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The stereochemical course of addition of allyltrimethylsilane to protected L-alaninals and L-serinals in the presence of Lewis acids. Total synthesis of *cis*-(2*R*,3*S*)-3-hydroxyproline†

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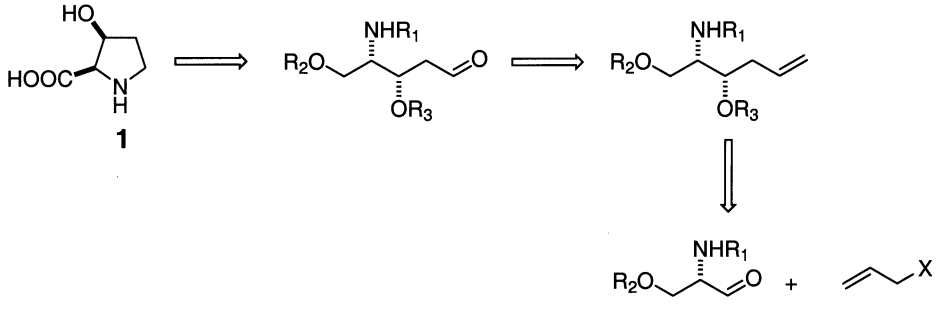
Abstract—The influence of Lewis acids on the diastereoselectivity of the addition of allyltrimethylsilane to variously protected L-alaninals and L-serinals was investigated and high levels of asymmetric induction were achieved. Stereochemical models for rationalisation of the results obtained are proposed. *cis*-(2*R*,3*S*)-3-Hydroxyproline was synthesised starting from *N*-Cbz,*O*-TBS-L-serinal, in which the crucial step involves addition of allyltrimethylsilane to the aldehyde in the presence of $SnCl_4$.

1. Introduction

The amino acyl–proline *cis*/*trans* isomerisation is a rate limiting step in protein folding[1] and modulates the biological activity of peptides.[2] Therefore, proline plays a particular role in protein structure and peptide conformation.[3] *cis*-(2*R*,3*S*)-3-Hydroxyproline **1** is a structural unit present in some biologically important compounds such as slaframine,[4] castanospermine,[5] and detoxinine.[6] They belong to the class of compounds known as polyhydroxylated amino sugars, which proved to be highly effective glycosidase inhibitors.[7] Because glycoproteins mediate cell–cell recognition,[8] it is reasoned that inhibitors of glycosidases should be of interest in alleviating viral infections. The development of improved synthetic methodologies for potential glycosidase inhibitors is still a challenging field. Various synthetic methodologies have been applied so far and the subject of the total synthesis of amino sugars has been covered in several general reviews.[9–15] Very often, the stereoselective C(3) elongation of the carbon skeleton is the crucial problem in the synthesis of amino sugars from α-amino acids and their derivatives.[16–18] We would like to propose a new pathway for the synthesis of *cis*-(2*R*,3*S*)-3-hydroxyproline **1**, a useful building block. The retrosynthetic analysis, shown in Scheme 1, suggests that *N*,*O*-protected-L-serinal and an allyl reagent could serve as starting materials.[19] Prelim-



Scheme 1.

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† Dedicated to Professor Marek Chmielewski on the occasion of his 60th birthday.

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inary results[20] concerning the diastereoselective addition of allyltrimethylsilane **2** to *N*,*O*-protected-L-serinals suggested that this process requires deeper studies in order to explain the influence of the *N*-protecting group and the *O*-protecting group and the Lewis acid used as a promoter.

2. Results and discussion

2.1. Addition of allyltrimethylsilane 2 to *N*-mono- and *N*,*N*-diprotected-L-alaninals

With the aim of studying the influence of Lewis acids and protecting groups on the addition of allyltrimethylsilane **2** to α-amino aldehydes, we decided to use the derivatives of L-alanine as the simplest case. *N*-Bn,*N*-Cbz-L-Alaninal **3**, *N*-Bn,*N*-Boc-L-alaninal **4** and *N*-Bn,*N*-Ts-L-alaninal **5** were selected as typical examples of *N*,*N*-diprotected derivatives. Each of these alaninals was obtained from the respective L-alaninol, using the TEMPO[21] oxidation method, since it gives α-amino aldehydes of high enantiomeric purity. Additions of allyltrimethylsilane **2** were initially carried out in the presence of Lewis acids such as $TiCl_4$, $SnCl_4$ (so-called chelating Lewis acids) and $BF_3{\cdot}OEt_2$, applying equimolar acid and aldehyde (Scheme 2, Table 1).

The reaction of *N*-Bn,*N*-Cbz-L-alaninal **3** with allyltrimethylsilane **2** in the presence of $TiCl_4$ gave the *syn*-isomer **3a** as the major product (Table 1, entry 1). This result was unexpected because, in the case of additions to *N*,*N*-diprotected L-alaninals, *anti*-diastereoselectivity[22,23] is usually observed due to the fact that an α-chelate cannot be formed and the addition occurs from the less-hindered side of the Felkin–Anh model. We propose that in our case a seven-membered chelate is formed as a result of coordination of titanium by two oxygen atoms (Fig. 1). The formation of a similar complex was proposed by Garner,[24] who observed *syn*-diastereoselectivity in the case of addition to *N*,*N*-diprotected derivative of serinal in the presence of $ZnCl_2$.

Surprisingly, the addition of **2** to **3**, in the presence of $SnCl_4$ (Table 1, entry 6), occurred with no diastereofacial selectivity. Presumably because attack by the allyl reagent occurs partially from the less hindered side of the Felkin–Anh model and partially from the less hindered side of the seven-membered chelate. The reaction of allyltrimethylsilane **2** with *N*-Bn,*N*-Cbz-L-alaninal **3** mediated by $BF_3{\cdot}OEt_2$ was slow, but gave both high yield and good *anti*-diastereoselectivity (12:88) (Table 1, entry 3). According to our expectations, we did not obtain any allylated adduct derived from *N*-Bn,*N*-Boc-L-alaninal **4**; this aldehyde is not stable enough under the reaction conditions. Furthermore, we studied the addition of **2** to *N*-Bn,*N*-Ts-L-alaninal **5**. In all reactions, the *anti*-diastereoisomer **5b** (Table 1, entries 2, 5

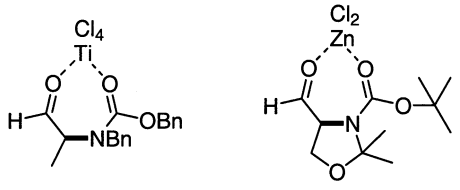
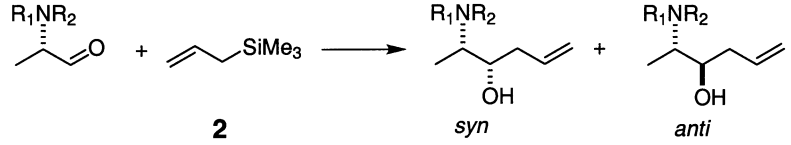


Figure 1.



2

syn *anti*

3 R_1 = Bn, R_2 = Cbz
4 R_1 = Bn, R_2 = Boc
5 R_1 = Bn, R_2 = Ts
6 R_1 = H, R_2 = Cbz
7 R_1 = H, R_2 = Ts

3a R_1 = Bn, R_2 = Cbz **3b**
4a R_1 = Bn, R_2 = Boc **4b**
5a R_1 = Bn, R_2 = Ts **5b**
6a R_1 = H, R_2 = Cbz **6b**
7a R_1 = H, R_2 = Ts **7b**

Scheme 2.

Table 1. Addition of allyltrimethylsilane **2** to variously protected L-alaninals

Entry	Aldehyde	Lewis acid	Reaction time (h)	*syn*/*anti* ratio	Yield (%)
1	**3**	$TiCl_4$	25	84:16	62[a]
2	**5**	$TiCl_4$	22	32:68	87
3	**3**	$BF_3{\cdot}OEt_2$	48	12:88	83[b]
4	**4**	$BF_3{\cdot}OEt_2$	18	–	0[b]
5	**5**	$BF_3{\cdot}OEt_2$	24	7:93	85[a]
6	**3**	$SnCl_4$	2	50:50	96
7	**4**	$SnCl_4$	18	–	0[b]
8	**5**	$SnCl_4$	1.5	34:66	34[b]

[a] Unreacted starting material was recovered.
[b] By-products were formed.

and 8) was formed as the major product and the best result was obtained when $BF_3{\cdot}OEt_2$ was used as a promoter (entry 5). Depending on the *N*-protecting group in the aldehyde and the promoter used, the *anti*- or *syn*-adduct may be the major product of the reactions of *N*,*N*-diprotected-L-alaninal and allyltrimethylsilane **2** catalysed by a Lewis acid.

