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A Total Synthesis of Hydroxylysine in Protected Form and Investigations of the Reductive Opening of *p*-Methoxybenzylidene Acetals

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A synthesis of (2*S*,5*R*)-5-hydoxylysine, based on (*R*)-malic acid and Williams glycine template as chiral precursors, has been developed. This afforded hydroxylysine, suitably protected for direct use in peptide synthesis, in 32% yield over the 13-step sequence. Regioselective reductive opening of a *p*-methoxybenzylidene acetal and alkylation of the Williams glycine template were key steps in the synthetic sequence. Surprisingly, the regioselectivity in opening of the *p*-methoxybenzylidene acetal was reversed as compared to what was expected. It was found that this was due to chelation of the trialkylsilyl choride, used as an electrophile in the reductive opening, to an adjacent azide functionality. It was also discovered that an equivalent amount of trialkylsilyl hydride was formed in the reaction, a finding that led to additional mechanistic insight into reductive openings of *p*-methoxybenzylidene acetals with sodium cyanoborohydride as reducing agent.

Introduction

Collagen is the most abundant protein found in mammals. This fibrous protein has structural functions and is found in slightly different forms in almost all organs. Lysine residues in collagen can undergo posttranslational hydroxylation to give (2*S*,5*R*)-5-hydroxylysine, which was first discovered in protein hydrolysates.[1,2] In addition, the hydroxylysine residues may be glycosylated, either with a β-D-galactopyranosyl- or an α-D-glucopyranosyl-(1→2)-β-D-galactopyranosyl moiety.[3] The structure of the naturally occurring (2*S*,5*R*)-5-hydroxylysine was determined in 1950,[4,5] and the first synthesis of racemic 5-hydroxylysine was reported at the same time.[6] Since then a number of syntheses leading to stereoisomeric mixtures of hydroxylysine have been published, and it has been shown that the four stereoisomers can be separated by fractional crystallization after derivatization.[7,8]

During recent years some approaches for stereoselective syntheses of (2*S*,5*R*)-5-hydroxylysine and its stereoisomers have been reported. Two routes starting from *S*-glutamic acid were based on nonstereoselective reductions of a carbonyl group at C-5 in the side chain, and thus required separation of the resulting diasteromers to provide optically pure material.[9,10] A procedure that combined the Schöllkopf method to generate the α-stereogenic center and a Sharpless asymmetric aminohydroxylation to create the 2-aminoethanol moiety of hydroxylysine turned out to be less suitable for preparation of the naturally occurring (2*S*,5*R*)-isomer than for synthesis of the (2*S*,5*S*)-isomer.[11] However, an attractive approach based on chiral glycine template methodology and use of (*R*)-hydroxynitrile lyase for the introduction of chirality at the α-position and in the side chain, respectively, has been described.[12] Two recent reports describe the synthesis of both (2*S*,5*R*)- and (2*S*,5*S*)-5-hydroxylysine through a route based on stereoselective hydroxylation of 6-substituted piperidin-2-ones.[13,14]

In view of our previous studies on the synthesis of glycosylated derivatives of hydroxylysine,[15,16] including a *C*-glycosidic analogue,[17] we were interested in the development of a synthetic route to (2*S*,5*R*)-5-hydroxy-

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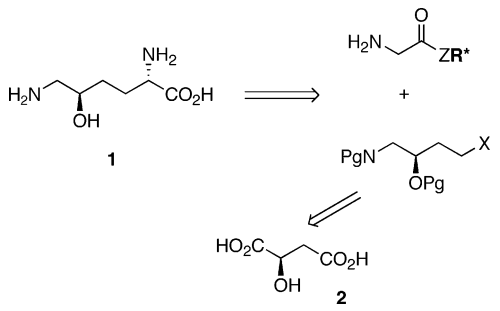
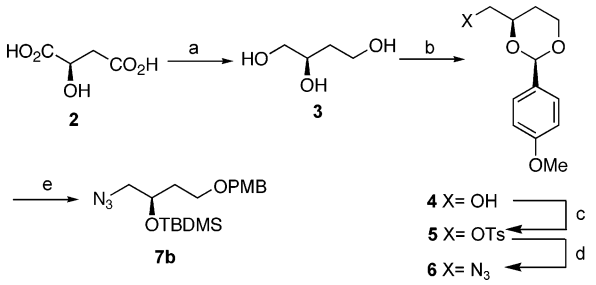


FIGURE 1. Retrosynthetic analysis of (2*S*,5*R*)-5-hydroxylysine (**1**).

SCHEME 1[a]



[a] Reagents and conditions: (a) BH_3·SMe_2, $B(OMe)_3$, THF, rt; (b) *p*-methoxybenzaldehyde, pyridinium toluene-4-sulfonate, CH_2Cl_2, reflux (89% from **2**); (c) TsCl, Et_3N, DMAP, CH_2Cl_2, rt (98%); (d) NaN_3, DMF, 55 °C (88%); (e) $NaCNBH_3$, TBDMSCl, CH_3CN, rt (89%).

lysine (**1**, Figure 1). Synthesis of hydroxylysine requires control of two stereogenic centers, the α-position and the hydroxylated C-5 in the side chain. In the synthetic route presented here the stereogenic integrity at C-5 was ascertained by preparing the side chain of hydroxylysine from (*R*)-malic acid (**2**), while chirality at the α-position was ensured by alkylation of a chiral glycine template (Figure 1).

Results and Discussion

Synthesis of a Hydroxylysine Side Chain Equivalent. The synthetic route to (2*S*,5*R*)-5-hydroxylysine (**1**) began by reduction of (*R*)-malic acid (**2**) with borane in the presence of trimethylborate (Scheme 1). This furnished triol **3**[18] without epimerization of the stereogenic center.[19] Although the reduction appeared to proceed in quantitative yield, purification of **3** by column chromatography reduced the reaction time and improved the yield in the next step. Selective acetalization[20] of the 1,3-diol in **3** was achieved by treatment with *p*-methoxybenzaldehyde and pyridinium *p*-toluenesulfonate in dichloromethane to give **4**[21] in 89% yield from **2**. Then tosylation of the hydroxyl group in **4**, followed by substitution of the tosylate with sodium azide in DMF, afforded **6** (86% from **4**).

