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Divergent reaction pathways in amine additions to β-lactone electrophiles. An application to β-peptide synthesis

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Abstract—β-Lactone electrophiles are subject to regioselective addition–elimination (AE) or S_N2 ring opening with various nitrogen-based nucleophiles. Primary and secondary amines promote AE ring opening to deliver products that are the functional equivalent of amide aldol adducts. Azide and sulfonamide anion nucleophiles engender S_N2 lactone ring opening to deliver *N*-protected β-amino acid derivatives. These nucleophile-dependent ring opening pathways, coupled with the convenient access to highly enantioenriched β-lactones afforded by acyl halide–aldehyde cyclocondensations, constitute versatile methodologies for asymmetric organic synthesis. The application of this reaction technology to a new method for β-peptide synthesis based on the optically active β-azido acids emerging from the AAC-ring opening sequence is also described.

1. Background

β-Lactones offer considerable versatility as intermediates for organic synthesis.[1] This utility is derived primarily from the reactivity β-lactones express as electrophiles toward a variety of carbon or heteroatom nucleophiles. Ring opening via nucleophilic addition at the carbonyl residue affords access to a variety of β-hydroxy ester or amide adducts depending on the choice of nucleophile (Fig. 1). The addition–elimination (AE) ring opening pathway reveals β-lactones as convenient surrogates for prototypical aldol adducts.[2] However, ring strain within the β-lactone nucleus can elicit electrophilic character reminiscent of that expressed by epoxides. Appropriate tuning of nucleophile reactivity can lead to scission of the C_{alkyl}–O bond in an S_N2 reaction pathway. As a result, β-lactones also afford access to β-disubstituted carboxylate derivatives including β-amino, β-thio, and β,β-dialkyl carboxylic acids.[3,4]

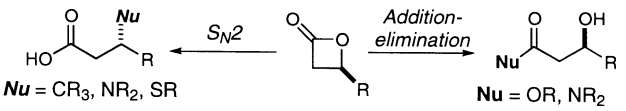

Figure 1. Nucleophile-dependent β-lactone ring opening pathways.

On the basis of the bifunctional electrophilic character expressed by β-lactones, we have been interested in developing optically active 4-substituted 2-oxetanones as generally useful platforms for asymmetric organic synthesis. Catalytic asymmetric acyl halide–aldehyde

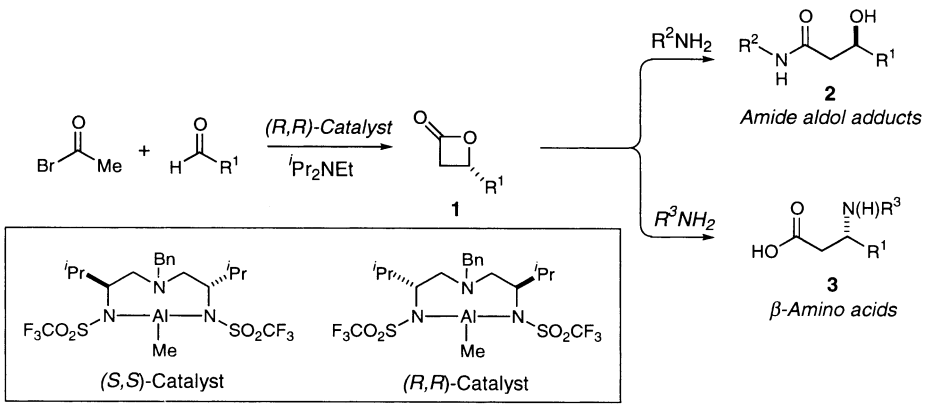

Figure 2. Alternative AAC-amine-mediated ring opening sequences.

Keywords: amino acids; asymmetric catalysis; lactones; nucleophilic additions; peptides.

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cyclocondensation (AAC) reactions have been developed as an operationally simple approach to highly enantiomerically enriched β-lactones **1** (Fig. 2).[2] This reaction technology provides convenient and economical access to the optically active β-lactones required for applications in asymmetric synthesis. In order to reveal β-lactones as versatile aldol surrogates, we envisioned that amine-promoted lactone opening via the addition–elimination pathway would afford enantioenriched β-hydroxy amides **2** constituting formal aldol adducts of amide enolates. However, we were also cognizant of the facile access to enantioenriched β-amino acids derivatives **3** afforded by β-lactones provided suitable conditions existed for securing amine-mediated S_N2 ring opening. Herein we outline the structural and electronic requirements for engaging enantioenriched β-lactones in regioselective addition–elimination or S_N2 ring opening with amine-based nucleophiles and the versatility the derived ring opened products provide in various synthesis activities.[5]

