Monocarbamates, Derived from (*S*)-2-(Dibenzylamino)butane-1,4-diol, and the Influence of the Second *O*-Protecting Group on the Regioselectivity of Deprotonation – Application to the Synthesis of the *Boletus* Toxin (2*S*,4*S*)-γ-Hydroxy-norvaline

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Abstract: Differentially protected 1-*O*- and 4-*O*-monocarbamates, derived from (*S*)-2-(dibenzylamino)butane-1,4-diol are prepared and investigated with respect to their capability of being deprotonated and forming the corresponding lithium carbanions. In the *1-O*-trityl and methyl 4-*O*-monocarbamates **6a** and **6b** the *pro-S*-4-H is removed by *sec*-butyllithium/(-)-sparteine with high diastereoselectivity. The 1-*O*-(2-methoxyethyl) 4-*O*-monocarbamate **(23e)** undergoes a highly selective, substrate-controlled abstraction of the *pro-S*-4-H without addition of any diamine. On the other hand, the 4-*O*-methyl 1-*O*-monocarbamate **7a** reacts with *sec*-butyllithium in diethyl ether with essentially complete stereoselectivity and forms the bicyclic chelate **33** complex with (*S*)-configuration at the lithiated C-1 atom. Trapping by means of iodomethane, CO_2, and other electrophiles proceed with complete stereoretention. The method is applied for the synthesis of *Boletus* toxin (2*S*,4*S*)-γ-hydroxy-norvaline in the form of the lactone hydrochloride. Further, evidence was found that the 2-(dimethylamino) group in the *1-O*-TBDMS 4-*O*-monocarbamate **16** induces a highly substrate-controlled deprotonation in the (4*S*)-position.

Key words: stereoselective lithiation, chiral aminodiols, directed lithiation, chiral carbanion, (–)-sparteine

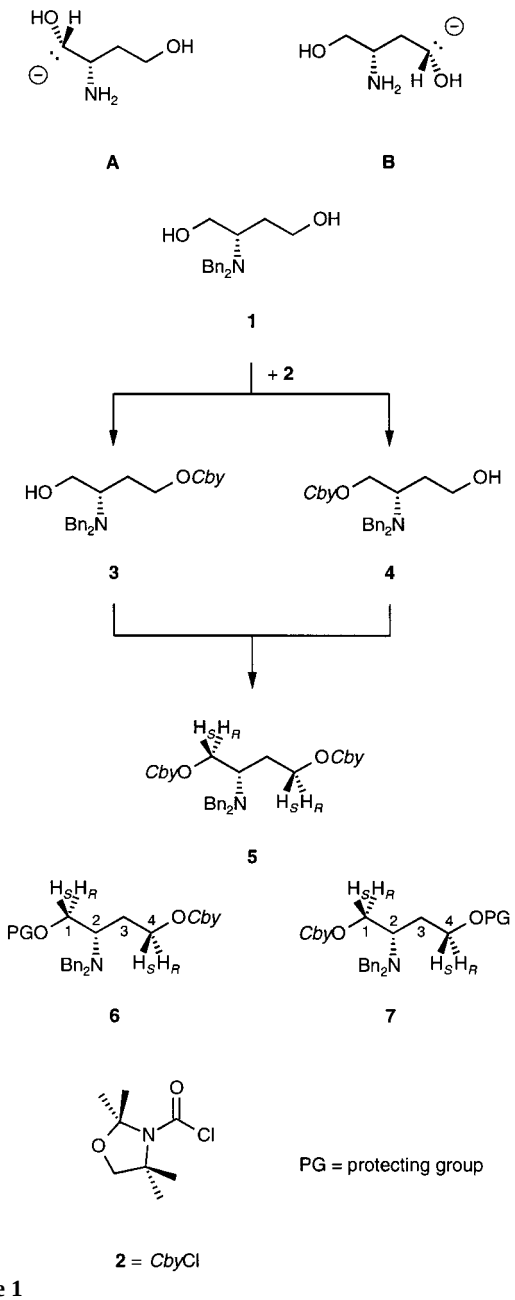
Introduction

In the preceding publication we reported on the highly regio- and diastereoselective lithiation of the enantiomerically pure dicarbamate **5**.[1] By substrate-induced chiral induction, the *pro-S*-1-H is removed by deprotonation with *sec*-butyllithium, providing a synthetic equivalent for the chiral synthon **A**.

Synthon **B** could be approached from **5** after substitution of the *pro-S*-1-H by deuterium, via the abstraction of the *pro-S*-4-H by means of *sec*-butyllithium/(–)-sparteine **(22)**.[1–3] For a more direct synthetic solution, a monocarbamate ester of type **6** is required, bearing a suitable protecting group PG at the 1-*O* atom which does not support lithiation at C-1. On the other hand, monocarbamate ester **7**, having the reverse protecting group pattern, may be useful too for preparing precursors of synthon **A**, in cases when the subsequent reactions require a differentiation between the 1- and 4-oxygen function.

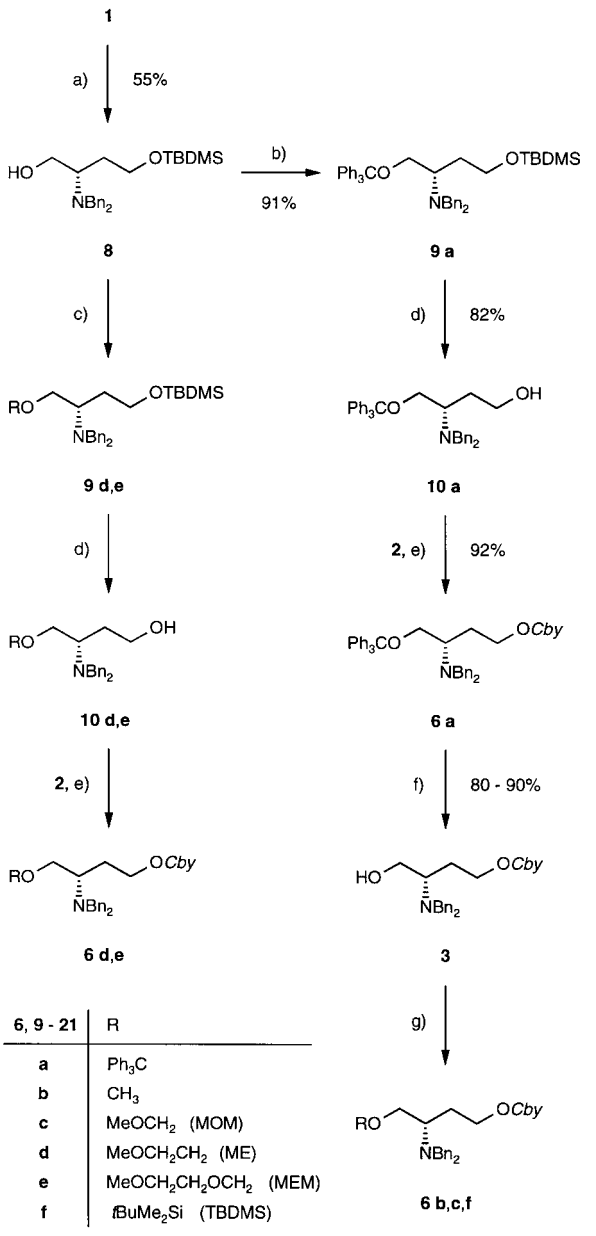
In principle, the ω-hydroxyalkyl carbamates **3** and **4**, which are intermediates in the preparation of dicarbamate **5** from diol **1**[1, 4] are easily accessible by monoacylation with the oxazolidine-3-carbonyl chloride **2** (combined yield 90%, ratio 3:1), but chromatographic separation on a preparative scale turned out to be very cumbersome.

Several methods have been developed in order to differentiate the two carbonyl groups in (*S*)-aspartic acid.[5] Further approaches utilize different (*S*)-amino acids with a four-carbon backbone such as (*S*)-methionine,[5g, 6] (*S*)-asparagine[7] or the expensive[8] (*S*)-homoserine for starting materials.



Scheme 1

Starting from diol **1**, the 4-*O*-TBDMS ether **8** serves as key intermediate, which is regioselectively formed.[4b, 9] Standard protecting group manipulations, followed by acylation of the corresponding alcohols by means of sodium hydride/2,2,6,6-tetramethyloxazolidine-3-carbonyl chloride (**2**, *Cby*Cl),[10] led to the 4-*O*-carbamates **3** and **6a–f** (Scheme 2, Table 1).



(a) TBDMSCl (1.2 equiv), Et_3N (1.2 equiv); DMAP (50 mol%), CH_2Cl_2, 0 °C, 10 min, then 40 °C, 8 h; (b) Ph_3CCl (1.2 equiv), Et_3N (1.9 equiv), DMAP (4 mol%), CH_2Cl_2, r.t., 14 h; (c) For **8** → **9d**: NaH (2.0 equiv), $MeOCH_2CH_2Br$ (3.2 equiv), Bu_4NI (11 mol%), DMAP (2 mol%), THF, 65 °C, 20 h; 45%. For **8** → **9e:** MEMCl (1.2 equiv), iPr_2NEt (1.2 equiv), CH_2Cl_2, 40 °C, 24 h; (d) TBAF (2.5 equiv), THF/Et_2O, r.t., 14 h; **10a** (82%); **10d** (99%); **10e** (90% over two steps). (e) i. NaH (1.5 equiv), THF, r.t., 3 h; ii. + *Cby*Cl (2, 1.3 equiv), 65 °C, 16 h; **6a** (92%); **6d** (88%); **6e** (72%); (f) TFA (21.5 equiv), MeOH/CH_2Cl_2, –5 °C, 0.5 h then r.t., 2 h; (g) For **3** → **6b**: i. NaH (3.0 equiv), THF, r.t., 0.5 h; ii. + MeI (4.0 equiv), 65 °C, 16 h; (95%). For **3** → **6c**: MOMCl (20 equiv), CH_2Cl_2, r.t., 7 d; 97%. For **3** → **6f**: TBDMSCl (1.2 equiv), Et_3N (5 equiv), CH_2Cl_2, r.t., 10 h; 97%.