Our aim was then to open the *p*-methoxybenzylidene acetal of **6** under reductive conditions to generate a primary alcohol while leaving the secondary alcohol protected as a *p*-methoxybenzyl ether. Several examples of regioselective reductions of *p*-methoxybenzylidene acetals in compounds closely related to **6** have been reported.[20−23] In these cases, use of DIBAL, which complexes with the sterically least hindered oxygen atom in the 1,3-dioxane moiety, resulted in unmasking of the primary hydroxyl group in high yields. Most unexpectedly, this selectivity was reversed when **6** was treated with DIBAL in dichloromethane, and secondary alcohol **7a** was obtained as the major product in 60% yield (Table 1, entry 1). Exchange of dichloromethane for diethyl ether or THF as solvent did not allow reduction with DIBAL. Several attempts toward reduction of **6** with borane and a Lewis acid under carefully controlled conditions resulted in either no reaction or reduction of the azide functionality. However, when Bu_2BOTf was used as Lewis acid **7a** was formed, but in a modest 37% yield (Table 1, entry 2).

In carbohydrate chemistry, sodium cyanoborohydride together with an electrophile is employed on a routine basis for regioselective reduction of both 4,6-*O*-benzylidene and 4,6-*O*-*p*-methoxybenzylidene acetals attached to hexopyranosides (Figure 2).[24−26] With a proton (TFA) as an electrophile, thermodynamic protonation at O-4 favors opening of *p*-methoxybenzylidene acetals to give the corresponding 6-*O*-*p*-methoxybenzyl ethers.[26] If a larger electrophile such as trimethylsilyl chloride is chosen, selectivity is reversed to favor formation of the 4-*O*-*p*-methoxybenzyl ether. In this case attack of the trimethylsilyl chloride occurs at O-6 and is assumed to be kinetically and/or sterically controlled. Reduction of **6** with sodium cyanoborohydride and trimethylsilyl chloride proceeded regioselectively, but again secondary alcohol **7a** was formed instead of the expected primary alcohol (Table 1, entry 3). Thus, the azidomethylene chain of **6** does not seem to impose sufficient steric hindrance to direct the electrophilic trimethylsilyl group to the primary oxygen atom. Alternatively, the azidomethylene group may be involved in directing the electrophile to the secondary oxygen atom of **6**. Use of larger silyl chlorides did not influence the regioselectivity, but the reductions proceeded to give mixtures of **7a** and the silylated derivatives **7b**−**d** (Table 1, entries 4−8). In all these reductions 2 equiv of sodium cyanoborohydride and the silyl chloride were used with acetonitrile as solvent at room temperature. Use of *tert*-butyldimethylsilyl chloride gave almost exclusive silylation of the secondary hydroxyl group and in acetonitrile **7b** was obtained in 89% yield (entry 5). By switching to DMF as solvent, the same selectivity was achieved and silylation was complete but the isolated yield of **7b** was lower. When even larger silyl chlorides, such as TIPSCl and TBDPSCl, were used, the reduction still proceeded, but silylation of the alcohol occurred to a lower extent (entries 7 and 8). In view of these results it was perhaps not surprising that use of

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(19) Triol **3** had $[\alpha]_D$ +26 (*c* 1.0, MeOH) [lit. +26 (*c* 1.0, MeOH, Sigma-Aldrich)].
(20) Toshima, H.; Maru, K.; Saito, M.; Ichihara, A. *Tetrahedron* **1999**, *55*, 5793−5808.
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(24) Garegg, P. J.; Hultberg, H. *Carbohydr. Res.* **1981**, *93*, c10−c11.
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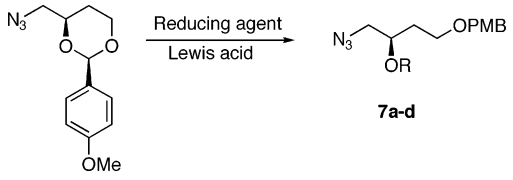
TABLE 1. Influence of Reducing Agent and Lewis Acid on the outcome of the Reductive Opening of the Benzylidene Acetal in 6



entry	reducing agent (2 equiv)	Lewis acid (2 equiv)	solvent, temp	**7a**, R = H	**7b**–**d**, R = SiR′$_3$
1	DIBAL	DIBAL	CH_2Cl_2, −78 °C	60%[a]	
2	BH_3·THF	Bu_2BOTf	CH_2Cl_2, −78 °C	37%	
3	$NaCNBH_3$	TMSCl	MeCN, rt	93%	
4	$NaCNBH_3$	TESCl	MeCN, rt	62%	**7c**, R = TES, 15%
5	$NaCNBH_3$	TBDMSCl	MeCN, rt	8%	**7b**, R = TBDMS, 89%
6	$NaCNBH_3$	TBDMSCl	DMF, rt	–	**7b**, R = TBDMS, 72%
7	$NaCNBH_3$	TBDPSCl	MeCN, rt	60%	**7d**, R = TBDPS, 30%
8	$NaCNBH_3$	TIPSCl	MeCN, rt	81%	
9	$NaCNBH_3$	TFA	MeCN, rt	85%	
10	$NaCNBH_3$	–	MeCN, rt	–	

[a] In addition, some formation of a product corresponding to **7a**, from which the PMB group had been cleaved off, was observed.

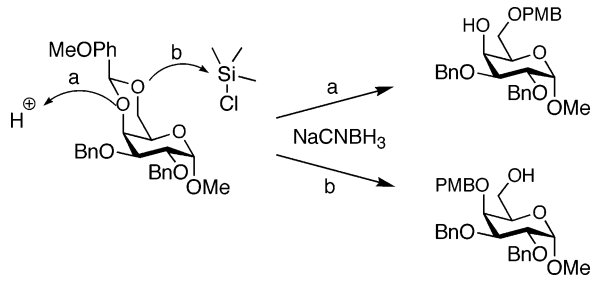


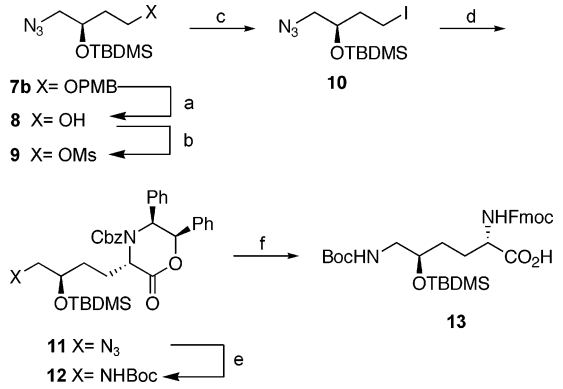
FIGURE 2. A schematic example of how the choice of electrophile determines the regioselectivity in reductive opening of 4,6-*O*-*p*-methoxybenzylidene acetals attached to carbohydrates.

