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Selective Side Chain Introduction onto Small Peptides Mediated by Samarium Diiodide: A Potential Route to Peptide Libraries

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Abstract: A mild and simple method for the selective introduction of carbinol side chains onto glycine residues in peptides is presented as a potential route for the preparation of peptide libraries. A series of di- and tripeptides, as well as one tetrapeptide, each possessing one glycine residue, were first selectively functionalized at this amino acid unit by a two-step sequence involving bromination with *N*-bromosuccinimide and then sulfide formation by treatment of the unstable glycyl bromide with 2-mercaptopyridine. These modified peptides were then reduced with samarium diiodide at room temperature in the presence of alkyl aldehydes and ketones, affording a series of peptides in yields of 40−65% containing serine/threonine derivatives as new functionalities. These reactions are quite efficient, considering the presence of as many as four amide protons in the enolate intermediate. The diastereoselectivities of these reactions are low or nonexistent, which is ascribed to either (a) the formation of single enolate, where the neighboring chiral centers impart no influence in the alkylation step or (b) the generation of an enolate mixture, where each stereoisomer leads to opposite enantiomers with respect to the newly formed amino acid upon alkylation. The successful nonselective double alkylation of the tripeptide, Bz-Gly-Val-Gly-OMe, suggests the possibility that the reductive samariation approach to the *C*-alkylation of peptides may be a viable route for the preparation of peptide libraries based on multiple serine/threonine derivatives. Finally, a preliminary investigation on one peptide has shown that the addition of 1% of nickel(II) iodide to these condensation reactions has a significant effect on the coupling yields.

Introduction

Small peptides are implicated in a wide range of roles in both plants and animals, acting as extracellular messengers—hormones, neurotransmitters, and neuromodulators—which influence essential functions such as metabolism, immune defense, respiratory functions, and reproduction to name a few. Because of these vital functions, bioorganic and medicinal chemists have developed a long-standing interest in the application of such peptides as pharmaceuticals for the treatment of diseases related to the above-mentioned biological processes. However, for efficient target screening and optimization of lead structures, flexible synthetic approaches are required for modifying natural peptides. Classical methods rely on stepwise syntheses of peptides through commercially available or synthetic nonnatural amino acids.[1] Such an approach is time-consuming and has led to the development of techniques such as parallel synthesis or combinatorial chemistry. A more convergent approach to the modification of biologically active peptides would be *to incorporate the side chain directly onto the peptide backbone*. This route would be more attractive and in particular more economical, as a multitude of analogues may be quickly synthesized from a single and intact peptide, without having to repeat the peptide synthesis for each modification.

(1) For a recent example on the modification of a peptide via the incorporation of nonnatural amino acids resulting in the improvement of its biological activity, see, De Filippis, V.; Quarzago, D.; Vindigni, A.; Di Cera, E.; Fontana, A. *Biochemistry* **1998**, *37*, 13507.

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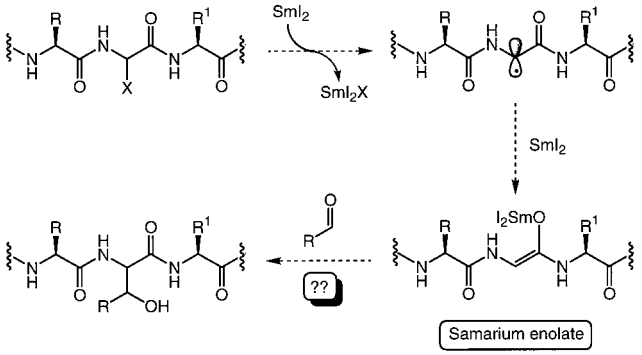
Various reactive intermediates have been employed for the C−C coupling step in a peptide chain including glycine enolates,[2−5] glycine cation equivalents,[6,7] as well as glycyl radicals.[8−12] Perhaps the most noteworthy in this respect represents the extensive work performed by Seebach and co-workers on the selective alkylation of glycine residues in a polylithiated peptide enolate.[2] With this approach, linear and cyclic peptides containing up to 11 amino acid residues could be alkylated at a glycine residue via the initial generation of a corresponding glycine enolate. The preparation of such enolates first requires a low-temperature multiple deprotonation step of the acidic amide protons with LDA, accompanied by a selective deprotonation of one of the α-CH protons of glycine. Successful enolate formation does, however, require that the C-terminal amide linkage of the glycine unit be alkylated. Resolution of this restriction was subsequently obtained by incorporating an electron withdrawing substituent on the glycine α-carbon such as an alkyl carboxylate or cyanide group.[2e] In this way, the pK_a of the α-C−H proton becomes sufficiently acidic such that deprotonation is selective only at this site. An ensuing reduction step is nevertheless necessary for removal of this assisting functionality, which also results in loss of any stereochemical information obtained in the alkylating step.

An alternative route to glycine enolates would be to perform a reductive metalation step of an appropriately α-*C*-functionalized glycine unit. Employing this route, the glycine enolate may be prepared directly via a glycyl radical intermediate without competitive deprotonation of amide protons with strong bases (Scheme 1). However, successful application of this approach would greatly depend on the stability of the enolate species toward either intra- or intermolecular protonation from the amide functionalities. The strong metal-complexing abilities of lanthanide(III) metal ions to oxygen in addition to the low basicity of alkyl lanthanide species suggested to us that the single-electron reducing agents, such as the well-known samarium diiodide (SmI_2), might be suitable for this purpose.[13] Evidence that SmI_2 may be ideal for such studies came about from our previous results in the divalent samarium-induced *C*-glycosylations.[14] In this work, we have demonstrated that C−C bond formations with an anomeric organosamarium could be accomplished even in the presence of an adjacent secondary amide group, implying that coupling is sufficiently fast compared to the protonation step.[14c,f,g] Whether these results could be adapted to carbon−carbon bond-forming reactions on peptides only protected at the terminal positions was therefore the subject of this investigation.

Scheme 1



In this paper, we disclose our findings on the use of a SmI_2-induced Reformatsky-type reaction for the selective introduction of carbinol side chains onto glycine residues. We have found that pyridyl sulfide glycyl units may indeed serve as an appropriate precursor to the required glycine enolates. The scopes and limitations on the application of such entities for the *C*-alkylation of peptides are discussed. This work lays the foundation for a possible route to the rapid and simple preparation of peptide libraries containing serine/threonine derivatives.[15]

Results and Discussions

Initial efforts for the development of a reductive samariation approach for the side-chain introduction onto peptides, first

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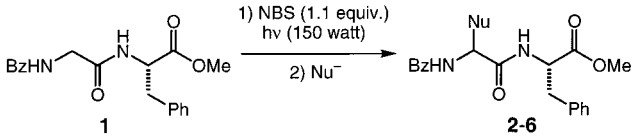
Table 1. Preparation of the Dipeptides **2**−**6**

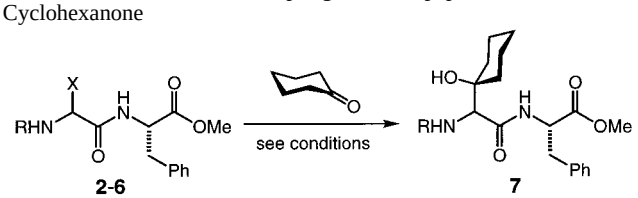


entry	Nu	conditions	modified dipeptide
1	S(2-Pyr)	(2-Pyr)SH (1.5 equiv) DIPEA (1.5 equiv)	**2** (87%)
2	SO_2Ph	(a) PhSH (1.5 equiv) DIPEA (1.5 equiv) (b) $RuCl_3/NaIO_4$	**3** (56%)
3	OAc	AcOH (1.5 equiv) DIPEA (1.5 equiv)	**4** (46%)
4	OBz	$PhCO_2H$ (1.5 equiv) DIPEA (1.5 equiv)	**5** (62%)
5	OMe	MeOH	**6** (26%)

required the identification of a suitable glycine enolate precursor. In our earlier work, we have established that a samarium diiodide (SmI_2)-induced Barbier reaction with glycosylpyridyl sulfones is a rapid and mild approach for the stereoselective construction of *C*-glycosides.[14,16,17] Crucial for the successful coupling of the intermediate anomeric organosamarium species to carbonyl substrates are the observations that such pyridyl sulfones are rapidly and selectively reduced by SmI_2, which is partly due to the generation of a stabilized anomeric radical.[16] On the other hand, a glycyl radical would be expected to display a greater stability due to the captodative effect (α-C−H bond dissociation energy of approximately 80 kcal/mol),[18] suggesting that with an appropriate electrophore on the α-carbon of a glycine residue, its SmI_2-induced reduction would be even faster than that for the corresponding glycosyl derivative.

