Practical Enzymatic Desymmetrization of 2-(Ethoxycarbonyl)propane-1,3-diyl Dihexanoate and Model Cyclization for the A – D Ring System of Lysergic Acid

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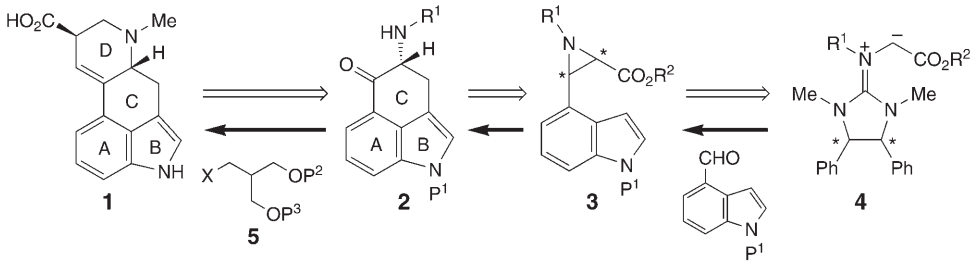
Porcine pancreas lipase-catalyzed hydrolysis of symmetrical 2-(ethoxycarbonyl)propane-1,3-diyl dihexanoate, under the modified conditions of the *Seebach* protocol, afforded a desymmetrized monohexanoate in 40–51% yield with 91–94% ee, even in a gram-scale reaction. The absolute configuration of a half-hydrolyzed (–)-product was determined to be (*R*) by conversion to a known 2-methylpropane-1,3-diol derivative. Samarium iodide-induced radical cyclization of 2-oxo-3-phenylethylamine with a C_4 unit on the N-atom, derived from the racemic monohexanoate, afforded a 3-phenylpiperidine derivative as a model construction of the A–D ring system of lysergic acid.

1. Introduction. – Lysergic acid (**1**), a tetracyclic indole derivative with two stereogenic centers, is the core unit of ergot alkaloids showing a wide spectrum of biological activities [1] such as prolactin inhibition, anti-*Parkinsonian* effect, and depression of hypertension. The total synthesis of racemic **1** has been reported by nine research groups [2], and two groups have successfully achieved the asymmetric synthesis [3]. We have explored a novel aziridination from guanidinium ylides and aromatic (or unsaturated) aldehydes, applicable to asymmetric synthesis [4], and designed the synthesis of bioactive N-containing compounds, including lysergic acid (**1**), using the formed aziridine as a key synthetic intermediate. Our retrosynthetic strategy of **1** is shown in *Scheme 1*, in which aziridine **3**, derived from guanidinium ylide **4** and 4-formyl-1*H*-indole, is reacted with an isobutyl-like C_4 unit **5** to build the D ring after construction of the A–B–C tricyclic ring system **2**. Recently, we reported the cyclization from the 4-position of the 1*H*-indole skeleton to the 3-position by application of the *Vilsmeier–Haack* reaction [5]. In this paper, we present the practical preparation of an optically active C_4 unit as the partial component of the D ring by enzymatic desymmetrization of 2-(ethoxycarbonyl)propane-1,3-diyl dihexanoate and the model cyclization for the A–D ring system of lysergic acid (**1**) by using the corresponding racemic C_4 unit.

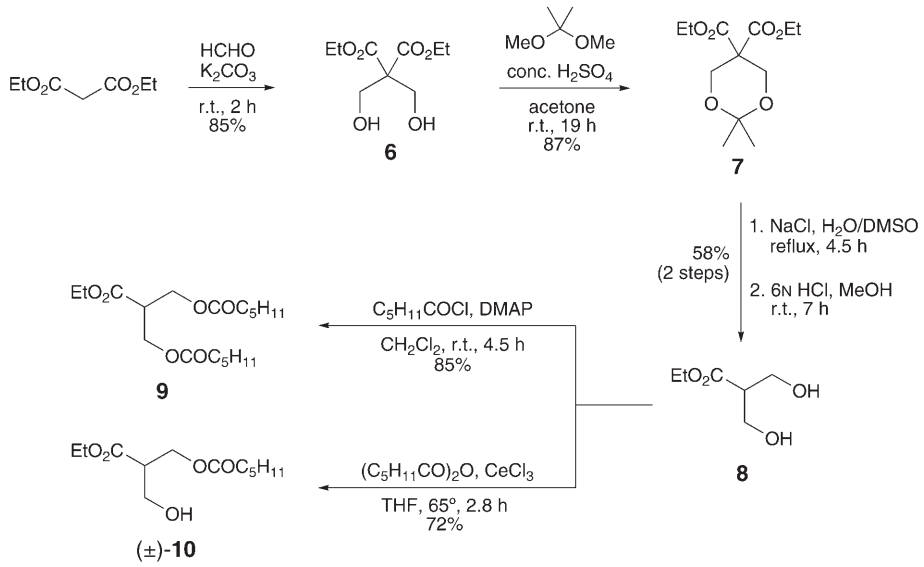
2. Results and Discussion. – 2.1. *Enzymatic Desymmetrization of 2-(Ethoxycarbonyl)propane-1,3-diyl Dihexanoate* (**9**). In 1990, *Ehrler* and *Seebach* reported the enzymatic desymmetrization of 2-(ethoxycarbonyl)propane-1,3-diyl dihexanoate (**9**) [6], in which a half-hydrolyzed (–)-monohexanoate (–)-**10** was obtained in 48% yield with 84% ee, when porcine pancreas lipase (PPL) was used as an enzyme in the

Scheme 1. *Retrosynthesis of Lysergic Acid* (**1**) *with Aziridine* **3** *as a Key Unit*



presence of MeOH as co-solvent. Therefore, we decided to re-examine *Seebach*'s protocol [6] using PPL and, thus, prepared the starting dihexanoate **9** and racemic monohexanoate (±)-**10**, as an authentic half-hydrolyzed product, from diethyl malonate according to the combination of reported procedures [6][1]) as shown in *Scheme 2*.

Scheme 2. *Preparation of 2-(Ethoxycarbonyl)propane-1,3-diyl Dihexanoate* (**9**) *and the Racemic Monohexanoate (±)-***10**

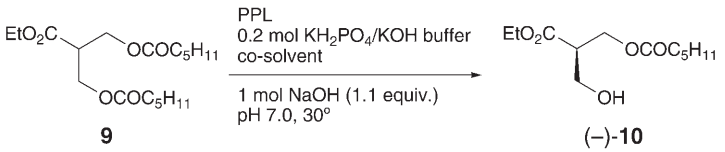


The results of the PPL-catalyzed desymmetrization are summarized in *Table 1*. At first, reactions with a small scale (0.1 g) of the dihexanoate **9** were examined as preliminary experiments (*Entries 1–7*). Application of the *Seebach*'s co-solvent system [6] of MeOH (*Entry 1*) as well as the use of THF as co-solvent (*Entry 7*) satisfactorily afforded an optically active half-hydrolyzed (–)-monohexanoate (–)-**10**, in spite of

[1]) For the conversion of diethyl malonate to **7**, see [7a–d]. For the conversion of **7** to **8**, see [7e]. For the conversion of **8** to (±)-**10**, see [7f].

long reaction time in the latter case. Next, gram-scale reactions were carried out under these two conditions. The product (−)-**10** was obtained in increased chemical yield without loss of enantioselectivity in the THF system (*Entry 9*), whereas lower enantioselectivity was observed in the MeOH one (*Entry 8*). Unfortunately, trial of further scale-up operation in the THF system resulted not only in longer reaction time, but also in lower enantioselectivity. Thus, it was concluded that a few gram scale operation in the THF system could be the best condition of this PPL-catalyzed desymmetrization of 2-(ethoxycarbonyl)propane-1,3-diyl dihexanoate (**9**).

Table 1. *PPL-Catalyzed Desymmetrization of 2-(Ethoxycarbonyl)propane-1,3-diyl Dihexanoate* (**9**)

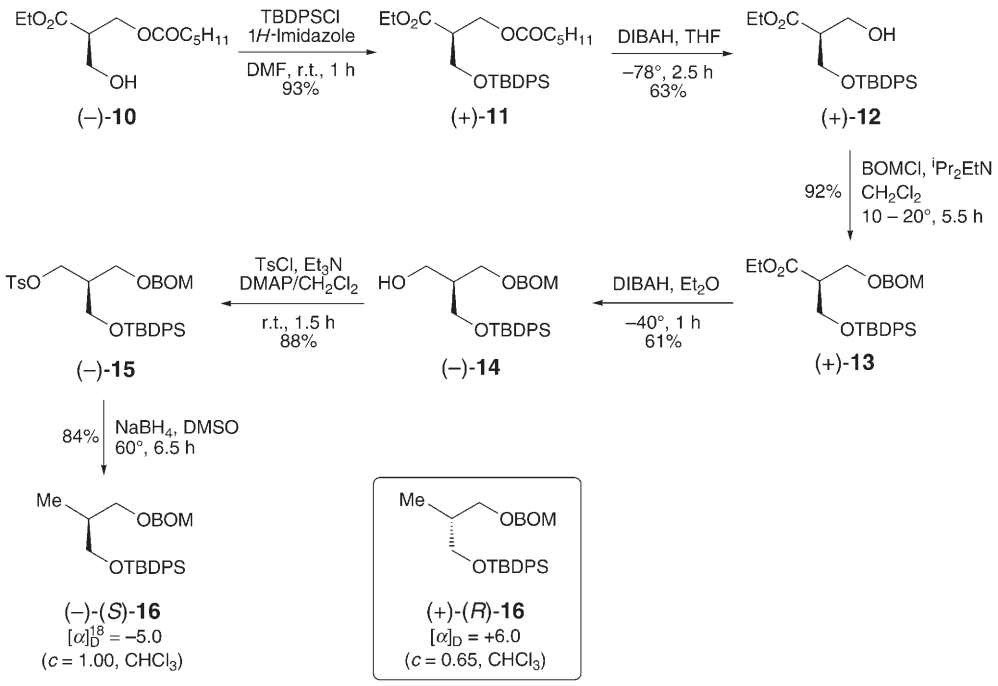


Entry	Scale [g]	Co-solvent[a])	Time [h]	(−)-**10**	
				Yield [%][b])	ee [%]
1	0.1	30% MeOH	1	25[c])	90
2	0.1	None	4	12	–[d])
3	0.1	10% ^{t}BuOH	2	1	–
4	0.1	10% DMSO	2	11	–
5	0.1	10% DMF	1	12	–
6	0.1	10% ^{i}Pr$_2$O	1	17	–
7	0.1	15% THF	20	30[c])	93
8	1	30% MeOH	1	34[c])	82
9	1	15% THF	7	51[c])	94
10	10	15% THF	168	38[c])	80

[a]) The percentage of co-solvent is a ratio to buffer solution. [b]) Estimated by ^{1}H-NMR. [c]) Isolated yield. [d]) Not measured.

Ehrler and *Seebach* had addressed the optical purity of the (−)-monohexanoate (−)-**10** by conversion to the corresponding *Mosher* ester [6]; however, we newly applied chiral HPLC method after benzoylation, in which a *CHIRALCEL OJ-H* column (hexane/^{i}PrOH 100:1) was used. The absolute configuration of the (−)-monohexanoate (−)-**10** has never been determined. Therefore, we determined it by chemical correlation with the known (+)-(*R*)-2-methyl-1,3-propanediol derivative (+)-(*R*)-**16** [8] as shown in *Scheme 3*. The (−)-monohexanoate (−)-**10** was reduced with diisobutylaluminum hydride (DIBAH) after protection of the OH moiety with the (*t*-Bu)Ph$_2$Si (TBDPS) group (→(+)-**11**). The obtained (+)-alcohol (+)-**12** was subjected to the successive treatments of protection with the (benzyloxy)methyl (BOM) group (→(+)-**13**), reduction with DIBAH (→(−)-**14**), introduction of a *p*-toluenesulfonyl (Ts) group (→(−)-**15**), and reductive cleavage with sodium borohydride ($NaBH_4$) in DMSO to give (−)-2-methylpropanediol derivative (−)-**16**. Thus, the opposite sign of optical rotation against the known (+)-compound with (*R*)-configuration indicated

Scheme 3. *Chemical Conversion of Enzymatically Hydrolyzed (−)-Monohexanoate (−)-***10** *to (−)-2-Methylpropane-1,3-diol Derivative (−)-***16**

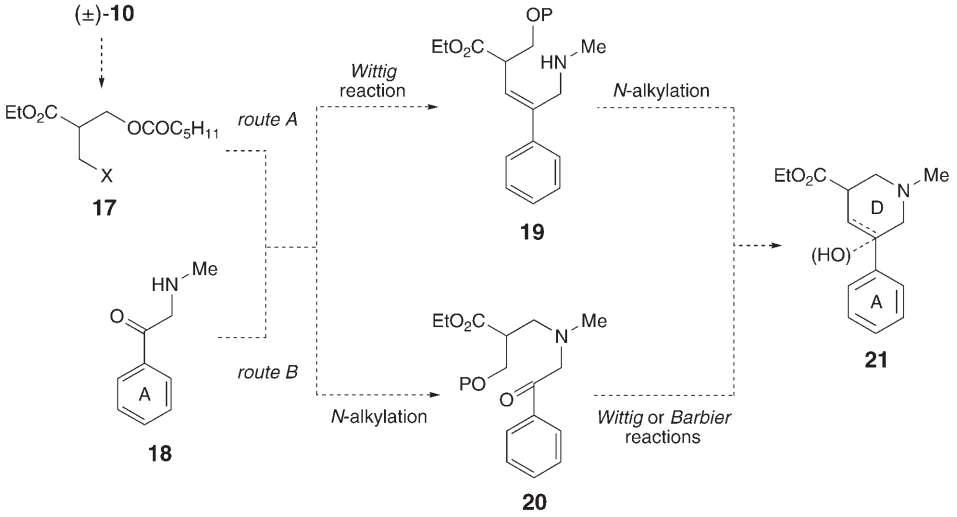


that the absolute configuration of (−)-monohexanoate (−)-**10**, obtained by PPL-catalyzed desymmetrization of dihexanote **9**, should be (*R*).