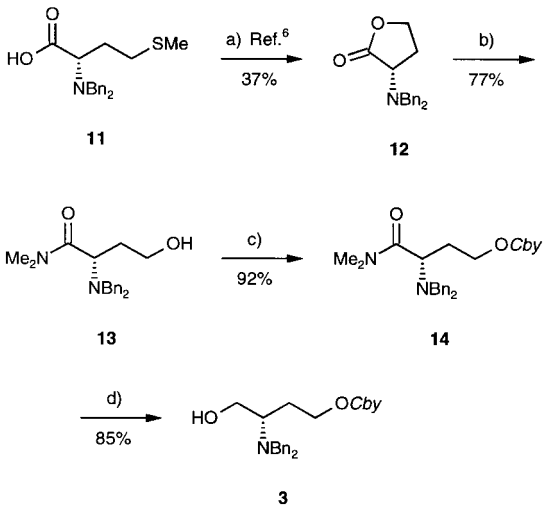
Scheme 2

Table 1. Differentially Protected Monocarbamates **3, 4, 6,** or **7** and Intermediates **8, 9, 10, 12, 13, 14, 15,** or **16** Leading to Them

Product[a]	Substrate (Scheme)		Yield (%)	mp[b] (°C)
3	**6a**	(2)	80–90	oil
	14	(3)	85	
4	**7a**	(5)	92	oil
6a	**10a**	(2)	92	66
6b	**3**	(2)	95	oil
6c	**3**	(2)	97	oil
6d	**10d**	(2)	88	oil
6e	**10e**	(2)	72	oil
6f	**3**	(2)	97	oil
7a	**8**	(5)	90	oil
7b	**4**	(5)	83	oil
8	**1**	(2)	55	oil
9a	**8**	(2)	91	oil
9d	**8**	(2)	45	oil
10a	**9a**	(2)	82	140
10d	**9d**	(2)	99	oil
10e	**9e**	(2)	90[c]	oil
12[d]	**11**	(3)	37	66
13	**12**	(3)	77	oil
14	**13**	(3)	92	oil
15	**6f**	(4)	84	oil
16	**15**	(4)	82	oil

[a] Satisfactory elemental analyses were obtained (C ± 0.30, H ± 0.30, N ± 0.30).
[b] From Et_2O.
[c] Over two steps.
[d] Ref. 6.

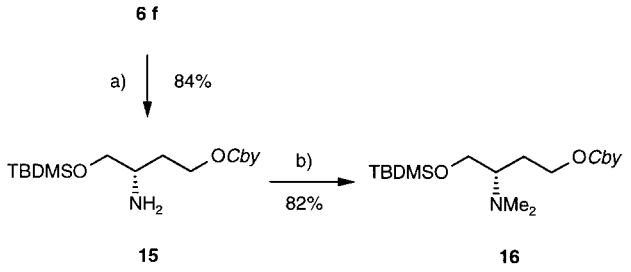
The 1-*O*-unprotected monocarbamate **3** was also prepared by a shorter route, starting from (*S*)-methionine **(11)** via the (*S*)-*N*,*N*-dibenzylhomoserine lactone **(12)** (according to Reetz),[6] aminolysis to the *N*,*N*-dimethylamide **13**, carbamoylation of the γ-hydroxy group and deaminative reduction[11] of the carbamate **14** by means of lithium triethylborohydride (Scheme 3, Table 1).[12]



(a) BnBr (3.0 equiv), K_2CO_3, NaOH, H_2O/MeOH, reflux, 45 min; (b) Me_2NH (11.2 equiv), EtOH/BnOH, 0 °C, 48 h; (c) i. NaH (1.5 equiv), THF, r.t., 3 h; ii. + *Cby*Cl (**2**, 1.5 equiv), 65 °C, 16 h; (d) $LiEt_3BH$ (4.8 equiv), THF, 0 °C; r.t., 12 h.

Scheme 3

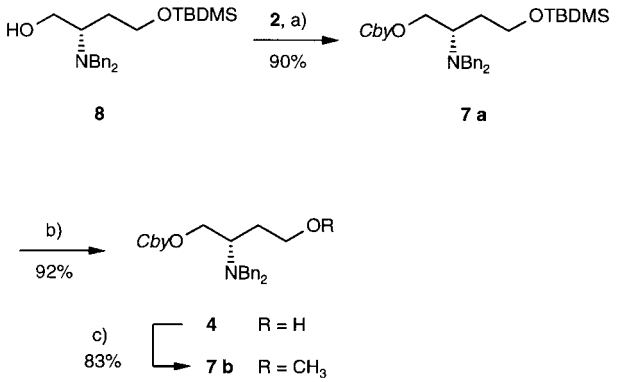
For the synthesis of the 3-(dimethylamino)butyl carbamate **16**, the *N*-benzyl groups in carbamate **6f** were removed by Pd-catalyzed transfer hydrogenolysis,[13] followed by reductive dimethylation, utilizing sodium cyanoborohydride as reacting agent (Scheme 4, Table 1).[14]



(a) cyclohexene (15 equiv), Pd/C (6 mol%), MeOH, reflux, 12 h; (b) i. $H_2C{=}O/H_2O$ (5 equiv), $NaBH_3CN$ (1.6 equiv), MeCN, r.t., 0.5 h; ii. HOAc.

Scheme 4

The 4-*O*-methyl- and 4-*O*-TBDMS-protected 1-*O*-carbamates **7a** and **7b**, respectively, and as well the free 1-alkanol **4**, are also conveniently prepared from the TBDMS ether **8** (Scheme 5, Table 1).



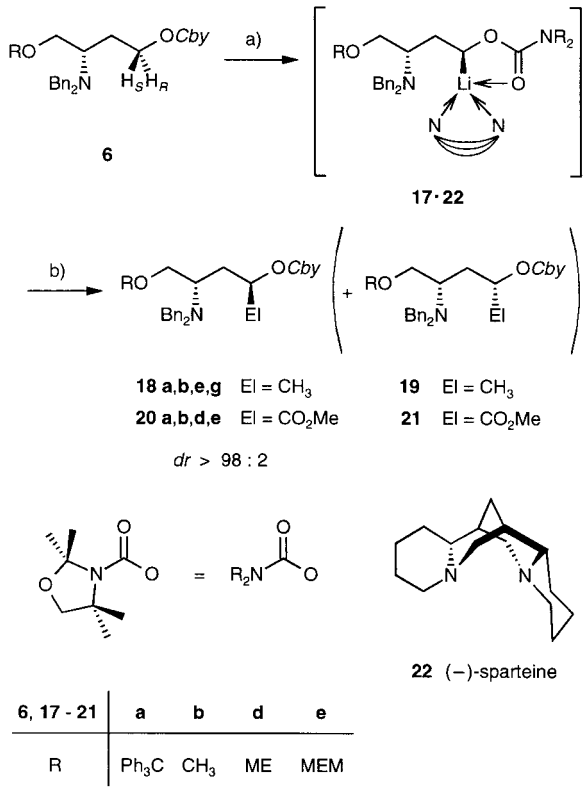
(a) i. NaH (1.2 equiv), THF, r.t., 2 h; ii. *Cby*Cl (**2**, 1.2 equiv), reflux, 16 h; (b) TBAF (2.5 equiv), THF, r.t., 40 min; (c) i. NaH (2.0 equiv), THF, r.t., 0.5 h; ii. + MeI (2.0 equiv), reflux, 15 h.

Scheme 5

The 1-*O*- and the 4-*O*-methyl derivatives **6b** and **7b** were also obtained by direct methylation of the sodium alkoxides of **3** and **4** (3:1) and could be separated on a small scale (1 g) by LC on silica gel.

Deprotonation and Electrophilic Substitution of 4-*O*-Monocarbamates 6

The 4-*O*-monocarbamates **6a**,**b**,**d**,**e** under the usual conditions[1] were smoothly deprotonated by 1.6 equivalents of *sec*-butyllithium/(–)-sparteine **(22)** in diethyl ether (reaction at –78 °C, quenching the solution of the assumed lithium intermediate **17·22** by iodomethane or carbon dioxide (followed by conversion of the crude acids), afforded the diastereomerically pure 4-substitution products **18a**,**b**,**e** and **20a**,**b**,**d**,**e**, respectively in good yields (Scheme 6, Table 3). If the deprotonation is assisted by (–)-sparteine the intermediate **17·22** has the (4*S*)-configuration and the external electrophilic substitution at the sp^3-C–Li bond will proceed with retention, since we never encountered an exception in an intermolecular reaction.[3] The correct configurational assignment was proven for the methylation product by its conversion into the known (2*S*,4*S*)-4-hydroxy-norvaline lactone hydrochloride **32** (see Scheme 10).



(a) *s*-BuLi (1.6 equiv), (–)-sparteine (**22**, 1.6 equiv), Et_2O, –78 °C, 5 h. (b) For **18**: MeI (1.6 equiv), 3 h at –78 °C, → r.t. For **19**: i. gaseous CO_2; ii. after workup CH_2N_2 in Et_2O.

