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Synthesis of a Hydroxyethylene Isostere of the Tripeptide Arg-Gly-Leu via a Convergent Acyl-like Radical Addition Strategy

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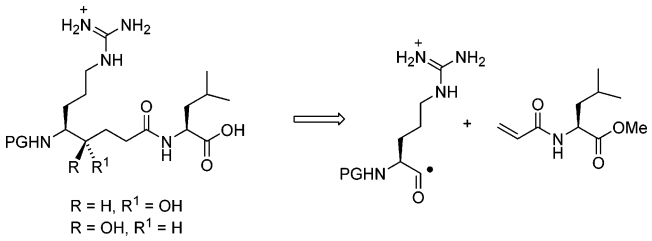

A hydroxyethylene isostere of the tripeptide Arg-Gly-Leu, representing an important fragment of a novel cyclic-peptide-based uPA inhibitor, was synthesized in few steps employing as the key step a samarium diiodide promoted coupling of either the 4-thiopyridyl ester of N^{α}-Fmoc- or N^{α}-Cbz-protected L-ornithine with the *N*-acryloyl derivative of L-leucine methyl ester. Epimerization under the coupling conditions at the chiral center in the α-position to the ketone was demonstrated not to take place. A stereoselective reduction of the Cbz-protected aminoketone obtained from this radical reaction was promoted by the same single-electron reducing agent in the presence of methanol providing the syn-amino alcohol with a diastereoselectivity of 85:15. With the use of lithium tri-*tert*-butoxyaluminum hydride in methanol, the corresponding anti-isomer was obtained almost exclusively. Subsequent elaboration of the ornithine moiety in the anti-isomer by introduction of the guanidine group followed by hydrolysis of the C-terminal ester bond and protection of the alcohol as its *tert*-butyldimethylsilyl ether provided the desired tripeptide mimic. The long reaction times required for the radical addition reactions with N^{δ}-Boc-L-ornithine (up to 5 days) led to a short study where a series of 4-thiopyridyl esters of Cbz-protected amino acids were reacted with two acrylates. Whereas N^{δ}-Boc-L-ornithine, alanine, phenylalanine, proline, and leucine all provided the aminoketone in 43−79% yield, valine only afforded traces of the coupling product.

Introduction

Urokinase-type plasminogen activator (uPA) is a serine protease which catalyses the conversion of the serine protease zymogen, plasminogen, into the active protease plasmin through cleavage of an Arg−Val bond in plasminogen. uPA-catalyzed plasmin generation has been implicated in the turn-over of extracellular matrix proteins in tissue remodeling.[1] Abnormal expression of uPA is believed to be responsible for tissue damage in several pathological conditions. In particular, abnormal expression of uPA is a key to a malignant tumor's capacity for invasion through basement membranes.[2,3]

Because of the pathophysiological functions of uPA, there has been extensive interest in generating specific uPA inhibitors. Several classes of synthetic low molecular weight inhibitors of uPA are known.[4] The binding modes for many of these have been characterized by X-ray crystal structure analysis. In general, such inhibitors have as a main constituent an Arg analogue inserting into the S1 pocket of the active site of uPA. With low molecular weight inhibitors, the challenge is to achieve selectivity for uPA over other serine proteases with P_1 Arg specificity, by utilizing small variations between the various proteases within the S1 pocket and its immediate surroundings.[4a,b,5−8] With the most promising of such inhibitors, a series of 6-halo-5-amidinoindole and 6-halo-

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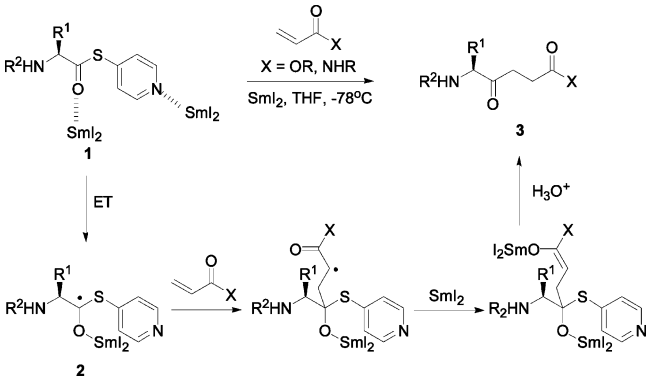
5-amidinobenzimidazole compounds, K_i values in the nanomolar range and 100−2000-fold selectivities for uPA over plasmin, trypsin, thrombin, tPA, and fXa were achieved.[9]

To find new principles for inhibiting the enzymatic activity of serine proteases, one of us (P.A.) has screened phage-displayed random peptide repertoires with uPA as bait. The most frequent of the isolated phage clones contained the disulfide bridge-constrained dodecapeptide sequence Cys-Ser-Trp-Arg-Gly-Leu-Glu-Asn-His-Arg-Met-Cys, which we have designated upain-1. A chemically synthesized peptide with this sequence inhibited uPA with a K_i of 30 μM and, importantly, exhibited a selectivity by factors of 50−500 over a number of other serine proteases, including trypsin, tPA, plasmin, thrombin, activated protein C, fXa, fVIIa, and plasma kallikrein.[10] This selectivity is comparable or superior to the most selective of the previously published small weight uPA inhibitors.[4] The fact that a reasonable affinity and an excellent selectivity were achieved in only a single selection step suggests that affinity maturation by a combined use of molecular biological methods and organic synthesis may eventually lead to highly specific and efficient uPA inhibitors and may give mechanistic information about serine protease catalysis and inhibition.

One of the possibilities in the chemical modification of peptide-based enzyme inhibitors is a stabilization of the scissile peptide bond toward nontarget proteases by replacing it with a nonamide bond. This will also allow studies of the importance of the nature of that bond for the mechanism of inhibition. For this reason, we set out to examine stable synthetic analogues of upain-1 with the incorporation of a hydroxyethylene isostere of the sequence Arg-Gly-Leu. In this report, we present our preliminary synthetic work on the construction of such a modified cyclic inhibitor dealing with the rapid preparation of the hydroxyethylene isostere of this tripeptide sequence.[11] Our synthetic approach exploits our newly discovered acyl-like radical addition reaction as the key carbon−carbon bond-forming step between two amino acid precursors, which provides a short and effective synthesis of the tripeptide analogue.