Since the additions in the presence of $TiCl_4$ did not give the expected good results and there was some evidence that this reaction depended on the amount of the Lewis acid added, as reported by Kiyooka et al.,[25] we considered it very interesting to study the influence of the amount of $TiCl_4$ used on the addition of allyltrimethylsilane **2** to *N*-mono- and *N*,*N*-diprotected-L-alaninals. For *N*-Cbz-L-alaninal **6** and *N*-Ts-L-alaninal **7**, the diastereoisomeric excess did not depend on the amount of the Lewis acid applied and it ranged about zero; a high yield was obtained when 1 equiv. of $TiCl_4$ per 1 equiv. of *N*-Cbz-L-alaninal **6** (Table 2, entry 3) and 2 equiv. for 1 equiv. *N*-Ts-L-alaninal **7** were used (Table 2, entry 12).

For *N*-Bn,*N*-Cbz-L-alaninal **3**, the dependence was more evident, the highest diastereoisomeric ratio (90:10) was obtained when 0.75 mmol of $TiCl_4$ per 1 mmol of aldehyde **3** was used (Table 3, entry 2). Increasing the amount of Lewis acid added led to a decrease in the *syn*-diastereoselection, but gave increased yields until the ratio of $TiCl_4$ reached 1.25 mmol per 1 mmol of aldehyde **3** (entry 4). In the case of *N*-Bn,*N*-Ts-L-alaninal **5**, the best result (5:95, 50% yield) was obtained when 0.5 mmol of $TiCl_4$ per 1 mmol of the aldehyde was used (entry 7). The yield increases (reaching 99%) with increasing amounts of $TiCl_4$ (2 mmol per 1 mmol of the aldehyde) (entry 12).

Table 2. The influence of the amount of $TiCl_4$ used on the addition of allyltrimethylsilane **2** to *N*-monoprotected L-alaninals

Entry	Amount of $TiCl_4$ (equiv.)	Aldehyde	*syn*/*anti* ratio	Yield (%)
1	0.50	**6**	60:40	40
2	0.75	**6**	58:42	99
3	1.00	**6**	58:42	99
4	1.25	**6**	55:45	92
5	1.50	**6**	52:48	86
6	2.00	**6**	52:48	71
7	0.50	**7**	50:50	39
8	0.75	**7**	–	0
9	1.00	**7**	50:50	41
10	1.25	**7**	–	0
11	1.50	**7**	–	0
12	2.00	**7**	63:37	67

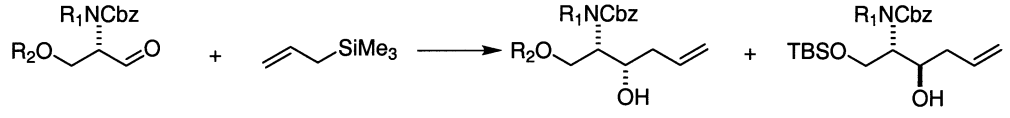
Table 3. The influence of the amount of $TiCl_4$ used on the addition of allyltrimethylsilane **2** to *N*,*N*-diprotected L-alaninals

Entry	Amount of $TiCl_4$ (equiv.)	Aldehyde	*syn*/*anti* ratio	Yield (%)
1	0.50	**3**	–	0
2	0.75	**3**	90:10	54
3	1.00	**3**	84:16	62
4	1.25	**3**	75:25	79
5	1.50	**3**	77:23	53
6	2.00	**3**	69:31	48
7	0.50	**5**	5:95	49
8	0.75	**5**	36:64	58
9	1.00	**5**	32:68	87
10	1.25	**5**	33:67	88
11	1.50	**5**	42:58	92
12	2.00	**5**	34:56	99

2.2. Addition of allyltrimethylsilane 2 to *N*-monoprotected-*O*-protected-L-serinals

We have reported the preliminary results of the diastereoselective addition of allyltrimethylsilane **2** to *N*,*O*-protected-L-serinals mediated by $TiCl_4$ and $SnCl_4$.[20] It was observed that it is possible to control the diastereoselectivity of this process by changing protecting groups as well as Lewis acids. Since C(3) elongation is the crucial step in the synthesis of *cis*-(2*R*,3*S*)-3-hydroxyproline **1**,[19] we decided to study addition of allyltrimethylsilane **2** to *N*,*O*-protected-L-serinals in detail (Scheme 3).

N,*O*-Protected L-serinals were obtained via oxidation of the respective alcohols using the TEMPO method.[21] *N*-Cbz,*O*-TBS-L-Serinal **8** and *N*-Bn,*N*-Cbz,*O*-TBS-L-serinal **10** were obtained with virtually no racemisation. Similar results were obtained for *N*-Cbz,*O*-BOM-L-serinal **9** and *N*-Bn,*N*-Cbz,*O*-BOM-L-serinal **11**. Having in hand the enantiomerically pure α-amino-β-hydroxy aldehydes, we investigated the addition of allyltrimethylsilane **2**. The reaction of *N*-Cbz,*O*-



2 *syn* *anti*

8 R_1 = H, R_2 = TBS
9 R_1 = H, R_2 = BOM
10 R_1 = Bn, R_2 = TBS
11 R_1 = Bn, R_2 = BOM

8a R_1 = H, R_2 = TBS **8b**
9a R_1 = H, R_2 = BOM **9b**
10a R_1 = Bn, R_2 = TBS **10b**
11a R_1 = Bn, R_2 = BOM **11b**

Scheme 3.

TBS-L-serinal **8** with **2**, irrespective of the Lewis acid used, gave the *syn*-diastereoisomer **8a** as the major product (Table 4).

This diastereoisomer can be obtained almost exclusively when $SnCl_4$ is applied as a mediator (Table 4, entry 1). We did not observe any significant influence of the amount of $TiCl_4$ added on the diastereoselectivity of the reaction of **2** with **8**, which remained at the level of 8:2–7:3 (entries 2–4). Increasing the amount of $TiCl_4$ caused an increase in the yield. In the case of less active Lewis acids such as $ZnBr_2$ or $ZnCl_2$, the reaction temperature had to be elevated in order to obtain the desired allylated adducts (**8a** and **8b**) but, as a consequence, the decrease in the diastereoselectivity was observed (entries 7 and 8). Reactions mediated by $MgBr_2{\cdot}OEt_2$ or $AlEt_3$ did not lead to allylated adducts (**8a** and **8b**) at all (entries 9 and 10).

The addition of allyltrimethylsilane **2** to *N*-Cbz,*O*-BOM-L-serinal **9**, in the presence of $SnCl_4$, gave predominantly the *syn*-adduct **9a**, but both the level of the diastereoselectivity and yield decreased (Table 5, entry 1). Very interesting results were obtained when the addition of **2** to **9** was carried out in the presence of $TiCl_4$ as a mediator (entries 2–4). Surprisingly, *anti*-diastereoselectivity was observed regardless of the amount of Lewis acid used. Reactions mediated by $ZnBr_2$, $ZnCl_2$ and $MgBr_2{\cdot}OEt_2$ failed to give the desired products **9a**, **9b** (entries 6–11). At room temperature, the formation of by-products occurs (entries 7, 9 and 11), whereas lowered temperature results in quantitative recovery of the substrate **9** (entries 6, 8 and 10).

2.3. Addition of allyltrimethylsilane 2 to *N*,*N*-diprotected-*O*-protected-L-serinals

The addition of allyltrimethylsilane **2** to *N*-Bn,*N*-CBz-*O*-TBS-L-serinal **10**, mediated by $TiCl_4$, gave the *syn*-diastereoisomer **10a** as the predominant product (Table 6, entries 2–4) and increasing the amount of $TiCl_4$ gave increases in both the diastereoselectivity and yield. When the addition was carried out in the presence of $SnCl_4$ or $BF_3{\cdot}OEt_2$, low to moderate *anti*-diastereoselectivity was observed (entries 1 and 6). At 4°C, weak Lewis acids did not promote the reaction of **2** with **10** at all (entries 8, 10 and 12); at room temperature, only low *syn*-diastereoselectivity and low yield were obtained (entries 7, 9 and 11).

N-Bn,*N*-CBz-*O*-BOM-L-Serinal **11** reacted with allyltrimethylsilane **2** to give the *anti*-adduct **11b** as a major product in the presence of all Lewis acids used (Table 7). Usually, the diastereoselectivity was moderate and the best result (18:82, 72% yield) was obtained for the reaction carried out in the presence of $TiCl_4$ (1.5 equiv.) (entry 4).