2. Reactivity of β-lactones

Techniques and procedures for achieving nucleophile-dependent regioselectivity in additions to α,β-unsaturated carbonyl electrophiles are widely recognized and exploited in organic synthesis.[6] The widespread utility of these addition reactions has resulted in extensive investigations of the factors affecting regiochemical preferences expressed by various nucleophiles.[7] However, similar analyses of the factors dictating regioselection in nucleophile additions to β-lactones have been less extensive, undoubtedly due to the relative obscurity of β-lactone electrophiles as compared to conjugated enones.[1] Indeed, the hard–soft nucleophile–electrophile matching arguments often used to rationalize preferences for 1,2- or 1,4-addition to enones correlate well with the nucleophile-dependent partioning of β-lactone ring opening (Fig. 3).[8] As expected, hard nucleophiles express a strong preference for addition to the lactone carbonyl, eliciting ring opening via an addition–elimination pathway.[9] Soft nucleophiles achieve better electronic matching with the electrophilic β-carbon, thereby promoting S_N2 displacement of the carboxylate residue.[10] While these considerations do not provide a comprehensive model for nucleophile-β-lactone additions, they are useful as a guideline for selecting the correct nucleophilic reaction partners required to elicit the desired mode of ring opening.

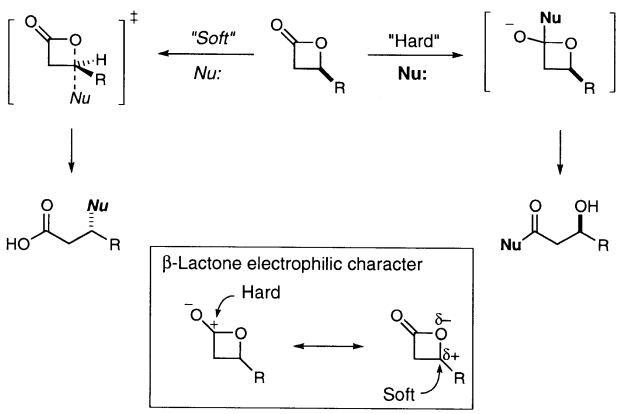
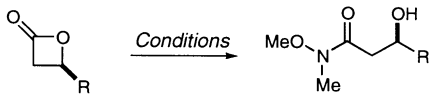


Figure 3. HSAB model for nucleophile additions to β-lactones.

3. Nucleophilic β-lactone ring opening

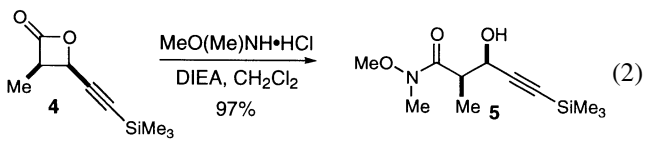
3.1. Amine-mediated addition–elimination

Primary and secondary amines are considered to be relatively non-polarizable, hard nucleophiles.[9] As a result, amine nucleophiles were expected to engage β-lactone electrophiles in facile AE ring opening owing to the activation of the carbonyl function engendered by the ring strain associated with the β-lactone. In examining these reactions, we were aware of one other example of an amine addition to an α-methylene β-lactone reported by Calter that adhered to this predicition.[11] Owing to the versatility of *N*-methoxy-*N*-methyl amides as conduits to other functional groups, we were especially interested in the potential for eliciting β-lactone ring opening using *N*,*O*-dimethyl-hydroxyl amine as the nucleophile.[12] The aluminum amide derived from *N*,*O*-dimethylhydroxylamine has proven to be the most generally effective reagent for converting various carbonyl functionalities to the corresponding Weinreb amides.[13] We had hoped that the enhanced electrophilicity of β-lactones relative to acylic ester derivatives would lead to nucleophilic ring opening using *N*,*O*-dimethylhydroxylamine without resorting to the more nucleophilic aluminum amide reagent (Eq. (1)). Indeed, reacting β-lactone **4** with *N*,*O*-dimethylhydroxyl-amine (Procedure A: MeO(Me)NH·HCl, Et_3N) delivered the desired Weinreb amide **5** in high yield (Eq. (2)).[2c] However, reactions utilizing the MeO(Me)NH·HCl/Et_3N reaction conditions did not afford uniformly high reaction yields for all of the β-lactones examined. For example, the β-lactone **6a** provides the derived amide **7a** in only 43% yield using Procedure A (Eq. (3)). For those β-lactone substrates that do not deliver high yields under the free-base (Procedure A) reaction conditions (cf. **6a** and **b**), application of the prototypical aluminum *N*,*O*-dimethylhydroxylamide reagent (Procedure B: MeO(Me)NH·HCl, Me_2AlCl) consistently delivered the derived amides (cf. **7a** and **b**) in high yields.



(1)

Procedure A: MeO(Me)NH·HCl, Et_3N, CH_2Cl_2.
Procedure B: MeO(Me)NH·HCl, Me_2AlCl, CH_2Cl_2.



