Amino Acids and Peptides; 75. Synthesis of Di- and Trihydroxyamino Acids – Construction of Lipophilic Tripalmitoyldihydroxy-α-amino Acids[1]

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Suitable protected derivatives of trihydroxynorleucines- [(2*S*,4*S*,5*S*)- and (2*R*,4*S*,5*S*)-2-amino-4,5,6-trihydroxyhexanoic acid,] of all isomeric dihydroxynorvalines [2-amino-4,5-dihydroxypentanoic acids), of all isomeric 2-amino-6,7-dihydroxyheptanoic acids and of (2*S*)-2-amino-6-hydroxymethyl-7-hydroxyheptanoic acid are synthesized via the corresponding α,β-didehydro compounds, which are hydrogenated with the optically active homogeneous catalyst [Rh(COD)(DIPAMP)]$^+$ BF_4^-.

Introduction

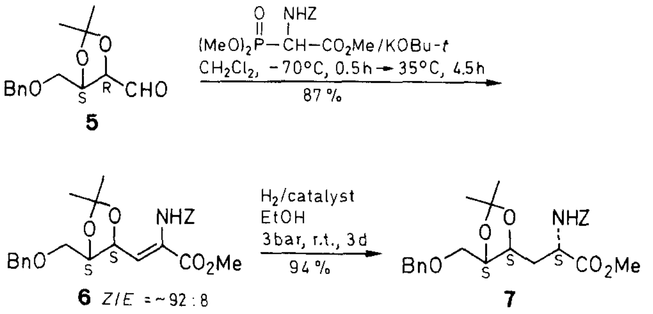
During the past 40 years, numerous unusual amino acids which differ structurally from the protein amino acids have been discovered. These unusual amino acids arise from the metabolisms of plants, bacteria, molds, and lower marine animals; they are often the characteristic units of biologically active peptides and peptolides. Many of these nonribosomal amino acids contain several hydroxy groups and thus border between amino acids and carbohydrates.[2]

In the following, we describe the stereoselective synthesis of di- and trihydroxyamino acids via the construction of the corresponding didehydroamino acids using the phosphonoglycinate method[3] and subsequent enantio- or diastereoselective hydrogenation of the latter. This methodology is superior to most of the other procedures for amino acid synthesis, since the conditions are so mild that polyhydroxyamino acids bearing benzyloxycarbonyl, benzyl, *tert*-butoxycarbonyl, and *tert*-butyl protecting groups and having the hydroxy groups masked as acetal functions can be obtained directly.

Hence, all protecting groups can be incorporated *a priori* in the starting materials used for the construction of the didehydroamino acids. In contrast, most of the enantioselective syntheses of amino acids, in particular the four-component condensation process and the Strecker synthesis, include an acid-catalyzed hydrolysis step and are, therefore, not suitable for the preparation of amino acids containing acid-labile groups. In all hydrogenation reactions involved in the preparation of (α*S*)-amino acids, the (*R*,*R*)-DIPAMP rhodium catalyst[4] (*R*,*R*)-**1** was used, since our experience has shown it to be superior in terms of stereoselectivity. As both enantiomers of the DIPAMP catalyst, namely (*R*,*R*)-**1** and (*S*,*S*)-**1**, are available, both (α*S*)- and (α*R*)-amino acids can be obtained.

Double Asymmetric Induction in the Hydrogenation of Optically Active Didehydroamino Acids with Optically Active Catalysts

The double asymmetric induction by the chiral catalysts **1**–**3** compared to nonchiral catalysts was studied for example of the hydrogenation of the didehydroamino acid **6** (Scheme A, Table 1). A significant effect in favor of the formation of the (α*S*)-configuration (2*S*,4*S*,5*S*)-**7** [de 31.4%] was apparent when using the nonchiral homogeneous catalyst **4**.[5] A weak induction but in the opposite direction to give (2*R*,4*S*,5*S*)-**7** was observed with rhodium/aluminum oxide (de 20%). When chiral catalyst (*R*,*R*)-**1** is used, the major diastereoisomer is the (2*S*,4*S*,5*S*)-**7** (de 94.4%); the double induction due to the chiral catalyst, on the one hand, and the chiral centres at the 4- and 5-positions, on the other, is complementary. However, with (*S*,*S*)-**1** these inductions were mutually opposed, giving (2*R*,4*S*,5*S*)-**7** in a de of only 57%. The superiority of (*R*,*R*)-**1** (de 94.4%) compared to **2**[6] and **3**[7] (de 85 and 67.6%, respectively) is apparent. The ratio of (2*S*)-**7**/(2*R*)-**7** were determined by analytical HPLC and the compounds purified by preparative MPLC.



Scheme A

The formation of diastereoisomers in the hydrogenation products of the optically active didehydroamino acid esters (*S*,*Z*)-**9** and (*R*,*Z*)-**9** using (*R*,*R*)-**1** and (*S*,*S*)-**1** could not be detected by HPLC. The small differences in the ^{13}C-NMR spectra of compounds (2*S*,4*S*)-**10** and (2*R*,4*S*)-**10**, respectively, could not be used to establish the exact de values. The corresponding diastereoisomers were only identifiable by HPLC after transformation into the lactones **11**: their absence implies a completely diastereoselective hydrogenation. The heterogeneous hydrogenation of (*S*,*Z*)-**9** with palladium on charcoal yielded a slight induction [(2*R*,4*S*)-**11**/(2*S*,4*S*)-**11** = 51:49 to 55:45].

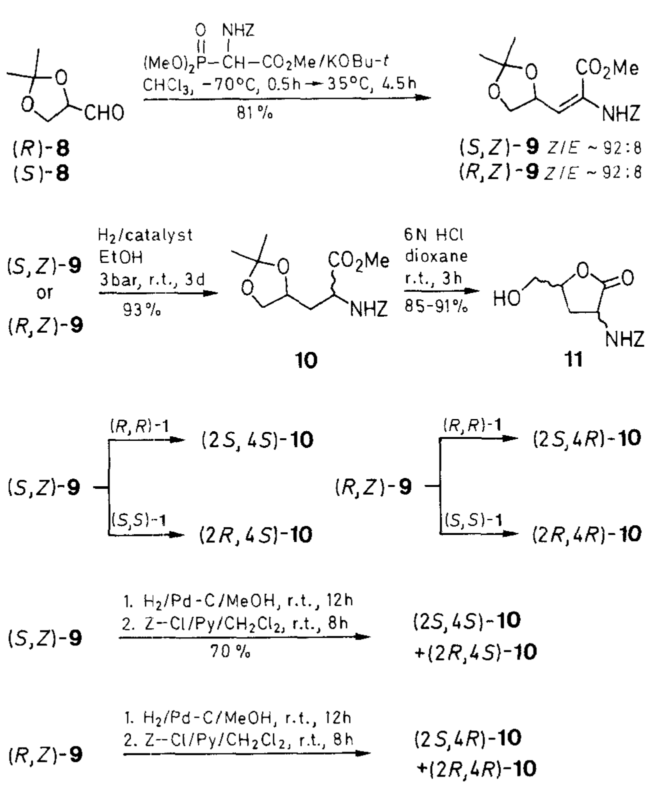
Only after transformation into the tripalmitoyl compounds **15** it was possible to demonstrate by HPLC that the diastereoselectivity in the hydrogenation of (*S*,*Z*)-**13** and (*R*,*Z*)-**13** with (*R*,*R*)-**1** and (*S*,*S*)-**1** was very high (de 100%).

