Synthesis of Dihydroxyethylene Isosteres of Dipeptides; 2. Isosteres of Leu-Ala and Leu-Val from Suitably Substituted 3-Dimethylphenylsilyl-4-octanolides

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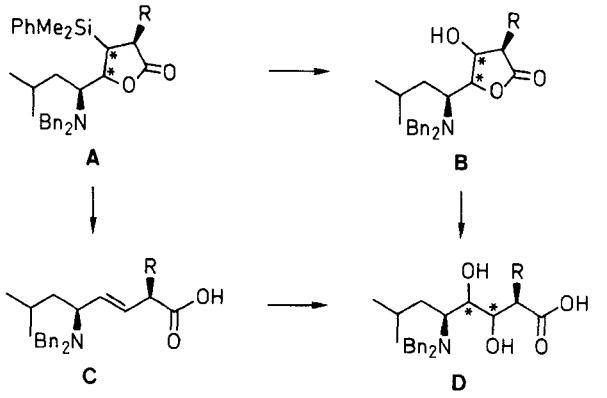
Dedicated to Professor E. Winterfeldt on the occasion of his 60th birthday

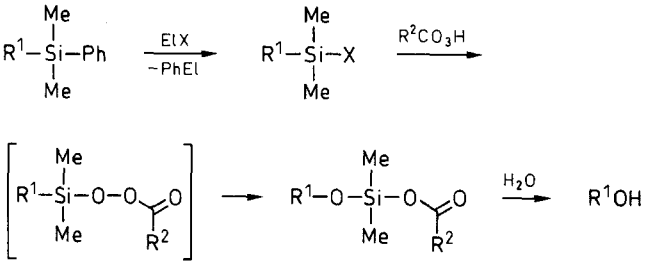
Homochiral 2-alkyl-5-amino-3-hydroxy-5-octanolides **4a,b**, **5b**, **6b** and **9a**, representing protected ψ [CHOHCHOH] dipeptides, were prepared by stereospecific oxydesilylation of the appropriate 3-dimethylphenylsilyl derivatives, **1a–c** and **7a**. Alternatively, anti-selective Peterson elimination of the diastereomeric 3,4-trans-substituted γ-lactones **1a** or **1b** followed by esterification yielded methyl (2*R*,3*E*,5*S*)-5-(*tert*-butoxycarbonylamino)-2,7-dimethyl-3-octenoate (**14a**), which on syn-bishydroxylation led to the 2*R*,3*S*,4*S*,5*S*- and 2*R*,3*R*,4*R*,5*S*-stereoisomers of ψ[CHOHCHOH]-L-leu-L-ala, **17a** and **18a**. In combination with the results of the preceding paper, a general procedure is outlined for the rapid synthesis of various diasteromers of dipeptide dihydroxyethylene isosteres.

Peptide surrogates, in which an amide moiety is replaced by a non-hydrolizable 1,2-dihydroxyethylene group play an important role as inhibitors of renin or HIV-proteases.[1] In the preceding publication[2] we reported on the synthesis of configurationally homogeneous 2-alkyl-5-dibenzylamino-3-dimethylphenylsilyl-4-octanolides of type **A** from (*S*)-*N*,*N*-dibenzylleucinal[3] by the combination of homoenolate[4] and enolate[5] methodology. In order to obtain the appropriate 3-hydroxy-4-octanolides **B**, which are valuable building blocks for the construction of dihydroxyethylene peptide isosteres,[1] the silyl function has to be exchanged for a hydroxy group (Scheme 1). This should be achieved by stereospecific oxydesilylation according to Fleming[6] and Tamao[7] or by anti-selective Peterson elimination,[8] which was found by Procter and co-workers[9] to proceed particularly smoothly in β-silyl-γ-lactones of type **A**, followed by bishydroxylation of **C**.



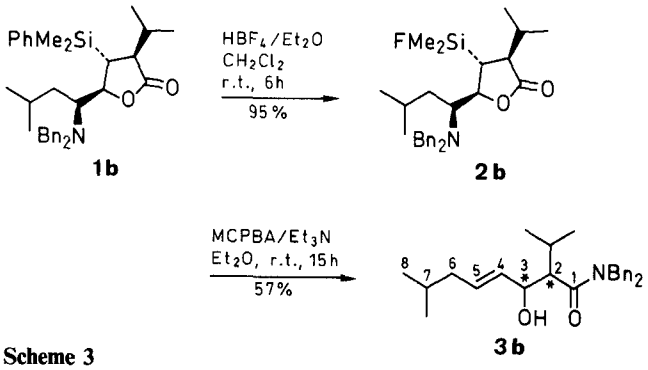
Scheme 1

In the first reaction step of the oxydesilylation sequence, the phenyl group usually is removed by electrophilic ipso-substitution with mercuric acetate,[6] bromine,[6] or tetrafluoroboric acid[10] (Scheme 2). The subsequent nucleophilic substitution at the silicon atom by peracid finally triggers an oxidative rearrangement with retention of configuration. The presence of a basic and oxidable amino group in the molecule of **A** was expected to bring problems to both steps.