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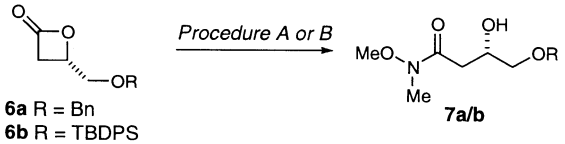


(3)

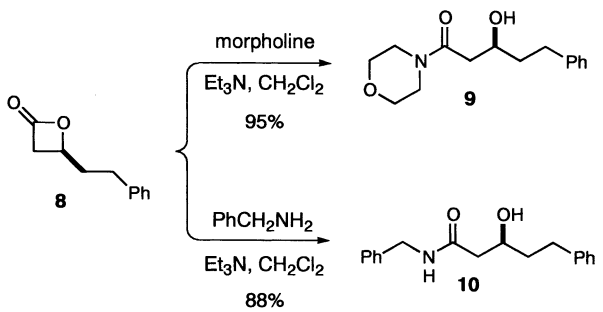
Procedure	lactone	% yield (amide)
A	**6a**	43 (**7a**)
B	**6a**	83 (**7a**)
B	**6b**	94 (**7b**)

Table 1. Azide-mediated ring opening reaction of β-lactones **1**

Entry	Lactone **1** (R)	% ee **1**[a]	% Yield **11**[b] (configuration)	% ee **11**
a	$BnOCH_2-$ (**1a**)	91	94 (*R*-**11a**)	92[c]
b	$PhCH_2CH_2-$ (**1b**)	97	95 (*S*-**11b**)	93[c]
c	Me_2CHCH_2- (**1c**)	95	95 (*S*-**11c**)	97[d]
d	$CH_3CH_2CH_2-$ (**1d**)	96	78 (*S*-**11d**)	
e	$CH_3(CH_2)_3-$ (**1e**)	97	83 (*S*-**11e**)	
f	$CH_2CH(CH_2)_8-$ (**1f**)	94	87 (*S*-**11f**)	
g	$^cC_6H_{11}-$ (**1g**)	99[e]	93 (*R*-**11g**)	
h	$^pNO_2C_6H_4-$ (*ent*-**1h**)[f]	97	83 (*S*-**11h**)	

[a] Lactones **1** were prepared and assayed using the procedures in Ref. 2a (except lactone **1g**).
[b] Lactone **1g** was obtained by the resolution procedure described in Ref. 22a.
[c] Reported yields are for materials obtained from the acid–base extractive work-up of the azide ring opening reactions.
[d] Enantiomer ratio determined by chiral HPLC (Chiralcel OD-H column) of the corresponding methyl ester.
[e] Enantiomer ratio determined by chiral HPLC (Chiralcel OD-H column) of the corresponding benzyl ester.
[f] (*R*)-4-(*p*-nitrophenyl)-2-oxetanone was used in this reaction.

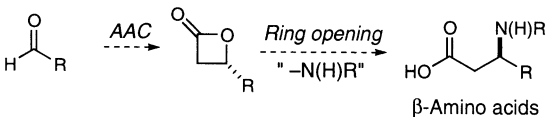
Primary and dialkyl amines are also efficient nucleophiles for promoting AE β-lactone ring opening (Eq. (4)). Preliminary investigations evaluating morpholine as a suitable nucleophile for addition–elimination β-lactone ring opening were inspired by the versatility the resulting amides would afford in accessing other functionalities.[14] Indeed, the optically active β-lactone **8** was subject to facile ring opening with morpholine at ambient temperatures to deliver the corresponding morpholine amide **9** in good yield (95%). Primary amine nucleophiles appear to function similarly to morpholine; reacting the enantioenriched β-lactone with benzyl amine afforded the corresponding benzyl amide **10** (88%).



(4)

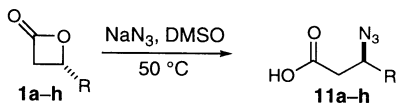
3.2. S_N2 ring opening

3.2.1. Azide nucleophiles. Optically active β-amino acids have become increasingly prevalent features in small-molecule chemotherapeutic agents[15] and are integral components of peptidic materials that exhibit unique structural properties.[16] As a result, efficient and economical preparation of enantiomerically enriched β-amino acids has become the focus of numerous synthesis studies.[17,18] We recognized that amine-mediated S_N2 ring opening of β-lactones would provide an especially attractive and straightforward entry to β-amino carbonyl relationships (Eq. (5)).[19,20] However, the evolution of this strategy as a general asymmetric synthesis of β-amino acids had previously been limited by the availability of the requisite optically active β-lactone electrophiles.[21] Catalytic asymmetric acyl halide–aldehyde cyclocondensation reactions coupled with appropriate reaction conditions for achieving regioselective S_N2 ring opening of enantiomerically enriched β-lactones was considered as an economical and efficient asymmetric synthesis of β-amino acids derivatives.