SCHEME 1



Results and Discussion

We have previously reported the samarium diiodide[12] promoted coupling of thioester derivatives of Cbz-protected amino acids to acrylamides and acrylates as a viable approach to 4-ketoamides and -esters via a formal acyl radical addition reaction in yields up to 90% (Scheme 1).[13] The mechanism for this reaction is believed to involve a SmI_2-promoted reduction of the thioester **1** to a ketyl radical type intermediate **2** followed by its radical addition to the α,β-unsaturated amide or ester. A second electron transfer from SmI_2 then affords a samarium(III) enolate which eventually undergoes protonation affording the aminoketone **3**.

Selective reduction of the keto-functionality to either of the two epimeric alcohols was also shown to be feasible,[14] revealing this two-step radical addition, ketone reduction sequence as an interesting alternative for the synthesis of peptides containing a hydroxyethylene isos-

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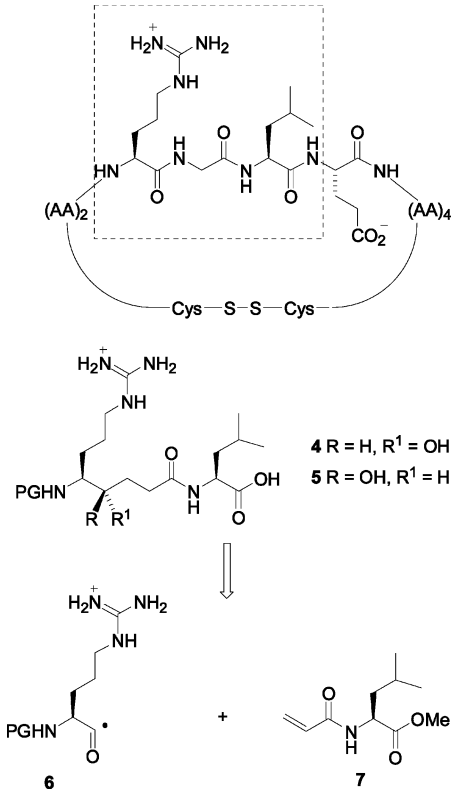
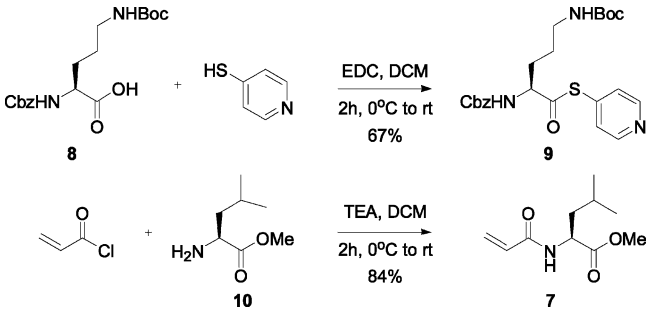


FIGURE 1. Retrosynthetic analysis for the synthesis of the tripeptide analogue of the Arg-Gly-Leu sequence.

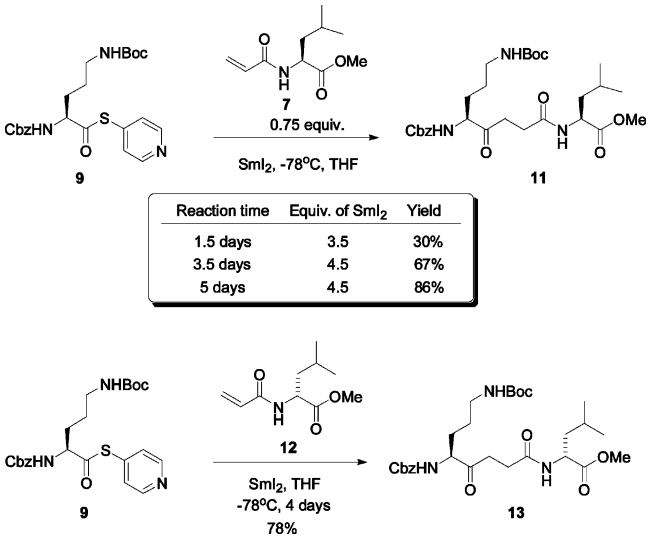
tere,[15] including the target tripeptide analogue of Arg-Gly-Leu. With these results in mind, the synthesis of the desired tripeptide mimic **4** or **5** would then simply require the coupling of an acyl-like radical equivalent of a suitably functionalized arginine **6** to the *N*-acryloyl derivative of leucine **7**, as depicted in Figure 1, followed by a stereoselective reduction.

Preparation of the two amino acid coupling partners for the radical addition reaction is illustrated in Scheme 2. To avoid a potential intervention of arginine's guanidine group in the SmI_2-mediated radical addition step, we commenced the synthesis with an arginine precursor represented by L-ornithine, introducing the guanidine functionality at a later stage of the synthesis. Hence, the thioester **9** was synthesized on a 7 mmol scale from N^{α}-Cbz-N^{δ}-Boc-L-ornithine (**8**) and 4-mercaptopyridine via an EDC coupling affording the desired product in an improved yield of 67% yield compared to our earlier report on a smaller reaction scale (1.3 mmol).[14] Reaction of acryloyl chloride with the methyl ester of L-leucine **10** in the presence of triethylamine in dichloromethane provided in a nondramatic fashion the acrylamide **7** in 84% yield.[16]

SCHEME 2



SCHEME 3



Reaction time	Equiv. of SmI_2	Yield
1.5 days	3.5	30%
3.5 days	4.5	67%
5 days	4.5	86%

Additionally, in our earlier publication, we reported that the coupling of the thioester **9** with the acrylamide **7** required a reaction time of 80 h in order to provide the ketone **11** in a 67% yield (Scheme 3).[14] This was somewhat surprising since similar coupling reactions performed with the thioesters of Cbz-protected phenylalanine or leucine afforded coupling products in similar yields but with greatly reduced reaction times (24 h).[13] When this reaction time was employed for the coupling of **7** and **9**, the product of radical addition **11** was only isolated in a 30% yield along with unreacted starting material. For this study, we extended the reaction time considerably to 5 days, which furnished **11** in a good 86% yield on a 0.3 mmol scale (79% on a 0.8 mmol scale). A supplementary point regarding the workup procedure for this C−C bond-forming reaction should be made. In our original procedure, a sodium hypochlorite solution was used to oxidize the thiol and disulfide byproducts obtained upon quenching of the reaction mixture with oxygen and ammonium chloride, thus facilitating their separation from the desired ketone.[13] Application of this procedure to the workup of **11** led to considerable amounts of selective N-chlorination of the ornithine side chain.[17] Omission of this oxidative workup provided the pure ketone after careful column chromatography.