2.2. *Model Construction of the A – D Ring System of Lysergic Acid* (**1**). Next, we planed to prepare 5-(ethoxycarbonyl)-1-methyl-3-phenylpiperidine core **21** by reaction of the C_4 unit **17**, derivable from (±)-2-(ethoxycarbonyl)propane-1,3-diyl monohexanoate (±)-**10**, and *N*-methyl-2-oxo-2-phenylethylamine (**18**) for the model construction of **21**, *i.e.*, the A – D ring system of lysergic acid (**1**) as outlined in *Scheme 4*.

The starting amino ketone **18** was prepared as a trifluoroacetate salt from 2-hydroxy-*N*-methyl-2-phenylethylamine (**22**) by *Swern* oxidation after protection of the amino group with (*tert*-butoxy)carbonyl (Boc) group, followed by treatment with trifluoroacetic acid (TFA). On the other hand, according to route *A* in *Scheme 4*, conversion of the (±)-monohexanoate (±)-**10** to phosphonium salt **27** through bromination was attempted, but only elimination of the hexanoic acid moiety from the bromo derivative **25** occurred to give an olefinic phosphonium salt **26**. Alternatively, introduction of a different leaving group to (±)-**10** based on route *B* was achieved by mesylation; however, trials for *N*-alkylation of the amino ketone **18** or amino alcohol **22** using the mesylate **28** were failed; instead, mainly demesylation of **28** occurred (*Scheme 5*). These facts led us to alter the use of a C_4 unit from the monohexanoate **17** to the propane-1,3-diol derivative **31** lacking ester function (*Scheme 6*).

Scheme 4. *Synthetic Plan of 5-(Ethoxycarbonyl)-1-methyl-3-phenylpiperidine Core* **21** *for the Model Construction of the A – D Ring System of Lysergic Acid* (**1**)

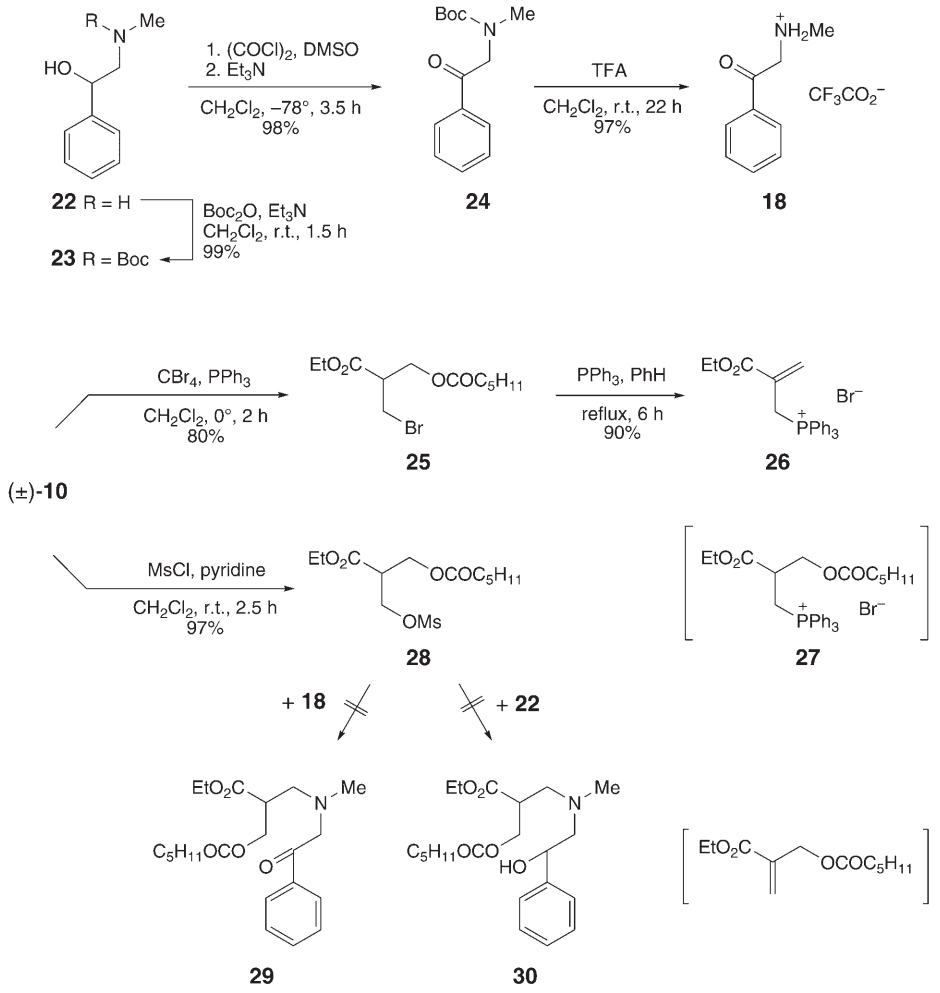


Preparation of some propane-1,3-diol derivatives without an ester function is depicted in *Scheme 7*. The key monosilyl derivative of 2-(ethoxycarbonyl)propane-1,3-diol **33** was prepared from (±)-**10** by silylation, followed by reductive hydrolysis. The monosilyl derivative **33** was also prepared by silylation of '2-(ethoxycarbonyl)propane-1,3-diol' (=ethyl 3-hydroxy-2-(hydroxymethyl)propanoate; **8**) under controlled conditions, in which the double-silylated product **34** was co-produced but could be re-used through desilylation. After protection of the OH group in **33** with the BOM or tetrahydropyranyl (THP) group, reduction with $LiBH_4$ afforded the corresponding diprotected 2-(hydroxymethyl)propane-1,3-diols **37** or **38**. Chemical modifications of them to bromides **39** and **40**, or methanesulfonates **41** and **42**, respectively, were achieved by either displacement of the OH group with Br or by mesylation.

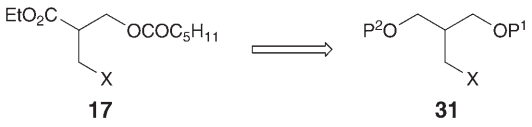
Trials for conversion of bromides **39** and **40** to the corresponding phosphonium salts for *Wittig* reaction resulted in the recovery of the starting materials. On the other hand, although trials for *N*-alkylation with methanesulfonates **41** or **42** by using the amino ketone **18** as a nucleophile failed, desired alkylation products **43** or **44** were obtained as an inseparable mixture of diastereoisomers in 61 and 73% yields, respectively, when amino alcohol **22** was treated with Et_3N and KI in DMF (*Scheme 8*). However, it was found that oxidation products such as **45**, produced by *Swern* oxidation, were quite labile in pure forms. Survey of the literature indicated no reports on the oxidation of amino alcohols like **43** or **44**, whereas smooth conversion of a 1-alkyl- [9] or an *N*-acyl-substituted amino alcohol, **46** and **48** [10], respectively, to the corresponding ketone products **47** and **49**, respectively, were observed. Therefore, the amines **43** or **44** for oxidation were changed to the corresponding *N*-Boc-protected derivatives.

Oxidation of *N*-Boc-amino alcohol **51**, derived from 2-hydroxy-2-phenylethylamine (**50**), with pyridinium dichromate (PDC) in DMF, as expected, gave the ketone **52** in

Scheme 5. *Preparation of* N*-Methyl-2-oxo-2-phenylethylamine* (**18**), *Manipulation of* (±)*-2-(Ethoxycarbonyl)propane-1,3-diyl Monohexanoate* (±)-**10**, *and Trials for* N*-Alkylation*

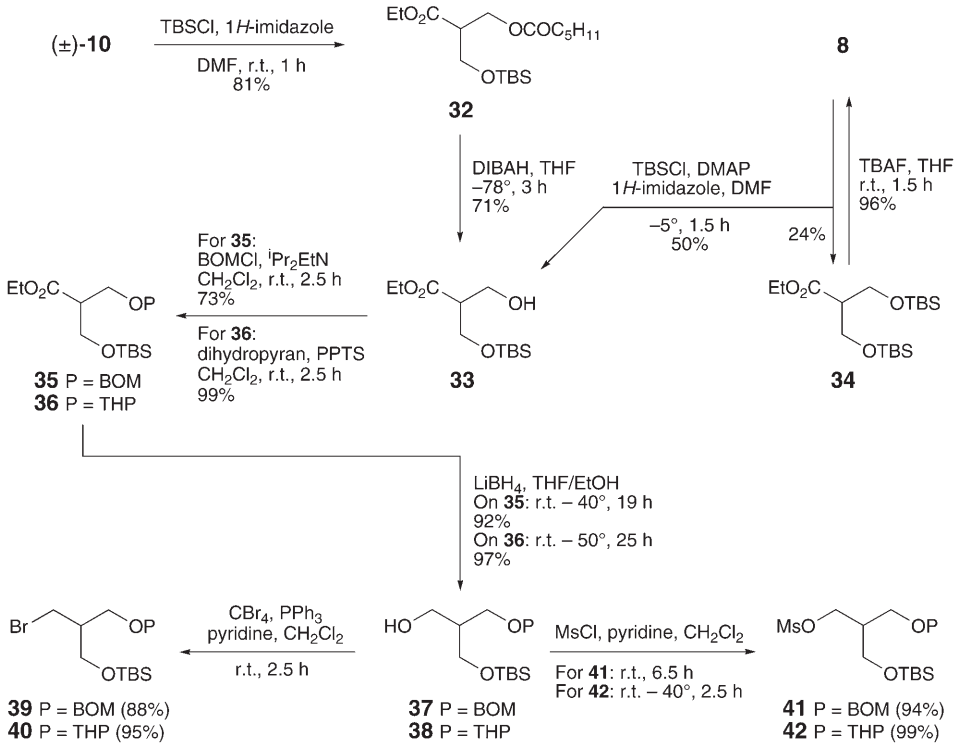


Scheme 6. *Alternation of a* C_4 *Unit from the Monohexanoate* **17** *to Propane-1,3-diol Derivative* **31** *without an Ester Function*



94% yield (*Scheme 9*). However, treatment of these *N*-Boc-protected amines **51** or **52** with BOM-protected methanesulfonate **41** did not afford alkylation products **53** or **54**. Fortunately, it was found that the original amino alcohol **50** itself could serve as a

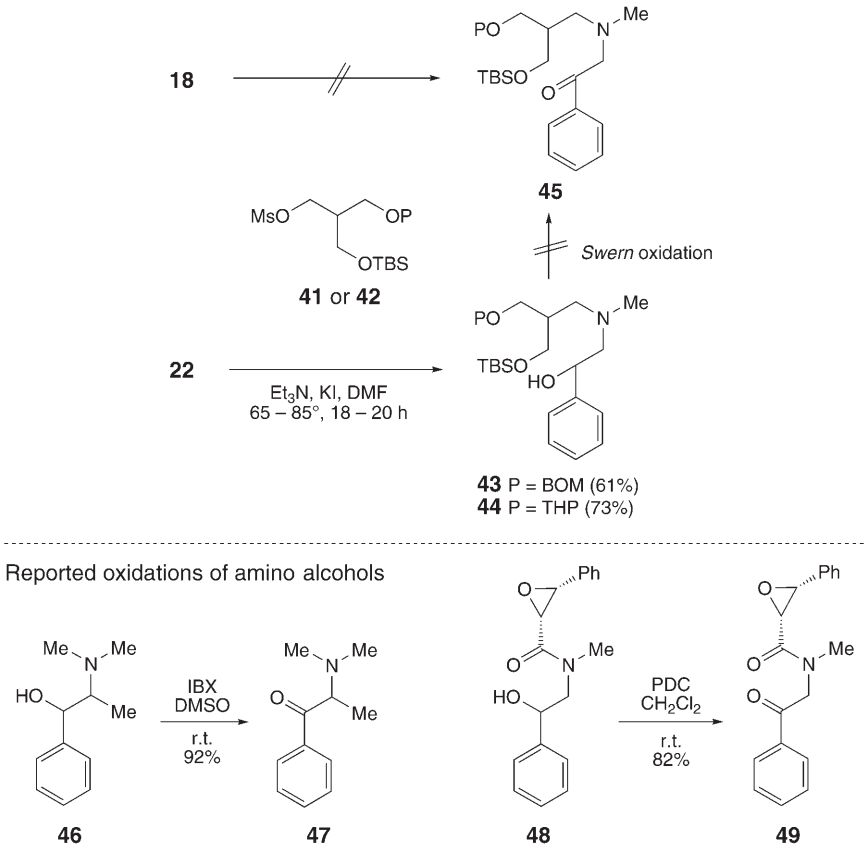
Scheme 7. *Preparation of Differently Diprotected Propane-1,3-diol Derivatives* **39**–**42**



nucleophile to give the desired alkylation product **55** although in moderate yield. The alcohol **55** was oxidized to *N*-Boc-amino ketone **54** by three kinds of methods with PDC in DMF (67%), by *Swern* oxidation (71%), and with MnO_2 in CH_2Cl_2 (83%), after protection of the amino function with Boc group. 2-Oxo-2-phenylethylamines **57** or **58** carrying an isobutyl-like C_4 unit as a precursor for the cyclization were prepared by deprotection of the (*t*-Bu)Me_2Si (TBS) group of **54**, followed by displacement of the OH group with a halogen atom (*Scheme 9*). The synthetic products **53**–**58** were formed as an inseparable mixture of diastereoisomers.