2-Amino-4,5,6-trihydroxyhexanoic Acids 7 and 2-Amino-4,5-dihydroxyhexanoic Acids 10

The four isomeric 2-amino-4,5,6-trihydroxyhexanoic acids, (2*S*,4*S*,5*S*)-**7**, (2*R*,4*S*,5*S*)-**7**, (2*S*,4*R*,5*R*)-**7** and (2*R*,4*R*,5*R*)-**7**, can be obtained depending upon the configuration of the protected 2,3,4-trihydroxybutyraldehyde **5**[8] and the hydrogenation catalyst.

Experimental details for the synthesis of the protected methyl (2*S*,4*S*,5*S*)-2-amino-4,5,6-trihydroxyhexanoic acid derivative **7** are given as an example. Starting material for the synthesis (Scheme A) was the (2*R*,3*S*)-4-benzyloxy-2,3-isopropylidenedioxybutyraldehyde **5**, obtained from (*R*,*R*)-tartaric acid, which was condensed with methyl (*Z*)-dimethoxyphosphorylglycinate to furnish the 2-hexenoic acid derivative **6** (*Z*/*E* ratio ~ 92:8). Homogeneous hydrogenation of **6** with (*R*,*R*)-**1** gave the protected (2*S*,4*S*,5*S*)-2-amino-4,5,6-trihydroxypentanoic acid with high diastereoselectivity (de 94.4%).

All four isomeric 2-amino-4,5-dihydroxypentanoic acids **10** are accessible from (*R*)- or (*S*)-2,3-*O*-isopropylideneglyceraldehyde[9] (*R*)-**8** or (*S*)-**8** (Scheme **B**). Preparation of the two 4*S*-isomers started from (*R*)-**8**, which was converted to the 2-pentenoic acid derivative (*S*,*Z*)-**9** (*Z*/*E* ratio ~92:8). Homogeneous hydrogenation using (*R*,*R*)-**1** furnished (2*S*,4*S*)-**10**, while use of (*S*,*S*)-**1** gave the diastereoisomer (2*R*,4*S*)-**10**. The optical induction at the α-position was very high. The ratio of the diastereoisomers could be estimated by HPLC after conversion to the lactones **11** (de >99%; i.e., the "wrong" diastereoisomer was not detected).



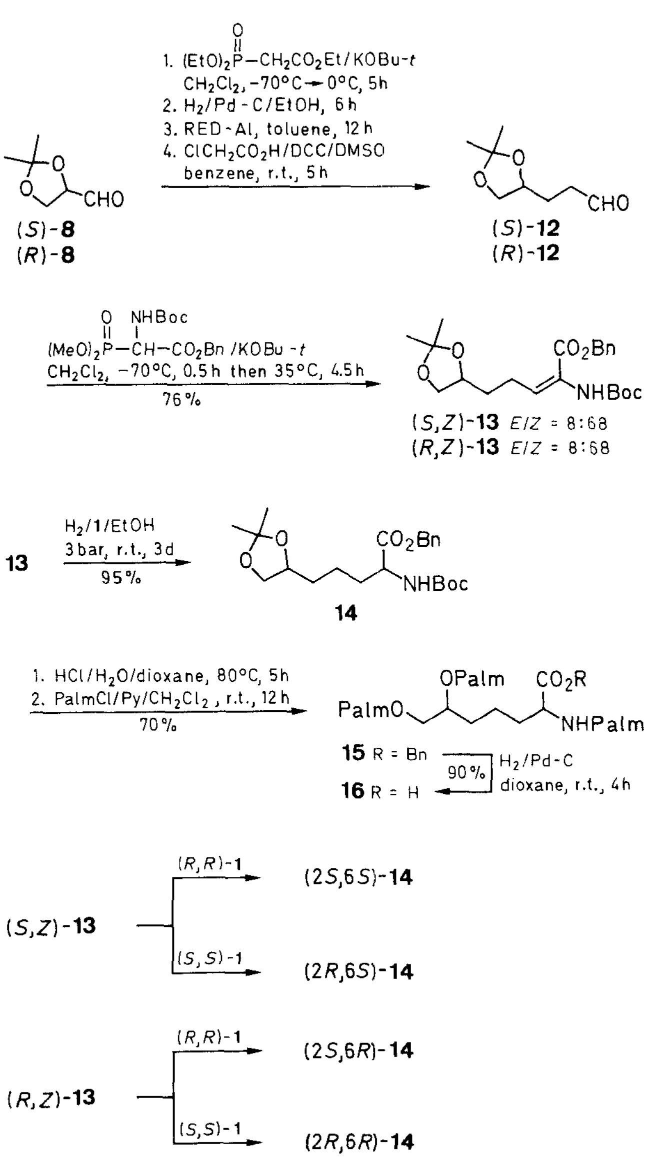
Scheme B

Acidic saponification of the acetal esters **10** proceeded smoothly and gave rise to the lactones **11**. The latter are valuable synthetic intermediates since the 5-hydroxy group can easily be transformed into other functional groups. Heterogeneous hydrogenation of the 2-pentenoic acids (*S*,*Z*)-**9** or (*R*,*Z*)-**9**, reacylation, and lactonization furnished diastereoisomeric mixtures of (2*S*,4*S*)-**11** and (2*R*,4*S*)-**11** (45:55) or (2*S*,4*R*)-**11** and (2*R*,4*R*)-**11** (45:55), respectively, wich could be separated by MPLC.