TFA as Lewis acid resulted in the same regioselectivity (entry 9). When the reduction was attempted in the absence of Lewis acid compound **6** remained unreacted (entry 10), confirming that electrophilic activation of the acetal is required for the reaction to proceed.

The unexpected regioselectivity obtained in the reductive opening of the benzylidene acetal of **6** prompted a slight modification of the original synthetic route. Thus, the synthesis of hydroxylysine was continued by deprotection of the *p*-methoxybenzyl ether of **7b** with DDQ (Scheme 2). Unfortunately, the *p*-methoxybenzaldehyde formed in this step turned out to be difficult to remove by column chromatography. Therefore the mixture of alcohol **8** and *p*-methoxybenzaldehyde was subjected to mesylation followed by substitution with sodium iodide before purification to give **10** (76% overall yield from **7b**). Alkyl iodide **10**, obtained in eight steps from (*R*)-malic acid, thus constitutes a building block corresponding to the side chain of hydroxylysine.

Preparation of Hydroxylysine by Enantioselective Alkylation. Several glycine equivalents are available for preparation of chiral amino acids, and we decided to evaluate templates **14**–**16** (Figure 3) in alkylations with iodide **10**. Myers and co-workers have described that glycine coupled to pseudoephedrine (i.e. **14**) can be alkylated with alkyl halides.[27] In our hands no reaction

SCHEME 2[a]



[a] Reagents and conditions: (a) DDQ, CH_3CN/H_2O, rt; (b) MsCl, triethylamine, DMAP, CH_2Cl_2, 0 °C; (c) NaI, acetone, reflux (76% over three steps); (d) **16b**, NaHMDS, 15-crown-5, THF, −78 to −20 °C (94%); (e) (i) PPh_3, THF/H_2O, microwave, (ii) Boc_2O, triethylamine, THF (85%); (f) (i) H_2 (65 psi), Pd/C, THF/H_2O, rt, (ii) FmocOSu, Na_2CO_3, acetone/H_2O (77%).

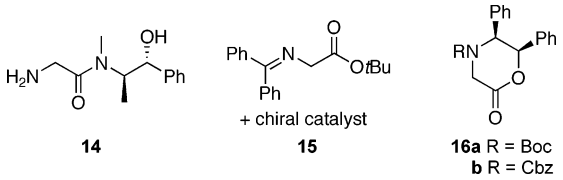


FIGURE 3. Chiral glycine templates investigated in alkylations with iodide **10**.

occurred between **14** and **10**, and the starting materials could usually be recovered. In a few of the attempts a deiodinated product, formed by transmetalation of **10** followed by protonation, could be isolated. Attention was then directed to the attractive method of catalytic enantioselective alkylation developed in the groups of Corey[28–30]

(27) Myers, A. G.; Gleason, J. L.; Yoon, T.; Kung, D. W. *J. Am. Chem. Soc.* **1997**, *119*, 656–673.
(28) Corey, E. J.; Xu, F.; Noe, M. C. *J. Am. Chem. Soc.* **1997**, *119*, 12414–12415.

and Lygo.[31−33] These research groups have reported several successful stereoselective alkylations of benzophenone-protected *tert*-butyl glycine **15** using a cinchonidinium-derived catalyst. Usually alkylations were performed with highly activated electrophiles, such as benzyl and allyl halides, but examples of nonactivated alkyl halides used in model studies also exist.[28,29] Disappointingly, alkylation according to this method failed for iodide **10**, and unreacted **10** was recovered from the reaction mixture.

Finally, the route developed by Williams relying on 2,3-diphenylmorpholinones **16** as α-amino acid templates was attempted.[34,35] This approach has previously been used in another synthesis of (2*S*,5*R*)-5-hydroxylysine by Brussee and co-workers.[12] Both enantiomers of morpholinones **16** are commercially available with the nitrogen atom protected with either a *tert*-butoxycarbonyl (Boc) or a benzyloxycarbonyl (Cbz) group (cf. **16a** and **16b**, respectively). The Boc-protected template has been reported to give better yields in alkylating reactions,[36] and this was also observed by Brussee and co-workers in their synthesis of hydroxylysine.[12] However, in the synthesis of amino acids that subsequently will be protected by an N^{α}-Fmoc group, the Cbz-protected template has the advantage that hydrogenolysis liberates both the α-amino and the α-carboxyl group. Gratifyingly, alkylation of Cbz-protected template **16b** with iodide **10**, using sodium hexamethyldisilazane as base in the presence of 15-crown-5, proceeded well and only a single diastereomer could be detected by HPLC and NMR spectroscopy (Scheme 2).[37] On a larger scale, better yields of **11** were obtained (94% for 1−3 mmol scales, as compared to 60−70% for 0.1 mmol scales) in accordance with previous experience of enolate-alkylations in our laboratory. In Brussee's synthesis of hydroxylysine, the steric bulk exerted by the protective group of the hydroxyl (TBDMS) and amino (Boc and *p*-methoxybenzyl) groups of the side chain equivalent used as alkylating agent led to low yields, which prompted a change in the synthetic route.[12] Such a problem was not observed in our case, in all probability due to the side chain N^{ϵ}-group being protected in the form of a small azido group.

To complete the synthesis of hydroxylysine, protected for use in Fmoc peptide synthesis, the azido group of **11** was reduced with triphenylphosphine, either by stirring overnight at room temperature or by heating in a microwave oven at 130 °C for 5 min. The resulting amino group was then directly protected with a *tert*-butoxycarbonyl group before compound **12** was purified by flash column chromatography (85% yield from azide **11**). Removal of the 2,3-diphenylmorpholinone auxiliary and the Cbz protective group from **12** was accomplished by hydrogenolysis at 65 psi. Finally, the hydroxylysine α-amino group was reprotected by treatment with Fmoc-succinimide, which gave orthogonally protected hydroxylysine **13** in 77% yield from **12**. Compound **13**, obtained in this manner, was compared to a sample of **13** prepared from hydroxylysine obtained from the chiral pool,[15] and was confirmed to be identical with respect to retention time on reversed-phase HPLC, optical rotation, as well as ^{1}H and ^{13}C NMR spectral data. Since both enantiomers of malic acid, as well as Williams template, are commercially available it is anticipated that the present synthetic strategy should allow all four stereoisomeres of hydroxylysine to be synthesized in a stereoselective manner.