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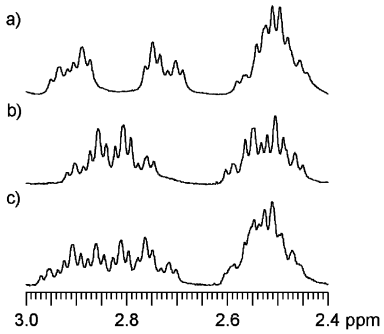
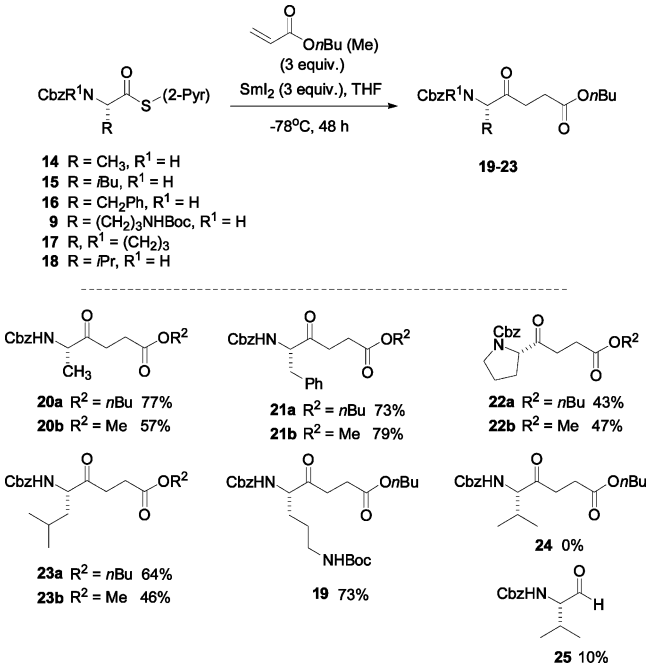


FIGURE 2. Section of ^{1}H NMR spectrum of (a) **11**, (b) **13**, and (c) an approximately 1:1 mixture of **11** and **13**.

To determine whether **11** had undergone any epimerization at the sensitive chiral center adjacent to the ketone under the reaction conditions or workup, a sample of the diastereomer **13** was prepared in a similar fashion from the coupling of the thioester **9** with the *N*-acryloyl derivative **12** of D-leucine (Scheme 3). The two diastereomeric ketones **11** and **13** were compared on the basis of their ^{1}H NMR spectra, and Figure 2 displays the region containing the proton signals from the ethylene spacer for (a) **11**, (b) **13**, and (c) as a mixture of the two. Analysis of the spectra recorded after the coupling of **9** with **7** revealed that if epimerization had occurred, the presence of the C3-epimer was less than 5%, representing the limit of detection. Hence, it can be concluded that these SmI_2-induced coupling reactions proceed under sufficiently mild conditions without significant levels of epimerization α to the ketone functionality.

The reactivity discrepancy observed between ornithine and phenylalanine or leucine was unanticipated and is undoubtedly related to the intervention of the ornithine side chain. A small study was initiated to examine in more detail the influence of the amino acid side chains on these radical addition reactions. Hence, the coupling reaction between six amino acid thioesters **9** and **14**−**18** and simple radical acceptors, such as butyl and methyl acrylate was investigated, the results of which are depicted in Scheme 4. All reactions were performed with excess samarium diiodide (3 equiv), and acrylate (3 equiv) with reaction times of 48 h. As indicated, the coupling yields for the thioesters **9** and **14**−**17** of Cbz-protected N^{δ}-Boc-L-ornithine, alanine, phenylalanine, proline, and leucine, interestingly all provided the coupling products **19**−**23** in acceptable to good yields. However, the thiopyridyl ester of Cbz-protected valine proved ineffective for the transformation of **18** to **24** with isolation of both recovered starting material (approximately 50%) and the aldehyde **25** (10%). These results suggests that α-substitution in the side chain of the amino acid thioester leads to considerable steric conestion in the transition state of the radical addition step where ultimately either hydrogen abstraction or reduction of the intermediate ketyl-like radical precedes the radical addition step, allowing for the formation of the aldehyde **25** upon workup. However, importantly no reaction discrepancy was noted in the coupling step between ornithine and the other reactive amino

SCHEME 4



acids, implying that the slow reactivity between **9** and **7** may be a result of the combination of these two derivatives.

The next step requires a stereoselective reduction of the ketone function. Various protocols exist for achieving this reduction step of α-aminoketones with high diastereomeric excess.[18,19] Luthman and co-workers have previously demonstrated the ability of (*S*)-alpine-hydride and (*S*)-enantride to be excellent reagents for achieving Felkin-Anh control[20] with essentially exclusive formation of the syn-amino alcohol.[18] We have also applied this protocol successfully with other di- and tripeptide mimics,[14,21] whereas application of the more common reducing agents was either low-yielding or displayed little facial selectivity. However, the aminoketone **11** proved quickly to deviate considerably from the results obtained from these earlier reduction studies, as illustrated in Table 1. Subjecting **11** to (*S*)-alpine-hydride, provided essentially a 1:1 mixture of diastereomeric amino alcohols **26** and **27** as determined by HPLC analysis of the crude reaction mixtures (entries 1 and 2). Undoubtedly, the ornithine side chain must again be intervening with this bulky borohydride reagent, and a potential solution would be to examine the influence of the nitrogen-protecting group on diastereoselectivities with this reducing agent. Whereas as this study would require us to modify the starting materials for this synthesis, instead a small study was initiated in an attempt to identify a more selective reducing reagent for this particular substrate **11**.