2-Amino-6,7-dihydroxyheptanoic Acids and 2-Amino-7-hydroxy-5-(hydroxymethyl)heptanoic Acid

Lipoprotein from the outer membrane of *Escherichia coli* constitutes a potent B lymphocyte mitogen and polyclonal activator in various species. The *N*-terminal amino acid of the lipoprotein has been identified as (*S*)-glyceryl-cysteine acylated with three fatty acids.[10] The synthetic tripalmitoyl derivative (Pam_3Cys)[11] has been linked to oligopeptides and conjugated with various antigens.[11–13] The resultant lipopeptides exhibit strong B-cell and macrophage activating effects similar to those of the native lipoprotein. A novel, low-molecular, synthetic vaccine against foot-and-mouth disease has been developed which contains tripalmitoyl-(*S*)-glyceryl-cysteinyl-seryl-serine as a built-in adjuvant linked to an α-helical T-cell epitope of the virus.[14]

The advantages of using conjugates consisting of Pam_3Cys and antigenic determinants for the coating of ELISA titer plates has been demonstrated in assays specific for HIV-1 and HIV-2.[15]



Scheme C

Since the two voluminous "paraffinic tails" mask the sulfur atom im Pam$_3$Cys, we considered the syntheses of the analogous carba-compounds and a study of their immunological properties to be a challenging task. Such compounds should possess several advantages over the sulfur-containing cysteine derivatives; for example, all four isomers should be easy to prepare, the variety of combinations of protecting groups will be considerably extended in peptide synthesis, and the lipoamino acids will be less sensitive to oxidation. The highly promising biological results obtained with lipopeptides having an *N*-terminal 2-palmitoylamino-6,7-dipalmitoyloxyheptanoic acid **16** will be published in due course.[16]

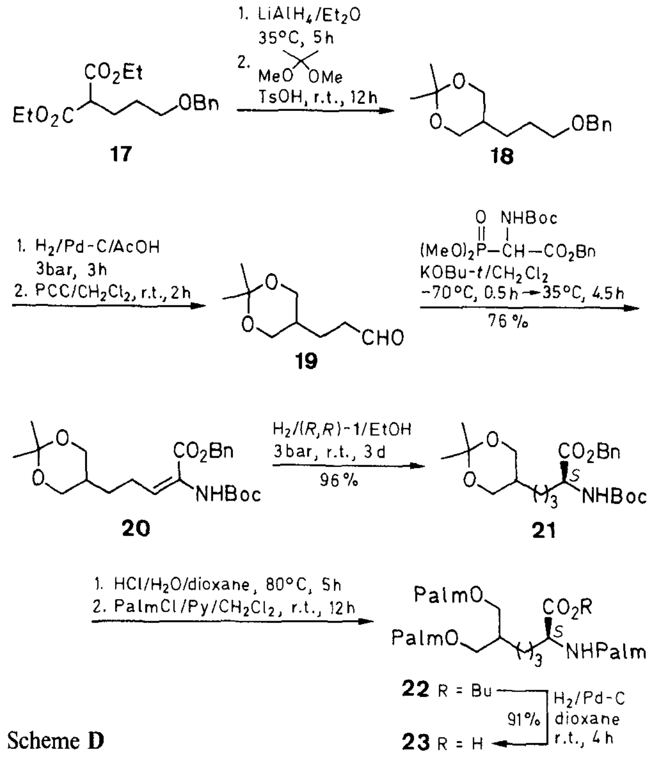
Starting materials for the construction of the 2-amino-6,7-dihydroxyheptanoic acids are the (4*R*)- and (4*S*)-4,5-isopropylidenedioxy-1-pentanols (Scheme **C**). The preparation of the (4*S*)-compound starting from glutamic acid[17] has been described but it is more conveniently obtained starting from the (2*R*)-2,3-*O*-isopropylideneglyceraldehydes via the Wittig–Horner reaction[18] and subsequent hydrogenation[19] and reduction.[17] The (4*R*)-4,5-isopropylidenedioxy-1-pentanol is accessible analogously.

Oxidation of the alcohols, condensation of the resultant enantiomeric aldehydes (*S*)-**12**[20] and (*R*)-**12** with benzyl 2-*tert*-butoxycarbonylamino-2-(dimethoxyphosphoryl)-acetate, and subsequent hydrogenation gave all four stereoisomers **14** depending upon the configuration of the starting aldehydes (*S*)-**8**, (*R*)-**8** and the catalyst (*R,R*)-**1**. It was not possible to check the diastereoselectivity of this hydrogenation process directly by HPLC. Acid hydrolysis of the products gave rise to the free benzyl 2-amino-6,7-dihydroxyheptanoates which were acylated to furnish the tripalmitoyl compounds **15**. Hydrogenolysis of the latter produced the 2-palmitoylamino-6,7-dipalmitoyloxyheptanoic acids **16**, which can be used for peptide synthesis.

The purity of the compounds **15** was checked by HPLC. The four diastereoisomers were easily separated, but the formation of diastereoisomers in the hydrogenation reaction could not be detected. This indicates that the hydrogenation process was completely diastereoselective.

The tripalmitoyl derivative of (2*S*)-2-amino-7-hydroxy-5-(hydroxymethyl)heptanoic acid has been prepared in a similar manner (Scheme **D**). The isopropylidenedioxyaldehyde **19** was synthesized from diethyl benzyloxypropylmalonate (**17**)[21] in a clean reaction sequence (**17**→**19**). Condensation of **19** with benzyl 2-*tert*-butoxycarbonylamino-2-(dimethoxyphosphoryl)acetate and subsequent enantioselective hydrogenation with (*R,R*)-**1** yielded the benzyl Boc-amino-isopropylidenedioxyalkanoate **21**, which was transformed into the (*S*)-2-palmitoylamino-7-palmitoyloxy-6-(palmitoyloxymethyl)heptanoic acid (**23**).

The optical purities of compounds **21**, **22**, and **23** could not be checked by HPLC on chiral columns; however, the results of analogous hydrogenations with (*R,R*)-**1** suggest that the diasteroisomeric excess of **23** is in the range 95–98%.



Scheme **D**

The ^{1}H- and ^{13}C-NMR spectra were recorded on a Bruker WP 80 (80 MHz) and a Bruker CXP 300 (300 MHz) respectively. $[\alpha]_D$ values were determined with a Perkin-Elmer 241 polarimeter. Melting points (Reichert microscope) are uncorrected. TLC was done on silica gel (Merck Silica 60 F$_{254}$ sheets) and medium pressure column chromatography used Merck LiChroprep Si 60 (15–25 μ). HPLC was done with a LKB Instrument and a silica gel column (Merck Hibar, LiChrosorb Si 60 5 μ).

