JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

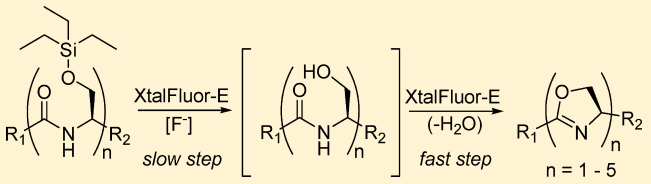
Synthesis of 2-Oxazolines by *in Situ* Desilylation and Cyclodehydration of β-Hydroxyamides

Marco Brandstätter, Fabian Roth, and Nathan W. Luedtke*

Department of Chemistry, University of Zürich, Winterthurerstrasse 190, CH-8057 Zürich, Switzerland

Supporting Information

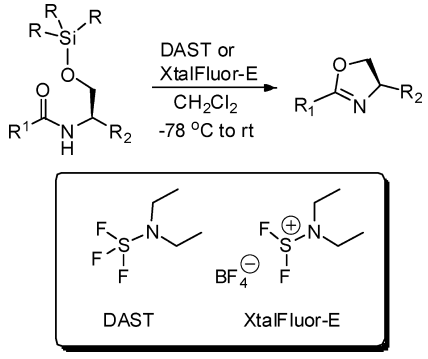
ABSTRACT: A powerful method for the synthesis of 2-oxazolines from silyl-protected β-hydroxyamides is reported. Using diethylaminosulfur trifluoride (DAST) or its tetrafluoroborate salt (XtalFluor-E), silyl-protected β-amidoalcohols can be *in situ* deprotected and dehydrated to give 2-oxazolines in good yields. The utility of this approach was demonstrated by preparing the first reported oligomer of [2,4′]-coupled 2-oxazoline units. By tuning the stability of the silyl protecting groups (ex. IPDMS < TES < TBS, etc.), the deprotection rate can be optimized so that all reaction intermediates remain soluble, allowing cyclodehydration to occur at all potential sites of ring closure. *N*-Terminal Ser residues containing an Fmoc carbamate are converted into 2-(9′-fluorenylmethyloxy)-2-oxazoline in high yield, thereby providing a new pathway for the synthesis of peptides capped with an *N*-terminal 2-alkoxy-2-oxazoline or 2-oxazolidinone unit.



INTRODUCTION

The discovery of oxazoline-containing bioactive natural products spawned widespread interest in the stereoselective synthesis of 2-oxazolines.[1] One common approach to this is the cyclodehydration of β-hydroxyamides.[2] While simple dehydrating reagents can be used (e.g., PCl_5, $POCl_3$, $COCl_2$, etc.), they exhibit low functional group compatibility and can cause epimerization of the α-position. In 1968, Burgess et al. reported methyl *N*-(triethylammoniumsulfonyl)carbamate, a mild dehydrating agent used for the elimination of secondary and tertiary alcohols.[3,4] Wipf and others utilized this reagent for the stereoselective cyclodehydration of β-hydroxyamides and thioamides.[5−7] The Burgess reagent, however, exhibits limited functional group tolerance, high moisture sensitivity, and a short shelf life even when it is stored at low temperature.[8] Diethylaminosulfur trifluoride (DAST) is a commercially available fluorinating agent that can be used to cyclodehydrate β-hydroxyamides in good yields and with little or no epimerization of the α-position.[9] Recently, diethylaminodifluorosulfinium tetrafluoroborate (XtalFluor-E)[10] has been reported as an attractive alternative to DAST, due to its enhanced thermal stability and reduced side product formation.[11] One drawback to the use of these common cyclodehydration reagents is that a relatively inert, apolar solvent must be used for cyclodehydration, most commonly CH_2Cl_2.[9−11] The inability of such solvents to solubilize large, polar molecules limits the scope of these reactions. This can be evidenced by the conspicuous absence of reported oligomers of [2,4′]-coupled 2-oxazolines that, at least conceptually, could be prepared via dehydration of Serine oligomers. We speculated that the solubility of such peptides in apolar solvents could be dramatically improved by protecting the Serine residues as silyl ethers, and that the fluoride ions generated during the course of the reaction would remove the silyl protective groups *in situ*, allowing for cyclodehydration to occur (Scheme 1). Such "direct" conversions of silyl ethers into other functional groups including aldehydes,[12] bromides,[13] acetates,[14] and one example of a 2-oxazoline have been previously demonstrated using similar approaches.[15]

Scheme 1. *In Situ* Desilylation and Cyclodehydration of β-Hydroxyamides by DAST or XtalFluor-E

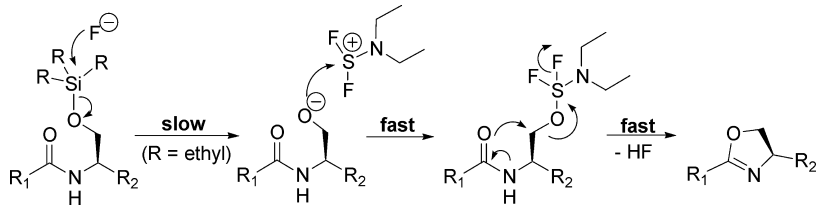


Herein we report a method for the synthesis of 2-oxazolines by combining silylated β-hydroxyamides with DAST or XtalFluor-E to facilitate *in situ* desilylation and cyclodehydration of β-hydroxyamides under standard reaction conditions (Scheme 1). By tuning the stability of the silyl protecting group (e.g., IPDMS < TES < TBS, etc.), the rate of deprotection can be modulated so that it is slower than cyclodehydration, yet faster than undesirable side reactions (Scheme 2). This feature

Received: July 23, 2014
Published: December 2, 2014

 © 2014 American Chemical Society dx.doi.org/10.1021/jo5016695 | J. Org. Chem. 2015, 80, 40−51

Scheme 2. Proposed Reaction Pathway for the Cyclodehydration of a Silyl-Protected β-Hydroxyamide by XtalFluor-E

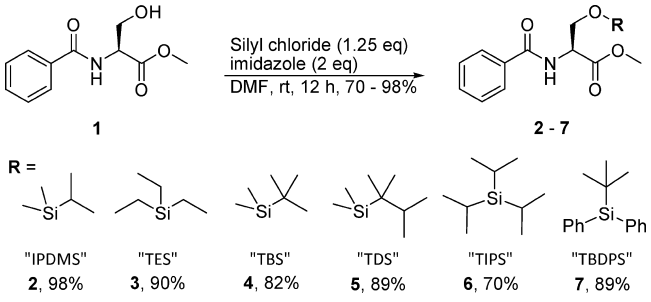


allows intermediates to remain soluble during the course of the reactions, so that cyclodehydration can occur at all potential sites within large, polar peptides containing multiple serine residues.

RESULTS AND DISCUSSION

Cyclodehydration of Silyl-Protected β-Hydroxyamides. To evaluate the impact of silyl group structure on cyclodehydration efficiency, the benzoylated serine methyl ester **1** was protected using isopropyldimethylsilyl chloride (IPDMS-Cl), triethylsilyl chloride (TES-Cl), *tert*-butyldimethylsilyl chloride (TBS-Cl), thexyldimethylsilyl chloride (TDS-Cl), triisopropylsilyl chloride (TIPS-Cl), or *tert*-butyldiphenylsilyl chloride (TBDPS-Cl) to give compounds **2**–**7** in isolated yields ranging from 70% to 98% (Scheme 3). Trimethylsilyl (TMS)

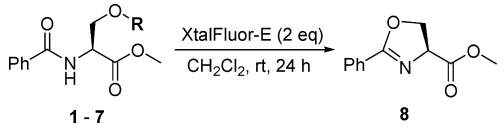
Scheme 3. Synthesis of Silyl-Protected β-Hydroxyamides 2–7



was not included in this series due to the low stability of TMS ethers.[16] Compounds **1**–**7** were reacted with 2 equiv of XtalFluor-E in CH_2Cl_2 at rt for 24 h. Consistent with previous studies,[9−11] the unprotected alcohol **1** was converted into oxazoline **8** with a good isolated yield of 81%. The use of silyl-protected β-hydroxyamides containing IPDMS (**2**) or TES (**3**) also provided **8** in good yields of 87% and 85%, respectively (Table 1). The larger silyl groups present in **4**–**7** caused dramatically lower yields ranging from 16% to 49% of **8**. According to HPLC and TLC analyses, compounds containing TDS (**5**), TIPS (**6**), and TBDPS (**7**) were not fully deprotected, as starting materials were still present in these reactions after 24 h. Deprotection was complete for the TBS derivative (**4**), but a mixture of alcohol **1** and oxazoline **8** was obtained, suggesting that XtalFluor-E decomposed over the course of the reaction with a rate similar to that of TBS deprotection.

To evaluate the relative rates of product formation, compounds **1**–**7** were reacted with 2 equiv of XtalFluor-E in CH_2Cl_2 at rt, and aliquots from each reaction were removed as a function of time, quenched with MeOH, and analyzed by quantitative HPLC (Figure 1). Under these conditions, the unprotected alcohol **1** is rapidly converted to oxazoline **8**,

Table 1. Cyclodehydration of 1–7 Using XtalFluor-E



compound	"R"	yield of **8** [%]	notes
1	H	81	
2	IPDMS	87	
3	TES	85	
4	TBS	41	*a*
5	TDS	45	*b*
6	TIPS	49	*b*
7	TBDPS	16	*b*

[a]Complete removal of silyl group after 24 h. [b]Remaining starting material observed after 24 h.

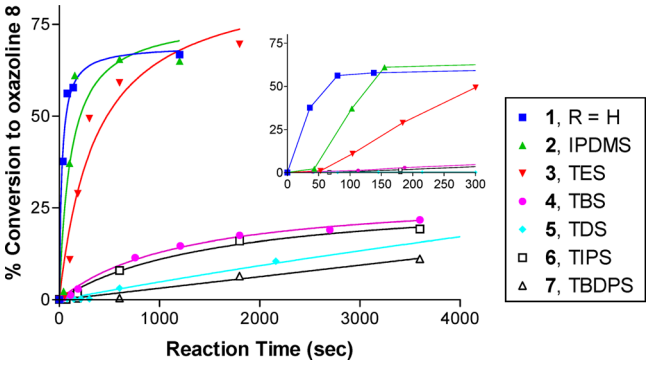


Figure 1. Percent conversion of compounds **1**–**7** into oxazoline **8** according to quantitative analytical HPLC analysis of crude reactions containing 75–95 nmoles of **1**–**7** and XtalFluor-E (2 equiv) in 2 mL of CH_2Cl_2 at rt.

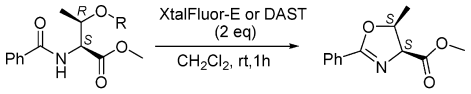
giving a 60% conversion after only 120 s, with an initial slope of 0–30 s ≈ 1.1 nmol/s. The silyl-protected substrates **2** and **3** exhibited a delay of roughly 50 s before any product formation could be observed. After this initiation period, the IPDMS-protected compound **2** gave a rapid rate of product formation (slope ≈ 0.58 nmol/s), nearly that of the free alcohol **1** (slope ≈ 1.1 nmol/s). The TES-protected compound **3**, in contrast, exhibited a significantly lower rate of product formation (slope ≈ 0.22 nmol/s). The lower rates exhibited by **2** and **3** did not negatively impact the yields of these reactions, giving similar % conversions for compounds **1**–**3** after 10 min. Substrates **4**–**7**, in contrast, exhibited dramatically lower cyclodehydration rates (slopes ≈ 0.004–0.015 nmol/s), consistent with the lower isolated yields from these reactions after 24 h (Table 1). The overall reaction rates for compounds **2**–**7** (IPDMS > TES ≫ TBS ≥ TIPS > TDS ≥ TBDPS) follow the known trends for nucleophilic substitution rates on silicon.[17] A 20-fold lower conversion rate was observed for **4** as compared to **2**, which is

dx.doi.org/10.1021/jo5016695 | J. Org. Chem. 2015, 80, 40–51

consistent with the general differences in S_N2 reaction rates for branched haloalkanes containing *t*Bu versus *i*Pr groups at the *β*-position.[18] In summary, these results demonstrate the feasibility of *in situ* desilylation and cyclodehydration of large polar molecules, where the triethylsilyl ether (TES) derivative **3** exhibited a markedly slower rate for deprotection as compared to the subsequent cyclodehydration reaction. This feature should prevent the accumulation of insoluble alcohol/alkoxide groups during the course of cyclodehydration reactions on substrates that contain multiple sites of ring closure. Importantly, the lower cyclodehydration rate for **3** did not negatively impact the isolated yield for its conversion into oxazoline **8** (Table 1). We therefore selected TES for further development of this methodology.