Regioselectivity in Reductive Opening of *p*-Methoxybenzylidene Acetals. As discussed above reductive opening of the benzylidene acetal in **6** with sodium cyanoborohydride, using *tert*-butyldimethylsilyl chloride as electrophile, surprisingly gave a mixture of **7a** and **7b** in which the *p*-methoxybenzyl group was located on the primary oxygen atom (Table 1 and Scheme 3). To investigate if the unexpected regioselectivity in the reduction of **6** was due to the presence of the azido group two oxygen analogues, **18**[38] and **21**,[39] and the nonfunctionalized analogue **25**,[21] were synthesized. Replacement of the azido group in this manner was done so as to vary both the steric hindrance and the field/inductive effect[40] (0.48, 0.29, and 0.42 for N_3, MeO, and AcO, respectively) of the substituent located in position four of the 1,3-dioxane ring. Methyl ether **18** and acetate **21** were both obtained from **4** in over 80% yields under standard conditions (Scheme 3). Analogue **25** was prepared from 1,3-butanediol **24** by acetalization under the same conditions as for conversion of triol **3** into **4**. When **18** was treated with sodium cyanoborohydride and *tert*-butyldimethylsilyl chloride the regioselectivity in the opening of the *p*-methoxybenzylidene acetal was reversed as compared to reduction of the acetal in azide **6**.[41] Consequently **19** (PMB on the primary oxygen atom) and **20** (PMB on the secondary oxygen atom) were obtained in a ratio of ∼1:3.[42] Reduction of acetate **21** under identical conditions led to an even more pronounced selectivity for location of the PMB group on the secondary oxygen atom. Thus compounds **22** and **23** were formed in a ratio of 15:85. In contrast reduction of analogue **25** led to a near 1:1 mixture of the two possible isomers **26** and **27**. Surprisingly, secondary alcohols **22** and **26** resisted silylation while the related secondary alcohols **7** and **19** were predominantly silylated during the reductive opening.

The regioselectivities obtained in the reductive opening of acetals **6**, **18**, **21**, and **25** may be rationalized as follows.

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(33) Lygo, B.; Crosby, J.; Peterson, J. A. *Tetrahedron* **2001**, *57*, 6447−6453.
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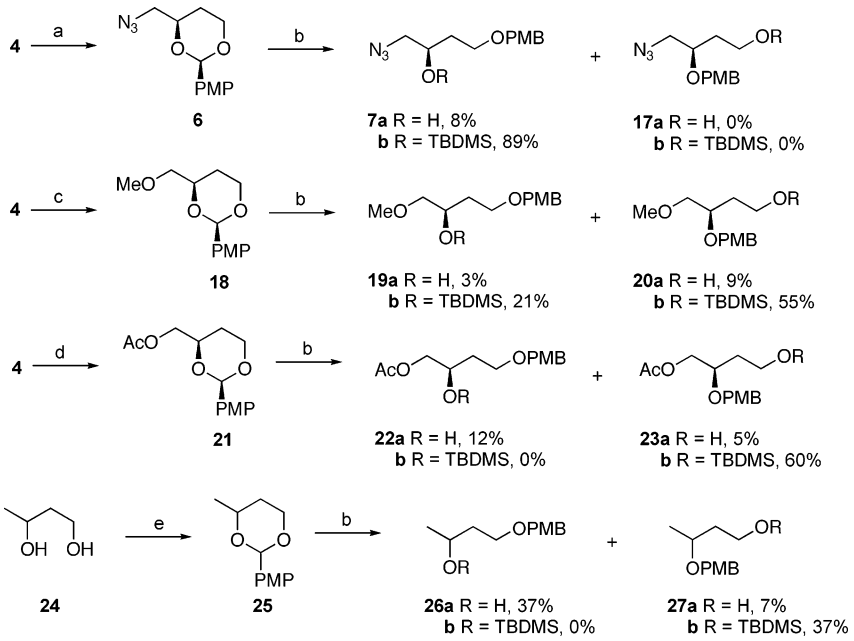
(35) Williams, R. M.; Im, M. N. *J. Am. Chem. Soc.* **1991**, *113*, 9276−9286.
(36) Baldwin, J. E.; Lee, V.; Schofield, C. J. *Synlett* **1992**, 249−251.
(37) Compound **11** was epimerized at the stereogenic center corresponding to Cα in hydroxylysine by treatment with NaHMDS (1 equiv) in THF. Analysis of the diasteromeric mixture by reversed-phase HPLC displayed two peaks having identical mass spectra. Only one of the two diastereomers was detected by HPLC when **11** was prepared by alkylation of **16b** with **10**.
(38) Sulikowski, G. A.; Lee, W.-M.; Jin, B.; Wu, B. *Org. Lett.* **2000**, *2*, 1439−1442.
(39) Herradón, B. *J. Org. Chem.* **1994**, *59*, 2891−2893.
(40) Hansch, C.; Leo, A.; Taft, R. W. *Chem. Rev.* **1991**, *91*, 165−195.
(41) Two equivalents of sodium cyanoborohydride and *tert*-butyldimethyl silyl chloride was used with acetonitrile as solvent at room temperature.

SCHEME 3[a]



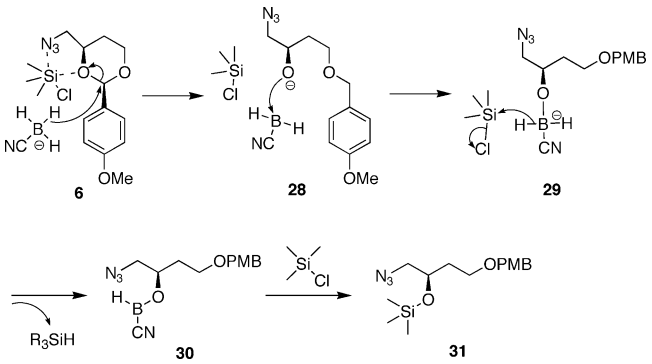
[a] Reagents and conditions: (a) (i) TsCl, triethylamine, DMAP, CH_2Cl_2, rt, (ii) NaN_3, DMF, 55 °C (86%); (b) $NaCNBH_3$, TBDMSCl, CH_3CN, rt; (c) MeI, NaH, THF, rt (83%); (d) AcCl, triethylamine, CH_2Cl_2, rt (85%); (e) *p*-methoxybenzaldehyde, pyridinium toluene-4-sulfonate, CH_2Cl_2, reflux (68%).