To test the reactivity of such modified glycine units, a variety of electrophores were first introduced on the simple dipeptide **1** (Table 1). This required though that a procedure for the selective functionalization of a glycine residue be available. Previous work by Easton and co-workers has demonstrated that glycine residues in small peptides readily undergo selective bromination when subjected to *N*-bromosuccinimide.[9,19] Hence, the dipeptide, Bz-Gly-Phe-OMe (**1**), was irradiated in CH_2Cl_2 with a 150-W lamp in the presence of NBS to afford the corresponding glycyl bromide derivative. Without isolation, this unstable halide was immediately subjected to a variety of nucleophiles, as depicted in Table 1. Good to modest yields of the modified dipeptides **2**−**6** were obtained. The sulfide pyridyl derivative **2** (entry 1), prepared in a satisfactory 87% yield, could not be oxidized to the corresponding and desired sulfone as this labile compound underwent spontaneous hydrolysis. As will be discussed below, this has no consequence with the subsequent coupling reactions. In contrast, the phenyl sulfide was oxidized to its sulfone **3** in 75% with the $RuCl_3/NaIO_4$ combination (entry 2).

Table 2. SmI_2-Mediated Coupling of the Dipeptides **2**−**6** with Cyclohexanone



entry	R	X	conditions	yield of **7**[a] (%)
1	Bz	S(2-Pyr)	SmI_2/THF 20 °C, 1 h	64
2	Bz	S(2-Pyr)	SmI_2/THF HMPA, 20 °C, then carbonyl cmpd	0
3	Bz	S(2-Pyr)	SmI_2/THF HMPA, −78 °C, then carbonyl cmpd	0
4	Bz	S(2-Pyr)	Cp_2TiCl_2/Mn/THF 20 °C	10
5	Bz	S(2-Pyr)	Cp_2TiCl_2/Zn/THF 20 °C	0
6	Bz	S(2-Pyr)	SmI_2/NiI_2 (1%) 0 °C, few s	75
7	Bz	S(2-Pyr)	SmI_2/NiI_2 (1%) −78 °C, 10 min	85
8	Bz	SO_2Ph	SmI_2/THF 20 °C, few s	32
9	Bz	OAc	SmI_2/THF 20 °C, few s	8
10	Bz	OBz	SmI_2/THF 20 °C, few s	39
11	Bz	OMe	SmI_2/THF 20 °C, 3 h	0
12	Boc	CN	SmI_2/THF 20 °C, 3 h	0

[a] In all cases, a diastereoselectivity of 1:1 was observed.

The results of the coupling experiments between the dipeptides **2**−**6** and cyclohexanone are shown in Table 2. Treatment of a THF solution of the pyridyl sulfide **2** and an excess of cyclohexanone (3 equiv) with 3 equiv of SmI_2, resulted in the consumption of **2** over a period of 0.5−1 h, affording a 1:1 diastereomeric mixture of alkylated dipeptides **7** in a promising yield of 64% (entry 1). Also isolated from the reaction mixture was the corresponding reduced peptide **1** in a 15% yield. Reaction of the pyridyl sulfide with SmI_2 prior to the addition of cyclohexanone produced only the dipeptide **1**. A similar result was also obtained in attempts to either accelerate the electron transfer or to stabilize the putative samarium enolate intermediate through the addition of the strong lanthanide complexing agent, hexamethylphosphoramide (HMPA),[20] as shown in entries 2 and 3. Substituting the reducing agent with the increasingly popular biscyclopentadienyltitanium chloride (Cp_2TiCl)[21] generated from Cp_2TiCl_2/Mn or Cp_2TiCl_2/Zn only resulted in the slow reduction of the pyridyl sulfide while affording a low yield of **7** in a single case (entries 4 and 5).

The report in 1996 by the group of Namy and Kagan that as low as 1 mol % NiI_2 premixed with SmI_2 accelerates the electron transfer from the divalent lanthanide metal to substrates such

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as alkyl halides,[22] prompted us to examine the effect of this catalyst on the yields of the SmI_2-promoted *C*-alkylation. Hence, a THF solution of the dipeptide **2** and cyclohexanone was subjected to 3 equiv of SmI_2 containing 1 mol % NiI_2 at 0 °C resulting in the fast consumption of **2** (few seconds). More importantly, the coupling yield had increased from 64 to 75% (entry 6).[23] Decreasing the reaction temperature to −78 °C, also led to a relatively fast reaction (few min), as well as a rise in the yield of **7** to an impressive 85% yield (entry 7). Interestingly, the diastereoselectivity was not effected by the temperature change.

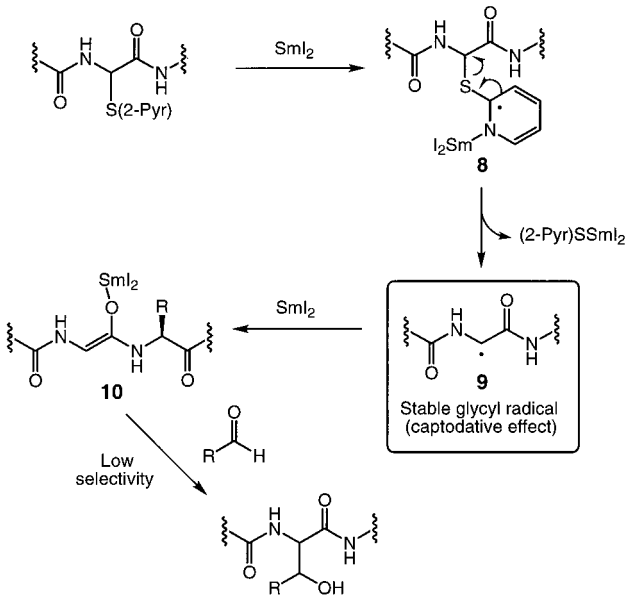
Although, we did not expect the phenyl sulfone derivative **3** to display an appreciable reactivity with the lanthanide-reducing reagent in comparison to previous results obtained in our *C*-glycosylation studies,[16] we were nevertheless surprised to observe that this compound reacted essentially instantaneously with SmI_2 (entry 8). Also unexpected, were the comparable and fast reactivities (few seconds) of the acetate **4** (entry 9) and the benzoate **5** (entry 10) with SmI_2, while the methoxide **6** remained untouched even after several hours of subjection to SmI_2 (entry 11). Whereas, their characteristically low coupling yields made these reactions synthetically undesirable, the different reactivity between the pyridyl sulfide **2** with **3**−**5** suggested the possibility that two mechanisms may be operating in the enolate formation step.

Finally, we also tested the cyanide derivative (entry 12), easily prepared via a peptide-coupling step with a cyano-containing amino acid building block.[2e] However, the peptide proved unreactive to SmI_2 alone at 20 °C and could only slowly be reduced to the unfunctionalized peptide in the presence of HMPA, conditions which are not adabtable for the succeeding alkylation step.[24]

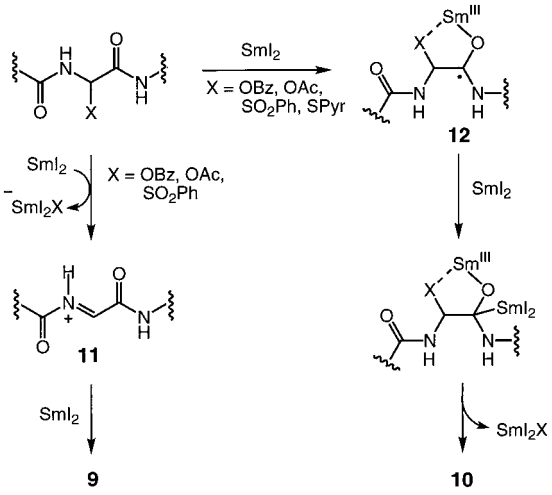
Although, an in-depth mechanistic investigation of the above coupling experiments was not pursued, a tentative explanation of these results is illustrated in Schemes 2 and 3. With the pyridyl sulfide group, activation of the carbon−nitrogen double bond through the coordination of the divalent lanthanide reagent could lead to the electron tranfer into the heteroaryl nucleus as with **8**. C−S bond fragmentation is thereafter facilitated by the formation of the captodatively stabilized glycyl radical **9**.[25] A subsequent reduction step with a second equivalent of SmI_2 then leads to the Sm^{III} enolate intermediate **10**. Although, the geometry of this enolate is unknown, the high oxophilicity of the lanthanide metal ion, including its ability to form strong complexes with amides, could suggest a coordination of the Sm^{III} ion to one of the adjacent amide groups of the peptide, leading to the possible formation of a cyclic enolate structure.[14c,f,g,27] Unfortunately, owing to the absence of any diastereoselectivity in this coupling event, it does not appear that the distal side chain on the adjacent amino acid has any directing abilities with respect to the incoming electrophile.[28] Another explanation may be that several enolate structures are produced under these conditions which lead to products of opposing diastereoselectivity in the coupling step to cyclohexanone.