Table 4. Addition of allyltrimethylsilane **2** to *N*-Cbz-*O*-TBS-L-serinal **8**

Entry	Lewis acid	Reaction time (h)	Temperature (°C)	*syn*/*anti* ratio	Yield (%)
1	$SnCl_4$	1	−78	98:2	88
2	$TiCl_4$, 0.5 equiv.	22	−78	80:20	40[a]
3	$TiCl_4$, 1.0 equiv.	20	−78	70:30	83
4	$TiCl_4$, 1.5 equiv.	20	−78	72:28	90
5	$BF_3{\cdot}OEt_2$	20.75	−78	58:42	33
6	$BF_3{\cdot}OEt_2$	2.2	−48	79:21	52
7	$ZnBr_2$	26.25	20	85:15	63
8	$ZnCl_2$	25.75	20	80:20	51
9	$MgBr_2{\cdot}OEt_2$	23.5	20	–	0[b]
10	$AlEt_3$	15	20	–	0[a]

[a] Unreacted starting material was recovered.
[b] By-products were formed.

Table 5. Addition of allyltrimethylsilane **2** to *N*-Cbz-*O*-BOM-L-serinal **9**

Entry	Lewis acid	Reaction time (h)	Temperature (°C)	*syn*/*anti* ratio	Yield (%)
1	$SnCl_4$	1.5	−78	82:18	68
2	$TiCl_4$, 0.5 equiv.	19	−78	2:98	17[a]
3	$TiCl_4$, 1.0 equiv.	16	−78	3:97	90
4	$TiCl_4$, 1.5 equiv.	16	−78	2:98	82[b]
5	$BF_3{\cdot}OEt_2$	23	−78	89:11	65
6	$ZnCl_2$	20	4	–	0[a,b]
7	$ZnCl_2$	20	20	–	0[b]
8	$ZnBr_2$	20	4	–	0[a]
9	$ZnBr_2$	40	20	–	0[b]
10	$MgBr_2{\cdot}OEt_2$	40	4	–	0[a]
11	$MgBr_2{\cdot}OEt_2$	40	20	–	0[a]

[a] Unreacted starting material was recovered.
[b] By-products were formed.

Table 6. Addition of allyltrimethylsilane **2** to *N*-Bn-*N*-Cbz-*O*-TBS-L-serinal **10**

Entry	Lewis acid	Reaction time (h)	Temperature (°C)	*syn*/*anti* ratio	Yield (%)
1	$SnCl_4$	1.5	−78	45:55	75
2	$TiCl_4$, 0.5 equiv.	20	−78	90:10	38[a]
3	$TiCl_4$, 1.0 equiv.	3	−78	94:6	70
4	$TiCl_4$, 1.5 equiv.	3	−78	97:3	79
5	$BF_3{\cdot}OEt_2$	19	−78	–	0[a]
6	$BF_3{\cdot}OEt_2$	5	−20	25:75	72
7	$ZnCl_2$	15	20	54:46	33[b]
8	$ZnCl_2$	5	4	–	0[a]
9	$ZnBr_2$	15	20	52:48	34[b]
10	$ZnBr_2$	5	4	–	0[a]
11	$MgBr_2{\cdot}OEt_2$	15	20	60:40	10[b]
12	$MgBr_2{\cdot}OEt_2$	5	4	–	0[a]

[a] Unreacted starting material was recovered.
[b] By-products were formed.

Table 7. Addition of allyltrimethylsilane **2** to *N*-Bn-*N*-Cbz-*O*-TBS-L-serinal **11**

Entry	Lewis acid	Reaction time (h)	Temperature (°C)	*syn*/*anti* ratio	Yield (%)
1	$SnCl_4$	3	−78	21:79	73
2	$TiCl_4$, 0.5 equiv.	20	−78	27:73	30[a]
3	$TiCl_4$, 1.0 equiv.	3.5	−78	26:74	59
4	$TiCl_4$, 1.5 equiv.	2.5	−78	18:82	72
5	$BF_3{\cdot}OEt_2$	15	−78	–	0[a]
6	$BF_3{\cdot}OEt_2$	21	−20	27:73	25[a]
7	$ZnCl_2$	36	20	24:76	23[a]
8	$ZnCl_2$	36	20	44:55	6[a]
9	$MgBr_2{\cdot}OEt_2$	36	20		0[a]

[a] Unreacted starting material was recovered.

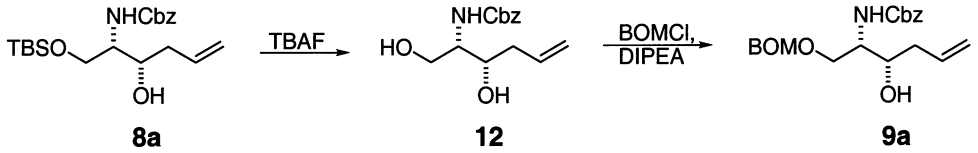
2.4. Chemical correlation

Having determined the extent of asymmetric induction, we studied the sense of induction by establishing the configuration of the products using the chemical correlation method. Adduct **8a**, obtained in the reaction of *N*-Cbz,*O*-TBS-L-serinal **8** with **2** in the presence of $SnCl_4$ (Table 4, entry 1), was transformed into the known *cis*-(2*R*,3*S*)-3-hydroxyproline **1**[19] which has the hydroxy and the hydroxymethyl groups in relation *cis* (Scheme 7). Therefore, compound **8a** bears the amino and the hydroxy groups unequivocally in the *syn*-orientation, this means that the C(3) stereogenic centre has (*S*)-absolute configuration. The other diastereoisomer **8b** possesses the opposite (*R*)-configuration.

In order to assign the stereochemical course of the allyl addition to *N*-Cbz,*O*-BOM-L-serinal **9**, the TBS group in *syn*-**8a** was replaced by the BOM group giving adduct **9a** (Scheme 4). The ^1H and ^{13}C NMR spectra taken for **9a** obtained from **8a** were identical to those taken for the major product from reaction of *N*-Cbz,*O*-BOM-L-serinal **9** with allyltrimethylsilane **2** mediated by $SnCl_4$. Therefore *syn*-configuration was assigned to compound **9a** and, consequently, *anti*-configuration was assigned to adduct **9b**.

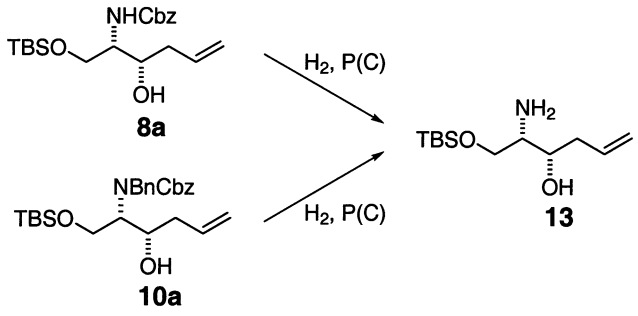
Hydrogenation of *syn*-*N*-Cbz,*O*-TBS adduct **8a** as well as the *N*-Bn,*N*-Cbz,*O*-TBS-derivative **10a**, being the major product of the addition reaction performed in the presence of $TiCl_4$ (Table 6, entry 4), gave the same *N*-deprotected compound **13** (Scheme 5), as determined by ^1H and ^{13}C NMR spectra. This indicates that *N*-Bn,*N*-Cbz,*O*-TBS derivative **10a** has the amino and hydroxy groups in the *syn*-orientation.

Hydrogenation of *syn*-*N*-Cbz,*O*-BOM-adduct **9a** gave fully deprotected dihydroxyamine, which was immediately (without purification) subjected to reaction with acetic anhydride, giving the triacetylated *syn*-product **14a**. As a result of hydrogenation of the *syn*/*anti* **11a**/**11b** mixture (18:82) (Table 7, entry 4), in the presence



8a **12** **9a**

Scheme 4.



Scheme 5.

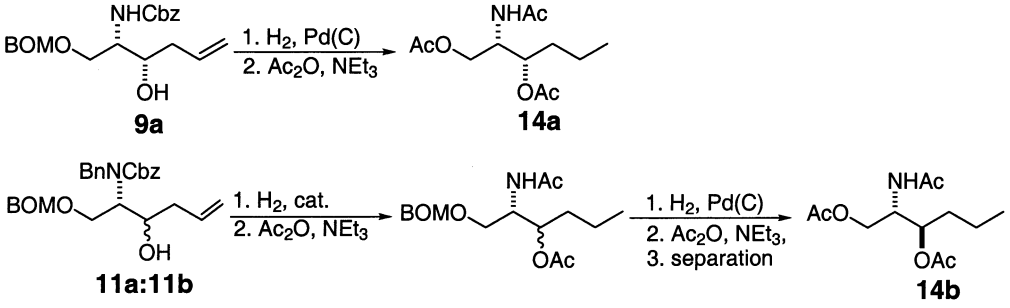
of the Degussa catalyst, the benzyl and carbobenzoxy groups were cleaved. Then the free amino and hydroxy groups were protected by treating with acetic anhydride. Further replacement of the BOM group with the acetyl group resulted mainly in the formation of the compound **14b**. Since the ^{1}H and ^{13}C NMR spectra of compounds **14a** and **14b** differ from each other, but relate to compounds of the same structure, we conclude that they have the opposite relative configurations. Thus, in the addition reaction of allyltrimethylsilane **2** to *N*-Bn,*N*-Cbz,*O*-BOM-L-serinal **11**, the *anti*-diastereoisomer **11b** was formed as the major product (Scheme 6).