For **25**, the slight steric hindrance from the methyl group should direct the chelating silyl chloride to the less hindered, primary oxygen atom resulting in regioselective location of the PMB group on the secondary oxygen atom (i.e. formation of **27**). However, the field/inductive effect from the methyl group increases the Lewis basicity of the secondary oxygen atom somewhat, thereby directing the silyl chloride to the secondary and the PMB group to the primary oxygen atom. As a consequence of these opposing effects **26** and **27** are formed in almost equal amounts. By analogy with reductive opening of *p*-methoxybenzylidene acetals attached to O-4 and O-6 of carbohydrates (cf. Figure 2), the field/inductive and steric effects from the methoxymethylene and acetoxymethylene groups in **18** and **21** both contribute to directing the chelating silyl chloride to the primary oxygen atom. In agreement with this prediction, formation of products **20** and **23**, in which the PMB group is located on the secondary oxygen atom dominate over the regioisomeric, primary PMB ethers **19** and **22**. As expected, the regioselectivity is enhanced by the increased electron-withdrawing effect of the acetate in **21** as compared to that of the methoxy group of **18**. Just as for **18** and **21**, steric and inductive effects from the azidomethylene group in **6** would be expected to direct the silyl chloride to the primary oxygen atom, thus resulting in formation of secondary PMB ethers **17** as the main products. However, if chelation of the silyl chloride occurred between the azide and the adjacent secondary oxygen atom in **6** this would provide a possible explanation for the unexpected regioselectivity that led to primary PMB ether **7**. In an initial attempt to investigate this hypothesis azide **6** and the methoxy analogue **18** were treated with 0.5−2 equiv of TDBSMCl in acetonitrile-d_3. However, no alterations in any of the ^1H and ^{13}C NMR chemical shifts of **6** and **18** could be detected, and chelation could thus not be confirmed. Instead, ^{15}N-enriched azide **6** was prepared from tosylate **4** and mono-^{15}N-labeled sodium azide. The ^{15}N NMR spectrum of ^{15}N-**6** consisted of two singlets with equal intensity set 36.7 ppm apart. The downfield signal was assumed to originate from the nitrogen atom attached to the methylene carbon and the other one from the distal nitrogen atom. In this case, addition of 1 equiv of TDBMSCl to a sample of ^{15}N-**6** in acetonitrile-d_3 caused another, sharp resonance to appear slightly upfield of the signal from the nitrogen bound to the methylene carbon atom, indicating chelation of the silyl chloride to the azido group.

Mechanistic Studies. If <2 equiv of *tert*-butyldimethylsilyl chloride were used for the reductive opening of the benzylidene acetal of **6** the reaction still proceeded completely to **7**, but at a slower rate and with a lower extent of silylation. When 1 equiv of the silyl chloride was employed no silylation to give **7b** was obtained and secondary alcohol **7a** was formed as the only product. With 1.5 equiv, partial silylation gave a 1:1 mixture of nonsilylated and silylated products **7a** and **7b**. Identical results were obtained for the oxygen analogues **18** and **21**. It thus appears that 1 equiv of the silyl chloride is

(42) Products were identified, and yields estimated, in the following way. After reductive opening of compound **18** the nonsilylated and silylated products were separated by flash column chromatography. This gave a mixture of **19a** and **20a** and another mixture consisting of **19b** and **20b**, and allowed the combined yields of **19a** + **20a** and **19b** + **20b** to be determined. The mixture of **19a** and **20a** was then acetylated, after which the structures were confirmed and the ratio between the two products was determined by using ^1H NMR spectroscopy. In a similar way treatment of the mixture of **19b** and **20b** with TBAF, followed by acetylation, allowed identification and an estimation of the yields to be performed. For the secondary hydroxyl group in **19a/b** acetylation led to a downfield ^1H NMR shift of ~1.15 ppm for the proximal hydrogen atom. As expected acetylation of the primary hydroxyl group in **20a/b** caused a smaller shift (~0.35 ppm) of the adjacent hydrogen atoms. The identity and the yields for compounds **22a/b**, **23a/b**, **26a/b**, and **27a/b** obtained after reductive opening of **21** and **25** were determined in the same manner.

SCHEME 4



consumed during the reductive acetal opening. The consumption of the silyl chloride may be explained by a mechanism that begins by electrophilic activation of the acetal of **6** which, in turn, enables reductive opening to form the PMB-protected intermediate **28** (Scheme 4). The alkoxide in **28** can then react with one of the two Lewis acids, i.e., the silyl chloride or the cyanoborane. Of these two the borane should be the stronger Lewis acid, and it reacts rapidly to form borate **29**. This in turn is a more powerful reducing agent than sodium cyanoborohydride and reduces the silyl chloride to a silane with simultaneous formation of **30**. Silanes require strong Lewis acids, such as borontrifluoride etherate, to reduce acetals, and it is therefore inert under these conditions. One equivalent of silyl chloride is thus consumed in the reduction whereas additional amounts react with boron ester **30** so that the stronger Si−O bond of silyl ether **31** is formed. In support of this mechanism, *tert*-butyldimethylsilane or triethylsilane was detected by GC when TBDMSCl or TESCl, respectively, was used as electrophile in the reductive opening of the acetal in **6**. In the GC analysis *t*BuMe$_2$SiH or Et$_3$SiH was added as internal reference to confirm the identity of the silanes. In addition, the silane hydrogen atom could easily be observed at 3.63 (*t*BuMe$_2$SiH) or 3.62 (Et$_3$SiH) ppm, using one-dimensional ^{1}H NMR spectroscopy and COSY experiments (H−Si−C−H couplings were used to confirm the assignment of Si−H). Moreover, integration of the NMR spectra from the crude products obtained in the reductive openings showed that the silanes were formed in approximately equivalent amounts as compared to products **7**.

It should be pointed out that, in addition to an increased understanding of how reductive opening of *p*-methoxybenzylidene acetals proceed, the above studies have led to a new method for orthogonal protection of 1,3-diols. Thus, regioselective reductive opening of a *p*-methoxybenzylidene acetal attached to a 1,3-diol results in protection of the two hydroxyl groups with *p*-methoxybenzyl and *tert*-butyldimethylsilyl groups, respectively, provided that 2 equiv of TBDMSCl are used. However, as illustrated by the examples shown in Scheme 3, the regioselective location of the two protective groups is determined by the adjacent functionalities.

