and 14). Moreover, this reaction has been applicable to the reduction of lactones (**1o** and **p**) to give desired cyclic ethers in good yields (entries 15 and 16).

The application is noted on Table 3 for the synthesis of β-amino ether by the reduction of methyl 4-(4-chlorophenyl)-2-methoxycarbonylamino-4-oxobutanoate (**4**). The ester (4) was easily prepared by Friedel–Crafts acylation of chlorobenzene with *N*-(methoxycarbonyl)aspartic anhydride.[6]

When the reduction of **4** was carried out using 5.0 mol equiv. of Et_3SiH in the presence of $TiCl_4$, reduction of both carbonyl moieties, ester and ketone groups took place to give the desired β-amino ethers (**5**) in 71% (>99% ee) yield for (*R*)-isomer from (*R*)-**4** and 75% (>99% ee) yield for (*S*)-isomer from (*S*)-**4** without racemization,[7] respectively (entries 1 and 2). On the other hand, in the case of the reduction of **4** using 3.0 mol equiv. of Et_3SiH, only the ketone moiety was reduced into methylene to give (**6**) in 87% (>99% ee) yield for (*R*)-isomer from (*R*)-**4** and in 84% (>99% ee) yield for (*S*)-isomer from (*S*)-**4** without racemization,[7] respectively (entries 3 and 4). We have already reported that the reduction of **4** using Et_3SiH and $TiCl_4$ gave **6** in 25% yield along with 4-chlorinated product (**7**) in 38% yield (entry 5).[6] These results suggest that the addition of TMSOTf into the Et_3SiH–$TiCl_4$ system prevents the chlorination of intermediate cation.

In conclusion, we have developed efficient methods for the preparation of aliphatic acyclic and cyclic ethers by the new reduction of their corresponding carboxylic esters with triethyl silane promoted through the combination of $TiCl_4$ and TMSOTf. Although there are a few effective reduction methods for converting carboxylic esters to ethers, this new

reduction proceeds smoothly even if the substrates are carboxylic esters of branched carboxylic acids, and is successfully applicable to the synthesis of optically active β-amino ethers.

3. Experimental

3.1. General

All melting points were taken in open capillary tubes on a melting point apparatus (Buchi 535) without correction. IR spectra were taken with an Analect RFX-65 spectrophotometer. ^{1}H NMR spectra were measured with a Gemini (Varian, 300 MHz), or a JNM GSX-400 (JEOL, 400 MHz) spectrometer with tetramethylsilane (TMS) as an internal standard. The mass spectra (MS), atmospheric pressure chemical ionization mass spectra (APCI-MS), electrospray ionization mass spectra (ESI-MS), electrical ionization mass spectra (EI-MS), and FAB-MS were obtained with a SSQ7000C (Finnigan MAT Inc.), an INCOS 50 (Finnigan MAT Inc.) or a JMS-HX 100 (JEOL) spectrometer. Optical rotations were measured on a Horiba SEPA-200 digital polarimeter. HPLC analysis was done with a Hitachi 638-30 (ultraviolet detection). Elemental analyses were obtained by using a Perkin–Elmer 2400, a Yanagimoto MT-3 or a YEW ion chromato IC-7000. Chromatography was performed using pre-coated Merck silica gel 60 GF_{254} plates, and Kanto silica gel 60 N (100–210 mesh) powder. In general, reactions were carried out in dry solvents under an argon atmosphere. Unless otherwise mentioned, all carboxylic esters were synthesized from the corresponding carboxylic acids and alcohols in a usual manner.

3.1.1. Methyl 3-(1-phenylsulfonylindol-3-yl)-propionate (1l). $SOCl_2$ (0.67 g, 5.63 mmol) was added dropwise to MeOH (10 ml) in an ice bath and the mixture was stirred at room temperature for 30 min. To this mixture was added 3-indole propionic acid (0.91 g, 4.81 mmol) at the same temperature. After being stirred at room temperature for 3 h, solvent was concentrated in vacuo. The residue was extracted with AcOEt. The AcOEt was washed with sat. $NaHCO_3$ solution and brine, and dried over Na_2SO_4. After removal of the solvent, the oily residue was purified by flash column chromatography on silica gel (eluent: hexane–AcOEt=2:1) to afford 0.97 g (99%) of methyl 3-(3-indolyl)-propionate as a colourless oil. IR (Neat): 3411, 1725, 1457, 1436, 1339, 1269, 1226, 1201, 1163 cm^{-1}. APCI-MS *m/z*: 204 (MH^+). ^{1}H NMR ($CDCl_3$) δ: 2.73 (2H, dd, *J*=8.7, 7.3 Hz), 3.11 (2H, dd, *J*=8.7, 7.3 Hz), 6.99–7.01 (1H, m), 7.09–7.22 (2H, m), 7.33–7.37 (1H, m), 7.58–7.62 (1H, m), 7.96 (1H, brs).