It is not exactly clear how NiI_2 exerts its rate-accelerating effect on the electron transfer to the pyridyl sulfide group, whether a SmI_2/NiI_2 complex or Ni(I) species is involved.[30] Nevertheless, the improved coupling yield observed with NiI_2,

Scheme 2. Mechanistic Proposal for the SmI_2-Induced Alkylation of Pyridyl Sulfide-Modified Peptides



Scheme 3. Alternative Mechanisms for the SmI_2-Promoted Reduction of α-Substituted Glycine Residues



(22) Machrouhi, F.; Hamann, B.; Namy, J.-L.; Kagan, H. B. *Synlett* **1996**, 633.

(23) Support for this study was recently provided by the group of Beau, demonstrating that the application of the Ni^{II} catalyst to the SmI_2-induced Barbier reaction of glycosylpyridyl sulfones with aldehydes has a dramatic positive influence on the coupling yields. Miquel, N.; Doisneau, G.; Beau, J.-M. *Angew. Chem., Int. Ed.*, in press.

(24) For other examples concerning the reductive removal of a cyanide group with SmI_2/HMPA, see: (a) Kang, H.-Y.; Hong, W. S.; Cho, Y. S.; Koh, H.-Y. *Tetrahedron Lett.* **1995**, *36*, 7661. (b) Molander, G. A.; Wolfe, J. P. *J. Brazilian Chem. Soc.* **1996**, *7*, 335.

(25) Similar mechanisms have recently been proposed in the *C*-glycosylation of glycosylpyridyl sulfones and the zinc-mediated reduction of alkylpyridyl sulfides (refs 16, 26).

(26) Boivin, J.; Lallemand, J.-Y.; Schmitt, A.; Zard, S. Z. *Tetrahedron Lett.* **1995**, *36*, 7243.

(27) (a) Kawatsura, M.; Dekura, F.; Shirahama, H.; Matsuda, F. *Synlett* **1996**, 373. (b) Molander, G. A.; McWilliams, J. C.; Noll, B. C. *J. Am. Chem. Soc.* **1997**, *119*, 1265.

(28) An alternative mechanism, which may explain the low diastereoselectivity observed, involves the addition of the intermediate and uncomplexed glycyl radical to the aldehyde or ketone. Although direct intermolecular addition to the carbonyl group is not likely due to the formation of a highly reactive oxygen centered radical, activation of this functionality by precomplexation to SmI_2 prior to the radical addition step would result in, (1) a lowering of the $\pi^*_{C=O}$ energy level, thus favoring radical addition, and (2) an immediate reduction of the reactive oxy-radical intermediate. However, the high stability of the glycyl radical as observed by the relatively weak α-C−H bond of a glycine unit in conformationally unrestricted peptides (ref 18) suggests that the reactivity of this intermediate towards addition reactions is probably unfavorable (ref 29).

(29) We have recently observed the reluctancy of the glycyl radical to add to alkenes under conditions which favor this addition step. Blakskjær, P.; Pedersen, L.; Skrydstrup, T. *J. Chem. Soc., Perkin Trans. 1*, in press.

could be explained by its ability to allow the reductive coupling to occur at low temperature, conditions where the rate of the competitive proton transfer to the enolate intermediate is substantially decreased compared to the room-temperature reactions.[31]

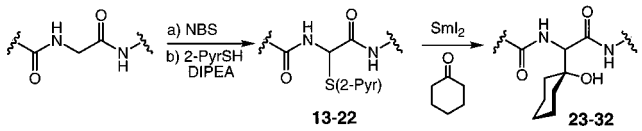
In previous work with *C*-glycosides, we noted that the order of decreasing reactivity of glycosyl arylsulfides and sulfones with SmI_2 was the following: $(2\text{-Pyr})SO_2$ > (2-Pyr)S > $PhSO_2$,[14,16] whereas glycosyl benzoates were completely inert.[32] The reversal of this order of reactivity with the modified dipeptide (Table 2, entries 1, 8−10), therefore suggests the possibility of two different mechanisms taking place in the initial reduction step to the glycyl radical. For the phenyl sulfone-, benzoate-, and acetate-derivative their complexation with SmI_2 may lead to their rapid expulsion through the formation of an iminium ion intermediate **11** (Scheme 3).[33] This reactive species is then immediately reduced to the α-carbon-centered radical. We do not yet understand the reason for the low coupling yields with these substrates, but reduction of the conjugated iminium ion may not necessarily afford the required glycyl radical, if the electron transfer occurs at one of the two neighboring carbonyl groups.

Finally, the known capacity for SmI_2 to promote the reductive removal of α-heterosubstituted carbonyl compounds,[34] including amides,[35] may suggest a completely different scenario for the formation of enolate **10** (Scheme 3). Hence, reversible electron transfer to the amide C═O bond leads to the carbon-centered radical **12**. Its reduction via a second electron transfer followed by a β-elimination step would then generate the enolate **10**. In these examples, the heterosubstituent not only provides an extra chelating site for the divalent samarium ion, but their electron-withdrawing properties would increase the carbonyl group's propensity to undergo reduction.

With the identification of the pyridyl sulfide group as an appropriate electrophore for C−C-bond formation reactions of the dipeptide **2**, we set out to examine the generality of this approach. A series of dipeptides, tripeptides, and one tetrapeptide were first subjected to the two-step bromination and thiopyridine introduction sequence, affording modest to good yields of the pyridyl sulfides **13**−**21** (Table 3, entries 1−9). In general, these reactions were quite clean though the reactivity of the glycine residue toward bromination diminished with increasing size of the peptide. In all cases, an approximately 1.6−1.7 mixture of diastereomers at the new stereocenter was obtained, the ratio of which had no consequence in the subsequent coupling step.

As with **2**, treatment of the peptides **13**−**21** with cyclohexanone and then SmI_2 afforded good yields of the *C*-alkylated peptides in the range of 40−63% (Table 3, entries 1−9), which are satisfactory considering the simplicity of the reaction

Table 3. Introduction of the Pyridyl Sulfide and Subsequent SmI_2-Mediated Alkylation of a Series of Peptides with Cyclohexanone



13-22 **23-32**

Entry	Starting Peptide	Pyridyl Sulfide (Yield)	Alkylated Peptide (Yield)[a]
1	BzHN, R = *i*Pr, OMe	**13** (85%)	**23** (63%, 1:1)
2	BzHN, R = CH_2CO_2Me, OMe	**14** (74%)	**24** (61%, 1:1)
3	BzHN, R = CH_3, OMe	**15** (42%)	**25** (43%, 1.1:1)
4	BzHN, OMe	**16** (46%)	**26** (54%, 1.8:1)
5	BzHN, OMe	**17** (49%)[b]	**27** (45%, 1.1:1)
6	BzHN, OMe	**18** (55%)	**28** (40%, 1.2:1)
7	BzHN, OMe, Ph	**19** (59%)[b]	**29** (50%, 2:1)
8	BzHN, OMe, Ph	**20** (34%)	**30** (46%, 1:1)
9	BzHN, OMe, Ph	**21** (42%)[b]	**31** (54%, 1.2:1)
10	BzHN, OMe	**22** (9%)	**32** (38%)

[a] Ratio refers to the diastereoselectivity observed. [b] Yield based on recovered starting material.

conditions. It was pleasing to observe that the coupling yields appeared independent of the peptide chain length as exemplified by the 54% yield obtained for the tetrapeptide **31** (entry 9) *even in the presence of four amide protons*. The simple reduction compounds were the major byproducts probably arising via the proton transfer from the amide groups or THF. As with the dipeptide **2**, essentially no stereoselectivity was noted for these coupling reactions, which is again quite remarkable, considering the number of potential sites for complexation with the Sm^{III} metal ion, and the high diastereoselectivities recently seen in the SmI_2-promoted Reformatzky reaction of α-bromoacetyl-2-oxazolidinones with aldehydes.[36] Possibly, deviation of the peptide from the normal linear conformation is energetically to costly to provide an additional complexation site on the Sm^{III} metal ion of the enolate.