Cyclodehydration of *β*-Substituted-Hydroxyamides. To evaluate the S_N2 character of the proposed ring-closing step (Scheme 2), cyclodehydration reactions were conducted on the threonine-derivative **9** and its TES-protected analogue **10** using XtalFluor-E and DAST. Good-to-excellent yields for the formation of a single 2-oxazoline diastereomer (according to NMR, see Supporting Information) were obtained for all four reactions. The specific rotation ($[\alpha]_D^{25}$, in deg dm^{-1} cm^3 g^{-1}) of the products were compared to literature values of +96.7 for (*R*,*S*)-**11** and +69.4 for (*S*,*S*)-**11**,[19] to reveal the formation of (*S*,*S*)-**11** (Table 2). These results indicate that an

Table 2. Inversion of Configuration upon Cyclodehydration of Threonine Derivatives



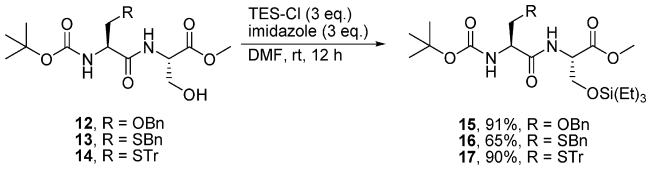
entry	substrate	R	reagent	yield [%]	$[\alpha]_D^{25}$	config.
1	**9**	H	XtalFluor-E	85	67.0	(*S*,*S*)
2	**9**	H	DAST	89	60.4	(*S*,*S*)
3	**10**	TES	XtalFluor-E	88	62.1	(*S*,*S*)
4	**10**	TES	DAST	94	64.1	(*S*,*S*)

inversion of configuration occurred during the cyclodehydration reactions of both silylated and nonsilylated substrates, consistent with an S_N2-like ring closing mechanism (Scheme 2).

Cyclodehydration of Dipeptides: Substrate Scope. The functional group tolerance of DAST and XtalFluor-E has been previously reported,[9−11] but their compatibility with common protecting groups used in peptide chemistry including benzyl (Bn), trityl (Tr), and *tert*-Butyl carbamate (Boc) has not been fully investigated. Acid-labile protective groups such as Tr and Boc are of particular concern,[20] due to the formation of HF during the course of cyclodehydration (Scheme 2). As model systems to evaluate the functional group compatibility of DAST and XtalFluor-E with 2-oxazoline formation, we prepared dipeptides **12**−**17** of the general formula Boc-Ser(Bn)-Ser(TES/OH)-OMe and Boc-Cys(Bn/Tr)-Ser(TES/OH)-OMe (Scheme 4).

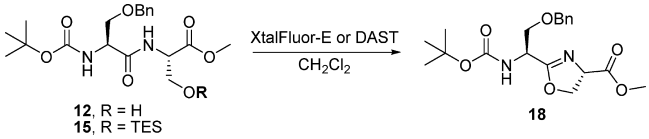
Paquin and co-workers previously demonstrated that XtalFluor-E can give excellent yields for cyclodehydration of simple *β*-hydroxyamides when the reactions were heated from rt to 90 °C.[11] When XtalFluor-E was mixed with dipeptide **12** at rt, a complex mixture of decomposition products was observed by TLC, none of which corresponded to the desired

Scheme 4. Silylation of Dipeptides



product **18** ("n.o.", Table 3). To prevent decomposition, the reaction temperature was lowered prior to the addition of

Table 3. Cyclodehydration of Boc-Ser(Bn)-Ser(TES/OH)-OMe



entry	substrate	R	reagent	*T* [°C]	base	yield [%]
1	**12**	H	XtalFluor-E	rt	–	n.o.[a]
2	**12**	H	XtalFluor-E	0 to rt	–	11
3	**12**	H	XtalFluor-E	−78 to rt	–	46
4	**12**	H	XtalFluor-E	−78 to rt	NEt_3	59[b]
5	**12**	H	XtalFluor-E	−78 to rt	DBU	76[b]
6	**12**	H	DAST	−78 to rt	–	85
7	**15**	TES	XtalFluor-E	−78 to rt	–	56
8	**15**	TES	DAST	−78 to rt	–	89

[a]"n.o." = no observed product, decomposition of starting material. [b]Mixture of diastereomers obtained.

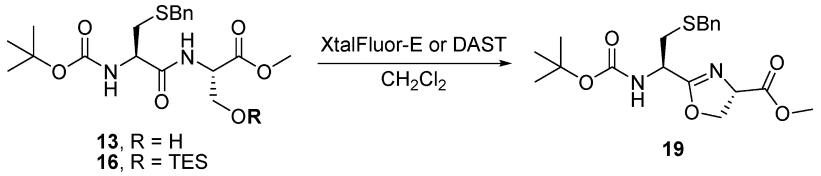
XtalFluor-E. By mixing the components at 0 °C or −78 °C, followed by slow warming to rt, oxazoline **18** could be isolated in low-to-modest yields of 11% and 46%, respectively (entries 2 and 3, Table 3).

Couturier and co-workers previously demonstrated that the addition of base can improve the yields for deoxofluorination of simple alcohols and carbonyl compounds by XtalFluor-E,[10] but it was hitherto unknown how added base would affect cyclodehydration efficiencies. This could, in principle, result in increased fluoride concentrations to facilitate silyl deprotection, while protecting Boc, Bn, and Tr groups from HF-mediated cleavage.[20] Indeed, the inclusion of 1.5 equiv of triethyl amine (TEA) to reactions containing **12** and XtalFluor-E increased the isolated yield of **18** to 59%. By using 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) the yield was further increased to 76%. Unfortunately, the use of base in both reactions caused epimerization, giving a mixture of diastereomers (entries 4 and 5, Table 3; see Supporting Information). Reactions lacking exogenous base that utilized DAST instead of XtalFluor-E furnished oxazoline **18** as a single diastereomer in an 85% isolated yield, representing a dramatic improvement as compared to the 46% obtained with XtalFluor-E (entries 3 and 6, Table 3). No loss of the Boc or Bn groups was observed when using DAST, despite the fact that HF concentrations were previously reported to be higher in DAST-containing reactions as compared to XtalFluor-E.[10] These results suggest that the higher Lewis acidity of XtalFluor-E as compared to DAST might cause compatibility problems with certain acid-labile protecting groups. The results obtained using SBn and STr groups support this notion *vide infra* (Tables 4 and 5).

Having optimized the yields for cyclodehydration of the alcohol-containing Ser-Ser dipeptide **12**, we next applied these

dx.doi.org/10.1021/jo5016695 | J. Org. Chem. 2015, 80, 40−51

Table 4. Cyclodehydration of Boc-Cys(Bn)-Ser(TES/OH)-OMe



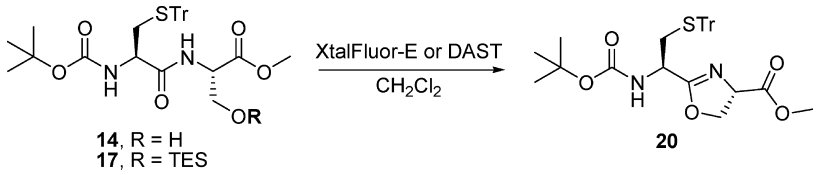
13, R = H
16, R = TES

19

entry	substrate	R	reagent	T [°C]	base	yield [%]
1	**13**	H	XtalFluor-E	rt	–	n.o.[a]
2	**13**	H	XtalFluor-E	0 to rt	–	n.o.[a]
3	**13**	H	XtalFluor-E	−78 to rt	–	44
4	**13**	H	XtalFluor-E	−78 to rt	DBU	50[b]
5	**13**	H	DAST	−78 to rt	–	61
6	**16**	TES	XtalFluor-E	−78 to rt	–	55
7	**16**	TES	XtalFluor-E	−78 to rt	DBU	60[b]
8	**16**	TES	DAST	−78 to rt	–	67

[a]"n.o." = no observed product, decomposition of starting material. [b]Mixture of diastereomers obtained.

Table 5. Cyclodehydration of Boc-Cys(Tr)-Ser(TES/OH) Dipeptide



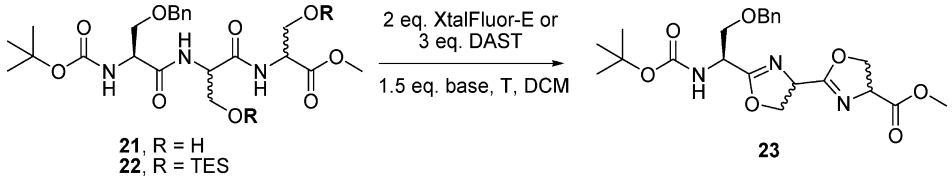
14, R = H
17, R = TES

20

entry	substrate	R	reagent	T [°C]	base	yield [%]
1	**14**	H	XtalFluor-E	0 to rt	–	n.o.[a]
2	**14**	H	XtalFluor-E	−78	–	12
3	**14**	H	XtalFluor-E	−78	DBU	39[b]
4	**14**	H	DAST	−78	–	79
5	**17**	TES	DAST	−78 to rt	–	85
6	**17**	TES	XtalFluor-E	−78 to rt	–	n.o.[a]

[a]"n.o." = no observed product, decomposition of starting material. [b]Mixture of diastereomers obtained.

Table 6. Cyclodehydration of Boc-Ser(Bn)-Ser(TES/OH)-Ser(TES/OH)



21, R = H
22, R = TES

23

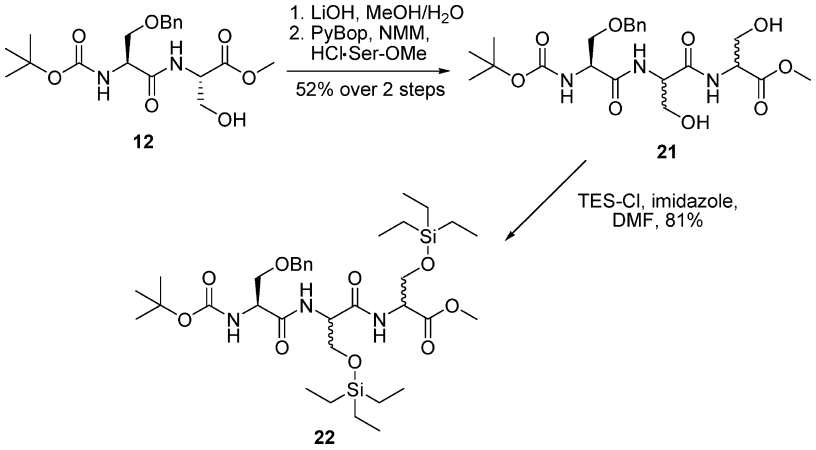
entry	substrate	R	reagent	T [°C]	base	yield [%]
1	**21**	H	XtalFluor-E	−78 to rt	–	27
2	**21**	H	DAST	−78 to rt	–	53
3	**22**	TES	XtalFluor-E	−78 to rt	–	12
4	**22**	TES	DAST	−78 to rt	–	73

conditions to the cyclodehydration of the TES-silylated peptide **15**. The presence of the TES group had a small, yet consistently positive effect on the isolated yields of oxazoline **18** that ranged from 56% to 89% (entries 7–8, Table 3). These yields represent improvements in the range of 4–10% as compared to the yields obtained for the corresponding free alcohol **12** (entries 3 and 6). Larger improvements upon silylation were observed for Cys-Ser dipeptide and $(Ser)_3$ tripeptides (Tables 4–6). In all cases, fewer byproducts were generated when using the silylated peptides, thereby facilitating product purification.

Cysteine is an important synthetic precursor of thiazole and thiazolinum,[21] but the compatibility of sulfur-containing peptides with DAST and XtalFluor-E is potentially problematic,[10] and peptides containing fused Cysteine-oxazoline units are only rarely reported.[22] Peptide **13** contains a Cys(Bn)-Ser(TES/OH) unit and was highly susceptible to decomposition at rt in reactions containing XtalFluor-E (entries 1 and 2, Table 4). By starting the reaction at −78 °C, a 44% isolated yield of oxazoline **19** could be obtained (entry 3). The addition of DBU improved the yield to 50%, but epimerization was again observed (entry 4). Reacting **13** with DAST yielded **19** in 61% as a single diastereomer (entry 6, Table 4). Approximately 10% higher yields were obtained in these reactions when using the silylated peptide **16** (entries 6–8) as compared to the free alcohol **13** (entries 3–6, Table 4).

dx.doi.org/10.1021/jo5016695 | J. Org. Chem. 2015, 80, 40–51

Scheme 5. Synthesis and Silylation of Boc-Ser(Bn)-Ser(TES/OH)-Ser(TES/OH)



In general, C−S bonds are about 20 kcal mol^{-1} weaker than C−O bonds[23] and are therefore more susceptible to cleavage by Lewis and Brønsted acids.[17] Accordingly, the yields obtained for the Cys(Bn)-containing peptides **13** and **16** (Table 4) were consistently lower than those for the corresponding Ser(Bn)-containing peptides **12** and **15** (Table 3). The highly labile trityl protective group (Tr) was even more problematic in the context of peptides **14** and **17** that contain a Cys(Tr) residue. Upon addition of XtalFluor-E, peptide **14** immediately decomposed in reactions maintained at 0 °C or above, giving an intensely colored yellow solution (entry 1, Table 5). When the temperature of the reaction was maintained at −78 °C, 12% of oxazoline **20** could be obtained from a complex mixture of decomposition products (entry 2, Table 5). A slightly higher yield of 39% was obtained by including DBU in the reaction, but epimerization was observed (entry 3, Table 5). At −78 °C, the reaction of **14** with DAST yielded 79% of the desired product as a single diastereomer (entry 4, Table 5). A slightly higher yield of 85% was obtained when using the corresponding TES-protected peptide **17**, upon warming the reaction to 0 °C to facilitate deprotection of the silyl group (entry 5, Table 5). Under the same conditions, the reaction of XtalFluor-E with TES-protected peptide **17** gave a complex mixture of decomposition products containing little or no desired product (entry 6, Table 5). Together, these results demonstrate that TES-protected Ser units in Cys-Ser dipeptides can serve as efficient oxazoline precursors, especially in cases where DAST is used as the cyclodehydrating reagent.