(5)

Pioneering observations by Vederas and Seebach had previously established azide nucleophiles to have the correct chemical potential to engage β-lactone electrophiles in the desired S_N2 ring openings.[19a–c] Indeed, this observation is consistent with hard–soft matching of nucleophile and electrophile, where the relatively polarizable azide anion would be expected to interact most strongly with the softer carboxylate carbon electrophile.[9,10] Based on this information, azide anion was initially evaluated as a suitable nucleophile for effecting the desired S_N2-mode of 2-oxetanone ring opening (Eq. (6)). Among the various solvent and azide salt combinations examined during reaction optimization, the optically active β-lactones **1a–h** were found to undergo S_N2 lactone ring opening most efficiently using sodium azide (2.0 equiv.) in DMSO (50°C) to directly afford the β-azido acids **11a–h** in 78–95% yield (Table 1). Highly polar reaction solvents are essential for achieving consistently high yields of the β-azido acids, with DMSO proving to be superior even to DMF in terms of reaction reproducibility. Under the optimized NaN_3–DMSO reaction conditions, azide-induced ring opening was insensitive to the structure of the lactone alkyl substituent, with lactones bearing aliphatic unbranched, alkoxy-substituted, α-branched,[22] and β-branched alkyl substituents being subject to efficient lactone ring opening with the anticipated inversion of stereochemistry.[23]



(6)

Precedent indicated that each of these S_N2 ring opening reactions would proceed with rigorous inversion of the 2-oxetanone stereocenter.[3,4] The absolute configuration of β-azido acids **11b–d** was established by conversion to the corresponding *N*-Boc amino esters **12b–d** ((i) CH_2N_2; (ii) H_2, Boc_2O, Pd–C) and correlation of their optical rotation to those of authentic samples of known configuration (Eq. (7)). The configuration of azido acid **11e** was established similarly by conversion to the corresponding *N*-Boc amino acid **12e** ((i) H_2, 10% Pd–C; (ii) Boc_2O, Et_3N); the configuration of the remaining β-azido acids (**11a**,**f**,**g**) was assigned by analogy to these determinations.[24] This stereochemical outcome was assumed to arise from a kinetic preference for azide addition at the β-lactone C_4 position (pathway a, Eq. (8)). However, a reaction mechanism involving competing addition–elimination cannot be discounted since the emergent acyl azide would be expected to revert to the β-lactone with concomitant ejection of the azide nucleophile (pathway b, Eq. (8)).[25] While no reaction by-products that would suggest the

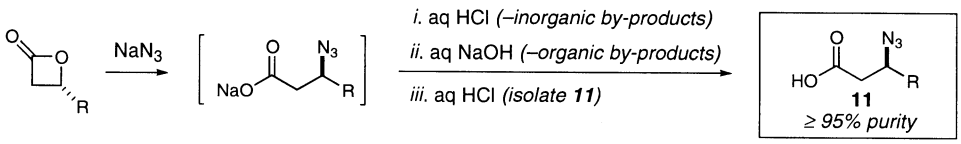
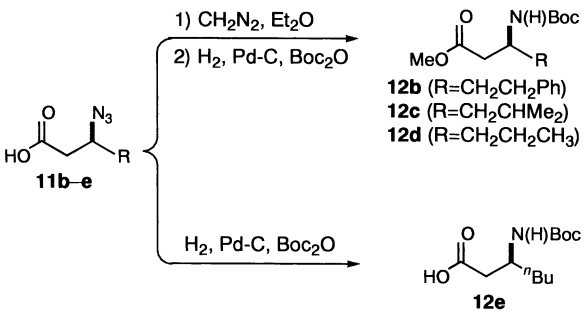


Figure 4. Purification of β-azido acids by extractive work-up.

intermediacy of the acyl azide were observed during these reactions, the participation of reversible carbonyl addition cannot be excluded.



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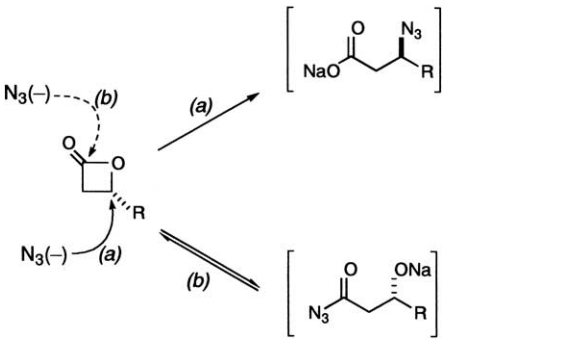
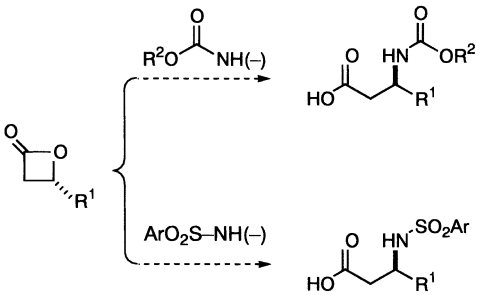


(8)

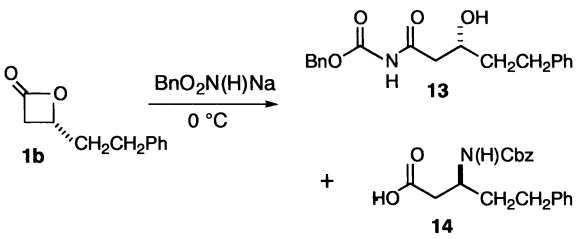
In addition to the high yields and enantioselectivities achieved in the AAC-based β-azido acid synthesis, the asymmetric AAC-azide ring opening sequence provides an operationally simple method for product isolation and purification. The carboxylic acid function that emerges from the ring opening reaction can be exploited in acid–base partitioning of the β-azido acid reaction products (Fig. 4). Typical product purification involved extracting the β-azido acid from an acidic aqueous wash to remove inorganic salts and excess DMSO.[26] Any remaining organic impurities were removed by extracting a basic aqueous solution of the carboxylate salt then reacidification to obtain the β-azido acid products. The β-azido acids **11** typically emerge from the extractive work-up in >95% purity.