Scheme 6

The argument, outlined above, requires that no substrate-catalyzed lithiation takes place. The 1-*O*-methyl and the 1-*O*-MOM derivative **6b** and **6c** did not react with *sec*-butyllithium in diethyl ether (–78 °C, 5 h) when (–)-sparteine was not present. This clearly demonstrates that neither these very donor-active γ-alkoxy groups nor the γ-dibenzylamino group[3c] are capable of intervening in the deprotonation step. The 1-O-MEM ether **6e** produced the (vinyloxymethyl) ether **24** via elimination of lithium methoxide (Scheme 7, Table 3). A smooth substrate-induced 4-deprotonation was achieved with the 1-(2-methoxyethyl) ether **6d**. The tentative tricyclic chelate complex **23e**, bearing four donor ligands for the lithium cation in optimal positions, obviously governs the structure of the transition state in the kinetically controlled deprotonation reaction. The diastereomerically pure ester **20d** was

Table 2a. Selected Data of Monocarbamates **3, 4, 6,** or **7**[a]

Compound	$[\alpha]_D^{20}$ [b]	IR (KBr/film) ν (cm^{-1})	^1H NMR ($CDCl_3$) δ, J (Hz)	^{13}C NMR ($CDCl_3$) δ, J (Hz)
3	+2.5	3430, 1680	1.63 (m, 3-H); 2.12 (m, 3-H); 2.96 (m, 2-H); 3.51 (m, 2 H, 1-H); 3.54 (d, 2 H, ^2J = 13.3, NCH_2Ph); 4.12 (m, 2 H, 4-H)	24.31 (C-3); 52.34 (2C, NCH_2Ph); 55.10 (C-2); 59.98[c]; 61.13 (C-1)[c]
4	–54.6	3440, 1680	2.05 (m, 2 H, 3-H); 3.12 (m, 2-H); 3.51 (m, 4 H, 4-H, NCH_2Ph); 3.89 (d, 2H, ^2J = 13.5, NCH_2Ph); 4.21 (dd, ^2J = 11.5, ^3J = 4.0 Hz, 1-H); 4.39 (dd, ^3J = 6.2)	31.15 (C-3); 54.04 (2C, NCH_2Ph); 56.48 (C-2); 62.26 (C-1); 63.14 (C-4)
6a	–62.7	1690, 1095, 1070, 760, 750, 710, 700	1.84 (m, 2 H, 3-H); 3.14 (m, 2 H, 1-H, 2-H); 3.41 (d, 2 H, ^2J = 13.7, NCH_2Ph); 3.42 (m, 1-H); 3.73 (d, 2 H, NCH_2Ph); 4.12 (m, 4-H); 4.25 (m, 4-H)	29.00 (C-3); 54.06 (2C, NCH_2Ph); 54.47 (C-2); 62.15 (C-1)[c]; 62.35 (C-4)[c]; 87.06 (CPh_3)
6b	–51.6	2840, 1680	1.78 (m, 3-H); 1.89 (m, 3-H); 2.95 (m, 2-H); 3.34 (s, 3 H, OCH_3); 3.48 (m, 1-H); 3.62 (m, 3 H, 1-H, NCH_2Ph); 3.82 (d, 2 H, ^2J = 13.8, NCH_2Ph); 4.14 (m, 2 H, 4-H)	26.88 (C-3); 52.09 (C-2); 52.50 (2C, NCH_2Ph); 57.12 (OCH_3); 60.70 (C-1); 70.87 (C-4)
6c	–44.3	2915, 1688, 1095, 1065, 745, 698	1.82 (m, 3-H); 1.92 (m, 3-H); 2.97 (m, 2-H); 3.38 (s, 3 H, OCH_3); 3.59 (d, 2 H, ^2J = 13.8, NCH_2Ph); 3.61 (m, 1-H); 3.78 (dd, ^2J = 10.0, ^3J = 5.8, 1-H); 3.85 (d, 2 H, NCH_2Ph); 4.20 (t, 2 H, ^3J = 6.3, 4-H); 4.62 (s , 2 H, OCH_2O)	28.80 (C-3); 53.88 (C-2); 54.24 (2C, NCH_2Ph); 55.33 (OCH_3); 62.36 (C-4)[c]; 67.05 (C-1)[c]; 96.57 (OCH_2O)
6d	–35.7	2930, 1690, 1095, 1070, 745, 700	1.81 (m, 3-H); 1.89 (m, 3-H), 2.98 (m, 2-H); 3.39 (s, 3 H, OCH_3); 3.61 (d, 2 H, ^2J = 13.8, NCH_2Ph); 3.50–3.71 (m, 5 H; 1-H, OCH_2CH_2O); 3.75 (dd, ^2J = 10.0, 1-H); 3.82 (d, 2 H, NCH_2Ph); 4.19 (t, 2 H, ^3J = 6.3, 4-H)	28.71 (C-3); 53.91 (C-2); 54.22 (2C, NCH_2Ph); 59.56 (OCH_3); 62.47 (C-4); 70.52, 71.10 (2C, OCH_2CH_2O)[c]; 72.11 (C-1)[c]
6e	–42.8	2910, 2850, 1680, 1085, 1060, 740, 690	1.80 (m, 3-H); 1.92 (m, 3-H); 2.97 (m, 2-H); 3.41 (s, 3 H, OCH_3); 3.55–3.75 (m, 5 H, 1-H, OCH_2CH_2O); 3.69 (d, 2 H, ^2J = 13.8, NCH_2Ph); 3.81 (dd, ^2J = 10.0, ^3J = 5.3, 1-H); 3.84 (d, 2 H, NCH_2Ph); 4.19 (m, 2 H, 4-H); 4.72 (s, 2 H, OCH_2O)	28.77 (C-3), 53.90 (C-2); 54.21 (2C, NCH_2Ph); 59.00 (OCH_3); 62.63 (C-4); 66.92, 67.18 (2C, OCH_2CH_2O)[c]; 71.80 (C-1)[c], 95.62 (OCH_2O)
6f	[d]	2980, 1690, 740, 695	0.09 (s, 6 H, $SiCH_3$); 0.91 [s, 9 H; C$(CH_3)_3$]; 1.74 (m, 2 H, 3-H); 2.80 (m, 2-H); 3.64 (d, 2 H, ^2J = 13.8, NCH_2Ph); 3.73 (dd, ^2J = 10.2, ^3J = 10.2, ^3J = 5.5, 1-H); 3.82 (dd, ^3J = 6.4, 1-H); 3.84 (d, 2 H, NCH_2Ph); 4.19 (m, 2 H, 4-H)	–5.47 (2C, $SiCH_3$); 17.99 [C$(CH_3)_3$]; 25.67 [3C, C$(CH_3)_3$]; 28.31 (C-3); 54.33 (2C, NCH_2Ph); 55.67 (C-2); 62.44 (2C, C-1, C-4)
7a	–14.4	1690, 1150	0.00 (s, 6 H; $SiCH_3$); 0.82 [s, 9 H, C$(CH_3)_3$]; 1.20–1.70 (m, 3-H)[e]; 1.94 (m, 3-H); 3.05 (m, 2-H); 3.55–3.88 (m, 6 H, 4-H, NCH_2Ph); 4.18 (dd, ^2J = 10.7, ^3J = 5.4, 1-H); 4.28 (dd, ^3J = 5.9, 1-H)	–5.28 (2C, $SiCH_3$); 18.32 [C$(CH_3)_3$]; 25.39 [3C, C$(CH_3)_3$]; 32.04 (C-3); 54.13 (2C, NCH_2Ph); 54.21 (C-2); 60.98 (C-1); 63.91 (C-4)
7b	–28.5	2840, 1680	1.71 (m, 3-H); 1.92 (m, 3-H); 3.08 (m, 2-H); 3.20 (s, 3 H; OCH_3); 3.35 (m, 4-H); 3.45 (m, 4-H); 3.72 (d, 2 H, ^2J = 13.4, NCH_2Ph); 3.85 (d, 2 H, NCH_2Ph); 4.25 (m, 2 H, 1-H)	29.18 (C-3); 53.97 (2C, NCH_2Ph); 53.97 (C-2); 58.47 (OCH_3); 63.76 (C-4); 70.27 (C-1)
16	–7.6	2090, 1690, 1095, 1065	0.05 (s, 6 H, $SiCH_3$); 0.89 [s, 9 H, C$(CH_3)_3$]; 1.79 (m, 2 H, 3-H); 2.34 (s, 6 H, NCH_3); 2.64 (m, 2-H); 3.60 (dd, ^2J = 10.4, ^3J = 5.4, 1-H); 3.74 (dd, ^3J = 5.2, 1-H); 4.18 (t, 2 H, 4-H)	–5.52 (2C, $SiCH_3$); 18.15 [C$(CH_3)_3$]; 25.86 [3C, C$(CH_3)_3$]; 27.72 (C-3); 41.41 (2C, NCH_3); 61.83 (C-2); 62.33 (C-1)[c]; 62.67 (C-4)[c]

[a] NMR data of the *Cby* group and the aromatic ring are omitted.
[b] c = 0.86–1.10 in $CHCl_3$.
[c] Assignment interchangeable.
[d] Not determined.
[e] As part of a multiplet.

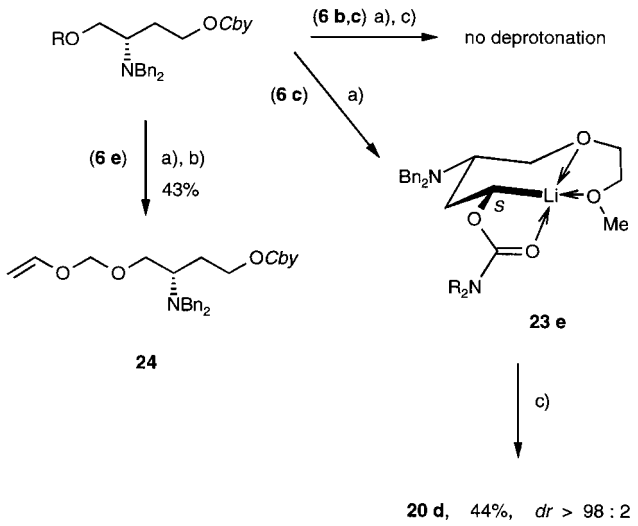
obtained by carboxylation/esterification. Fortunately, the (–)-sparteine- and the substrate-induced stereoselectivities match and, consequently, the stereochemical outcome is not influenced by the 1-alkoxy group.