The potential for the application of this approach to the multiple alkylation of a single peptide, was examined with the tripeptide **22** containing two pyridyl sulfide groups (entry 10).

(30) Previous experiments in the laboratory of Namy have demonstrated that mixing stoichiometric quantities of the nickel catalyst with SmI_2 does not lead to a reactive electron-donating agent. Machrouhi, F. Ph.D. Thesis, Université de Paris XI, 1999.

(31) The application of the NiI_2 catalysis was discovered at a late stage of the project and hence was not further pursued in the alkylation of other peptides. We are currently examining the effect of this catalyst in other systems, the work of which will be reported in a subsequent paper.

(32) Skrydstrup, T.; Beau, J.-M., unpublished results.

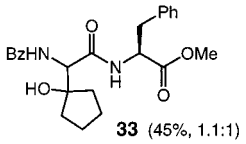
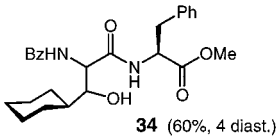
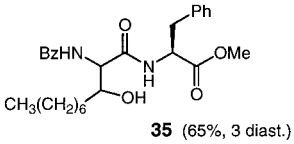
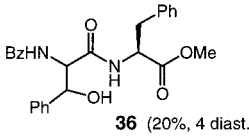
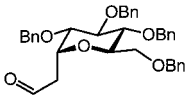
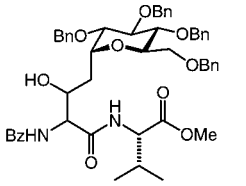
(33) For other samarium diiodide-promoted C−C bond forming reactions with a putative iminium ion intermediate, see: Aurrecoechea, J. M.; Fernández, A.; Gorgojo, J. M.; Saornil, C. *Tetrahedron* **1999**, *55*, 7345 and references therein.

(34) Molander, G. A.; Hahn, G. *J. Org. Chem.* **1986**, *51*, 1135. See also ref 13e for a more elaborate account on the reduction of α-substituted carbonyl compounds.

(35) (a) Molander, G. A.; Stengel, P. J. *Tetrahedron* **1997**, *53*, 8887. (b) Concellón, J. M.; Pérez-Andrés, J. A.; Rodríguez-Solla, H. *Angew. Chem., Int. Ed.* **2000**, *39*, 2773.

(36) Fukuzawa, S.; Matsuzawa, H.; Yoshimitsu, S. *J. Org. Chem.* **2000**, 65, 1702.

Table 4. Coupling of Dipeptides **2** and **13** with Other Carbonyl Compounds

Entry	Pyridyl Sulfide	Carbonyl Cmpd	Alkylated peptide (Yield)[a]
1	**2**	cyclopentanone	 **33** (45%, 1.1:1)
2	**2**	cyclohexane-carboxaldehyde	 **34** (60%, 4 diast.)
3	**2**	*n*-octanal	 **35** (65%, 3 diast.)
4	**2**	benzaldehyde	 **36** (20%, 4 diast.)
5	**13**	 **37**	 **38** (46%, 4 diast.)

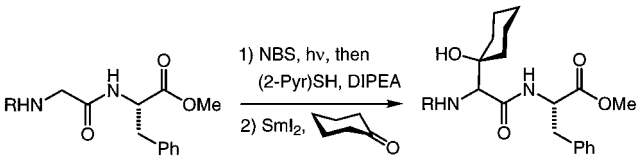
[a] Ratio refers to the diastereoselectivity observed.

Whereas, the preparation of **22** from Bz-Gly-Val-Gly-OMe was unexceptional, we were delighted to find that its coupling with cyclohexanone led to the isolation of the dialkylated peptide **32** as a mixture of four stereoisomers in an unoptimized yield.

Other carbonyl substrates were tested with the dipeptides **2** and **13** as shown in Table 4. The simple alkyl aldehydes worked well, leading to a mixture of stereoisomers (entries 2 and 3), as detected by ^{1}H NMR spectroscopy. On the other hand, benzaldehyde led to a poor coupling yield most likely due to the competitive reduction of this compound to the corresponding ketyl (entry 4). This was confirmed by the isolation of the pinacol coupling product, hydrobenzoin, in addition to the dipeptide **1** as the major compounds from this reaction.[37]

Entry 5 represents an interesting example of a potentially new route for the direct introduction of a carbohydrate onto a peptide backbone. The *C*-glycopeptide **38** was prepared by the coupling of the readily available aldehyde **37** in 46% yield,[38] although the carbohydrate moiety imparted no sufficient diastereoselectivity at either of the two newly created stereogenic centers.[39]

Table 5. Effect of the N-Terminal Nitrogen Protecting Group on the Introduction of the Pyridyl Sulfide Group and the Subsequent SmI_2-Promoted Coupling



entry	R	pyridyl sulfide yield (%)	alkylated dipeptide yield (%)
1	CH_3CO	**39** (46)	**43** (58)
2	$TolSO_2$	**40** (0)	
3	tBuO(CO)	**41** (0)	
4	BnO(CO)	**42** (18)	**44** (62)

Finally, a small study was undertaken to investigate the importance of the N-terminal nitrogen-protecting group on the coupling yields (Table 5). As anticipated, the *N*-acetyl group had little influence on either the introduction of mercaptopyridine or the *C*-alkylation yield with cyclohexanone (entry 1). However, in attempts to brominate the dipeptide R-Gly-Phe-OMe possessing either the tosyl, *tert*-butyloxycarbonyl, or the benzyloxycarbonyl group, extensive decomposition was observed, affording either none or low yields of the corresponding sulfide upon subjection with 2-mercaptopyridine (entries 2−4). This was surprising in particular with the example possessing a Boc group, considering the similar successful brominations of Boc-protected glycine esters.[40,41] Only in the latter case (entry 4) could we isolate the pyridyl sulfide **42**, in a disappointing 18% yield. Its subsequent SmI_2-promoted coupling to cyclohexanone proved none the less satisfactory, affording the branched peptide **44** in 62%. Although problems with the introduction of the aryl sulfide group were encountered, the latter result does suggest that alkyloxycarbonyl groups (including the Boc group, see Table 2, entry 12) can serve as nitrogen-protecting groups in the divalent lanthanide-promoted alkylation step. In any case, these final results including the low yields previously encountered in the bromination of other peptides (see Table 3) only stress the point that an alternative and more effective method for the introduction of the pyridyl sulfide group is required.

Conclusions

We have demonstrated in this work that reductive samariation can be a viable approach for the introduction of carbinol side-chains onto small peptides containing pyridyl sulfide-modified glycine residues. These Reformatsky-type couplings are quite efficient, taking into consideration that the peptide substrates tested contain up to four amide protons. In one example, we have also shown that multiple alkylation may be possible. It is not exactly clear why these coupling reactions lead to poor diastereoselectivities, but none the less this characteristic allows one to prepare peptides containing both an unnatural D- or L-amino acid unit, which is a significant feature for the application of this approach to the generation of peptide libraries, although random in these cases. If this low selectivity is the

(37) A similar result was observed in the attempted coupling of either a mannosyl or a glucosylpyridyl sulfone with benzaldehyde (refs 14a, e).

(38) Hosomi, A.; Sakata, Y.; Sakurai, H. *Carbohydrate Res.* **1987**, *171*, 125.

(39) For some recent syntheses of *C*-glycosyl amino acids and peptides, see (a) Burkhart, F.; Hoffmann, M.; Kessler, H. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1191. (b) Lay, L.; Meldal, M.; Nicotra, F.; Panza, L.; Russo, G. *Chem. Commun.* **1997**, 1469. (c) Debenham, S. D.; Debenham, J. S.; Burk, M. J.; Toone, E. J. *J. Am. Chem. Soc.* **1997**, *119*, 9897. (d) Dondoni, A.; Marra, A.; Massi, A. *Chem. Commun.* **1998**, 1741. (e) Dondoni, A.; Marra, A.; Massi, A. *Tetrahedron Lett.* **1998**, *39*, 6601. (f) Dondoni, A.; Marra, A.; Massi, A. *Tetrahedron* **1998**, *54*, 2827. (g) Ben, R. N.; Orellana, A.; Arya, P. *J. Org. Chem.* **1998**, *63*, 4817. (h) Arya, P.; Ben, R. N.; Qin, H. *Tetrahedron Lett.* **1998**, *39*, 6131. (i) Urban, D.; Skrydstrup, T.; Beau, J.-M. *Chem. Commun.* **1998**, 955. (j) Pearce, A. J.; Ramaya, S.; Thorn, S. N.; Bloomberg, G. B.; Walter, D. S.; Gallagher, T. *J. Org. Chem.* **1999**, *64*, 5453.