Conclusions

A synthesis of (2*S*,5*R*)-5-hydroxylysine, protected for use in peptide synthesis, has been accomplished in 13 steps with an overall yield of 32%. Alkylation of a chiral glycine equivalent, with a side chain building block prepared in eight steps from (*R*)-malic acid, constitutes a key step in the synthetic route. In the present case only alkylation of William's 2,3-diphenylmorpholinone α-amino acid template was successful. In contrast, glycine coupled to pseudoephedrine, or benzophenone-protected *tert*-butyl glycine in the presence of a cinchonidinium-derived catalyst, could not be successfully alkylated. The regioselective reductive opening of a *p*-methoxybenzylidene acetal with sodium cyanoborohydride in the presence of a trialkylsilyl chloride constitutes another key step in the synthesis. Unexpectedly, it was discovered that a neighboring azido group reversed the regioselectivity of this opening, compared with what could be predicted from previous reports in the literature. This was found to be due to complexation between the silyl chloride and the azido group. It was also discovered that 1 equiv of silyl chloride was reduced to a silane during the reductive opening, whereas additional amounts led to silylation of one of the hydroxyl groups originally protected in the acetal. In addition to providing an increased mechanistic understanding of the reductive openings of *p*-methoxybenzylidene acetals our studies also revealed a new route for orthogonal protection of the two hydroxyl groups of 1,3-diols with *p*-methoxybenzyl and *tert*-butyldimethylsilyl groups, respectively.

Experimental Section

General experimental details are provided in the Supporting Information.

[(2*R*,4*R*)-2-(4-Methoxyphenyl)-1,3-dioxan-4-yl]methanol (4). A solution of (*R*)-malic acid (**2**, 10.0 g, 74.6 mmol) in THF (50 mL) was transferred to a solution of BH_3·SMe_2 (2 M in THF, 120 mL, 240 mmol) and $B(OMe)_3$ (27 g, 260 mmol) in THF (50 mL) cooled to 0 °C. After the mixture was stirred at room temperature for 16 h MeOH (75 mL) was added and the solution was concentrated. The crude product was purified by flash column chromatography (CH_2Cl_2:MeOH 9:1−5:1) and the solvents were evaporated. The residue was suspended in CH_2Cl_2 (270 mL) and 4-methoxybenzaldehyde (15.2 g, 112 mmol) and pyridinium toluene-4-sulfonate (187 mg, 0.746 mmol) were added. The resulting mixture was heated at reflux overnight in a Soxhlet apparatus containing 4 Å molecular sieves. $NaHCO_3$ (250 mg) was added and the solvent was evaporated. Flash column chromatography (heptane:ethyl acetate 2:1−1:1) gave alcohol **4**[21] (14.9 g, 89%) as a colorless oil.

[(2*R*,4*R*)-2-(4-Methoxyphenyl)-1,3-dioxan-4-yl]methyl 4-Methylbenzenesulfonate (5). Triethylamine (13.5 mL, 97 mmol), 4-(*N*,*N*-dimethylamino)pyridine (790 mg, 6.47 mmol), and toluene-4-sulfonyl chloride (13.6 g, 71.1 mmol) were added to a solution of alcohol **4** (14.5 g, 64.7 mmol) in CH_2Cl_2 (110 mL). The solution was stirred for 15 min, precipitated triethylammonium chloride was filtered off ,and the solvent was evaporated. Flash column chromatography (heptane:ethyl acetate 4:1−1:1) gave tosylate **5** (23.8 g, 98%) as a slightly yellow solid. $[\alpha]_D$ +2.3 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.78 (d, J = 8.3 Hz, 2H, Ph), 7.32 (d, J = 8.6 Hz, 2H, Ph), 7.29 (d, J = 8.3 Hz, 2H, Ph), 6.86 (d, J = 8.6 Hz, 2H, Ph), 5.41 (s, 1H, $PhCHO_2$), 4.26 (ddd, J = 11.6, 5.3, 1.3 Hz, 1H, CH_2OTs), 4.14−4.01 (m, 3H, CH_2OTs, 2 OCH_2CH$_2$), 3.93 (dt, J = 11.6, 2.5 Hz, 1H, CHCH$_2$OTs), 3.80 (s, 3H, OCH_3), 2.43 (s, 3H, PhCH_3), 1.93 (dq, J = 12.0, 5.1 Hz, 1H, CCH_2C), 1.51−1.49 (m, 1H, CCH_2C); ^{13}C NMR ($CDCl_3$) δ 159.9 (Ph), 144.8 (Ph), 132.6 (Ph), 130.4 (Ph), 129.7 (Ph), 127.9 (Ph), 127.3 (Ph), 113.4 (Ph), 100.8 (Ph*C*HO$_2$), 73.9 (*C*HCH$_2$OTs), 71.5 (O*C*H$_2$CH$_2$), 66.1 (OCH_3), 55.2 (TsO*C*H$_2$), 27.0 (*C*H$_3$Ph), 21.5 (OCH$_2$*C*H$_2$); HR-MS (FAB) calcd for $C_{19}H_{22}O_6S$ 379.1215 $[M]^+$, found 379.1214.

(2*R*,4*S*)-4-(2-Azidoethyl)-2-(4-methoxyphenyl)-1,3-dioxane (6). NaN_3 (20.2 g, 312 mmol) was added to a solution of tosylate **5** (23.6 g, 62.4 mmol) in DMF (170 mL) and the mixture was heated at 55 °C for 24 h, then poured onto H_2O and EtOAc. The organic phase was washed five times with H_2O, dried over Na_2SO_4, filtered, and concentrated. Flash column chromatography (heptane:ethyl acetate 3:1) gave azide **6** (13.7 g, 88%) as a colorless oil. $[\alpha]_D$ −11.1 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.43 (d, J = 8.6 Hz, 2H, Ph), 6.89 (d, J = 8.6 Hz, 2H, Ph), 5.52 (s, 1H, PhC*H*O_2), 4.30 (ddd, J = 11.3, 5.1, 1.2 Hz, 1H, OC*H*$_2$$CH_2$), 4.12−4.05 (m, 1H, C*H*CH_2N_3), 3.98 (dt, J = 12.0, 1.2 Hz, 1H, OC*H*$_2$$CH_2$), 3.80 (s, 3H, OCH_3), 3.43 (dd, J = 13.0, 6.8 Hz, 1H, N_3CH_2), 3.29 (dd, J = 13.0, 3.9 Hz, 1H, N_3CH_2), 1.93 (dq, J = 12.0, 5.1 Hz, 1H, CCH_2C), 1.51−1.49 (m, 1H, C*H*$_2$$CH_2O$); ^{13}C NMR ($CDCl_3$) δ 159.9 (Ph), 130.6 (Ph), 127.2 (Ph), 113.5 (Ph), 100.9 (Ph*C*HO_2), 75.9 (*C*HCH_2N_3), 66.4 (O*C*H_2CH_2), 55.2 (OCH_3), 54.7 (N_3CH_2), 28.1 (CCH_2C); HR-MS (FAB) calcd for $C_{12}H_{16}N_3O_3$ 250.1192 $[M + H]^+$, found 250.1197.