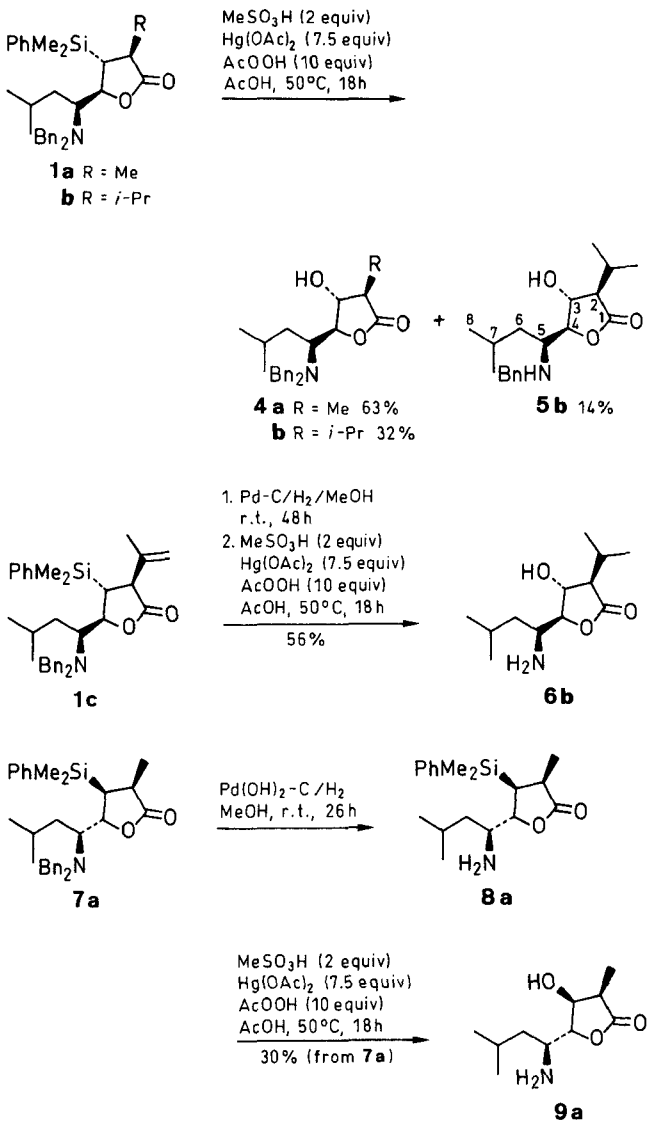
Scheme 2

When lactone **1b** was treated with tetrafluoroboric acid, analytical pure fluorosilane **2b** was isolated with 95% yield, however, the subsequent reaction with 3-chloroperoxybenzoic acid (MCPBA) resulted in the formation of a sensitive, optical active and diastereomerically pure rearrangement product **3b** (Scheme 3). No attempts were made to elucidate the relative configuration or the mode of formation of **3b**.



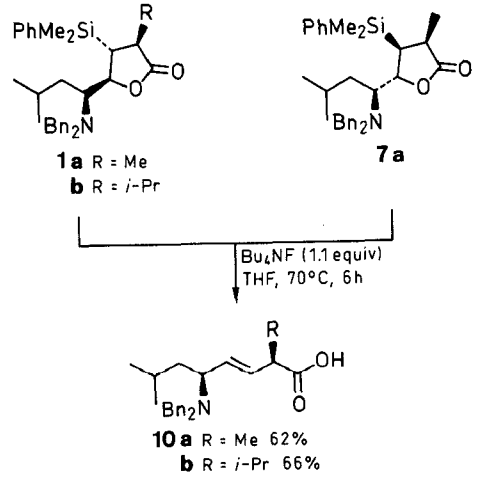
Scheme 3

The reaction of the ammonium methanesulfonates derived from **1a,b** with excess mercuric acetate and peracetic acid furnished the 3-hydroxylactones **4a** (63%) and **4b** (32%) (Scheme 4); **4b** was accompanied by the monobenzyl derivative **5b** (14%) and starting material **1b** (36%). It proved to be advantageous debenzylating **1b** before oxydesilylation. After hydrogenolysis of **1b** (obtained by in situ hydrogenation of the isopropenyl derivative **1c**) and the above described treatment, the free amine **6b** was isolated with 56% yield. Similarly the 2,3-cis-diastereomer **8a** prepared from the *N*,*N*-dibenzyl derivative **7a** afforded amine **9a** with 30% yield. The low yields are in part caused by losses during aqueous workup and chromatographic purification due to the high polarity of the hydroxy amines.