Well-chelating diamines, such as *N*,*N*,*N'*,*N'*-tetramethylethylenediamine (TMEDA), compete successfully with the intramolecular chelation. In these cases, only the steric bulk of the 2-dibenzylamino group causes a small direct-

Table 2b. Selected Data of Intermediates **8, 9, 10, 12, 13, 14, 15,** or **16**

Compound	$[\alpha]_D^{20}$ [b]	^{1}H NMR ($CDCl_3$) δ, J (Hz)				^{13}C NMR ($CDCl_3$) δ, J (Hz)		
		1-H	2-H	3-H	4-H	C-1/C-2	C-2	C-3
8	+ 43.4	3.53	2.96 (ddt, $^3J_{1a,2}$ = 3.5, $^3J_{1b,2}$ = 5.9)	1.46 (dddd, ^2J = 13.7), 2.02	3.63	61.07/ 61.40[c]	56.81	28.95
9a	–41.6	3.13 (dd, ^2J = 9.5, $^3J_{1,2}$ = 4.0), 3.29 (dd, $^3J_{1,2}$ = 5.9)	3.01	1.65, 1.84	3.56	61.48/ 63.36[c]	54.73	32.45
9d	–20.2	3.50–3.80[d]	3.01	1.69, 1.90	3.50–3.80[d]	61.57/ 70.63	53.95	32.32
10a	–98.0	3.55 (ddd, $^3J_{1,2}$ = 3.4), 3.73	3.10–3.21[d]	1.58, 1.92	3.10–3.21[d], 3.40	62.14/ 62.44[c]	53.35	31.03
10d	–80.5	3.40–3.78[d], 3.78 (dd, ^2J = 9.8, $^3J_{1,2}$ = 5.7)	3.09	1.53, 1.92	3.40–3.78[d]	62.29/ 70.51	56.74	30.84
10e	–80.4	3.40–3.78[d], 3.85 (dd, ^2J = 10.0, $^3J_{1,2}$ = 5.5)	3.08	1.54, 1.93	3.40–3.78[d]	62.29/ 67.01	56.62	30.71
12[e]	–37.0	–	3.75 (dd, $^3J_{2,3}$ = 9.8)	2.28	4.08 (ddd, ^2J = 9.3, $^3J_{3,4}$ = 8.1), 4.33 ($^3J_{3a,4}$ = 3.6, $^3J_{3b,4}$ = 7.6)	175.88/ 65.21	57.74	24.89
13	+10.2	–	3.69–3.78[d]	2.12	3.69–3.78[d]	173.10/ 60.64	56.23	27.45
14	+12.3	–	3.76	2.22	4.09, 4.21	171.89/ 62.33	54.65	25.90
15	–3.1	3.41 (dd, ^2J = 9.8, $^3J_{1,2}$ = 6.8), 3.57 (dd, $^3J_{1,2}$ = 4.5)	2.93	1.36–1.56[a], 1.81	4.23	68.27/ 61.73[c]	50.11	33.46

[a] NMR data of the *Cby* group and the aromatic ring are omitted.
[b] c = 1.00 in $CHCl_3$.
[c] Assignment interchangeable.
[d] As part of a multiplet.
[e] Ref. b.



(a) *s*-BuLi (1.6 equiv), Et_2O, –78 °C, 5 h. (b) MeI (1.6 equiv), 3 h at –78 °C, → r.t. (c) i. gaseous CO_2; ii. after workup CH_2N_2 in Et_2O.
Scheme 7

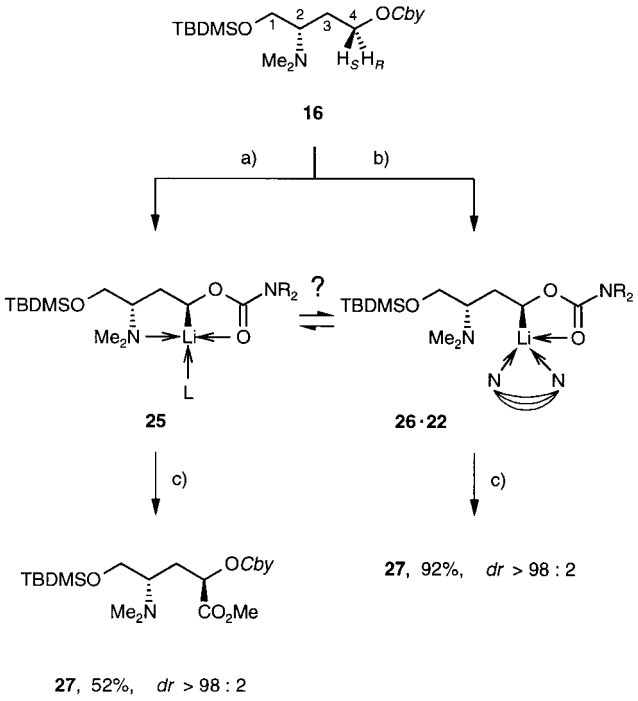
ing effect in the diastereotopic selection: when the deprotonations of **6a**,**b**,**e** were carried out in the presence of TMEDA, inseparable mixtures of the epimeric carboxylic esters **20a**,**b**,**e** and **21a**,**b**,**e** were isolated (yields 68–89%, dr 75–80:25–20, see Table 3).

In earlier work we experienced that γ-dimethylamino groups are powerful ligands in alkyl carbamate lithiation, which prevail over (–)-sparteine.[15] Since the γ-dimethylamino group in the 4-monocarbamate **16** is attached to a stereogenic center, a high stereodirecting power is expected to operate. Indeed, *sec*-butyllithium in diethyl ether (5 h at –78 °C) and the subsequent trapping reaction furnished the diastereomerically pure carboxylic ester **27**, arising from the formal substitution of the *pro-S*-4-H, with 52% yield (Scheme 8, Table 2). The yield increased to 92% when (–)-sparteine was used as an additive. These experiments demonstrate that the bicyclic chelate complex **25** is formed with a very good selectivity. Presumably, the (–)-sparteine addition opens an additional depro-

Table 3. Substitution Products via Lithiation of Functionalized 4-*Q*-Monocarbamates

Product[a]	Substrate (Scheme)	R	El	ElX	Yield (%) (*dr*) Diamine			mp[b] (°C)
					(–)-Sparteine (Method 1)	TMEDA (Method 2)	Without (Method 3)	
18a	**6a** (6)	Ph_3C	CH_3	CH_3I	91[c]	[d]	[h]	49.5
18b	**6b** (6)	Me	CH_3	CH_3I	84[c]	85 (85 : 15)	[h]	oil
18e [**18g**][e]	**6e** (6, 7)	MEM	CH_3	CH_3I	63[c] [25][c,e]	68 (74 : 26)	[f]	oil [oil][e]
20a	**6a** (6)	Ph_3C	CO_2Me	CO_2[g]	90[c]	85 (77 : 23)	[h]	57.5
20b	**6b** (6)	Me	CO_2Me	CO_2[g]	90[c]	89 (82 : 18)	[h]	oil
20d	**6d** (6, 7)	$MeOCH_2CH_2$	CO_2Me	CO_2[g]	59[c]	[d]	44 (≥ 28 : 2)	oil
20e	**6e** (6, 7)	MEM	CO_2Me	CO_2[g]	69[c]	76 (71 : 29)	[d]	oil
27	**16** (8)	TBDMS	CO_2Me	$ClCO_2Me$	92[c]	[d]	52 (≥ 98 : 2)	oil

[a] Satisfactory elemental analyses were obtained (C ± 0.30, H ± 0.29, N ± 0.29).
[b] From Et_2O.
[c] dr ≥ 98.2.
[d] Not carried out.
[e] Substituted elimination product.
[f] Only elimination product **24**.
[g] The crude acid was converted into the methyl ester by treatment with diazomethane.
[h] No deprotonation achieved (≥ 98 : 2).



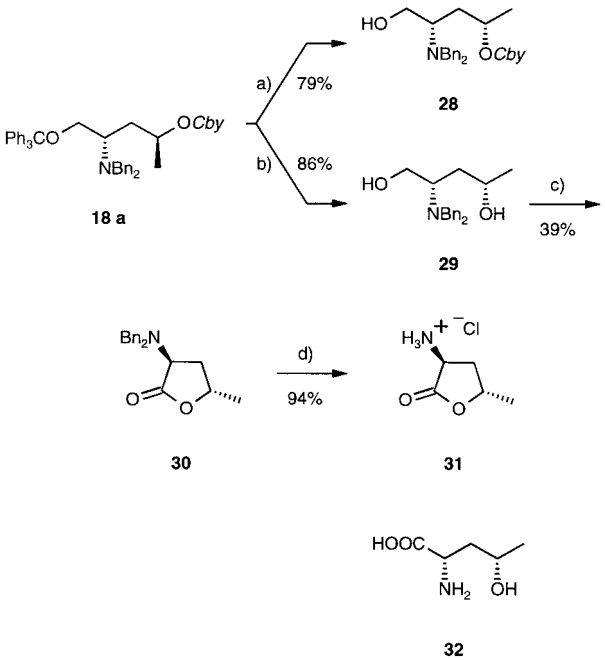
(a) *s*-BuLi (2.0 equiv), Et_2O, –78 °C, 5 h. (b) *s*-BuLi (2.0 equiv), (–)-sparteine (**22**, 2.0 equiv), Et_2O, –78 °C, 5 h. (c) $ClCO_2Me$ (3.0 equiv).