(*S*)- or (*R*)-4,5-(Isopropylidenedioxy)pentanal (*S*)-12[20] and (*R*)-12; General Procedure:

Dichloroacetic acid (2.92 g, 22.6 mmol) is added dropwise to a solution of (4*S*)- or (4*R*)-4,5-isopropylidenedioxy-1-pentanol[17] (7.25 g, 45.3 mmol) and DCC (10.65 g, 51.8 mmol) in benzene/DMSO (220 mL, 1:1). After stirring for 5 h at r.t. the reaction mixture is treated with 1 N aq NaHCO$_3$ (35 mL) and Et$_2$O (100 mL). The organic layer is separated and the water phase extracted with Et$_2$O (5 × 50 mL). The combined organic layers are dried (MgSO$_4$), evaporated and Kugelrohr distilled to give the aldehydes (*S*)-**12** or (*R*)-**12**; yield: 6.5 g (90%); bp 35°C/0.1 mbar; (*S*)-**12**: $[\alpha]_D^{20}$ −0.95° (*c* = 1.42, CH$_2$Cl$_2$); (*R*)-**12**: $[\alpha]_D^{20}$ 1.00 (*c* = 1.30, CH$_2$Cl$_2$).

C$_8$H$_{14}$O$_3$	calc.	C 60.74	H 8.91
(158.2)	(*S*)-**12**:found	60.36	8.82
	(*R*)-**12**:found	60.42	8.87

(*S*)-**12** or (*R*)-**12** (identical ^{1}H-NMR spectra). ^{1}H-NMR (80 MHz, CDCl$_3$/TMS): δ = 1.33 (s, 3 H), 1.40 (s, 3 H), 1.93 (m, 2 H), 2.62 (t, 2 H, *J* = 7 Hz), 3.57 (m, 1 H), 4.10 (m, 2 H), 9.80 (br s, 1 H).

5-(3-Benzyloxypropyl)-2,2-dimethyl-1,3-dioxane (18):

5-Benzyloxy-2-hydroxymethyl-1-pentanol:

To a suspension of LiAlH$_4$ (12.0 g; 0.32 mol) in Et$_2$O (400 mL) under argon, ethyl 5-benzyloxy-2-(ethoxycarbonyl)pentaneoate[21] **17** (65 g, 0.21 mol) dissolved in Et$_2$O (100 mL) is added slowly at 0°C. The mixture is allowed to come to r.t., refluxed for 5 h and finally hydrolyzed with 2N HCl (320 mL). The organic layer is separated, the aqueous layer extracted with Et$_2$O (3 × 100 mL) and the combined organic layers are dried (MgSO$_4$) filtered and evaporated *in vacuo*. Distillation of the residue (140°C/0.1 mbar) gives 5-benzyloxy-2-hydroxymethyl-1-pentanol which can be recrystallized from Et$_2$O/hexane; yield: 38.8 g (82%); mp 46°C.

$C_{13}H_{20}O_3$	calc.	C 69.61	H 8.99
(224.3)	found	69.86	9.05

^{1}H-NMR (80 MHz, $CDCl_3$/TMS): δ = 1.9–1.1 (m, 5H), 2.97 (br s, 2H), 3.47 (t, 2H, J = 6 Hz), 3.65 (m, 4H), 4.48 (s, 2H), 7.32 (s, 5H).

5-(3-Benzyloxypropyl)-2,2-dimethyl-1,3-dioxane (**18**):

5-Benzyloxy-2-hydroxymethyl-1-pentanol (22.4 g, 0.1 mol) dissolved in 2,2-dimethoxypropane (100 g, 0.9 mol) is stirred in presence of a catalytic amount of TsOH at r.t. over 12 h. After addition of Na_2CO_3 (5 g, 47 mol) the mixture is evaporated *in vacuo*. The solution of the residue in CH_2Cl_2 (300 mL) is washed with 1 N aq $NaHCO_3$, dried ($MgSO_4$), filtered and evaporated. Kugelrohr distillation of the residue gives the desired ketal **18**; yield: 23.5 g (89%); bp 70°C/0.05 mbar.

$C_{16}H_{24}O_3$	calc.	C 72.69	H 9.15
(264.4)	found	72.03	8.99

^{1}H-NMR (80 MHz, $CDCl_3$/TMS): δ = 1.42 (s, 6H), 2.1–1.1 (m, 5H), 3.47 (t, 2H, J = 6 Hz), 4.05–3.40 (m, 4H), 4.5 (s, 2H), 7.36 (s, 5H).

5-Formylethyl-2,2-dimethyl-1,3-dioxane (19):

5-(3-Hydroxypropyl)-2,2-dimethyl-1,3-dioxane:

A solution of 5-(3-benzyloxypropyl)-2,2-dimethyl-1,3-dioxane (**18**, 8.6 g, 32 mmol) in AcOH (50 mL) is hydrogenated (3 bar) in presence of Pd–C (0.5 g, 5%) for 3 h. The reaction mixture is filtered, evaporated *in vacuo*, twice diluted with toluene (2 × 30 mL) and evaporated. The residue is dissolved in CH_2Cl_2 (100 mL) and the solution is washed with 1 N aq $KHCO_3$, dried ($MgSO_4$) and evaporated. The crude product is purified by Kugelrohr distillation; yield: 4.1 g (72%); bp 65–70°C/0.04 mbar.

Table 1. Double Asymmetric Induction in the Hydrogenation of **6**[a]

Entry	Catalyst	Product[a] (2*S*,4*S*,5*S*)-**7**/(2*R*,4*S*,5*S*)-**7**	de (%)
1	[Rh (1.5 COD) (*R*,*R*)-DIPAMP]$^+$$BF_4^-$ [b] (*R*,*R*)-**1**	97.2/2.8	94.4
2	[Rh(1.5 COD) (*S*,*S*)-DIPAMP]$^+$$BF_4^-$ [c] (*S*,*S*)-**1**	21.5/78.5	57
3	[Rh (1.5 COD) (R)-prophos]$^+$$Cl^-$ [d] **2**	92.5/7.5	85
4	[Rh (1.5 COD) (*N*-benzyl-3,4-bis(diphenylphosphino)-pyrrolidine)]$^+$$BF_4^-$ **3**	83.8/16.2	67.6
5	[Rh (diphos)]$_2^+$ $(BF_4)_2^-$ [e] **4**	65.7/34.3	31.4
6	5% Rh/aluminum oxide/H_2, 1 bar	47/53	6
7	5% Rh/aluminum oxide/H_2, 3 bar	40/60	20

[a] a HPLC of compounds **7** was done with a Merck Hibar column (LiChrosorb Si 60, 5 μ); solvent: hexane/EtOAc 8 : 2. (2*S*,4*S*,5*S*)-**7**: R_t = 10.4 min, (2*R*,4*S*,5*S*)-**7**: R_t = 9.3 min.