(40) See ref 11 and references therein.

(41) The exact reasons for the poor bromination yields with the Boc-protecting group are not fully understood, as attempted bromination with an acid scavenger was likewise unsuccessful. However, in the case of the tosyl and Cbz groups, possibly competitive bromination of these protecting groups could be responsible for the low yields observed.

result of an unbiased facial selectivity of a single enolate structure present in solution, or from an enolate mixture, the addition of asymmetric ligands to the lanthanide ion could influence both the enolate structure and the facial selectivity in the alkylation. In this way, access to either of the two diastereomers may be possible by the choice of the appropriate ligand. A number of enantiomerically pure ligands will be examined in the future although little has been explored in the realm of asymmetric synthesis with SmI_2-promoted reactions.[27b,36,42]

In this study, peptides possessing only lipophilic side chains have so far been studied, where future work will have to examine the compatibility of other amino acid side chains in the SmI_2-promoted *C*-alkylation step. Although, the functional group selectivity of this mild one-reducing suggests that this method will be adabtable even in the presence of a wide range of side chains, more concern is put forth regarding the ability to perform the initial bromination step, where various protected amino acids may simply not be compatible to such conditions (e.g., cysteine, methionine). Hence, work is currently underway to identify a new electrophore, which may be incorporated into an amino acid building block, such that no modification of the peptide prior to the alkylation step would be required. The successful identification of this group would likewise allow for the multiple alkylation of peptides containing more than one glycine residue, or for the selective alkylation at one or several glycine sites in the presence of others not functionalized. This method could allow for a rapid approach to a new series of peptide libraries based on serine/threonine derivatives for combinatorial chemistry.

Experimental Section

General Methods. The SmI_2-promoted coupling reactions were performed under Ar, while all other reactions were carried out under N_2. THF was dried and freshly distilled over sodium/benzophenone. Dichloromethane was freshly distilled over P_2O_5. DMF was distilled and stored over molecular sieves (4 Å). ^1H and ^{13}C NMR spectra were recorded on a Varian Gemini 2000 (200 and 50 MHz, respectively) using $CDCl_3$ as solvent unless otherwise stated and TMS as an internal standard for ^1H NMR. High-resolution mass spectral analyses were performed with a Micromass LC-TOF instrument. Analytical thin-layer chromatography was performed on Merck silica gel 60 F_{254} plates. Compounds were visualized using a cerium sulfate−ammonium molybdate solution, blue stain solution, or *p*-anisaldehyde solution followed by heating. Flash column chromatography was performed using Fluka silica gel 60 (0.04−0.063 mm). All peptides were synthesized using standard peptide coupling procedures with 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide (EDC) and 1-hydroxy-1H-benzotriazole (HOBt). For details on the oligopeptide syntheses see the standard procedure.[43] Samarium diiodide was prepared according to the literature.[44]

General Procedure for the Preparation of the Pyridyl Sulfide Derivatives. Bz-((2-Pyr)S)Gly-Phe-OMe (2). A solution of *N*-bromosuccinimide (226 mg, 1.29 mmol) and the dipeptide **1** (400.0 mg, 1.18 mmol) in CH_2Cl_2 (14 mL) was irradiated with a 150-W lamp for 3 h. The heat from the lamp was sufficient to maintain refluxing. The solution was then cooled to 0 °C, after which 2-mercaptopyridine (198.0 mg, 1.77 mmol) and diisopropylethylamine (308 μL, 1.77 mmol) were added. The reaction mixture was stirred for 3 h at 0 °C and then diluted with CH_2Cl_2 and washed with water (2×) and brine. The organic phase was dried ($MgSO_4$) and evaporated to dryness, whereafter the residue was purified by flash chromatography (pentane/EtOAc, 7/3) to afford a diastereomeric mixture (1.6:1.0 as determined by ^1H NMR analysis) of the pyridyl sulfide **2** (462 mg, 87%) as a light yellow foam. IR (KBr) 3310, 1745, 1660 cm^{-1}; ^1H NMR δ = 9.26 (1H, d, J = 8.0 Hz), 9.15 (1H, d, J = 8.2 Hz), 8.24 (1H, m), 8.06 (1H, m), 7.74−7.90 (6H, m), 6.88−7.64 (22H, m), 6.42 (1H, d, J = 7.6 Hz), 6.38 (1H, d, J = 7.0 Hz), 4.86−5.02 (2H, m), 3.75 (3H, s), 3.57 (3H, s), 2.99−3.20 (4H, m); ^{13}C NMR δ = 171.3, 171.2, 168.9, 168.6, 165.6, 157.5, 149.1, 136.8, 136.0, 135.4, 133.3, 132.1, 129.4, 129.1, 128.7, 128.0, 127.3, 127.2, 126.8, 123.2, 123.0, 120.5, 54.1, 53.9, 52.4, 52.2, 38.2, 38.0; HR-MS (ES) calcd for $C_{24}H_{23}N_3O_4SNa$ (M + Na): 472.1307, found: 472.1307.

General Procedure for the SmI_2-Promoted Coupling with Carbonyl Compound. A 0.1 M solution of SmI_2 in THF (5.5 mL, 0.55 mmol) was added to a stirred solution of the pyridyl sulfide (0.20 mmol) and cyclohexanone (62 μL, 0.60 mmol) in THF (0.5 mL) at 20 °C. After stirring for 1 h, saturated aqueous NH_4Cl (2 mL) was added to the reaction mixture, which was then extracted with CH_2Cl_2 (2 × 10 mL). The combined organic phases were washed with water, filtered through Celite, dried with $MgSO_4$, and evaporated to dryness. Flash chromatography afforded the alkylated peptide **7**, **23**−**35**, **38**, **43**, **44**. Yields are described in Tables 3, 4, and 5. Diastereomeric ratios were determined by ^1H NMR analysis.

Bz-(1-hydroxycyclohexyl)Gly-Phe-OMe (7): Chromatography (pentane/EtOAc, 2/1). Colorless solid (1.0:1.0 diastereomeric mixture). IR (KBr) 3279, 1750, 1630 cm^{-1}; ^1H NMR δ = 7.75−7.85 (4H, m), 7.38−7.61 (6H, m), 7.00−7.33 (14H, m), 4.78−4.94 (2H, m), 4.57 (1H, d, J = 8.0 Hz), 4.53 (1H, d, J = 8.4 Hz), 3.88 (1H, bs), 3.81 (1H, bs), 3.74 (3H, s), 3.67 (3H, s), 3.23 (1H, dd, J = 5.2, 14.0 Hz), 3.16 (1H, dd, J = 5.2, 14.0 Hz), 3.02 (1H, dd, J = 8.8, 14.0 Hz), 2.97 (1H, dd, J = 7.4, 14.0 Hz), 1.56−1.81 (20H, m); ^{13}C NMR δ = 171.5, 167.9, 167.7, 133.7, 132.2, 129.3, 128.8, 127.4, 127.3, 73.1, 72.9, 58.1, 53.4, 52.7, 37.9, 35.4, 33.7, 33.6, 25.7, 21.9, 21.6; HR-MS (ES) calcd for $C_{25}H_{30}N_2O_5Na$ (M + Na): 461.2052, found: 461.2055.

Bz-(1-Hydroxycyclohexyl)Gly-Val-OMe (23): Chromatography (pentane/EtOAc, 3/1). Colorless solid (1.0:1.0 diastereomeric). IR (KBr) 3292, 1748, 1634 cm^{-1}; ^1H NMR (300 MHz) δ = 7.77−7.84 (4H, m), 7.40−7.56 (6H, m), 7.05−7.21 (3H, m), 6.98 (1H, d, J = 5.8 Hz), 4.59 (1H, d, J = 5.6 Hz), 4.56 (1H, d, J = 5.4 Hz), 4.50 (1H, dd, J = 5.9, 3.3 Hz), 4.46 (1H, dd, J = 5.8, 3.2 Hz), 3.76 (3H, s), 3.64 (3H, s), 2.21 (2H, m), 1.19−1.86 (20H, m), 0.97 (3H, d, J = 4.9 Hz), 0.94 (3H, d, J = 4.9 Hz), 0.91 (3H, d, J = 4.4 Hz), 0.90 (3H, d, J = 4.4 Hz), 2 OH signals missing; ^{13}C NMR (75 MHz) δ = 172.0, 171.5, 168.1, 168.0, 133.7, 132.1, 128.8, 127.3, 127.2, 73.0, 72.8, 58.3, 57.8, 57.6, 57.4, 52.4, 52.3, 35.7, 35.4, 33.9, 33.6, 30.9, 25.7, 21.9, 21.8, 21.6, 19.2, 19.1, 18.0, 17.7; HR-MS (ES) calcd for $C_{21}H_{30}N_2O_5Na$ (M + Na) 413.2052, found: 413.2043.