To a suspension of NaH (0.17 g, 4.25 mmol) in DMF (5 ml) was added dropwise a solution of methyl 3-(3-indolyl)-propionate (0.77 g, 3.79 mmol) in DMF (8 ml) in an ice bath and the mixture was stirred at the same temperature for 1 h. To this mixture was added dropwise a solution of $PhSO_2Cl$ (0.81 g, 4.59 mmol) in DMF (2 ml) at the same temperature. After being stirred at room temperature over night, the mixture was poured into ice water. The aqueous layer was extracted with AcOEt. The combined organic layer was washed with H_2O and brine, and dried over Na_2SO_4. After removal of the solvent, the oily residue was purified by column chromatography on silica gel (eluent: hexane–AcOEt=4:1) to afford 0.92 g (70%) of **1l** as pale yellow oily semi solid. IR (Nujol): 1729, 1456, 1447, 1363, 1176 cm^{-1}. APCI-MS *m/z*: 376 (M^++MeOH). ^{1}H NMR ($CDCl_3$) δ: 2.69 (2H, t, *J*=8.1 Hz), 3.00 (2H, t, *J*=8.1 Hz), 3.67 (3H, s), 7.21–7.55 (8H, m), 7.85 (2H, d, *J*=8.4 Hz), 7.99 (1H, d, *J*=8.2 Hz). Anal. calcd for $C_{18}H_{18}NO_4S$: C, 62.77; H, 5.27; N, 4.07; S, 9.31. Found: C, 62.95; H, 5.31; N, 4.20; S, 9.44.

3.1.2. (±)-α-Benzyl-γ-butyrolactone (1o). To a solution of benzaldehyde (2.00 g, 18.7 mmol) and γ-butyrolactone (3.22 g, 37.4 mmol) in toluene (40 ml) was added sodium methoxide (1.32 g, 24.5 mmol) at −10°C. After being stirred at the same temperature for 5 min, then at room temperature for 1.5 h, the mixture was diluted with AcOEt (30 ml). To this mixture was added dropwise conc. H_2SO_4 (1.35 ml) and H_2O (20 ml) in an ice bath. The organic layer was washed with sat. $NaHCO_3$ solution, H_2O and brine, and dried over Na_2SO_4. After removal of the solvent, the residue was washed with *i*-Pr_2O to afford 2.64 g (80%) of (±)-α-benzylidene-γ-butyrolactone as colourless crystals, mp 116–117°C. IR (Nujor): 1737, 1649 cm^{-1}. EI-MS *m/z*: 174 (M^+), 129, 115. ^{1}H NMR ($CDCl_3$) δ: 3.26 (2H, dt, *J*=3.0, 7.3 Hz), 4.47 (2H, t, *J*=7.3 Hz), 7.37–7.54 (5H, m), 7.58 (1H, t, *J*=3.0 Hz). Anal. calcd for $C_{11}H_{10}O_2$: C, 75.84; H, 5.79. Found: C, 75.81; H, 5.78.

A mixture of (±)-α-benzylidene-γ-butyrolactone (2.00 g, 11.5 mmol) and 10% Pd/C (210 mg) in EtOH (40 ml)–MeOH (10 ml) was stirred vigorously under 1 atm. H_2 for 2 h. Catalyst was removed by filtration. The solvent was removed in vacuo to afford 2.00 g (99%) of (±)-α-benzyl-γ-butyrolactone (**1o**) as a colourless oil. IR (Neat): 1769, 1454, 1375, 1204, 1185, 1149, 1023 cm^{-1}. GC–MS *m/z*: 176 (M^+), 147, 91. ^{1}H NMR ($CDCl_3$) δ: 1.92–2.06 (1H, m), 2.19–2.30 (1H, m), 2.75 (1H, dd, *J*=13.4, 9.5 Hz), 2.79–2.90 (1H, m), 3.26 (1H, dd, *J*=13.4, 3.5 Hz), 4.14 (1H, dt, *J*=9.2, 6.6 Hz), 4.23 (1H, dt, *J*=9.1, 3.2 Hz), 7.19–7.34 (5H, m). Anal. calcd for $C_{11}H_{12}O_2$: C, 74.98; H, 6.86. Found: C, 74.82; H, 7.01.