2.5. Stereochemical course of the additions

syn-Diastereoselectivity was observed for all additions of **2** to *N*-Cbz,*O*-TBS-L-serinal **8**, irrespective of the Lewis acid used. In the case of the chelating Lewis acids,[26–28] the direction of asymmetric induction can be explained by the transition state A, as shown in Fig. 2. Attack by the allyl reagent occurs from the less-hindered side of the cyclic model **A**. Surprisingly, the addition in the presence of non-chelating acids such as $BF_3{\cdot}OEt_2$[26,27,29] also resulted in *syn*-adduct **8a**, as a consequence of H-bonding between the NH and carbonyl groups—model **B** (Fig. 2), which resembles model A. Therefore, the allyl reagent approaches from the same side as in model **A**, giving predominantly *syn*-**8a**. Similar effects[16] were observed in the hetero-Diels–Alder reaction of α-amino aldehydes. Since we did not observe any *anti*-diastereoselectivity, the formation of β-chelate (model **C**) between the hydroxy group (protected with the TBS group) and the carbonyl group is presumably excluded due to the steric hindrance.

N-Cbz,*O*-BOM-L-Serinal **9** can form α-chelates, (**A**) or (**B**), and β-chelates (**C**) (Fig. 2) since the BOM group does not influence strongly the coordination by the ether oxygen atom. In the presence of $SnCl_4$ and $BF_3{\cdot}OEt_2$ the addition of allyltrimethylsilane **2** to aldehyde **9** afforded *syn*-adduct **9a** as a major product. In both cases, the α-chelates should be formed because, for $SnCl_4$, the reaction proceeds via α-chelate (**A**). Since $BF_3{\cdot}OEt_2$ cannot form cyclic chelates, model **B** should operate in this case. Although $TiCl_4$ is regarded as a strong Lewis acid, the reaction mediated by $TiCl_4$ gave predominantly the *anti*-product **9b**. It is highly unlikely that this reaction proceeds via the Felkin–Anh model, therefore we assume that $TiCl_4$ and aldehyde **9** form a six-membered β-chelate (**C**) and attack by the allyl reagent occurs from the side opposite of the amino group leading to *anti*-diastereoisomer **9b**.

The most interesting result was observed for the addition of **2** to *N*-Bn,*N*-Cbz,*O*-TBS-L-serinal **10** when the *syn*-adduct **10a** was mainly formed in the presence of $TiCl_4$. Since the formation of α-chelate is excluded by the presence of steric hindrance, there should be some other interactions resulting in another stable conformation. We propose that titanium is coordinated by two carbonyl oxygen atoms (CHO and COOBn) forming a seven-membered chelate—model **D** (Fig. 2) and, therefore, attack of the allyl reagent from the less hindered side leads to the *syn*-product **10a**. A similar chelate was first proposed by Kunz,[30] who proved the formation of



Scheme 6.

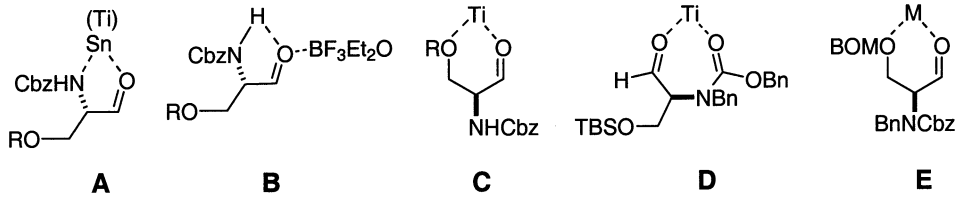


Figure 2.

such a complex by ^{13}C NMR. Later, Garner[24] assumed that in the presence of $ZnCl_2$ the cycloaddition to diprotected L-serinal proceeds via such a seven-membered α-chelate.

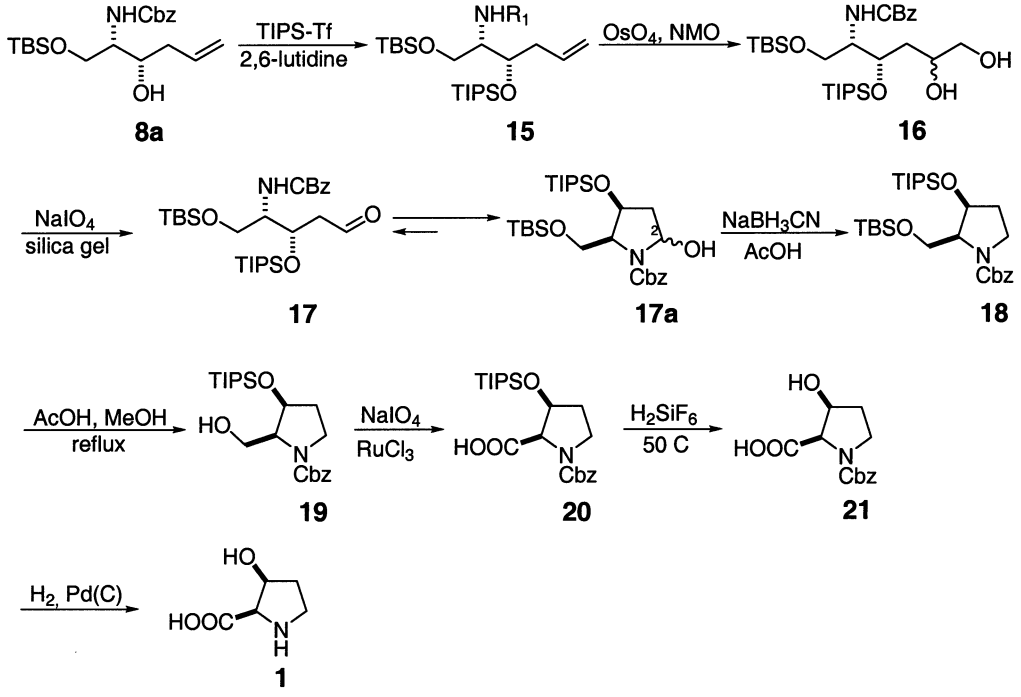
In all cases of the addition to *N*-Bn,*N*-Cbz,*O*-BOM-L-serinal **11**, the major product results from the β-chelation-controlled reaction (model **E**) that gives mainly the 1,2-*anti*-isomer **11a**, showing that the *O*-BOM oxygen atom is able to coordinate to Lewis acids such as $SnCl_4$, $TiCl_4$, $ZnCl_2$ and $ZnBr_2$. Of course, we are aware of the fact that attack of the allyl reagent from the less-hindered side of the Felkin–Anh model gives the same result as represented by the reaction mediated by $BF_3{\cdot}OEt_2$.

2.6. Total synthesis of *cis*-(2*R*,3*S*)-3-hydroxyproline, 1

Having in hand a very good method for the synthesis of diastereoisomerically pure *syn*-adduct **8a**, we pursued the synthesis of *cis*-(2*R*,3*S*)-3-hydroxyproline **1** (Scheme 7). Protection of the hydroxy group of the *syn*-adduct **8a** using triisopropylsilyl triflate, followed by *syn*-dihydroxylation with NMO and OsO_4[31] gave the polyhydroxy amine **16**, which, without purification, was subjected to oxidative cleavage using sodium periodate[32] to afford the aldehyde **17** in 81% yield. Analysis of ^1H and ^{13}C NMR data proved that **17** adopts the cyclic conformation **17a**. In ^1H NMR spectra of **17**, there are no signals for the CHO and NH protons, instead a broad signal characteristic of an OH proton appears at 6.45–6.56 ppm as well as a doublet of doublets at 5.36 ppm, which is assigned to the amine carbon C(2). Treatment of **17** with $NaBH_3CN$, followed by selective deprotection of the primary hydroxy group, afforded the pyrrolidine derivative **19** in 91% yield. Oxidation of the hydroxy group in **19** with $NaIO_4$ in the presence of $RuCl_3$ in a biphasic system[33] resulted in the protected amino acid **20**. The silyl protective group was removed using H_2SiF_6[34] to provide the corresponding derivative **21** in 81% yield. Deprotection of **21** by hydrogenolysis (H_2, Pd/C) then gave the desired **1**. For independent verification of the *cis*-correlation of the substituents, the free *cis*-(2*R*,3*S*)-3-hydroxyproline was transformed into the corresponding hydrochloride **22**. Compound **22** had ^1H and ^{13}C NMR spectra consistent with those reported in the literature.[34]

3. Conclusions

The diastereoselective synthesis of *cis*-(2*R*,3*S*)-3-hydroxyproline **1** proceeds in 52% yield over eight steps, starting from the suitably protected L-serinal **8**. This synthetic strategy proves the utility of C(3)-elongation of α-amino aldehydes. During the course of our studies we found that the addition of allyltrimethylsilane **2** to α-amino aldehydes strongly depends on the Lewis acid used and the *N*,*O*-protecting groups present in the aldehyde. We have observed that when $TiCl_4$ is used as a mediator for the reaction of allyltrimethylsilane **2** and α-amino aldehydes preferentially forms the seven-membered chelates. Furthermore, we are able to obtain the *anti*- and *syn*-adducts, derived from L-alaninal and L-serinal, in good yields and enantiomeric purity.