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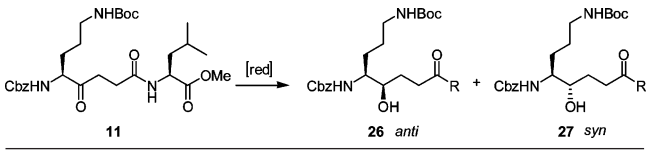
TABLE 1. Survey of Reducing Agents for the Stereoselective Reduction of the α-Amino Ketone 11



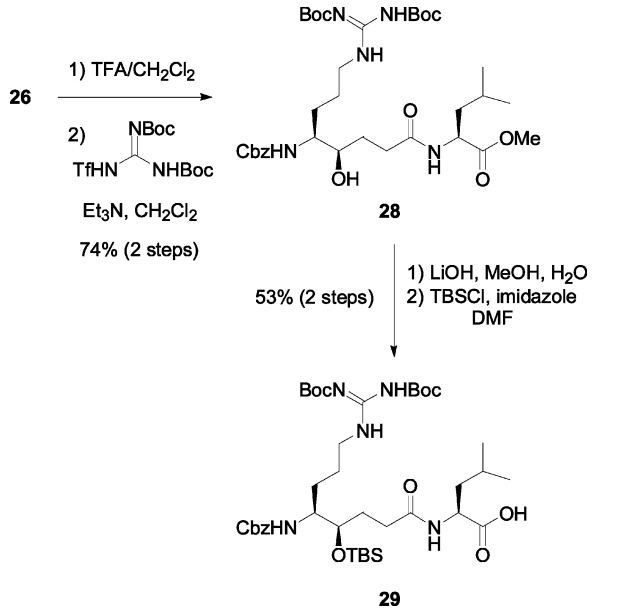
entry	reducing reagent	solvent	temp °C	time	yield	anti/syn[a]
1	(*S*)-alpine-hydride	THF	−78	5 h	nd[b]	42:58
2	(*S*)-alpine-hydride	THF	−78	16 h	nd[b]	44:56
3	DIBALH	THF	−78	24 h	30%[c]	36:64
4	LS-selectride	THF	−78	20 h	71%[c]	80:20
5	SmI_2 (3 equiv) MeOH (1.2 equiv)	THF	20	5 h	61%[d]	15:85
6	SmI_2 (3 equiv) MeOH (2 equiv)	THF	20	6.5 h	nd[b]	19:81
7	SmI_2 (3 equiv) MeOH (10 equiv)	THF	20	10 min	nd[b]	33:67
8	$NaBH_4$	MeOH	−78	3.5 h	93%[c]	57:43
9	$NaBH_4$	EtOH	−78	3.5 h	66%[c]	65:35
10	$NaBH_4$, $CeCl_3$	MeOH	−78	45 min	98%[c]	69:31
11	$NaBH_4$, $CeCl_3$	EtOH	−78	45 min	97%[c]	86:14
12	$LiAlH(O\text{-}t\text{-}Bu)_3$ (6 equiv)	MeOH	−78	16 h	60%[d]	>95:5

[a] The anti/syn ratio was determined by HPLC. [b] Not determined. [c] Yield obtained from ^1H NMR spectra with the remaining material being unreacted ketone. [d] Isolated yield.

DIBALH reductions usually furnish the Felkin-Anh product, but with the ketone **11** the selectivity was only moderate (entry 3). Selectrides have previously been reported to predominantly yield the syn-isomer,[18] or show no selectivity,[19] but in the case of **11**, employing LS−selectride (entry 4), the major product was the anti-isomer. On the other hand, reduction with the single-electron transferring reagent, samarium diiodide, in the presence of a proton source provided an alternative route for accessing the syn-isomer **27**. In particular, it was found that subjecting **11** to SmI_2 with 1.2 equiv of methanol at 20 °C (entry 5) afforded the syn-amino alcohol **27** in a yield of 61% where the diastereomeric ratio attained a value of 85:15.[22] It is important that the reaction time does not exceed the 5 h used for this reduction as prolonged subjection to these conditions led to extensive decomposition and hence reduced yields of **27**. Increasing the number of equivalents of MeOH had an adverse effect on the diastereoselectivity of the reduction (entries 6 and 7), yet with 20 equiv the reaction time was reduced to only 10 min.

Of the various hydride-based reducing agents tested, only the lithium tri-*tert*-butoxyaluminum hydride proved to be sufficiently selective, though in favor of the anti-product **26** with an anti/syn ratio greater than 95:5 (entry 12). The stereochemical assignments were tentatively made based on earlier reduction studies of aminoketones with this reagent by the Hoffman group.[19] In the $NaBH_4$ reductions (entries 8−11) an increase in the anti-selectivity in favor of the Cram chelate product **26**[23] is observed on going from MeOH to EtOH as the solvent and also upon the addition of $CeCl_3$.[24] These results nicely illustrate the importance of the size of the reactive alkoxyborohydride species on the selectivity of the reduction.

SCHEME 5



Finally, completion of the tripeptide mimic required a selective deprotection of the nitrogen-containing side chain of the ornithine unit followed by introduction of the guanidine group, the transformations of which were attempted with the anti-isomer **26**. Hence, removal of the Boc group with trifluoroacetic acid and treatment of the primary amine with *N*,*N*′-di-Boc-*N*″-triflylguanidine as reported by Goodman and co-workers afforded the arginine derivative **28** in a yield of 74% (Scheme 5).[25] To provide a more appropriately functionalized mimic, **28** was submitted to basic hydrolysis followed by an alcohol protection step to afford the silyl ether **29** in 53% yield.

We next examined the possibility of exploiting other nitrogen-protecting groups other than CBz for the radical-coupling step. To this end, the coupling efficiencies of three phenylalanine thioesters possessing three different nitrogen-protecting groups with acrylamide **7** were compared in a model study as shown in Scheme 6. Whereas the Cbz-protected derivative **16** afforded a high yield of the aminoketone **32** in the SmI_2-promoted radical addition reaction as previously reported,[13] the corresponding Boc-protected amino acid **30** essentially and unexpectedly led to no conversion to the corresponding Boc-protected aminoketone **33**. Fortunately, a coupling reaction performed with the Fmoc-protected phenylalanine **31** led to the desired coupling product **34** in a satisfactory yield of 76%, demonstrating the compatibility of this protecting group with these radical addition reactions. Finally, in light of these results, a coupling attempt with the N^{α}-Fmoc-N^{δ}-Boc-L-ornithine derivative **35** was made. Quite pleasingly, the tripeptide analogue **36** was generated in a 43% yield after a reaction time of 4 days.