3.1.3. 4-Phenyl-6-hexanolide (1p). The mixture of 4-phenylcyclohexanone (1.2 g, 6.9 mmol) and *m*CPBA (1.8 g, 8.4 mmol) in $CHCl_3$ (24 ml) was stirred at room temperature for 20 h. The reaction mixture was diluted with AcOEt, washed with sat. $NaHCO_3$ solution, H_2O and brine, and dried over Na_2SO_4. After removal of the solvent, the residue was recrystallized from AcOEt–hexane to afford 1.05 g (80%) of **1p** as colourless needles, mp 100–101°C. IR (Nujol): 1743, 1457, 1389, 1247, 1174, 1150 cm^{-1}. EI-MS *m/z*: 190 (M^+), 148, 117, 91. ^{1}H NMR ($CDCl_3$) δ: 1.78–1.92 (1H, m), 2.00–2.20 (3H, m), 2.71–2.90 (3H, m), 4.31 (1H, ddd, *J*=13.4, 9.5, 1.5 Hz, 6-H), 4.40 (1H, ddd, *J*=15.6, 4.9, 2.6 Hz, 6-H), 7.16–7.27 (3H, m, aromatic), 7.29–7.36 (2H, m, aromatic). Anal. calcd for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42. Found: C, 75.76; H, 7.45.

3.1.4. (*R*)-Methyl 4-(4-chlorophenyl)-2-methoxycarbonylamino-4-oxobutanoate ((*R*)-4). $SOCl_2$ (1.5 g, 12.6 mmol) was added dropwise to a solution of (*R*)-4-(4-chlorophenyl)-2-methoxycarbonylamino-4-oxobutanoic acid[6] (2.3 g, 8.2

mmol) in MeOH (35 mL) at 0°C. The mixture was stirred at 0°C for 16 h. The reaction mixture was concentrated in vacuo. The residue was extracted with AcOEt. The AcOEt was washed with sat. $NaHCO_3$ solution and brine, and dried over Na_2SO_4. After removal of the solvent, the residue was purified by column chromatography on silica gel. Elution with AcOEt–hexane (1:2) gave 1.8 g (75%; >99% ee) of (*R*)-**4** as a colourless oil. IR (Neat): 3359, 1726, 1687 cm^{-1}. APCI-MS *m/z*: 302 and 300 (MH^+). ^1H NMR (DMSO-d_6) δ: 3.45–3.48 (2H, m, 3-H), 3.54 (3H, s, $NHCO_2Me$), 3.64 (3H, s, CO_2Me), 4.57–4.65 (1H, m, 2-H), 7.57–7.66 (1H, m, NH), 7.62 (2H, d, *J*=8.8 Hz, aromatic), 7.97 (2H, d, *J*=8.8 Hz, aromatic). Anal. calcd for $C_{13}H_{14}NO_5Cl$: C, 52.10; H, 4.71; N, 4.67; Cl, 11.83. Found: C, 52.22; H, 4.91; N, 4.42; Cl, 11.57.

3.1.5. (*S*)-Methyl 4-(4-chlorophenyl)-2-methoxycarbonylamino-4-oxobutanoate ((*S*)-4). This compound was obtained from (*S*)-4-(4-chlorophenyl)-2-methoxycarbonylamino-4-oxobutanoic acid[6] in 95% (>99% ee) yield as a colourless oil. IR (Neat): 3359, 1726, 1687 cm^{-1}. APCI-MS *m/z*: 302 and 300 (MH^+). ^1H NMR (DMSO-d_6) δ: 3.45–3.48 (2H, m, 3-H), 3.54 (3H, s, $NHCO_2Me$), 3.64 (3H, s, CO_2Me), 4.57–4.65 (1H, m, 2-H), 7.57–7.66 (1H, m, NH), 7.62 (2H, d, *J*=8.8 Hz, aromatic), 7.97 (2H, d, *J*=8.8 Hz, aromatic). Anal. calcd for $C_{13}H_{14}NO_5Cl$: C, 52.10; H, 4.71; N, 4.67; Cl, 11.83. Found: C, 52.08; H, 4.74; N, 4.57; Cl, 11.67. Chiral HPLC analysis was carried out under the following conditions: column, chiralcel OD-R (4.6× 150 mm); eluent, MeCN–H_2O (7:13), 0.5 mL/min; detector, 254 nm; retention time, (*R*)-**4** (26 min), (*S*)-**4** (24 min).