Scheme 8

tonation pathway via the complex **26•22**, as it was observed in a related case.[15, 16]

Conversion of 18a into (2*S*,4*S*)-γ-Hydroxy-norvaline Lactone Hydrochloride (31)

(2*S*,4*S*)-γ-Hydroxy-norvaline **(32)** has been isolated from the fruit bodies of *Boletus satanas Lenz*.[17] Several syntheses are known for other diastereomers of γ-hydroxy-norvaline, but only one in the form of lactone **32** or its hydrochloride **31**.[18–20] The methylation products **18** already have the correct array of **32** except for the oxidation state at C-1 (Scheme 9). The 1-*O*-trityl derivative **18a** was deprotected (TFA in CH_2Cl_2/MeOH)[21] to give the alcohol **28** (yield 79%) or, under more forced conditions (5 N aq HCl in THF), to yield the diol **29** in 86% yield. Oxidation of **29** by tris(triphenylphosphine)ruthenium(II) dichloride/sodium carbonate[22] furnished the dibenzylamino-γ-lactone **30** (yield 39%), which was debenzylated by transfer hydrogenolysis,[13] to give the amino lactone, isolated in the form of the hydrochloride **31**.[23] Its mp and the specific optical rotation are in good agreement with the published data.[20]



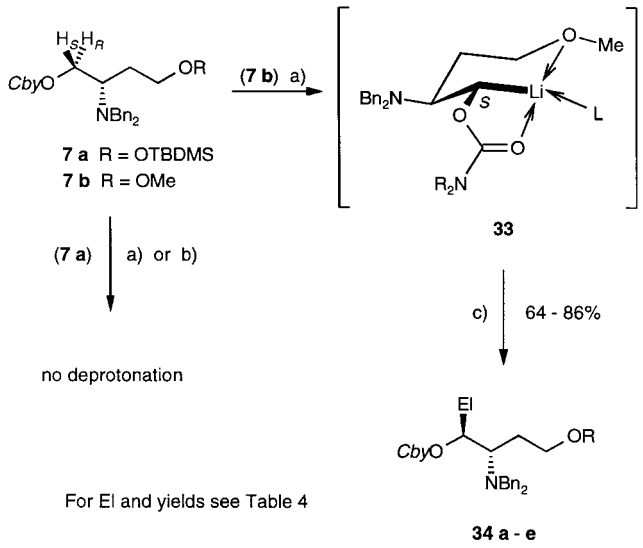
(a) TFA (21.5 equiv), MeOH/CH_2Cl_2, –5 °C, 0.5 h, r.t., 2 h; (b) 5 N HCl, THF, reflux, 16 h; (c) i. $(Ph_3P)_3RuCl_2$ (1.2 equiv), C_6H_6, r.t., 24 h; ii. + Na_2CO_3 (14 equiv), r.t., 48 h. (d) cyclohexene (15 equiv), Pd/C (6 mol%), MeOH, reflux, 12 h.

Scheme 9

Deprotonation of 4-*O*-Protected 1-*O*-Monocarbamates 7

Can selective deprotonations be achieved also at orthogonally protected 1-*O*-carbamates, derived from 2-aminobutane-1,4-diol?

The 4-*O*-TBDMS ether **7a**, under the usual conditions (1.6 equiv *sec*-butyllithium, Et_2O, 5 h at –78 °C), reacted neither in the presence of (–)-sparteine nor in the absence of diamines (Scheme 10). Good substrate-induced stereoselectivity was achieved with the 4-*O*-methyl ether **7b**. The intermediate lithium derivative, presumably the bischelate **33**, could be trapped by several electrophiles to yield the diastereomerically pure substitution products **34a–e** (Scheme 10, Table 4). It is expected, that this reaction course is followed, independent of the 4-alkoxy group, as long as the Lewis basicity of the 4-oxygen atom is not diminished by an electron-withdrawing or a bulky group. Thus, this method can be a useful extension of the dicarbamate deprotonation.[1]



(a) *s*-BuLi (1.6 equiv), Et_2O, –78 °C, 5 h. (b) *s*-BuLi (1.6 equiv), (–)-sparteine (22, 1.6 equiv), Et_2O, –78 °C, 5 h. (c) + ElX (1.6 equiv), 3 h at –78 °C, → r.t.

Scheme 10

Table 4. Substitution Products **33** via Lithiation of Functionalized 1-*O*-Monocarbamate **7a** (Scheme 10)

Product **34**[a,b]	El	ElX	Yield (%)	mp (°C)
a	CO_2Me	CO_2[c]	86	oil
b	$SiMe_3$	$ClSiMe_3$	65	oil
c	$(CH_3)_2COH$	$(CH_3)_2C{=}O$	64	oil
d	$C_2H_5(=O)$	$C_2H_5(=O)Cl$	64	oil
e	[e]	[f]	78	oil

[a] All products with *ds* ≥ 98 : 2.
[b] Satisfactory elemental analyses were obtained (C ± 0.30, H ± 0.29, N ± 0.29).
[c] The crude acid was converted into the methyl ester by treatment with diazomethane.
[d] (*E*)-$CH_3CH{=}CHC(=O)$.
[e] (*E*)-$CH_3CH{=}CHC(=O)Cl$.

In conclusion, by selecting the *O*- and *N*-protecting groups properly, efficient routes to equivalents of the synthons **A** and **B** are easily achieved.

All reactions were carried out under argon. All solvents were purified by distillation and dried, if necessary, prior to use. ^1H and ^{13}C NMR spectra were recorded on Bruker WM 300, AM 360 or U 600 spectrometers. Optical rotations were recorded on a Perkin–Elmer polarimeter 241. Mps were obtained on a Gallenkamp melting point apparatus MFB-595 and are uncorrected. Products were purified by flash-column chromatography on silica gel (40–63 μm). (+)-(*S*)-2-(*Dibenzylamino)butane-1,4-diol* (**1**) was preparing according to ref. 1 and 4.

(+)-(*S*)-4-(*tert*-Butyldimethylsilyloxy)-2-(dibenzylamino)butan-1-ol (8):[4b,9]

A solution of Et_3N (1.21 g, 12.0 mmol), DMAP (0.61 g, 5.00 mmol), and TBDMSCl (1.76 g, 12.0 mmol), dissolved in CH_2Cl_2 (60 mL), was added to diol **1** in anhyd CH_2Cl_2 (40 mL). The mixture was refluxed for 8 h. After cooling to r.t., water (50 mL) was added, the organic layer was separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried ($MgSO_4$) and evaporated in vacuo. The residue was purified by flash chromatography (silica gel, Et_2O/pentane 1:4) to yield the silyl ether **8** (2.20 g, 55%) as a colorless oil;
R_f 0.39 (Et_2O/pentane 1:2); $[\alpha]_D^{20}$ +39.7 (*c* = 1.00, $CHCl_3$) [ref.[9] $[\alpha]_D^{23}$ +43 (*c* = 1, $CHCl_3$)].

(–)-(*S*)-4-(*tert*-Butyldimethylsilyloxy)-2-(dibenzylamino)-1-(triphenylmethoxy)butane (9a):

To a solution of **8** (7.71 g, 19.3 mmol) in CH_2Cl_2 (150 mL) was added Et_3N (3.65 g, 36.1 mmol) and subsequently trityl chloride (6.46 g, 23.2 mmol) and DMAP (0.10 g, 0.80 mmol), dissolved in CH_2Cl_2 (10 mL). After stirring for 14 h at r.t., water (50 mL) was added. The CH_2Cl_2 layer was separated and the aqueous phase was extracted with CH_2Cl_2 (2 × 40 mL). The collected extracts were dried ($MgSO_4$) and the solvents were evaporated in vacuo. The crude product was purified by flash chromatography (silica gel, Et_2O/pentane 1:3) to yield pure **9a** (9.36 g, 91%) as a viscous oil. (Data see Table 2b.)

(–)-(*S*)-4-(*tert*-Butyldimethylsilyloxy)-2-(dibenzylamino)-1-(2-methoxyethoxy)butane (9d):

A solution of **8** (7.42 g, 18.6 mmol) in anhyd THF (40 mL) was added dropwise to a suspension of NaH (1.48 g, 37.1 mmol, 60% in mineral oil) in THF (10 mL). The mixture was stirred at r.t for 4 h, before 2-bromoethyl methyl ether (7.74 g, 60.0 mmol), Bu_4NI (0.69 g, 2.00 mmol), and DMAP (40 mg, 0.33 mmol) were added. After heating under reflux for 20 h and cooling to r.t., water (15 mL) was poured carefully into the mixture. The organic layer was separated and the aqueous solution extracted with Et_2O (3 × 25 mL). The collected extracts were dried ($MgSO_4$) and the solvents evaporated in vacuo. The crude product was purified by flash chromatography (silica gel, Et_2O/pentane 1:6) to yield pure **9d** (3.29 g, 44%) as a viscous oil and **8** (3.48g, 45%).(Data see Table 2b.)

(–)-(*S*)-3-(*tert*-Butyldimethylsilyloxy)-3-(dibenzylamino)-4-(2-methoxyethoxymethoxy)butane (9e):

To a solution of **8** (16.24 g, 40.6 mmol) in CH_2Cl_2 (50 mL) were added MEMCl (7.58 g, 60.9 mmol) and iPr_2NEt (7.87 g, 60.9 mmol). After heating under reflux for 24 h and cooling to r.t., water (15 mL) was added. The CH_2Cl_2 layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 40 mL). The collected extracts were dried ($MgSO_4$). After removal of the solvent in vacuo, the residue was used without purification.

Table 5. Selected Data of Substituted Monocarbamates **18, 19, 27, 33**[a]

