Pergamon

Tetrahedron, Vol. 53, No. 8, pp. 2823-2834, 1997

0040-4020/97 $17.00 + 0.00

PII: S0040-4020(97)00050-1

Barbier-Type Allylation of Chiral α-Aminoaldehydes : Dependence of the Stereochemical Outcome on Metal and Allylic Halide

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Abstract: The chiral β-hydroxy-α-aminoaldehydes of type 1 react smoothly with allyl-, 3,3-dimethylallyl bromide and 2-bromo-cyclohexene in the presence of tin or zinc dust to give the homoallylic alcohols of type **3**. For the first time it is shown that the diastereoselectivity in the Barbier reaction can be influenced by the choice of metal and / or allylic halide.

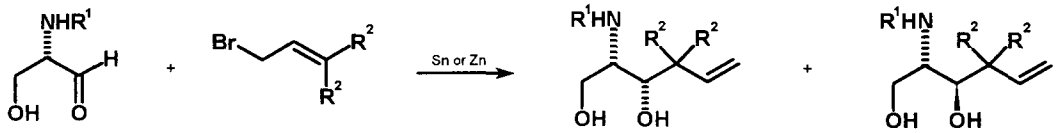
Chiral α-aminoaldehydes are important building blocks in the synthesis of various natural products and drugs.[1] However, their chemical and configurational instability hitherto prevented their widespread use in organic chemistry. Besides the many strategies developed to overcome these problems by using suitable protective groups,[2] the β-hydroxy-α-aminoaldehydes **1** (*L*-serinals)[3,4] proved to be stable and easy to handle due to their oligomeric or polymeric structure. So far, we have shown their potential in the synthesis of vinylogous amino acids[3] and peptides,[4] pseudopeptides containing an aminomethylene moiety, and chiral piperazinones.[5] Recently, we became interested in homoallylic alkohols of type **3**, which could be obtained from the β-hydroxy-α-aminoaldehydes of type **1** by addition of allylic compounds, and which are important building blocks in the synthesis of hydroxyethylene peptide isosteres.[6-8] Furthermore, the homoallylic alcohols provide access to amino-deoxy-sugars **7** which are components of naturally occurring antibiotics.[9-11]

Chain elongation at the aldehyde group of **1** raises the problem of racemisation / epimerisation as well as fragmentation of the β-hydroxy-α-aminoaldehydes. Our own experiences with organometallic reagents have shown that instead of yielding the expected products, fragmentation of the aldehydes occurred. As the β-hydroxy-α-aminoaldehydes we use are obtained in form of their hydrates, methods employing water sensitive organometallic reagents to allylate carbonyl compounds seemed to be unsuitable in this case.

The allylation of aldehydes and ketones with allylic halides in the presence of metals in aqueous solutions is known as a type of Barbier reaction,[12] the mechanism of which remains to be elucidated despite of its frequent use in organic synthesis.[13] Many different metals like tin, zinc or indium are employed in the reaction after activation by different protocols. From the known methods of activation we chose ultrasound, which was reported from Luche,[14] Whitesides[15] and Schmid,[16] as well as reaction in presence of ammonium chloride,[14] which both seemed to be most suitable for our purposes.

So far, no chiral α-aminoaldehydes were used in the reaction with allylic halides and tin or zinc. It was even claimed they couldn't be reacted at all.[17]

Here we now report the metal mediated allylation of β-hydroxy-α-aminoaldehydes **1** furnishing the homoallylic alcohols of type **3**. Furthermore, we report for the first time that the stereochemical outcome of the reaction is dependent on the metal as well as on the nature of the allylic halide.



1 **2** *syn* **3a-f** *anti*

Scheme 1 : R^1 = Boc, *N*-Cbz-Val, *N*-Cbz-Phe, R^2 = H, CH_3

The reaction of the α-aminoaldehydes **1** with allylic halides **2** proceeds smoothly to give the desired homoallylic alcohols **3** (Scheme 1) as a mixture of *syn* and *anti* diastereomers. When employing tin, independently from the reaction conditions used (aq. EtOH / ultrasound or sat. aq. NH_4Cl solution / THF), the major isomer found shows an *anti* relation between the amino group and the newly created hydroxy group (entries 1, 3, 5, 7, 9 and 11 in Table 1).

Most interestingly, the ratio of isomers can be changed in favor of the *syn* diastereomer by using 3,3-dimethylallyl bromide and zinc instead of tin (entries 2, 4, 8, 12 in Table 1).

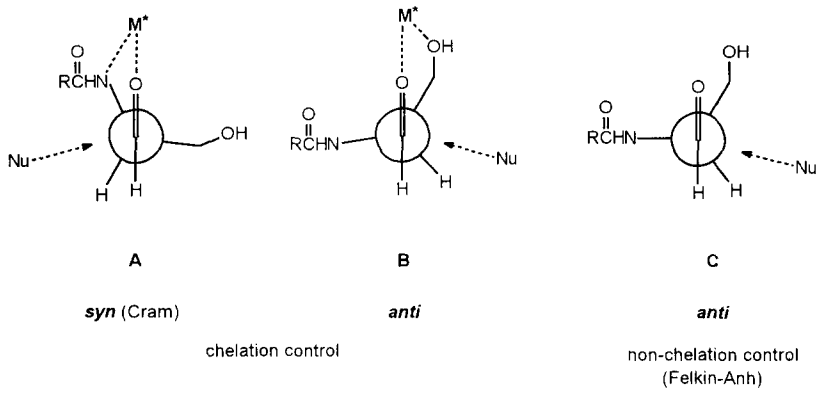
On the other hand, with unsubstituted allyl bromide this effect is not observed, suggesting also a strong influence of the nature of the allylic compound.