For C–C bond-formation of the halides **57** or **58** under *Wittig* reaction conditions, trials of conversion to the corresponding phosphonium salts were unsuccessful. Thus, we turned our attention to radical cyclization. Although almost no reaction occurred in the use of triethylborane-oxygen condition, application of samarium iodide (SmI_2)-induced cyclization to the iodide **58** in the presence of hexamethylphosphoric triamide (HMPA) afforded the desired 3-phenylpiperidine **59** as a separable *ca.* 1:1 mixture of diastereoisomers, albeit in 23% yield (see, *Entry 1* in *Table 2*). Thus, we examined this *Barbier*-type reaction under various conditions (*Table 2*), and slightly increased formation of the cyclized product **59** (32%) was observed, when an excess of samarium (Sm) [11] was used in the presence of HMPA under dilute concentration of the iodide **58** in THF (*Entry 5*). A cleaved product **60** was a major side-product in these reactions.

Scheme 8. *Trials for Preparation of 2-Oxo-2-phenylethylamines with an Isobutyl-Like C_4 Unit and Reported Oxidations of 2-Hydroxy-2-phenylethylamine Derivatives* **46** *and* **48**



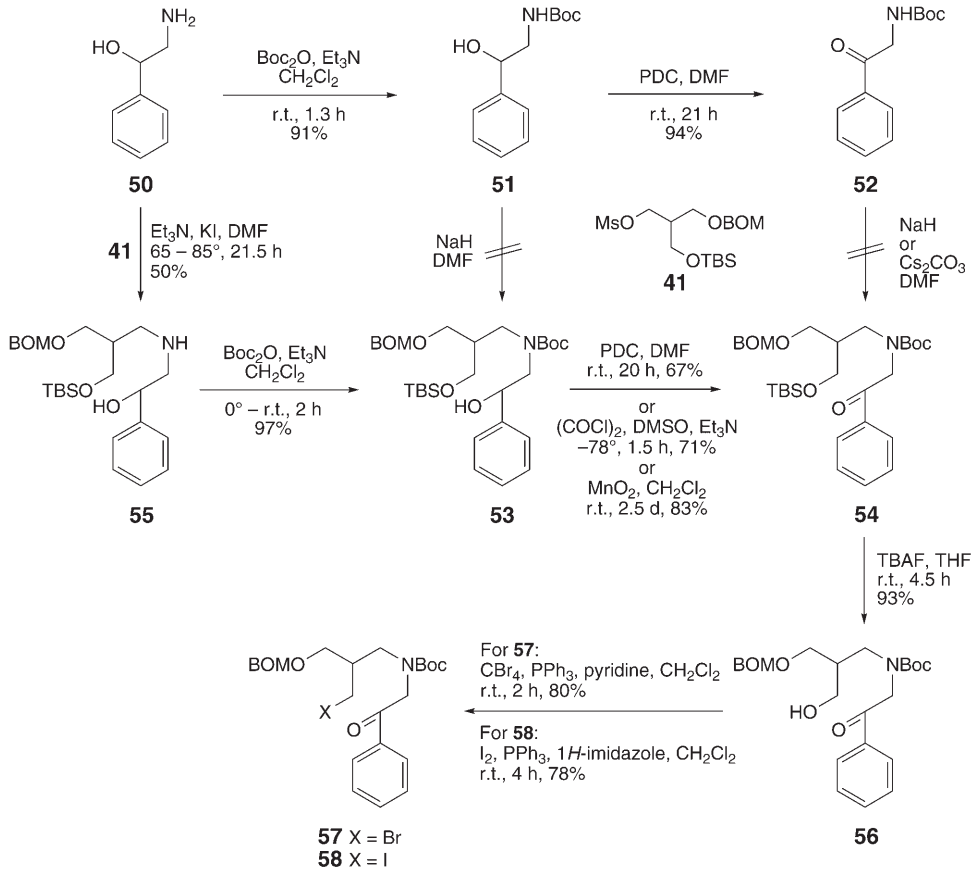
3. Conclusions. – In summary, we established the practical PPL-catalyzed desymmetrization of 2-(ethoxycarbonyl)propane-1,3-diyl dihexanoate, in which the best result in a few gram scale was obtained by the use of THF as co-solvent, and the absolute configuration of the desymmetrized (–)-monohexanoate was determined to be (*R*) by chemical conversion. Furthermore, SmI_2-induced radical cyclization of 2-oxo-3-phenylethylamine with an isobutyl-like C_4 unit on the N-atom, derived from the racemic monohexanoate, afforded 3-phenylpiperidine derivative as a model construction of A–D ring system of lysergic acid.

We thank *Dr. Takeshi Sugai*, Keio University, Japan, for his kind technical suggestion to enzymatic hydrolysis.

Experimental Part

General. Anh. THF, CH_2Cl_2, and DMF, were purchased from *Wako* or *Kanto Chemicals.* PPL Powder (Type *II*, *Batch#114K0617*) was purchased from *Sigma*. Et_3N, MeCN, and MeOH were distilled

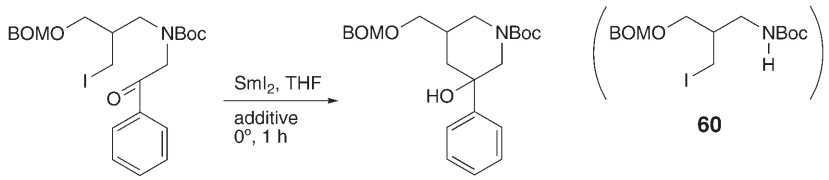
Scheme 9. *Preparation of Precursors for Model Cyclization of the A – D Ring System of Lysergic Acid* (**1**)



from KOH, CaH_2, and Mg turnings, resp. Benzene and EtOH were stored with Na and mol. sieves (3 Å), resp., after distillation. Org. solns. obtained in extractions were dried ($MgSO_4$). For column chromatography (CC), *Kanto Chemicals*, silica gel *60* (acidic) or silica gel *60N* (neutral), and *Fujisilicia*, *Chromatorex NH-DM1020* (NH-type), and, for prep. TLC *Merck*, TLC plates silica gel *60* F_{254}, were used. M.p.: *Yanaco MP-S3*; uncorrected. $[\alpha]_D$ Values: *JASCO P-1020*. IR Spectra: *JASCO FT/IR-300E* spectrophotometer. ^{1}H-NMR Spectra: in $CDCl_3$ on a *JEOL JNM ECP-400* (400 MHz) or *ALPHA-500* (500 MHz) instruments, TMS as an internal standard, unless otherwise stated. ^{13}C-NMR Spectra: *JEOL JNM ECP-400* (100 MHz) or *ALPHA-500* (125 MHz), with the middle resonance of $CDCl_3$ (77.0 ppm) as an internal standard. LR- and HR-EI-MS: *JEOL GC-mate* with direct inlet. HR-FAB-MS: *JEOL JMS-HX 110A* with 3-nitrobenzyl alcohol as a matrix.

Benzoylation of (±)-2-(Ethoxycarbonyl)-3-hydroxypropyl Hexanoate ((±)-**10**). To an ice-cooled stirred soln. of (±)-**10** (44 mg, 0.18 mmol) and pyridine (0.5 ml) was added a soln. of PhCOCl (BzCl) in CH_2Cl_2 (0.1 ml), which was prepared from BzCl (0.22 ml, 1.9 mmol) in CH_2Cl_2 (0.8 ml), under Ar. After stirring for 0.5 h under the same conditions, the mixture was diluted with Et_2O (15 ml). The org. soln. was washed with 2N aq. HCl (4 ml), sat. aq. $NaHCO_3$ (4 ml), H_2O (4 ml), and brine (4 ml), dried, and evaporated. Purification of the residue by CC (acidic; hexane/AcOEt 20:1) afforded the benzoate (57 mg, 91%) as a colorless oil. Chiral HPLC (*DAICEL CHIRALCEL OJ-H*, 254 nm, 0.5 ml/min,

Table 2. *SmI_2-Induced Cyclization of Iodide* **58**



58 **59** **60**

Entry	SmI_2 [equiv.]	Conc. [μM]	Additive ([equiv.])	Yields [%][a])		
				59	**58**	**60**
1	3	30	HMPA (7)	23	18	5
2	5	30	None	–	36	36
3	3	30	HMPA (7)/DMAE (3)	–	50	–
4	3	30	HMPA (17)/Sm (5)	20	3	–
5	4	5	HMPA (19)/Sm (6)	32	4	–
6	4	5	DMPU (18)/Sm (6)	–	45	18
7	3	5	$Fe(acac)_3$ (cat)/Sm (5)	–	24	38
8	3	5	NiI_2 (cat)/Sm (6)	–	22	25

[a]) Yield of isolated products.

hexane/^{i}PrOH 100:1): 31.7 and 33.5 min. IR (ATR): 1726 (CO). ^{1}H-NMR (400 MHz): 0.88 (*t*, *J* = 6.8, Me); 1.24–1.32 (*m*, CH_2); 1.26 (*t*, *J* = 7.1, Me); 1.61 (*quint.*, *J* = 7.5, CH_2); 2.31 (*t*, *J* = 7.5, CH_2); 3.17 (*quint.*, *J* = 6.0, CH); 4.21 (*q*, *J* = 7.1, CH_2); 4.41 (*dd*, *J* = 11.0, 6.1, CH_2); 4.46 (*dd*, *J* = 11.0, 6.1, CH_2); 4.56 (*dd*, *J* = 11.0, 5.6, CH_2); 4.62 (*dd*, *J* = 11.0, 5.6, CH_2); 7.44 (*t*, *J* = 7.5, arom. H); 7.57 (*t*, *J* = 7.5, arom. H); 8.01 (*d*, *J* = 7.5, arom. H). ^{13}C-NMR (100 MHz): 13.8; 14.1; 22.2; 24.5; 31.1; 34.0; 44.2; 61.1; 61.2; 61.8; 128.4; 129.5; 133.1; 166.0; 170.3; 173.3. HR-EI-MS: 350.1702 (M^+, $C_{19}H_{26}O_6^+$; calc. 350.1729).

Enzymatic Hydrolysis of 2-(Ethoxycarbonyl)propane-1,3-diyl Dihexanoate (**9**; *Entry 9* in *Table 1*). A mixture of **9** (1.04 g, 3.0 mmol) in 0.2 mol aq. KH_2PO_4 (28 ml), 0.2 mol aq. KOH (16 ml), and anh. THF (7.8 ml) was sonicated for 5 min, to which PPL powder (0.1 g) was added. The mixture was stirred at 30° (inner temp.) for 7 h and maintained at pH 6.9–7.1 by adding 1 mol aq. NaOH (total 3.3 ml, 3.3 mmol) during the stirring. After ice-cooling, cold acetone (350 ml), followed by *Celite* (*ca.* 0.5 g), was, in one portion, added, and the whole mixture was stirred for 1.5 h under ice-cooling. The *Celite*-absorbing PPL was removed by filtration and washed with a small amount of AcOEt. After evaporation of the filtrate, brine (3 ml) was added to the residue, and the mixture was extracted with AcOEt (3 × 200 ml). The org. soln. was dried and evaporated to give a pale yellow oil (quant.), purification of which by CC (acidic, hexane/AcOEt 5:1) afforded (−)-**10** (0.380 g, 51%) and **8** (0.195 g, 44%).

(−)-2-(Ethoxycarbonyl)-3-hydroxypropyl Hexanoate ((−)-**10**): Colorless oil. *Benzoate:* Chiral HPLC: 31.7 (97%) and 33.5 (3%) min (*DAICEL CHIRALCEL OJ-H*; 254 nm, 0.5 ml/min, hexane/^{i}PrOH 100:1). $[\alpha]_D^{19} = -10.2$ (*c* = 1.1, EtOH). IR (ATR): 3444 (OH), 1736 (CO). ^{1}H-NMR (400 MHz): 0.90 (*t*, *J* = 7.0, Me); 1.27–1.35 (*m*, Me, 2 CH_2); 1.58–1.65 (*m*, CH_2); 2.31 (*t*, *J* = 7.6, CH_2); 2.43 (*t*, *J* = 6.7, HO); 2.88 (*quint.*, *J* = 5.8, CH); 3.83 (*dd*, *J* = 11.3, 6.3, 1 H, CH_2); 3.89 (*dd*, *J* = 11.3, 6.3, 1 H, CH_2); 4.21 (*q*, *J* = 3.6, CH_2); 4.37 (*dd*, *J* = 16.9, 5.8, 1 H, CH_2); 4.41 (*dd*, *J* = 16.9, 5.8, 1 H, CH_2).

(+)-(S)-3-[(tert-Butyl)diphenylsilyloxy]-2-(ethoxycarbonyl)propyl Hexanoate ((+)-**11**). A soln. of (−)-**10** (173 mg, 0.70 mmol), 1*H*-imidazole (76 mg, 1.12 mmol), and (*t*-Bu)Ph_2SiCl (TBDPSCl) (0.23 ml, 0.88 mmol) in DMF (0.95 ml) was stirred at r.t. for 1 h under Ar, the reaction was quenched with H_2O (10 ml), and the mixture was extracted with AcOEt (3 × 20 ml). The org. soln. was washed with H_2O (5 × 10 ml) and brine (10 ml), dried, and evaporated. Purification of the residue by CC (acidic, hexane/AcOEt 50:1) afforded (+)-**11** (315 mg, 93%). Colorless oil. $[\alpha]_D^{21} = +4.6$ (*c* = 1.0, $CHCl_3$). IR (ATR):

1738 (CO). ^{1}H-NMR (400 MHz): 0.88 (*t*, *J* = 7.0, Me); 1.03 (*s*, 3 Me); 1.25–1.29 (*m*, 2 CH_2); 1.26 (*t*, *J* = 7.1, Me); 1.57 (*quint.*, *J* = 7.5, CH_2); 2.24 (*t*, *J* = 7.5, CH_2); 2.90 (*quint.*, *J* = 6.0, CH); 3.89 (*dd*, *J* = 10.0, 5.4, 1 H, CH_2); 3.93 (*dd*, *J* = 10.0, 5.4, 1 H, CH_2); 4.21 (*q*, *J* = 7.1, CH_2); 4.37 (*dd*, *J* = 11.0, 6.5, 1 H, CH_2); 4.43 (*dd*, *J* = 11.0, 6.5, 1 H, CH_2); 7.36–7.45 (*m*, arom. H); 7.64 (diffused *t*, *J* = 6.4, arom. H). ^{13}C-NMR (100 MHz): 13.9; 14.2; 19.2; 22.3; 24.5; 26.7; 31.2; 34.1; 47.2; 60.7; 61.2; 61.3; 127.7; 129.7; 133.1; 135.5; 171.4; 173.4. HR-FAB-MS: 485.2706 ($[M+H]^+$, $C_{28}H_{41}O_5Si^+$; calc. 485.2723).