Tandem [2,4′]-coupled 2-oxazoline units can be prepared via cyclodehydration reactions of peptides containing multiple serine residues.[21] We therefore compared the ability of XtalFluor-E and DAST to generate two consecutive 2-oxazolines from peptides containing Ser(OH) or Ser(TES) residues. To provide starting material for these reactions, peptide **12** was elongated by one serine moiety in a two-step procedure, where the methyl ester was hydrolyzed using LiOH in H_2O/MeOH, followed by peptide coupling with L-serine methyl ester hydrochloride to give an inseparable mixture of diastereomers (Scheme 5). Silylation of tripeptide **21** was performed using TES-Cl and imidazole in DMF (81%). **21** was reacted with XtalFluor-E at −78 °C to give a 27% isolated yield of the desired products containing two consecutive 2-oxazoline units (entry 1, Table 6). The reaction of tripeptide **21** with DAST at −78 °C gave a moderate yield of 53%, which could be further improved to 73% by utilizing the TES-protected peptide **22**. This improvement in yield was only observed when using DAST, and not in the case of XtalFluor-E (entries 3 and 4, Table 6). These reactions provide rare examples of simultaneous synthesis of two tandem [2,4′]-fused 2-oxazoline units and further demonstrate the potential advantages of using silyl-protected Ser units in the starting material.

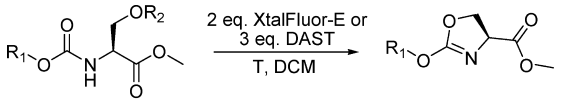
Cyclodehydration of β-Hydroxycarbamates. Carbamates are ubiquitous groups in peptide synthesis, where *tert*-butoxycarbonyl (Boc), fluorenylmethyloxycarbonyl (Fmoc), and benzyl carbonate (Cbz) are used to protect the *N*-terminal amines. It is well-known that *O*-protected, *N*-terminal serine residues containing Cbz or Boc remain stable in the presence of DAST, giving good to excellent yields for cyclodehydration reactions at remote β-hydroxyamides (Tables 3 − 6).[9] However, little or nothing is reported about the reactivity of Boc, Cbz, and Fmoc groups in the context of β-hydroxycarbamates, where the *N*-terminal Ser residue carries a free alcohol. In this case, cyclodehydration could conceivably furnish 2-alkoxy-2-oxazolines. In general, only a few methods have been reported for the synthesis of 2-alkoxy-2-oxazolines,[24] the most common being the *O*-alkylation of 2-oxazolidinones to give 2-ethoxy-[25] and 2-benzoxyoxazolines.[26] To investigate the potential synthesis of *N*-terminal 2-alkoxy-2-oxazolines from β-hydroxycarbamates, substrates **24**−**28** were prepared and reacted with DAST or XtalFluor-E (Table 7).

Boc-protected carbamate **24** was reacted with XtalFluor-E at rt or at −78 °C, but no oxazoline **29** could be observed by TLC or ESI-MS. The reaction of Cbz-protected **25** with XtalFluor-E gave oxazoline **30** in a 16% isolated yield, while the reaction of TES-protected **26** with DAST gave a complex mixture of products containing no detectable product **30**. The cyclodehydration of Fmoc-protected **27** using XtalFluor-E and DAST gave **31** in 45% and 61% isolated yields, respectively. When using the TES-protected derivative **28**, the isolated yield of **31** increased to 71% with little or no byproduct formation. These results suggest that *N*-terminal Fmoc/TES-protected serine residues are especially well suited for cyclodehydration reactions to give an *N*-terminal 2-alkoxy-2-oxazoline. We therefore selected Fmoc as the *N*-terminal protecting group for the synthesis of oligomers containing [2,4′]-coupled 2-oxazoline units.

Cyclodehydration of $(Ser)_5$. Little is known about the synthesis or physical properties of linear oligomers of oxazoline units. The longest reported example is an intermediate from the total synthesis of thiangazole, containing only three consecutive

dx.doi.org/10.1021/jo5016695 | J. Org. Chem. 2015, 80, 40−51

Table 7. Cyclodehydration of Carbamates Using XtalFluor-E and DAST



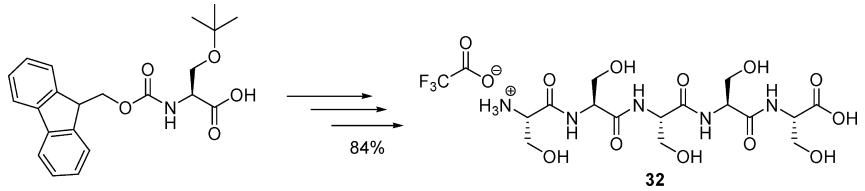
24, R_1 = *t*Bu, R_2 = H
25, R_1 = Bn, R_2 = H
26, R_1 = Bn, R_2 = TES
27, R_1 = 9-fluorenylmethyl, R_2 = H
28, R_1 = 9-fluorenylmethyl, R_2 = TES

29, R_1 = *t*Bu
30, R_1 = Bn
31, R_1 = 9-fluorenylmethyl

entry	substrate	carbamate	R_2	product	reagent	*T* [°C]	yield [%]
1	**24**	Boc	H	**29**	XtalFluor-E	rt	n.o.[a]
2	**24**	Boc	H	**29**	DAST	−78	n.o.[a]
3	**25**	Cbz	H	**30**	XtalFluor-E	−78	16
4	**25**	Cbz	H	**30**	DAST	−78	n.o.[a]
5	**26**	Cbz	TES	**30**	DAST	−78 to rt	n.o.[a]
6	**27**	Fmoc	H	**31**	XtalFluor-E	−78	45
7	**27**	Fmoc	H	**31**	DAST	−78	61
8	**28**	Fmoc	TES	**31**	DAST	−78 to rt	71

[a]"n.o." = no observed product, decomposition of starting material.

Scheme 6. Solid-Phase Peptide Synthesis of $(Ser)_5$ 32



32

units.[21] To evaluate the synthesis of oxazoline oligomers by in situ desilylation and cyclodehydration of *β*-hydroxyamide oligomers, **32** was synthesized via Fmoc solid-phase synthesis and isolated as a crude product in an 84% yield (Scheme 6).

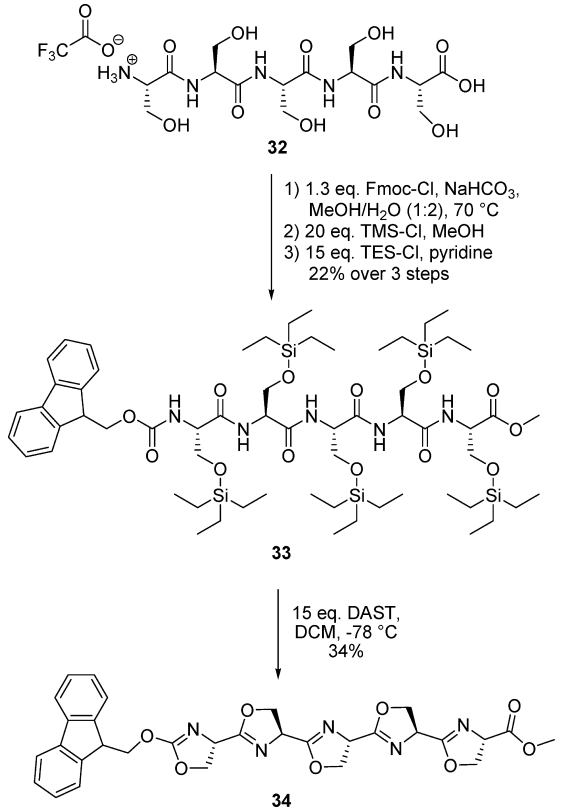
Crude peptide **32** was protected on each termini and silylated in a three-step procedure to obtain silylated pentaserine **33** (Scheme 7). The N-terminal amine was protected using Fmoc-Cl and $NaHCO_3$ in a $MeOH/H_2O$ (1:2) solution. After the protection was complete, the product was precipitated using DCM and directly used for the esterification. The methyl ester was formed by adding excess TMS-Cl to a stirring suspension of the crude material in MeOH. The product was again precipitated and directly used for silylation. Reaction with TES-Cl in pyridine and purification by silica gel column chromatography provided pure peptide **33** in a 22% isolated yield over three steps.

Peptide **33** was reacted with 15 equiv of DAST at −78 °C in DCM and slowly warmed to 0 °C over 4 h, during which **33** and all reaction intermediates remained soluble.[27] The reaction was then quenched with MeOH and purified by silica gel column chromatography. Pentaoxazoline **34** was thereby obtained in a 34% isolated yield as a single diastereomer, representing a >80% yield for cyclodehydration at each independent position. This molecule represents the first example of a linear oligomer of oxazoline containing more than three units, and it contains a novel, *N*-terminal 2-(9′-fluorenylmethyloxy)-2-oxazoline.

CONCLUSIONS

We have developed a method to synthesize 2-oxazolines from silyl-protected *β*-amido alcohols in a tandem two-step reaction comprising deprotection and cyclodehydration upon addition of a deoxofluorinating agent. After screening various silyl groups, we found that triethylsilyl (TES) was optimal, giving a rate of deprotection that was significantly slower than the

Scheme 7. Synthesis of Silyl-Protected Fmoc-$(Ser)_5$ 33 and Its Cyclodehydration to 34



dx.doi.org/10.1021/jo5016695 | J. Org. Chem. 2015, 80, 40−51

cyclodehydration reaction. This prevents accumulation of highly polar and insoluble alcohol/alkoxide groups during the course of cyclodehydration reactions on substrates containing multiple sites of ring closure. This provides a means to synthesize 2-oxazolines from highly polar starting materials that would otherwise be insoluble under standard reaction conditions. As a demonstration, we synthesized the first oxazoline oligomer containing five linear units from a Fmoc-$(Ser)_5$ peptide. During the course of the reaction, the *N*-terminal F-moc protected Ser residue was converted into a 2-(9′-fluorenylmethyloxy)-2-oxazoline unit, thereby revealing a new pathway for the synthesis of peptides capped with an *N*-terminal 2-alkoxy-2-oxazoline or, following deprotection, a 2-oxazolidinone unit.[28]

EXPERIMENTAL SECTION

General Information. Starting materials were obtained in the highest commercial grades and used without further purification. All reactions sensitive to moisture and/or air were carried out under an atmosphere of argon or nitrogen in dry, freshly distilled solvents and oven-dried glassware. Commercially available dichloromethane (CH_2Cl_2) was purified by distillation prior to use. Commercially available anhydrous pyridine was used directly without further drying. For all aq. solutions, H_2O was purified on a Purelab Ultra MK2 apparatus from ELGA Labwater. Analytical thin-layer chromatography was performed on precoated 250 μm layer thickness silica gel 60 F254 plates. Visualization was performed by ultraviolet light and staining with a $KMnO_4$ solution. Flash column chromatography was performed using 40−63 μm silica gel and compressed air. ^{1}H NMR spectra were recorded on 300, 400, and 500 MHz spectrometers; tetramethylsilane or the residual solvent peaks were used as internal standards: DMSO (quint, δH = 2.50 ppm), $CHCl_3$ (s, δH = 7.26 ppm). ^{13}C NMR spectra were recorded on 75, 100, and 125 MHz spectrometers, with δ relative to DMSO (δ 40.5 ppm) or $CHCl_3$ (δ 77.23 ppm). Coupling constants (J) are reported in hertz (Hz). The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet−doublet, ddd = doublet−doublet−doublet, dt = doublet−triplet, br = broad. Mass spectra were obtained on a quadrupole ion trap instrument equipped with an atmospheric pressure ion (API) source. High-resolution electrospray mass spectra (HR-ESI MS) were recorded on a QTOFMS instrument. Infrared spectra were recorded on an FTIR spectrometer. Optical rotation ($[\alpha]_D^{25}$) was measured at room temperature with a PerkinElmer 241MC polarimeter, and values are given in deg cm^3 g^{-1} dm^{-1}; concentration c is given in g (100 mL)$^{-1}$.

Synthesis of Hydroxyamide Derivatives. General Procedure A.[29] To a stirring solution of amine (1 mmol) in EtOH at rt, the carboxylic acid (1.03 mmol), NMM (2.2 mmol), and HOBt (0.15 mmol) were subsequently added. The solution was then cooled to 0 °C, and EDC (1.2 mmol) was added. The reaction was stirred at rt overnight, followed by the addition of 0.1 M citric acid. The mixture was then extracted with EtOAc (3×). The combined organic phases were washed with brine (1×), dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The crude material was purified by column chromatography to give the indicated product.

Synthesis of Silylated Hydroxyamide Derivatives. General Procedure B.[30] To a stirring solution of the hydroxyamide derivative (1 mmol) in DMF or DCM, the corresponding silyl chloride (1.3−3 mmol) was added at rt. After the solution stirred for 30 min, imidazole or NEt_3 (2−5 mmol) was added and stirred overnight. The solution was diluted with EtOAc and washed with 0.1 M citric acid and brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude material was purified by column chromatography to give the desired product.

Synthesis of 2-Oxazolines via Cyclodehydration. General Procedure C. To a stirring solution of β-hydroxyamide or silylated β-hydroxyamide (1 mmol) in DCM (2 mL), DAST or XtalFluor-E (2−3 mmol) and DBU or NEt_3 (1.5 mmol, optionally) were added. The solution was then stirred at −45 or −78 °C and allowed to warm to 0 °C or rt. After completion, the reaction was quenched by sat. $NaHCO_3$ in MeOH or MeOH and dried using a rotary evaporator. The crude material was purified by column chromatography to give the desired product.