Table 1 : Allylation of α-Aminoaldehydes (see Scheme 1)

Entry	Compound	R^1	R^2	Metal	Yield (%)	anti : syn [a]
1	**3a**	*N*-Cbz-*L*-Val	CH_3	Sn	69	3 : 1
2	**3a**	*N*-Cbz-*L*-Val	CH_3	Zn	56	1 : 3
3	**3b**	*N*-Cbz-*D*-Val	CH_3	Sn	51	3.3 : 1
4	**3b**	*N*-Cbz-*D*-Val	CH_3	Zn	50	1 : 4
5	**3c**	*N*-Cbz-*L*-Val	H	Sn	78	1.5 : 1 [c]
6	**3c**	*N*-Cbz-*L*-Val	H	Zn	57	2 : 1 [c]
7	**3d**	*N*-Cbz-*L*-Phe	CH_3	Sn	44	6 : 1
8	**3d**	*N*-Cbz-*L*-Phe	CH_3	Zn	71	1 : 4
9	**3e**	*N*-Cbz-*L*-Phe	H	Sn	58	3 : 1 [c]
10	**3e**	*N*-Cbz-*L*-Phe	H	Zn	60	1.5 : 1 [c]
11	**3f**	Boc	CH_3	Sn	56	5 : 1
12	**3f**	Boc	CH_3	Zn	62	1 : 5
13	**5a**	*N*-Cbz-*L*-Val	[b]	Zn	46	1 : 1 [d]
14	**5b**	Boc	[b]	Sn	30	12 : 1
15	**5b**	Boc	[b]	Zn	35	4 : 1

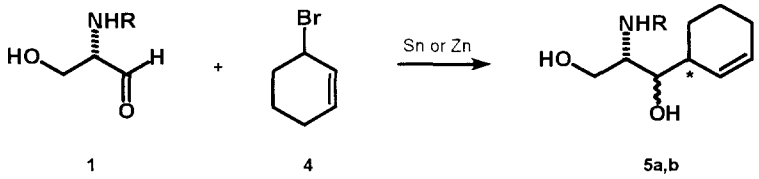
[a] the diastereomeric ratio was determined by ^{1}H NMR; [b] cyclohexenyl (Scheme 3); Boc = *tert.*-butyloxycarbonyl, Cbz = benzyloxycarbonyl; [c] separated after conversion to the dioxanes **6**; [d] not separated

The *syn* products obtained can be explained by a chelation-controlled mechanism of type A (Scheme 2), involving a 5-membered cyclic chelate (Cram). For the formation of the *anti* isomers two different reaction pathways can be considered: chelation control (type B) or sterical approach control (Felkin-Anh[18]) according to type C.



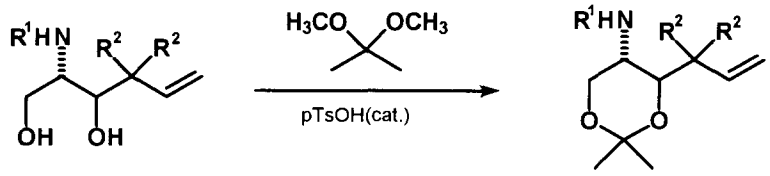
Scheme 2 : * M = metal surface; whether ionic or radical species are involved remains unclear.[12]

In accordance with the findings of Luche[19] only the formation of the γ-regioisomer was observed. Furthermore, reaction with the secondary cyclohexenyl bromide **4** was also accomplished using this protocol.[20] However, in case of the peptide aldehydes the reaction failed when using tin, whereas in the presence of zinc the desired product **5** was obtained. When employing cyclohexenyl bromide (entries 17 and 18) independently from the metal, formation of the *anti* isomer was favored, whereas with tin a significantly increased selectivity was found (12 : 1 vs. 4 : 1). The diastereomeric ratio was determined after removal of the second stereogenic center (* in Scheme 3) by catalytic hydrogenation. This observation again underlines the influence not only of the metal but also of the nature of the allylic halide.



Scheme 3 : R = *N*-Cbz-*L*-Val **5a**; R = Boc **5b**

The resulting configuration at the newly generated stereogenic center was determined after conversion of the homoallylic alcohols **3** to the 1,3-dioxans of type **6**, which was easily achieved by treatment with dimethoxy propane in the presence of a catalytic amount of p-TsOH. By measuring the $^{3}J_{HH}$ coupling constants the configuration at C-3 was unambiguously assigned.



3a-f6a-f

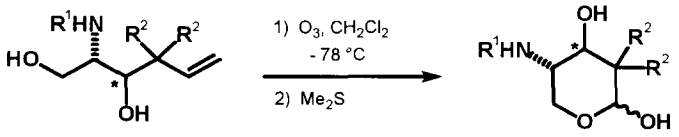
Scheme 4: R^1 = Boc, N-Cbz-Val, N-Cbz-Phe, R^2 = H, CH_3

In case of the peptide aldehydes, separation of the diastereomers was achieved by column chromatography, whereas in case of *N*-Boc-*L*-serinal the isomers were inseparable. Thus, the diastereomeric homoallylic alcohols **3f** were obtained after conversion into the corresponding dioxane derivatives **6** and subsequent acidic cleavage of the acetals.

The Barbier reaction proceeds without racemisation of the α-aminoaldehydes **1**. For the peptide aldehydes only simple sets of signals could be observed in the ^{1}H NMR spectra. Determination of the enantiomeric purity of the other compounds derived from *N*-Boc-*L*-serinal was achieved as exemplified for ***syn*-3f** by conversion to the known derivative ***syn*-3a** (removal of the Boc group with aq. HCl, followed by DCC / HOBT coupling with *N*-Cbz-*L*-Phe). The ^{1}H NMR spectra obtained was identical with the data of the reference sample, and again only simple sets of signals were found.

To investigate the influence of the stereogenic center of the amino acid in case of the peptide aldehydes, in entries 3 and 4 the peptide aldehyde derived from *D*-valine was employed, but showed to have no effect on the stereochemical outcome of the reaction.

The homoallylic alcohols **3**, after separation of the diastereomers, were transformed by ozonolysis to give the new 4-amino-4-deoxy-sugars of type 7 (Scheme 5), which is exemplified for several compounds in Table 2.



3 **7a-e**

Scheme 5

Table 2: Ozonolysis of Homoallylic Alcohols Affording 4-Amino-4-deoxy-sugars

Compound	R^1	R^2	C-3	Yield [%]
7a	*N*-Cbz-Val	CH_3	*R*	50
7b	*N*-Cbz-Val	CH_3	*S*	53
7c	*N*-Cbz-Phe	CH_3	*S*	41
7d	Boc	CH_3	*S*	31
7e	Boc	CH_3	*R*	40

In conclusion we have achieved the diastereoselective allylation of chiral β-hydroxy-α-aminoaldehydes with primary and secondary allylic bromides in aqueous media under mild conditions. To our knowledge, this represents the first case showing a dependence of the stereochemical outcome of a Barbier reaction on the metal as well as on the halide used. So far only the influence of the substrate and its substituents as well as the influence of the solvent on the course of the Barbier reaction was reported.[21]

EXPERIMENTAL

Unless otherwise noted, materials were obtained from commercial suppliers and were used without further purification. Solvents were purified in the usual way. The ultrasonic bath used was a commercial ultrasonic cleaning bath (Bandelin Sonorex RK 100). Melting points are uncorrected and were measured with a Büchi SMP 20 apparatus. Thin layer chromatography: Merck precoated TLC plates, silica gel 60; column chromatography: silica gel 60 (Merck, 40-63 μm). ^{1}H NMR: Bruker AC-200, Bruker AM-400. Mass spectrometry: A. E. I. MS-30 and MS-50, ion source 180°C, FAB: Kratos Concept 1H, matrix = m-nitrobenzylic alcohol. Elemental analyses were performed at the Institute of Organic Chemistry and Biochemistry, Bonn, microanalytical department.