3.2. Reduction of esters or lactones (1) with Et_3SiH–$TiCl_4$–TMSOTf

The general procedure is exemplified by the reduction of methyl 4-phenylbutanoate (**1a**). To a solution of $TiCl_4$ (240 mg, 1.27 mmol) in CH_2Cl_2 (1.5 ml) was added dropwise a solution of TMSOTf (581 mg, 2.61 mmol) in CH_2Cl_2 (1 ml) in an ice bath. After being stirred at room temperature for 4 h, a solution of **1a** (147 mg, 0.83 mmol) and Et_3SiH (485 mg, 4.17 mmol) in CH_2Cl_2 (2 ml) was added in an ice bath. After being stirred at room temperature for 20 h, the reaction mixture was poured into ice-water. The aqueous layer was extracted with AcOEt. The combined organic layer was washed with H_2O and brine, and dried over Na_2SO_4. After removal of the solvent, the oily residue was subjected to silica gel preparative TLC (eluent: hexane–AcOEt=20:1) to afford 110 mg (81%) of 4-phenylbutyl methyl ether (**2a**) as a colourless oil. IR (Neat): 1603, 1496, 1453, 1387, 1152 cm^{-1}. GC–MS *m/z*: 164 (M^+), 132, 117, 104, 91, 45. ^1H NMR ($CDCl_3$) δ: 1.56–1.74 (2H, m), 2.63 (2H, t, *J*=7.5 Hz), 3.32 (3H, s), 3.39 (2H, t, *J*=7.9 Hz), 7.14–7.19 (3H, m), 7.24–7.30 (2H, m). Anal. calcd for $C_{11}H_{16}O$: C, 80.44; H, 9.82. Found: C, 80.15; H, 9.83.

3.2.1. 4-Phenylbutyl ethyl ether (2b). This compound was obtained from **1b** in 78% yield as a colourless oil. IR (Neat): 1495, 1453, 1377, 1353, 1127, 1112 cm^{-1}. GC–MS *m/z*: 178 (M^+), 132, 117, 104, 91, 59. ^1H NMR ($CDCl_3$) δ: 1.19 (3H, t, *J*=7.1 Hz), 1.57–1.74 (4H, m), 2.64 (2H, t, *J*=7.5 Hz), 3.42 (2H, t, *J*=6.2 Hz), 3.46 (2H, q, *J*=7.1 Hz), 7.14–7.19 (3H, m), 7.24–7.30 (2H, m). Anal. calcd for $C_{12}H_{18}O$: C, 80.85; H, 10.18. Found: C, 81.13; H, 9.98.

3.2.2. 4-Phenylbutyl butyl ether (2c). This compound was obtained from **1c** in 79% yield as a colourless oil. IR (Neat): 1496, 1453, 1373, 1115 cm^{-1}. GC–MS *m/z*: 206 (M^+), 132, 117, 104, 91. ^1H NMR ($CDCl_3$) δ: 0.92 (3H, t, *J*=6.4 Hz), 1.30–1.42 (2H, m), 1.50–1.74 (6H, m), 2.63 (2H, t, *J*=7.7 Hz), 3.40 (2H, q, *J*=6.4 Hz), 3.42 (2H, t, *J*=7.7 Hz), 7.13–7.19 (3H, m), 7.24–7.30 (2H, m). Anal. calcd for $C_{14}H_{12}O$: C, 81.50; H, 10.75. Found: C, 81.31; H, 10.67.