Bz-(1-Hydroxycyclohexyl)Gly-Asp-OMe (24): Chromatography (pentane/EtOAc, 2/3). Colorless solid (1.0:1.0 diastereomeric mixture). IR (KBr) 3278, 1743, 1633 cm^{-1}; ^1H NMR δ = 7.78−7.87 (4H, m), 7.73 (1H, d, J = 8.0 Hz), 7.61 (1H, d, J = 8.4 Hz), 7.36−7.56 (6H, m), 7.15−7.28 (2H, m), 4.90 (1H, ddd, J = 4.8, 5.0, 8.6 Hz), 4.84 (1H, ddd, J = 5.0, 5.2, 8.0 Hz), 4.67 (1H, d, J = 8.6 Hz), 4.66 (1H, d, J = 8.8 Hz), 3.74 (3H, s), 3.66 (3H, s), 3.65 (3H, s), 3.62 (3H, s), 3.50 (2H, bs), 2.74−3.07 (4H, m), 1.12−1.85 (20H, m); ^{13}C NMR δ = 171.4, 171.3, 171.1, 171.0, 170.8, 170.6, 167.9, 167.7, 133.7, 133.5, 132.0, 128.7, 127.3, 73.3, 73.0, 58.7, 58.4, 53.6, 52.2, 48.9, 48.6, 36.0, 35.9, 35.4, 35.3, 33.7, 33.4, 25.6, 21.8, 21.6; HR-MS (ES) calcd for $C_{21}H_{28}N_2O_7Na$ (M + Na): 443.1794, found: 443.1767.

Bz-(1-Hydroxycyclohexyl)Gly-Ala-OMe (25): Chromatography (pentane/EtOAc, 1/1). Pale yellow solid (1.1:1.0 diastereomeric mixture). IR (KBr) 3290, 1750, 1635 cm^{-1}; ^1H NMR δ = 7.78−7.88 (4H, m), 7.39−7.58 (6H, m), 7.06−7.30 (4H, m), 4.45−4.67 (4H, m), 4.04 (1H, bs), 3.90 (1H, bs), 3.75 (3H, s), 3.65 (3H, s), 1.19−1.86 (26H, m); ^{13}C NMR δ = 172.9, 172.6, 171.4, 171.3, 168.0, 167.8, 133.7, 132.1, 128.8, 128.5, 127.3, 73.2, 72.9, 58.3, 57.9, 52.7, 48.3, 35.5, 35.4, 33.8, 33.5, 25.7, 21.8, 21.6, 18.0, 17.8; HR-MS (ES) calcd for $C_{19}H_{26}N_2O_5Na$ (M + Na): 385.1739, found: 385.1736.

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Bz-(1-Hydroxycyclohexyl)Gly-Pro-OMe (26): Chromatography (pentane/EtOAc, 3/2). Colorless solid (1.8:1.0 diastereomeric mixture). IR (KBr) 3431, 1752, 1630 cm^{-1}; ^1H NMR δ = 7.77−7.85 (4H, m), 7.38−7.57 (6H, m), 7.12 (1H, d, J = 9.0 Hz), 7.04 (1H, d, J = 9.5 Hz), 4.93 (1H, d, J = 9.5 Hz), 4.86 (1H, d, J = 9.5 Hz), 4.46−4.54 (1H, m), 3.68−3.91 (1H, m), 4.14 (2H, s), 3.75 (3H, s), 3.67 (3H, s), 1.90−2.36 (8H, m), 1.20−1.90 (20H, m); ^{13}C NMR δ = 172.2, 171.33, 171.28, 167.4, 167.3, 133.4, 133.5, 131.9, 128.6, 127.22, 127.17, 73.3, 73.0, 59.0, 58.8, 55.4, 55.2, 52.4, 47.9, 34.9, 33.9, 33.8, 29.3, 25.7, 24.9, 24.6, 21.7, 21.6, 21.5, 21.4; HR-MS (ES) calcd for $C_{21}H_{28}N_2O_5$-Na (M + Na): 411.1896, found 411.1903.

Bz-Leu-(1-hydroxycyclohexyl)Gly-OMe (27): Chromatography (pentane/EtOAc, 3/2). Colorless solid (1.1:1.0 diastereomeric mixture). IR (KBr) 3332, 1745, 1637 cm^{-1}; ^1H NMR δ = 7.72−7.82 (4H, m), 7.33−7.54 (6H, m), 7.15−7.29 (2H, m), 6.85−6.96 (2H, m), 4.73−4.88 (2H, m), 4.60 (1H, d, J = 9.0 Hz), 4.57 (1H, d, J = 9.0 Hz), 3.75 (3H, s), 3.69 (3H, s), 2.98 (1H, bs), 2.79 (1H, bs), 1.12−1.82 (26H, m), 0.91−1.02 (12H, m); ^{13}C NMR δ = 172.7, 172.4, 171.9, 171.6, 167.7, 167.5, 134.0, 131.9, 128.7, 127.2, 73.1, 72.8, 59.4, 52.4, 52.3, 42.7, 41.4, 35.3, 35.1, 34.5, 25.5, 25.1, 25.0, 23.2, 23.0, 22.4, 22.3, 21.7; HR-MS (ES) calcd for $C_{22}H_{32}N_2O_5Na$ (M + Na): 427.2209, found: 427.2209.

Bz-Leu-(1-hydroxycyclohexyl)Gly-Val-OMe (28): Chromatography (pentane/EtOAc, 3/2). Colorless solid (1.2:1.0 diastereomeric mixture). IR (KBr) 3334, 1745, 1640 cm^{-1}; ^1H NMR δ = 7.75−7.84 (4H, m), 7.33−7.54 (8H, m), 7.02−7.22 (4H, m), 4.72−4.88 (2H, m), 4.48−4.62 (2H, m), 4.36−4.47 (2H, m), 4.05 (1H, bs), 3.80 (1H, bs), 3.74 (3H, s), 3.54 (3H, s), 0.78−2.34 (52H, m); ^{13}C NMR δ = 173.3, 173.1, 172.5, 172.0, 171.6, 167.4, 167.3, 133.9, 131.8, 128.5, 127.4, 72.8, 72.5, 58.5, 57.9, 57.5, 57.1, 53.6, 52.4, 52.2, 52.1, 41.8, 41.7, 35.6, 35.2, 34.3, 33.7, 33.1, 32.1, 31.1, 30.6, 29.8, 25.7, 25.5, 25.2, 25.0, 23.0, 22.8, 22.5, 22.3, 21.8, 21.6, 21.4, 19.1, 17.9, 17.8.

Bz-Leu-(1-hydroxycyclohexyl)Gly-Phe-OMe (29): Chromatography (pentane/EtOAc, 1/1). Colorless solid (2.0:1.0 diastereomeric mixture). IR (KBr) 3292, 1747, 1637 cm^{-1}; ^1H NMR δ = 7.75−7.91 (5H, m), 7.05−7.65 (21H, m), 4.75−4.98 (4H, m), 4.63 (1H, d, J = 8.8 Hz), 4.52 (1H, d, J = 8.8 Hz), 4.01 (1H, bs), 3.65 (3H, s), 3.60 (1H, bs), 3.51 (3H, s), 2.87−3.23 (4H, m), 1.10−1.80 (26H, m), 0.84−1.02 (12H, m); ^{13}C NMR δ = 172.9, 172.1, 171.7, 171.1, 170.9, 167.5, 136.2, 135.9, 134.0, 131.7, 129.2, 128.7, 128.6, 128.5, 127.4, 127.2, 127.1, 73.0, 72.7, 58.9, 53.4, 52.4, 52.1, 41.9, 41.4, 38.1, 34.9, 33.5, 33.1, 25.5, 25.0, 23.2, 23.1, 22.4, 22.2, 21.4; HR-MS (ES) calcd for $C_{31}H_{41}N_3O_6Na$ (M + Na): 574.2893, found: 574.2869.