Scheme 7.

4. Experimental

4.1. General

All chemicals were used as received unless otherwise noted. Reagent grade solvents ($CHCl_3$, CH_2Cl_2, hexanes, AcOEt) were distilled prior use. All reported NMR spectra were recorded with a Bruker spectrometer at 500 (^{1}H NMR) and 125 (^{13}C NMR) MHz or a Bruker spectrometer at 400 (^{1}H NMR) and 100 (^{13}C NMR) MHz or a Varian Gemini spectrometer at 200 (^{1}H NMR) and 50 (^{13}C NMR) MHz. Chemical shifts are reported as δ values relative to TMS peak defined at $\delta = 0.00$ (^{1}H NMR) or $\delta = 0.0$ (^{13}C NMR). IR spectra were obtained on a Perkin–Elmer 1640 FTIR. Mass spectra were obtained on an AMD-604 Intectra instrument using the EI or LSIMS technique. Chromatography was performed on silica (Kiesel gel 60, 200–400 mesh). Optical rotations were recorded using a JASCO DIP-360 polarimeter with a thermally jacketed 10 cm cell.

4.2. Addition of allyltrimethylsilane 2 to α-amino aldehydes, general procedure

The α-amino aldehyde (0.23 mmol) was dissolved in dry CH_2Cl_2 (2 mL) under argon and cooled to −78°C, then the Lewis acid (0.23 mmol) was added. After 5 min, allyltrimethylsilane **2** (0.46 mmol) was added and the reaction mixture was stirred for another 1.5 h at −78°C. The mixture was diluted with saturated aqueous NH_4F and extracted with ether. The organic phase was dried over $MgSO_4$, rotary evaporated, and chromatographed (silica, hexane/ethyl acetate).

4.2.1. (1*S*,2*S*)-[1-(*tert*-Butyldimethylsilanyloxymethyl)-2-hydroxypent-4-enyl]carbamic acid benzyl ester, 8a. ^{1}H NMR (400 MHz, 363 K, toluene-d_8) −0.08 (s, 6H), 0.80 (s, 9H), 2.0–2.1 (m, 3H), 3.5–3.6 (m, 1H), 3.6–3.7 (m, 2H), 3.73 (dt, $J_t = 5.3$ Hz, $J_d = 3.3$ Hz, 1H), 4.8–5.0 (m, 5H), 5.58 (ddt, $J_t = 6.5$ Hz, $J_d = 17.9$ Hz, 1H), 6.9–7.2 (m, 5H); ^{13}C NMR (100 MHz, 363 K, toluene-d_8) −5.7, 25.8, 38.9, 55.2, 64.9, 66.6, 71.1, 117.2, 128.4, 128.6, 128.8, 137.3; IR (film) 697, 778, 837, 1028, 1099, 1216, 1258, 1471, 1509, 1703, 2856, 2929, 3068, 3437; LSIMSHR $C_{20}H_{34}NO_4Si$ $(M+H)^+$ calcd 380.2257, found 380.2256; $[\alpha]_D^{20}$ +20.5 (*c* 1.47, $CHCl_3$).

4.2.2. (1*S*,2*R*)-[1-(*tert*-Butyldimethylsilanyloxymethyl)-2-hydroxypent-4-enyl]carbamic acid benzyl ester, 8b. ^{1}H NMR (500 MHz, 363 K, toluene-d_8) −0.03 (s, 3H), −0.03 (s, 3H), 0.85 (s, 9H), 2.1–2.2 (m, 3H), 3.5–3.6 (m, 2H), 3.67 (ABM/2, $J_{AB} = 10.3$ Hz, $J_{AM} = 3.9$ Hz, 1H), 3.79 (ABM/2, $J_{AB} = 10.3$ Hz, $J_{BM} = 3.5$ Hz, 1H), 4.9–5.0 (m, 2H), 5.03 (s, 2H), 5.04 (m, 1H), 5.76 (ddt, $J_t = 7.0$ Hz, $J_d = 17.2$, 10.3 Hz, 1H), 7.0–7.2 (m, 5H); ^{13}C NMR (100 MHz, 363 K, toluene-d_8) −5.4, 18.5, 26.1, 39.5, 56.3, 63.2, 67.0, 72.3, 117.5, 128.5, 128.7, 128.9, 137.6, 156.4; IR (film) 697, 779, 837, 1045, 1084, 1216, 1255, 1470, 1510, 1705, 2857, 2930, 3440; LSIMSHR $C_{20}H_{34}NO_4Si$ $(M+H)^+$ calcd 380.2257, found 380.2248; $[\alpha]_D^{20}$ +27.3 (*c* 1.56, $CHCl_3$).

4.2.3. (1*S*,2*S*)-[1-(Benzyloxymethyl)-2-hydroxypent-4-enyl]carbamic acid benzyl ester, 9a. ^{1}H NMR (500 MHz, 363 K, toluene-d_8) 2.16 (t, $J = 7.1$, 2H), 3.54 (ABM/2, $J_{AB} = 9.9$ Hz, $J_{BM} = 4.9$ Hz, 1H), 3.59 (ABM/2, $J_{AB} = 10.3$ Hz, $J_{AM} = 5.9$ Hz, 1H), 3.72 (dt, $J_t = 6.6$ Hz, $J_d = 2.1$ Hz, 1H), 3.8–3.9 (m, 1H), 4.41 (s, 2H), 4.49 (s. 2H), 4.9–5.0 (m, 2H), 5.05 (s, 2H), 5.11 (d, $J = 8.1$ Hz, 1H), 5.74 (ddt, $J_t = 7.2$ Hz, $J_d = 17.3$, 10.2 Hz, 1H), 7.0–7.3 (m, 10H); ^{13}C NMR (100 MHz, 363 K, toluene-d_8) 38.8, 54.1, 66.7, 69.3, 70.0, 70.9, 95.2, 117.2, 128.0, 128.1, 128.4, 128.6, 128.8, 137.3; LSIMSHR $C_{22}H_{28}NO_5$ $(M+H)^+$ calcd 386.1967, found 386.1979; $[\alpha]_D^{20}$ −1.5 (*c* 0.85, $CHCl_3$).

4.2.4. (1*S*,2*R*)-[1-(Benzyloxymethyl)-2-hydroxypent-4-enyl]carbamic acid benzyl ester, 9b. ^{1}H NMR (400 MHz, 363 K, toluene-d_8) 2.0–2.1 (m, 2H), 3.5–3.7 (m, 4H), 4.32 (s, 2H), 4.39 (s, 2H), 4.8(5)–4.9 (m, 3H), 4.95 (s, 2H), 5.66 (ddt, $J_t = 6.9$ Hz, $J_d = 17.2$, 10.3 Hz, 1H), 6.9–7.1(5) (m, 10H); ^{13}C NMR (100 MHz, 363 K, toluene-d_8) 38.9, 55.2, 66.7, 67.6, 69.9, 71.8, 95.2, 117.2, 127.8, 128.0, 128.1, 128.8, 128.6, 128.8, 137.3; LSIMSHR $C_{22}H_{28}NO_5$ $(M+H)^+$ calcd 386.1967, found 386.1964; the diastereoisomeric purity of this compound was 90%.