[(1*R*)-1-Azidomethyl-3-(4-methoxybenzyloxy)propyl]oxy-*tert*-butyldimethylsilane (7b). TBDMSCl (16.2 g, 108 mmol) and $NaCNBH_3$ (6.8 g, 108 mmol) were added to a solution of azide **6** (13.4 g, 53.8 mmol) in CH_3CN (300 mL). After being stirred for 30 min, the reaction was quenched by the addition of $NaHCO_3$ (aq, sat.). The mixture was extracted three times with CH_2Cl_2, and the combined organic phases were washed with $NaHCO_3$ (aq, sat.) and H_2O, dried over Na_2SO_4, filtered, and concentrated. Flash column chromatography (heptane:ethyl acetate 3:1) gave **7b** (17.5 g, 89%) as a colorless oil. $[\alpha]_D$ +1.1 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.24 (d, J = 8.6 Hz, 2H, Ph), 6.88 (d, J = 8.6 Hz, 2H, Ph), 4.45 (s, 2H, Ph*C*HO_2), 4.01−3.94 (m, 1H, N_3CH_2C*H*), 3.80 (s, 3H, OCH_3), 3.69 (ddd, J = 9.4, 5.9, 4.5 Hz, 1H, PMBOC*H*$_2$), 3.62 (ddd, J = 9.4, 7.9, 4.2 Hz, 1H, PMBOC*H*$_2$), 3.32−3.22 (m, 1H, N_3CH_2), 3.20 (d, J = 3.3 Hz, 1H, N_3CH_2), 1.86−1.69 (m, 2H, $PMBOCH_2$-
C*H*$_2$), 0.93 (s, 9H, *t*Bu), 0.13 (s, 6H, $SiCH_3$); ^{13}C NMR ($CDCl_3$) δ 159.2 (Ph), 130.0 (Ph), 128.1 (Ph), 113.5 (Ph), 72.6 (CH_2Ph), 69.2 (N_3CH_2CH), 65.9 (PMBO*C*H_2), 56.9 ($N_3C$$H_2$), 56.2 ($OCH_3$), 35.0 ($PMBOCH_2C$$H_2$), 25.7 (C(*C*$H_3$)$_3$), 17.6 (*C*($CH_3$)$_3$), −4.6 ($SiCH_3$), −4.9 ($SiCH_3$); HR-MS (FAB) calcd for $C_{18}H_{32}N_3O_3Si$ 366.2213 $[M + H]^+$, found 366.2215.

[(1*R*)-1-Azidomethyl-3-iodopropyl]oxy-*tert*-butyldimethylsilane (10). DDQ (1.13 g, 4.96 mmol) was added to a solution of **7b** (1.51 g, 4.13 mmol) in CH_2Cl_2:H_2O 8:1 (v:v, 30 mL). After the solution was stirred for 20 min, the solids were filtered off through a pad of Celite that was washed with CH_2Cl_2. The solution was concentrated and the residue was purified by flash column chromatography (heptane:ethyl acetate 3:1) to afford a mixture of alcohol **8** and *p*-methoxybenzaldehyde. Triethylamine (627 mg, 6.20 mmol), DMAP (50 mg, 0.413 mmol), and methanesulfonyl chloride (710 mg, 6.20 mmol) were added to this mixture dissolved in CH_2Cl_2 (6 mL) at 0 °C. After being stirred for 10 min the mixture was poured onto HCl (0.1% aq) and CH_2Cl_2 at 0 °C. The organic phase was washed with NaCl (aq, sat.), dried over Na_2SO_4, filtered, and concentrated. The residue (crude **9**) was dissolved in acetone (10 mL), NaI (1.24 g, 8.26 mmol) was added, and the resulting slurry was heated to reflux for 1 h. The reaction was quenched by the addition of NaCl (aq, sat.) and the organic phase was extracted twice with CH_2Cl_2. The combined organic phases were dried over Na_2SO_4, filtered, and concentrated. Flash column chromatography (heptane:ethyl acetate 15:1) gave iodide **10** (1.11 g, 76%) as a colorless oil of low viscosity. $[\alpha]_D$ +13.5 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 3.91 (dq, J = 6.7, 4.8 Hz, 1H, C*H*OTBDMS), 3.34 (dd, J = 12.6, 4.8 Hz, 1H, N_3CH_2), 3.24−3.17 (m, 2H, ICH_2), 3.16 (dd, J = 12.6, 4.8 Hz, 1H, N_3CH_2), 2.09−2.01 (m, 2H, ICH_2C*H*$_2$), 0.91 (s, 9H, C(CH_3)$_3$), 0.14 (s, 6H, Si(CH_3)$_2$); ^{13}C NMR ($CDCl_3$) δ 71.4 (*C*HOTBDMS), 56.1 (N_3CH_2), 38.6 (ICH_2), 25.8 (C(*C*H_3)$_3$), 18.0 (*C*(CH_3)$_3$), 1.8 (ICH_2*C*H_2), −4.6 ($SiCH_3$), −4.8 ($SiCH_3$); HR-MS (FAB) calcd for $C_{10}H_{23}IN_3O_3Si$ 356.0655 $[M + H]^+$, found 356.0658.

Benzyl (3*S*,5*S*,6*R*)-3-[(3*R*)-4-Azido-3-(*tert*-butyldimethylsilyloxy)butyl]-2-oxo-5,6-diphenylmorpholine-4-carboxylate (11). Iodide **10** (917 mg, 2.58 mmol) was added to a solution of 15-crown-5 (1.13 g, 5.16 mmol), William's template **16b**, and NaHMDS (498 mg, 2.58 mmol) in THF (60 mL) cooled to −78 °C. After 30 min at −78 °C the solution was allowed to attain −20 °C during 4 h, poured onto H_2O, and extracted three times with EtOAc. The combined organic phases were dried over Na_2SO_4, filtered, and concentrated. Flash column chromatography (heptane:ethyl acetate 4:1) gave **11** (1.50 g, 94%) as a white amorphous solid. $[\alpha]_D$ −25.7 (*c* 1.0, $CHCl_3$); ^1H NMR (DMSO-d_6, run at 368 K to avoid duplication of the spectrum due to the presence of morpholine conformers) δ 7.30−7.01 (m, 13H, Ph), 6.57 (d, J = 7.3 Hz, 2H, Ph), 6.18 (d, J = 2.3 Hz, 1H, COOC*H*Ph), 5.29 (d, J = 2.3 Hz, 1H, NC*H*Ph), 5.05−4.92 (m, 2H, PhC*H*$_2$OCO), 4.79 (d, J = 7.3 Hz, OCOC*H*N), 3.97−3.89 (m, 1H, N_3CH_2C*H*), 3.42−3.34 (m, 1H, N_3CH_2), 3.28−3.20 (m, 1H, N_3CH_2), 2.23−2.12 (m, 2H, OCOCHC*H*$_2$), 1.79−1.70 (m, 2H, N_3CH_2CHC*H*$_2$), 0.90 and 0.87 (2s, 9H, C(CH_3)$_3$), 0.12 and −0.02 (2s, 6H, Si(CH_3)$_2$);[43] HR-MS (FAB) calcd for $C_{34}H_{43}N_4O_5Si$ 615.3003 $[M + H]^+$, found 615.3007.