To conclude these studies, we examined the possibility of incorporating a fourth amino acid directly into the

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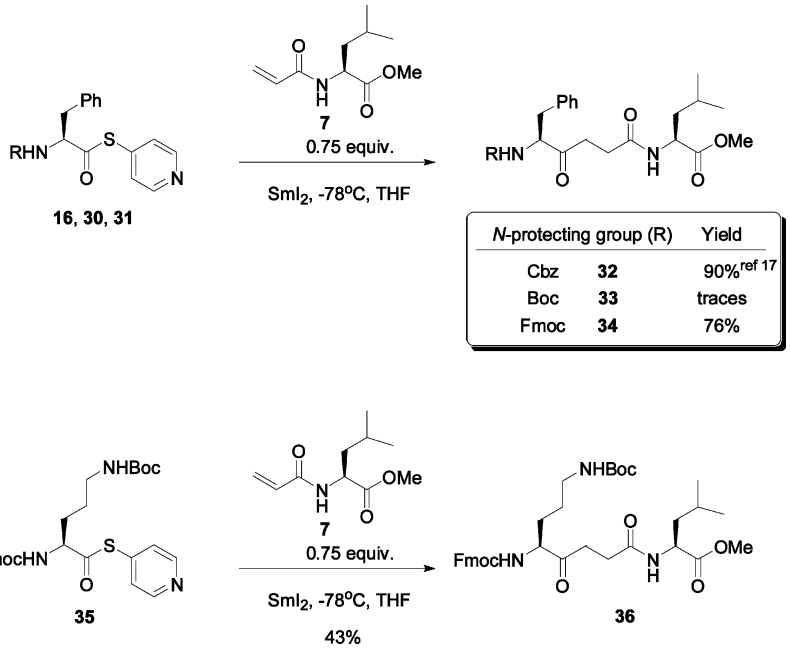
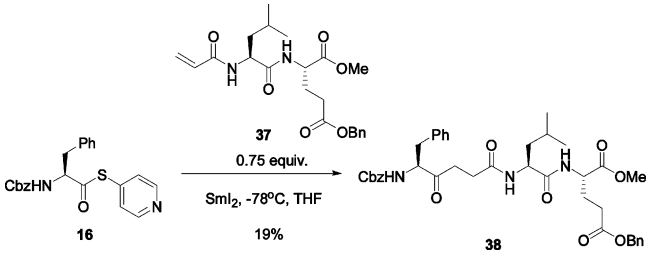
(24) Gemal, A. L.; Luche, J.-L. *J. Am. Chem. Soc.* **1981**, *103*, 5454.
(25) (a) Feichtinger, K.; Zapf, C.; Sings, H. L.; Goodman, M. *J. Org. Chem.* **1998**, *63*, 3804. (b) Baker, T. J.; Luedtke, N. W.; Tor, Y.; Goodman, M. *J. Org. Chem.* **2000**, *65*, 9054.

SCHEME 6



SCHEME 7



peptide mimic before further elaboration on the solid-phase synthesis. As illustrated in the Introduction, the leucine residue is flanked by a glutamate unit at the C-terminal end. We have commenced studies for preparing a similar hydroxyethylene mimic of this extended peptide structure and have already examined the radical coupling step between the model, phenyl alanine thioester **16**, and the acryloyl derivative of the protected dipeptide Leu-Glu **37** (Scheme 7). Under similar coupling conditions as for the preparation of **11**, only a 19% yield was obtained for the tetrapeptide analogue **38**. Repeated attempts with longer reaction times did not improve the coupling efficiency. Again, it is difficult to provide a plausible explanation for this loss of reactivity, taking into consideration our previous successful formation of other tetrapeptide analogues using this radical addition chemistry.[13] It is becoming increasingly apparent that this C−C bond-forming reaction is particularly sensitive to the amino acid structures of both the radical donor and acceptor.

Conclusions

We have successfully applied our acyl-like radical addition chemistry to a short synthesis of a hydroxyethylene isostere of the tripeptide sequence Arg-Gly-Leu, with the eventual goal of incorporating this fragment into the cyclic peptide based inhibitor of the urokinase plasminogen activator. The key steps for this synthesis involved a samarium diiodide promoted carbon−carbon bond formation followed by a stereoselective ketone reduction mediated by the same single-electron reducing agent for the obtention of the syn-amino alcohol. Alternatively, the anti-isomer was prepared by reduction with lithium tri-*tert*-butoxyaluminum hydride. An investigation was undertaken to examine appropriate protecting groups on the amino acid precursors such that the eventual tripeptide fragment could be made adaptable to solid-phase peptide synthesis. The Fmoc nitrogen-protecting group was shown to be compatible with the SmI_2-induced radical addition reaction. Further work is now underway where the results of this work will be exploited to prepare a suitably protected tripeptide mimic for the completion of the synthesis of a potential inhibitor of the protease, uPA. This work will be reported in due course.

Experimental Section

(2*S*)-2-Acryloylamino-4-methylpentanoic Acid Methyl Ester (7): General Procedure for the Formation of Acrylamides. The hydrochloride salt of L-Leu-OMe (2.20 g, 15.2 mmol) was transferred to a flame-dried flask, and the flask was flushed with nitrogen. Dry dichloromethane (100 mL) and triethylamine (4.3 mL, 30.8 mmol) were added, and the solution was cooled to 0 °C before distilled acryloyl chloride (1.25 mL, 15.2 mmol) was added in a dropwise manner. The mixture was allowed to warm to room temperature and left stirring for 2 h. The reaction was quenched by addition of an aqueous solution of $NaHCO_3$, and the solution was extracted with dichloromethane (3 times). The combined organic phases were washed with saturated $NaHCO_3$ and dried over $MgSO_4$. After concentration in vacuo, 2.59 g was obtained of the crude product **7** (84% yield) as a yellow powder which was of sufficient purity to be used in the subsequent transformations. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 6.32 (dd, 1H, J = 16.8, 1.2 Hz), 6.15 (dd, 1H, J = 16.8, 10.0 Hz), 6.05 (br d, 1H, J = 6.8 Hz), 5.68 (dd, 1H, J = 10.0, 1.2 Hz), 4.75 (dt, 1H, J = 8.4, 4.8 Hz), 3.75 (s, 3H), 1.72−1.64 (m, 2H), 1.63−1.53 (m, 1H), 0.96 (d, 3H, J = 6.0 Hz), 0.95 (d, 3H, J = 6.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 174.0, 165.5, 130.6, 127.3, 52.5,

50.9, 41.8, 25.0, 23.0, 22.1. HRMS $C_{10}H_{17}NO_3$ [M + Na^+]: calculated, 222.1106; found, 222.1098.