General procedure for the allylation of α-amino aldehydes with allylic bromides and tin or zinc dust

The β-hydroxy-α-aminoaldehyde **(1)** (1 equivalent) was dissolved in a mixture of a saturated aqueous solution of ammonium chloride and THF (4 : 1). After addition of allylic bromide and zinc dust (2 equivalents each), the reaction mixture was stirred at room temperature until analysis by TLC (eluent - see below) indicated complete consumption of starting material. The residue was filtered off and the filtrate was extracted with diethyl ether. The collected organic layers were dried over magnesium sulphate and the oily residue obtained on removal of the solvent was subjected to chromatography to afford the product.

Alternatively the following procedure can be used: To a solution of the β-hydroxy-α-aminoaldehyde (1 equivalent) in aqueous ethanol, tin dust and allylic bromide was added (2 equivalents each). After 6 h of sonication at 0°C the reaction mixture has turned light yellow and was treated with 2 N hydrochloric acid and a saturated aqueous solution of ammonium chloride. The remaining residue was filtered off and the filtrate was then extracted with diethyl ether. The collected organic layers were dried over magnesium sulphate and the solvent was removed under reduced pressure. The remaining oily residue was purified by chromatography on silica gel to yield the product.

2-(S)-(*N*-Benzyloxycarbonylamino-*L*-valinoyl-amino)-4,4-dimethyl-1-hydroxy-3-(*R,S*)-hydroxy-hex-5-ene (3a)

***anti*-3a** : 500 mg of *N*-Cbz-*L*-ValSerCHO was treated with Sn dust according to the general procedure.
Yield: 420.7 mg (69 %) of an mixture of diastereomers (anti : syn = 3 : 1) from which ***anti*-3a** could be separated by column chromatography; colorless oil; R_f (anti) = 0.20 (CH_2Cl_2 : MeOH = 5 : 1);
^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.93 (d, 7 Hz, 3 H, 1′-CH_3); 0.97 (d, 7 Hz, 3 H, 1′-CH_3); 1.08 (s, 6 H, 2x CH_3); 2.13 (m, 1 H, 2′-CH); 3.04 (br, 1 H, OH); 3.16 (br, 1 H, OH); 3.49 (m, 1 H, 3-CH); 3.63 (m, 1 H, 2-CH); 3.96 (m, 3 H, 3′-CH, 1-CH_2); 4.98-5.17 (m, 4 H, $PhCH_2$, 6-CH_2); 5.40 (d, 8 Hz, 1 H, carbamate-NH); 5.94 (dd, 17.6 Hz, 11.2 Hz, 1 H, 5-CH); 6.87 (d, 8.6 Hz, 1 H, amide-NH); 7.30 (m, 5 H, Ph).
Analysis: $C_{21}H_{32}N_2O_5$ * 1/16 H_2O (393.36) calcd. (%): C 64.26, H 8.22, N 7.14; found (%): C 64.08, H 8.23, N 7.12.
MS (HR-MS): $C_{21}H_{32}N_2O_5$ $[M]^+$, calcd.: m/z = 392.2311, found: m/z = 392.2338.
***syn*-3a** : 500 mg of *N*-Cbz-*L*-ValSerCHO was treated with Zn dust according to the general procedure.
Yield: 340 mg (56 %) of a mixture of diastereomers (anti : syn = 1 : 3) from which ***syn*-3a** could be separated by column chromatography; colorless oil; R_f (syn) = 0.17 (CH_2Cl_2 : MeOH = 5 : 1);
^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.93 (d, 7 Hz, 3 H, 1′-CH_3); 0.97 (d, 7 Hz, 3 H, 1′-CH_3); 1.08 (s, 6 H, 2x CH_3); 2.15 (m, 1 H, 2′-CH); 2.84 (br, 1 H, OH); 2.99 (br, 1 H, OH); 3.59 (m, 1 H, 3-CH); 3.68-4.20 (m, 4 H, 2-CH, 3′-CH, 1-CH_2); 4.93-5.19 (m, 4 H, $PhCH_2$, 6-CH_2); 5.36 (d, 8 Hz, 1 H, carbamate-NH); 5.80 (dd, 17.6 Hz, 11.2 Hz, 1 H, 5-CH); 6.65 (d, 8.6 Hz, 1 H, amide-NH); 7.32 (m, 5 H, Ph).

2-(S)-(*N*-Benzyloxycarbonylamino-*D*-valinoyl-amino)-4,4-dimethyl-1-hydroxy-3-(*R,S*)-hydroxy-hex-5-ene (3b)