3.2.2. Sulfonamide anion nucleophiles. In anticipation of the demands that multistep synthesis applications might place on the β-amino acid derivatives emerging from this procedure, we were interested in developing methods for directly installing the protected β-amine function in the correct oxidation state. Ring-opening of optically active β-lactones with stabilized amine anions would afford an asymmetric synthesis of β-amino acids in which the nitrogen function would incorporate an electron-withdrawing protecting group. Based on the HSAB model for nucleophilic β-lactone ring opening, resonance stabilized amide anions were expected to exhibit the correct electronic properties for achieving S_N2 ring opening (Eq. (9)). Thus, carbamate nucleophiles would afford direct access to *N*-protected β-amino acids incorporating ubiquitous *t*-butyloxycarbonyl (Boc) or benzyloxycarbonyl (Cbz) amine protecting groups. Sulfonamide anions were expected to exhibited attenuated basicity relative to the carbamate-derived nucleophiles, thereby offering an alternative for identifying amide anions possessing the correct electronic properties ('softness') to elicit S_N2 β-lactone ring opening.



(9)

Recognizing the utility of *N*-Boc and *N*-Cbz functionalities in peptide synthesis, preliminary investigations of carbamate anion-mediated β-lactone ring openings utilized nucleophles derived from *t*-butyl- or benzyl carbamate. However, reacting lactone **1b** with a variety of carbamate salts (M=Li, Na, K, MgBr) afforded imide **13** derived from addition–elimination ring opening as the major product (Eq. (10));[27] only minor amounts of the desired β-amino acid derivative **14** could be isolated using carbamate-based nucleophiles. No salient reaction parameter (solvent, temperature, etc.) could be identified that rendered S_N2 ring opening as the predominant reaction mode for carbamate nucleophiles.



Solvent	13:14
THF	100:0
DMSO	80:20

(10)

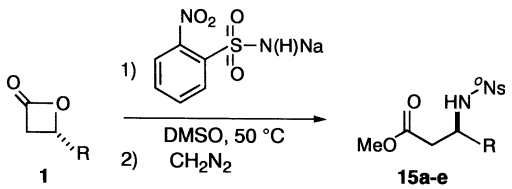
Inadequate attenuation of amide anion basicity by the carboalkoxy function, leading to a harder nitrogen nucleophile, was considered responsible for the predominant carbonyl addition by carbamate nucleophiles. Believing that further attenuation of nitrogen basicity would lead to enhanced selectivity for the S_N2 ring opening mode, the anion derived from *o*-nitrobenzenesulfonamide was next examined as a suitable nucleophile based on the sulfonyl function's ability to stabilize the amide anion. Furthermore, these sulfonamide anions would successfully install the nitrogen functionality in protected form as nosylate (^{o}Ns) groups had previously been developed as nitrogen protecting

Table 2. Sulfonamide anion-mediated β-lactone ring opening

Entry	Lactone **1** (R)	% Yield **15**[a] (configuration)	% ee **15**[b] (% ee lactone **1**)
a	**1a** ($BnOCH_2-$)	64 (*R*-**15a**)	
b	**1b** ($PhCH_2CH_2-$)	72 (*S*-**15b**)	≥95 (97)
c	**1c** (Me_2CHCH_2-)	74 (*S*-**15c**)	93 (95)
d	**1f** ($CH_2CH(CH_2)_8-$)	83 (*S*-**15d**)	
e	**1g** ($^cC_6H_{11}-$)	43 (*R*-**15e**)[c]	≥95 (99)

[a] Reported values are for chromatographically purified materials.
[b] Enantiomer ratios determined by ^1H NMR analysis of corresponding (*S*)-α-methoxyphenylacetamides; see Section 6.
[c] 38% of regioisomer isolated.

groups (Eq. (11)).[28] Thus, reacting the enantiomerically enriched β-lactones **1a–c**,**f**,**g** with the sodium salt of *o*-nitrobenzenesulfonamide in DMSO (50°C) afforded the *N*-protected β-amino acids **15a–e** in good yields (64–83%) accompanied by little (≤10%) to none of the imide product arising from carbonyl addition (Table 2). Steric bulk adjacent to the electrophilic carbon atom, however, alters the regioselectivity of nucleophilic addition to the β-lactones; sulfonamide anion addition to the cyclohexyl-substituted lactone **1g** suffers from significant competition between the S_N2 and carbonyl addition reaction pathways (Table 2, entry e). In this regard, the azide-mediated ring opening reactions that do not exhibit substrate-dependent regioselectivity represent attractive complements to sulfonamide anion addition reactions. Since *o*-nitrobenzenesulfonyl-protected nitrogen functionalities are conveniently unmasked with thiolate ion, this procedure constitutes a convenient two-step synthesis of versatile *N*-protected β-amino acids.