3.2.3. 2-Phenylethyl methyl ether (2g). This compound was obtained from **1g** in 40% yield as a colourless oil. IR (Neat): 1496, 1454, 1383, 1154 cm^{-1}. GC–MS *m/z*: 136 (M^+), 104, 91, 45. ^1H NMR ($CDCl_3$) δ: 2.89 (2H, t, *J*=7.1 Hz), 3.36 (3H, s), 3.61 (2H, t, *J*=7.1 Hz), 7.20–7.33 (5H, m). Anal. calcd for $C_9H_{12}O$: C, 79.37; H, 8.88. Found: C, 79.55; H, 8.76.

3.2.4. 2-(4-Bromophenyl)ethyl methyl ether (2h). This compound was obtained from **1h** in 80% yield as a colourless oil. IR (Neat): 1489, 1382, 1117, 1072, 1011 cm^{-1}. GC–MS *m/z*: 216 and 214 (M^+), 171 and 169, 135, 45. ^1H NMR ($CDCl_3$) δ: 2.83 (2H, t, *J*=7.0 Hz), 3.34 (3H, s), 3.58 (2H, t, *J*=7.0 Hz), 7.10 (2H, d, *J*=8.4 Hz), 7.41 (2H, d, *J*=8.4 Hz). Anal. calcd for $C_9H_{11}BrO$: C, 50.26; H, 5.15; Br, 37.15. Found: C, 50.11; H, 5.34; Br, 37.21.

3.2.5. 2-(4-Nitrophenyl)ethyl methyl ether (2i). This compound was obtained from **1i** in 72% yield as a colourless oil. IR (Neat): 1506, 1462, 1344, 1153 cm^{-1}. GC–MS *m/z*: 181 (M^+), 151, 45. ^1H NMR ($CDCl_3$) δ: 2.98 (2H, t, *J*=6.5 Hz), 3.35 (3H, s), 3.65 (2H, t, *J*=6.5 Hz), 7.39 (2H, d, *J*=8.8 Hz), 8.15 (2H, d, *J*=8.8 Hz). Anal. calcd for $C_9H_{11}NO_3$: C, 59.66; H, 6.12; N, 7.73. Found: C, 59.43; H, 6.17; N, 7.81.

3.2.6. 3-Phenylpropyl methyl ether (2j). This compound was obtained from **1j** in 75% yield as a colourless oil. IR (Neat): 1496, 1454, 1386, 1155 cm^{-1}. GC–MS *m/z*: 150 (M^+), 117, 91, 45. ^1H NMR ($CDCl_3$) δ: 1.84–1.94 (2H, m), 2.69 (2H, t, *J*=7.5 Hz), 3.34 (3H, s), 3.39 (2H, t, *J*=6.4 Hz), 7.15–7.21 (3H, m), 7.26–7.31 (2H, m). Anal. calcd for $C_{10}H_{14}O$: C, 79.96; H, 9.39. Found: C, 80.15; H, 9.53.

3.2.7. 3-(4-Methoxyphenyl)propyl methyl ether (2k). This compound was obtained from **1k** in 89% yield as a colourless oil. IR (Neat): 1512, 1463, 1299, 1246, 1177, 1118, 1037 cm^{-1}. GC–MS *m/z*: 180 (M^+), 148, 121, 91, 77, 45. ^1H NMR ($CDCl_3$) δ: 1.81–1.91 (2H, m), 2.63 (2H, dd, *J*=7.3, 8.1 Hz), 3.34 (3H, s), 3.38 (2H, t, *J*=6.4 Hz), 3.79 (3H, s), 6.83 (2H, d, *J*=8.8 Hz), 7.10 (2H, d *J*=8.8 Hz). Anal. calcd for $C_{11}H_{16}O_2$: C, 73.11; H, 8.99. Found: C, 73.30; H, 8.95.

3.2.8. 3-(1-Phenylsulfonylindol-3-yl)propyl methyl ether (2l). This compound was obtained from **1l** in 43% yield as a yellow oil. IR (Neat): 1447, 1369, 1175, 1119 cm^{-1}. APCI-MS *m/z*: 362 (M^++MeOH), 347 (M^++NH_4), 330 (MH^+). ^1H NMR ($CDCl_3$) δ: 1.89–1.99 (2H, m), 2.72–2.77 (2H, m),

3.34 (3H, s), 3.39 (2H, t, J=6.2 Hz), 7.20–7.34 (3H, m), 7.38–7.45 (2H, m), 7.47–7.54 (2H, m), 7.83–7.88 (2H, m), 7.99 (1H, dt, J=8.1, 0.9 Hz). Anal. calcd for $C_{18}H_{19}NO_3S$: C, 65.63; H, 5.81; N, 4.25; S, 9.73. Found: C, 65.46; H, 6.01; N, 4.33; S, 9.91.