Benzyl (3*S*,5*S*,6*R*)-3-[(3*R*)-4-(*tert*-Butoxycarbonylamino)-3-(*tert*-butyldimethylsilyloxy)butyl]-2-oxo-5,6-diphenylmorpholine-4-carboxylate (12). PPh_3 (599 mg, 2.28 mmol) was added to a solution of azide **11** (936 mg, 1.52 mmol) in moist THF (14 mL). This solution was heated in a microwave oven for 5 min at 130 °C in three portions (4.7 mL each). Alternatively, the solution could be stirred at room temperature for 16 h. Boc_2O (498 mg, 2.28 mmol) and triethylamine (185 mg, 1.83 mmol) were added, and the resulting solution was stirred for 20 min after which 5 drops of H_2O_2 (30% aq) was added and allowed to react for 5 min. Evaporation of the solvents and purification of the residue by flash column chromatography (heptane:ethyl acetate 9:1−4:1) gave **12** (891 mg, 85%) as a white amorphous solid. $[\alpha]_D$ −23.8 (*c* 1.0, $CHCl_3$); ^1H NMR (DMSO-d_6, run at 368 K to avoid duplication of the spectrum due to the presence of morpholine conformers) δ 7.20−6.91 (m, 13H, Ph), 6.56 (d, J = 7.7 Hz, 2H, Ph), 6.31 (br s, 1H, Boc*H*N), 6.19 (d, J = 3.3 Hz, 1H, COOC*H*Ph), 5.29 (d, J = 3.3 Hz, 1H, NC*H*Ph), 5.01−4.92 (m, 2H, PhC*H*$_2$OCO), 4.79 (d, J = 7.5 Hz, OCOC*H*N), 3.84−3.76 (m, 1H, N_3CH_2C*H*), 3.06−2.98 (m, 2H, N_3CH_2), 2.24−2.15 (m, 2H, OCOCHC*H*$_2$), 1.71−1.55 (m, 2H, N_3CH_2CHC*H*$_2$), 1.36 (s, 9H, OC(CH_3)$_3$), 0.88 and 0.86 (2s, 9H, SiC(CH_3)$_3$), 0.08 and 0.06 (2s, 6H, Si(CH_3)$_2$);[43] HR-MS (FAB):calcd for $C_{39}H_{53}N_2O_7Si$ 689.3622 $[M + H]^+$, found 689.3625.

(5*R*)-*N*$^{\alpha}$-(Fluoren-9-ylmethoxycarbonyl)-*N*$^{\epsilon}$-(*tert*-butoxycarbonyl)-5-*O*-(*tert*-butyldimethylsilyl)-5-hydroxy-L-lysine (13). Pd/C (10%, 580 mg) was added to a solution of **12** (580 mg, 0.842 mmol) in THF:H_2O (1:1, 18 mL) containing 1 drop of AcOH. The mixture was hydrogenated overnight at 65 psi, filtered through Celite, and concentrated. The solid residue was dissolved in acetone (10 mL), and *N*-(9*H*-fluorene-2-ylmethoxycarbonyloxy)succinimide (298 mg, 0.884 mmol) and Na_2CO_3 (10% aq, 8 mL) were added. After being stirred overnight the homogeneous solution was poured onto HCl (0.1 M aq) and extracted three times with EtOAc. The organic phases were then dried over Na_2SO_4, filtered, and concentrated. Purification by flash column chromatography (heptane: ethyl acetate 9:1−3:1) gave amino acid **13** (386 mg, 77%). Optical rotation and ^1H and ^{13}C NMR data were identical with values previously reported.[15] HR-MS (FAB) calcd for $C_{32}H_{47}N_2O_7Si$ 599.3153 $[M + H]^+$, found 599.3145.

(2*R*,4*R*)-4-Methoxymethyl-2-(4-methoxyphenyl)-1,3-dioxane (18). NaH (75 mg, 3.1 mmol) and MeI (117 μL, 1.9 mmol) were added to a solution of alcohol **4** (350 mg, 1.6 mmol) in THF (5 mL) and the mixture was stirred at room temperature for 5 min, then poured onto NH_4Cl (aq) and EtOAc. The organic phase was washed NaCl (aq, sat.) and dried over Na_2-

(43) The TBDMS group underwent slow cleavage at room temperature, which prevented recording of ^{13}C NMR data.

SO_4, filtered, and concentrated to afford methyl ether **18** (308 mg, 83%) as a slightly yellow oil. ^1H and ^{13}C NMR data were identical with values previously reported.[38]

[(2*R*,4*R*)-2-(4-Methoxyphenyl)-1,3-dioxan-4-yl]methyl Acetate (21). Acetyl chloride (137 μL, 1.9 mmol) and triethylamine (337 μL, 2.4 mmol) were added to a solution of alcohol **4** (362 mg, 1.6 mmol). After 15 min at room temperature, the solution was poured onto HCl (0.1 M, aq) and CH_2Cl_2. The organic phase was washed with NaCl (aq, sat.), dried over Na_2SO_4, filtered, and concentrated. To remove *p*-methoxybenzaldehyde formed through hydrolysis the residue was dissolved in CH_2Cl_2 and treated with $TsNHNH_2$ on polystyrene. After filtration and concentration, acetate **21** (366 mg, 85%) was obtained as a colorless oil. ^1H and ^{13}C NMR data were identical with values previously reported.[39]

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Supporting Information Available: General methods and materials; ^1H NMR and ^{13}C NMR spectra for compounds **5**, **6**, **7b**, **10**, **11**, and **12**; ^{15}N NMR spectra for ^{15}N-labeled **6**, in the presence and absence of TBDMSCl; HPLC chromatograms illustrating the diastereomeric purity of compounds **11** and **13**. This material is available free of charge via the Internet at http://pubs.acs.org.

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