***N*-Benzoyl-(*S*)-serine Methyl Ester (1).** To a suspension of HCl·Ser-OMe (3.00 g, 19.28 mmol) at 0 °C in CH_2Cl_2 (50 mL) was added a solution of Bz-Cl (2.50 mL, 21.50 mmol) in CH_2Cl_2 (20 mL) and successively a solution of NEt_3 (5.40 mL, 38.96 mmol) in CH_2Cl_2 (30 mL) over a period of 20 min. The reaction mixture was maintained at 4 °C for 2 h and allowed to slowly warm to rt. After completion, 0.1 M citric acid was added. The resulting solution was extracted with DCM (3×) and the combined organic layers were washed with brine (1×), dried over $MgSO_4$, filtered, and evaporated *in vacuo*. The crude material was subjected to column chromatography on silica gel (hexane/EtOAc, gradient from 2:1 to 1:2) to give a white solid which was recrystallized (hexane/CH_2Cl_2, 1:1) to give **1** as white needles (2.61 g, 11.68 mmol, 61%): R_f (hexane/EtOAc, 1:1) 0.21; IR (neat) ν = 3349, 2953, 1739, 1639, 1578, 1528, 1488, 1442, 1348, 1209, 1160, 1073, 713, 691, 530 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.81 (*d*, *J* = 9.0, 2 H), 7.51 (*t*, *J* = 6.0, 1 H), 7.42 (*t*, *J* = 6.0, 2 H), 7.12 (*d*, *J* = 6.0, 1H), 4.87−4.84 (*m*, 1H), 4.09−3.99 (*m*, 2H), 3.80 (*s*, 3H), 2.49 (*s*, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.3, 167.9, 133.6, 132.2, 128.9, 127.4, 63.8, 55.4, 53.1; HRMS (ESI-TOF) *m*/*z*: [M + Na]$^+$ calculated for $C_{11}H_{14}NO_4Na$ 246.0737, found 246.0734.

***N*-Benzoyl-*O*-((1-methylethyl)dimethylsilyl)-(*S*)-serine Methyl Ester (2).** Following general procedure B on a 2.24 mmol scale of **1** using IPDMS-Cl (453 μL, 2.69 mmol) and imidazole (305 mg, 4.48 mmol) in DMF (1 mL), the desired product (714 mg, 2.21 mmol, 98%) was isolated as colorless oil by extraction: R_f (hexane/EtOAc, 3:1) 0.57; IR (neat) ν = 3448, 3333, 2953, 2865, 1745, 1653, 1518, 1486, 1348, 1302, 1251, 1207, 1163, 1104, 999, 883, 829, 776, 712, 691, 520 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.81 (*d*, *J* = 6.0, 2 H), 7.56−7.43 (*m*, 3 H), 6.97 (*d*, *J* = 7.8, 1 H), 4.87 (dt, *J* = 1.8, 8.1, 1 H), 4.15 (*dd*, J_1 = 2.7, J_2 = 10.2, 1 H), 3.95 (*dd*, J_1 = 3.0, J_2 = 10.0, 1 H), 3.79 (*s*, 3 H), 0.93 (*d*, *J* = 6.3, 6H), 0.88−0.79 (*m*, 1H), 0.04 (*s*, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.2, 167.2, 134.2, 131.9, 128.8, 127.3, 63.4, 54.8, 52.7, 16.9, 14.5, −4.4; HRMS (ESI-TOF) *m*/*z*: [M + Na]$^+$ calculated for $C_{16}H_{25}NO_4SiNa$ 346.1445, found 346.1446.

***N*-Benzoyl-*O*-(triethylsilyl)-(*S*)-serine Methyl Ester (3).** Following general procedure B on a 2.24 mmol scale of **1** using TES-Cl (451 μL, 2.69 mmol) and imidazole (305 mg, 4.48 mmol) in DMF (1 mL) the desired product (679 mg, 2.00 mmol, 90%) was isolated as a colorless oil by silica gel column chromatography: R_f (hexane/EtOAc, 9:1) 0.21; IR (neat) ν = 3448, 3333, 2953, 2911, 2876, 1746, 1655, 1516, 1485, 1465, 1350, 1296, 1243, 1207, 1163, 1104, 1004, 973, 814, 712 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79 (*d*, *J* = 6.0, 2 H), 7.53−7.41 (*m*, 3 H), 6.98 (*d*, *J* = 6.0, 1 H), 4.86 (dt, *J* = 3.0, 9.0, 1 H), 4.15 (*dd*, J_1 = 3.0, J_2 = 12.0, 1 H), 3.95 (*dd*, J_1 = 3.0, J_2 = 12.0, 1 H), 3.77 (*s*, 3 H), 0.91 (*t*, *J* = 6.0, 9H), 0.56 (*q*, *J* = 6.0, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.2, 167.2, 134.2, 132.0, 128.8, 127.3, 63.5, 54.9, 52.7, 6.8, 4.4; HRMS (ESI-TOF) *m*/*z*: [M + Na]$^+$ calculated for $C_{17}H_{27}NO_4SiNa$ 360.1602, found 360.1600.

***N*-Benzoyl-*O*-((*tert*-butyl)-dimethylsilyl)-(*S*)-serine Methyl Ester (4).** Following general procedure B on a 4.48 mmol scale of **1** using TBS-Cl (960 μL, 5.38 mmol) and imidazole (762 mg, 11.99 mmol) in DMF (2 mL), the desired product (1.23 g, 3.66 mmol, 82%) was isolated as a colorless oil by silica gel column chromatography (hexane/EtOAc, 6:1): R_f (hexane/EtOAc, 6:1) 0.55; IR (neat) ν = 3442, 3333, 2953, 2929, 2856, 2348, 1745, 1653, 1518, 1486, 1471, 1436, 1385, 1350, 1302, 1253, 1207, 1163, 1105, 1046, 833, 777, 712, 691, 666 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83−7.80 (*m*, 2 H), 7.50−7.45 (*m*, 3 H), 6.96 (*d*, *J* = 9.0, 1 H), 4.68−4.85 (*m*, 1 H), 4.16 (*dd*, J_1 = 3.0, J_2 = 10.5, 1 H), 3.96 (*dd*, J_1 = 3.0, J_2 = 9.0, 1 H), 3.78 (*s*, 3 H), 0.87 (*s*, 9H), 0.03 (*s*, 3 H), 0.03 (*s*, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.8, 167.7, 134.6, 132.3, 129.2, 127.6, 63.7, 54.8, 52.5, 25.6, 18.0, 5.9, 5.8; HRMS (ESI-TOF) *m*/*z*: [M + Na]$^+$ calculated for $C_{17}H_{27}NO_4SiNa$ 360.1602, found 360.1604.

***N*-Benzoyl-*O*-((2,3-dimethyl-2-butyl)-dimethylsilyl)-(*S*)-serine Methyl Ester (5).** Following general procedure B on a 1.17 mmol

dx.doi.org/10.1021/jo5016695 | J. Org. Chem. 2015, 80, 40−51

scale of **1** using TDS-Cl (299 μL, 1.52 mmol) and imidazole (161 mg, 2.34 mmol) in DMF (1 mL), the desired product (376 mg, 1.03 mmol, 89%) was isolated as a colorless oil by silica gel column chromatography (hexane/EtOAc, 6:1): R_f (hexane/EtOAc, 6:1) 0.61; IR (neat) ν = 3448, 3338, 2954, 2870, 1746, 1666, 1514, 1485, 1467, 1437, 1380, 1350, 1252, 1206, 1166, 1104, 1040, 827, 777, 711, 691, 494 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.80 (*d*, *J* = 1.8, 2 H), 7.53−7.43 (*m*, 3 H), 6.96 (*d*, *J* = 7.2, 1 H), 4.88 (dt, *J* = 2.7, 5.4, 1 H), 4.15 (*dd*, J_1 = 3.0, J_2 = 10.0, 1 H), 3.95 (*dd*, J_1 = 3.0, J_2 = 9.9, 1 H), 3.78 (*s*, 3 H), 1.64−1.55 (*m*, 1H), 0.87 (*d*, *J* = 6.9, 6 H), 0.83 (*s*, 6H), 0.1 (*s*, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.2, 167.1, 134.3, 132.0, 128.9, 127.3, 63.7, 54.9, 52.7, 34.5, 25.3, 20.4, 18.7, −3.5; HRMS (ESI-TOF) *m*/*z*: $[M + Na]^+$ calculated for $C_{19}H_{31}NO_4SiNa$ 388.1915, found 388.1913.

***N*-Benzoyl-*O*-(triisopropyl)-(*S*)-serine Methyl Ester (6).** Following general procedure B on a 4.51 mmol scale of **1** using TIPS-Cl (1.11 mL, 5.67 mmol) and imidazole (765 mg, 11.18 mmol) in DMF (2 mL), the desired product (1.19 g, 3.13 mmol, 70%) was isolated as a colorless oil by silica gel column chromatography (hexane/EtOAc, 6:1): R_f (hexane/EtOAc, 3:1) 0.69; IR (neat) ν = 3442, 3333, 2943, 2866, 2354, 1746, 1666, 1516, 1485, 1464, 1437, 1380, 1349, 1296, 1245, 1206, 1163, 1110, 1066, 1040, 994, 881, 799, 735, 712, 683, 661 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.83−7.80 (*m*, 2 H), 7.50−7.45 (*m*, 3 H), 7.03 (*d*, *J* = 9.0, 1 H), 4.91−4.86 (*m*, 1 H), 4.27 (*dd*, J_1 = 3.0, J_2 = 6.0, 1 H), 3.96 (*dd*, J_1 = 3.0, J_2 = 6.0, 1 H), 3.78 (*s*, 3 H), 1.07−0.99 (*m*, 21H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.8, 167.7, 134.7, 132.3, 129.2, 127.6, 64.3, 54.8, 52.5, 17.7, 17.6, 11.6; HRMS (ESI-TOF) *m*/*z*: $[M + Na]^+$ calculated for $C_{20}H_{33}NO_4SiNa$ 402.2071, found 402.2072.

***N*-Benzoyl-*O*-(*tert*-butyldiphenylsilyl)-(*S*)-serine Methyl Ester (7).** Following general procedure B on a 2.24 mmol scale of **1** using TBDPS-Cl (757 μL, 2.91 mmol) and imidazole (305 mg, 4.48 mmol) in DMF (1 mL), the desired product (925 mg, 2.00 mmol, 89%) was isolated as a white solid by silica gel column chromatography (hexane/EtOAc, 9:1): R_f (hexane/EtOAc, 3:1) 0.58; IR (neat) ν = 3442, 3338, 2953, 2932, 2885, 2854, 1745, 1665, 1514, 1484, 1472, 1428, 1349, 1247, 1207, 1162 1106, 823, 736, 700, 690, 613, 488 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.68−7.03 (*m*, 15H), 7.02 (*d*, *J* = 6.0, 1H), 4.20 (*dd*, J_1 = 3.0, J_2 = 9.0, 1H), 4.01 (*dd*, J_1 = 3.0, J_2 = 9.0, 1H), 3.77 (*s*, 3H), 1.03 (*s*, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.0, 166.9, 135.5, 134.8, 133.9, 132.9, 131.8, 130.0, 129.6, 128.6, 127.8, 127.7, 127.1, 64.5, 54.6, 52.6, 26.7, 19.3; HRMS (ESI-TOF) *m*/*z*: $[M + Na]^+$ calculated for $C_{27}H_{31}NO_4SiNa$ 484.1915, found 484.1919.

(4*S*)-4-Methoxycarbonyl-2-phenyl-2-oxazoline (8). Following general procedure C on a 0.10 mmol scale of **3** using XtalFluor-E (46 mg, 0.20 mmol) in CH_2Cl_2 and sat. $NaHCO_3$ in MeOH to quench the reaction, the desired product (18 mg, 0.09 mmol, 87%) was isolated as a colorless oil by silica gel column chromatography (hexane/EtOAc, 2:1): R_f (hexane/EtOAc, 1:1) 0.64; $[\alpha]_D^{25}$ +123.2 (*c* = 1.0, $CHCl_3$) {(Lit.[31] $[\alpha]_D^{25}$ + 122.7 (*c* =1.0, $CHCl_3$)}; IR (neat) ν = 2953, 1738, 1639, 1450, 1436, 1360, 1296, 1272, 1203, 1176, 1088, 1068, 1059, 1039, 1025, 970, 945, 778, 693 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.00−7.98 (*m*, 2 H, Ph), 7.52−7.48 (*m*, 1H, Ph), 7.43−7.40 (*m*, 2H, Ph), 4.96 (*dd*, J_1 = 8.0, J_2 = 10.5, 1H, C*H*CH_2O), 4.70 (*dd*, J_1 = 8.0, J_2 = 9.0, 1H, CH_2O), 4.60 (*dd*, J_1 = 8.5, J_2 = 10.5, 1H, CH_2O), 3.82 (*s*, 3H, OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.8, 166.6, 132.1, 128.85, 128.6, 127.1, 69.8, 68.8, 53.0; HRMS (ESI-TOF) *m*/*z*: $[M + Na]^+$ calculated for $C_{11}H_{11}NO_3Na$ 228.0631, found 228.0627.