3.2.9. 2-Isobutyl 4-phenylbutyl ether (2m). This compound was obtained from **1m** in 72% yield as a colourless oil. IR (Neat): 1447, 1369, 1175, 1119 cm^{-1}. GC–MS *m/z*: 206 (M^+), 131, 104. ^1H NMR ($CDCl_3$) δ: 0.89 (6H, d, J=6.8 Hz), 1.57–1.75 (4H, m), 1.85 (1H, sept, J=6.6 Hz), 2.64 (2H, t, J=7.7 Hz), 3.15 (2H, d, J=6.8 Hz), 3.42 (2H, t, J=6.2 Hz), 7.14–7.19 (3H, m), 7.24–7.31 (2H, m). Anal. calcd for $C_{14}H_{22}O$: C, 81.50; H, 10.75. Found: C, 81.59; H, 10.75.

3.2.10. 2,2-Dimethylpropyl 4-phenylbutyl ether (2n). This compound was obtained from **1n** in 65% yield as a colourless oil. IR (Neat): 1447, 1369, 1175, 1119 cm^{-1}. GC–MS *m/z*: 220 (M^+). ^1H NMR ($CDCl_3$) δ: 0.90 (9H, s), 1.56–1.76 (4H, m), 2.64 (2H, t, J=7.3 Hz), 3.42 (2H, t, J=6.3 Hz), 7.14–7.20 (3H, m), 7.25–7.30 (2H, m). Anal. calcd for $C_{15}H_{24}O$: C, 81.76; H, 10.98. Found: C, 81.58; H, 10.98.

3.2.11. 3-Benzyltetrahydrofuran (2o). This compound was obtained from **1o** in 67% yield as a colourless oil. IR (Neat): 3416, 1453, 1239, 1083, 1048, 1016 cm^{-1}. GC–MS *m/z*: 162 (M^+), 92, 70. ^1H NMR ($CDCl_3$) δ: 1.56–1.68 (1H, m), 1.94–2.05 (1H, m), 2.44–2.59 (1H, m), 2.68–2.71 (2H, m), 3.46 (1H, dd, J=8.4, 6.8 Hz), 3.72–3.94 (3H, m), 7.15–7.23 (3H, m), 7.25–7.32 (2H, m). Anal. calcd for $C_{11}H_{14}O$: C, 81.44; H, 8.70. Found: C, 81.42; H, 8.75.

3.2.12. 4-Phenyloxepane (2p). This compound was obtained from **1p** in 40% yield as a colourless oil. IR (Neat): 1492, 1451, 1136, 1123 cm^{-1}. GC–MS *m/z*: 176 (M^+), 132, 117, 104, 91. ^1H NMR ($CDCl_3$) δ: 1.77–1.99 (6H, m, 3-H, 5-H, 6-H), 2.75–2.85 (1H, m, 4-H), 3.64–3.79 (2H, m, 2-H or 7-H), 3.85–3.94 (2H, m, 7-H or 2-H), 7.15–7.23 (3H, m, aromatic), 7.27–7.33 (2H, m, aromatic). Anal. calcd for $C_{12}H_{16}O$: C, 81.77; H, 9.15. Found: C, 81.53; H, 9.26.