(11)

4. β-Azido acids in peptide synthesis

β-Peptides have emerged recently as important tools for deconvoluting structural imperatives for protein secondary structure and function.[16] The β-peptide materials pioneered by Seebach[29] and Gellman[30] exhibit a considerably greater propensity for adopting well-defined secondary structures than the corresponding materials derived from natural α-amino acids. Moreover, direct biomedical applications of these β-peptidic materials have also been discovered; helical β-peptide oligomers exhibit potent antibacterial activity, reminiscent of the ubiquitous α-peptide antibacterial agents such as cephalosporin.[31,32] However, diversity within these β-peptide materials has been somewhat limited by the availability of the requisite enantioenriched β-amino acid building blocks. The β-azido acids emerging from the AAC-azide ring opening sequence were considered to be ideal building blocks for constructing structurally diverse β-peptide units (Fig. 5). Specifically, β-peptide construction would proceed by formatting a β-azido acid unit as the peptide C terminus using a two step esterification-azide reduction sequence. The active ester coupling partner required for peptide elongation would be derived from a similar β-azido acid; significantly, coupling can be accomplished by direct activation of the carboxylate function as the amine function would already exist in protected form. The resulting azide-terminated peptide chain would then be ready for iterative application of the azide reduction–peptide coupling sequence with the next β-azido acid unit.

Assemblying the enantioenriched β-azido acids into peptide units was initiated by first esterifying the amino acid unit that would become the peptide C terminus, rendering methyl ester **16** as the starting point for peptide elongation (Scheme 1). To format the resulting azido ester **16** for peptide coupling, the azide function was reduced to the corresponding primary amine **17** (H_2, Pd–C). The activated coupling partner required for amide bond construction is available by directly activating β-azido acid **18** as the corresponding β-azido acyl halide **19** (oxalyl chloride, DMF, CH_2Cl_2). Peptide coupling then involved simple acylation of the primary amine **16** with the acid chloride **19** (Et_3N, CH_2Cl_2) to afford the dipeptides **20a–d** (74–83%). Further elongation of the peptide chain could be accomplished by reiteration of the azide reduction–amine acylation sequence (Eq. (12)). Thus, azide reduction of the dipeptide **20a** and acylation with acid chloride **19** (R=CH_2CHMe_2) afforded the tri-β-peptide **21** (74%).

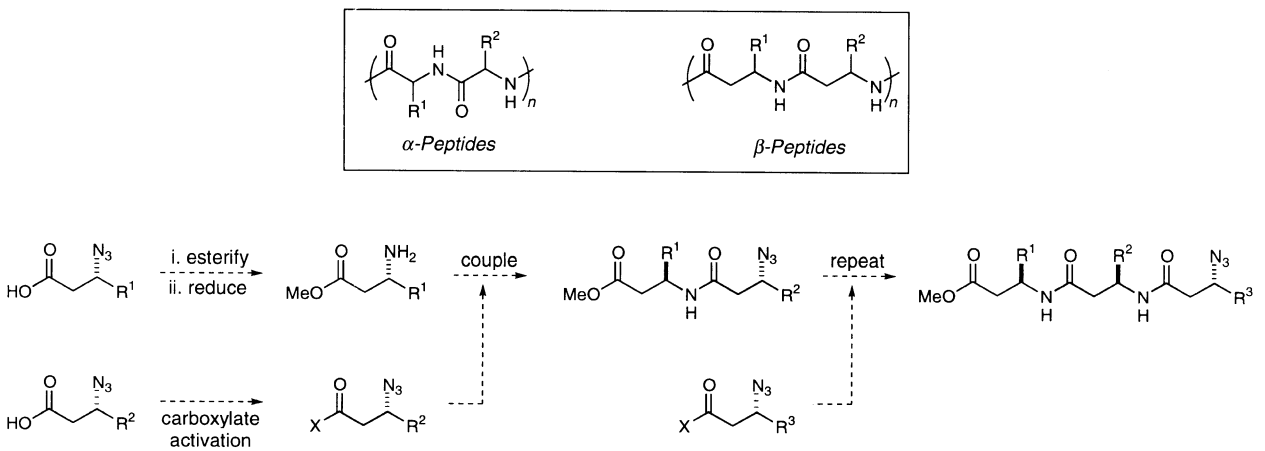
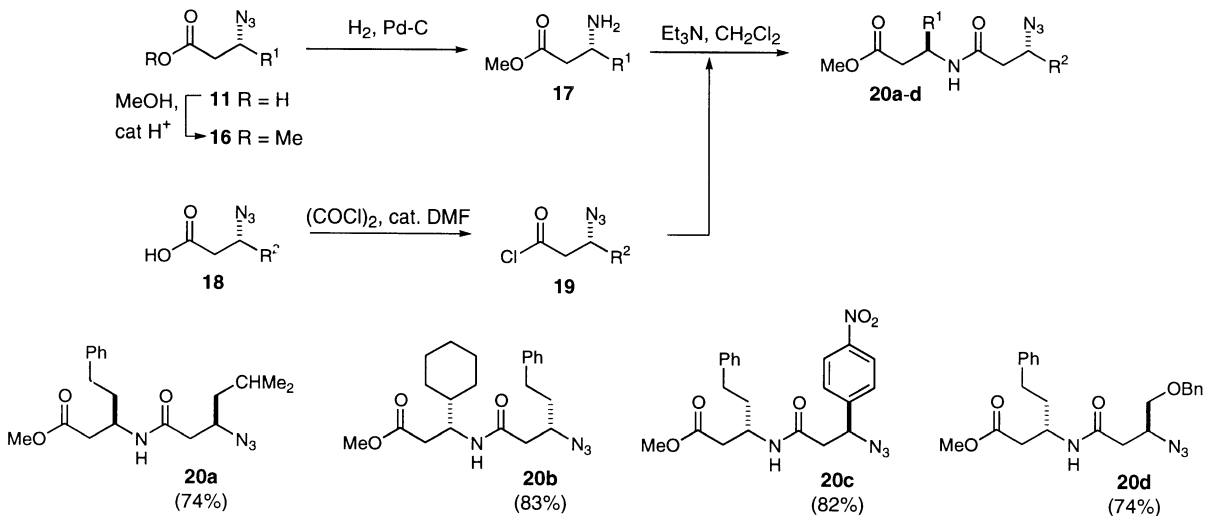
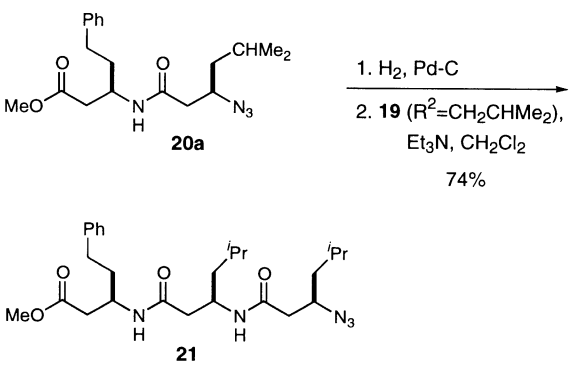