***anti*-3b** : 200 mg of *N*-Cbz-*D*-ValSerCHO was treated with Sn dust according to the general procedure.
Yield: 124 mg (51 %) of a colorless oil; R_f = 0.59 (petroleum ether : acetone = 3 : 2); ratio of diastereomers: anti : syn = 3.3 : 1 from which ***anti*-3b** could be separated by column chromatography;
^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.91 (d, 7 Hz, 3 H, 1′-CH_3); 0.95 (d, 7 Hz, 3 H, 1′-CH_3); 0.99 (s, 3 H, 4-CH_3); 1.00 (s, 3 H, 4-CH_3); 2.00-2.20 (m, 1 H, C<u>H</u>(CH_3)$_2$); 2.78 (m, 1 H); 3.42-3.79 (m, 2 H); 3.90 (dd, 8 Hz, 6.4 Hz, 1 H); 3.85-4.18 (m, 1 H); 4.90-5.17 (m, 4 H, $PhCH_2$ and CH=C<u>H</u>$_2$); 5.39 (d, 8 Hz, 1 H, carbamate-NH); 5.96 (dd, 17.6 Hz, 11.2 Hz, 1 H, C<u>H</u>=CH_2); 6.83 (d, 8 Hz, 1 H, amide-NH); 7.25-7.42 (m, 5 H, Ph).
MS (EI-MS): $C_{21}H_{33}N_2O_5$ $[M+H]^+$, calcd.: m/z = 393.2, found: m/z = 393.
***syn*-3b** : 500 mg of *N*-Cbz-*D*-ValSerCHO was treated with Zn dust according to the general procedure.
Yield: 121 mg (50 %); m.p. 123 °C; R_f = 0.53 (petroleum ether : acetone = 3 : 2); ratio of diastereomers: anti : syn = 1 : 4 from which ***syn*-3b** could be separated by column chromatography;
^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.91 (d, 7 Hz, 3 H, 1′-CH_3); 0.95 (d, 7 Hz, 3 H, 1′-CH_3); 0.99 (s, 3 H, 4-CH_3); 1.00 (s, 3 H, 4-CH_3); 2.00-2.20 (m, 1 H, C<u>H</u>(CH_3)$_2$); 2.78 (d, 3.2 Hz, 1 H); 3.42-3.79 (m, 2 H); 3.92 (dd, 8 Hz, 6.4 Hz, 1 H); 4.05-4.18 (m, 1 H); 4.90-5.17 (m, 4 H, $PhCH_2$ and CH=C<u>H</u>$_2$); 5.38 (d, 8 Hz, 1 H, carbamate-NH); 5.79 (dd, 17.6 Hz, 11.2 Hz, 1 H, C<u>H</u>=CH_2); 6.64 (d, 8.6 Hz, 1 H, amide-NH); 7.25-7.42 (m, 5 H, Ph).
Analysis: $C_{21}H_{32}N_2O_5$ * ¼ H_2O (396.73) calcd. (%) C 63.52, H 8.26 N 7.06; found (%) C 63.83, H 8.11, N 7.04.
MS (EI-MS): $C_{21}H_{33}N_2O_5$ $[M+H]^+$, calcd.: m/z = 393.2, found: m/z = 393.

2-(S)-(*N*-Benzyloxycarbonylamino-*L*-valinoyl-amino)-1-hydroxy-3-(*R,S*)-hydroxy-hex-5-ene (3c)

500 mg of *N*-Cbz-*L*-ValSerCHO was treated with Sn dust according to the general procedure.
Yield: 441.8 mg (78.3 %) of an mixture of diastereomers (anti : syn = 1.5 : 1); m.p. 116 °C; R_f = 0.29 (petroleum ether / acetone = 3 : 2);
^{1}H NMR (400 MHz, $CDCl_3$) (mixture of diastereomers): δ = 0.90-1.00 (m, 6 H, 2x 1′-CH_3); 2.09 (m, 1 H, 2′-CH); 2.20 (m, 1 H, 4-CH_2); 2.31 (m, 1 H, 4-CH_2); 3.00 (br, 1 H, OH); 3.20 (br, 1 H, OH); 3.65-3.82 (m, 2 H, 1-CH_2); 3.83-4.00 (m, 3 H, 3-CH, 2-CH, 3′-CH); 5.00-5.20 (m, 4 H, $PhCH_2$, 6-CH_2); 5.54 (d, 8.44 Hz, 0.4 H, carbamate-NH); 5.59 (d, 8.31 Hz, 0.6 H, carbamate-NH); 5.78 (m, 1 H, 5-CH); 6.78 (d, 8.56 Hz, 0.6 H, amide-NH); 6.97 (d, 7.82 Hz, 0.4 H, amide-NH); 7.32 (m, 5 H, Ph).
Analysis: $C_{19}H_{28}N_2O_5$ (364.20) calcd. (%): C 62.62, H 7.74, N 7.69; found (%): C 62.77, H 8.03, N 7.47.
MS (HR-MS): $C_{19}H_{28}N_2O_5$ $[M]^+$, calcd.: m/z = 364.1998, found: m/z = 364.2014.

2-(*S*)-(*N*-Benzyloxycarbonylamino-*L*-phenylalaninoyl-amino)-4,4-dimethyl-1-hydroxy-3-(*R,S*)-hydroxy-hex-5-ene (3d)

500 mg of *N*-Cbz-*L*-PheSerCHO was treated with Sn dust according to the general procedure.

Yield: 262 mg (44 %) of a mixture of diastereomers (anti : syn = 6 : 1); colorless oil; from which the diasteromers could be separated by column chromatography.

***syn*-3d** : R_f = 0.43 (petroleum ether : acetone = 3 : 2);

^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.88 (s, 6 H, CH_3); 2.65-3.17 (m, 5 H); 3.48-3.62 (m, 1 H); 3.63-3.79 (m, 1 H); 3.95-4.07 (m, 1 H); 4.26-4.39 (m, 1 H, 2´-CH); 4.88-5.38 (m, 5 H, $PhCH_2$, 6-CH_2, carbamate-NH); 5.60-5.78 (m, 1 H, 5-CH); 6.67 (d, 7.6 Hz, 1 H, amide-NH); 7.06-7.48 (m, 10 H, 2x Ph).

***anti*-3d** : R_f = 0.48 (petroleum ether : acetone = 3 : 2);

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.03 (s, 6 H, CH_3); 2.40-3.24 (m, 4 H, 1´-CH_2, 2x OH); 3.44-3.61 (m, 1 H; 3.77-3.98 (m, 2 H); 4.27-4.40 (m, 1 H, 2´-CH); 4.85-5.16 (m, 4 H, $PhCH_2$, 6-CH_2); 5.38 (d, 7.6 Hz, 1 H, carbamate-NH); 5.78-5.94 (m, 1 H, 5-CH); 6.55 (d, 8.2 Hz, 1 H, amide-NH); 7.06-7.48 (m, 10 H, 2x Ph).

MS (FAB-MS): $C_{25}H_{33}N_2O_5$ $[M+H]^+$, calcd.: m/z = 441.2389, found: m/z = 441.2.

2-(*S*)-(*N*-Benzyloxycarbonylamino-*L*-phenylalaninoyl-amino)-1-hydroxy-3-(*R,S*)-hydroxy-hex-5-ene (3e)

500 mg of *N*-Cbz-*L*-PheSerCHO was treated with Sn dust according to the general procedure.