3.3. Reduction of methyl 4-(4-chlorophenyl)-2-methoxycarbonylamino-4-oxobutanoate (4) with Et_3SiH–$TiCl_4$–TMSOTf

3.3.1. Preparation of (*R*)-2-methoxycarbonylamino-4-(4-chlorophenyl)butyl methyl ether ((*R*)-5). To a solution of $TiCl_4$ (330 mg, 1.74 mmol) in CH_2Cl_2 (2 ml) was added dropwise a solution of TMSOTf (782 mg, 3.52 mmol) in CH_2Cl_2 (1 ml) in an ice bath. After being stirred at room temperature for 4 h, a solution of (*R*)-**4** (174 mg, 0.58 mmol) and Et_3SiH (358 mg, 3.08 mmol) in CH_2Cl_2 (2 ml) was added in an ice bath. After being stirred at room temperature for 20 h, the reaction mixture was poured into ice-water. The aqueous layer was extracted with AcOEt. The combined organic layer was washed with H_2O and brine, and dried over Na_2SO_4. After removal of the solvent, the oily residue was subjected to silica gel preparative TLC (eluent: hexane–AcOEt=2:1) to afford 112 mg (71%; >99% ee) of (*R*)-2-methoxycarbonylamino-4-(4-chlorophenyl)butyl methyl ether ((*R*)-**5**) as colourless crystals, mp 43.5–45°C. $[\alpha]_D^{20}$=+3.2° (c 0.5, $CHCl_3$). IR (Neat): 3350, 1691 cm^{-1}. APCI-MS *m/z*: 274 and 272 (MH^+, 1:3). ^1H NMR ($CDCl_3$) δ: 1.75–1.87 (2H, m, 3-H), 255–2.73 (2H, m, 4-H), 3.33 (3H, s, OMe), 3.39 (2H, d, J=3.9 Hz, 1-H), 3.68 (3H, s, CO_2Me), 3.72–3.85 (1H, m, 2-H), 4.81–4.95 (1H, m, NH), 7.12 (2H, d, J=8.4 Hz, aromatic), 7.24 (2H, d, J=8.4 Hz, aromatic). Anal. calcd for $C_{13}H_{18}NO_3Cl$: C, 57.46; H, 6.68; N, 5.15; Cl, 13.05. Found: C, 57.40; H, 6.55; N, 5.03; Cl, 13.01.

3.3.2. (*S*)-2-Methoxycarbonylamino-4-(4-chlorophenyl)-butyl methyl ether ((*S*)-5). This compound was obtained from (*S*)-**4** in 75% (>99% ee) yield as colourless crystals, mp 43.5–45°C. $[\alpha]_D^{20}$=−3.2° (c 0.5, $CHCl_3$). IR (Neat): 3350, 1705 cm^{-1}. APCI-MS *m/z*: 274 and 272 (MH^+, 1:3). ^1H NMR ($CDCl_3$) δ: 1.75–1.87 (2H, m, 3-H), 2.55–2.73 (2H, m, 4-H), 3.33 (3H, s, OMe), 3.39 (2H, d, J=3.9 Hz, 1-H), 3.68 (3H, s, CO_2Me), 3.72–3.85 (1H, m, 2-H), 4.81–4.95 (1H, m, NH), 7.12 (2H, d, J=8.4 Hz, aromatic), 7.24 (2H, d, J=8.4 Hz, aromatic). Anal. calcd for $C_{13}H_{18}NO_3Cl$: C, 57.46; H, 6.68; N, 5.15; Cl, 13.05. Found: C, 57.18; H, 6.59; N, 5.36; Cl, 12.89. Chiral HPLC analysis was carried out under the following conditions: column, chiralpak AD (4.6×250 mm); eluent: hexane–EtOH (9:1), 1.0 mL/min; detector, 220 nm; retention time, (*R*)-**5** (14 min), (*S*)-**5** (9 min).

3.3.3. Preparation of methyl 4-(4-chlorophenyl)-2-(methoxycarbonylamino)-butanoate ((*R*)-6). To a solution of $TiCl_4$ (214 mg, 1.13 mmol) in CH_2Cl_2 (1.5 ml) was added dropwise a solution of TMSOTf (514 mg, 2.31 mmol) in CH_2Cl_2 (1 ml) in an ice bath. After being stirred at room temperature for 4 h, a solution of (*R*)-**4** (223 mg, 0.74 mmol) and Et_3SiH (266 mg, 2.29 mmol) in CH_2Cl_2 (2 ml) was added in an ice bath. After being stirred at room temperature for 20 h, the reaction mixture was poured into ice-water. The aqueous layer was extracted with AcOEt. The combined organic layer was washed with H_2O and brine, and dried over Na_2SO_4. After removal of the solvent, the oily residue was subjected to silica gel preparative TLC (eluent: hexane–AcOEt=2:1) to afford 184 mg (87%; >99% ee) of (*R*)-methyl 4-(4-chlorophenyl)-2-(methoxycarbonylamino)butanoate ((*R*)-**6**) as a colourless oil. $[\alpha]_D^{20}$=−45.8° (c 1.1, $CHCl_3$). IR (Neat): 3335, 1725, 1533 cm^{-1}. APCI-MS *m/z*: 288 and 286 (MH^+, 1:3). ^1H NMR ($CDCl_3$) δ: 1.86–2.01 (1H, m, 3-H), 2.09–2.23 (1H, m, 3-H), 2.60–2.70 (2H, m, 4-H), 3.70 (3H, s, $NHCO_2Me$), 3.73 (3H, s, CO_2Me), 4.34–4.46 (1H, m, 2-H), 5.20–5.33 (1H, m, NH), 7.11 (2H, d, J=8.4 Hz, aromatic), 7.25 (2H, d, J=8.4 Hz, aromatic). Anal. calcd for $C_{13}H_{16}NO_4Cl$: C, 54.65; H, 5.64; N, 4.90; Cl, 12.41. Found: C, 54.39; H, 5.45; N, 4.66; Cl, 12.13.