[b] Ligand: (*R*,*R*)-1,2-ethanediylbis[(*o*-methoxyphenyl)phenylphosphine].

[c] Ligand: (*S*,*S*)-1,2-ethanediylbis[(*o*-methoxyphenyl)phenylphosphine].

[d] Ligand: (*R*)-(+)-1,2-bis(diphenylphosphine)propane.

[e] Ligand: 1,2-ethanediylbis(diphenylphosphine).

Table 2. Didehydroamino acids **6**, **9**, **13**, **20** Prepared

Product	Yield (%)	Rf (hexane/ EtOAc)	$[\alpha]_D^{26}$ (*c*, solvent)	Molecular Formula[a]	^{1}H-NMR (80 MHz, $CDCl_3$/TMS) δ, J(Hz)
(*Z*)-**6**	87	0.31 (7 : 3)	+20.4 (1.4, $CHCl_3$)	$C_{25}H_{29}NO_7$ (455.5)	1.40 (s, 6H), 3.58–3.73 (m, 2H), 3.76 (s, 3H), 3.90–4.15 (m, 1H), 4.61 (s, 2H), 4.73 (dd, 1H, J_1 = 7.5, J_2 = 7), 5.15 (s, 2H), 6.32 (d, 1H, J = 7.5), 7.27 (br s, 1H), 7.35 (s, 5H), 7.38 (s, 5H)
(*S*,*Z*)-**9**	81	0.63 (7 : 3)	−1.3 (0.3, $CHCl_3$)	$C_{17}H_{21}NO_6$ (335.4)	(*S*,*Z*)-**9**/(*R*,*Z*)-**9**: 1.35 (s, 3H), 1.45 (s, 3H), 3.77 (s, 3H), 4.30 (dd, 1H, J_1 = 8, J_2 = 7), 4.82 (dd, 1H, J_1 = 8, J_2 = 7), 4.87 (dt, 1H, J_1 = 8, J_2 = 6.5), 5.15 (s, 2H), 6.50 (d, 1H, J = 8), 6.88 (br s, 1H), 7.38 (s, 5H)
(*R*,*Z*)-**9**	81	0.63 (7 : 3)	+1.4 (0.5, $CHCl_3$)		
(*S*,*E*)-**13**	8	0.5 (8 : 2)	+5.2 (0.93, CH_2Cl_2)	$C_{22}H_{31}NO_6$ (405.5)	(*S*,*E*)-**13**/(*R*,*E*)-**13**: 1.30 (s, 3H), 1.35 (s, 3H), 1.45 (s, 9H), 1.70 (m, 4H), 2.62 (m, 2H), 3.45 (m, 1H), 4.0 (m, 2H), 5.27 (s, 2H), 6.65 (br s, 1H), 6.72 (t, 1H, J = 8), 7.40 (s, 5H)
(*R*,*E*)-**13**	8	0.5 (8 : 2)	−5.0 (0.82, CH_2Cl_2)		
(*S*,*Z*)-**13**	68	0.38 (8 : 2)	+15.2 (1.02, CH_2Cl_2)		(*S*,*Z*)-**13**/(*R*,*Z*)-**13**: 1.35 (s, 3H), 1.40 (s, 3H), 1.45 (s, 9H), 1.85 (m, 4H), 2.35 (m, 2H), 3.52 (m, 1H), 4.07 (m, 2H), 5.22 (s, 2H), 6.45 (br s, 1H), 6.55 (t, 1H, J = 8), 7.37 (s, 5H)
(*R*,*Z*)-**13**	68	0.38 (8 : 2)	−14.5 (0.4, CH_2Cl_2)		
(*Z*)-**20**	76	0.54 (7 : 3)	–	$C_{23}H_{33}NO_6$ (419.5)	1.42 (s, 6H), 1.43 (s, 9H), 1.5–2.05 (m, 3H), 2.25 (m, 1H), 3.40–4.05 (m, 4H), 5.25 (s, 2H), 6.07 (br s, 1H), 6.61 (t, 1H, J = 7), 7.42 (s, 5H)

[a] Satisfactory microanalyses obtained: C ±0.19, H ±0.12, N ±0.26.