Yield: 322.9 mg (58 %) of a mixture of diastereomers (anti : syn = 3 : 1); m.p. 109 °C; R_f (anti) = 0.59 and R_f (syn) = 0.53 (CH_2Cl_2 : MeOH = 5 : 1);

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.90 (m, 1 H, 1-CH_2); 2.17 (m, 1 H, 1-CH_2); 2.49 (m, 1 H, OH); 2.78 (m, 1 H, OH); 3.06 (m, 2 H, 1´-CH_2); 3.47-3.93 (m, 4 H, 2-CH, 3-CH, 4-CH_2); 4.39 (dd, 7.35 Hz, 1 H, 2´-CH); 5.05 (m, 2 H, $PhCH_2$); 4.95-5.15 (m, 2 H, 6-CH_2); 5.53 (d, 7.72 Hz, 1 H, carbamate-NH); 5.50-5.80 (m, 1 H, 5-CH); 6.57 (d, 7.91 Hz, 0.75 H, amide-NH); 6.64 (d, 8.64 Hz, 0.25 H, amide-NH); 7.10-7.40 (m, 10 H, 2x Ph).

Analysis: $C_{23}H_{28}N_2O_5$ * ¼ H_2O (416.70) calcd. (%): C 66.23, H 6.89, N 6.72; found (%): C 66.07, H 6.92, N 6.75.

MS (HR-MS): $C_{23}H_{28}N_2O_5$ $[M]^+$, calcd.: m/z = 412.1998, found: m/z = 412.1994.

2-(S)-*tert.*-Butyloxycarbonylamino-4,4-dimethyl-1-hydroxy-3-(*R,S*)-hydroxy-hex-5-ene (3f)

***anti*-3f :** 500 mg of *N*-Boc-*L*-serinal was treated with Sn dust according to the general procedure.

Yield: 164 mg (24%) of a colorless oil; R_f = 0.28 (petroleum ether / ethyl acetate = 1 : 1); mixture of diastereomers (anti : syn = 5 : 1) from which ***anti*-3f** could be separated after conversion to **6c** and subsequent cleavage of the acetal.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.08 (s, 3 H, CH_3); 1.09 (s, 3 H, CH_3); 1.42 (s, 9 H, $(CH_3)_3$); 2.52-2.80 (br, 2 H, OH); 3.48-3.57 (m, 1 H, 3-CH); 3.60-3.73 (m, 2 H, 1-CH_2); 3.93-4.07 (m, 1 H, 2-CH); 5.00-5.15 (m, 2 H, 6-CH_2); 5.28-5.39 (m, 1 H, NH); 5.94 (dd, 17 Hz, 11 Hz, 1 H, 5-CH).

Analysis: $C_{13}H_{26}NO_4$ * ¾ H_2O (272.69) calcd. (%): C 57.23, H 9.79, N 5.13; found (%): C 57.54, H 9.47, N 4.50.

MS (HR-MS): $C_{13}H_{27}NO_4$ $[M+H]^+$, calcd.: m/z = 260.1861, found: m/z = 260.1853.

***syn*-3f :** 500 mg of *N*-Boc-*L*-serinal was treated with Zn dust according to the general procedure.

Yield: 426 mg (62%) of a colorless oil; R_f = 0.28 (petroleum ether / ethyl acetate = 1 : 1); mixture of diastereomers (anti : syn = 1 : 5) from which ***syn*-3f** could be separated after conversion to **6c** and subsequent cleavage of the acetal.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.04 (s, 3 H, CH_3); 1.05 (s, 3 H, CH_3); 1.42 (s, 9 H, $(CH_3)_3$); 2.24-2.47 (br, 2 H, OH); 3.50-3.57 (m, 1 H, 3-CH); 3.64-3.70 (m, 2 H, 1-CH_2); 3.80-3.85 (m, 1 H, 2-CH); 4.80-5.11 (m, 2 H, 6-CH_2); 5.12-5.20 (m, 1 H, NH); 5.82 (dd, 17 Hz, 11 Hz, 1 H, 5-CH).

MS (HR-MS): $C_{13}H_{27}NO_4$ $[M+H]^+$, calcd.: m/z = 260.1861, found: m/z = 260.1853.

2-(*S*)-(*N*-Benzyloxycarbonylamino-*L*-valinoyl-amino)-1-hydroxy-3-(*R,S*)-hydroxy-3-cyclohex-5-enyl-propane (5a)

100 mg *N*-Cbz-*L*-ValSerCHO was treated with Zn dust according to the general procedure.

Yield: 58 mg (46 %) of a colorless oil; R_f = 0.75 (petroleum ether : acetone = 3 : 2);

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.72-1.08 (m, 6 H, 2x CH_3); 1.10-2.40 (m, 8 H); 2.72-3.10 (m, 1 H, OH); 3.20-4.18 (m, 5 H); 4.94-5.18 (m, 2 H, $PhCH_2$); 5.39-5.63 (m, 1 H, CH=CH); 5.68-5.92 (m, 1 H, CH=CH); 6.70-7.04 (m, 1 H, NH); 7.27-7.47 (m, 5 H, Ph).
MS (HR-MS): $C_{22}H_{32}N_2O_5$ $[M]^+$, calcd.: m/z = 404.2311, found: m/z = 404.2300.

2(S)-*tert.*-Butyloxycarbonylamino-1-hydroxy-3-(*R,S*)-hydroxy-3-(1′(*R,S*)-cyclohex-2′-enyl)-propane (5b)
500 mg of *N*-Boc-*L*-serinal was treated with Sn dust according to the general procedure.
Yield: 259 mg (36 %) of a colorless oil;
***syn*-5b:**
R_f = 0.37 (petroleum ether / ethyl acetate = 1 : 1);
^{1}H NMR (200 MHz, $CDCl_3$) (syn): δ = 1.40 (m, 13 H, $(CH_3)_3$, CH_2); 1.68 (m, 2 H, CH_2); 1.92 (m, 2 H, CH_2); 2.18 (m, 1 H, 1′-CH); 3.10-3.60 (m, 4 H, 2-CH_2, 3-CH, 4-CH); 4.40 (m, 1 H, OH); 4.55 (dd, 11.6 Hz, 5.6 Hz, 1 H, OH); 5.70 (m, 2 H, 2′-CH, NH); 6.35 (t, 7.8 Hz, 1 H, 1′-CH).
MS (FAB-MS) $C_{14}H_{27}NO_4$ $[M+H]^+$, calcd.: m/z = 272.2, found: m/z = 272.2.
***anti*-5b:**
R_f = 0.34 (petroleum ether / ethyl acetate = 1 : 1);
^{1}H NMR (200 MHz, $CDCl_3$) (anti): δ = 1.40 (m, 13 H, $(CH_3)_3$, CH_2); 1.68 (m, 2 H, CH_2); 1.92 (m, 2 H, CH_2); 2.18 (m, 1 H, 1′CH); 3.10-3.60 (m, 4 H, 2-CH_2, 3-CH, 4-CH); 4.40 (m, 1 H, OH); 4.55 (dd, 11.6 Hz, 5.6 Hz, 1 H, OH); 5.70 (m, 2 H, 2′-CH, NH); 6.35 (t, 7.8 Hz, 1 H, 1′-CH).
MS (FAB-MS) $C_{14}H_{27}NO_4$ $[M+H]^+$, calcd.: m/z = 272.2, found: m/z = 272.2.