4.2.5. (1*S*,2*S*)-Benzyl-[1-(*tert*-butyldimethylsilanyloxymethyl)-2-hydroxypent-4-enyl]carbamic acid benzyl ester, 10a. ^{1}H NMR (400 MHz, 363 K, toluene-d_8) −0.10 (s, 6H), 0.81 (s, 9H), 2.0–2.1 (m, 2H), 3.6–3.7 (m, 1H), 3.8–3.9 (m, 3H), 4.48 (d, $J = 15.6$ Hz, 1H), 4.56 (d, $J = 15.6$ Hz, 1H), 4.86 (s, 1H), 4.9 (m, 2H), 4.97 (s, 1H), 4.98 (s, 1H), 5.7–5.8 (m, 1H), 6.9–7.2 (m, 10H); ^{13}C NMR (100 MHz, 363 K, toluene-d_8) −5.7, 18.2, 25.9, 39.6, 52.5, 62.8, 65.0, 67.5, 70.7, 116.5, 127.1, 127.4, 127.9, 128.2, 128.4, 128.6, 128.8, 135.4; IR (film) 698, 777, 837, 1104, 1253, 1471, 1679, 1698, 2856, 2929, 3435; LSIMSHR $C_{27}H_{40}NO_4Si$ $(M+H)^+$ calcd 470.2727, found 470.2725; $[\alpha]_D^{20}$ +13.9 (*c* 1.6, $CHCl_3$).

4.2.6. (1*S*,2*R*)-Benzyl-[1-(*tert*-butyldimethylsilanyloxymethyl)-2-hydroxypent-4-enyl]carbamic acid benzyl ester, 10b. ^{1}H NMR (400 MHz, 363 K, toluene-d_8) −0.07 (s, 3H), −0.07 (s, 3H), 0.81 (s, 1H), 0.83 (s, 9H), 2.0–2.1 (m, 2H), 3.5–3.6 (m, 1H), 3.9–4.1 (m, 3H), 4.35 (d, $J = 16.8$ Hz, 1H), 4.67 (d, $J = 16.8$ Hz, 1H), 4.8–4.9 (m, 2H), 4.99 (s, 2H), 5.54 (ddt, $J_t = 6.3$ Hz, $J_d = 16.5$, 9.8 Hz, 1H), 6.9–7.1 (m, 10H); ^{13}C NMR (100 MHz, 363 K, toluene-d_8) −5.7, 18.2, 25.9, 40.0, 67.4, 72.6, 116.7, 127.4, 127.7, 127.9, 128.2, 128.4, 128.6, 135.2, 136.3; IR (film) 699, 777, 837, 1005, 1101, 1253, 1471, 1679, 1698, 2929, 3447; LSIMSHR $C_{27}H_{40}NO_4Si$ $(M+H)^+$ calcd 470.2726, found 470.2725; $[\alpha]_D^{20}$ −10.8 (*c* 0.9, $CHCl_3$).

4.2.7. (1*S*,2*R*)-Benzyl-[1-(benzyloxymethyl)-2-hydroxypent-4-enyl]-carbamic acid benzyl ester, 11b. ^{1}H NMR (500 MHz, 363 K, toluene-d_8) 2.14 (s, 2H), 3.6–3.7 (m, 1H), 3.89 (s, 1H), 3.97 (dd, $J = 10.3$, 4.0 Hz, 1H), 4.06 (s, 1H), 4.38 (d, $J = 5.1$ Hz, 1H), 4.42 (d, $J = 4.5$ Hz, 2H), 4.44 (m, 1H), 4.51 (dd, $J = 19.8$, 6.3 Hz, 2H), 4.69 (d, $J = 15.4$ Hz, 1H), 4.8–4.9 (m, 2H), 5.06 (s, 2H), 5.58 (ddt, $J_t = 7.0$ Hz, $J_d = 17.2$, 10.3 Hz, 1H), 7.0–7.2(5) (m,

15H); ^{13}C NMR (100 MHz, 363 K, toluene-d_8) 40.2, 66.6, 67.8, 69.9, 73.1, 95.3, 117.3, 127.5, 127.8, 128.1, 128.2, 128.3, 128.5, 128.6, 128.7, 128.8, 128.9, 129.1, 135.5, 137.3, 138.9, 157.3; IR (film) 698, 736, 1048, 1114, 1239, 1419, 1454, 1678, 1696, 2887, 2938, 3031, 3065, 3451; LSIMSHR $C_{29}H_{34}NO_5$ $(M+H)^+$ calcd 476.2437, found 476.2436; $[\alpha]_D^{20}$ −10.1 (*c* 1.76, $CHCl_3$). Diastereoisomer **11a** was not isolated in pure form.

4.2.8. (1*S*,2*S*)-(2-Hydroxy-1-hydroxymethylpent-4-enyl)-carbamic acid benzyl ester, 12. To a solution of adduct **8a** (646 mg, 1.70 mmol) in THF (7 mL) was added $Bu_4NF{\cdot}3H_2O$ (1.02 g, 3.23 mmol). After 1.5 h, the reaction mixture was diluted with saturated aqueous $NaHCO_3$ and extracted with ether. The chromatography (silica, hexane/ethyl acetate, gradually from 8:2 to 1:1) gave 354 mg (82%) of the desired product. ^{1}H NMR (500 MHz, 363 K, toluene-d_8) 2.1–2.1(6) (m, 2H), 3.51 (ABM/2, $J_{AB}=10.9$ Hz, $J_{BM}=4.6$ Hz, 1H), 3.56 (ABM/2, $J_{AB}=10.9$ Hz, $J_{AM}=5.2$ Hz, 1H), 3.6–3.6(4) (m, 1H), 3.67 (dt, $J_t=6.8$ Hz, $J_d=2.1$ Hz, 1H), 4.9(6)–5.0 (m, 2H), 5.04 (s, 2H), 5.31 (d, $J=6.0$ Hz, 1H), 5.70 (ddt, $J_t=7.1$ Hz, $J_d=17.0$, 11.5 Hz, 1H), 7.0–7.2(5) (m, 5H); ^{13}C NMR (125 MHz, D_2O) 39.2, 55.8, 64.7, 67.2, 71.7, 117.7, 127.8, 128.0, 128.2, 128.7, 128.9, 129.1, 134.9, 157.2; IR (film) 698, 1028, 1066, 1252, 1340, 1527, 1698, 2941, 3401 cm^{-1}; LSIMSHR $C_{14}H_{20}NO_4$ $(M+H)^+$ calcd 266.1392, found 266.1392; $[\alpha]_D^{20}$ +3.0 (*c* 2.9, $CHCl_3$).

4.2.9. (2*S*,3*S*)-[2-Amino-1-(*tert*-butyldimethylsilanyloxy)hex-5-en]-3-ol, 13. Hydrogenation of the adduct **8a** or **10a** in the presence of Pd/C (10%) gave the title compound. ^{1}H NMR (500 MHz, 363 K, toluene-d_8) 0.04 (s, 6H), 0.87 (s, 9H), 0.91 (t, $J=7.0$ Hz, 3H), 1.3–1.5 (m, 5H), 2.14 (s, 2H), 2.66 (dt, $J_t=4.2$ Hz, $J_d=5.9$ Hz, 1H), 3.48 (dt, $J_t=4.2$ Hz, $J_d=8.3$ Hz, 1H), 3.58 (ABM/2, $J_{AB}=10.0$ Hz, $J_{AM}=5.9$ Hz, 1H), 3.65 (ABM/2, $J_{AB}=10.0$ Hz, $J_{BM}=4.2$ Hz, 1H); ^{13}C NMR (125 MHz, 273 K, $CDCl_3$) −5.6, −5.5, 14.0, 18.1, 18.9, 25.8, 36.5, 56.0, 66.4, 71.3; IR (film) 777, 837, 1097, 1256, 1472, 1583, 2858, 2956, 3360 cm^{-1}; LSIMSHR $C_{12}H_{30}NO_2Si$ $(M+H)^+$ calcd 248.2046, found 248.2044; $[\alpha]_D^{20}$ −15.9 (*c* 1.28, $CHCl_3$).

4.2.10. (2*S*,3*S*)-1,3-Diacetoxy-2-acetamidohexane, 14a. Compound **9a** after hydrogenation in the presence of Pd/C (10%) was dissolved in CH_2Cl_2, and treated with an excess of Ac_2O and NEt_3 and a catalytic amount of DMAP. The reaction mixture was stirred for 2 h. Extraction followed by chromatography (silica, hexanes/AcOEt) gave **14a** as a colourless oil. ^{1}H NMR (200 MHz, 273 K, $CDCl_3$) 0.9–1.0 (m, 3H), 1.2–1.6 (m, 4H), 2.05 (s, 3H), 2.07 (s, 3H), 2.13 (s, 3H), 4.2–4.3 (m, 2H), 5.0–5.3 (m, 2H), 5.68 (d, $J=8.5$ Hz, 1H); ^{13}C NMR (50 MHz, 273 K, $CDCl_3$) 13.9, 18.4, 18.5, 20.8, 20.9, 33.7, 53.1, 61.3, 72.1; LSIMSHR $C_{12}H_{22}NO_5$ $(M+H)^+$ calcd 260.1498, found 260.1500.