Table 3. Amino Acid Esters **7**, **10**, **14**, **21** Prepared

Product	Yield (%)	R_f (hexane/EtOAc)	$[\alpha]_D^{20}$ (c, $CHCl_3$)	Molecular Formula[a]	^1H-NMR ($CDCl_3$/TMS) δ, J(Hz)	^{13}C-NMR (75MHz, $CDCl_3$/TMS) δ
(2*S*,4*S*,5*S*)-**7**	94	0.28 (7:3)	−8.1 (2.1)	$C_{25}H_{31}NO_7$ (457.5)	1.36 (s, 3H), 1.39 (s, 3H), 2.0 (m, 1H), 2.15 (m, 1H), 3.48 (dd, 1H, $J_1 = 4.6$, $J_2 = 10.2$), 3.59 (dd, 1H, $J_1 = 5.1$, $J_2 = 10$), 3.71 (s, 3H), 3.85 (m, 2H), 4.49–4.59 (m, 1H), 4.55 (s, 2H), 5.09 (d, 1H, J = 17.7), 5.15 (d, 1H, J = 17.7), 5.69 (br d, 1H, J = 8.2), 7.25–7.40 (m, 1H)[b]	
(2*R*,4*S*,5*S*)-**7**	94	0.29 (7:3)	−23.2 (0.79)		1.34 (s, 3H), 1.35 (s, 3H), 2.02 (m, 1H), 2.19 (m, 1H), 3.49 (dd, 1H, $J_1 = 4.7$, $J_2 = 10.2$), 3.59 (dd, 1H, $J_1 = 5$, $J_2 = 10.2$), 3.72 (s, 3H), 3.86 (m, 2H), 4.47 (m, 1H), 4.55 (s, 2H), 5.10 (s, 2H), 5.69 (br d, 1H, J = 6.6), 7.25–7.40 (m, 10H)[b]	
(2*S*,4*S*)-**10**	93	0.15 (4:6)	−31.5 (0.72)	$C_{17}H_{23}NO_6$ (337.4)	(2*S*,4*S*)-**10** or (2*R*,4*R*)-**10**: 1.30 (s, 3H), 1.37 (s, 3H), 1.85–2.23 (m, 2H), 3.74 (s, 3H), 3.40–3.83 (m, 1H), 3.90–4.30 (m, 2H), 4.30–4.70 (m, 1H), 5.14 (s, 2H), 5.75 (br d, 1H, J = 6.5), 7.39 (s, 5H)[c] (2*S*,4*R*)-**10** or (2*R*,4*S*)-**10**: 1.33 (s, 3H), 1.41 (s, 3H), 2.02 (m, 2H), 3.62 (m, 1H), 3.77 (s, 3H), 3.90–4.35 (m, 2H), 4.55 (m, 1H), 5.28 (s, 2H), 5.80 (br d, 1H, J = 8), 7.24 (s, 5H)[c]	25.61, 26.93, 35.71, 52.34, 52.54, 67.00, 69.27, 73.08, 109.60, 128.10, 128.15, 128.35, 128.51, 136.37, 156.04, 172.34 25.62, 26.93, 35.72, 52.35, 52.45, 67.00, 69.28, 73.09, 109.61, 128.10, 128.16, 128.29, 128.52, 128.66, 136.38, 156.04, 172.35
(2*R*,4*S*)-**10**	93	0.15 (4:6)	+17.9 (0.24)			
(2*S*,4*R*)-**10**	93	0.15 (4:6)	−17.2 (0.83)			
(2*R*,4*R*)-**10**	93	0.15 (4:6)	+32.9 (1.09)			
(2*S*,6*S*)-**14**	95	0.7 (7:3)	+1.5 (1.05)	$C_{22}H_{33}NO_6$ (467.5)	(2*S*,6*S*)-**14** or (2*R*,6*R*)-**14**: 1.33 (s, 3H), 1.38 (s, 3H), 1.43 (s, 9H), 1.40–1.70 (m, 5H), 1.83 (m, 1H), 3.43 (m, 1H), 3.98 (m, 2H), 4.34 (m, 1H), 5.05 (d, 1H, J = 7.7), 5.11 (d, 1H, J = 12.3), 5.21 (d, 1H, J = 12.3), 7.35 (s, 5H)[b] (2*S*,6*R*)-**14** or (2*R*,6*S*)-**14**: 1.33 (s, 3H), 1.38 (s, 3H), 1.43 (s, 9H), 1.40–1.70 (m, 5H), 1.83 (m, 1H), 3.44 (m, 1H), 4.01 (m, 2H), 4.34 (m, 1H), 5.02 (d, 1H, J = 7.7), 5.12 (d, 1H, J = 12.3), 5.21 (d, 1H, J = 12.3), 7.35 (s, 5H)[b]	21.69, 25.72, 26.94, 28.32, 32.69, 33.04, 53.39, 67.02, 69.36, 75.79, 79.92, 108.77, 128.32, 128.45, 128.61, 135.44, 155.39, 172.64 21.59, 25.71, 26.92, 28.31, 32.55, 32.98, 53.42, 67.02, 69.30, 75.66, 79.94, 108.78, 128.34, 128.45, 128.61, 135.44, 155.35, 172.61
(2*R*,6*S*)-**14**	95	0.7 (7:3)	+12.1 (0.98)			
(2*S*,6*R*)-**14**	95	0.7 (7:3)	−12.4 (0.87)			
(2*R*,6*R*)-**14**	95	0.7 (7:3)	−1.5 (1.39)			
21	96	0.66 (1:1)	+21.4 (0.3)	$C_{23}H_{33}NO_6$ (421.0)	1.40 (s, 3H), 1.47 (s, 12H), 1.10–2.40 (m, 7H), 3.35–4.10 (m, 4H), 4.35 (m, 1H), 5.10 (brd, 1H, J = 7), 5.25 (m, 2H), 7.45 (s, 5H)	

[a] Satisfactory microanalyses obtained: C ±0.37, H ±0.13, N ±0.18. [b] 300 MHz. [c] 80 MHz.

Table 4. Lactones **11** Prepared

Product	Yield (%)	R_f (EtOAc)	mp[a] (°C)	$[\alpha]_D^{20}$ (c, MeOH)	Molecular Formula[b]	^1H-NMR (300 MHz, DMSO-d_6/TMS) δ, J(Hz)
(2*S*,4*S*)-**11**	85	0.43	118	+6.6 (0.24)	$C_{13}H_{15}NO_5$ (265.3)	(2*S*,4*S*)-**11** or (2*R*,4*R*)-**11**: 2.20–2.38 (m, 2H), 3.45–3.65 (m, 2H), 4.5 (dd, 1H, $J_1 = 18.6$, $J_2 = 10.0$), 4.59 (dd, 1H, $J_1 = 8.8$, $J_2 = 2.2$), 5.05 (s, 2H), 5.19 (t, 1H, J = 5.2), 7.30–7.40 (m, 5H), 7.79 (d, 1H, J = 8.5) (2*S*,4*R*)-**11** or (2*R*,4*S*)-**11**: 1.94 (dd, 1H, $J_1 = 22.6$, $J_2 = 11.8$), 2.31–2.40 (m, 1H), 3.45–3.64 (m, 2H), 4.41–4.50 (m, 1H), 4.55 (dt, 1H, $J_1 = 11.8$, $J_2 = 8.8$), 5.05 (s, 2H), 5.11 (t, 1H, J = 5.7), 7.29–7.40 (m, 5H), 7.80 (d, 1H, J = 8.6)
(2*R*,4*S*)-**11**	90	0.5	121	+47.9 (0.52)		
(2*S*,4*R*)-**11**	91	0.5	123	−50.9 (0.48)		
(2*R*,4*R*)-**11**	89	0.43	116	−7.1 (0.37)		

[a] Solvent: Et_2O/hexane.

[b] Satisfactory microanalyses obtained: C ±0.41, H ±0.10, N ±0.17.

$C_9H_{18}O_3$	calc.	C 62.04	H 10.41
(174.2)	found	61.85	10.14

^{1}H-NMR (80 MHz, $CDCl_3$/TMS) δ = 1.42 (s, 6 H), 2.0–1.1 (m, 5 H), 2.1 (s, 1 H), 4.05–3.45 (m, 6 H).