General procedure for the synthesis of 1,3-dioxan derivatives
The corresponding diols are dissolved in anhydrous CH_2Cl_2, then 1.5 eq. of 2,2-dimethoxy propane and a catalytical amount of pTSA are added. The mixture is stirred at r.t. until the reaction is complete according to TLC analysis. The solution is extracted with sat. aq. NH_4Cl and water, dried over magnesium sulphate, and the solvent is removed under reduced pressure. The diastereomers could be separated by column chromatography.

5(R)-(*N*-Benzyloxycarbonylamino-*L*-valinoyl)-amino-4(S)-(1',1'-dimethylprop-2-enyl)-2,2-dimethyl-1,3-dioxan (6a)
55 mg of ***anti*-3a** were treated according to the general procedure.
Yield: 60 mg (99 %); m.p. 125°C; R_f = 0.77 (petroleum ether / ethyl acetate = 3 : 2);
^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.87 (d, 6.49 Hz, 3 H, 1′-CH_3); 0.95 (d, 6.49 Hz, 3 H, 1′-CH_3); 0.98 (s, 3 H, CH_3); 1.02 (s, 3 H, CH_3); 1.31 (s, 3 H, 2-CH_3); 1.34 (s, 3 H, 2-CH_3); 2.14 (m, 1 H, 2′-CH); 3.14 (d, $^3J_{HH(ax\text{-}ax)}$ = 7.33 Hz, 1 H, 4-CH); 3.35 (dd, 11.65 Hz, 1.5 Hz, 1 H, 6-CH_2); 3.79 (dd, 11.78 Hz, 4.02 Hz, 6-CH_2); 3.92 (dd, 8.77 Hz, 5.65 Hz, 1 H, 5-CH); 4.07 (m, 1 H, 3′-CH); 4.95-5.15 (m, 4 H, $PhCH_2$, olefinic-CH_2); 5.27 (d, 8.53 Hz, 1 H, carbamate-NH); 5.85 (dd, 17.3 Hz, 10.5 Hz, 1 H, olefinic-CH); 6.20 (d, 8.65 Hz, 1 H, amide-NH); 7.30-7.40 (m, 5 H, Ph).
MS (HR-MS): $C_{24}H_{36}N_2O_5$ $[M]^+$, calcd.: m/z = 432.2624, found: m/z = 432.2613.

5(R)-(*N*-Benzyloxycarbonylamino-*L*-phenylalaninoyl)-amino-4(R)-(1',1'-dimethylprop-2-enyl)-1,3-dioxan (*syn*-6b)
100 mg of **3e** were treated according to the general procedure.
Yield: 25 mg (23 %); Rf = 0.46 (petroleum ether / ethyl acetate = 3 : 2);
^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.31 (s, 3 H, CH_3); 1.41 (s, 3 H, CH_3); 1.80-1.95 (m, 2 H, allylic-CH_2); 3.10 (d, 6 Hz, 2 H, $PhCH_2$); 3.63 (d, 12 Hz, 1 H, 6-CH_2); 3.80 (dd, 9.4 Hz, 1.77 Hz, 1 H, 5-CH); 3.89 (td, 6.8 Hz, 1.77 Hz, 1 H, 4-CH); 3.99 (dd, 12 Hz, 1.77 Hz, 1 H, 6-CH_2); 4.40-4.55 (m, 1 H, 2′-CH); 4.93-5.15 (m, 4 H, $PhCH_2$, olefinic-CH_2); 5.29 (d, 8.4 Hz, 1 H, carbamate-NH); 5.60-5.72 (m, 1 H, olefinic-CH); 6.49 (d, 8.7 Hz, 1 H, amide-NH); 7.15-7.38 (m, 10 H, 2x Ph).
MS (HR-MS): $C_{26}H_{32}N_2O_5$ $[M]^+$, calcd.: m/z = 452.2311, found: m/z = 452.2331.

5(R)-(*N*-Benzyloxycarbonylamino-*L*-phenylalaninoyl)-amino-4(S)-(1',1'-Dimethylprop-2-enyl)-1,3-dioxan (*anti*-6b)
100 mg of **3e** were treated according to the general procedure.
Yield: 79 mg (72 %); R_f= 0.58 (petroleum ether / ethyl acetate = 3 : 2);
^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.32 (s, 3 H, CH_3); 1.33 (s, 3 H, CH_3); 2.00-2.10 (m, 2 H, allylic-CH_2); 2.92-3.15 (m, 2 H, $PhCH_2$); 3.31-3.45 (m, 2 H); 3.72-3.84 (m, 2 H); 4.26-4.38 (m, 1 H, 2'-CH); 4.96-5.14 (m, 4 H, $PhCH_2$, olefinic-CH_2); 5.29 (d, 8.4 Hz, 1 H, carbamate-NH); 5.61 (d, 8.7 Hz, 1 H, amide-NH); 5.64-5.78 (m, 1 H, olefinic-CH); 7.13-7.38 (m, 10 H, 2x Ph).
MS (HR-MS): $C_{26}H_{32}N_2O_5$ $[M]^+$, calcd.: m/z = 452.2311, found: m/z = 452.2307.

5(R)-*tert.*-Butyloxycarbonylamino-4(S)-(1',1'-dimethylprop-2-enyl)-2,2-dimethyl-1,3-dioxan (6c)
150 mg of **3f** were treated according to the general procedure.
Yield: 88 mg (52 %); m.p. 71°C; R_f= 0.68 (petroleum ether / ethyl acetate = 7 : 1);
^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.03 (s, 3 H, CH_3); 1.05 (s, 3 H, CH_3); 1.26 (s, 3 H, CH_3); 1.28 (s, 3 H, CH_3); 1.43 (s, 9 H, $(CH_3)_3$); 3.13 (d, 7.5 Hz, 1 H, 4-CH); 3.43 (m, 1 H, 6-CH); 3.75 (m, 2 H, 6'-CH, 5-CH); 4.73 (d, $^3J_{HH}$ = 8.7 Hz, 1 H, NH); 4.97 (d, $^3J_{HH}$ = 3.4 Hz, 1 H, 3'-CH); 5.05 (d, 10.3 Hz, 1 H, 3'-CH); 5.90 (dd, 17.6 Hz, 11.7 Hz, 1 H, 2'-CH).
MS (FAB-MS): $C_{16}H_{31}NO_4$ $[M+H]^+$, calcd.: m/z = 300.2, found: m/z = 300.2.