***N*-Bz-Thr-OMe (9).** To a suspension of HCl·Thr-OMe (2.00 g, 11.6 mmol) at 0 °C in CH_2Cl_2 (40 mL) was added a solution of Bz-Cl (1.56 mL, 11.56 mmol) in CH_2Cl_2 (10 mL) and successively a solution of NEt_3 (3.29 mL, 23.6 mmol) in CH_2Cl_2 (40 mL) over a period of 30 m. The reaction mixture was allowed to slowly warm up to rt overnight. After completion, 0.1 M citric acid was added. The resulting solution was extracted with DCM (3×), and the combined organic layers were washed with brine (1×), dried over $MgSO_4$, filtered, and evaporated *in vacuo*. The crude material was subjected to column chromatography on silica gel (hexane/EtOAc, gradient from 2:1 to 1:2) to give **1** as a slightly yellow powder (2.64 g, 11.1 mmol, 96%): R_f (hexane/EtOAc, 1:1): 0.24; IR (neat) ν = 3375, 2974, 2359, 2333, 1740, 1643, 1579, 1524, 1488, 1437, 1316, 1211, 1165, 1080, 1017, 1000, 927, 884, 838, 713, 691, 665, 541, 412 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.85 (*d*, *J* = 6.0, 2H), 7.53−7.45 (*m*, 3H), 6.93 (*br s*, 1H), 4.85−4.81 (*m*, 1H), 4.49−4.43 (*m*, 1H), 3.80 (*s*, 3H), 2.17 (*br s*, 1H), 1.29 (*d*, *J* = 6.0, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.4, 168.7, 134.4, 132.5, 129.2, 127.7, 68.5, 57.7, 52.8, 20.0; HRMS (ESI-TOF) *m*/*z*: $[M + Na]^+$ calculated for $C_{12}H_{15}NO_4Na$ 260.0893, found 260.0890.

***N*-Bz-Thr(TES)-OMe (10).** Following general procedure B on a 1.77 mmol scale of **1** using TES-Cl (350 μL, 2.12 mmol) and NEt_3 (320 μL, 2.30 mmol) in CH_2Cl_2 (5 mL), the desired product (522 mg, 1.49 mmol, 84%) was isolated as a colorless oil by silica gel column chromatography (hexane/EtOAc, 3:1): R_f (hexane/EtOAc, 3:1): 0.36; IR (neat) ν = 2954, 2913, 2876, 2361, 2335, 1748, 1670, 1513, 1484, 1439, 1381, 1349, 1317, 1239, 1207, 1167, 1126, 1092, 1004, 963, 840, 712, 527, 465 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.84 (*d*, *J* = 6.0, 2H), 7.54−7.44 (*m*, 3H), 6.85 (*d*, *J* = 9.0, 1H), 4.78−4.75 (*m*, 1H), 4.60−4.53 (*m*, 1H), 3.76 (*s*, 3H), 1.26 (*d*, *J* = 6.0, 3H), 0.95 (*t*, *J* = 9.0, 9H), 0.59 (*q*, *J* = 9.0, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.0, 168.5, 134.9, 132.3, 129.2, 127.7, 69.1, 58.3, 52.4, 21.1, 6.5, 4.6; HRMS (ESI-TOF) *m*/*z*: $[M + Na]^+$ calculated for $C_{18}H_{29}NO_4SiNa$ 374.1758, found 374.1762.

(4*S*,5*S*)-4-Carboxymethoxy-5-methyl-2-phenyloxazoline (11). Following general procedure C on a 0.21 mmol scale of **1** using DAST (55 μL, 0.41 mmol) in CH_2Cl_2 and sat. $NaHCO_3$ in MeOH to quench the reaction, the desired product (40 mg, 0.18 mmol, 89%) was isolated as a colorless oil by silica gel column chromatography (hexane/EtOAc, 3:1): R_f (hexane/EtOAc, 3:1): 0.41. $[\alpha]_D^{25}$ +60.36 (*c* = 0.92, $CHCl_3$); IR (neat) ν = 2984, 2950, 2361, 2340, 1737, 1645, 1583, 1493, 1449, 1436, 1349, 1244, 1197, 1174, 1082, 1066, 1044, 1027, 932, 841, 778, 734, 694, 491 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.99−7.96 (*m*, 2H), 7.47−7.36 (*m*, 3H), 5.10−5.02 (*m*, 1H), 4.97 (*d*, *J* = 10.2, 1H), 3.75 (*s*, 3H), 1.36 (*d*, *J* = 6.0, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.4, 166.5, 132.2, 128.7, 128.5, 78.0, 71.6, 52.3, 16.4; HRMS (ESI-TOF) *m*/*z*: $[M + Na]^+$ calculated for $C_{12}H_{13}NO_3Na$ 242.0788, found 242.0787.

***N*-Boc-Ser(Bn)-Ser-OMe (12).** Following general procedure A on a 5.57 mmol scale of HCl·Ser-OMe using Boc-Ser(OBn)-OH (1.70 g, 5.74 mmol), EDC (1.29 g, 6.69 mmol), NMM (1.35 mL, 12.25 mmol), and HOBt (112.93 mg, 0.84 mmol) in EtOH (20 mL), the desired product (1.96 g, 4.93 mmol, 86%) was isolated as colorless oil by silica gel column chromatography (hexane/EtOAc, 3:1): R_f (hexane/EtOAc, 1:1) 0.27; IR (neat) ν = 3342, 2978, 2354, 1744, 1665, 1498, 1455, 1439, 1392, 1366, 1248, 1163, 1072, 1025, 862, 735, 699, 461 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.35−7.28 (*m*, 5H), 5.46 (*d*, *J* = 7.0), 4.65−4.62 (*m*, 1H), 4.54 (*s*, 2H), 4.32 (*br s*, 1H), 3.91−3.88 (*m*, 3H), 3.75 (*s*, 3H), 3.62 (*dd*, J_1 = 5.5, J_2 = 9.5, 1H), 1.44 (*s*, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.8, 170.7, 155.8, 137.5, 128.7, 128.2, 128.1, 80.7, 73.7, 70.0, 63.0, 60.6, 55.2, 52.9, 28.5; HRMS (ESI-TOF) *m*/*z*: $[M + Na]^+$ calculated for $C_{19}H_{28}N_2O_7Na$ 419.1789, found 419.1791.

***N*-Boc-Cys(Bn)-Ser-OMe (13).** *N*-Boc-Cys(Bn)-OH (10.54 g, 34 mmol) and HOBt·H_2O (5.03 g, 37 mmol, 1.1 equiv) were dissolved into 100 mL of dry DMF, and *N*,*N*′-diisopropylcarbodiimide (5.80 mL, 37 mmol, 1.1 equiv) was added and stirred at rt under N_2 for 30 min, whereupon HCl·Ser-OMe (5.80 g, 37 mmol, 1.1 equiv) was added and the mixture was sonicated in a bath sonicator. Triethylamine (30 mL, 216 mmol, 6.4 equiv) was added to the reaction and stirred at rt under N_2 for 2.5 h. A white precipitate was removed from the reaction by filtration and washed with 50 mL of ethyl acetate. The combined filtrate was diluted into 500 mL of ethyl acetate and washed four times with 0.1 M citric acid (4 × 60 mL), saturated sodium bicarbonate (2 × 100 mL), and brine (1 × 100 mL), dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The crude material was dissolved into CH_2Cl_2 and loaded onto silica gel (350 mL). The column was washed with CH_2Cl_2, and the product was eluted using a gradient of hexane/EtOAc from a ratio of 2:1 to 1:2, with the combined fractions concentrated to yield 9.53 g (68%). R_f (hexane/EtOAc, 1:1) 0.43; IR (neat) ν = 3306, 2979, 2364, 1744, 1657, 1517, 1454, 1437, 1366, 1245, 1163, 1050, 1023, 864, 769, 736, 702, 561

dx.doi.org/10.1021/jo5016695 | *J. Org. Chem.* 2015, 80, 40−51

cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.36−7.29 (*m*, 5H), 5.43 (*d*, *J* = 5.0, 1H), 4.61−4.58 (*m*, 1H), 4.24−4.21 (*m*, 1H), 3.90−3.88 (*m*, 2H), 3.72 (*s*, 3H), 3.71 (*s*, 2H), 2.78 (*d*, *J* = 10.0, 2H), 1.40 (*s*, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.8, 171.3, 156.3, 138.4, 129.5, 129.1, 127.7, 80.8, 62.7, 55.0, 52.7, 42.33, 36.5, 33.6, 28.2; HRMS (ESI-TOF) *m*/*z*: $[M + Na]^+$ calculated for $C_{19}H_{28}N_2O_6SNa$ 435.1560, found 435.1556.

***N*-Boc-Cys(Tr)-Ser-OMe (14).** Following general procedure A on a 3.15 mmol scale of HCl·Ser-OMe using Boc-Cys(Tr)-OH (1.50 g, 3.25 mmol), EDC (742.32 mg, 3.78 mmol), NMM (762 μL, 6.93 mmol), and HOBt (65.20 mg, 0.47 mmol) in EtOH (20 mL), the desired product (1.59 g, 2.81 mmol, 89%) was isolated as a white solid by silica gel column chromatography (hexane/EtOAc, 3:1): R_f (hexane/EtOAc, 1:1) 0.43; IR (neat) ν = 3392, 3319, 3055, 2974, 2358, 2335, 1745, 1671, 1491, 1444, 1391, 1367, 1248, 1166, 1030, 861, 743, 701, 627 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.29−7.21 (*m*, 15H), 6.79 (*d*, *J* = 8.1, 1H), 4.77 (*d*, *J* = 5.7, 1H), 4.76−4.54 (*m*, 1H), 4.03 (*dd*, J_1 = 2.7, J_2 = 9.9, 1H), 3.94 (*m*, 1H), 3.76 (*dd*, J_1 = 3.0, J_2 = 10.1, 1H), 3.69 (*s*, 3H), 2.78 (*dd*, J_1 = 5.7, J_2 = 13.2, 1H), 2.54 (*dd*, J_1 = 4.8, J_2 = 12.6, 1H), 1.42 (*s*, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.8, 170.6, 144.5, 129.8, 128.4, 128.3, 127.2, 80.3, 67.5, 62.7, 55.3, 54.2, 52.9, 34.2, 28.5; HRMS (ESI-TOF) *m*/*z*: $[M + Na]^+$ calculated for $C_{31}H_{36}N_2O_6SNa$ 587.2186, found 587.2189.

***N*-Boc-Ser(Bn)-Ser(TES)-OMe (15).** Following general procedure B on a 0.63 mmol scale of **12** using TES-Cl (316 μL, 1.89 mmol) and imidazole (129 mg, 1.89 mmol) in DMF (1 mL), the desired product (294 mg, 0.58 mmol, 91%) was isolated as a colorless oil by silica gel column chromatography (hexane/EtOAc, 9:1): R_f (hexane/EtOAc, 7:1) 0.25; IR (neat) ν = 3333, 2954, 2876, 2359, 2333, 1749, 1717, 1680, 1497, 1456, 1366, 1247, 1206, 1167, 1109, 1047, 1017, 858, 743, 698 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.34−7.29 (*m*, 5H), 5.39 (*s*, 1H), 4.67−4.64 (*m*, 1H), 4.58 (*s*, 2H), 4.35 (*br s*, 1H), 4.08 (*dd*, J_1 = 3.0, J_2 = 10.3, 1H), 3.89 (*dd*, J_1 = 5.0, J_2 = 9.3, 1H), 3.80 (*dd*, J_1 = 3.5, J_2 = 10.0, 1H), 3.72 (*s*, 3H), 3.59 (*dd*, J_1 = 6.5, J_2 = 9.3, 1H), 1.45 (*s*, 9H), 0.90 (*t*, *J* = 7.5, 9H), 0.54 (*q*, *J* = 7.5, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.7, 170.5, 155.6, 137.7, 128.6, 128.0, 127.9, 80.3, 73.7, 70.1, 63.4, 54.6, 54.0, 52.5, 28.5, 6.8, 4.4; HRMS (ESI-TOF) *m*/*z*: $[M + Na]^+$ calculated for $C_{25}H_{42}N_2O_7SiNa$ 533.2654, found 533.2653.

***N*-Boc-Cys(Bn)-Ser(TES)-OMe (16).** Following general procedure B on a 0.49 mmol scale of **13** using TES-Cl (108 μL, 0.64 mmol) and imidazole (168 mg, 2.46 mmol) in DCM (5 mL), the desired product (167 mg, 0.32 mmol, 65%) was isolated as a white solid by silica gel column chromatography (hexane/EtOAc, 7:1): R_f (hexane/EtOAc, 7:1) 0.30; IR (neat) ν = 3286, 2953, 2874, 1743, 1710, 1673, 1650, 1508, 1452, 1366, 1241, 1164, 1105, 1045, 1019, 1005, 869, 746, 733, 717, 699 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.36−7.23 (*m*, 5H), 7.12 (*d*, *J* = 7.5, 1H), 5.33 (*br s*, 1H), 4.61 (*ddd*, J_1 = 5.5, J_2 = 6.0, J_3 = 8.0, 1H), 4.32 (*br s*, 1H), 4.09 (*dd*, J_1 = 2.5, J_2 = 10.0, 1H), 3.82 (*dd*, J_1 = 3.0, J_2 = 10.3, 1H), 3.78 (*s*, 2H), 3.73 (*s*, 3H), 2.87 (*dd*, J_1 = 5.5, J_2 = 14.0, 1H), 2.78 (*dd*, J_1 = 7.0, J_2 = 14.0, 1H), 1.46 (*s*, 9H), 0.93 (*t*, *J* = 8.0, 9H), 0.57 (*q*, *J* = 8.0, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7, 170.6, 138.1, 129.3, 128.8, 127.4, 77.4, 63.2, 54.7, 53.0, 52.6, 36.7, 34.2, 28.5, 6.8, 4.4; HRMS (ESI-TOF) *m*/*z*: $[M + Na]^+$ calculated for $C_{25}H_{42}N_2O_6SSiNa$ 549.2425, found 549.2432.