3.3.4. (*S*)-Methyl 4-(4-chlorophenyl)-2-(methoxycarbonylamino)butanoate ((*S*)-6). This compound was obtained from (*S*)-**6** in 84% (>99% ee) yield as a colourless oil. $[\alpha]_D^{20}$=+45.6° (c 1.1, $CHCl_3$). IR (Neat): 3335, 1725, 1533 cm^{-1}. APCI-MS *m/z*: 288 and 286 (MH^+, 1:3). ^1H NMR ($CDCl_3$) δ: 1.86–2.01 (1H, m, 3-H), 2.09–2.23 (1H, m, 3-H), 2.60–2.70 (2H, m, 4-H), 3.70 (3H, s, $NHCO_2Me$), 3.73 (3H, s, CO_2Me), 4.34–4.46 (1H, m, 2-H), 5.20–5.33 (1H, m, NH), 7.11 (2H, d, J=8.4 Hz, aromatic), 7.25 (2H, d,

J=8.4 Hz, aromatic). Anal. calcd for $C_{13}H_{16}NO_4Cl$: C, 54.65; H, 5.64; N, 4.90; Cl, 12.41. Found: C, 54.83; H, 5.61; N, 4.74; Cl, 12.49. Chiral HPLC analysis was carried out under the following conditions: column, chiralpak AD (4.6×250 mm); eluent: hexane–EtOH (4:1), 1.0 mL/min; detector, 220 nm; retention time, (*R*)-**6** (8 min), (*S*)-**6** (12 min).

References

1. (a) Pettit, R. G.; Piatak, D. M. *J. Org. Chem.* **1962**, *27*, 2127–2130. (b) Pettit, R. G.; Kasturi, T. R. *J. Org. Chem.* **1961**, *26*, 4553–4556. (c) Pettit, R. G.; Ghatak, U. R.; Green, B.; Kasturi, T. R.; Piatak, D. M. *J. Org. Chem.* **1961**, *26*, 1685–1686.
2. Tsurugi, J.; Nakao, R.; Fukumoto, T. *J. Am. Chem. Soc.* **1969**, *91*, 4587–4588.
3. Mao, Z.; Gregg, B. T.; Cutler, A. R. *J. Am. Chem. Soc.* **1995**, *117*, 10139–10140.
4. Homma, K.; Takenoshita, H.; Mukaiyama, T. *Bull. Soc. Chem. Jpn* **1990**, *63*, 1898–1915.
5. (a) Noftle, R. E.; Cady, G. H. *Inorg. Chem.* **1966**, *5*, 2182–2185. (b) Miyashita, M.; Shiina, I.; Miyoshi, S.; Mukaiyama, T. *Bull. Chem. Soc. Jpn* **1993**, *66*, 1516–1527. (c) Miyashita, M.; Shiina, I.; Mukaiyama, T. *Bull. Chem. Soc. Jpn* **1994**, *67*, 210–215. (d) Yoshida, Y.; Hayashi, R.; Sumihara, H.; Tanabe, Y. *Tetrahedron Lett.* **1997**, *38*, 8727–8730.
6. (a) Yato, M.; Homma, K.; Ishida, A. *Heterocycles* **1995**, *41*, 17–20. (b) Yato, M.; Homma, K.; Ishida, A. *Heterocycles* **1998**, *49*, 233–254.
7. Optical purity of the products was determined with HPLC analysis. See Section 3.