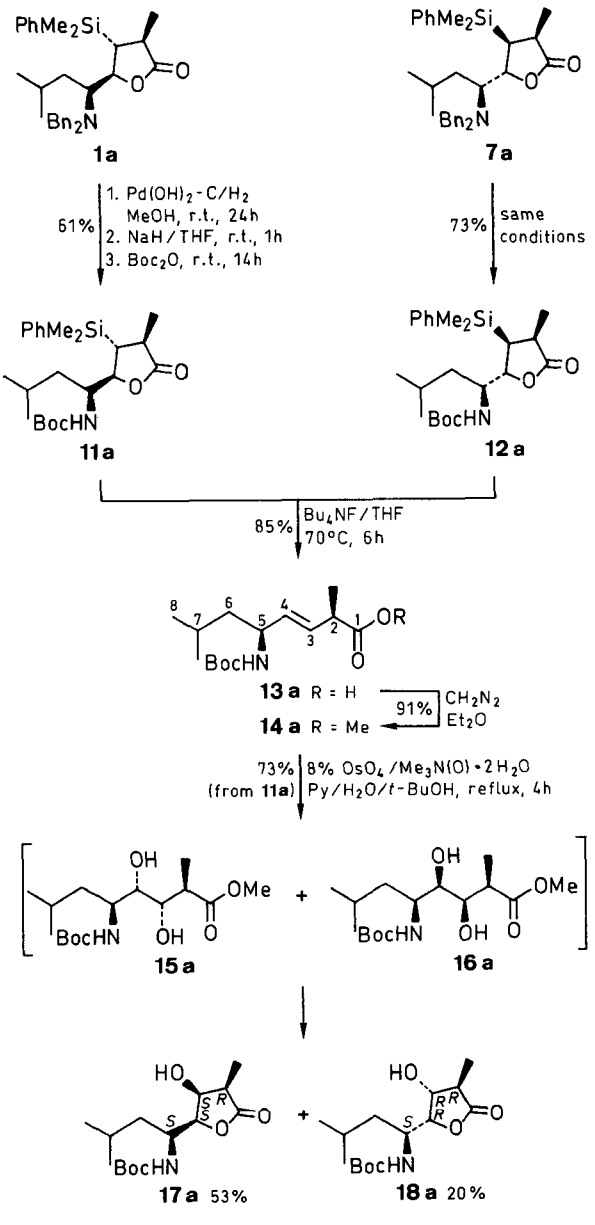
Scheme 4

According to a procedure developed by Procter and co-workers[9] for simpler γ-lactones, the *N,N*-dibenzyl derivatives **1a,b** and **7a** furnished on treatment with tetrabutylammonium fluoride in a clean anti-elimination the corresponding (2*R*,3*E*,5*S*)-5-amino-3-alkenoic acids **10a,b** (Scheme 5). Thus, the two diastereomers formed initially in the homoaldol reaction[2,3] can be converted stereoconvergently to a single stereoisomer **10**. Although compounds of type **10** are regarded as ethylene dipeptide isosteres[11-13] and have been used frequently in the construction of enzyme inhibitors,[14] they seem to be of little value due to their low polarity and their metabolic instability. Thus, the preparative value of compounds **10** lies in their facile transformation into the bishydroxyethylene analogues.[1]



Scheme 5

However, all attempts to accomplish an osmium tetroxide-mediated syn-bishydroxylation[15] on the *N,N*-dibenzyl derivatives **10a** and **b** failed. Thus we undertook an exchange of the protecting groups. **1a** and **7a** afforded the respective *N*-*tert*-butoxycarbonyl (Boc) derivatives **11a** and **12a** by hydrogenolytic debenzylation and *tert*-butoxycarbonylation without isolation of the intermediate primary amines (Scheme 6). Treatment of both **11a** and **12a** with tetrabutylammonium fluoride[9] gave rise to the diastereomerically pure *N*-Boc-δ-amino acid **13a**, which