Compound	$[a]_D^{20}$ [b]	IR (KBr/film) ν (cm^{-1})	^1H NMR ($CDCl_3$) δ, J (Hz)	^{13}C NMR ($CDCl_3$) δ, J (Hz)
18a	+37.8	2960, 1730, 745, 695	0.94 (d, 3 H, $^3J_{4,5}$ = 6.0, 5-H); 1.56 (m, 3-H); 1.98 (m, 3-H); 2.97 (m, 2-H); 3.24 (dd, ^2J = 9.5, $^3J_{1,2}$ = 5.3, 1-H); 3.38 (dd, $^3J_{1,2}$ = 5.5, 1-H); 3.41 (d, 2 H, ^2J = 13.7, NCH_2Ph); 3.73 (d, 2 H, NCH_2Ph); 5.02 (m, 4-H)	19.84 (C-5); 36.41 (C-3); 54.15 (2C, N*C*H_2Ph); 54.39 (C-2); 62.51 (C-1); 67.08 (C-4); 87.13 (*C*Ph_3)
18b	–12.6	2840, 1690	0.92 (d, 3 H, 5-H); 1.82 (m, 2 H, 3-H); 2.90 (m, 2-H); 3.28 [3.24][c] (s, 3 H, OCH_3); 3.48 (m, 2 H, 1-H); 3.62 (m, 2 H, NCH_2Ph); 3.82 (d, 2H, ^2J = 13.8, NCH_2Ph); 5.12 (m, 4-H)	20.21 (C-5); 26.88 (C-3); 52.09 (C-2); 52.50 (2C, N*C*H_2Ph); 57.12 (OCH_3); 65.83 (C-1); 68.78 (C-4)
18e	–15.3	2970, 2930, 2870, 1685, 1050, 1090, 765, 748, 730, 700	0.97 (d, 3 H, $^3J_{4,5}$ = 6.2, 5-H); 1.63 (m, 3-H); 1.98 (m, 3-H); 2.90 [2.96][c] (m, 2-H); 3.41 (s, 3 H, OCH_3); 3.55–3.85 (m, 6 H; OCH_2CH_2O, 1-H); 3.57 (d, 2 H, ^2J = 13.6, NCH_2Ph); 3.83 (d, 2 H, NCH_2Ph); 4.74 [4.70][c] (s, 2 H, OCH_2O); 5.08 (m, 4-H)	19.90 [20.93][c] (C-5); 35.88 [36.57][c] (C-3); 53.54 (C-2); 54.22 [54.49][c] (2C, N*C*H_2Ph); 59.03 (OCH_3); 66.98, 67.34 (2-C, O*C*H_2*C*H_2)[d]; 68.97 (C-4); 71.84 (C-1)[d]; 95.78 (OCH_2O)
18g	–17.1	2970, 2890, 1700, 1065, 750, 700	0.97 (d, 3 H, $^3J_{1,2}$ = 6.2, 5-H); 1.65 (m, 3-H); 1.96 (m, 3-H); 2.90 (m, 2-H); 3.56 (d, 2 H, ^2J = 13.6, NCH_2Ph); 3.72–3.87 (m, 2 H, 1-H); 3.81 (d, 2 H, NCH_2Ph); 4.18 (dd, ^2J = 1.7, ^3J = 6.6, OCHCH_2); 4.52 (dd, ^3J = 14.1, OCHCH_2); 4.92 (s, 2 H, OCH_2O); 5.06 (m, 4-H); 6.43 (dd, OC*H*CH_2)	14.06 (C-5); 35.84 (C-3); 53.37 (C-2); 54.19 (2C, N*C*H_2Ph); 67.81 (C-1); 68.87 (C-4); 91.05, 94.25 (2C, OCH_2O, OCH*C*H_2); 149.65 (O*C*HCH_2)
20a	–43.8	2950, 1750, 1090, 1070, 765, 745, 700, 705	2.06 (m, 3-H); 2.13 (m, 3-H); 3.23 (m, 4-H); 3.35 (m, 2 H, 5-H); 3.53 (d, ^2J = 14.1, NCH_2Ph); 3.65 [3.72][c] (s, 3 H, OCH_3); 3.69 (d, 2 H, NCH_2Ph); 4.97 [5.32, d][c] (dd, $^3J_{2,3a}$ = 5.0, $^3J_{2,3b}$ = 9.3 [10.7][c] 2-H)	31.45 (C-3); 51.97 (OCH_3); 54.36 [53.76][c] (C-4); 54.53 (2C, N*C*H_2Ph); 62.21 (C-5); 70.59 [70.01][c] (C-2); 86.94 (Ph_3C); 171.74 [172.53][c] (C-1)
20b	–4.3	2840, 1730, 1680	1.84 (m, 3-H); 1.92 (m, 3-H); 3.05 (m, 4-H); 3.34 (s, 3H, OCH_3); 3.56 (s, 3 H; $COOCH_3$); 3.62 (m, 4 H, 5-H, NCH_2Ph); 3.87 (d, 2 H, ^2J = 13.8, NCH_2Ph); 5.14 [5.31][c] (dd, $^3J_{2,3a}$ = 5.1, $^3J_{2,3b}$ = 6.5, 2-H)	27.15 (C-3); 53.11 (C-4); 54.50 (2C, N*C*H_2Ph); 56.12 (OCH_3); 58.86 ($COOCH_3$); 69.97 (C-5); 75.04 (C-2); 170.23 (C-1)
20d	–22.7	2890, 1750, 1700, 1095, 1070, 745, 700	2.04 (m, 3-H); 2.19 (m, 3-H); 3.10 (m, 4-H); 3.38 (s, 3 H; OCH_3); 3.51–3.79 (m, 8 H, NCH_2Ph, 5-H, OCH_2CH_2); 3.65 (s, 3 H, $COOCH_3$); 3.73 (d, 2 H, ^2J = 14.3, NCH_2Ph); 5.13 (dd, $^3J_{2,3a}$ = 4.6, $^3J_{2,3a}$ = 9.4, 2-H)	31.10 (C-3); 51.95 ($COOCH_3$); 53.58 (C-4); 54.52 (2C, N*C*H_2Ph); 59.01 (OCH_3); 70.43 (C-2); 70.49, 70.73, 72.05 (3C, C-5, O*C*H_2*C*H_2); 171.72 (C-1)
20e	–20.6	2920, 2880, 1750, 1695, 1095, 1070, 750, 700	2.07 [1.86][c] (m, 3-H); 2.22 (m, 3-H); 3.11 [2.97][c] (m, 4-H); 3.40 [3.42][c] (s, 3 H, $COOCH_3$); 3.66 [3.72] (s, 3 H, OCH_3); 3.67 (d, ^2J = 12.9, NCH_2Ph); 3.78 [3.91][c] (d, 2 H; NCH_2Ph); 3.53–3.85 (m, 6 H, 5-H, OCH_2CH_2); 4.73 [4.72, s][c] (d, 2 H, OCH_2O); 5.13 [5.31, d][c]; dd, $^3J_{2,3a}$ = 4.8, $^3J_{2,3b}$ = 9.5 [10.7][c] 2-H)	31.00 [31.81][c] (C-3); 51.96 ($COOCH_3$); 53.50 [53.04][c] (C-4); 54.52 [54.04][c] (2C, N*C*H_2Ph); 59.00 (OCH_3); 67.02 [66.27][c] (2C, O*C*H_2*C*H_2)[d]; 70.30 [69.92][c] (C-2); 71.80 (C-5)[d]; 95.70 (OCH_2); 171.64 (C-1)
27	–21.6	2915, 2900, 2865, 1745, 1690, 1075, 1045	0.61 (s, s, 6 H, $SiCH_3$); 0.89 [s, 9 H, $C(CH_3)_3$]; 2.03 (m, 2 H, 3-H); 2.31 (s, 6 H, NCH_3), 2.82 (m, 4-H); 3.50–3.85 (m, 5 H, OCH_3, 5-H); 5.18 (dd, $^3J_{2,3a}$= 4.5, $^3J_{2,3b}$ = 6.0, 2-H)	–5.56 (2C, $OSiCH_3$); 18.12 [*C*$(CH_3)_3$]; 25.84 [3C, C(*C*$H_3)_3$]; 30.09 (C-3); 41.03 (2C, NCH_3); 51.58 (OCH_3); 60.57 (C-4); 59.78–61.66 (C-5)[e]; 70.21 (C-2); 175.75 (C-1)
34a	–27.3	2840, 1700, 1690	1.85 (m, 2 H, 4-H); 2.19 (m, 3-H); 3.30 (s, 3 H, OCH_3); 3.35–3.50 (m, 5 H, 3-H, 5-H, NCH_2Ph); 3.53 (s, 3 H, $COOCH_3$); 3.90 (m, 2 H, ^2J = 13.2, NCH_2Ph); 5.35 (d, $^3J_{2,3}$ = 4.3, 2-H)	24.29 (C-4); 51.76 (OCH_3); 54.87 (2C, N*C*H_2Ph); 55.77 (C-3); 58.67 ($COOCH_3$); 69.92 (C-5); 75.02 (C-2); 170.11 (C-1)
34b	–27.1	2820, 1670	0.00 (s, 9 H, $SiCH_3$); 1.28–1.85 (m, 3-H)[e]; 3.15 (s, 3 H, OCH_3); 3.18–3.80 (m, 7-H, 2-H, 4-H, 5-H, ^2J = 13.9, NCH_2Ph); 4.97 (d, $^3J_{1,2}$ = 6.9, 1-H)	0.00 (3C, $SiCH_3$); 29.82 (C-3); 56.28 (2C, N*C*H_2Ph); 59.43 (C-2); 60.01 (OCH_3); 72.21 (C-4); 72.85 (C-1)
34c	+1.8	3420, 2830, 1710	0.40, 1.03 [s, s, 6 H, $C(CH_3)_2$]; 1.75 (m, 2 H, 2-H); 2.18 (m, 3-H); 3.40 (s, 3 H, OCH_3); 3.42–3.75 (m, 6 H, 1-H, ^2J = 13.2, NCH_2Ph); 4.61 (OH); 4.86 (d, $^3J_{3,4}$ = 3.1, 4-H)	23.51 (C-2); 26.39, 26.68 [2C, C(*C*$H_3)_2$]; 54.87 (2C, N*C*H_2Ph); 55.05 (C-3); 59.05 (OCH_3); 69.81 (C-1); 74.09 (C-5); 76.99 (C-4)
34d	–51.2	2830, 1730, 1690	0.93 (t, 3 H, $^3J_{1,2}$ = 7.2, 1-H); 1.91 (m, 6-H); 2.18 (m, 6-H); 3.37 (s, 3 H, OCH_3); 3.31–3.71 (m, 6 H, 2-H, ^2J = 13.5, NCH_2Ph); 3.95 (m, 2 H, 7-H); 5.35 (d, $^3J_{4,5}$ = 5.0, 4-H)	7.01 (C-1); 23.12 (C-2); 31.64 (C-6); 54.52 (2C, N*C*H_2Ph); 54.86 (C-5); 58.77 (OCH_3); 69.79 (C-7); 80.16 (C-4); 205.96 (C-3)
34e	–51.2	2830, 1730, 1690	0.93 (t, 3 H, $^3J_{1,2}$ = 7.2, 1-H); 1.91 (m, 6-H); 2.18 (m, 6-H); 3.37 (s, 3 H, OCH_3); 3.31–3.71 (m, 6 H, 2-H, ^2J = 13.5, NCH_2Ph); 3.95 (m, 2 H, 7-H); 5.35 (d, $^3J_{4,5}$ = 5.0, 4-H)	7.01 (C-1); 23.12 (C-2); 31.64 (C-6); 54.52 (2C, N*C*H_2Ph); 54.86 (C-5); 58.77 (OCH_3); 69.79 (C-7); 80.16 (C-4); 205.96 (C-3)

[a] NMR data of the *Cby* group and the aromatic ring are omitted.
[b] c = 0.96–1.02 in $CHCl_3$, only **18a**: c = 0.36.
[c] Spectroscopic data of the minor diastereomer.
[d] Assignment interchangeable.
[e] As a part of a overlay of signals.