4.2.11. (2*S*,3*R*)-1,3-Diacetoxy-2-acetamidohexane, 14b. A mixture of compounds **11a** and **11b** (18:82) following hydrogenation in the presence of Degussa catalyst (50% of H_2O) was dissolved in CH_2Cl_2 and treated with an excess of Ac_2O and NEt_3 and a catalytic amount of DMAP. The reaction mixture was stirred for 2 h. After standard work-up the reaction mixture was again hydrogenated in the presence of 10% Pd/C followed by reaction with acetic anhydride. The reaction mixture was stirred for 2 h at rt and then extracted with CH_2Cl_2. Column chromatography (silica, hexanes/AcOEt) gave **14b** as the main product. ^{1}H NMR (200 MHz, 273 K, $CDCl_3$) 0.92 (t, $J=7.2$ Hz, 3H), 1.2–1.7 (m, 4H), 2.02 (s, 3H), 2.08 (s, 3H), 2.09 (s, 3H), 4.08 (ABM/2, $J_{AB}=11.4$ Hz, $J_{AM}=3.9$ Hz, 1H), 4.27 (ABM/2, $J_{AB}=11.4$ Hz, $J_{BM}=5.9$ Hz, 1H), 4.3–4.5 (m, 1H), 4.94 (dt, $J_t=5.3$ Hz, $J_d=7.7$ Hz, 1H), 5.91 (d, $J=8.5$ Hz, 1H); ^{13}C NMR (125 MHz, 273 K, $CDCl_3$) 13.9, 16.7, 20.9, 21.1, 23.5, 33.7, 50.6, 62.7, 73.8; LSIMSHR $C_{12}H_{22}NO_5$ $(M+H)^+$ calcd 260.1498, found 260.1499.

4.2.12. (1*S*,2*S*)-[1-(*tert*-Butyldimethylsilanyloxymethy)-2-triisopropylsilanyloxypent-4-enyl]carbamic acid benzyl ester, 15. To the solution of adduct **8a** (3.3 g, 8.7 mmol) in CH_2Cl_2 (20 mL) at 0°C under argon, 2,6-lutidine (2.1 mL, 18.1 mmol) and triisopropylsilyl trifluoromethanesulfonate (3.1 mL, 12 mmol) were added. After stirring for 18 h at 20°C, the reaction mixture was diluted with water and extracted with ether to give an oil (4.7 g), which was used without purification for the next reaction. For analytical purposes, a sample of the crude reaction mixture was chromatographed (silica, hexane/ethyl acetate, 9:1) ^{1}H NMR (500 MHz, 363 K, toluene-d_8) 0.07 (s, 3H), 0.09 (s, 3H), 0.93 (s, 9H), 1.08 (s, 18H), 1.09 (s, 3H), 2.3–2.4 (m, 1H), 2.4–2.5 (m, 1H), 3.69 (t, $J=9.2$ Hz, 1H), 3.7–3.8 (m, 1H), 3.9–4.1 (m, 1H), 4.3–4.4 (m, 1H), 5.0–5.1 (m, 5H), 5.7–5.8 (m, 1H), 7.0–7.4 (m, 5H); ^{13}C NMR (125 MHz, 363 K, toluene-d_8) −5.2, −5.1, 12.8, 13.4, 18.3, 18.4, 18.5, 26.1, 26.2, 39.7, 55.4, 62.6, 66.9, 70.9, 118.0, 125.5, 128.3, 128.4, 128.6, 134.4; IR (film) 680, 777, 839, 1028, 1107, 1211, 1251, 1463, 1497, 1728, 2867, 2947, 3447; LSIMSHR $C_{29}H_{54}NO_4Si_2$ $(M+H)^+$ calcd 536.3591, found 536.3584; $[\alpha]_D^{20}$ +5.6 (*c* 1.7, $CHCl_3$).

4.2.13. (1*S*,2*S*,4*S*,*R*)-[1-(*tert*-Butyldimethylsilanyloxymethyl)-4,5-dihydroxy-2-triisopropylsilanyloxypentyl]-carbamic acid benzyl ester, 16. Compound **15** (4.7 g, 8.7 mmol) was dissolved in a mixture of acetone (50 mL) and water (7 mL) then treated sequentially with 4-methylmorpholine *N*-oxide (1.66 g, 14.2 mmol) and a solution of OsO_4 in *tert*-butanol (6.1 mL, 0.05 M). The reaction mixture was stirred overnight at room temperature. Saturated aqueous $KHSO_3$ was added and, after 10 min, the reaction mixture was extracted with ethyl acetate. Chromatography (silica, hexane/ethyl acetate, gradually from 9:1 to 6:4) gave **16** as a mixture of two epimers (4 g, 81%). ^{1}H NMR (500 MHz, 363 K, toluene-d_8) 0.06 (s, 3H), 0.07 (s, 3H), 0.08 (s, 3H), 0.10 (s, 3H), 0.92 (s, 9H), 0.95 (s, 9H), 1.08 (s, 18H), 1.08 (s, 3H), 1.09 (s, 18H), 1.09 (s, 3H), 1.6–1.7 (m, 2H), 1.80 (dt, $J_t=8.3$ Hz, $J_d=14.4$ Hz, 1H), 2.10 (brs, 1H), 2.53 (brs, 1H), 3.13 (dd, $J=10.7$, 7.0 Hz,

1H), 3.24 (dd, $J=10.7$, 6.6 Hz, 1H), 3.28 (dd, $J=10.8$, 3.6 Hz, 1H), 3.38 (dd, $J=10.8$, 3.9 Hz, 1H), 3.7–3.8 (m, 8H), 4.0–4.1(5) (m, 2H), 4.39 (ddd, $J=8.2$, 4.8, 2.2 Hz, 1H), 4.60 (ddd, $J=9.3$, 4.5, 1.5 Hz, 1H), 5.0–5.1 (m, 6H), 5.24 (d, $J=9.0$ Hz, 1H), 7.0–7.1 (m, 10H); ^{13}C NMR (125 MHz, 363 K, toluene-d_8) −5.2, −5.2, −5.1, −5.1, 13.5, 18.5, 18.5, 26.2, 26.2, 38.3, 39.0, 55.7, 57.0, 62.7, 63.2, 67.1, 67.2, 67.5, 67.5, 69.0, 69.5, 69.9, 70.4, 128.2, 128.3, 128.5, 128.8, 128.9, 129.1, 137.7; LSIMSHR $C_{29}H_{56}NO_6Si_2$ $(M+H)^+$ calcd 570.3646, found 570.3653.

4.2.14. (1*S*,2*S*)-[1-(*tert*-Butyldimethylsilanyloxymethyl)-4-oxo-2-triisopropylsilanyloxybutyl]carbamic acid benzyl ester, 17. To a magnetically stirred suspension of silica gel (14 g) in CH_2Cl_2 (112 mL) was added a solution of $NaIO_4$ (1.95 g, 9.1 mmol) in water (14 mL) dropwise, followed by a solution of diol **16** (4.0 g, 7.0 mmol) in CH_2Cl_2 (17 mL) and the resulting mixture was stirred overnight at room temperature. Silica gel was removed by filtration and the filtrate was washed with water and brine, and dried over $MgSO_4$. The crude product (3.8 g) was used for the next reaction. For analytical purposes, a sample of the crude reaction mixture was chromatographed (silica, hexane/ethyl acetate, 9:1). ^{1}H NMR (500 MHz, 363 K, toluene-d_8) 0.0–0.1 (m, 6H), 0.9–1.0(5) (m, 30H), 2.19 (dt, $J_t=7.2$ Hz, $J_d=12.8$ Hz, 1H), 2.3–2.4 (m, 1H), 3.9–3.9(6) (m, 2H), 4.02 (d, $J=3.3$ Hz, 1H), 4.80 (dt, $J_t=7.4$ Hz, $J_d=10.7$ Hz, 1H), 5.0–5.0(5) (m, 1H), 5.11 (s, 1H), 5.36 (dd, $J=12.1$, 6.1 Hz, 1H), 5.5–5.7 (s, 1H), 7.0–7.3 (m, 5H); ^{13}C NMR (125 MHz, 363 K, toluene-d_8) −5.3, −5.2, 12.8, 12.8, 18.3, 18.3, 26.2, 26.4, 62.3, 67.1, 70.6, 80.9, 128.6, 1238.9, 129.1; IR (film) 875, 1111, 1255, 1410, 1715, 2880, 2960, 3480 cm^{-1}; LSIMSHR $C_{28}H_{52}NO_5Si_2$ $(M+H)^+$ calcd 560.3204, found 560.3212.