Scheme 6

Table 1. Compounds Prepared

Starting Materials	Product	Configuration	Molecular Formula[a]	Yield (%)	$[\alpha]_D^{20}$ (c[b])	mp (°C) (solvent[c])	R_f[c,d]	IR (neat) ν (cm^{-1})
1b	**2b**	(2*S*,3*R*,4*S*,5*S*)	$C_{28}H_{40}FNO_2$ (469.7)	95	−41.4, A (0.6)	76 (D)	0.68, C (1:1)	1750
2b	**3b**		$C_{26}H_{35}NO_2$ (393.6)	57	+44.6, A (1.0)	oil	0.86, C (1:1)	3400, 1700
1a	**4a**	(2*R*,3*R*,4*S*,5*S*)	$C_{24}H_{31}NO_3$ (381.5)	63	−59.3, B (2.0)	oil	0.55, D (1:1)	3440, 1760
1b	**4b**	(2*R*,3*R*,4*S*,5*S*)	$C_{26}H_{35}NO_3$ (409.6)	32	−59.9, B (1.2)	105 (D)	0.81, D (1:1)	3420, 1760
1b	**5b**	(2*R*,3*R*,4*S*,5*S*)	$C_{19}H_{29}NO_3$ (319.4)	14	–	oil	0.56, D (1:1)	3420, 1760
1b	**6b**	(2*R*,3*R*,4*R*,5*S*)	$C_{12}H_{23}NO_3$ (229.3)	56	−17.6, A (0.5)	oil	0.29, D (1:1)	3400, 1760
	7a	(2*S*,3*S*,4*R*,5*S*)	$C_{32}H_{41}NO_2Si$ (499.8)	53	−46.9, A (0.9)	oil	0.45, C (1:4)	1770
7a	**8a**	(2*S*,3*S*,4*R*,5*S*)	$C_{18}H_{29}NO_2Si$ (319.5)	44	+27.1, A (1.6)	60 (D)	0.18, D (1:1)	3380, 1750
8a	**9a**	(2*R*,3*S*,4*R*,5*S*)	$C_{10}H_{19}NO_3$ (201.3)	30	−26.8, A (0.6)	oil	0.2, D (1:1)	3400, 1760
1a	**10a**	(2*R*,3*E*,5*S*)	$C_{24}H_{31}NO_2$ (365.5)	62	−50.7, A (1.1)	oil	0.24, D (1:4)	1700
1b	**10b**	(2*R*,3*E*,5*S*)	$C_{26}H_{35}NO_2$ (393.6)	66	−84.4, A (1.4)	oil	0.29, C (1:4)	1700, 1650
1a	**11a**	(2*S*,3*R*,4*S*,5*S*)	$C_{23}H_{37}NO_4Si$ (419.6)	61	−52.1, A (1.2)	oil	0.33, D (1:10)	1770, 1700
7a	**12a**	(2*S*,3*S*,4*R*,5*S*)	$C_{23}H_{37}NO_4Si$ (419.6)	73	+6.3, A (1.0)	oil	0.66, D (1:1)	1770, 1700
11a	**13a**	(2*R*,3*E*,5*S*)	$C_{15}H_{27}NO_4$ (285.4)	84	−25.1, A (1.2)	oil	0.23, C (1:1)	3300, 1700
12a				85				
13a	**14a**	(2*R*,3*E*,5*S*)	$C_{16}H_{29}NO_4$ (299.4)	91	−34.4, A (0.9)	oil	0.68, D (1:1)	3400, 1740
11a	**17a**	(2*R*,3*S*,4*S*,5*S*)	$C_{15}H_{27}NO_5$ (301.4)	53 (+**18a**)	−72.6, A (0.4)	173 (D)	0.18, D (1:4)	3340, 1780, 1670
12a								
11a	**18a**	(2*R*,3*R*,4*R*,5*S*)	$C_{15}H_{27}NO_5$ (301.4)	20 (+**17a**)	−34.6, A (0.5)	201 (D)	0.23, D (1:4)	3340, 1780, 1670
12a								

[a] All new compounds gave satisfactory C,H analyses (C ± 0.19, H ± 0.14); exceptions are **2b, 3b, 5b, 6b, 9a, 12a**.
[b] Solvents used A CH_2Cl_2, B MeOH.
[c] C Et_2O/pentane, D EtOAc/hexane.
[d] Silica gel.