Figure 5. β-Azido acid-based peptide synthesis.



Scheme 1.



(12)

5. Conclusion

Uniting asymmetric AAC reaction methodology with regioselective amine-mediated β-lactone ring opening provides an operationally simple and economical enantioselective synthesis of amide aldol and β-amino acid derivatives. Amine nucleophiles afford addition–elimination lactone ring opening to deliver optically active β-hydroxy amides. Alternatively, azide and sulfonamide anion nucleophiles elicit S_N2 ring opening to deliver enantioenriched β-amino acid derivatives in which the amine function is introduced directly in protected from. The availability of either enantiomer of the cyclocondensation catalyst affords convenient access to β-amino acids in either enantiomeric series. This methodology has been exploited in developing an efficient synthesis of β-peptide fragments based on β-azido acid building blocks.

6. Experimental

6.1. General

Lactones **1a**–**f**, **1h**, **6a**, **6b**,[2a] **1g**,[22a] and **4**[2c] were prepared according to the published procedures. The (*R*,*R*)- and (*S*,*S*)-catalyst complexes (Fig. 2) were prepared according to the published procedure.[2a]

6.1.1. *N*-Methoxy-*N*-methyl-2-(*R*)-methyl-3-(*R*)-hydroxy-5-trimethylsilyl-4-pentynamide (5). To a solution of 180 mg of lactone **4** (1.0 mmol) and 250 μL of diisopropylethylamine (1.5 mmol, 1.5 equiv.) in 2 mL of CH_2Cl_2 was added 150 mg of *N*,*O*-dimethylhydroxyamine·HCl salt (1.5 mmol, 1.5 equiv.) and the reaction was stirred 10 h at ambient temperature. A saturated aqueous solution of NH_4Cl was added and the resulting mixture was extracted with ether (3×15 mL). The combined organic portions were washed with brine and dried ($MgSO_4$). The volatiles were evaporated in vacuo and the crude product mixture was subjected to silica gel chromatography (10% ethyl acetate in hexane) to afford 235 mg of amide **5** (97%) as a colorless oil. $[\alpha]_D=-16$ (*c* 2.8, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ 4.68 (d, *J*=3.0 Hz, 1H), 3.72 (s, 3H), 3.18 (s, 3H), 3.02 (b, 1H), 3.03 (dq, *J*=7.5, 3.0 Hz, 1H), 1.32–1.34 (d, *J*=7.5 Hz, 3H), 0.15 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.6, 104.3, 89.8, 63.8, 61.8, 40.7, 32.0, 11.6, −0.02. IR (NaCl) 3404, 2248, 2175, 1640, 1251, 845 cm^{-1}. MS (EI, 70 eV): *m*/*z* 244 $(M+1)^+$, 228 $(M-Me)^+$, 226 $(M-OH)^+$. HRMS *m*/*z* calcd for $C_{10}H_{18}NO_3Si$ $(M-Me)^+$: 228.1056; found 228.1057.