*Ethyl (+)-(*S*)-3-[(*tert*-Butyl)diphenylsilyloxy]-2-hydroxymethylpropanoate* ((+)-**12**). A mixture of (+)-**11** (349 mg, 0.72 mmol) in THF (5.6 ml) and 1M soln. of DIBAH in toluene (1.4 ml, 1.4 mmol) was stirred at −78° for 2.5 h under Ar. After quenching with H_2O (2 ml) at the same temp., H_2O (8 ml), Et_2O (40 ml), and 1N aq. HCl (10 ml) were added, and the resulting mixture was extracted with Et_2O (2 × 30 ml). The org. soln. was washed with brine (10 ml), dried, and evaporated. Purification of the residue by CC (acidic, hexane/AcOEt 20:1) afforded (+)-**12** (175 mg, 63%) as a colorless oil together with the starting (+)-**11** (84 mg, 24%). $[\alpha]_D^{19} = +5.6$ (*c* = 1.1, $CHCl_3$). IR (ATR): 3415 (OH), 1730 (CO). ^{1}H-NMR (400 MHz): 1.04 (*s*, 3 Me); 1.26 (*t*, *J* = 7.1, Me); 2.36 (*t*, *J* = 6.4, HO); 2.79 (*tt*, *J* = 6.5, 5.1, CH); 3.87 (*ddd*, *J* = 11.3, 6.7, 4.9, 1 H, CH_2); 3.91 (*dd*, *J* = 10.0, 4.9, 1 H, CH_2); 3.98 (*dd*, *J* = 10.0, 6.2, 1 H, CH_2); 4.03 (*ddd*, *J* = 11.3, 6.2, 6.2, 1 H, CH_2); 4.16 (*dd*, *J* = 10.7, 7.1, 1 H, CH_2); 4.18 (*dd*, *J* = 10.7, 7.1, 1 H, CH_2); 7.37–7.46 (*m*, arom. H); 7.64–7.67 (*m*, arom. H). ^{13}C-NMR (100 MHz): 14.1; 19.2; 26.7; 49.7; 60.7; 61.2; 62.2; 127.70; 127.73; 129.8; 132.98; 133.0; 135.48; 135.51; 172.9. HR-FAB-MS: 387.1996 ($[M+H]^+$, $C_{22}H_{31}O_4Si^+$; calc. 387.1992).

*Ethyl (+)-(*S*)-2-{[(Benzyloxy)methoxy]methyl}-3-[(*tert*-butyl)diphenylsilyloxy]propanoate* ((+)-**13**). To a soln. of (+)-**12** (99 mg, 0.26 mmol) and ^{i}Pr$_2$EtN (0.13 ml, 0.76 mmol) in CH_2Cl_2 (0.70 ml) was added a soln. of (benzyloxy)methyl chloride (BOMCl) (0.05 ml, 0.36 mmol) in CH_2Cl_2 (0.30 ml) under Ar. The mixture was stirred at 10–20° for 5.5 h, the reaction was quenched with aq. NH_4Cl (5 ml), and the mixture was extracted with AcOEt (3 × 15 ml). The org. soln. was washed with brine (10 ml), dried, and evaporated. Purification of the residue by CC (acidic, hexane/Et_2O 20:1) afforded (+)-**13** (120 mg, 92%). Colorless oil. $[\alpha]_D^{18} = +1.6$ (*c* = 1.0, $CHCl_3$). IR (ATR): 1734 (CO). ^{1}H-NMR (400 MHz): 1.03 (*s*, 3 Me); 1.26 (*t*, *J* = 7.2, Me); 2.89 (*quint.*, *J* = 6.0, CH); 3.82 (*dd*, *J* = 9.8, 6.1, CH_2); 3.89–3.96 (*m*, CH_2); 4.17 (*q*, *J* = 7.2, CH_2); 4.53, 4.56 (*AB*, *J* = 12.2, CH_2 (benzyl)); 4.71 (*s*, CH_2; 7.31–7.42 (*m*, arom. H); 7.64–7.66 (diffused *d*, *J* = 7.8, arom. H). ^{13}C-NMR (100 MHz): 14.2; 19.2; 26.7; 48.6; 60.6; 61.7; 65.4; 69.2; 94.7; 127.7; 127.9; 128.4; 129.7; 133.3; 135.5; 137.7; 172.3. HR-FAB-MS: 545.2078 ($[M+K]^+$, $C_{30}H_{38}KO_5Si^+$; calc. 545.2126).

*(−)-(*S*)-2-{[(Benzyloxy)methoxy]methyl}-3-[(*tert*-butyl)diphenylsilyloxy]propan-1-ol* ((−)-**14**). A soln. of (+)-**13** (42 mg, 0.08 mmol) and 1M soln. of DIBAH in toluene (0.42 ml, 0.42 mmol) in Et_2O (0.83 ml) was stirred at −40° for 1 h under Ar. After quenching with H_2O (1 ml) at the same temp., AcOEt (10 ml) and 1N aq. HCl (6 ml) were added, and the resulting mixture was extracted with AcOEt (2 × 10 ml). The org. soln. was washed with brine (6 ml), dried, and evaporated. Purification of the residue by CC (acidic, hexane/AcOEt 50:1) afforded (−)-**14** (24 mg, 61%). Colorless oil. $[\alpha]_D^{22} = -2.4$ (*c* = 1.0, $CHCl_3$). IR (ATR): 3448 (OH). ^{1}H-NMR (400 MHz): 1.06 (*s*, 3 Me); 2.08 (*sept.*, *J* = 5.9, CH); 2.43 (br. *s*, HO); 3.69 (*dd*, *J* = 9.5, 6.3, 1 H, CH_2); 3.70 (*dd*, *J* = 9.5, 5.9, 1 H, CH_2); 3.76 (*dd*, *J* = 10.2, 6.1, 1 H, CH_2); 3.80 (*dd*, *J* = 10.2, 5.4, 1 H, CH_2); 3.81 (br. *s*, CH_2); 4.55 (*s*, CH_2); 4.71 (*s*, CH_2); 7.27–7.45 (*m*, arom. H); 7.65–7.68 (diffused *d*, *J* = 8.0, arom. H). ^{13}C-NMR (100 MHz): 19.2; 26.8; 43.2; 63.6; 67.3; 69.4; 94.8; 127.69; 127.72; 127.8; 128.4; 129.8; 133.14; 133.18; 135.53; 135.54; 137.7. HR-FAB-MS: 465.2422 ($[M+H]^+$, $C_{28}H_{37}O_4Si^+$; calc. 465.2461).

*(−)-(*S*)-2-{[(Benzyloxy)methoxy]methyl}-3-[(*tert*-butyl)diphenylsilyloxy]propan-1-yl* p-*Toluenesulfonate* ((−)-**15**). A mixture of (−)-**14** (148 mg, 0.32 mmol), TsCl (167 mg, 0.88 mmol), DMAP (24 mg, 0.20 mmol), and Et_3N (0.13 ml, 0.93 mmol) in CH_2Cl_2 (1.5 ml) was stirred at r.t. for 1.5 h under Ar. After quenching with NH_4Cl (71 mg, 1.33 mmol), followed by H_2O (8 ml) under ice-cooling, the resulting mixture was extracted with Et_2O (3 × 25 ml). The org. soln. was washed with brine (12 ml), dried, and evaporated. Purification of the residue by CC (acidic, hexane/AcOEt 15:1) afforded (−)-**15** (173 mg, 88%). Colorless oil. $[\alpha]_D^{22} = -0.4$ (*c* = 1.1, $CHCl_3$). ^{1}H-NMR (400 MHz): 0.98 (*s*, 3 Me); 2.18 (*quint.*, *J* = 5.7, CH); 2.41 (*s*, Me); 3.54 (*dd*, *J* = 9.4, 5.9, 1 H, CH_2); 3.57 (*dd*, *J* = 9.4, 5.3, 1 H, CH_2); 3.61 (*dd*, *J* = 10.1, 6.3, 1 H, CH_2); 3.66 (*dd*, *J* = 10.1, 5.4, 1 H, CH_2); 4.16 (*dd*, *J* = 10.6, 5.6, 1 H, CH_2); 4.20 (*dd*, *J* = 10.6, 5.6, 1 H, CH_2); 4.48 (*s*, CH_2); 4.61 (*s*, CH_2); 7.26–7.44 (*m*, arom. H); 7.58 (*d*, *J* = 7.1, arom. H);

7.76 (*d*, *J* = 7.9, arom. H). ^{13}C-NMR (100 MHz): 19.2; 21.6; 26.7; 41.6; 61.0; 65.0; 68.2; 69.4; 94.7; 127.7; 127.85; 127.91; 128.4; 129.7; 129.8; 132.9; 133.1; 135.5; 137.7; 144.6. HR-FAB-MS: 657.2137 ($[M+K]^+$, $C_{35}H_{42}KO_6SSi^+$; calc. 657.2108).

*(−)-(*S*)-3-[(Benzyloxy)methoxy]-2-methylpropyl (*tert*-Butyl)diphenylsilyl Ether* ((−)-**16**). A mixture of (−)-**15** (194 mg, 0.31 mmol) and $NaBH_4$ (128 mg, 3.38 mmol) in DMSO (16 ml) was stirred at 60° for 6.5 h under Ar. After quenching with H_2O (6 ml) and 5% aq. NH_4Cl (15 ml) under ice-cooling, the resulting mixture was extracted with Et_2O (3 × 40 ml). The org. soln. was washed with brine (10 ml), dried, and evaporated. Purification of the residue by CC (acidic, hexane/AcOEt 30:1) afforded (−)-**16** (118 mg, 84%). Colorless oil. $[\alpha]_D^{18} = -5.0$ ($c = 1.0$, $CHCl_3$). ^{1}H-NMR (400 MHz): 0.97 (*d*, *J* = 7.0, Me); 1.05 (*s*, 3 Me); 1.99 (*sext.*, *J* = 6.3, CH); 3.51 (*dd*, *J* = 9.4, 6.1, 1 H, CH_2); 3.60 (*dd*, *J* = 10.2, 5.6, 1 H, CH_2); 3.63 (*dd*, *J* = 10.2, 5.6, 1 H, CH_2); 3.64 (*dd*, *J* = 9.4, 6.1, 1 H, CH_2); 4.57 (*s*, CH_2); 4.73 (*s*, CH_2); 7.26–7.42 (*m*, arom. H); 7.66 (diffused *d*, *J* = 5.7, arom. H). ^{13}C-NMR (100 MHz): 14.1; 19.3; 26.9; 36.3; 65.8; 69.2; 70.2; 94.8; 127.6; 127.9; 128.4; 129.5; 133.9; 135.6; 138.0. FAB-MS: 487 ($[M+K]^+$); 449 ($[M+H]^+$).

tert-*Butyl* N-*(2-Hydroxy-2-phenylethyl)*-N-*methylcarbamate* (**23**). A mixture of **22** (203 mg, 1.34 mmol), Et_3N (0.21 ml, 1.51 mmol), and Boc_2O (328 mg, 1.50 mmol) in CH_2Cl_2 (2 ml) was stirred at r.t. for 1.5 h under Ar. After dilution with CH_2Cl_2 (10 ml), the mixture was washed with 10% aq. citric acid (5 ml), sat. aq. $NaHCO_3$ (5 ml), and brine (5 ml), and dried, and evaporated. Purification of the residue by CC (neutral, $CHCl_3$) afforded **23** (335 mg, 99%) as a colorless oil, which was solidified on standing (m.p. 48.5–50°). IR (ATR): 3413 (OH), 1664 (CO). ^{1}H-NMR (400 MHz; 2:1 mixture of rotamers): 1.49 (*s*, 3 Me); 2.35 (*s*, 0.33 HO); 2.79 (br. *s*, 0.66 Me); 2.90 (br. *s*, 0.33 Me); 3.38–3.60 (*m*, CH_2); 4.21 (br. *s*, 0.66 HO); 4.95 (br. *s*, CH); 7.27–7.30 (*m*, arom. H); 7.34–7.38 (*m*, arom. H). FAB-MS: 503 ($[2M+H]^+$), 274 ($[M+Na]^+$), 252 ($[M+H]^+$).

tert-*Butyl* N-*Methyl*-N-*(2-oxo-2-phenylethyl)carbamate* (**24**). To a soln. of oxalyl chloride (0.43 ml, 4.93 mmol) in CH_2Cl_2 (9 ml) was added a soln. of DMSO (0.55 ml, 7.75 mmol) in CH_2Cl_2 (4 ml), followed by a soln. of **23** (879 mg, 3.5 mmol) in CH_2Cl_2 (4 ml) at −78° under Ar, and then the mixture was stirred at the same temp. for 1 h. After addition of Et_3N (2.4 ml, 17.2 mmol) at the same temp., the mixture was stirred for 3.5 h, and the reaction was quenched with H_2O (5 ml). After further addition of H_2O (5 ml) at r.t., the mixture was extracted with CH_2Cl_2 (3 × 50 ml). The org. soln. was washed with H_2O (5 × 15 ml) and brine (15 ml), and dried and evaporated. Purification of the residue by CC (acidic, hexane/AcOEt 10:1) afforded **24** (852 mg, 98%). Colorless oil. IR (ATR): 1687 (CO). ^{1}H-NMR (400 MHz): 1.38 (*s*, Me); 1.49 (*s*, Me); 2.94, 2.98 (2*s*, Me); 4.59 (*s*, CH_2); 4.69 (*s*, CH_2); 7.45–7.51 (*m*, arom. H); 7.56–7.63 (*m*, arom. H); 7.94 (*t*, *J* = 7.7, arom. H). EI-MS: 250 ($[M+H]^+$), 249 (M^+).