Table 2. ^1H NMR Data[a,b] of the New Compounds

Compound	2-H $J_{2,3}$	3-H $J_{3,4}$	4-H $J_{4,5}$	5-H $J_{5,6}$	2-R $J_{1',2}$	3-$(CH_3)_2$SiPh	5-N$(CH_2Ph)_2$ $J_{A,B}$	8-H_3 and $J_{7,7'}$	7-CH_3 $J_{7,8}$
1a	2.42 (*11.8*)	1.24 (*10.8*)	4.86 (*1.1*)	2.72 (*10.1*)	0.98 (*6.9*)	0.13, 0.24	3.54, 3.93 (*14.4*)	0.63 (*6.6*)	0.94 (*6.8*)
1b	2.35 (*11.0*)	1.46 (*10.0*)	4.78 (*1.7*)	2.70 (*9.2*)	2.01 (*3.5*)	0.15, 0.25	3.53, 3.85 (*14.4*)	0.68 (*6.5*)	0.84 (*6.9*)
1c	3.13 (*12.8*)	1.79 (*11.1*)	4.84 (*1.2*)	2.79 (*9.6*)	–	0.1, 0.2	3.57 (*14.5*)	0.67 (*6.5*)	0.94 (*6.8*)
2b	2.35 (*11.1*)	1.46 (*10.0*)	4.75 (*1.7*)	2.70 (*9.3*)	2.00 (*3.7*)	0.15, 0.25	3.53, 3.85 (*14.4*)	0.68 (*6.3*)	0.84 (*6.8*)
3b	2.25 (*6.0*)	3.76 (*8.9*)	5.31 (*15.4*)	5.42 (*6.2*)	1.69 (*8.9*)	–	3.82, 3.86 (*12.9*)	0.84 (*6.6*)	0.87 (*6.6*)
4a	2.56 (*10.0*)	3.25 (*7.7*)	4.17 (*7.7*)	2.86 (*6.2*)	1.16 (*7.1*)	–	3.59, 3.72 (*13.3*)	0.83 (*6.5*)	0.93 (*6.6*)
4b	2.47 (*9.4*)	3.42 (*7.6*)	4.10 (*7.8*)	2.82 (*6.3*)	2.11 (*4.5*)	–	3.57, 3.74 (*13.0*)	0.73 (*6.9*)	0.87 (*6.5*)
5b	2.5 (*9.0*)	3.7 (*9.0*)	4.1 (*6.0*)	2.9	2.2 (*4.5*)	–	3.8 (*12.0*)	0.95 (*6.0*)	0.95 (*6.6*)
6b	2.55 (*10.2*)	4.14 (*7.9*)	3.63 (*8.9*)	2.81 (*5.5*)	2.24 (*4.6*)	–	–	0.94 (*6.5*)	1.11 (*6.3*)
7a	3.11 (*11.1*)	1.78 (*3.1*)	4.33 (*5.8*)	2.40 (*6.2*)	1.22 (*7.5*)	0.22, 0.30	3.51, 3.79 (*13.4*)	0.62 (*6.5*)	0.63 (*6.6*)
8a	2.93 (*9.3*)	2.27 (*8.2*)	4.30 (*3.2*)	2.42 (*5.3*)	1.24 (*7.6*)	0.43, 0.43	–	0.76 (*6.6*)	0.82 (*6.5*)
9a	2.59 (*3.2*)	5.05 (*8.6*)	4.84 (*2.2*)	3.55 (*6.9*)	1.36 (*7.0*)	–	–	0.94 (*6.3*)	0.99 (*6.4*)
10a	3.20 (*6.8*)	5.60 (*15.4*)	5.51 (*7.7*)	3.08 (*7.2*)	1.37 (*7.2*)	–	3.31, 3.77 (*13.6*)	0.66 (*6.5*)	0.76 (*6.6*)
10b	2.79 (*8.8*)	5.56 (*15.4*)	5.45 (*8.9*)	3.11 (*7.5*)	2.10 (*7.9*)	–	3.32, 3.79 (*13.5*)	0.66 (*6.5*)	0.76 (*6.6*)
11a	2.42 (*11.5*)	1.31 (*11.4*)	4.39 (*2.4*)	3.76 (*2.6*)	1.12 (*7.0*)	0.48, 0.51	–	0.84 (*6.6*)	0.91 (*6.7*)
12a	2.85 (*9.6*)	2.13 (*8.2*)	4.41 (*1.5*)	1.3	1.18 (*7.6*)	0.43, 0.46	–	0.84 (*6.5*)	0.88 (*6.4*)
13a	3.15 (*7.1*)	5.69 (*15.5*)	5.48 (*5.9*)	1.35	1.28 (*7.1*)	–	–	0.91 (*6.6*)	0.91 (*6.6*)
14a	3.13 (*7.5*)	5.67 (*15.5*)	5.44 (*6.4*)	1.33 (*6.6*)	1.25 (*7.1*)	–	–	0.91 (*6.6*)	0.92 (*6.6*)
17a	2.67 (*4.4*)	4.26 (*2.2*)	3.75 (*10.2*)	1.75	1.30 (*7.0*)	–	–	0.92 (*6.1*)	0.96 (*6.5*)
18a	2.26 (*10.2*)	4.18 (*2.6*)	3.91 (*8.6*)	1.75	1.29 (*7.2*)	–	–	0.92 (*6.1*)	0.96 (*6.5*)

[a] 300 MHz, $CDCl_3$, δ, J_{vic} (Hz).
[b] Numbering according to the open-chain compounds.

Table 3. ^{13}C NMR Data[a, b] of the New Compounds

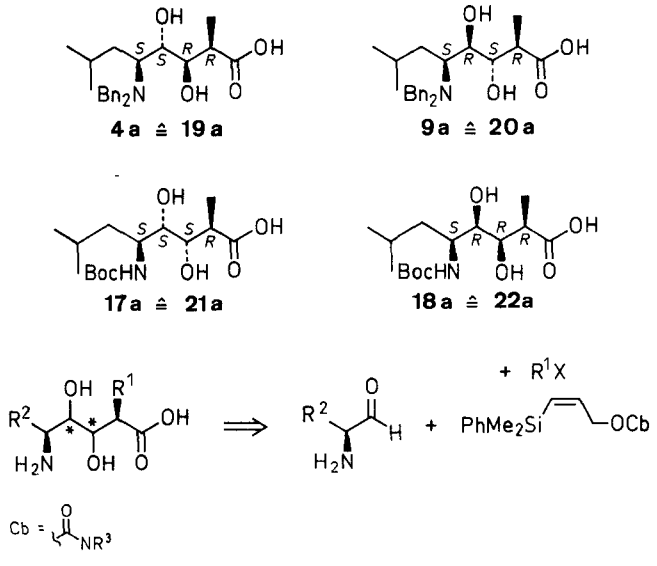
Compound	C-1	C-2	C-3	C-4	C-5	2-R	3-($\underline{C}H_3$)$_2$SiPh	5-N($\underline{C}H_2$Ph)$_2$	C-8 and C-7'
1a	179.76	37.25	34.27	80.43	58.51	16.93	−4.57, −3.72	54.56	21.72, 23.98
1b	177.75	47.70	29.57	80.33	59.13	29.57	−1.12, −0.26	54.60	22.03, 23.85
1c	176.94	51.24	30.14	81.02	58.48	140.19	−3.96, −3.74	54.24	21.91, 23.91
2b	177.89	47.78	29.98	80.46	59.30	29.63	−4.40, −3.54	54.70	22.07, 23.86
3b	178.69	55.63	82.77	127.91	134.71	26.97	–	62.61	22.16, 22.46
4a	176.54	42.62	78.11	82.17	57.27	12.33	–	54.37	22.55, 23.19
4b	175.05	52.89	73.35	82.16	57.88	26.74	–	54.44	18.52, 19.85
6b	177.14	55.58	75.91	86.42	58.51	26.85	–	–	21.39, 22.32
7a	180.25	36.29	29.58	81.90	57.84	14.77	−3.27, −2.57	55.14	22.65, 22.84
8a	180.43	38.13	30.29	84.49	51.02	14.99	−3.27, −2.57	–	21.65, 23.25
9a	170.52	38.22	76.06	78.22	50.73	10.56	–	–	22.20, 22.71
10a	180.47	43.05	130.05	132.15	57.59	17.76	–	53.76	22.48, 22.94
10b	180.18	56.92	128.99	133.13	57.82	30.56	–	53.88	22.48, 22.90
11a	179.53	38.02	33.28	84.23	51.21	16.82	−4.20, −3.75	–	21.33, 23.78
12a	180.55	38.11	30.20	83.06	51.23	15.22	−2.47, −2.26	–	22.20, 22.94
13a	179.68	42.39	128.89	133.05	50.56	17.14	–	–	22.44, 22.73
14a	175.01	42.42	129.02	132.92	50.49	17.24	–	–	22.45, 22.69
17a	177.89	40.67	69.98	81.65	47.05	8.11	–	–	21.14, 23.53
18a	177.24	41.13	75.62	84.59	47.37	13.73	–	–	21.37, 22.92