(2*S*)-2-Benzyloxycarbonylamino-5-*tert*-butoxycarbonylaminothiopentanoic Acid *S*-Pyridin-4-yl Ester (9): General Procedure for the Formation of 4-Pyridyl Thioesters. EDC (1.71 g, 8.90 mmol) was added to a stirred solution of N^{α}-Cbz-N^{δ}-Boc-L-ornithine (**8**) (2.72 g, 7.40 mmol) and 4-mercaptopyridine (0.824 g, 7.40 mmol) in dichloromethane (80 mL) at 0 °C under a nitrogen atmosphere. After 10 min the solution was warmed to 20 °C and left stirring for an additional 1.2 h. The reaction was quenched with water, and the organic phase was washed with water (4 times) and brine. The organic phase was dried over Na_2SO_4, filtered, and concentrated in vacuo to yield the crude thioester. The crude product was purified by flash chromatography using pentane/ethyl acetate (2:3) as the eluant, affording 2.28 g of the thioester (67% yield) as a slightly yellow powder. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.62 (d, 2H, J = 5.6 Hz), 7.37−7.34 (m, 7H), 5.77 (br s, 1H), 5.17 (s, 2H), 4.63 (br t, 1H, J = 5.8 Hz), 4.55−4.50 (m, 1H), 3.22−3.08 (m, 2H), 2.02−1.92 (m, 1H), 1.77−1.68 (m, 1H), 1.64−1.56 (m, 2H), 1.43 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 197.3, 156.4, 156.3, 150.1 (2C), 138.8, 136.2, 128.8 (2C), 128.6, 128.4 (2C), 128.4 (2C), 79.7, 67.7, 61.5, 40.0, 29.5, 28.6 (3C), 26.6. HRMS $C_{23}H_{29}N_3O_5S$ [M+Na^+]: calculated, 482.1726; found, 482.1736.

(2*S*)-2-[(5*S*)-5-Benzyloxycarbonylamino-8-*tert*-butoxycarbonyl-amino-4-ox o-octanoylamino]-4-methylpentanoic Acid Methyl Ester (11): General Procedure for SmI_2-Promoted Coupling of a Thioester and an Acrylamide. The thioester **9** (201 mg, 0.43 mmol) and acrylamide **7** (58 mg, 0.29 mmol) were flushed with argon before THF (3 mL) was added. The solution was added dropwise over 15 min via a syringe pump to a solution of 0.1 M SmI_2 in THF (19 mL, 1.9 mmol) cooled to −78 °C under an argon atmosphere, and the solution was left stirring at this temperature for 5 days. The excess SmI_2 was oxidized by flushing the mixture with oxygen from a balloon. To the now yellow solution was added saturated NH_4Cl(aq) at −78 °C followed by warming the solution to room temperature. The THF was evaporated off, and 10% citric acid or 0.5 M HCl was added followed by extraction (3 times) with EtOAc. The combined organic phases were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The coupling product was purified by flash chromatography on silica gel using pentane/ethyl acetate (1:1 to 1:3) as the eluant, affording 137 mg of **11** (86%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.35 (s, 5H), 6.02 (br d, 1H, J = 7.6 Hz), 5.59 (br d, 1H, J = 7.2 Hz), 5.01 (s, 2H), 4.76 (br s, 1H), 4.62−4.57 (m, 1H), 4.45−4.41 (m, 1H), 3.71 (s, 3H), 3.13 (d, 2H, J = 10 Hz), 2.98−2.90 (m, 1H), 2.77−2.70 (m, 1H), 2.59−2.46 (m, 2H), 2.00−1.90 (m, 1H), 1.72−1.59 (m, 6H), 1.43 (s, 9H), 0.93 (d, 3H, J = 5.2 Hz), 0.92 (d, 3H, J = 4.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 208.1, 173.8, 171.4, 156.3 (2C), 136.5, 128.7 (2C), 128.4, 128.3 (2C), 79.3, 67.2, 59.5, 52.5, 51.0, 41.8, 40.2, 34.7, 29.6, 28.8, 28.6 (3C), 25.6, 25.0, 23.0, 22.1. IR (KBr, cm^{-1}): 2958, 1744, 1682, 1650, 1526. HRMS $C_{28}H_{43}N_3O_8$ [M + Na^+]: calculated, 572.2948; found, 572.2932.

Methyl 8-[[(1,1-dimethylethyl)carbonyl]amino]-4-oxo-(5*S*)-5-[[(phenylmethoxy)carbo nyl]-amino]octanoate (19): General Method for the Coupling of Thioesters with Acrylates. The thioester **9** (215 mg, 0.469 mmol) was dissolved in anhydrous THF (7.5 mL), and the reaction vessel was flushed with argon for 10 min. Methyl acrylate (111 μL, 1.50 mmol) and *tert*-butyl alcohol (135 μL, 1.50 mmol) were added, after which the solution was cooled to −78 °C, before a 0.1 M solution of SmI_2 (15 mL, 1.50 mmol) was added slowly via syringe over 10 min. The reaction mixture was stirred at −78 °C for 48 h, and then the flask was flushed with O_2 before saturated NH_4Cl(aq) (2 mL) was added and the mixture warmed to 20 °C. The mixture was poured into 0.5 M HCl (40 mL) and extracted with EtOAc (3 × 20 mL). The combined organic phases were washed with saturated $Na_2S_2O_3$ (30 mL), dried ($MgSO_4$), filtered, and evaporated in vacuo. The pure product was obtained by column chromatography on silica gel (20−50% EtOAc in pentane) giving 76% yield as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.26 (m, 5H), 5.60 (d, J = 6.8 Hz, 1H), 5.08 (s, 2H), 4.64−4.73 (m, 1H), 3.38−4.46 (m, 1H), 3.64 (s, 3H), 3.05−3.17 (m, 2H), 2.86 (dt, J = 18.4, 6.4 Hz, 1H), 2.51−2.78 (m, 3H), 1.89−1.99 (m, 1H), 1.40−1.65 (m, 3H), 1.42 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 207.3, 173.0, 156.2 (2C), 136.3, 128.6 (2C), 128.3 (2C), 79.3, 67.1, 59.4, 52.0, 40.0, 34.3, 28.7, 28.5, 27.6, 25.7. HRMS $C_{22}H_{32}N_2O_7$ [M + Na^+]: calculated, 459.2107; found, 459.2107.