(Methyl)(2-oxo-2-phenylethyl)ammonium Trifluoroacetate (**18**). A soln. of **24** (150 mg, 0.6 mmol) and TFA (0.1 ml, 1.3 mmol) in CH_2Cl_2 (0.5 ml) was stirred at r.t. for 22 h under Ar. After evaporation of the TFA and the solvent, trituration of the residue with hexane/Et_2O 1:1, followed by recrystallization from CH_2Cl_2, afforded **18** as TFA salt (154 mg, 97%). IR (ATR): 1739, 1682 (CO). ^{1}H-NMR (400 MHz, in $CDCl_3 + CD_3OD$): 2.83 (*s*, Me); 3.76 (br. *s*, NH_2); 4.61 (*s*, CH_2); 7.54 (*t*, *J* = 7.8, 2 arom. H); 7.69 (*tt*, *J* = 7.4, 1.4, 1 arom. H); 7.97 (diffused *dd*, *J* = 8.4, 1.3, 2 arom. H). ^{13}C-NMR (100 MHz, in $CDCl_3 + CD_3OD$): 32.4; 53.4; 116.3; 127.6; 128.6; 132.9; 134.5; 161.9; 190.8. HR-EI-MS: 149.0841 ($[M-TFA]^+$, $C_9H_{11}NO^+$; calc. 149.0811).

3-Bromo-2-(ethoxycarbonyl)propyl Hexanoate (**25**). A mixture of (±)-**10** (166 mg, 0.67 mmol), CBr_4 (346 mg, 1.02 mmol), and PPh_3 (304 mg, 1.16 mmol) in CH_2Cl_2 (3 ml) was stirred for 2 h under ice-cooling and Ar. After removal of precipitate by filtration, the filtrate was evaporated and purified by CC (acidic, hexane/AcOEt 50:1) to afford **25** (181 mg, 80%). Colorless oil. IR (ATR): 1738 (CO). ^{1}H-NMR (400 MHz): 0.90 (*t*, *J* = 6.9, Me); 1.23–1.37 (*m*, 2 CH_2); 1.29 (*t*, *J* = 7.1, Me), 1.62 (*quint.*, *J* = 7.5, CH_2); 2.31 (*t*, *J* = 7.5, CH_2); 3.11 (*quint.*, *J* = 5.9, CH); 3.61 (*dd*, *J* = 10.4, 6.0, 1 H, CH_2); 3.66 (*dd*, *J* = 10.5, 5.9, 1 H, CH_2); 4.22 (*q*, *J* = 7.1, CH_2); 4.37 (*dd*, *J* = 11.2, 6.1, 1 H, CH_2); 4.43 (*dd*, *J* = 11.3, 5.6, 1 H, CH_2). ^{13}C-NMR (100 MHz): 13.9; 14.1; 22.3; 24.5; 29.0; 31.2; 34.0; 46.6; 61.4; 62.2; 170.0; 173.3. HR-EI-MS: 308.0622 ($[M+H]^+$, $C_{12}H_{21}BrO_4^+$; calc. 308.0623).

Trial for the Preparation of [2-(Ethoxycarbonyl)-3-hexanoyloxypropyl]triphenylphosphonium Bromide (**27**): *[2-(Ethoxycarbonyl)prop-2-enyl]triphenylphosphonium Bromide* (**26**). A mixture of **25** (53 mg, 0.15 mmol) and PPh_3 (38 mg, 0.15 mmol) in benzene (0.8 ml) was refluxed for 6 h under Ar.

After removal of the solvent, the residue was purified by trituration with hexane/Et_2O to afford **26** (59 mg, 90%). Colorless solid. IR (ATR): 1712 (CO). ^{1}H-NMR (400 MHz): 1.06 (*t*, *J* = 7.1, Me); 3.81 (*q*, *J* = 7.1, CH_2); 5.28 (*d*, *J* = 15.0, CH_2); 6.54 (*d*, *J* = 5.7, CH_2); 7.66–7.71 (*m*, arom. H); 7.79 (*t*, *J* = 7.5, arom. H); 7.90 (*dd*, *J* = 12.7, 7.2, arom. H). FAB-MS: 376 ($[M+H]^+$); 375 (M^+).

2-(Ethoxycarbonyl)-3-hexanoylpropyl Methanesulfonate (**28**). A soln. of (±)-**10** (194 mg, 0.79 mmol), MsCl (0.12 ml, 1.6 mmol), and pyridine (0.39 ml, 4.82 mmol) in CH_2Cl_2 (2 ml) was stirred at r.t. for 2.5 h under Ar. After dilution with CH_2Cl_2 (20 ml), the soln. was washed with sat. aq. $CuSO_4$ (10 ml), sat. aq. $NaHCO_3$ (10 ml), and brine (10 ml), and dried and evaporated. Purification of the residue by CC (acidic, hexane/AcOEt 30:1 then $CHCl_3$/Et_2O 10:1) afforded **28** (248 mg, 97%). Colorless oil. IR (ATR): 1734 (CO). ^{1}H-NMR (400 MHz): 0.90 (*t*, *J* = 6.9, Me); 1.27–1.32 (*m*, 2 CH_2); 1.29 (*t*, *J* = 7.1, Me), 1.61 (*quint.*, *J* = 7.5, CH_2); 2.32 (*t*, *J* = 7.5, CH_2); 3.05 (*s*, Me); 3.11 (*quint.*, *J* = 6.0, CH); 4.22 (*q*, *J* = 7.1, CH_2); 4.37 (*dd*, *J* = 11.3, 6.0, 1 H, CH_2); 4.40 (*dd*, *J* = 11.3, 6.0, 1 H, CH_2); 4.44 (*dd*, *J* = 10.2, 6.0, 1 H, CH_2); 4.52 (*dd*, *J* = 10.2, 6.0, 1 H, CH_2). ^{13}C-NMR (100 MHz): 13.7; 13.9; 22.1; 24.3; 31.1; 33.8; 37.1; 44.2; 60.3; 61.5; 66.0; 169.2; 173.1. HR-FAB-MS: 325.1304 ($[M+H]^+$, $C_{13}H_{25}O_7S^+$; calc. 325.1321).

*3-[(*tert*-Butyl)dimethylsilyloxy]-2-(ethoxycarbonyl)propyl Hexanoate* (**32**). A soln. of (±)-**10** (240 mg, 0.98 mmol), 1*H*-imidazole (172 mg, 2.52 mmol), and TBSCl (228 mg, 1.48 mmol) in DMF (1.8 ml) was stirred at r.t. for 1 h under Ar, the reaction was quenched with H_2O (10 ml), and the mixture was extracted with AcOEt (3 × 20 ml). The org. soln. was washed with H_2O (3 × 10 ml) and brine (10 ml), and dried and evaporated. Purification of the residue by CC (acidic, hexane/AcOEt 50:1) afforded **32** (285 mg, 81%). Colorless oil. IR (ATR): 1739 (CO). ^{1}H-NMR (400 MHz): 0.04 (*s*, 2 Me); 0.87 (*s*, 3 Me); 0.89 (*t*, *J* = 6.8, Me); 1.24–1.31 (*m*, CH_2); 1.26 (*t*, *J* = 7.1, Me); 1.61 (*quint.*, *J* = 7.5, CH_2); 2.29 (*t*, *J* = 7.5, CH_2); 2.85 (*quint.*, *J* = 6.0, CH); 3.86 (*d*, *J* = 6.0, CH_2); 4.16 (*q*, *J* = 7.1, CH_2); 4.32 (*dd*, *J* = 10.9, 6.0, 1 H, CH_2); 4.35 (*dd*, *J* = 10.9, 6.0, 1 H, CH_2). ^{13}C-NMR (100 MHz): −5.7; 13.8; 14.1; 18.1; 22.2; 24.6; 25.7; 31.2; 34.1; 47.4; 60.6; 61.3; 171.4; 173.4. HR-FAB-MS: 361.2386 ($[M+H]^+$, $C_{18}H_{37}O_5Si$; calc. 361.2410).

*Ethyl (±)-3-{[(*tert*-Butyl)dimethylsilyloxy]methyl}-2-hydroxypropanoate* (**33**). To a soln. of **32** (75 mg, 0.21 mmol) in THF (1.4 ml) was added 1M soln. of DIBAH in toluene (0.7 ml, 0.7 mmol). The mixture was stirred at −78° for 3 h under Ar, and the reaction was quenched with H_2O (3 ml) at the same temp. After further addition of H_2O (10 ml) at r.t., the mixture was extracted with AcOEt (30 ml). The org. soln. was washed with 0.1% aq. HCl (5 × 10 ml), and the HCl washings were extracted with AcOEt (2 × 30 ml). The org. solns. were combined and washed with brine (15 ml), and dried and evaporated. Purification of the residue by CC (acidic, hexane/AcOEt 30:1) afforded **33** (39 mg, 71%). Colorless oil. IR (ATR): 3458 (OH), 1734 (CO). ^{1}H-NMR (400 MHz): 0.06 (*s*, 2 Me); 0.88 (*s*, 3 Me); 1.28 (*t*, *J* = 7.1, Me); 2.68 (br. *s*, HO); 2.75 (*quint.*, *J* = 5.7, CH); 3.87–3.96 (*m*, 2 CH_2); 4.18 (*q*, *J* = 7.1, CH_2). ^{13}C-NMR (100 MHz): −5.8; −5.7; 14.1; 18.0; 25.6; 49.7; 60.6; 61.1; 61.6; 172.8. HR-FAB-MS: 263.1665 ($[M+H]^+$, $C_{12}H_{27}O_4Si^+$; calc. 263.1679).

Silylation of Ethyl 3-Hydroxy-2-(hydroxymethyl)propanoate (**8**). A soln. of **8** (962 mg, 6.49 mmol), 1*H*-imidazole (665 mg, 9.76 mmol), DMAP (237 mg, 1.94 mmol), and TBSCl (1.2 g, 7.81 mmol) in DMF (6.7 ml) was kept at −5° for 1.5 h under Ar, the reaction was quenched with H_2O (10 ml), and the mixture was extracted with AcOEt (3 × 20 ml). The org. soln. was washed with H_2O (3 × 20 ml) and brine (20 ml), and dried and evaporated. Purification of the residue by CC (acidic, hexane/AcOEt 20:1) afforded **33** (846 mg, 50%) and **34** (576 mg, 24%). Colorless oil.

*Ethyl 3-[(*tert*-Butyl)dimethylsilyloxy]-2-{[(*tert*-butyl)dimethylsilyloxy]methyl}propanoate* (**34**): IR (ATR): 1738 (CO). ^{1}H-NMR (400 MHz): 0.04 (*s*, 4 Me); 0.87 (*s*, 6 Me); 1.26 (*t*, *J* = 7.1, Me); 2.69 (*quint.*, *J* = 6.0, CH); 3.83 (*dd*, *J* = 9.9, 6.1, CH_2); 3.86 (*dd*, *J* = 9.9, 5.9, CH_2); 4.14 (*q*, *J* = 7.1, CH_2). ^{13}C-NMR (100 MHz): −5.6; −5.5; 14.2; 18.2; 25.8; 50.9; 60.2; 60.3; 172.6. HR-FAB-MS: 377.2537 ($[M+H]^+$, $C_{18}H_{41}O_4Si_2^+$; calc. 377.2543).

Desilylation of **34**. To a soln. of **34** (3.5 g, 9.16 mmol) in THF (8 ml) was added 1 mol soln. of TBAF in THF (20 ml, 20 mmol). The mixture was stirred at r.t. for 1.5 h, quenched with sat. aq. NH_4Cl (8 ml), and extracted with AcOEt (3 × 70 ml). The org. soln. was washed with brine (30 ml), and dried (Na_2SO_4) and evaporated. Purification of the residue by CC (acidic, hexane/AcOEt 1:1) afforded **8** (1.30 g, 96%).

*Ethyl 2-{[(Benzyloxy)methoxy]methyl}-3-[(*tert*-butyl)dimethylsilyloxy]propanoate* (**35**). To an ice-cooled soln. of **33** (90 mg, 0.34 mmol) and $^{i}Pr_2EtN$ (0.17 ml, 1.0 mmol) in CH_2Cl_2 (0.7 ml) was added a soln. of BOMCl (0.06 ml, 0.41 mmol) in CH_2Cl_2 (0.2 ml) under Ar. The mixture was stirred at r.t. for 2.5 h, the reaction was quenched with (2 ml), and the mixture was extracted with AcOEt (3 × 10 ml). The org. soln. was washed with sat. aq. $NaHCO_3$ (10 ml) and brine (10 ml), and dried and evaporated. Purification of the residue by CC (neutral, hexane/Et_2O 30:1) afforded **35** (96 mg, 73%). Labile colorless oil. IR (ATR): 1736 (CO). ^{1}H-NMR (400 MHz): 0.04 (*s*, 2 Me); 0.87 (*s*, 3 Me); 1.26 (*t*, *J* = 7.1, Me); 2.84 (*quint.*, *J* = 6.0, CH); 3.81 (*dd*, *J* = 9.8, 6.0, 1 H, CH_2); 3.83–3.90 (*m*, 3 H, CH_2); 4.16 (*q*, *J* = 7.1, CH_2); 4.58 (*s*, CH_2); 4.75 (*s*, CH_2); 7.26–7.35 (*m*, arom. H). ^{13}C-NMR (100 MHz): −5.62; −5.58; 14.2; 18.1; 25.7; 48.7; 60.5; 60.9; 65.3; 69.2; 94.7; 127.6; 127.9; 128.4; 137.7; 172.3. HR-FAB-MS: 383.2239 ($[M+H]^+$, $C_{20}H_{35}O_5Si$; calc. 383.2254).