[a] $CDCl_3$, δ.

[b] Numbering according to the open-chain compounds.

was converted from the crude product into the methyl ester **14a** by the use of diazomethane. The bishydroxylation of **14a** with trimethylamine *N*-oxide, catalyzed by osmium tetroxide,[15] gave smoothly a 73:27 mixture of the diastereomeric β-hydroxylactones **17a** and **18a** with 73% yield (based on **11a**) which were seperated by silica gel chromatography. Obviously, the intermediate β,γ-dihydroxycarboxylates **15a** and **16a** undergo rapid lactone ring closure under the reaction conditions.

By the protocols, outlined above, all four possible diastereomers of ψ[CHOHCHOH]-L-leu-L-ala were prepared (Scheme 7), starting from (*S*)-*N*,*N*-dibenzylleucinal. The sequence offers a general approach for the "brick-box synthesis" of a manifold of dihydroxyethylene dipeptide isosteres from simple building blocks with few steps, starting from readily available and configurationally stable (*S*)-2-(dibenzylamino)alkanals[3] by chain-



Scheme 7

elongation with a homoenolate[16] reagent, followed by highly stereoselective introduction of R^1 and functional group interchange.

^1H and ^{13}C NMR spectra were recorded on Varian XL-200, FT 80A, and Bruker AM 300 spectrometer. IR spectra were recorded on Perkin-Elmer 298 or 283b spectrophotometer. Optical rotations were recorded on Perkin-Elmer polarimeter 241. Et_2O, used for metaloorganic reactions, was dried by distillation from $LiAlH_4$ in an Ar atmosphere.

(2*S*,3*R*,4*S*,5*S*)-5-Dibenzylamino-3-fluorodimethylsilyl-2-isopropyl-7-methyl-4-octanolide (2b):
To a solution of (2*S*,3*R*,4*S*,5*S*)-5-dibenzylamino-3-dimethylphenylsilyl-2-isopropyl-7-methyl-4-octanolide[2] (**1b**; 95 mg, 0.18 mmol) in CH_2Cl_2 (3 mL) an excess of 54% HBF_4 (2.3 mL) in Et_2O was added and the mixture stirred at r.t. for 6 h. Aqueous $NaHCO_3$ (10 mL) and Et_2O (10 mL) were added to the solution and the aqueous solution was extracted with Et_2O (3 × 10 mL). The etheral solution was dried (Na_2SO_4) and the solvent removed in vacuum. The residue was chromatographed on silica gel (20 g) with EtOAc/hexane (1:1) affording **2b** (80 mg, 95%); data see Tables 1, 2 and 3.

(4*E*)-5-Dibenzyl-3-hydroxy-2-isopropyl-7-methyl-4-octenamide (3b):
To a solution of **2b** (109 mg, 0.24 mmol) in Et_2O (3 mL), Et_3N (121 mg, 1.2 mmol) and MCPBA (174 mg, 80% purity, 0.84 mmol) were added and the mixture was stirred at r.t. for 15 h. The solution was reduced with Me_2S (0.1 mL), and 1 N HCl (10 mL), Et_2O (10 mL) were added. The aqueous solution was extracted with Et_2O (3 × 10 mL), washed with $NaHCO_3$ and dried with (Na_2SO_4). The solvent was removed in vacuum and the residue chromatographed on silica gel (20 g) with EtOAc/hexane (1:1) affording **3b** (54 mg, 57%).