***N*-Boc-Cys(Tr)-Ser(TES)-OMe (17).** Following general procedure B on a 0.45 mmol scale of **14** using TES-Cl (226 μL, 1.35 mmol) and imidazole (92 mg, 1.35 mmol) in DMF (1 mL): R_f (hexane/EtOAc, 3:1), the desired product (274 mg, 0.40 mmol, 90%) was isolated as a white solid by silica gel column chromatography (hexane/EtOAc, gradient from 9:1 to 3:1): 0.71; IR (neat) ν = 3412, 3334, 2954, 2912, 2876, 2361, 1748, 1716, 1672, 1490, 1444, 1366, 1248, 1207, 1167, 1110, 1047, 1016, 862, 753, 700, 676, 618 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.35−7.28 (*m*, 5H), 5.46 (*d*, *J* = 7.0), 4.65−4.62 (*m*, 1H), 4.54 (*s*, 2H), 4.32 (*br s*, 1H), 3.91−3.88 (*m*, 3H), 3.75 (*s*, 3H), 3.62 (*dd*, J_1 = 5.5, J_2 = 9.5, 1H), 1.44 (*s*, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.8, 170.7, 155.8, 137.5, 128.7, 128.2, 128.1, 80.7, 73.7, 70.0, 63.0, 60.6, 55.2, 52.9, 28.5; HRMS (ESI-TOF) *m*/*z*: $[M + Na]^+$ calculated for $C_{37}H_{50}N_2O_6SSiNa$ 701.3051, found 701.3054.

2-[(1*S*)-1-[[(1,1-Dimethylethoxy)carbonyl]amino]-2-(phenylmethoxy)ethyl]2-(4*S*)-oxazoline Methyl Ester (18). Following general procedure C on a 0.13 mmol scale of **12** using DAST (50 μL, 0.38 mmol) at −78 °C and warming up to rt in CH_2Cl_2 (2 mL), the desired product (41 mg, 0.11 mmol, 85%) was isolated by silica gel column chromatography (hexane/EtOAc, 3:1): R_f (hexane/EtOAc, 1:1) 0.62; $[\alpha]_D^{25}$ +63.2 (*c* = 1.0, $CHCl_3$); IR (neat) ν = 2971, 2360, 2334, 1741, 1713, 1664, 1498, 1458, 1366, 1249, 1203, 1164, 1024, 971, 918, 862, 734, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.28−7.20 (*m*, 5H), 5.41 (*d*, *J* = 7.5, 1H), 4.71−4.69 (*m*, 1H), 4.55−4.37 (*m*, 6H), 3.72−3.63 (*m*, 5H), 1.36 (*s*, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.3, 168.6, 155.4, 138.0, 128.5, 127.9, 127.7, 80.1, 73.3, 70.3, 70.1, 68.2, 52.9, 49.5, 28.5; HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calculated for $C_{19}H_{27}N_2O_6$ 379.1864, found 379.1863.

2-[(1*S*)-1-[[(1,1-Dimethylethoxy)carbonyl]amino]-2-(thiobenzyl)ethyl]2-(4*S*)-oxazoline Methyl Ester (19). Following general procedure C on a 0.1 mmol scale of **13** using DAST (41 μL, 0.31 mmol) at −45 °C and warming up to rt in CH_2Cl_2 (2 mL), the desired product (25 mg, 0.061 mmol, 61%) was isolated by silica gel column chromatography (hexane/EtOAc, 3:1): R_f (hexane/EtOAc, 5:1) 0.21; $[\alpha]_D^{25}$ +45.4 (*c* = 1.0, $CHCl_3$); IR (neat) ν = 3391, 2979, 2920, 1742, 1713, 1662, 1496, 1454, 1366, 1332, 1247, 1208, 1167, 1047, 1017, 766, 704 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.24−7.16 (*m*, 5 H), 5.35 (*d*, J = 7.5, 1H), 4.73−4.68 (*m*, 1H), 4.62−4.59 (*m*, 1H), 4.51−4.47 (*m*, 1H), 4.41 (*dd*, J_1 = 8.8, J_2 = 10.6, 1H), 3.71 (*s*, 3H), 3.66 (*d*, J = 1.5, 2H), 2.82 (*dd*, J_1 = 5.3, J_2 = 14.1, 1H), 2.73 (*dd*, J_1 = 5.6, J_2 = 14.0, 1H), 1.37 (*s*, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.1, 169.0, 155.1, 138.0, 129.1, 128.7, 127.3, 80.2, 70.4, 68.1, 52.9, 48.7, 36.8, 34.5, 28.5; HRMS (ESI-TOF) *m*/*z*: $[M + Na]^+$ calculated for $C_{19}H_{26}N_2O_5SNa$ 417.1455, found 417.1459.

2-[(1*S*)-1-[[(1,1-Dimethylethoxy)carbonyl]amino]-2-((triphenylmethyl)thio)ethyl]2-(4*S*)-oxazoline Methyl Ester (20). Following general procedure C on a 0.09 mmol scale of **14** using DAST (37 μL, 0.28 mmol) at −78 °C and warming up to rt in CH_2Cl_2 (2 mL), the desired product (40 mg, 0.07 mmol, 79%) was isolated by silica gel column chromatography (hexane/EtOAc, 3:1): R_f (hexane/EtOAc, 3:1) 0.27; $[\alpha]_D^{25}$ +48.5 (*c* = 1.0, $CHCl_3$); IR (neat) ν = 2976, 2361, 1743, 1715, 1661, 1491, 1444, 1366, 1265, 1248, 1209, 1165, 1035, 981, 964, 849, 767, 738, 700, 676, 620 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.33−7.30 (*m*, 6H), 7.21−7.11 (*m*, 9H), 5.09 (*br s*, 1H), 4.68−4.64 (*m*, 1H), 4.48−4.31 (*m*, 2H), 3.67 (*s*, 3H), 2.52(*d*, *J* = 5.4, 2H), 1.34 (*s*, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2, 168.9, 154.9, 144.6, 129.7, 128.1, 127.0, 80.1, 70.4, 68.1, 66.9, 52.8, 48.1, 35.2, 28.5; HRMS (ESI-TOF) *m*/*z*: $[M + Na]^+$ calculated for $C_{31}H_{34}N_2O_5SNa$ 569.2081, found 569.2086.

***N*-Boc-Ser(Bn)-Ser-Ser-OMe (21).** To a stirring solution of **12** (1.72 g, 4.35 mmol) at rt in MeOH (30 mL) was added a solution of LiOH (625.20 mg, 26.09 mmol) in H_2O (15 mL) and stirred for 4 h. After completion, approximately 2/3 of the MeOH was removed by a rotary evaporator. The solution was then acidified by adding 40 mL of 1 M $NaHSO_4$ whereon a white precipitate was formed. The suspension was extracted with EtOAc (3×), and the combined organic phases were dried with $MgSO_4$, filtered, and evaporated *in vacuo* to yield the carboxylic acid (1.60 g, 4.11 mmol, 96%) as a white solid. The crude material was directly used for peptide bond formation. To individual stirring solutions of the carboxylic acid (1.55 g, 4.05 mmol) and HCl·Ser-OMe (630.62 mg, 4.05 mmol), DMF was added (each 20 mL) and NMM (each 1.23 mL, 12.16 mmol)·PyBop (3.17 g, 6.08 mmol) was added to the stirring solution of carboxylic acid, followed by the solution of H-Ser-OMe. The reaction solution was stirred overnight at rt. After completion, most of the DMF was removed on a rotary evaporator; diluted with EtOAc (30 mL); washed with 0.1 M citric acid (2×), sat. $NaHCO_3$ (2×), and brine; dried over $MgSO_4$; filtered; and evaporated *in vacuo*. The crude material was purified by column chromatography (gradient from 0 to 10% MeOH in $CHCl_3$) to give **21** (1.09 g, 2.25 mmol, 56%) as a mixture of four diastereomers: R_f ($CHCl_3$/MeOH, 9:1) 0.31; ^1H NMR (500 MHz, $CDCl_3$) δ 7.35−7.28 (*m*, 20H), 5.62−5.52 (*m*, 4H), 4.60−4.56 (*m*, 8H), 4.29 (*br-s*, 4H), 4.08−3.82 (*m*, 16H), 3.75−3.73 (*m*, 12H), 3.69−3.66 (*m*, 8H), 1.42 (*s*, 36H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.4, 171.3, 170.9, 170.8, 137.5, 137.4, 137.4, 137.4, 173.4, 137.3, 128.8, 128.8, 128.7, 128.4, 128.3, 128.2, 128.2, 128.1, 128.1,

dx.doi.org/10.1021/jo5016695 | *J. Org. Chem.* 2015, 80, 40−51

128.1, 128.1, 81.2, 73.8, 73.7, 73.6, 62.9, 62.6, 62.5, 62.5, 56.0, 55.3, 55.3, 54.8, 53.1, 53.0, 53.0, 52.9, 46.7, 28.5, 28.5, 28.5, 28.4, 26.6, 26.5, 26.5, 26.4; HRMS (ESI-TOF) m/z: $[M + Na]^+$ calculated for $C_{22}H_{33}N_3O_9Na$ 506.2109, found 506.2105.

***N*-Boc-Ser(Bn)-Ser(TES)-Ser(TES)-OMe (22).** Following general procedure B on a 0.59 mmol scale of **21** using TES-Cl (498 μL, 2.96 mmol) and imidazole (243 mg, 3.56 mmol) in DMF (2 mL), the desired product (344 mg, 0.48 mmol, 85%) was isolated as a mixture of four diastereomers as a colorless oil by column chromatography (hexane/EtOAc, 5:1): R_f (hexane/EtOAc, 3:1) 0.43; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35−7.28 (*m*, 20H), 0.83 (*s*, 4H), 4.68−4.65 (*m*, 4 H), 4.62−4.51 (*m*, 8H), 4.48−4.43 (*m*, 4H), 4.32 (*br s*, 4H), 4.07−4.02 (*m*, 8H), 3.90−3.77 (*m*, 8H), 3.73−3.71 (*m*, 12H), 3.62−3.56 (*m*, 8H), 1.44 (*s*, 36H), 0.98−0.89 (*m*, 72H), 0.66−0.55 (*m*, 48H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 170.4, 170.3, 170.3, 170.3, 170.2, 169.9, 169.9, 169.8, 155.5, 137.5, 128.5, 128.5, 128.4, 128.4, 128.4, 127.8, 127.8, 127.8, 127.8, 127.7, 127.7, 73.4, 73.4, 73.3, 69.9, 69.8, 69.6, 69.6, 63.3, 63.2, 54.6, 54.6, 54.4, 54.4, 54.3, 54.3, 54.3, 54.2, 28.3, 28.2, 28.3, 6.7, 6.6, 6.6, 4.2, 4.2; HRMS (ESI-TOF) m/z: $[M + Na]^+$ calculated for $C_{34}H_{61}N_3O_9Si_2Na$ 734.3839, found 734.3834.

2-[(1*S*)-1-[[(1,1-Dimethylethoxy)carbonyl]amino]-2-(phenylmethoxy)ethyl]2-[2,4′:2′,4″]-bis-oxazoline Methyl Ester (23). Following general procedure C on a 0.07 mmol scale of **21** using DAST (53 μL, 0.40 mmol) at −78 °C and warming up to rt in CH_2Cl_2 (2 mL), the desired product (16 mg, 0.04 mmol, 53%) was isolated by silica gel column chromatography (1% MeOH in $CHCl_3$) as a mixture of four diastereomers: R_f (1% MeOH in $CHCl_3$) 0.50; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34−7.28 (*m*, 20H), 6.52 (*d*, *J* = 9.5, 4H), 5.64 (*d*, *J* = 7.5, 4H), 5.45 (*s*, 4H), 4.83−4.73 (*m*, 4H), 4.65−4.50 (*m*, 20H), 4.65 (*s*, 4H), 3.95 (*s*, 4H), 3.80−3.72 (*m*, 12H), 3.63−3.57 (*m*, 8H), 1.46−1.45 (*m*, 36H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.5, 172.0, 171.9, 171.9, 171.8, 171.3, 171.2, 169.5, 169.2, 169.1, 169.0, 168.9, 168.8, 138.0, 137.9, 129.0, 129.0, 129.0, 128.9, 128.8, 128.4, 128.4, 128.3, 128.2, 128.1, 128.0, 128.0, 81.1, 80.7, 73.6, 73.5, 70.5, 70.4, 70.2, 68.1, 68.0, 67.7, 54.6, 54.5, 53.5, 52.6, 52.6, 52.5, 49.9, 49.9, 49.7, 49.4, 49.4, 28.2, 28.2, 28.2, 28.1; HRMS (ESI-TOF) m/z: $[M + Na]^+$ calculated for $C_{22}H_{29}N_3O_7Na$ 470.1898, found 470.1897.