Bz-(1-Hydroxycyclohexyl)Gly-Leu-Phe-OMe (30): Chromatography (pentane/EtOAc, 3/2). Colorless solid (1.0:1.0 diastereomeric mixture). IR (KBr) 3316, 1743, 1624 cm^{-1}; ^1H NMR δ = 7.74−7.82 (4H, m), 7.37−7.54 (6H, m), 7.07−7.36 (12H, m), 6.96 (1H, d, J = 7.6 Hz), 6.90 (1H, d, J = 8.8 Hz), 6.89 (1H, d, J = 8.4 Hz), 6.66 (1H, d, J = 7.8 Hz), 4.85 (1H, dt, J = 6.0, 8.0 Hz), 4.76 (1H, dt, J = 5.8, 8.0 Hz), 4.58 (1H, d, J = 8.8 Hz), 4.33−4.49 (2H, m), 4.40 (1H, d, J = 7.8 Hz), 3.97 (1H, s), 3.94 (1H, s), 3.70 (3H, s), 3.49 (3H, s), 3.12 (2H, d, J = 6.0 Hz), 3.10 (1H, dd, J = 5.8, 14.0 Hz), 2.99 (1H, dd, J = 8.0, 14.0 Hz), 1.16−1.82 (26H, m), 0.90 (3H, d, J = 6.2 Hz), 0.88 (3H, d, J = 6.2 Hz), 0.83 (3H, d, J = 6.2 Hz), 0.79 (3H, d, J = 5.8 Hz); ^{13}C NMR δ = 171.7 (2), 171.6, 171.4 (2), 171.1, 168.5, 167.9, 136.3, 135.8, 133.6, 133.1, 132.2, 132.1, 129.3, 128.7, 128.6 (2), 128.4, 127.3, 127.2, 127.1, 126.9, 73.2, 72.4, 59.0, 58.7, 53.3 (2), 52.4, 52.2 (3), 40.6, 40.3, 37.9, 37.7, 35.4, 35.3, 34.0, 32.9, 29.7 (2), 25.5 (2), 24.9, 24.7, 23.0, 22.9, 21.8, 21.5 (2), 21.4, 21.3; HR-MS (ES) calcd for $C_{31}H_{41}N_3O_6Na$ (M + Na): 574.2893, found 574.2863.

Bz-Leu-(1-hydroxycyclohexyl)Gly-Leu-Phe-OMe (31): Chromatography (pentane/EtOAc, 7/3 to 1/1). Colorless solid (1.2:1.0 diastereomeric mixture). IR (KBr) 3293, 1748, 1635 cm^{-1}; ^1H NMR δ = 8.11 (1H, d, J = 8.4 Hz), 7.75−7.92 (7H, m), 7.01−7.53 (20H, m), 4.32−5.10 (8H, m), 3.65 (3H, s), 3.64 (3H, s), 2.88−3.16 (4H, m), 1.07−1.88 (32H, m), 0.73−1.05 (24H, m), 2 OH signals missing; ^{13}C NMR δ = 173.8, 173.1, 172.1, 171.9, 171.7, 171.6, 171.0, 168.0, 167.5, 136.2, 135.9, 134.1, 132.1, 131.6, 129.3, 129.2, 128.7, 128.5, 128.4, 127.6, 127.5, 127.2, 127.0, 73.0, 72.4, 59.1, 58.6, 53.8, 52.9, 52.5, 52.3, 51.7, 41.5, 41.3, 40.5, 37.9, 35.4, 35.1, 33.9, 33.0, 29.8, 25.5, 25.1, 24.9, 23.0, 22.7, 22.3, 21.9, 21.3; HR-MS (ES) calcd for $C_{37}H_{52}N_4O_7Na$ (M + Na): 687.3734, found: 687.3736.

A small fraction of one of the two diastereomers could be isolated from the same chromatographic separation. ^1H NMR δ = 7.75−7.85 (2H, m), 7.69 (1H, m), 7.00−7.63 (10H, m), 6.94 (1H, d, J = 8.2 Hz), 4.88 (1H, m), 4.65 (1H, m), 4.21−4.42 (2H, m), 3.64 (3H, s), 3.10 (1H, dd, J = 6.0, 14.0 Hz), 2.94 (1H, dd, J = 8.0, 13.6 Hz), 1.04−1.86 (16H, m), 0.68−1.03 (12H, m).

Bz-(1-Hydroxycyclohexyl)Gly-Val-(1-hydroxycyclohexyl)Gly-OMe (32). A 0.1 M solution of SmI_2 in THF (2.6 mL, 0.26 mmol) was added to a stirred solution of the pyridyl sulfide **22** (24.7 mg, 0.043 mmol) and cyclohexanone (27 μL, 0.26 mmol) in THF (0.5 mL) at 20 °C. After workup according to the general procedure for the preparation of **7**, flash chromatography (pentane/EtOAc 7/3 to 1/1) gave the tripeptide **32** (8.9 mg, 38%) as a colorless solid in a 3.4:1.5:1.4:1.0 diastereomeric mixture as determined by ^1H NMR analysis. IR (KBr) 3200, 1720, 1661 cm^{-1}; ^1H NMR (300 MHz at 45 °C) δ = 7.78−7.87 (8H, m), 7.40−7.59 (12H, m), 6.84−7.32 (12H, m), 4.30−4.70 (12H, m), 3.76 (3H, s), 3.70 (3H, s), 3.67 (3H, s), 3.62 (3H, s), 2.18−2.60 (4H, m), 1.09−1.96 (80H, m), 0.83−1.03 (24H, m), 8 OH signals missing; ^{13}C NMR (75 MHz) δ = 172.1, 172.0, 171.9, 171.8, 171.7, 171.6, 171.5, 171.4, 171.1, 170.9, 170.7, 167.8, 167.7, 133.5, 132.2, 132.1, 131.9, 131.8, 128.7, 128.5, 127.3, 127.2, 127.1, 73.5, 73.1, 72.8, 72.6, 72.4, 72.1, 72.0, 71.8, 59.5, 59.1, 59.0, 58.9, 58.8, 58.7, 58.5, 58.4, 58.2, 52.1, 51.9, 35.6, 35.4, 35.2, 35.0, 34.9, 34.8, 34.6, 34.4, 34.2, 34.1, 34.0, 30.2, 29.9, 29.4, 29.3, 25.4, 25.3, 25.2, 21.8, 21.7, 21.6, 21.5, 21.4, 21.3, 19.7, 19.4, 19.3, 19.2, 19.1, 17.6, 17.3, 17.1, 17.0, 16.8; HR-MS (ES) calcd for $C_{29}H_{43}N_3O_7Na$ (M + Na): 568.2998, found: 568.2993.

Bz-(1-Hydroxycyclopentyl)Gly-Phe-OMe (33): Chromatography (pentane/EtOAc, 7/3 to 3/2). Colorless solid (1.1:1.0 diastereomeric mixture). IR (KBr) 3280, 1749, 1631 cm^{-1}; ^1H NMR δ = 7.73−7.83 (4H, m), 7.09−7.61 (20H, m), 4.75−4.90 (2H, m), 4.50 (1H, d, J = 8.4 Hz), 4.43 (1H, d, J = 8.2 Hz), 4.05 (1H, bs), 3.99 (1H, bs), 3.74 (3H, s), 3.64 (3H, s), 3.20 (1H, dd, J = 5.2, 14.0 Hz), 3.16 (1H, dd, J = 5.0, 14.0 Hz), 3.02 (1H, dd, J = 8.4, 14.0 Hz), 2.97 (1H, dd, J = 8.0, 14.0 Hz), 1.44−1.94 (16H, m); ^{13}C NMR δ = 171.7, 171.6, 168.1, 167.7, 136.0, 135.7, 133.5, 132.2, 129.2, 128.7, 128.6, 127.3, 127.1, 82.8, 82.6, 58.9, 58.6, 53.4, 52.6, 38.8, 38.7, 37.8, 37.3, 24.5, 24.4, 24.0, 23.8; HR-MS (ES) calcd for $C_{24}H_{28}N_2O_5Na$ (M + Na): 447.1896, found: 447.1894.

Bz-(1-Hydroxy(cyclohexyl)methyl)Gly-Phe-OMe (34): Chromatography (pentane/EtOAc, 2/1). Colorless foam (2.5:1.8:1.1:1.0 diastereomeric mixture). IR (KBr) 3280, 1745, 1635 cm^{-1}; ^1H NMR δ = 7.72−7.84 (8H, m), 6.94−7.61 (40H, m), 4.62−4.97 (8H, m), 4.01−4.18 (2H, m), 3.80−3.94 (2H, m), 3.74 (3H, s), 3.73 (3H, s), 3.66 (3H, s), 3.64 (3H, s), 2.88−3.30 (8H, m), 0.78−2.15 (44H, m), 4 OH signals missing; ^{13}C NMR δ = 171.6, 167.9, 167.5, 136.0, 135.7, 133.4, 132.1, 129.2, 128.7, 128.6, 128.5, 127.4, 127.2, 127.1, 74.6, 53.7, 53.4, 52.6, 41.0, 37.7, 29.7, 29.4, 29.1, 28.7, 26.3, 26.0, 25.8; HR-MS (ES) calcd for $C_{26}H_{32}N_2O_5Na$ (M + Na): 475.2209, found: 475.2200.