5-Formylethyl-2,2-dimethyl-1,3-dioxane (**19**):

To a solution of 5-(3-hydroxypropyl)-2,2-dimethyl-1,3-dioxane (**19**, 4 g, 23 mmol) in CH_2Cl_2 (70 mL), pyridinium chlorochromate (7.5 g, 34.8 mmol) and NaOAc (1 g, 12.2 mmol) are added and the heterogeneous reaction mixture is stirred at r.t. for 2 h. Filtration on silica gel (hexane/EtOAc 7:3) and Kugelrohr distillation gives rise to aldehyde **19**; yield: 2.26 g (57 %); bp 50 °C/0.05 mbar.

$C_9H_{16}O_3$	calc.	C 62.77	H 9.36
(172.2)	found	62.41	9.18

^{1}H-NMR (80 MHz, $CDCl_3$/TMS) δ = 1.42 (s, 6 H), 1.75–1.5 (m, 3 H), 2.48 (t, 2 H, J = 7 Hz), 4.05–3.45 (m, 4 H), 9.75 (s, 1 H).

Preparation of Didehydroamino Acids 6, (*S,Z*)-9, (*R,Z*)-9, (*S,Z*)-13, (*R,Z*)-13 and 20; General Procedure:

To a suspension of KOBu-*t* (36 mmol) in CH_2Cl_2 (20 mL) at −70 °C is added methyl 2-benzyloxycarbonylamino-2-(dimethoxyphosphoryl)acetate (36 mmol) for the formation of **6**, and **9** or benzyl 2-*tert*-butoxycarbonylamino-2-(dimethoxyphosphoryl) acetate (36 mmol) for the formation of **13**, and **20**. After 15 min the corresponding aldehyde **5**[8], (*S*)-**8**[9], (*R*)-**8**, (*S*)-**12**, (*R*)-**12** or **19** is added. The mixture is kept for 0.5 h at −70 °C, then slowly warmed up to 35 °C over 4.5 h and evaporated *in vacuo*. The solution of the residue in EtOAc is washed with cold water, filtered and evaporated. Chromatography on silica gel with petroleum ether/EtOAc gives the product (Table 2).

Table 5. Palmitoyl Amino Acid Esters **15** and **22** Prepared

Product	Yield (%)	R_f[a]	mp[b] (°C)	$[\alpha]_D^{20}$ (*c*, $CHCl_3$)	Molecular Formula[c]	^{1}H-NMR (300 MHz, $CDCl_3$/TMS) δ, *J*(Hz)
(2*S*,6*S*)-**15**	70	0.77	54	−0.2 (0.58)	$C_{62}H_{111}NO_7$ (892.4)	(2*S*,6*S*)-**15** or (2*R*,6*R*)-**15**: 0.88 (t, 9H, *J* = 6.5), 1.20–1.5 (m, 78H), 1.50–1.75 (m, 5H), 1.85 (m, 1H), 2.17–2.30 (m, 6H), 3.97 (dd, 1H, J_1 = 6.7, J_2 = 11.9), 4.15 (dd, 1H, J_1 = 4.1, J_2 = 11.9), 4.62 (dt, 1H, J_1 = 5.2, J_2 = 7.8), 5.01 (m, 1H), 5.13 (d, 1H, *J* = 12.2), 5.19 (d, 1H, *J* = 12.2), 5.97 (d, 1H, *J* = 7.8), 7.35 (m, 5H) (2*R*,6*S*)-**15** or (2*S*,6*R*)-**15**: 0.88 (t, 6H, *J* = 6.5), 1.18–1.5 (m, 78H), 1.5–1.70 (m, 5H), 1.85 (m, 1H), 2.18–2.30 (m, 6H), 3.95 (dd, 1H, J_1 = 6.7, J_2 = 11.9), 4.17 (dd, 1H, J_1 = 3.4, J_2 = 11.9), 4.64 (dt, 1H, J_1 = 5.6, J_2 = 7.9), 5.0 (m, 1H), 5.13 (d, 1H, *J* = 12.2), 5.19 (d, 1H, *J* = 12.2), 5.97 (d, 1H, *J* = 7.9), 7.35 (m, 5H)
(2*R*,6*S*)-**15**	70	0.72	76	−1.2 (0.98)		
(2*S*,6*R*)-**15**	70	0.72	70–71	+1.3 (0.81)		
(2*R*,6*R*)-**15**	70	0.77	51	+0.2 (0.80)		
22	72	0.75	60.5	+4.7 (0.25)	$C_{63}H_{103}NO_7$ (996.6)	0.88 (t, 9H, *J* = 6.5), 1.15–1.38 (m, 78H), 1.55–1.70 (m, 6H), 1.87 (m, 1H), 2.21 (t, 2H, *J* = 7.5), 2.28 (t, 4H, *J* = 7.5), 3.92–4.05 (m, 4H), 4.66 (dt, 1H, J_1 = 5.4, J_2 = 7.2), 5.13 (d, 1H, *J* = 12.2), 5.20 (d, 1H, *J* = 12.2), 5.98 (d, 1H, *J* = 8), 7.35 (s, 5H)

[a] Hexane/EtOAc, 8:2.

[b] Acetone.

[c] Satisfactory microanalyses obtained: C ±0.22, H ±0.23, N ±0.23.

Table 6. Palmitoyl Amino Acids **16** and **23** Prepared

Product	Yield (%)	R_f[a]	mp[b] (°C)	$[\alpha]_D^{20}$ (*c*, $CHCl_3$)	Molecular Formula[c]	^{1}H-NMR (300 MHz, $CDCl_3$/TMS) δ, *J*(Hz)
(2*S*,6*S*)-**16**	90	0.4	74	+6.0 (0.41)	$C_{55}H_{105}NO_7$ (892.4)	(2*S*,6*S*)-**16** or (2*R*,6*R*)-**16**: 0.88 (t, 9H, *J* = 6.5), 1.15–1.40 (m, 78H), 1.40–1.80 (m, 5H), 1.93 (m, 1H), 2.22–2.33 (m, 6H), 4.04 (dd, 1H, J_1 = 6.9, J_2 = 11.8), 4.19 (dd, 1H, J_1 = 3.4, J_2 = 11.8), 4.49 (m, 1H), 5.10 (m, 1H), 6.21 (d, 1H, *J* = 7), 7.1 (br s, 1H) (2*R*,6*S*)-**16** or (2*S*,6*R*)-**16**: 0.88 (t, 9H, *J* = 6.5), 1.15–1.50 (m, 78H), 1.40–1.78 (m, 5H), 1.92 (m, 1H), 2.22–2.40 (m, 6H), 4.0 (dd, 1H, J_1 = 6.8, J_2 = 12.0), 4.24 (dd, 1H, J_1 = 3.3, J_2 = 12.0), 4.49 (m, 1H), 5.06 (m, 1H), 6.08 (d, 1H, *J* = 7.3), 7.1 (br s, 1H)
(2*R*,6*S*)-**16**	90	0.4	72	−6.2 (0.04)		
(2*S*,6*R*)-**16**	90	0.4	71	+5.9 (0.43)		
(2*R*,6*R*)-**16**	90	0.4	76	−6.1 (0.55)		
23	91	0.45	64	+15.6 (0.25)	$C_{56}H_{107}NO_7$ (906.5)	0.88 (t, 9H, *J* = 6.5), 1.15–1.5 (m, 78H), 1.52–1.82 (m, 7H), 2.25 (t, 2H, *J* = 7.5), 2.30 (t, 4H, *J* = 7.5), 3.96–4.12 (m, 4H), 4.58 (m, 1H), 6.23 (d, 1H, *J* = 7.4), 6.4–7.1 (br s, 1H)