(2*R*,3*R*,4*S*,5*S*)-5-Dibenzylamino-3-hydroxy-2,7-dimethyl-4-octanolide (4a):
To a solution of (2*S*,3*R*,4*S*,5*S*)-5-dibenzylamino-3-dimethylphenylsilyl-2,7-dimethyl-4-octanolide[2] (**1a**; 264 mg, 0.5 mmol) in Et_2O (1 mL) $MeSO_3H$ (32.5 μL) was added and the solvent removed in vacuum. The residue was stirred with $Hg(OAc)_2$ (1.20 g, 3.75 mmol), $MeSO_3H$ (65 μL, 1.00 mmol), and 40% AcOOH in AcOH (5 mL) at 50°C for 18 h. The mixture was cooled to r.t. and reduced with Me_2S (1 mL) until the solution became clear. H_2O (3 mL) and solid $KHCO_3$ (2 g) were cautiously added and the solution extracted with

EtOAc (3 × 10 mL). The combined EtOAc solution was dried ($MgSO_4$) and the solvent removed at the rotavapor. The residue was chromatographed on silica gel (45 g) with EtOAc/hexane (1:3, 1:1) affording **4a** (140 mg, 63%).

(2*R*,3*R*,4*S*,5*S*)-5-Dibenzylamino-3-hydroxy-2-isopropyl-7-methyl-4-octanolide (4b) and (2*R*,3*R*,4*S*,5*S*)-5-Benzylamino-3-hydroxy-2-isopropyl-7-methyl-4-octanolide (5b):
To a solution of **1b** (202 mg, 0.38 mmol) in Et_2O (1 mL), $MeSO_3H$ (25 µL) was added and the solvent removed in vacuum. $Hg(OAc)_2$ (0.909 g, 2.85 mmol), $MeSO_3H$ (50 µL, 0.76 mmol), and 40% AcOOH in AcOH (5 mL) were added and the mixture stirred at 50°C for 18 h. The solution was allowed to warm to r.t. and was reduced with Me_2S (1 mL). H_2O (2 mL) and solid $KHCO_3$ (250 mg) was added and the mixture extracted with EtOAc (3 × 10 mL). The combined EtOAc solution was dried (Na_2SO_4) and the solvent removed in vacuum. The residue was chromatographed on silica gel (45 g) with EtOAc/hexane (1:1) affording **4b** (50 mg, 32%), R_f = 0.81, mp = 105°C (EtOAc/hexane) and **5b** (17 mg, 14%), oil and **1b** (72 mg, 36%).

(2*R*,3*R*,4*S*,5*S*)-5-Amino-3-hydroxy-2-isopropyl-7-methyl-4-octanolide (6b) from 1c:
To a solution of (2*S*,3*R*,4*S*,5*S*)-5-dibenzylamino-3-dimethylphenylsilyl-2-isopropenyl-7-methyl-4-octanolide[2] (**1c**; 263 mg, 0.50 mmol) in MeOH (5 mL), 10% Pd-C (263 mg) was added and the suspension stirred in H_2 atmosphere for 48 h. The mixture was filtered on silica gel and the residue treated as described for **4b**, affording **6b** (64 mg, 56%), oil.

(2*S*,3*S*,4*R*,5*S*)-5-Amino-3-dimethylphenylsilyl-2,7-dimethyl-4-octanolide (8a):
To a solution of (2*S*,3*S*,4*R*,5*S*)-5-dibenzylamino-2,7-dimethyl-3-dimethylphenylsilyl-4-octanolide[2] (**7a**; 300 mg, 0.6 mmol) in MeOH (4 mL), 20% $Pd(OH)_2$-C (225 mg) was added and the suspension was stirred under H_2 atmosphere for 26 h. The mixture was filtered through silica gel (20 g) and the solvent removed in vacuum. The residue was chromatographed on silica gel (45 g) with EtOAc/hexane (1:1) affording **8a** (84 mg, 44%), R_f = 0.18 mp = 60°C (EtOAc/hexane). **8a** was used in the following sequence without purification.

(2*R*,3*S*,4*R*,5*S*)-5-Amino-3-hydroxy-2,7-dimethyl-4-octanolide (9a):
Compound **8a** (383 mg, 1.2 mmol) was treated as described for **4a** affording **9a** (72 mg, 30%), oil.

(2*R*,3*E*,5*S*)-5-Dibenzylamino-2,7-dimethyl-3-octenoic Acid (10a):
To a solution of **1a** and **7a** (297 mg, 0.59 mmol) in THF (5 mL), a solution of 1 M Bu_4NF (0.65 mL, 0.65 mmol) in THF was added and the solution stirred at 70°C for 6 h. The mixture was allowed to warm to r.t. and Et_2O (20 mL) and sat. aq. $NaHCO_3$ (10 mL) were added. The aqueous solution was extracted with Et_2O (3 × 10 mL) and the etheral solutions were dried (Na_2SO_4). After removal of the solvent in vacuum the residue was chromatographed on silica gel (45 g) with EtOAc/hexane (1:4) affording **10a** (135 mg, 62%), oil.

(2*R*,3*E*,5*S*)-5-Dibenzylamino-2-isopropyl-7-methyl-3-octenoic Acid (10b):
(2*S*,3*R*,4*S*,5*S*)-5-Dibenzylamino-3-dimethylphenylsilyl-2-isopropyl-7-methyl-4-octanolide[2] (**1b**; 275 mg, 0.52 mmol) was treated as described for **10a** affording **10b** (135 mg, 66%), oil.