Bz-(1-Hydroxyoctyl)Gly-Phe-OMe (35): Chromatography (pentane/EtOAc, 2/1). Colorless solid (2.2:2.1:1.0 diastereomeric mixture). IR (KBr) 3289, 1742, 1635 cm^{-1}; ^1H NMR δ = 7.73−7.85 (6H, m), 7.02−7.64 (30H, m), 4.76−4.92 (3H, m), 4.56−4.68 (3H, m), 4.02−4.28 (2H, m), 3.76 (1H, m), 3.74 (3H, s), 3.72 (3H, s), 3.67 (3H, s), 2.91−3.26 (6H, m), 1.06−1.72 (33H, m), 0.78−0.94 (12H, m), 3 OH signals missing; ^{13}C NMR δ = 171.7, 171.4, 170.9, 170.5, 168.1, 167.7, 136.0, 135.7, 133.4, 132.1, 129.2, 128.7, 127.4, 73.7, 73.6, 57.2, 56.6, 53.4, 52.6, 37.7, 33.9, 33.6, 31.9, 29.5, 29.3, 26.0, 22.7, 14.2; HR-MS (ES) calcd for $C_{27}H_{36}N_2O_5Na$ (M + Na): 491.2522, found: 491.2523.

Bz-(2-(2,3,4,6-Tetra-*O*-benzylglucopyranosyl)-1-hydroxy-ethyl)-Gly-Val-OMe (38): Chromatography (pentane/EtOAc, 7/3). Thick colorless syrup. Although 4 signals for the OMe group were observed, their overlap with other signals made it impossible to determine the diasteromeric ratio from the proton integrations. IR (film) 3301, 1742, 1644 cm^{-1}; ^1H NMR (300 MHz) δ = 7.76−7.91 (8H, m), 7.02−7.70 (100H, m), 4.00−4.94 (48H, m), 3.30−3.90 (24H, m), 3.70 (3H, s), 3.67 (3H, s), 3.65 (3H, s), 3.62 (3H, s), 1.80−2.34 (12H, m), 0.78−1.03 (24H, m), 4 OH signals missing; ^{13}C NMR (75 MHz) δ = 171.8, 171.6, 171.5, 170.9, 170.8, 170.7, 168.0, 167.8, 167.7, 167.6, 138.5,

138.4, 138.3, 138.2, 138.0, 137.9, 137.8, 137.7, 137.6, 137.5, 133.6, 133.5, 133.4, 131.9, 131.8, 131.7, 128.6, 128.5, 128.3, 128.2, 127.9, 127.8, 127.7, 127.6, 127.5, 127.1, 127.0, 81.9, 81.8, 81.6, 79.5, 79.2, 79.1, 78.4, 77.9, 77.7, 77.5, 75.6, 75.5, 75.3, 75.2, 75.0, 74.6, 74.5, 73.4, 73.3, 73.2, 73.1, 73.0, 72.9, 72.2, 71.9, 71.8, 71.6, 71.5, 71.3, 70.6, 70.1, 69.2, 69.1, 68.9, 68.6, 57.5, 57.4, 57.3, 56.6, 56.2, 56.0, 52.0, 30.7, 30.6, 30.2, 29.6, 29.4, 29.2, 29.1, 19.1, 19.0, 18.9, 17.7, 17.5, 17.4; HR-MS (ES) calcd for $C_{51}H_{58}N_2O_{10}Na$ (M + Na): 881.3989, found: 881.3996.

Ac-(1-Hydroxycyclohexyl)Gly-Phe-OMe (43): Chromatography (pentane/EtOAc, 1/2). Colorless solid (2.7:1.0 diastereomeric mixture). IR (KBr) 3328, 1741, 1645 cm^{-1}; ^1H NMR δ = 7.08−7.35 (11H, m), 6.95 (1H, d, J = 8.2 Hz), 6.41−6.52 (2H, m), 4.76−4.91 (2H, m), 4.32 (1H, d, J = 8.8 Hz), 4.31 (1H, d, J = 8.8 Hz), 3.78 (1H, bs), 3.73 (3H, s), 3.72 (3H, s), 3.21 (1H, dd, J = 5.2, 14.0 Hz), 3.17 (1H, dd, J = 5.6, 14.0 Hz), 3.02 (1H, dd, J = 7.8, 14.0 Hz), 2.98 (1H, dd, J = 8.2, 14.0 Hz), 2.01 (3H, s), 1.98 (3H, s), 1.12−1.70 (20H, m), 1 OH signal missing; ^{13}C NMR δ = 171.5, 171.4, 170.7, 170.5, 136.0, 135.7, 129.3, 129.2, 128.7, 127.2, 72.7, 72.6, 57.8, 57.4, 53.3, 52.6, 38.0, 37.8, 35.3, 33.5, 25.6, 23.1, 21.8, 21.7, 21.5; HR-MS (ES) calcd for $C_{20}H_{28}N_2O_5Na$ (M + Na): 399.1896, found: 399.1888.

A small fraction of one of the two diastereomers could be isolated from the same chromatographic separation. ^1H NMR δ = 7.07−7.38 (5H, m), 6.79 (1H, bd), 6.36 (1H, bd), 4.84 (1H, m), 4.32 (1H, d, J = 8.8 Hz), 3.73 (3H, s), 3.17 (1H, dd, J = 5.6, 14.0 Hz), 3.02 (1H, dd, J = 7.8, 14.0 Hz), 1.98 (3H, s), 1.12−1.70 (10H, m), OH signal missing; ^{13}C NMR δ = 171.5, 170.7, 170.5, 135.7, 129.2, 128.7, 127.2, 72.7, 57.8, 53.3, 52.6, 37.8, 35.3, 33.5, 25.6, 23.1, 21.7, 21.5.

Cbz-(1-Hydroxycyclohexyl)Gly-Phe-OMe (44): Chromatography (pentane/EtOAc, 3/1). Colorless solid (1.2:1.0 diastereomeric mixture). IR (KBr) 3339, 1734, 1693 cm^{-1}; ^1H NMR δ = 7.04−7.41 (20H, m), 6.65−6.87 (2H, m), 5.66−5.79 (2H, m), 5.02−5.17 (4H, m), 4.79−4.96 (2H, m), 4.02 (1H, d, J = 8.8 Hz), 4.01 (1H, d, J = 8.8 Hz), 3.72 (3H, s), 3.70 (3H, s), 3.48 (1H, bs), 3.41 (1H, bs), 2.93−3.26 (4H, m), 1.10−1.68 (20H, m); ^{13}C NMR δ = 171.7, 171.3, 156.7, 136.2, 135.9, 129.2, 128.7, 128.6, 128.2, 128.0, 127.3, 72.9, 72.7, 67.2, 60.2, 59.9, 53.2, 52.6, 37.9, 37.7, 35.1, 33.2, 33.0, 25.5, 21.6, 21.5, 21.4; HR-MS (ES) calcd for $C_{26}H_{32}N_2O_6Na$ (M + Na): 491.2158, found: 491.2138.

SmI_2-Promoted Coupling of Dipeptide 2 with Cyclohexanone in the Presence of 1% NiI_2. A 0.01 M solution of NiI_2 in THF (0.6 mL, 6.0 μmol) was added to a 0.1 M solution of SmI_2 in THF (6.0 mL, 0.60 mmol) and then allowed to stir for 15 min, after which the solution was cooled to 0 °C. This solution was then added dropwise to a stirred solution of the pyridyl sulfide **2** (89.8 mg, 0.20 mmol) and cyclohexanone (62 μL, 0.60 mmol) in THF (0.5 mL) at −78 °C. TLC analysis showed that the reaction was complete after 10 min. The reaction mixture was then warmed to 20 °C and saturated aqueous NH_4Cl (1 mL) was added. Workup according to the general procedure and flash chromatography gave the dipeptide **7** (74.9 mg, 85%) as a colorless solid in a 1:1 diastereomeric mixture as determined by ^1H NMR analysis.

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Supporting Information Available: Full experimental detail and characterization for compounds **13**−**22**, **39**, and **42** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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