[a] Hexane/EtOAc, 3:7.

[b] Acetone.

[c] Satisfactory microanalyses obtained: C ±0.23, H ±0.07, N ±0.03.

Preparation of Amino Acid Esters 7, 10, 14, and 21 by Diastereoselective Hydrogenation with (*R*,*R*)-1 or (*S*,*S*)-1; General Procedure:

A solution of one of the didehydroamino acid esters (**6**, **9**, **13** or **20**) (4 mmol) in EtOH (30 mL) and (*R*,*R*)-**1** (15 mg) for the formation of (αS)-amino acids; [(*S*,*S*)-**1** was used for the formation of (α*R*)-amino acids] is hydrogenated (3 bar) at r.t. over 3 d. The reaction mixture is evaporated and the residue chromatographed on silica gel (petroleum ether/EtOAc). Hydrogenation of didehydroamino acid **6** with the catalysts **2** (prepared *in situ*) and **4** are performed in the same way. Hydrogenation of **6** with catalyst **3** is performed at 50 bar H_2 pressure (Table 3).

Preparation of the Diastereoisomeric Mixtures of Amino Acid Esters (2*S*,4*S*)-10/(2*R*,4*S*)-10 and (2*S*,4*R*)-10/(2*R*,4*R*)-10; General Procedure:

A solution of one of the didehydroamino acid esters [(*S*,*Z*)-**9** or (*R*,*Z*)-**9**] (10 mmol) in MeOH (50 mL) is hydrogenated at 3 bar in the presence of Pd–C (1 g, 5 %) over 12 h. When the reaction is complete (DC control), the catalyst is filtered off and the filtrate is evaporated *in vacuo*. The residue is dissolved in CH_2Cl_2 (20 mL) and pyridine (20 mmol) and benzyl chloroformate (15 mmol) are added. After 8 h the reaction mixture is evaporated *in vacuo*, the residue dissolved in EtOAc (50 mL) and washed successively with 1 N $KHSO_4$ and 1 N $NaHCO_3$ solutions. The organic layer is dried ($MgSO_4$), filtered and evaporated. Purification of the residue by silica gel chromatography (EtOAc) gives the (α*S*,*R*) mixtures of amino acid esters in yields of 70 %.

Preparation of Lactones 11; General Procedure:

One of the optically pure amino acid esters (2*S*,4*S*)-**10**, (2*R*,4*S*)-**10**, (2*S*,4*R*)-**10** or (2*R*,4*R*)-**10** or one of the diastereoisomeric mixtures (2*S*,4*S*)-**10**/(2*R*,4*S*)-**10** or (2*S*,4*R*)-**10**/(2*R*,4*R*)-**10** is dissolved in dioxane (20 mL) containing 6N HCl (1 mL). After 3 h at r.t., dioxane is evaporated *in vacuo*, the residue diluted with water and extracted with $CHCl_3$ (3 × 10 mL). The combined organic layers are dried ($MgSO_4$), filtered and evaporated *in vacuo*. When the diastereoisomeric mixtures (2*S*,4*S*)-**10**/(2*R*,4*S*)-**10** or (2*S*,4*R*)-**10**/(2*R*,4*R*)-**10** are reacted, the resulting diastereoisomeric lactones (2*S*,4*S*)-**11**/(2*R*,4*S*)-**11** and (2*S*,4*R*)-**11**/(2*R*,4*R*)-**11** can be separated easily by MPLC on silica gel (EtOAc). All lactones **11** can be recrystallized from Et_2O/hexane (Table 4).

Preparation of the Palmitoyl Amino Acid Esters 15 and 22; General Procedure:

A solution of one of the amino acid esters (2*S*,6*S*)-**14**, (2*R*,6*S*)-**14**, (2*S*,6*R*)-**14**, (2*R*,6*R*)-**14** or **21** (4.17 mmol) in dioxane (10 mL) containing conc HCl (0.5 mL) is heated at 80 °C over a period of 5 h. After evaporation the residue is dried *in vacuo* to give the *N*,*O*-unprotected amino acid ester derivatives, the solutions of which in CH_2Cl_2 (20 mL) and pyridine (22 mmol) at 0 °C are treated with palmitinic acid chloride (14.5 mmol). The mixtures are allowed to react at r.t. overnight, washed with 2N H_2SO_4 (15 mL), dried ($MgSO_4$) and filtered through silica gel eluting with petroleum ether/EtOAc to give the tripalmitoyl derivatives (2*S*,6*S*)-**15**, (2*R*,6*S*)-**15**, (2*S*,6*R*)-**15**, (2*R*,6*R*)-**15** and **22**, which can be recrystallized from acetone (Table 5). In case of compounds **15** the diastereoisomeric purity for each synthesized isomer can be determined by HPLC chromatography on silica gel (Merck Hibar, LiChrosorb Si 60, 5 μ; EtOAc/hexane 9 : 1). (2*S*,6*S*) and (2*R*,6*R*): R_t = 13.06 min; (2*R*,6*S*) and (2*S*,6*R*): R_t = 13.57 min.

Preparation of the Palmitoyl Amino Acids 16 and 23; General Procedure:

One of the amino acid esters **15** or **22** (1 mmol), dissolved in dioxane (50 mL) is hydrogenated with Pd–C (100 mg, 5 %) at r.t. over 4 h. Filtration from the catalyst, evaporation and recrystallization from acetone yields the tripalmitoyl amino acids (2*S*,6*S*)-**16**, (2*R*,6*S*)-**16**, (2*S*,6*R*)-**16**, (2*R*,6*R*)-**16** or **23** (Table 6).

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