*Ethyl 3-[(*tert*-Butyl)dimethylsilyloxy]-2-[(3,4,5,6-tetrahydropyran-2-yl)oxymethyl]propanoate* (**36**). A soln. of **33** (532 mg, 2.03 mmol), 3,4-dihydro-2*H*-pyran (0.28 ml, 3.1 mmol), and pyridinium *p*-toluenesulfonate (53 mg, 0.21 mmol) in CH_2Cl_2 (5 ml) was stirred at r.t. for 2.5 h. After addition of AcOEt (50 ml), the mixture was washed with sat. aq. $NaHCO_3$ (5 ml), H_2O (5 ml), and brine (5 ml), and dried and evaporated. Purification of the residue by CC (neutral, benzene/Et_2O 40:1) afforded **36** (695 mg, 99%). Colorless oil. IR (ATR): 1736 (CO). ^{1}H-NMR (400 MHz): 0.04 (*s*, 2 Me); 0.87 (*s*, 3 Me); 1.26 (*t*, *J* = 7.1, Me); 1.49–1.80 (*m*, CH_2); 2.83 (*dddd*, *J* = 12.0, 6.0, 6.0, 4.2, CH); 3.48–3.70 (*m*, CH_2); 3.60 (*dd*, *J* = 9.9, 6.6, 1 H, CH_2); 3.66 (*dd*, *J* = 9.7, 6.4, 1 H, CH_2); 3.80–3.90 (*m*, CH_2); 3.93 (*dd*, *J* = 9.7, 6.0, 1 H, CH_2); 3.98 (*dd*, *J* = 9.9, 6.6, 1 H, CH_2); 4.16 (*q*, *J* = 7.1, CH_2); 4.62 (*t*, *J* = 3.3, CH). ^{13}C-NMR (100 MHz): −5.6; −5.4; 14.2; 18.1; 19.1; 25.4; 25.7; 30.4; 48.6; 48.7; 60.3; 60.9; 61.7; 64.5; 64.7; 98.6; 98.7; 172.4. HR-FAB-MS: 347.2222 ($[M+H]^+$, $C_{17}H_{35}O_5Si^+$; calc. 347.2254).

*2-{[(Benzyloxy)methoxy]methyl}-3-[(*tert*-butyl)dimethylsilyloxy]propan-1-ol* (**37**). A soln. of **35** (35 mg, 0.09 mmol) and $LiBH_4$ (8 mg, 0.36 mmol) in THF (0.4 ml) and EtOH (0.1 ml) was stirred at r.t. for 11 h and then at 40° for 8 h under Ar, the reaction was quenched with sat. aq. NH_4Cl (1 ml), followed by H_2O (3 ml) under ice-cooling, and the mixture was extracted with AcOEt (3 × 8 ml). The org. soln. was washed with brine (3 ml), and dried and evaporated. Purification of the residue by CC (acidic, hexane/AcOEt 15:1) afforded **37** (29 mg, 92%). Colorless oil. IR (ATR): 3415 (OH). ^{1}H-NMR (400 MHz): 0.07 (*s*, 2 Me); 0.89 (*s*, 3 Me); 2.01 (*sept.*, *J* = 5.7, CH); 2.76 (br. *s*, HO); 3.65 (*d*, *J* = 10.6, 1 H, CH_2); 3.69 (*d*, *J* = 10.6, 1 H, CH_2); 3.73 (*dd*, *J* = 10.0, 6.0, 1 H, CH_2); 3.77 (br. *s*, CH_2); 3.79 (*dd*, *J* = 10.0, 5.3, 1 H, CH_2); 4.59 (*s*, CH_2); 4.74 (*s*, CH_2); 7.27–7.30 (*m*, arom. H); 7.35 (*d*-like, arom. H). ^{13}C-NMR (100 MHz): −5.7; −5.6; 18.1; 25.8; 42.9; 63.2; 63.7; 67.0; 69.4; 94.8; 127.7; 127.8; 128.4; 137.7. HR-FAB-MS: 341.2120 ($[M+H]^+$, $C_{18}H_{33}O_4Si^+$; calc. 341.2148).

*3-[(*tert*-Butyl)dimethylsilyloxy]-2-[(3,4,5,6-tetrahydropyran-2-yl)oxymethyl]propan-1-ol* (**38**). A soln. of **36** (153 mg, 0.44 mmol) and $LiBH_4$ (45 mg, 1.84 mmol) in THF (14 ml), and EtOH (0.9 ml) was stirred at r.t. for 17.5 h and then at 50° for 7.5 h under Ar, the reaction was quenched with sat. aq. NH_4Cl (2 ml), followed by H_2O (4 ml) under ice-cooling, and the mixture was extracted with AcOEt (3 × 15 ml). The org. soln. was washed with brine (5 ml), and dried and evaporated. Purification of the residue by CC (neutral, hexane/AcOEt 50:1) afforded **38** (131 mg, 97%). Colorless oil. IR (ATR): 3410 (OH). ^{1}H-NMR (400 MHz): 0.07 (*s*, 2 Me); 0.90 (*s*, 3 Me); 1.49–1.62 (*m*, CH_2); 1.69–1.83 (*m*, 2 CH_2); 2.02–2.04 (*m*, CH); 2.85 (br. *s*, HO); 3.51 (*dd*, *J* = 9.1, 6.0, 1 H, CH_2); 3.53 (*dd*, *J* = 9.8, 6.0, 1 H, CH_2); 3.70–3.87 (*m*, CH_2); 4.58 (diffused *t*, *J* = 3.4, CH). ^{13}C-NMR (100 MHz): −5.7; 18.1; 19.5; 25.3; 25.7; 30.5; 43.0; 43.1; 62.2; 62.9; 63.5; 66.5; 99.0; 99.1. HR-FAB-MS: 305.2137 ($[M+H]^+$, $C_{15}H_{32}O_4Si^+$; calc. 305.2148).

*3-[(Benzyloxy)methoxy]-2-(bromomethyl)propyl (*tert*-Butyl)dimethylsilyl Ether* (**39**). A mixture of **37** (98 mg, 0.29 mmol), CBr_4 (218 mg, 0.65 mmol), pyridine (0.09 ml, 1.11 mmol), and PPh_3 (173 mg, 0.66 mmol) in CH_2Cl_2 (0.9 ml) was stirred at r.t. for 2.5 h under Ar and poured into AcOEt (20 ml). The org. soln. was washed with 10% aq. $CuSO_4$ (20 ml), sat. aq. $NaHCO_3$ (20 ml), H_2O (10 ml), and brine (10 ml), and dried and evaporated. Purification of the residue by CC (acidic, hexane/AcOEt 50:1) afforded **39** (102 mg, 88%). Colorless oil. ^{1}H-NMR (400 MHz): 0.06 (*s*, 2 Me); 0.89 (*s*, 3 Me); 2.16 (*sept.*, *J* = 5.8, CH); 3.56 (*d*, *J* = 5.5, CH_2); 3.61 (*dd*, *J* = 9.7, 6.5, 1 H, CH_2); 3.64 (*dd*, *J* = 9.9, 5.8, 1 H, CH_2); 3.66 (*dd*, *J* = 9.7, 5.8, 1 H, CH_2); 3.71 (*dd*, *J* = 9.9, 5.3, 1 H, CH_2); 4.60 (*s*, CH_2); 4.75 (*s*, CH_2); 7.29–7.32 (*m*, arom. H); 7.34–7.36 (*m*, arom. H); 7.36 (*d*-like, arom. H). ^{13}C-NMR (100 MHz): −5.5; 18.2; 25.8;

32.8; 43.6; 61.6; 66.6; 69.4; 94.8; 127.7; 127.9; 128.4; 137.8. HR-FAB-MS: 403.1274 ($[M+H]^+$, $C_{18}H_{32}BrO_3Si$; calc. 403.1304).

*2-(Bromomethyl)-3-[2-(3,4,5,6-tetrahydropyran-2-yl)]propyl (*tert*-Butyl)dimethylsilyl Ether* (**40**). A mixture of **38** (51 mg, 0.17 mmol), CBr_4 (116 mg, 0.34 mmol), pyridine (0.05 ml, 0.62 mmol), and PPh_3 (90 mg, 0.34 mmol) in CH_2Cl_2 (0.6 ml) was stirred at r.t. for 2.5 h under Ar and poured into AcOEt (15 ml). The org. soln. was washed with 10% aq. $CuSO_4$ (5 ml), sat. aq. $NaHCO_3$ (5 ml), and brine (5 ml), and dried and evaporated. Purification of the residue by CC (neutral, hexane/AcOEt 50:1) afforded **40** (58 mg, 95%). Colorless oil. ^{1}H-NMR (400 MHz; mixture of diastereoisomers): 0.06 (*s*, 2 Me); 0.89 (s, 3 Me); 1.48–1.63 (*m*, 2 CH_2); 1.67–1.84 (*m*, CH_2); 2.16 (*sept.*, $J=5.9$, CH); 3.39 (*dd*, $J=$ 9.8, 6.6, 0.5 H, CH_2); 3.44 (*dd*, $J=9.8$, 5.9, 0.5 H, CH_2); 3.49–3.60 (*m*, 1 H, CH_2); 3.56 (diffused *d*, $J=5.7$, CH_2); 3.64 (*dd*, $J=9.9$, 6.2, 0.5 H, CH_2); 3.66 (*dd*, $J=9.8$, 6.0, 0.5 H, CH_2); 3.716 (*dd*, $J=9.9$, 5.3, 0.5 H, CH_2); 3.719 (*dd*, $J=10.1$, 5.1, 0.5 H, CH_2); 3.76 (*dd*, $J=9.8$, 6.6, 0.5 H, CH_2); 3.80 (*dd*, $J=9.8$, 5.6, 0.5 H, CH_2); 3.82–3.89 (*m*, 1 H, CH_2); 4.59 (*t*, $J=3.4$, CH). ^{13}C-NMR (100 MHz): −5.5; 18.2; 19.3; 19.4; 25.4; 25.8; 30.5; 33.0; 33.1; 43.65; 43.69; 61.6; 61.7; 61.99; 62.3; 66.1; 66.2; 98.8; 99.0. HR-FAB-MS: 405.0858 ($[M+K]^+$, $C_{15}H_{31}BrKO_3Si^+$; calc. 405. 0863).

*2-{[(Benzyloxy)methoxy]methyl}-3-[(*tert*-butyl)dimethylsilyloxy]propyl Methanesulfonate* (**41**). A soln. of **37** (661 mg, 1.94 mmol), MsCl (0.23 ml, 2.97 mmol), and pyridine (0.60 ml, 7.42 mmol) in CH_2Cl_2 (1 ml) was stirred at r.t. for 6.5 h under Ar. After dilution with AcOEt (50 ml), the soln. was washed with 10% aq. $CuSO_4$ (2 × 10 ml), sat. aq. $NaHCO_3$ (2 × 10 ml), and brine (10 ml), and dried and evaporated. Purification of the residue by CC (acidic, hexane → hexane/$CHCl_3$ 1:1) afforded **41** (764 mg, 94%). Colorless oil. ^{1}H-NMR (400 MHz): 0.05 (*s*, 2 Me); 0.89 (*s*, 3 Me); 2.23 (*sept.*, $J=5.9$, CH); 2.98 (*s*, Me); 3.60 (*dd*, $J=10.0$, 6.6, 1 H, CH_2); 3.63 (*dd*, $J=11.4$, 5.9, 1 H, CH_2); 3.68 (*dd*, $J=11.4$, 6.0, 1 H, CH_2); 3.71 (*dd*, $J=10.0$, 5.3, 1 H, CH_2); 4.32 (*d*, $J=5.7$, CH_2); 4.60 (*s*, CH_2); 4.75 (*s*, CH_2); 7.28–7.40 (*m*, arom. H). ^{13}C-NMR (100 MHz): −5.5; 18.2; 25.8; 37.0; 41.7; 60.1; 65.1; 68.0; 69.5; 94.9; 127.75; 127.81; 128.4; 137.7. HR-FAB-MS: 457.1480 ($[M+K]^+$, $C_{19}H_{34}KO_6SSi^+$; calc. 457.1482).

*3-[(*tert*-Butyl)dimethylsilyloxy]-2-[(3,4,5,6-tetrahydropyran-2-yl)oxymethyl]propyl Methanesulfonate* (**42**). A soln. of **38** (457 mg, 1.50 mmol), MsCl (0.27 ml, 3.4 mmol), and pyridine (0.72 ml, 8.91 mmol) in CH_2Cl_2 (4 ml) was stirred at r.t. for 1 h and then at 40° for 1.5 h under Ar. After addition of H_2O (5 ml), the mixture was extracted with AcOEt (3 × 30 ml). The org. soln. was washed with 10% aq. $CuSO_4$ (10 ml), sat. aq. $NaHCO_3$ (10 ml), and brine (10 ml), and dried and evaporated. Purification of the residue by CC (neutral, hexane/$CHCl_3$ 1:1) afforded **42** (568 mg, 99%). Colorless oil. ^{1}H-NMR (400 MHz): 0.06 (*s*, 2 Me); 0.89 (*s*, 3 Me); 1.48–1.62 (*m*, CH_2); 1.68–1.83 (*m*, CH_2); 2.24 (*sept.*, $J=6.0$, CH); 3.01 (*s*, Me); 3.41 (*dd*, $J=9.8$, 6.7, 1 H, CH_2); 3.44 (*dd*, $J=9.8$, 6.0, 1 H, CH_2); 3.48–3.54 (*m*, CH_2); 3.63–3.85 (*m*, CH_2); 4.33–4.36 (*m*, CH_2); 4.56 (*m*, CH). ^{13}C-NMR (100 MHz): complicated. HR-FAB-MS: 383.1919 ($[M+H]^+$, $C_{16}H_{35}O_6SSi^+$; calc. 383.1924).