5(R)-*tert.*-Butyloxycarbonylamino-4(R)-(1',1'-dimethylprop-2-enyl)-2,2-dimethyl-1,3-dioxan (6d)
150 mg of **3f** were treated according to the general procedure.
Yield: 70 mg (45 %); colorless oil; R_f= 0.31 (petroleum ether / ethyl acetate = 7 : 1);
^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.05 (s, 3 H, CH_3); 1.42 (s, 6 H, 2x CH_3); 1.44 (s, 9 H, $(CH_3)_3$); 1.56 (s, 3 H, CH_3); 3.45 (m, 1 H, 4-CH); 3.62 (m, 1 H, 5-CH); 3.74 (m, 2 H, 6-CH_2); 4.63 (s, 1 H, NH); 5.06 (m, 2 H, 3'-CH_2); 5.84 (m, 1 H, 2'-CH).
MS (HR-MS): $C_{16}H_{31}NO_4$ $[M+H]^+$, calcd.: m/z = 300.2163, found: m/z = 300. 2175.

5(S)-*tert.*-Butyloxycarbonylamino-4(R)-(1'(R/S)-cyclohex-2'-enyl)-2,2-dimethyl-1,3-dioxan (*anti*-6e)
200 mg of **5b** were treated according to the general procedure.
Yield: 114 mg (50 %), yellowish oil; R_f = 0.53 (petroleum ether / ethyl acetate = 5 : 1);
^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.27 (s, 3 H, CH_3); 1.31 (s, 3 H, CH_3); 1.35 (s, 9 H, $(CH_3)_3$); 1.45 (m, 2 H, 6'-CH_2); 1.72 (m, 2 H, 5'-CH_2); 1.92 (m, 1.6 H, 4'-CH_2); 1.98 (m, 0,4 H, 4'-CH_2); 2.30 (m, 1 H, 1'-CH); 3.29 (dd, 9.1 Hz, 4.6 Hz, 1 H, 4-CH); 3.37 (m, 0.2 H, 6-CH); 3.43 (m, 0.8 H, 6-CH); 3.75 (m, 1 H, 5-CH); 3.85 (m, 1 H, 6-CH); 4.45 (m, 1 H, NH); 5.65 (m, 2 H; 2'-CH, 3'-CH).
MS (FAB-MS): $C_{17}H_{31}NO_4$ $[M+H]^+$, calcd.: m/z = 312.2, found: m/z = 312.2.

5(S)-*tert.*-Butyloxycarbonylamino-4(S)-(1'(R/S)-cyclohex-2'-enyl)-2,2-dimethyl-1,3-dioxan (*syn*-6e)
150 mg of **5b** were treated according to the general procedure.
Yield: 86 mg (50 %); R_f = 0.36 (petroleum ether / ethyl acetate = 5 : 1);
^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.42 (m, 12 H, CH_3, $(CH_3)_3$); 1.51 (m, 5 H, CH_3, 6'-CH_2); 1.70 (m, 2 H, 5'-CH_2); 1.93 (m, 2 H, 4'-CH_2); 2.18 (m, 1 H, 1'CH); 3.55 (m, 0.4 H, 6-CH, 4-CH); 3.65 (m, 1.6 H, 6-CH, 4-CH); 3.82 (m, 1 H, 5-CH); 4.07 (m, 0.8 H, 6-CH); 4.12 (m, 0.2 H, 6-CH); 5.75 (m, 2 H, 2'-CH, 3'-CH).
MS (FAB-MS): $C_{17}H_{31}NO_4$ $[M+H]^+$, calcd.: m/z = 312.2, found: m/z = 312.2.

5(S)-*tert.*-Butyloxycarbonylamino-4(R)-(cyclohexanyl)-2,2-dimethyl-1,3-dioxan (6f)
86 mg of **6e** were hydrogenated over Pd/C in methanol.
Yield: 61 mg (70 %) of a colorless oil; R_f= 0.55 (petroleum ether / ethyl acetate = 5 : 1);
^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.00-1,80 (m, 11 H, cyclohexanyl); 1.28 (s, 3 H, CH_3); 1.30 (s, 3 H, CH_3); 1.37 (s, 9 H, $(CH_3)_3$); 3.18 (dd, 9.1 Hz, 3.6 Hz, 1 H, 4-CH); 3.41 (dd, 11.5 Hz, 5.9 Hz, 1 H, 6-CH); 3.69 (m, 1 H, 5-CH); 3.82 (dd, 11.5 Hz, 4.9 Hz, 1 H, 6-CH); 4.39 (d, 9.1 Hz, 1 H, NH).
MS (FAB-MS): $C_{17}H_{33}O_4$ $[M+H]^+$, calcd.: m/z = 314.3, found: m/z = 314.3.

General procedure for the preparation of amino-deoxy-sugars
The allylic compounds were dissolved in CH_2Cl_2 : MeOH = 5 : 1 and cooled to -78 °C. Ozone was bubbled through the solution for 30 minutes, followed by nitrogen for 5 minutes. After addition of dimethylsulfide the mixture was stirred overnight at r.t.. The solvent was removed under reduced pressure and the remaining residue was purified by chromatography on silica gel to yield the product.

2,4-Dideoxy-2,2-dimethyl-4-*N*-(*N'*-benzyloxycarbonyl-*L*-valinoyl)-amino-*L*-erythro-pentopyranose (7a)
Yield: 77.2 mg (50 %); m.p. 127 °C; R_f = 0.53 (petroleum ether : acetone = 3 : 2);
^{1}H NMR (400 MHz, DMSO-d_6): δ = 0.74-1.00 (m, 12 H, 4x CH_3); 1.83-2.05 (m, 1 H, C<u>H</u>$(CH_3)_2$); 3.20-3.55 (m, 2 H); 3.56-3.95 (m, 2 H); 4.19 (d, 5.2 Hz, 0.4 H); 4.45 (d, 6.4 Hz, 0.6 H); 4.56 (d, 3.9 Hz, 0.6 H); 4.62 (d, 6.4 Hz, 0.4 H); 4.97-5.10 (m, 2 H, $PhCH_2$); 6.08 (d, 3.9 Hz, 0.6 H); 6.47 (d, 5.2 Hz, 0.4 H); 7.18 (d, 9.1 Hz, 0.6 H); 7.22 (d, 8.9 Hz, 0.4 H); 7.25-7.44 (m, 5 H); 7.58 (d, 7.6 Hz, 0.4 H); 7.64 (d, 7.6 Hz, 0.6 H); 8.3 (s, 1 H, amide-NH).
MS (FAB-MS): $C_{20}H_{29}N_2O_6$ $[M-H]^+$, calcd.: m/z = 393.2026, found: m/z = 393.2.