(2*S*,3*R*,4*S*,5*S*)-5-(*tert*-Butoxycarbonylamino)-2,7-dimethyl-3-dimethylphenylsilyl-4-octanolide (11a):
To a solution of **1a** (283 mg, 0.57 mmol) in MeOH (3 mL), 20% $Pd(OH)_2$-C (213 mg) was added and the suspension stirred in H_2 atmosphere for 24 h. The mixture was filtered on silica gel and the residue dissolved in THF (3 mL). 80% NaH in mineral oil (20 mg, 0.68 mmol) was added and the mixture stirred for 1 h. Boc_2O (122 mg, 0.56 mmol) in THF (1 mL) was added dropwise and stirring was continued for 14 h. Et_2O (15 mL) and H_2O (10 mL) were added, the aqueous solution was extracted with Et_2O (3 × 10 mL) and the combined etheral solutions dried (Na_2SO_4). After removal of the solvent in vacuum, the residue was chromatographed on silica gel (45 g) with EtOAc/hexane (1:10) affording **11a** (142 mg, 61%), oil.

(2*S*,3*S*,4*R*,5*S*,)-5-(*tert*-Butoxycarbonylamino)-2,7-dimethyl-3-dimethylphenylsilyl-4-octanolide (12a):
To a solution of **7a** (67 mol, 0.21 mmol) in MeOH, 20% $Pd(OH)_2$-C (50 mg) was added and the suspension stirred in H_2 atmosphere for 24 h. The mixture was filtered on silica gel and the residue, dissolved in THF (2 mL). 80% NaH in mineral oil (7 mg, 0.25 mmol) in THF (1 mL) was added and the mixture stirred for 1 h. Boc_2O (46 mg, 0.21 mmol) was added and stirring continued for 18 h. Et_2O (10 mL) and H_2O (5 mL) were added and the aqueous solution extracted was with Et_2O (3 × 10 mL). The etheral solutions were dried (Na_2SO_4) and the solvent removed in vacuum. The residue was chromatographed on silica gel (20 g) with EtOAc/hexane (1:1) affording **12a** (64 mg, 73%), oil.

(2*R*,3*E*,5*S*)-5-(*tert*-Butoxycarbonylamino)-2,7-dimethyl-3-octenoic Acid (13a):
To a solution of **12a** (244 mg, 0.58 mmol) in THF (5 mL) a solution of 1 M Bu_4NF (0.7 mL, 0.7 mmol) in THF was added and the mixture stirred at 70°C for 6 h. Et_2O (20 mL) and sat. aq $NaHCO_3$ was added and the aqueous solution extracted with Et_2O (3 × 10 mL). The etheral solutions were dried (Na_2SO_4) and the solvent was removed in vacuum. The residue was chromatographed on silica gel (45 g) with Et_2O/pentane (1:1) affording **13a** (141 mg, 85%), R_f = 0.23, oil.

Methyl (2*R*,3*E*,5*S*)-5-(*tert*-Butoxycarbonylamino)-2,7-dimethyl-3-octenoate (14a):
To a solution of **13a** (42 mg, 0.15 mmol) in Et_2O (3 mL) a solution of CH_2N_2 in Et_2O was added until the mixture turned to a yellow color. Silica gel (10 mg) was added and the solution extracted with Et_2O (10 mL). The etheral solutions were dried (Na_2SO_4) and the solvent was removed in vacuum. The residue was chromatographed on silica gel (9 g) with EtOAc/hexane (1:1) affording **14a** (41 mg, 91%), R_f = 0.68, oil.

(2*R*,3*S*,4*S*,5*S*)- and (2*R*,3*R*,4*R*,5*S*)-5-(*tert*-Butoxycarbonylamino)-3-hydroxy-2,7-dimethyl-4-octanolide (17a) and (18a):
Compound **11a** (198 mg, 0.47 mmol) was treated with Bu_4NF (0.57 mmol) as described for **13a**. A solution of CH_2N_2 in Et_2O (1 mL) was added to a solution of the crude product in Et_2O (3 mL). After removal of the solvent in vacuum, the residue was dissolved in *t*-BuOH (5 mL) and trimethylamine oxide dihydrate (192 mg, 1.73 mmol), pyridine (0.1 mL), H_2O (1.5 mL), and 2.5% OsO_4 in *t*-BuOH (0.5 mL) were added and the solution stirred under reflux for 4 h. The mixture was reduced with aq sat. Na_2SO_3 (8 mL) and refluxing was continued for 1 h. Aq sat. $NaHCO_3$ (10 mL) and EtOAc (15 mL) were added and the aqueous solutions were extracted with EtOAc (3 × 10 mL). The EtOAc solutions were dried (Na_2SO_4) and the solvent was removed in vacuum. The residue was chromatographed on silica gel (45 g) with EtOAc/hexane (1:4) affording **17a**, R_f = 0.18, mp = 173°C (EtOAc/hexane) and **18a** (103 mg, 73%), R_f = 0.23, mp = 201°C (EtOAc/hexane).

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