***N*-Boc-Ser-OMe (24).** To a stirring solution of H-Ser-OMe·HCl (10 g, 64.3 mmol) at rt in CH_2Cl_2 (150 mL) was added Et_3N (20 mL, 140 mmol), and the resulting suspension was cooled to 0 °C in an ice bath. After 30 min, Boc_2O (15.5 g, 71 mmol) was added and the suspension was stirred overnight while slowly warming to rt. After completion, the suspension was diluted with CH_2Cl_2 and washed with 1 M $NaHSO_4$ (3×), sat. $NaHCO_3$ (1×), and brine (1×). All aq. layers were back extracted with CH_2Cl_2, and the combined organic layers were dried over $MgSO_4$, filtered, and evaporated *in vacuo* to give **24** as a colorless oil (14.31 g, 65.3 mmol, 99%). R_f (hexane/EtOAc, 3:1) 0.10; IR (neat) ν = 3412, 2979, 2364, 1743, 1693, 1506, 1458, 1438, 1392, 1367, 1350, 1249, 1210, 1159, 1059, 1030, 853, 780, 736, 702 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.49 (*br s*, 1 H), 4.40 (*br s*, 1 H), 3.94 (*dd*, J_1 = 10.1, J_2 = 3.7, 2 H), 3.79 (*s*, 3 H), 1.45 (*s*, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ171.2; 155.7; 80.3, 63.5, 55.6; 52.6; 28.2; HRMS (ESI-TOF) m/z: $[M + Na]^+$ calculated for $C_9H_{17}NO_5Na$ 242.0999, found 242.1003.

***N*-[(Phenlymethoxy)carbonyl]-(*S*)-serine Methyl Ester (25).** To a stirring solution of HCl·Ser-OMe (458 mg, 2.95 mmol) at rt in H_2O/MeOH (8:3, 5.5 mL) was added $NaHCO_3$ (744 mg, 8.84 mmol), followed by cooling to 0 °C. Benzyl chloroformate (505 μL, 3.54 mmol) was added to yield a white suspension that was slowly warmed to rt and then refluxed at 70 °C for 6 h. The reaction mixture was allowed to cool to rt, diluted with sat. $NaHCO_3$, extracted with EtOAc (3×), dried over $MgSO_4$, filtered, and evaporated *in vacuo*. The crude material was purified by column chromatography on silica gel (hexane/EtOAc, 3:1) to give **25** as a white solid (535 mg, 2.11 mmol, 72%): R_f (hexane/EtOAc, 1:1) 0.30; IR (neat) ν = 3426, 2956, 2361, 1703, 1516, 1450, 1341, 1266, 1210, 1059, 1028, 977, 733, 697, 474 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36−7.31 (*m*, 5H), 5.78 (*d*, *J* = 6.9, 1H), 5.12 (*s*, 2H), 4.47−4.42 (*m*, 1H), 3.99 (*dd*, J_1 = 3.6, J_2 = 11.1, 1H), 3.90 (*dd*, J_1 = 3.3, J_2 = 11.1, 1H), 3.77 (*s*, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.3, 156.4, 136.2, 128.8, 128.5, 128.3, 67.4, 63.4, 56.2, 53.0; HRMS (ESI-TOF) m/z: $[M + Na]^+$ calculated for $C_{12}H_{15}NO_5Na$ 276.0842, found 276.0839.

***N*-[(Phenlymethoxy)carbonyl]-*O*-(triethylsilyl)-(*S*)-serine Methyl Ester (26).** Following general procedure B on a 0.46 mmol scale of **25** using TES-Cl (233 μL, 0.1.39 mmol) and imidazole (96 mg, 1.39 mmol) in DMF (1 mL), the desired product (86 mg, 0.23 mmol, 51%) was isolated as a colorless oil by silica gel column chromatography (hexane/EtOAc, 7:1): R_f (hexane/EtOAc, 3:1) 0.49; IR (neat) ν = 2954, 2877, 2361, 1725, 1505, 1456, 1438, 1381, 1343, 1297, 1239, 1203, 1174, 1109, 1084, 1063, 1028, 1005, 979, 821, 732, 697 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34−7.31 (*m*, 5H), 5.73 (*d*, *J* = 8.4, 1H), 5.13 (*d*, *J* = 2.4, 2H), 4.44−4.40 (*m*, 1H), 4.07 (*dd*, J_1 = 2.7, J_2 = 10.1, 1H), 3.84 (*dd*, J_1 = 3.0, J_2 = 10.1, 1H), 3.75 (*s*, 3H), 0.91 (*t*, *J* = 8.1, 9H), 0.54 (*q*, *J* = 7.8, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2, 156.2, 136.5, 128.7, 128.4, 128.3, 67.2, 63.5, 56.2, 52.6, 6.7, 4.4; HRMS (ESI-TOF) m/z: $[M + Na]^+$ calculated for $C_{18}H_{29}NO_5Na$ 390.1707, found 390.1709.

***N*-[(9-Fluorenylmethoxy)carbonyl]-(*S*)-serine Methyl Ester (27).** To a stirring solution of HCl·Ser-OMe (316 mg, 2.03 mmol) at rt in H_2O/MeOH (8:3, 5.5 mL) was added $NaHCO_3$ (512 mg, 6.10 mmol), which was subsequently cooled to 0 °C. At 0 °C, Fmoc-Cl (632 mg, 2.44 mmol) was added to give a white suspension that was slowly warmed to rt and then refluxed overnight at 70 °C. The reaction mixture was allowed to cool to rt, diluted with sat. $NaHCO_3$, extracted with EtOAc (3×), dried over $MgSO_4$, filtered, and evaporated *in vacuo*. The crude material was purified by column chromatography on silica gel (hexane/EtOAc, 3:1) to give **27** as a white solid (350 mg, 1.03 mmol, 51%): R_f (hexane/EtOAc, 1:1) 0.36; IR (neat) ν = 3412, 3061, 2950, 2868, 2354, 2334, 1704, 1519, 1449, 1338, 1265, 1209, 1104, 1057, 976, 759, 735, 702, 621, 568, 534, 519, 507, 426 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60−7.30 (*m*, 8H), 5.81 (*d*, *J* = 7.5, 1H), 4.46−4.24 (*m*, 3H), 4.22 (*t*, *J* = 7.0), 4.00 (*dd*, J_1 = 2.5, J_2 = 11.0, 1H), 3.91 (*dd*, J_1 = 2.5, J_2 = 11.5, 1H), 3.78 (*s*, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.2, 156.5, 144.0, 143.8, 141.5, 141.5, 128.0, 127.3, 127.3, 125.3, 120.2, 120.2, 67.4, 63.4, 56.8, 53.0, 47.3; HRMS (ESI-TOF) m/z: $[M + Na]^+$ calculated for $C_{19}H_{19}NO_5Na$ 364.1155, found 364.1152.

***N*-[(9-Fluorenylmethoxy)carbonyl]-*O*-(triethylsilyl)-(*S*)-serine Methyl Ester (28).** Following general procedure B on a 0.28 mmol scale of **27** using TES-Cl (138 μL, 0.82 mmol) and imidazole (57 mg, 0.82 mmol) in DMF (1.5 mL), the desired product (64 mg, 0.14 mmol, 51%) was isolated as a colorless oil by silica gel column chromatography (hexane/EtOAc, 7:1): R_f (hexane/EtOAc, 3:1) 0.69; IR (neat) ν = 2955, 2876, 2361, 1722, 1506, 1449, 1341, 1242, 1204, 1106, 1082, 1059, 1006, 979, 756, 736, 543 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60−7.29 (*m*, 8H), 5.69 (*d*, *J* = 8.7), 4.47−4.41 (*m*, 1H), 4.37 (*d*, *J* = 6.9, 1H), 4.26 (*t*, *J* = 7.2, 1H), 4.10 (*dd*, J_1 = 2.7, J_2 = 10.4, 1H), 3.88 (*dd*, J_1 = 3.3, J_2 = 10.2, 1H), 3.77 (*s*, 3H), 0.95 (*t*, *J* = 7.9, 9H), 0.59 (*q*, *J* = 8.1, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.0, 156.0, 143.8, 141.3, 127.7, 127.1, 125.2, 125.1, 120.0, 67.2, 63.4, 56.0, 52.4, 47.1, 6.6, 4.2; HRMS (ESI-TOF) m/z: $[M + Na]^+$ calculated for $C_{25}H_{33}NO_5SiNa$ 478.2020, found 478.2019.

(4*S*)-4-Methoxycarbonyl-2-benzyloxy-2-oxazoline (30). Following general procedure C on a 0.11 mmol scale of **25** using XtalFluor-E (50 mg, 0.22 mmol) at −78 °C and warming up to rt in CH_2Cl_2 (2 mL), the desired product (5 mg, 0.02 mmol, 16%) was isolated by silica gel column chromatography (hexane/EtOAc, 3:1): R_f (hexane/EtOAc, 5:1) 0.21; IR (neat) ν = 1740, 1438, 1414, 1363, 1217, 1202, 1176, 1090, 1062, 1030, 1001, 937, 758, 741,701, 672, 593, 457 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35−7.24 (*m*, 5H), 4.90 (*d*, *J* = 15.0, 1H), 4.44−4.38 (*m*, 1H), 4.34 (*dd*, J_1 = 4.8, J_2 = 8.9, 1H), 4.24 (*d*, *J* = 15, 1H), 4.10 (*dd*, J_1 = 5.1, J_2 = 9.5, 1H), 3.74 (*s*, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7, 158.3, 135.6, 129.5, 129.1, 128.8, 64.5, 56.0, 52.9, 47.4; HRMS (ESI-TOF) m/z: $[M + Na]^+$ calculated for $C_{12}H_{13}NO_4Na$ 258.0737, found 258.0734.

(4*S*)-2-(9-Fluorenylmethoxy)-4-methoxycarbonyl-2-oxazoline (31). Following general procedure C on a 0.11 mmol scale of **27** using DAST (44 μL, 0.33 mmol) at −78 °C and warming up to rt in CH_2Cl_2 (2 mL), the desired product (21 mg, 0.07 mmol, 61%) was isolated by silica gel column chromatography (hexane/EtOAc, 3:1): R_f

dx.doi.org/10.1021/jo5016695 | *J. Org. Chem.* 2015, 80, 40−51

(hexane/EtOAc, 3:1) 0.31; IR (neat) ν = 1742, 1660, 1477, 1449, 1404, 1354, 1306, 1249, 1209, 1181, 1100, 1059, 964, 760, 742 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.77 (*d*, *J* = 9, 2H), 7.63 (*d*, *J* = 9, 2H), 7.43−7.38 (*m*, 2H), 7.34−7.29 (*m*, 2H), 4.70−4.52 (*m*, 5H), 4.34 (*t*, *J* = 9, 1H), 3.77 (*s*, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.2, 164.8, 143.4, 143.3, 141.5, 128.1, 127.3, 125.5, 120.2, 73.4, 70.5, 65.4, 52.8, 46.8; HRMS (ESI-TOF) *m*/*z*: [M + Na]$^+$ calculated for $C_{19}H_{17}NO_4Na$ 346.1050, found 346.1051.

Solid-Phase Synthesis of TFA·H_2N-[Ser]$_5$-OH (32). Fmoc-Ser(O*t*Bu)-OH (2.36 g, 6.14 mmol) and DIEA (2.09 mL, 12.28 mmol) in CH_2Cl_2 (30 mL) were stirred at rt for 5 min. The solution was added to a preactivated and swelled 2-chlorotrityl chloride resin (8.19 g), which was agitated at rt for 4.5 h. The resin was washed with CH_2Cl_2 (3 × 30 mL), DMF (3 × 30 mL), and CH_2Cl_2 (3 × 30 mL). Unreacted resin positions were capped by adding a solution of CH_2Cl_2/MeOH/DIEA (80:15:5, 3 × 30 mL), which was agitated at rt for 3 × 10 min. The resin was then washed with CH_2Cl_2 (4 × 30 mL) and dried over KOH *in vacuo*. A solution of 25% piperidine in DMF (6 × 15 mL) was added to the resin, which was agitated for 6 × 10 min. The resin was then washed with DMF (3 × 30 mL), CH_2Cl_2 (2 × 30 mL), and DMF (2 × 30 mL). Fmoc-Ser(OtBu)-OH (3.64 g, 9.51 mmol), DIEA (4.04 mL, 23.76 mmol), HOBt (1.25 g, 9.27 mmol), and HBTU (3.52 g, 9.27 mmol) were dissolved in DMF (30 mL) at rt and stirred for 10 min. The solution was added to the preswelled resin which was agitated at rt for 4.5 h. The resin was then washed with DMF (5 × 30 mL) and dried *in vacuo*. Fmoc deprotection of resin bound dipeptide and loading of Fmoc-Ser(OtBu)-OH were then repeated three times. Fmoc-removal was carried out using piperidine as described above. A solution of TFA/H_2O/TIS (95:2.5:2.5, 40 mL) was added to the resin and agitated at rt for 2 h. The resin was filtered off, and the pentapeptide **32** was precipitated by adding diisopropyl ether (−20 °C) to the filtrate. The peptide was centrifuged, washed with Et_2O (3×), and dried *in vacuo*. The peptide was redissolved in a solution of H_2O/CH_3CN (2:1, 10 mL) and lyophilized to give crude **32** (2.26 g, 3.99 mmol, 84%) as a slightly yellow powder. The crude peptide was used without further purification. ^1H NMR (500 MHz, DMSO-d_6) δ 8.58 (*d*, *J* = 7.5, 1H), 8.06 (*d*, *J* = 7.5, 1H), 7.98−7.94 (*m*, 2H), 4.49−4.45 (*m*, 1H), 4.40−4.35 (*m*, 2H), 4.27−4.24 (*m*, 1H), 3.92−3.90 (*m*, 1H), 3.71−3.56 (*m*, 10H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.6, 171.4, 171.3, 170.9, 170.5, 68.2, 62.5, 62.3, 61.7, 61.2, 58.9, 57.9, 57.4, 56.4, 55.7, 55.4; HRMS (ESI-TOF) *m*/*z*: [M − TFA + H]$^+$ calculated for $C_{15}H_{28}N_5O_{11}$ 454.1780, found 454.1781.