Desilylation of Silyl Ethers 7a, 9a,d,e; Preparation of the Alcohols 4, 10a,d,e; General Procedure:
To a solution of the TBDMS ether **7** or **9** (5.0 mmol) in Et_2O was added 1.0 M TBAF in THF (12.5 mL, 12.5 mmol). After stirring at r.t. for 14 h, water (20 mL) was added. Stirring was continued for 0.5 h, and the organic layer was separated. The aqueous layer was extracted with Et_2O (3 × 25 mL), the combined solutions were dried ($MgSO_4$), and evaporated in vacuo. The crude product was purified by flash chromatography (silica gel, Et_2O/pentane 1:1) to yield the pure alcohol **4** (92%), **10a** (82%), **10d** (99%), or **10e** (90%, over two steps). (Data see Table 1a, for **4**, and Table 2b.)

Carbamoylation of the Alcohols 1, 8, 10a,d,e, 13; Preparation of the Monocarbamates 3, 4, 7a, 6a,d,e, and 14; General Procedure:
A solution of the alcohol (60 mmol) in anhyd THF (30 mL) was added dropwise to a suspension of NaH (3.60 g, 90 mmol, 60% in mineral oil) in THF (60 mL). The mixture was stirred for 3 h at r.t., before 2,2,4,4-tetramethyloxazolidine-3-carbonyl chloride[10] (*Cby*Cl, **2**, 14.98 g, 78 mmol) in THF (20 mL) was added. After heating under reflux for 16 h and cooling to r.t., water (50 mL) and Et_2O (50 mL) were added carefully to the mixture. The organic layer was separated and the aqueous solution extracted with Et_2O (3 × 50 mL). The collected extracts were dried ($MgSO_4$). The solvents were evaporated in vacuo and the crude product was purified by flash chromatography (silica gel, Et_2O/pentane 1:1) to yield pure carbamates **7a** (90%), **6a** (92%), **6d** (88%), **6e** (72%), or **14**[12] (92%).(Data see Table 2a, for **14** see Table 2b.) For carbamoylation of **1** (1.43 g, 5.0 mmol) in THF (10 mL): With NaH (3.60 g, 90 mmol, 80% in mineral oil) in THF (10 mL) and *Cby*Cl (**2**, 1.15 g, 6.0 mmol) in THF (5 mL). Chromatography (silica gel, Et_2O/pentane 1:5) afforded a 1:3 mixture of **3** and **4** (1.98 g, 90%) with partial separation.

Detritylation of 6a, 18a; Preparation of the Alcohols 3, 28; General Procedure:
To a solution of the trityl ether **6a** (4.22 g, 6.18 mmol) in CH_2Cl_2 (7 mL) and MeOH (7 mL) at –5 °C TFA (10.2 mL, 133 mmol) was added dropwise.[21] After stirring the yellow mixture at –5 °C for 0.5 h and 2 h at r.t. water (15 mL) was added. Sat. K_2CO_3 was added carefully to the mixture until the formation of gas stopped. The organic layer was separated and the aqueous solution extracted with CH_2Cl_2 (3 × 25 mL). The collected extracts were dried ($MgSO_4$). The solvents were evaporated in vacuo and the crude product was purified by flash chromatography (silica gel, Et_2O/pentane 1:2 → 1:0) to yield pure alcohol **3** (2.28 g, 84%) as a colorless oil. (Data see Table 2a.)

(+)-(2*S*,4*S*)-4-(Dibenzylamino)-5-hydroxy-1-methylbutyl 2,2,4,4-Tetramethyloxazolidine-3-carboxylate (28):
From **18a** (166 mg, 0.24 mmol) in CH_2Cl_2/MeOH (1 mL/1 mL); yield: 86 mg (79%); colorless solid; mp 124 °C; R_f 0.23 (Et_2O/pentane 1:1); $[\alpha]_D^{20}$ +37.8 (*c* = 0.36, $CHCl_3$).
IR (film): ν = 3400 (OH), 1730 (C=O), 750, 695 cm^{-1} (arom).
^1H NMR ($CDCl_3$, 300 MHz): δ = 1.13–1.57 (m, 12H, *Cby*-CH_3); 1.23 (d, 3H, $^3J_{1,2}$ = 6.2 Hz, 5-H); 2.10 (m, 3-H); 2.97 (m, 3-H); 3.07 (m, OH); 3.51 (d, 2H, ^2J = 13.6 Hz, NCH_2Ph); 3.40–3.75 (m, 3H, 1-H, 2-H); 3.67, 3.68 (s, s, 2H, *Cby*-CH_2); 3.81 (d, 2H, NCH_2Ph); 3.97 (m, 4-H); 7.17–7.37 (m, 10H, Ph).
^{13}C NMR ($CDCl_3$, 75 MHz): δ = 20.90 (C-5); 23.97, 24.20, 25.17, 25.35, 25.60, 26.53, 26.90 (4C, *Cby*-CH_3); 32.86 (C-3); 53.48 (2C, NCH_2Ph); 55.87 (C-4); 59.52, 60.61 [N$C(CH_3)_2CH_2$]; 61.42 (C-1); 68.61 (C-2); 76.03, 76.27 (*Cby*-CH_2); 94.60, 95.87 [O$C(CH_3)_2$N]; 127.15, 127.81, 128.45, 128.83, 129.30, 139.27 (12C, Ph); 152.46, 153.11 (C=O).
Anal. Calcd for $C_{27}H_{38}N_2O_4$ (454.61): C, 71.34; H, 8.43. Found: C, 71.66; H, 8.51.

Etherification of 3, 4; Preparation of Methyl Ether 6b, 7b; General Procedure:
A solution of **3** or **4** (441 mg, 1.0 mmol) in anhyd THF (5 mL) was added dropwise to a suspension of NaH (120 mg, 3.0 mmol, 60% in mineral oil) in THF (5 mL). The mixture was stirred at r.t for 0.5 h, before MeI (568 mg, 4.0 mmol) was added. After heating under reflux for 16 h and cooling to r.t., water (10 mL) was introduced carefully to the mixture. The organic layer was separated and the aqueous solution extracted with Et_2O (3 × 20 mL). The collected extracts were dried ($MgSO_4$) and the solvents evaporated in vacuo. The crude product was purified by flash chromatography (silica gel, Et_2O/pentane 1:1) to yield the pure methyl ether **6b** (432 mg, 95%) or **7b** (380 mg, 85%). (Data see Table 2a.)

(–)-(*S*)-[3-(Dibenzylamino)-4-(methoxymethoxy)butyl] 2,2,4,4-Tetramethyloxazolidine-3-carboxylate (6c):
To a solution of **3** (1.10 g, 2.50 mmol) in CH_2Cl_2 (15 mL) was added MOMCl (6.46g, 50 mmol).[24] The mixture was stirred at r.t. for 7 d. The solvent was evaporated in vacuo and the crude product was purified by flash chromatography on silica gel to yield **6c** (1.18 g, 97%) as a colorless oil. (Data see Table 2a.)

(*S*)-[4-(*tert*-Butyldimethylsilyloxy)-3-(dibenzylamino)butyl] 2,2,4,4-Tetramethyloxazolidine-3-carboxylate (6f):
A solution of Et_3N (3.39 g, 33.5 mmol) and TBDMSCl (1.21 g, 8.04 mmol), dissolved in CH_2Cl_2 (3 mL), was added to the alcohol **3** (2.96 g, 6.70 mmol) in anhyd CH_2Cl_2 (50 mL). After stirring the mixture at r.t. for 10 h water (50 mL) was added. The organic layer was separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic layers were dried ($MgSO_4$) and evaporated in vacuo. The residue was purified by flash chromatography (silica gel, Et_2O/pentane 1:2) to yield the silyl ether **6f** (3.61 g, 97%) as a colorless oil. (Data see Table 2a.)

(–)-(*S*)-2-(Dibenzylamino)-4-butanolide (12):[6]
To a solution of (*S*)-methionine (14.92 g, 100 mmol), K_2CO_3 (15.62 g, 114 mmol) and NaOH (4.55 g, 114 mmol) in MeOH/H_2O (75 mL/75 mL) at 95 °C (bath temperature) was added dropwise BnBr (51.31 g, 300 mmol); refluxing and stirring was continued for 40 min. To the cooled mixture was added Et_2O (100 mL), the aqueous layer was extracted with Et_2O (3 × 50 mL) and the collected extracts were dried ($MgSO_4$). After removal of the solvent in vacuo, the residue was purified by flash chromatography (silica gel, Et_2O/pentane 1:4) to afford a mixture of **12** and BnOH. The pure lactone **12** (10.33 g, 37%) was obtained by crystallization. (Data see Table 2a.)

(+)-(*S*)-2-(Dibenzylamino)-4-hydroxy-*N*,*N*-dimethylbutanamide (13):
To a solution of lactone **12** (2.81 g, 10.0 mmol) containing BnOH (1.2 g) in anhyd EtOH (40 mL) was added 5.6 M Me_2NH in EtOH (20 mL, 112 mmol) at 0 °C. After stirring for 48 h at 0 °C the solvent was evaporated in vacuo at r.t. The residue was purified by flash chromatography (silica gel, Et_2O/pentane 1:4 → MeOH/CH_2Cl_2 1:20) afford **13** (2.50 g, 77%) as yellow oil. (Data see Table 2b.) 0.59 g (21%) of **12** was recovered.