(2*S*)-2-[(4*R*),(5*S*)-5-Benzyloxycarbonylamino-8-*tert*-butoxycarbonyl-amino-4-hydroxy-octanoylamino]-4-methylpentanoic Acid Methyl Ester (26). Dry MeOH (2 mL) was cooled to −78 °C before adding $LiAlH(O\text{-}t\text{-}Bu)_3$ (118 mg, 0.46 mmol). A solution of ketone **11** (63 mg, 0.11 mmol) in MeOH (1 mL) was added dropwise to the solution, and the reaction mixture was stirred at −78 °C for 16 h. The reaction was quenched with 10% citric acid, warmed to 20 °C, and extracted 3 times with EtOAc. The combined organic phases were washed with water and brine, dried over Na_2SO_4, and the solvent was removed in vacuo. Reverse phase HPLC analysis of the crude mixture showed the desired alcohol **26** was obtained in a >95:5 anti/syn ratio, and flash chromatography on silica gel using pentane/ethyl acetate (2:3 to 1:5) afforded 37.9 mg (60% yield) of the product **26**. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.35−7.32 (m, 5H), 6.22 (br d, 1H, J = 6.8 Hz), 5.11 (br t, 1H, J = 7.2 Hz), 5.08 (s, 2H), 4.66−4.56 (m, 2H), 3.89 (br s, 1H), 3.71 (s, 3H), 3.66−3.59 (m, 2H), 3.16−3.07 (m, 2H), 2.48−2.36 (m, 2H), 1.81−1.49 (m, 9H), 1.43 (s, 9H), 0.92 (d, 6H, J = 6.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 173.8, 173.7, 157.0, 156.2, 136.6, 128.6 (2C), 128.2 (3C), 79.2, 74.0, 66.9, 55.7, 52.5, 51.0, 41.5, 40.4, 33.1, 28.5 (5C), 26.8, 25.0, 22.9, 22.0. HRMS $C_{28}H_{45}N_3O_8$ [M +N a^+]: calculated, 574.3104; found, 574.3107.

(2*S*)-2-[(4*S*),(5*S*)-5-Benzyloxycarbonylamino-8-*tert*-butoxycarbonyl-amino-4-hydroxy-octanoylamino]-4-methylpentanoic Acid Methyl Ester (27). Ketone **11** (22 mg, 0.040 mmol) was flushed with argon before adding THF (2 mL) and MeOH (2 μL, 0.05 mmol). SmI_2 (1.7 mL, 0.1 M, 0.17 mmol) was added dropwise to the solution, and the mixture was left stirring at room temperature for 5 h. The reaction was quenched by adding oxygen until the blue color disappeared and the reaction mixture was yellow. Diethyl ether (5 mL) and 10% citric acid (0.5 mL) were added, and the mixture was allowed to stir for 10 min. The solution was extracted with Et_2O (3 times), and the combined organic phases were washed with $Na_2S_2O_3$(aq) and brine, dried over Na_2SO_4, and concentrated in vacuo. Reverse phase HPLC showed the desired alcohol **27** was obtained in a 85:15 syn/anti ratio, and flash chromatography using pentane/ethyl acetate (3:1 to 5:1) yielded 14.3 mg (65%) of **27**. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.35−7.29 (m, 5H), 6.15 (br s, 1H), 5.16 (br d, 1H, J = 9.6 Hz), 5.10 (d, 1H, J = 12.2 Hz), 5.06 (d, 1H, J = 12.2 Hz), 4.66−4.56 (m, 2H), 4.10 (br s, 1H), 3.72 (s, 3H), 3.67−3.54 (m, 2H), 3.15−3.07 (m, 2H), 2.48−2.14 (m, 2H), 1.88−1.47 (m, 9H), 1.43 (s, 9H), 0.93 (d, 6H, J = 6.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 173.8, 173.6, 157.0, 156.2, 136.7, 128.6 (2C), 128.2, 128.1 (2C), 79.2, 72.9, 66.8, 55.2, 52.5, 51.0, 41.6, 40.4, 33.5, 30.1, 30.0, 28.6 (3C), 26.8, 25.0, 22.9, 22.1. HRMS $C_{28}H_{45}N_3O_8$ [M + Na^+]: calculated, 574.3104; found, 574.3106.

(2*S*)-2-[(4*R*),(5*S*)-8-(2,3-bis(*tert*-Butoxycarbonyl)guanidino)-5-benzyloxycar bonylamino-4-hydroxy-octanoylamino]-4-methylpentanoic Acid Methyl Ester (28). Amino alcohol **26** (27 mg, 0.048 mmol) was treated with trifluoroacetic acid (0.5 mL) and dichloromethane (2 mL) for 30 min before evaporating the solvent off. To a solution of the crude product and triethylamine (0.030 mL, 0.22 mmol) in dichloromethane (2 mL) was added *N*,*N*′-di-Boc-*N*″-triflylguanidine (21 mg, 0.053 mmol). The reaction mixture was left stirring for 2 h and 15 min before adding dichloromethane. The organic phase was washed with 2 M $NaHSO_4$(aq), saturated $NaHCO_3$(aq), and brine and dried over Na_2SO_4. After filtration, the organic