4.2.15. (2*S*,3*S*)-[2-(*tert*-Butyldimethylsilanyloxymethyl)-3-triisopropylsilanyloxy]pyrrolidine-1-carboxylic acid benzyl ester, 18. To the solution of compound **17** (3.8 g, crude) in a mixture of concentrated acetic acid (38 mL) and methanol (38 mL) was added $NaBH_3CN$ (8 g, 127 mmol) and the temperature was maintained below 30°C. When the reaction was complete by TLC, the reaction mixture was diluted with water and neutralised with solid $NaHCO_3$. Extraction with ethyl acetate afforded an oil (3.8 g), which was used in the next reaction without purification. For analytical purposes, a sample of the crude reaction mixture was chromatographed (silica, hexane/ethyl acetate, 9:1). ^{1}H NMR (500 MHz, 363 K, toluene-d_8) 0.03 (s, 3H), 0.05 (s, 3H), 0.92 (s, 9H), 1.0–1.1 (m, 21H), 1.78 (ddt, $J_t=7.4$ Hz, $J_d=12.3$, 2.6 Hz, 1H), 3.2–3.4 (m, 1H), 3.5–3.5(6) (m, 1H), 3.82 (s, 1H), 3.97 (d, $J=9.2$ Hz, 1H), 4.08 (s, 1H), 4.25 (dt, $J_t=7.2$ Hz, $J_d=9.6$ Hz, 1H), 5.1–5.2 (m, 3H), 7.0–7.1 (m, 5H); ^{13}C NMR (125 MHz, 363 K, toluene-d_8) −5.3, 12.8, 12.9, 18.3, 26.3, 33.1, 44.3, 61.6, 66.9, 72.5, 128.6, 128.7, 128.9, 154.9; IR (film) 829, 1085, 1110, 1410, 1710, 2880, 2960 cm^{-1}; LSIMSHR $C_{22}H_{52}NO_4Si_2$ $(M+H)^+$ calcd 522.3435, found 522.3428; $[\alpha]_D^{20}$ 27.6 (*c* 1.5, $CHCl_3$).

4.2.16. (2*S*,3*S*)-[2-(Hydroxymethyl)-3-triisopropylsilanyloxy]pyrrolidine-1-carboxylic acid benzyl ester 19. Compound **18** (3.8 g) was dissolved in a mixture of concentrated acetic acid (10 mL) and methanol (30 mL), and the resulting solution was heated under reflux for 1 h, then cooled to room temperature, diluted with water, and neutralised with solid $NaHCO_3$. Extraction with CH_2Cl_2 followed by chromatography (silica, hexane/ethyl acetate, 9:1) gave a colourless oil (2.6 g, 91% starting from **16**). ^{1}H NMR (500 MHz, 363 K, toluene-d_8) 0.9–1.0 (m, 21H), 1.6–1.8 (m, 2H), 3.1–3.2 (m, 1H), 3.3–3.4 (m, 1H), 3.8–3.8(6) (m, 1H), 3.89 (m, 1H), 4.02 (s, 1H), 4.21 (dd, $J=7.3$, 6.9 Hz, 1H), 5.02 (AB/2, $J=12.4$ Hz, 1H), 5.10 (AB/2, $J=12.4$ Hz, 1H), 6.9(5)–7.2(5) (m, 5H); ^{13}C NMR (125 MHz, 363 K, toluene-d_8) 12.8, 18.2, 33.4, 44.1, 62.9, 67.3, 73.5, 128.7, 128.8, 129.1, 137.6; IR (film) 684, 882, 999, 1088, 1131, 1359, 1418, 1703, 2866, 2944, 3446 cm^{-1}; LSIMSHR $C_{22}H_{38}NO_4Si$ $(M+H)^+$ calcd 408.2570, found 408.2566.

4.2.17. (2*R*,3*S*)-3-Triisopropylsilanyloxypyrrolidine-1,2-dicarboxylic acid-1-benzyl ester, 20. Alcohol **19** (770 mg, 1.9 mmol) was dissolved in the mixture of CCl_4 (3.8 mL) and acetonitrile (3.8 mL) then water (5.7 mL), $NaIO_4$ (1.67 g, 7.8 mmol) and $RuCl_3{\cdot}xH_2O$ (10 mg, 0.05 mmol) were added. The resulting biphasic mixture was vigorously stirred overnight at rt. CH_2Cl_2 (10 mL) was added and the phases were separated. The upper aqueous phase was extracted with CH_2Cl_2 and the combined organic extracts were dried ($MgSO_4$) and concentrated to afford the crude product (790 mg). For analytical purposes, a sample of the crude reaction mixture was chromatographed (silica, hexane/ethyl acetate). ^{1}H NMR (500 MHz, 363 K, toluene-d_8) 1.0–1.0(7) (m, 21H), 1.7–1.7(6) (m, 1H), 2.0–2.1 (m, 1H), 3.2–3.3 (m, 1H), 3.6–3.7 (m, 1H), 4.36 (q, $J=7.4$ Hz, 1H), 4.44 (s, 1H), 5.07 (AB/2, $J=12.4$ Hz, 1H), 5.12 (AB/2, $J=12.4$ Hz, 1H), 7.0–7.3 (m, 5H); ^{13}C NMR (125 MHz, 363 K, toluene-d_8) 12.8, 18.2, 33.0, 44.4, 63.6, 67.4, 73.4, 128.3, 128.8, 129.1, 154.7, 173.8; IR (film) 870, 1122, 1352, 1410, 1710, 2880, 2960, 2500–3600 m^{-1}; LSIMSHR $C_{22}H_{36}NO_5Si$ $(M+H)^+$ calcd 422.2363, found 422.2364; $[\alpha]_D^{20}$ −7.3 (*c* 2.3, $CHCl_3$).

4.2.18. *cis*-(2*R*,3*S*)-3-Hydroxyproline, 1. Compound **20** (131 mg, 0.31 mmol) was dissolved in acetonitrile (1.5 mL) in a Teflon Erlenmayer flask. Hydrofluoric acid (0.4 mL, 40%) and silica gel (40 mg) were added, and the resulting mixture was stirred for 50 min at 50–60°C. The excess hydrofluoric acid was decomposed by addition of silica gel (250 mg). The solvents were removed and the remaining silica gel was loaded onto the top of a silica column for chromatography. Chromatography (silica, CH_2Cl_2/methanol, solvent gradient from 95:5 to 70:30 with the addition of 0.3% HCOOH from the beginning) afforded the desired product **21** (67 mg, 81%). Hydrogenation of the hydroxy acid **21** (49 mg, 0.2 mmol) in methanol (1 mL) in the presence of Pd/C (10%) for 18 h followed by filtration through Celite and evaporation gave white crystals of **1** (24 mg, 99%). ^{1}H NMR (500 MHz, D_2O) 2.0–2.1 (m, 1H), 2.1(4)–2.2 (m, 1H), 3.33 (dt, $J_t=11.7$ Hz, $J_d=2.8$ Hz, 1H), 3.49 (dt, $J_t=10.8$ Hz, $J_d=7.7$ Hz, 1H), 3.99 (d, $J=4.1$ Hz, 1H),

4.63 (m, 1H); ^{13}C NMR (125 MHz, D_2O) 36.4, 46.6, 70.5, 74.4; IR (film) 870, 1122, 1352, 1410, 1710, 2880, 2960, 2500–3600 m^{-1}; EI MSHR $C_5H_9NO_3$ $(M)^+$ calcd 131.0582, found 131.0583; $[\alpha]_D^{20}$ +89 (*c* 0.7, H_2O), mp 225–235°C {lit. 220–230°C}.

4.2.19. *cis*-(2*R*,3*S*)-3-Hydroxyproline hydrochloride 22. To a solution of compound **18** (100 mg, 0.25 mmol) in THF (1 mL) was added $Bu_4NF{\cdot}3H_2O$ (150 mg, 0.48 mmol) and the reaction mixture was stirred for 1.5 h at room temperature. Aqueous $NaHCO_3$ was added and the reaction mixture was extracted with ether. Column chromatography (silica, hexane/ethyl acetate, from 1:1 to 3:7) afforded the deprotected compound (57 mg, 92%). Hydrogenation in the presence of Pd/C (10%) followed by the addition of AcCl (0.1 mL, 1.4 mmol) gave compound **22** (31 mg, 90%). ^{1}H NMR (200 MHz, D_2O) 1.9–2.4 (m, 2H), 3.4–4.1 (m, 6H); ^{13}C NMR (50 MHz, D_2O) 33.4, 44.0, 58.4, 66.1, 70.6; IR (film) 1058, 1395, 1462, 1674, 2743, 2958, 3361 cm^{-1}; EI MSHR for free amine $C_5H_{11}NO_2$ $(M)^+$ calcd 117.0790, found 117.0790; $[\alpha]_D^{20}$ +16.9 (*c* 1.1, MeOH).

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