Reductive Deamination of 14; Preparation of 3:
To a solution of **14** (560 mg, 1.16 mmol) in THF (12 mL) was added 1 M $LiEt_3BH$ in THF (3.6 mL, 3.60 mmol) dropwise at 0 °C.[11] The mixture was stirred at r.t. for 12 h and further $LiEt_3BH$ (2.0 mL, 2.00 mmol) was added. After stirring for 1 h, the mixture was quenched with water (10 mL) and the separated aqueous layer was extracted with Et_2O (3 × 15 mL). The collected organic layers were dried ($MgSO_4$) and the solvent removal in vacuo. The residue was purified by flash chromatography (silica gel, Et_2O/pentane 4:1) to yield **3** (436 mg, 85%). (Data see Table 2a.)

Debenzylation of 6f, 30; Preparation of 15, 31; General Procedure:
To a solution of **6f** (5.95 g, 10.0 mmol) in MeOH (40 mL) was added 5% Pd/C (1.20 g, 0.56 mmol) and cyclohexene (12.3 g, 150 mmol). After heating under reflux for 12 h and cooling to r.t. Et_2O (10 mL) was added. The mixture was stirred at r.t. for 0.5 h. The solids were filtered off and thoroughly extracted with Et_2O (50 mL). The solvents were evaporated in vacuo and for analyses the crude product was purified by flash chromatography on silica gel with Et_2O/pentane/Et_3N (4:1:0.1) to yield the amine **15** (3.76 g, 84%). (Data see Table 2b.)

(+)-(2*S*,4*S*)-2-Amino-4-pentanolide Hydrochloride (31):
From **30** (40 mg, 0.14 mmol) with Pd/C (25 mg, 0.01 mmol) in MeOH (2 mL). The crude product was dissolved in 6 M HCl (2 mL) and stirred at r.t. for 1 h. The solvent was evaporated in vacuo and the residue was crystallized from MeOH/Et_2O; yield: 20 mg (94%); colorless solid: mp 193 °C; $[\alpha]_D^{20}$ –41.0 (*c* = 0.50, MeOH) [ref.[20] mp 198–200 °C; $[\alpha]_D^{20}$ –44 (*c* = 1.1, MeOH).

(–)-(*S*)-[4-(*tert*-Butyldimethylsilyloxy)-3-(dimethylamino)butyl] 2,2,4,4-Tetramethyloxazolidine-3-carboxylate (16):
To a solution of **15** (562 mg, 1.50 mmol) in MeCN (5 mL) and 37% aq CH_2O (0.7 mL) was added $NaBH_3CN$ (150 mg, 2.40 mmol).[14] The mixture was stirred at r.t. for 0.5 h and the solution neutralized with HOAc. The solvent was evaporated in vacuo before the residue was dissolved in 15% aq NaOH (10 mL). After extraction with Et_2O (5 × 15 mL), the combined Et_2O extracts were dried ($MgSO_4$), evaporated and the residue purified by flash chromatography (silica gel, Et_2O/pentane/Et_3N 1:2:0.1) to yield **16** (496 mg, 82%) as a colorless oil. (Data see Table 2a.)

Deprotonation of Monocarbamate 6, 7, 16 with *s*-BuLi and Preparation of C-1 Substituted Products 9; General Procedure:
Method 1: (–)-Sparteine (**22**, 422 mg, 1.80 mmol) was dissolved in anhyd Et_2O (4.5 mL) under argon and 1.4 M *s*-BuLi in cyclohexane/hexane (1.29 mL, 1.80 mmol) was added dropwise. After stirring for 15 min, the monocarbamate, dissolved in Et_2O (2.5 mL), was added. Stirring was continued for 5 h before the electrophile was introduced. (See Method A or B.)

Method 2: TMEDA (209 mg, 1.80 mmol) was dissolved in anhyd Et_2O (4.5 mL) under argon and 1.4 M *s*-BuLi in cyclohexane/hexane (1.29 mL, 1.80 mmol) was added dropwise. After stirring for 15 min, the monocarbamate, dissolved in Et_2O (2.5 mL), was added. Stirring was continued for 5 h before the electrophile was introduced. (See Method A or B.)

Method 3: Deprotonation without diamine. To a solution of the carbamate (1.0 mmol) in anhyd Et_2O or THF (8 mL) under argon at –78 °C 1.4 M *s*-BuLi in cyclohexane/hexane (1.29 mL, 1.80 mmol) was added dropwise. Stirring was continued for 5 h before the electrophile was introduced. (See Method A or B.)

Method A:
For carboxylation, after stirring at –78 °C for 5 h, a stream of dry CO_2 was introduced to the solution of the deprotonated carbamate via a syringe for 10 min. After warming to r.t., hydrolysis with water (10 mL) and extraction with Et_2O (3 × 25 mL), the collected organic layers were dried ($MgSO_4$) and concentrated. The residue was dissolved in Et_2O (5 mL) and treated with ethereal CH_2N_2 solution until remaining yellow. After stirring for 1 h, silica gel (20 mg) was added and the mixture was stirred for 15 min in order to destroy the excess of CH_2N_2. The subsequent flash chromatographic purification (Et_2O/pentane 1:1 to 1:4) yielded the methyl ester **20** or **33a**.

Method B:
After stirring at –78 °C for 5 h, the electrophile (1.8 mmol) was slowly introduced with a syringe. The mixture was allowed to warm up to r.t. for 12 h and water (10 mL) was added. The Et_2O layer was separated and the aqueous phase was extracted with Et_2O (3 × 25 mL). The combined Et_2O were dried ($MgSO_4$) and evaporated in vacuo. The residue was purified by flash chromatography (silica gel, Et_2O/pentane 1:1 to 1:4) to afford the C-1 substituted carbamate **18**.

(+)-(2*S*,4*S*)-2-(Dibenzylamino)pentane-1,4-diol (29):
A solution of **18a** (3.48 g, 5.00 mmol) in THF (5 mL) and 5 M HCl (25 mL) was refluxed for 16 h. After cooling to r.t., the mixture was neutralized with 5 M NaOH (25 mL) and extracted with Et_2O (5 × 25 mL). The collected extracts were dried ($MgSO_4$) and the solvents were evaporated in vacuo. The crude product was purified by flash chromatography (silica gel, Et_2O/pentane 1:3 → 1:0) to yield pure diol **29** (1.28 g, 86%) as a viscous oil; oil; R_f 0.24 (Et_2O/pentane 4:1); $[\alpha]_D^{20}$ +4.8 (*c* = 1.00, $CHCl_3$).
IR (film): ν = 3450 (OH), 1050 (C–O), 750, 700 cm^{-1} (arom).
^1H NMR ($CDCl_3$, 300 MHz): δ = 1.14 (d, 3H, $^3J_{4,5}$ = 6.2 Hz, 5-H); 1.37 (ddd, ^2J = 14.3 Hz, $^3J_{2,3}$ = 5.8 Hz, 3-H); 1.75 (ddd, $^3J_{2,3}$ = 7.6 Hz, $^3J_{3,4}$ = 9.5 Hz, 3-H); 2.51 (m, OH); 3.06 (m, 2-H); 3.53–3.80 (m, 3H, 1-H, 4-H); 3.62 (d, 2H, ^2J = 13.0 Hz, NCH_2Ph); 3.76 (d, 2H, NCH_2Ph); 4.36 (m, OH); 7.13–7.35 (m, 10H, Ph).
^{13}C NMR ($CDCl_3$, 75 MHz): δ = 23.83 (C-5); 35.18 (C-3); 53.68 (2C, N*C*H_2Ph); 58.15 (C-2); 61.26 (C-1); 67.36 (C-4); 127.24, 128.46, 129.25, 138.71 (12C, Ph).
MS (EI) $C_{19}H_{25}NO_2$ (299.41):calcd. 299.18853, found 299.18782.

(–)-(2*S*,4*S*)-2-(Dibenzylamino)-4-pentanolide (30):
To a solution of **29** (156 mg, 0.52 mmol) in anhyd benzene (10 mL) was added $(Ph_3P)_3RuCl_2$ (600 mg, 0.62 mmol).[22] The mixture was stirred for 24 h at r.t., before Na_2CO_3 (827 mg, 7.80 mmol) was added; stirring was continued for 48 h. The solids were filtered off over silica gel and the solvents evaporated in vacuo. The crude product was purified by flash chromatography (silica gel, Et_2O/pentane 1:2) to afford **30** (60 mg, 39%); oil; R_f 0.50 (Et_2O/pentane 1:1); $[\alpha]_D^{20}$ –33.1 (*c* = 0.93, $CHCl_3$).
IR (film): ν = 1180 (C–O), 1769 (C=O), 740, 695 cm^{-1} (arom).
^1H NMR ($CDCl_3$, 300 MHz): δ = 1.28 (d, 3H, $^3J_{4,5}$ = 6.5 Hz, 5-H); 1.97 (ddd, ^2J = 13.1 Hz, $^3J_{2,3}$ = 9.5 Hz, $^3J_{3,4}$ = 3.4 Hz, 3-H); 2.41 (ddd, $^3J_{2,3}$ = 8.7 Hz, $^3J_{3,4}$ = 8.6 Hz, 3-H); 3.67 (d, 2H, ^2J = 13.4 Hz, NCH_2Ph); 3.82 (m, 2-H); 3.87 (d, 2H, NCH_2Ph); 4.66 (ddq, 4-H); 7.18–7.44 (m, 10H, Ph).
^{13}C NMR ($CDCl_3$, 75 MHz): δ = 22.03 (C-5); 31.60 (C-3); 54.75 (2C, N*C*H_2Ph); 57.19 (C-2); 74.30 (C-4); 127.24, 128.38, 128.69, 138.83 (12C, Ph); 175.91 (C-1).
Anal. Calcd for $C_{19}H_{21}NO_2$ (295.38): C, 77.26; H, 7.17; N, 4.74. Found: C, 76.87; H, 7.01; N, 4.89.

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