*2-[(2-{[(Benzyloxy)methoxy]methyl}-3-[(*tert*-butyl)dimethylsilyloxy]propyl)(methyl)amino]-1-phenylethanol* (**43**). A soln. of **22** (79 mg, 0.52 mmol) in DMF (1 ml) was added to a mixture of **41** (169 mg, 0.40 mmol), KI (68 mg, 0.41 mmol), and Et_3N (0.11 ml, 0.79 mmol) in DMF (0.8 ml), and the resulting mixture was stirred at 65° for 17 h and then at 85° for 2.5 h. After addition of sat. aq. $NaHCO_3$ (3 ml), followed by H_2O (3 ml), the mixture was extracted with AcOEt (3 × 30 ml). The org. soln. was washed with half-sat. brine (5 × 6 ml) and brine (6 ml), and dried (K_2CO_3) and evaporated. Purification of the residue by CC (acidic, hexane/AcOEt 20:1) afforded **43** (116 mg, 61%). Colorless oil. IR (ATR): 3427 (OH). ^{1}H-NMR (400 MHz; mixture of diastereoisomers): 0.05 (*s*, 2 Me); 0.89 (*s*, 3 Me); 2.01 (*sext.*, $J=6.0$, CH); 2.35 (*s*, Me); 2.33–2.37 (*m*, 0.5 H, CH_2); 2.41 (*dd*, $J=12.6$, 6.7, 0.5 H, CH_2); 2.45–2.50 (*m*, CH_2); 2.57 (*dd*, $J=12.5$, 7.7, 0.5 H, CH_2); 2.63 (*dd*, $J=12.5$, 8.1, 0.5 H, CH_2); 3.58–3.71 (*m*, 2 CH_2); 4.61 (*s*, CH_2); 4.69 (*dd*, $J=9.4$, 4.5, CH); 4.75 (*d*, $J=7.7$, 1 H, CH_2); 4.77 (*d*, $J=7.7$, 1 H, CH_2); 7.24–7.38 (*m*, arom. H). ^{13}C-NMR (100 MHz): −5.5; 18.3; 25.9; 39.9; 42.4; 42.6; 56.7; 56.8; 61.6; 61.9; 66.8; 66.9; 67.2; 67.4; 69.35; 69.43; 95.0; 125.9; 127.4; 127.7; 127.8; 128.3; 128.4; 137.9; 142.1. HR-FAB-MS: 474.3054 ($[M+H]^+$, $C_{27}H_{44}NO_4Si^+$; calc. 474.3040).

*2-({3-[(*tert*-Butyl)dimethylsilyloxy]-2-[(3,4,5,6-tetrahydropyran-2-yl)oxymethyl]propyl}(methyl)amino)-1-phenylethanol* (**44**). A soln. of **22** (1.14 g, 7.53 mmol) in DMF (18 ml) was added to a mixture of **42** (2.22 g, 5.79 mmol), KI (965 mg, 5.81 mmol), and Et_3N (1.6 ml, 11.5 mmol) in DMF (10 ml), and the resulting mixture was stirred at 65° for 15.5 h and then at 85° for 2.5 h. After addition of sat. aq. $NaHCO_3$

(10 ml), followed by H_2O (10 ml), the mixture was extracted with AcOEt (3 × 150 ml). The org. soln. was washed with half-sat. brine (5 × 30 ml) and brine (30 ml), and dried (K_2CO_3) and evaporated. Purification of the residue by CC (neutral, hexane/AcOEt 10:1) afforded **44** (1.86 g, 73%). Colorless oil. IR (ATR): 3460 (OH). ^{1}H-NMR (400 MHz; mixture of diastereoisomers): 0.05, 0.06 (2*s*, 2 Me); 0.90 (*s*, 3 Me); 1.48–1.62 (*m*, 2 CH_2); 1.68–1.74 (*m*, 1 H, CH_2); 1.76–1.85 (*m*, 1 H, CH_2); 2.01 (*sept.*, *J* = 6.0, CH); 2.29–2.65 (*m*, 2 CH_2); 2.35 (*s*, Me); 3.40–3.46 (*m*, 1 H, CH_2); 3.48–3.53 (*m*, 1 H, CH_2); 3.62–3.75 (*m*, CH_2); 3.78 (*dd*, *J* = 9.5, 4.6, 0.5 H, CH_2); 3.83 (*dd*, *J* = 9.8, 5.8, 0.5 H, CH_2); 3.84–3.90 (*m*, 1 H, CH_2); 4.57 (*dd*, *J* = 4.2, 2.7, CH); 4.66–4.72 (*m*, CH); 7.26 (*tt*, *J* = 6.7, 1.6, arom. H); 7.33 (*dd*, *J* = 7.7, 7.3, 2 arom. H); 7.37 (diffused *d*, *J* = 8.2, 2 arom. H). ^{13}C-NMR (100 MHz): −5.5; 18.3; 19.5; 19.6; 19.7; 25.4; 25.9; 30.6; 39.7; 39.9; 42.4; 42.5; 56.45; 56.49; 56.8; 56.9; 61.4; 61.7; 61.8; 61.9; 62.2; 62.3; 62.4; 66.1; 66.28; 66.34; 66.5; 66.8; 66.9; 66.97; 67.04; 69.4; 69.5; 69.6; 98.98; 99.03; 99.26; 99.32; 125.8; 127.3; 128.2; 142.18; 142.22; 142.24; 142.3. HR-FAB-MS: 438.3037 ($[M+H]^+$, $C_{24}H_{44}NO_4Si^+$; calc. 438.3040).

tert-*Butyl* N-*(2-Hydroxy-2-phenylethyl)carbamate* (**51**). A mixture of **50** (358 mg, 2.48 mmol), Et_3N (0.52 ml, 3.75 mmol), and Boc_2O (647 mg, 2.97 mmol) in CH_2Cl_2 (4 ml) was stirred at r.t. for 1.3 h under Ar. After addition of sat. aq. NH_4Cl (10 ml), the mixture was extracted with CH_2Cl_2 (3 × 20 ml). The org. soln. was washed with H_2O (5 ml) and brine (10 ml), and dried (Na_2SO_4) and evaporated. Recrystallization of the residue from benzene afforded **51** (537 mg, 91%). Colorless needles. M.p. 122–124.5°. IR (ATR): 3363 (OH); 1674 (CO). ^{1}H-NMR (400 MHz): 1.45 (*s*, 3 Me); 3.00 (*s*, HO); 3.27 (*ddd*, *J* = 13.6, 8.0, 5.6, CH_2); 3.47–3.52 (*m*, CH_2); 4.84 (*m*, CH); 4.91 (br. *s*, HN); 7.28–7.31 (*m*, arom. H); 7.34–7.37 (*m*, arom. H). EI-MS: 237 (M^+).

tert-*Butyl (2-Oxo-2-phenylethyl)carbamate* (**52**). To a soln. of pyridinium dichromate (PDC; 268 mg, 0.70 mmol) in DMF (0.5 ml) was added an ice-cooled soln. of **51** (41 mg, 0.17 mmol) in DMF (0.5 ml) under Ar, and then the mixture was stirred at r.t. for 21 h. After addition of brine (10 ml), followed by H_2O (5 ml), the mixture was extracted with Et_2O (3 × 10 ml). The org. soln. was washed with brine (10 ml), and dried and evaporated. Purification of the residue by CC (acidic, hexane/AcOEt 10:1) afforded **52** (38 mg, 94%). Colorless oil. IR (ATR): 3356 (OH), 1714 (CO), 1685 (CO). ^{1}H-NMR (400 MHz): 1.48 (*s*, 3 Me); 4.67 (*d*, *J* = 4.4, CH_2); 5.56 (br. *s*, HN); 7.49 (*t*, *J* = 7.6, arom. H); 7.61 (diffused *t*, *J* = 6.0, arom. H); 7.96 (diffused *d*, *J* = 8.3, arom. H). FAB-MS: 258 ($[M+Na]^+$), 236 ($[M+H]^+$).

*2-(2-{[(Benzyloxy)methoxy]methyl}-3-[(*tert*-butyl)dimethylsilyloxy]propylamino)-1-phenylethanol* (**55**). A soln. of **50** (225 mg, 1.56 mmol) in DMF (3.5 ml) was added to a mixture of **41** (498 mg, 1.19 mmol), KI (195 mg, 1.18 mmol), and Et_3N (0.36 ml, 2.59 mmol) in DMF (2.5 ml), and the resulting mixture was stirred at 65° for 18.5 h and then at 85° for 3 h. After addition of sat. aq. $NaHCO_3$ (2 ml), followed by H_2O (5 ml), the mixture was extracted with AcOEt (3 × 30 ml). The org. soln. was washed with brine (10 ml), dried (K_2CO_3), and evaporated. Purification of the residue by CC (NH-type, hexane/benzene 5:1) afforded **55** (275 mg, 50%). Colorless oil. IR (ATR): 3315 (OH). ^{1}H-NMR (400 MHz): 0.04 (*s*, 2 Me); 0.88 (*s*, 3 Me); 1.96 (*sept.*, *J* = 5.9, CH); 2.64–2.72 (*m*, CH_2); 2.76 (*dd*, *J* = 6.0, 4.0, 1 H, CH_2); 2.79 (*dd*, *J* = 6.4, 4.6, 1 H, CH_2); 2.87 (*dd*, *J* = 3.4, 1.7, 1 H, CH_2); 2.90 (*dd*, *J* = 3.4, 1.7, 1 H, CH_2); 3.57–3.71 (*m*, CH_2); 4.58 (*s*, CH_2); 4.66 (*dd*, *J* = 3.5, 2.0, 0.5 H, CH); 4.68 (*dd*, *J* = 3.5, 2.0, 0.5 H, CH); 4.730 (*s*, 1 H, CH_2); 4.734 (*s*, 1 H, CH_2); 7.24–7.37 (*m*, arom. H). ^{13}C-NMR (100 MHz): −5.5; 18.2; 25.8; 41.5; 49.1; 57.4; 62.5; 62.6; 67.6; 67.7; 69.3; 71.39; 71.43; 94.8; 125.8; 127.4; 127.6; 127.8; 128.3; 128.4; 137.8; 142.6. HR-FAB-MS: 460.2871 ($[M+H]^+$, $C_{26}H_{42}NO_4Si^+$; calc. 460.2883).

tert-*Butyl* N-*(2-Hydroxy-2-phenylethyl)*-N-*(2-{[(benzyloxy)methoxy]methyl}-3-[(*tert*-butyl)dimethylsilyloxy]propyl)carbamate* (**53**). A mixture of **55** (124 mg, 0.19 mmol), Et_3N (0.05 ml, 0.36 mmol), and Boc_2O (62 mg, 0.29 mmol) in CH_2Cl_2 (1.5 ml) was stirred under ice-cooling for 1 h and then at r.t. for 1 h under Ar. After addition of H_2O (2 ml), followed by sat. aq. $NaHCO_3$ (4 ml), the mixture was extracted with AcOEt (3 × 20 ml). The org. soln. was washed with brine (10 ml), dried (K_2CO_3), and evaporated. Purification of the residue by CC (acidic, hexane/AcOEt 10:1) afforded **53** (100 mg, 97%). Colorless oil. IR (ATR): 3425 (OH); 1693 (CO). ^{1}H-NMR (400 MHz): 0.00 (*s*, Me); 0.02 (*s*, Me); 0.87, 0.88 (2*s*, 3 Me); 1.47 (*s*, 3 Me); 2.11 (br. *s*, CH); 3.14 (*dd*, *J* = 14.2, 6.7, 1 H, CH_2); 3.24 (br. *s*, 1 H, CH_2); 3.38–3.60 (*m*, CH_2); 4.54 (*s*, 1 H, CH_2); 4.56 (*s*, 1 H, CH_2); 4.696 (*s*, 1 H, CH_2); 4.704 (*s*, 1 H, CH_2); 4.93–4.95 (*m*, CH); 7.22–7.37 (*m*, arom. H). ^{13}C-NMR (100 MHz): −5.6; 18.2; 25.8; 28.4; 41.2; 41.3; 48.3; 56.9; 61.3; 61.4; 66.5; 66.7; 69.2; 74.1; 80.6; 94.8; 125.7; 125.8; 127.4; 127.6; 127.7; 128.3; 137.7; 142.4; 158.1. HR-FAB-MS: 582.3256 ($[M+Na]^+$, $C_{31}H_{49}NNaO_6Si^+$; calc. 582.3227).

Oxidation of **53**: tert-*Butyl* N-*(2-{[(Benzyloxy)methoxy]methyl}-3-[(*tert-*butyl)dimethylsilyloxy]-propyl)*-N-*(2-oxo-2-phenylethyl)carbamate* (**54**). 1) *With PDC*. An ice-cooled soln. of **53** (40 mg, 0.07 mmol) in DMF (0.45 ml) was added to a soln. of PDC (60 mg, 0.94 mmol) in DMF (0.2 ml) under Ar, and then the mixture was stirred at r.t. for 20 h. After addition of brine (3 ml), followed by H_2O (2 ml), the mixture was extracted with Et_2O (3 × 10 ml). The org. soln. was washed with brine (10 ml), dried, and evaporated. Purification of the residue by CC (acidic, hexane/AcOEt 20:1) afforded **54** (27 mg, 67%). Colorless oil. IR (ATR): 1705 (CO). ^{1}H-NMR (400 MHz): 0.03 (*s*, 2 Me); 0.85 (*s*, 3 Me); 1.34, 1.49 (2*s*, 3 Me); 2.09 (*sept.*, J = 6.2, CH); 3.27 (*dd*, J = 14.7, 7.0, 1 H, CH_2); 3.30 (*dd*, J = 14.3, 7.1, 1 H, CH_2); 3.40 (*dd*, J = 14.7, 7.0, 1 H, CH_2); 3.47 (*dd*, J = 14.3, 6.8, 1 H, CH_2); 3.60–3.70 (*m*, CH_2); 4.54–4.65 (*m*, 2 CH_2); 4.70–4.77 (*m*, CH_2); 7.29–7.34 (*m*, arom. H); 7.42–7.49 (*m*, arom. H); 7.54–7.61 (*m*, arom. H); 7.91 (*dd*, J = 9.0, 8.3, arom. H). ^{13}C-NMR (100 MHz): −5.51; −5.49; 18.2; 25.8; 28.1; 28.4; 41.4; 41.6; 47.7; 54.3; 54.9; 61.4; 66.8; 66.9; 69.3; 79.9; 80.2; 94.95; 95.01; 127.6; 127.8; 128.4; 128.6; 128.7; 133.3; 135.4; 135.5; 137.8; 138.0; 155.7; 156.2; 194.9. HR-FAB-MS: 596.2763 ($[M+K]^+$, $C_{31}H_{47}KNO_6Si^+$; calc. 596.2810).