***N*-Fmoc-[Ser]$_5$-OMe (33).** To a stirring solution of **32** (205 mg, 0.36 mmol) at rt in H_2O/MeOH (8/3) was added $NaHCO_3$ (121 mg, 1.44 mmol) and Fmoc-Cl (121 mg, 0.47 mmol), and the resulting mixture was refluxed at 70 °C overnight. The reaction mixture was then dried down, transferred to a 50 mL falcon tube, washed, and centrifuged with DCM (2×). After drying *in vacuo*, the crude material was suspended in MeOH (10 mL) at rt and TMS-Cl (916 μL, 7.22 mmol) was added dropwise. The reaction mixture was stirred overnight and diluted with Et_2O (50 mL). The precipitate was collected by centrifugation, washed with Et_2O (3×), and dried *in vacuo*. The crude material was suspended in pyridine (5 mL) at rt, and TES-Cl (909 μL, 5.42 mmol) was added dropwise and stirred overnight. The reaction mixture was diluted with EtOAc and washed with 0.1 M citric acid (2×) and brine (2×), dried over $MgSO_4$, filtered, and dried by rotary evaporator. The remaining pyridine was removed by coevaporation with toluene (2 × 5 mL). The crude material was purified by silica gel column chromatography (hexane/EtOAc, gradient from 7:1 to 4:1) to give **33** (100 mg, 0.079 mmol, 22%) as a white solid: R_f (hexane/EtOAc, 5:1) 0.21; IR (neat) ν = 3299, 2954, 2911, 2876, 2361, 2333, 1753, 1636, 1512, 1463, 1239, 1112, 1037, 1007, 973, 811, 738, 668 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 8.58 (*d*, *J* = 7.5, 1H), 8.06 (*d*, *J* = 7.5, 1H), 7.98−7.94 (*m*, 2H), 4.49−4.45 (*m*, 1H), 4.40−4.35 (*m*, 2H), 4.27−4.24 (*m*, 1H), 3.92−3.90 (*m*, 1H), 3.71−3.56 (*m*, 10H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.2, 169.7, 169.6, 169.5, 169.5, 169.5, 141.3, 141.3, 127.7, 127.1, 125.2, 125.2, 120.0, 72.6, 63.6, 63.2, 62.7, 62.5, 55.1, 54.8, 54.6, 52.5, 47.5, 7.1, 7.1, 7.1, 7.1, 7.0, 6.3, 4.7, 4.7, 4.6, 4.6; HRMS (ESI-TOF) *m*/*z*: [M + Na]$^+$ calculated for $C_{61}H_{109}N_5O_{13}Si_5Na$ 1282.6760, found 1282.6760.

2-(9-Fluorenylmethyl)-[2,4′:2′,4″:2″,4‴:2‴,4⁗]-pentoxazoline Methyl Ester (34). To a stirring solution of **33** (36 mg, 0.029 mmol) in CH_2Cl_2 at −78 °C was added DAST (43 μL, 0.33 mmol). The reaction was stirred for 4 h, while being slowly warmed to 0 °C. The reaction was quenched using MeOH, and the solvent was removed by rotary evaporator. The crude material was subjected to silica gel column chromatography (2% MeOH in $CHCl_3$) to give **34** as a single diastereoisomer (5.9 mg, 0.010 mmol, 34%): ^1H NMR (500 MHz, $CDCl_3$) δ 7.77 (*d*, *J* = 7.5, 2H), 7.60 (*t*, *J* = 7.5, 2H), 7.49 (*d*, J = 8.0, 1H), 7.39 (*t*, *J* = 7.5, 2H), 7.31 (*t*, *J* = 7.5, 2H), 5.76 (*s*, 1H), 4.70−4.67 (*m*, 1H), 4.42−4.38 (*m*, 4H), 4.25−4.22 (*m*, 2H), 4.07−4.02 (*m*, 4H), 3.99 (*dd*, J_1 = 4.5, J_2 = 9.5, 1H), 3.78 (*dd*, J_1 = 3.5, J_2 = 10.0, 1H), 3.72 (*s*, 3H), 3.69−3.65 (*m*, 2H,), 3.58−3.55 (*m*, 2H), 0.99−0.90 (*m*, 45H), 0.69−0.53 (*m*, 30H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.5, 141.8, 141.5, 132.4, 127.8, 127.3, 124.9, 120.3, 110.2, 71.2, 70.5, 68.1, 65.4, 63.3, 52.9, 50.6, 47.0, 29.9, 27.5; HRMS (ESI-TOF) *m*/*z*: [M + Na]$^+$ calculated for $C_{31}H_{29}N_5O_8Na$ 622.1908, found 622.1909.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of ^1H NMR and ^{13}C NMR spectra of compounds **1**−**34**. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: nathan.luedtke@chem.uzh.ch.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank Dr. Martin Seyfried and Olivia Schmidt for technical assistance. This work was made possible by support from the Swiss National Science Foundation (#146754) and the University of Zurich.

■ REFERENCES

(1) For examples see: (a) Perez, L. J.; Faulkner, D. J. *J. Nat. Prod.* **2003**, *66*, 247. (b) Kim, M. Y.; Vankayalapati, H.; Shin-ya, K.; Wierzba, K.; Hurley, L. H. J. *J. Am. Chem. Soc.* **2002**, *124*, 2098. (c) Parsons, R. L.; Heathcock, C. H. *J. Org. Chem.* **1994**, *59*, 4733. (d) Wipf, P. In *Alkaloids: Chemical and Biological Perspective*; Pelletier, S. W., Ed.; Pergamon: New York, 1998; p 187.

(2) For examples see: (a) Vorbrüggen, H.; Krolikiewicz, K. *Tetrahedron Lett.* **1981**, *22*, 4471. (b) Lutomski, K. A.; Meyers, A. I. *J. Am. Chem. Soc.* **1982**, *104*, 879. (c) Panek, J. S.; Masse, C. E. *J. Org. Chem.* **1998**, *63*, 2382. (d) Ishihara, M.; Togo, H. *Tetrahedron* **2007**, *63*, 1474. (e) Hamada, Y.; Shibata, M.; Shiori, T. *Tetrahedron Lett.* **1985**, *26*, 6501. (f) Vorbrüggen, H.; Krolikiewicz, K. *Tetrahedron* **1993**, *49*, 9353. (g) Jouin, P.; Poncet, J.; Montagne, C.; Galéotti, N. *Tetrahedron Lett.* **1992**, *33*, 2807. (h) Miller, C. P.; Wipf, P. *Tetrahedron Lett.* **1992**, *33*, 907.

(3) Atkins, G. M.; Burgess, E. M. *J. Am. Chem. Soc.* **1968**, *90*, 4744.

(4) For a review, see: Khapli, S.; Dey, S.; Mal, D. J. *Indian Inst. Sci.* **2001**, *81*, 461.

(5) Miller, C. P.; Wipf, P. *Tetrahedron Lett.* **1992**, *33*, 907.

(6) Fritch, P. C.; Wipf, P. *Tetrahedron Lett.* **1994**, *35*, 5397.

(7) (a) Fritch, P. C.; Wipf, P. *J. Am. Chem. Soc.* **1996**, *118*, 12358. (b) Okonya, J. F.; Kolasa, T.; Miller, M. J. *J. Org. Chem.* **1995**, *60*, 1932. (c) Liyanage, W.; Weerasinghe, L.; Strong, R. K.; Del Valle, J. R. *J. Org. Chem.* **2008**, *73*, 7420. (d) Grant, C. M.; Miller, P.; Wipf, P. *Tetrahedron* **2000**, *56*, 9143. (e) Doi, T.; Yoshida, M.; Shin-ya, K.; Takahashi, T. *Org. Lett.* **2006**, *8*, 4165. (f) Plant, A.; Stieber, F.; Scherkenbeck, J.; Lösel, P.; Dyker, H. *Org. Lett.* **2001**, *3*, 3427. (g) Boyce, R. J.; Mulqueen, G. C.; Pattenden, G. *Tetrahedron Lett.*

1994, *35*, 5705. (h) Castellano, S.; Kuck, D.; Sala, M.; Novellino, E.; Lyko, F.; Sbardella, G. *J. Med. Chem.* **2008**, *51*, 2321. (i) Jing, Y.; Hong, J. *Tetrahedron Lett.* **2007**, *48*, 8104. (j) You, S.; Kelly, J. W. *Tetrahedron Lett.* **2005**, *46*, 2567.
(8) Metcalf, T. A.; Simionescu, R.; Hudlicky, T. *J. Org. Chem.* **2010**, *75*, 3447.
(9) (a) Phillips, A. J.; Uto, Y.; Wipf, P.; Reno, M. J.; Williams, D. R. *Org. Lett.* **2000**, *2*, 1165. (b) Burrell, G.; Evans, J. M.; Jones, G. E.; Stemp, G. *Tetrahedron Lett.* **1990**, *31*, 3649. (c) Lafargue, P.; Guenot, P.; Lellouche, J.-P. *Heterocycles* **1995**, *41*, 947.
(10) L'Heureux, A.; Beaulieu, F.; Bennett, C.; Bill, D. R.; Clayton, S.; LaFlamme, F.; Mirmehrabi, M.; Tadayon, S.; Tovell, D.; Couturier, M. *J. Org. Chem.* **2010**, *75*, 3401.
(11) Pouliot, M.; Angers, L.; Hamel, J.; Paquin, J. *Tetrahedron Lett.* **2012**, *53*, 4121.
(12) Mohammadopoor-Baltork, I.; Pouranshirvani, S. *Synthesis* **1997**, *7*, 756.
(13) Kim, S.; Park, J. H. *J. Org. Chem.* **1988**, *53*, 3111.
(14) Danishefsky, S. J.; Mantlo, N. *J. Am. Chem. Soc.* **1988**, *110*, 8129.
(15) Metaferia, B. B.; Fetterolf, B. J.; Shazad-ul-Hussan, S.; Moravec, M.; Smith, J. A.; Ray, S.; Gutierrez-Lugo, M.-T.; Bewley, C. A. *J. Med. Chem.* **2007**, *50*, 6326.
(16) Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190.
(17) Wuts, P. G. M.; Green, T. W. *Greene's Protective Groups in Organic Synthesis*; John Wiley & Sons, Inc.: Hoboken, NJ, 1999; p 113.
(18) Schore, N. E.; Vollhardt, K. P. C. *Organic Chemistry*, 6th ed; W. H. Freeman and Company: New York, NY, 2009; p 240.
(19) Ait-Haddou, H.; Hoarau, O.; Cramailére, D.; Pezet, F.; Daran, J.; Balavoine, G. G. A. *Chem.—Eur. J.* **2004**, *10*, 699.
(20) Walker, J. M. *Peptide Synthesis Protocols: Methods in Molecular Biology*; Pennington, M. W., Dunn, B. M., Eds.; Humana Press Inc.: NJ, 1994; pp 41−62.
(21) Venkatraman, S.; Wipf, P. *J. Org. Chem.* **1995**, *60*, 7224.
(22) Riedrich, M.; Harkal, S.; Arndt, H.-D. *Angew. Chem., Int. Ed.* **2007**, *46*, 2701.
(23) Smith, M. B.; March, J. *March's Adcanced Organic Chemistry: Reactions, Mechanisms, and Structure*; John Wiley & Sons, Inc.: Hoboken, NJ, 2007; p 29.
(24) (a) Ambroise, L.; Dumez, E.; Szeki, A.; Jackson, R. F. W. *Synthesis* **2002**, *15*, 2296. (b) Pandit, N.; Singla, R. K.; Shrivastava, B. *Int. J. Med. Chem.* **2012**, doi: 10.1155/2012/159285.
(25) Rein, K.; Giocoechea-Pappas, M.; Anklekar, T. V.; Hart, G. C.; Smith, G. A.; Gawley, R. E. *J. Am. Chem. Soc.* **1989**, *111*, 2211.
(26) Seki, M.; Matsumoto, K. *Synthesis* **1999**, *6*, 924.
(27) The limited solubility properties of peptide **32** and its termini-protected derivatives prevented their purification and evaluation as cyclodehydration substrates.
(28) (a) Fujino, M.; Kobayashi, S.; Obayashi, M.; Fukuda, T.; Shinagawa, S.; Yamazaki, I.; Nakayama, R.; White, W. F.; Rippel, R. H. *Biochem. Biophys. Res. Commun.* **1972**, *49*, 698. (b) Vlieghe, P.; Liswoski, V.; Martinez, J.; Khreestchatisky, M. *Drug Disc. Tod.* **2010**, *15*, 40.
(29) Martin, V. S.; Hernandez, J. N. *J. Org. Chem.* **2004**, *69*, 3590.
(30) Cunico, R. F.; Bedell, L. *J. Org. Chem.* **1980**, *45*, 4797.
(31) Fukuhara, T.; Hasegawa, C.; Hara, S. *Synthesis* **2007**, *10*, 1528.