2,4-Dideoxy-2,2-dimethyl-4-*N*-(*N'*-benzyloxycarbonyl-*L*-valinoyl)-amino-*L*-threo-pentopyranose (7b)
Yield: 47 mg (53 %); m.p. 121 °C; R_f = 0.49 (petroleum ether : acetone = 3 : 2);
^{1}H NMR (400 MHz, DMSO-d_6): δ = 0.74-1.00 (m, 12 H, 4x CH_3); 1.83-2.05 (m, 1 H, C<u>H</u>$(CH_3)_2$); 3.20-3.55 (m, 2 H); 3.56-3.95 (m, 2 H); 4.19 (d, 5.2 Hz, 0.4 H); 4.45 (d, 6.4 Hz, 0.6 H); 4.56 (d, 3.9 Hz, 0.6 H); 4.62 (d, 6.4 Hz, 0.4 H); 4.97-5.10 (m, 2 H, $PhCH_2$); 6.08 (d, 3.9 Hz, 0.6 H); 6.47 (d, 5.2 Hz, 0.4 H); 7.18 (d, 9.1 Hz, 0.6 H); 7.22 (d, 8.9 Hz, 0.4 H); 7.25-7.44 (m, 5 H); 7.58 (d, 7.6 Hz, 0.4 H); 7.64 (d, 7.6 Hz, 0.6 H); 8.3 (s, 1 H, Amid-NH).
MS (FAB-MS): $C_{20}H_{30}N_2O_6$ $[M-H]^+$, calcd.: m/z = 393.2026, found: m/z = 393.2.
and $C_{20}H_{28}N_2O_5$ $[M-H_2O]^+$, calcd.: m/z = 376.1998, found: m/z = 376.2.

2,4-Dideoxy-2,2-dimethyl-4-*N*-(*N'*-benzyloxycarbonyl-*L*-phenylalaninoyl)-amino-*L*-threo-pentopyranose (7c)
Yield: 64.4 mg (41 %); m.p. 74-78 °C; R_f = 0.39 (petroleum ether : acetone = 3 : 2);
^{1}H NMR (400 MHz, DMSO-d_6): δ = 0.82-0.93 (m, 6 H, 2x CH_3); 2.68-2.81 (m, 1 H); 2.91-3.2 (m, 2 H); 3.36-3.83 (m, 3 H); 4.57-4.63 (m, 1.2 H); 4.78 (d, 5.9 Hz, 0.4 H); 4.89-5.01 (m, 2 H); 6.13 (d, 3.9 Hz, 0.6 H); 6.51 (d, 5.2 Hz, 0.4 H); 7.1-7.4 (m, 10 H); 7.42 (d, 8.8 Hz, 0.6 H); 7.46 (d, 8.6 Hz, 0.4 H); 7.74 (d, 7.6 Hz, 0.4 H); 7.82 (d, 7.8 Hz, 0.6 H).
Analysis: $C_{24}H_{30}N_2O_6$ * 1/3 H_2O (448.21), calcd. (%) C 64.26, H 6.90, N 6.25; found (%) C 64.04, H 6.82, N 5.94.
MS (HR-MS): $C_{24}H_{28}N_2O_5$ $[M-H_2O]^+$, calcd.: m/z = 424.1998, found: m/z = 424.1994.
FAB-MS: $C_{24}H_{31}N_2O_6$ $[M+H]^+$, calcd.: m/z = 443.2182, found: m/z = 443.2.

2,4-Dideoxy-2,2-dimethyl-4-*N-tert.*-butyloxycarbonylamino-*L*-threo-pentopyranose (7d)
Yield: 35 mg (35 %); m.p. 75°C; R_f = 0.30 (petroleum ether / ethyl acetate = 1 : 1), anomeric ratio = 3 : 1;
^{1}H NMR (400 MHz, DMSO-d_6): δ = 0.71 (s, 0.75 H, CH_3); 0.75 (s, 2.25 H, CH_3); 0.97 (s, 3 H, CH_3); 1.33 (s, 2.25 H, $(CH_3)_3$); 1.38 (s, 6.75 H, $(CH_3)_3$); 3.38 (m, 1 H, 4-CH); 3.63 (m, 3 H, 5-CH_2, 3-CH); 3.79 (m, 1 H, OH); 4.29 (d, 7.3 Hz, 1 H, 1-CH); 4.52 (m, 1 H, OH).
MS (FAB-MS): $C_{12}H_{19}NO_3$ $[M-H_2O]^+$, calcd.: m/z = 244.1, found: m/z = 244.1.

2,4-Dideoxy-2,2-dimethyl-4-*N-tert.*-butyloxycarbonylamino-*L*-erythro-pentopyranose (7e)
Yield: 31 mg (31 %); m.p. 82°C, R_f = 0.28 (petroleum ether / ethyl acetate = 1 : 1), anomeric ratio = 1.1 : 1;
^{1}H NMR (400 MHz, DMSO-d_6): δ = 0.72 (s, 3 H, CH_3); 0.93 (s, 3 H, CH_3); 1.41 (s, 9 H, $(CH_3)_3$); 3.28 (m, 1 H, 4-CH); 3.51 (m, 0.94 H, 5-CH_2); 3.59 (m, 1.06 H, 5-CH_2); 3.80 (m, 0.53 H, 3-CH); 3.89 (m, 0.47 H, 3-CH); 4.40 (m, 0.47 H, OH); 4.47 (m, 0.53 H, OH); 4.53 (m, 0.53 H, 1-CH); 4.58 (m, 0.47 H, 1-CH), 4.88 (m, 0.53 H, OH); 4,95 (m, 0.47 H, OH).
MS (FAB-MS): $C_{12}H_{19}NO_3$ $[M-H_2O]^+$, calcd.: m/z = 244.1, found: m/z = 244.1.

Acknowledgement: This work was supported by the Deutsche Forschungsgemeinschaft (Gi 204/1-2).

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(*Received in Germany* 20 *November* 1996; *accepted* 13 *January* 1997)