2) *By* Swern *Oxidation*. To a soln. of oxalyl chloride (0.01 ml, 0.12 mmol) in CH_2Cl_2 (0.1 ml) was added a soln. of DMSO (0.01 ml, 0.17 mmol) in CH_2Cl_2 (0.1 ml), followed by a soln. of **53** (45 mg, 0.08 mmol) in CH_2Cl_2 (0.4 ml) at −78° under Ar, and then the mixture was stirred at the same temp. for 1 h. After addition of a soln. of Et_3N (0.06 ml, 0.40 mmol) in CH_2Cl_2 (0.1 ml) at the same temp., the mixture was stirred for 1.5 h, the reaction was quenched with H_2O (2 ml), and then the mixture was extracted with CH_2Cl_2 (3 × 10 ml). The org. soln. was washed with brine (8 ml), dried, and evaporated. Purification of the residue by CC (acidic, hexane/AcOEt 10:1) afforded **54** (32 mg, 71%).

3) *With* MnO_2. A mixture of **53** (503 mg, 0.90 mmol) and MnO_2 (3.12 g) in CH_2Cl_2 (5 ml) was stirred at r.t. for 2 d under Ar. After further addition of MnO_2 (0.52 g), the resulting mixture was stirred under the same conditions for 10 h. After removal of the MnO_2 through *Celite*® pad, the filtrate was evaporated. Purification of the residue by CC (acidic, hexane/AcOEt 15:1) afforded **54** (417 mg, 83%).

tert-*Butyl* N-*(3-{[(Benzyloxy)methoxy]methyl}-2-(hydroxymethyl)propyl)*-N-*(2-oxo-2-phenylethyl)carbamate* (**56**). To a soln. of **54** (362 mg, 0.65 mmol) in THF (3.5 ml) was added 1 mol soln. of TBAF in THF (0.78 ml, 0.78 mmol), and the mixture was stirred at r.t. for 4.5 h under Ar, and the reaction was quenched with sat. aq. NH_4Cl (2 ml), followed by H_2O (15 ml), and the mixture was extracted with AcOEt (3 × 20 ml). The org. soln. was washed with brine (20 ml), dried, and evaporated. Purification of the residue by CC (acidic, hexane/AcOEt 2:1) afforded **56** (266 mg, 93%). Colorless oil. IR (ATR): 3427 (OH); 1699 (CO). ^{1}H-NMR (400 MHz): 1.36, 1.44 (2*s*, 3 Me); 1.99 (br. *s*, CH); 3.22–3.32 (*m*, CH_2); 3.46 (br. *s*, HO); 3.55–3.67 (*m*, CH_2); 3.75 (br. *s*, CH_2); 4.51–4.66 (*m*, CH_2); 4.56 (*s*, 1 H, CH_2); 4.60 (*s*, 1 H, CH_2); 4.72 (*s*, 1 H, CH_2); 4.74 (*s*, 1 H, CH_2); 7.27–7.34 (*m*, 5 arom. H); 7.46 (*dd*, J = 7.3, 6.8, 2 arom. H); 7.57 (*t*, J = 6.8, arom. H); 7.89 (*d*, J = 7.3, 2 arom. H). ^{13}C-NMR (100 MHz): 28.1; 28.4; 40.8; 47.0; 47.5; 54.4; 55.1; 60.4; 62.4; 67.9; 68.5; 69.6; 69.7; 80.7; 80.9; 95.0; 127.7; 127.8; 127.9; 128.4; 128.7; 128.8; 133.6; 135.2; 137.7; 157.0; 194.5. HR-FAB-MS: 482.1920 ($[M+K]^+$, $C_{25}H_{33}KNO_6^+$; calc. 482.1945).

tert-*Butyl* N-*(2-{[(Benzyloxy)methoxy]methyl}-3-bromopropyl)*-N-*(2-oxo-2-phenylethyl)carbamate* (**57**). A mixture of **56** (25 mg, 0.06 mmol), CBr_4 (79 mg, 0.24 mmol), pyridine (0.03 ml, 0.32 mmol), and PPh_3 (67 mg, 0.25 mmol) in CH_2Cl_2 (0.25 ml) was stirred at r.t. for 2 h under Ar and poured into AcOEt (20 ml). The org. soln. was washed with 10% aq. $CuSO_4$ (4 ml), sat. aq. $NaHCO_3$ (2 ml), H_2O (2 ml), and brine (2 ml), and dried and evaporated. Purification of the residue by CC (acidic, hexane/AcOEt 10:1) afforded **57** (23 mg, 80%). Colorless oil. IR (ATR): 1697 (CO). ^{1}H-NMR (400 MHz): 1.34, 1.50 (2*s*, 3 Me); 2.31 (*sept.*, J = 6.0, 0.5 H, CH); 2.38 (*sept.*, J = 6.0, 0.5 H, CH); 3.32–3.52 (*m*, CH_2); 3.56–3.73 (*m*, CH_2); 4.60 (*s*, CH_2); 4.62 (*s*, CH_2); 4.70 (*s*, CH_2); 4.76 (*s*, CH_2); 7.29–7.36 (*m*, arom. H); 7.44–7.51 (*m*, arom. H); 7.56–7.62 (*m*, arom. H); 7.91 (*t*, J = 8.5, arom. H). ^{13}C-NMR (100 MHz): 28.1; 28.4; 33.9; 34.1; 40.6; 40.7; 49.1; 49.5; 54.7; 55.4; 67.1; 69.5; 69.6; 80.4; 80.7; 94.9; 127.7; 127.9; 128.39; 128.41; 128.7; 128.8; 133.5; 135.1; 137.6; 137.8; 155.7; 155.9; 194.7. HR-FAB-MS: 544.1083 ($[M+K]^+$, $C_{25}H_{32}BrKNO_5^+$; calc. 544.1101).

tert-*Butyl* N-*(2-{[(Benzyloxy)methoxy]methyl}-3-iodopropyl)*-N-*(2-oxo-2-phenylethyl)carbamate* (**58**). A mixture of 1*H*-imidazole (152 mg, 2.24 mmol) and PPh_3 (294 mg, 1.12 mmol), and I_2 (285 mg, 1.12 mmol) in CH_2Cl_2 (1 ml) was vigorously stirred at r.t. under Ar. To the resulting yellow suspension

was added a soln. of **56** (248 mg, 0.56 mmol) in CH_2Cl_2 (1.3 ml), and the mixture was stirred at r.t. for 4 h. After removal of insoluble materials by filtration, the filtrate was evaporated. Purification of the residue by CC (acidic, hexane/AcOEt 10:1) afforded **58** (242 mg, 78%). Pale yellow oil. IR (ATR): 1701 (CO). ^{1}H-NMR (400 MHz): 1.34, 1.50 (2*s*, 3 Me); 1.97 (*sept.*, $J = 5.6$, 0.5 H, CH); 2.06 (*sept.*, $J = 5.6$, 0.5 H, CH); 3.28–3.45 (*m*, CH_2); 3.53 (*dd*, $J = 9.9$, 6.6, 1 H, CH_2); 3.57 (*dd*, $J = 9.8$, 6.3, 1 H, CH_2); 3.65 (*dd*, $J = 9.5$, 4.4, 1 H, CH_2); 3.69 (*dd*, $J = 9.9$, 4.6, 1 H, CH_2); 4.61 (*s*, CH_2); 4.70 (*d*, $J = 7.1$, CH_2); 4.76 (*s*, CH_2); 7.22–7.30 (*m*, arom. H); 7.32–7.37 (*m*, arom. H); 7.44–7.52 (*m*, arom. H); 7.56–7.62 (*m*, arom. H); 7.92 (*t*, $J =$ 8.3, arom. H). ^{13}C-NMR (100 MHz): 8.5; 8.8; 28.1; 28.4; 40.2; 50.4; 50.7; 54.7; 55.4; 68.7; 69.6; 69.7; 80.4; 80.8; 94.9; 127.7; 127.9; 128.4; 128.7; 128.8; 133.5; 135.1; 135.2; 137.6; 137.8; 155.7; 155.9; 194.7. HR-FAB-MS: 554.1415 ($[M+H]^+$, $C_{25}H_{33}INO_5^+$; calc. 554.1404).

tert-*Butyl (5-{[(Benzyloxy)methoxy]methyl}-3-hydroxy-3-phenylpiperidin-1-yl)carbamate* (**59**; *Entry 5* in *Table 2*). A soln. of CH_2I_2 (0.03 ml, 0.31 mmol) in THF (0.1 ml) was added to a suspension of Sm metal (128 mg, 0.85 mmol) in THF (2 ml) at r.t. under sonication in Ar atomsphere. After addition of further THF (20 ml), the mixture was vigorously stirred for 1 h under sonication and for additional 0.5 h without sonication, and cooled to 0°. After addition of HMPA (0.28 ml, 1.61 mmol), the mixture was stirred under the same conditions for 20 min, to which a soln. of **58** (48 mg, 0.09 mmol) in THF (1 ml) was slowly added, and the mixture was stirred at 0° for 1 h. After quenching with sat. aq. *Roschelle* salt (6 ml), insoluble materials were filtered through *Celite*® pad, and the filtrate obtained was extracted with AcOEt (3×10 ml). The org. soln. was washed with H_2O (10×3 ml) and brine (10 ml), and dried and evaporated. Purification of the residue by CC (acidic, hexane/AcOEt 8:1), followed by prep. TLC (hexane/acetone 5:1, triple developments), afforded **59** as a mixture of the (3*R**,5*R**)- (5 mg, 13%; a colorless oil) and the (3*S**,5*R**)-diastereoisomers (7 mg, 19%; a colorless oil).

*Data of the (3*R*,*5*R*)-*Isomer*: IR (ATR): 3442 (OH); 1685 (CO). ^{1}H-NMR (400 MHz at 55°; 1:1 mixture of rotamers): 1.48 (*s*, 3 Me); 1.70 (*t*, $J = 12.9$, 1 H, CH_2); 1.92, 1.95 (2*quint.*, $J = 1.9$, 1 H, CH_2); 2.23 (br. *s*, HO); 2.31–2.41 (*m*, CH); 2.58 (*t*, $J = 12.5$, 1 H, CH_2); 3.02 (*d*, $J = 13.7$, 1 H, CH_2); 3.46 (*dd*, $J =$ 9.8, 6.2, 1 H, CH_2); 3.53 (*dd*, $J = 9.8$, 4.9, 1 H, CH_2); 4.11 (*d*, $J = 13.7$, 1 H, CH_2); 4.32 (br. *d*, $J = 11.0$, 1 H, CH_2); 4.59 (*s*, CH_2); 4.72 (*d*, $J = 8.2$, 1 H, CH_2); 4.74 (*d*, $J = 8.2$, 1 H, CH_2); 7.26–7.38 (*m*, arom. H); 7.50 (diffused *d*, $J = 7.9$, arom. H). ^{13}C-NMR (100 MHz at 55°): 28.5; 32.7; 40.5; 47.5; 54.9; 69.7; 70.5; 72.4; 80.2; 95.0; 124.8; 127.4; 127.8; 127.9; 128.45; 128.48; 138.0; 145.6; 156.2. HR-EI-MS: 427.2368 (M^+, $C_{25}H_{33}NO_5^+$; calc. 427.2359).

*Data of the (3*S*,*5*R*)-*Isomer*: IR (ATR): 3406 (OH); 1687 (CO). ^{1}H-NMR (400 MHz at 55°; 1:1 mixture of rotamers): 1.45 (*s*, 3 Me); 1.78 (*dd*, $J = 13.6$, 7.9, 1 H, CH_2); 1.90 (br. *s*, CH); 2.28 (br. *s*, HO); 2.29 (*d*, $J = 8.6$, 1 H, CH_2); 3.31 (br. *s*, 1 H, CH_2); 3.44 (*d*, $J = 11.9$, 1 H, CH_2); 3.63 (*d*, $J = 6.2$, 1 H, CH_2); 3.68 (br. *s*, 1 H, CH_2); 3.97 (*d*, $J = 13.5$, 1 H, CH_2); 4.58 (*d*, $J = 11.8$, 1 H, CH_2); 4.62 (*d*, $J = 11.8$, 1 H, CH_2); 4.72 (*d*, $J = 10.3$, 1 H, CH_2); 4.76 (*d*, $J = 10.3$, 1 H, CH_2); 7.26–7.36 (*m*, arom. H); 7.54 (diffused *d*, $J = 7.9$, arom. H). ^{13}C-NMR (100 MHz at 55°): 28.5; 34.1; 40.5; 46.0; 54.1; 69.6; 70.7; 72.0; 79.9; 95.1; 125.7; 127.6; 127.7; 127.9; 128.4; 138.0; 144.9; 155.0. HR-FAB-MS: 428.2436 ($[M+H]^+$, $C_{25}H_{34}NO_5$; calc. 428.2437).

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