phase was concentrated in vacuo. Flash chromatography on silica gel using dichloromethane/methanol (60:1) as eluant afforded 25 mg of **28** (74%) as a colorless film. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 11.45 (br s, 1H), 8.34 (br s, 1H), 7.35−7.32 (m, 5H), 6.10 (br d, 1H, J = 7.6 Hz), 5.66 (br d, 1H, J = 8.4 Hz), 5.10 (s, 2H), 4.63−4.57 (m, 1H), 3.88 (br s, 1H), 3.72 (s, 3H), 3.68−3.64 (m, 2H), 3.54−3.48 (m, 2H), 3.36−3.29 (m, 2H), 2.48−36 (m, 2H), 1.81−53 (m, 7H), 1.49 (s, 9H), 1.46 (s, 9H), 0.93 (d, 6H, J = 6.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 174.0, 173.8, 163.9, 157.4, 156.8, 153.7, 137.0, 128.9 (2C), 128.5 (3C), 83.3, 79.4, 74.2, 66.9, 56.3, 52.5, 51.0, 41.7, 40.7, 33.3, 28.4 (4C), 28.2 (3C), 26.6, 25.8, 25.0, 22.9, 22.1. HRMS $C_{34}H_{55}N_5O_{10}$ [M + Na^+]: calculated, 716.3046; found, 716.3937.

(2*S*)-2-[(4*R*,5*S*)-8-(2,3-bis(*tert*-Butoxycarbonyl)guanidino)-5-benzyloxycarb onylamino-4-*tert*-butyldimethylsilyloxy-octanoylamino]-4-methylpentanoic Acid (29). Methyl ester **28** (186 mg, 0.27 mmol) was dissolved in methanol (5.5 mL) and treated with LiOH (23 mg, 0.54 mmol) in water (1.8 mL) for 6 h. Et_2O and 10% citric acid were added to the reaction mixture, and the aqueous phase was extracted with Et_2O (3 times). The combined organic phases were washed with water and brine and then dried over Na_2SO_4. After evaporation in vacuo the resulting film was redissolved in DMF (2 mL). Imidazole (393 mg, 5.77 mmol) and TBDMS−Cl (394 mg, 2.61 mmol) were added to the solution followed by stirring for 66 h. MeOH (16.5 mL) was added, and the solution was stirred for another 3.5 h. The reaction mixture was evaporated, and EtOAc was added. The organic phase was washed with 10% citric acid, H_2O (4 times), and brine before drying over Na_2SO_4. The organic phase was filtered and evaporated to dryness. Flash chromatography on silica gel using dichoromethane/methanol (40:1) with 0.1% HCOOH afforded 112 mg of 29 (53%) as a colorless film. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.39 (br s, 1H), 7.36−7.28 (m, 5H), 6.68 (br d, 1H, J = 8.0 Hz), 5.10 (br s, 1H), 5.08 (s, 2H), 4.52 (m, 1H), 3.71−3.60 (m, 2H), 3.49−3.41 (m, 1H), 3.34−3.25 (m, 1H), 2.37−2.21 (m, 2H), 1.89−1.78 (m, 2H), 1.71−1.53 (m, 7H), 1.48 (s, 9H), 1.46 (s, 9H), 0.92 (d, 6H, J = 6.0 Hz), 0.86 (s, 9H), 0.05 (s, 3H), 0.01 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 175.6, 173.2, 163.2, 156.5, 156.4, 153.3, 136.5, 128.6 (2C), 128.2, 128.0 (2C), 83.4, 79.6, 74.1, 66.9, 53.6, 51.2, 41.3, 40.8, 31.5, 29.2, 28.3 (3C), 28.2 (3C), 25.9 (4C), 25.5, 25.0, 23.0, 22.0, 18.1, −4.2, −4.7. ES-MS $C_{39}H_{67}N_5O_{10}Si$ [M + Na^+]: 816.2.

(2*S*)-2-[(5*S*)-5-(9*H*-Fluoren-9-ylmethoxycarbonylamino)-8-*tert*-butoxycarbonylamino-4-oxo-octanoylamino]-4-methylpentanoic Acid Methyl Ester (36). Thioester **35** (103 mg, 0.19 mmol) and acrylamide **7** (26 mg, 0.13 mmol) were reacted according to the general procedure for the preparation of compound **11** with a reaction time of 4 days. The coupling product was purified by flash chromatography on silica gel using pentane/ethyl acetate (2:1 to 1:4) as the eluant, affording 35 mg of **35** (43% yield) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.76 (d, 2H, J = 8.8 Hz), 7.59 (d, 2H, J = 6.8 Hz), 7.39 (dt, 2H, J = 7.6, 0.6 Hz), 7.31 (dt, 2H, J = 7.6, 0.6 Hz), 6.06 (br d, 1H, J = 8.4 Hz), 5.67 (br d, 1H, J = 6.4 Hz), 4.78 (br s, 1H), 4.62−4.57 (m, 2H), 4.40 (d, 2H, J = 6.8 Hz), 4.20 (t, 1H, J = 6.8 Hz), 3.71 (s, 3H), 3.13 (br d, 2H, J = 5.6 Hz), 2.95−2.87 (m, 1H), 2.77−2.70 (m, 1H), 2.60−2.47 (m, 2H), 1.99−1.91 (m, 1H), 1.67−1.48 (m, 6H), 1.44 (s, 9H), 0.93 (d, 3H, J = 4.0 Hz), 0.92 (d, 3H, J = 4.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 208.0, 173.7, 171.3, 156.3, 156.2, 144.0, 143.9, 141.5 (2C), 127.8 (2C), 127.2 (2C), 125.2 (2C), 120.1 (2C), 79.3, 67.0, 59.5, 52.4, 50.9, 47.4, 41.8, 40.1, 34.6, 29.6, 28.5 (4C), 25.6, 24.9, 22.9, 22.0. HRMS $C_{35}H_{47}N_3O_8$ [M + Na^+]: calculated, 660.3261; found, 660.3282.

Acknowledgment. We are indebted to the Danish National Science Research Council, the Lundbeck Foundation, and the University of Aarhus for generous financial support.

Supporting Information Available: Experimental protocol for the preparation of compounds **13**−**18**, **20**−**23**, **31**, **34**, **37**, and **38**; copies of ^{1}H NMR and ^{13}C NMR spectra for compounds **7**, **9**, **11**, **13**, **19**−**23**, **26**−**29**, **31**, and **34**−**38**; HPLC chromatograms in the reduction studies of the aminoketone **11**. This material is available free of charge via the Internet at http:// pubs.acs.org.

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