6.1.2. 4-(*tert*-Butyldiphenylsilanyloxy)-(3*S*)-hydroxy-*N*-methoxy-*N*-methylbutyramide (7b). To a 0°C solution containing 1.36 g of methoxymethylamine hydrochloride (14 mmols) in 30 mL methylene chloride was added 14 mL of dimethylaluminum chloride (14 mmols) as a 1 M solution in hexanes. The solution was allowed to warm to room temperature and stir for 1 h. A 5 mL methylene chloride solution containing 2.39 g of lactone **6b** (7.0 mmol) was transferred via cannula to the amine solution at room temperature. After stirring the reaction mixture for 12 h at room temperature, 42 mL of pH=8 hydrogen phosphate buffer was added to the reaction. The reaction was filtered through a pad of celite to remove the solid aluminum salts. The resulting biphasic solution was separated, and the aqueous layer was washed with methylene chloride (2×10 mL). The combined organics were dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude oil was purified by silica gel chromatography (30:70 EtOAc/hexanes) to provide 2.64 g of amide **7b** (94%) as a white solid. $[\alpha]_{546}^{23}=-16$ (91% ee, *c* 1.1, $CHCl_3$). ^1H NMR

($CDCl_3$) δ 7.72 (dd, *J*=5.0, 1.8 Hz, 4H), 7.44–7.36 (m, 6H), 4.24 (m, 1H), 3.85 (d, *J*=3.2 Hz, 1H), 3.80 (dd, *J*=10.1, 4.7 Hz, 1H), 3.72 (dd, *J*=10.0, 5.0 Hz, 1H), 3.64 (s, 3H), 3.16 (s, 3H), 2.78 (d, *J*=15.6 Hz, 1H), 2.67 (dd, *J*=8.3, 15.2 Hz, 1H), 1.11 (s, 9H). ^{13}C NMR ($CDCl_3$) δ 173.1, 135.4, 133.2, 129.7, 127.7, 68.6, 67.0, 61.1, 53.4, 34.9, 31.7, 26.8, 19.2. IR (NaCl) 3441, 3069, 3046, 2954, 2931, 2891, 2855, 1640, 1465, 1426, 1386, 1184, 1109, 998, 828, 741, 705, 610. EI-MS (70 eV) 344 $(M-{}^tBu)^+$, 266, 241, 223, 199, 181, 163, 153, 135, 123. HRMS *m/z* calcd for $C_{10}H_{18}NO_3Si$ $(M-Me)^+$: 344.1322; found 344.1318.

6.2. General procedure A: S_N2 addition of NaN_3 to β-lactone 1

To a 50°C solution of 72 mg of NaN_3 (2.0 mmols, 2.0 equiv.) in 3.4 mL of anhydrous DMSO (0.3 M in lactone) was added 176 mg of β-lactone **1** (1.0 mmol) via syringe. The resulting homogeneous solution was stirred until all the lactone had been consumed as monitored by TLC (~6 h). After cooling the reaction mixture to ambient temperature, 3 mL of saturated aqueous $NaHCO_3$ was added. The resulting heterogeneous mixture was triturated with water until all the precipitated salts dissolved. The resulting mixture was extracted with ethyl acetate (2×5 mL) and the aqueous layer was separated and acidified with 1 M HCl. The acidic aqueous layer was extracted with ethyl acetate (3×5 mL) and the combined organic portions were washed with water (2×5 mL) and brine (2×5 mL). The organic portion was dried (Na_2SO_4) and evaporated in vacuo to afford the β-azido acid **11**.

6.2.1. (*R*)-3-Azido-4-benzyloxybutanoic acid (11a). General procedure A was followed employing 192 mg of β-lactone **1a** (1.0 mmol). Extractive work-up gave 221 mg (94%) of the title compound. $[\alpha]_D^{25}=+27$ (*c* 5.5, CH_2Cl_2). ^1H NMR ($CDCl_3$, 300 MHz) δ 7.40–7.24 (m, 5H), 4.59 (s, 2H), 4.04 (m, 1H), 3.60 (d, *J*=5.5 Hz, 2H), 2.67 (dd, *J*=16.6, 5.0 Hz, 1H), 2.54 (dd, *J*=16.6, 8.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 176.8, 137.7, 128.7 (2C), 128.1, 127.8 (2C), 73.5, 71.8, 57.7, 36.1. IR (NaCl) 3089, 3065, 3034, 2927, 2863, 2673, 2127, 2095, 1711, 1414, 1267, 1093, 741, 701 cm^{-1}. MS (EI, 70 eV): *m/z* 207 $(M-N_2)^+$, 130, 91. MS (FAB, Na-ethylene glycol): *m/z* 258 $(M+Na)^+$. Conversion of **11a** to the corresponding methyl ester (CH_2N_2, Et_2O) and separation of the enantiomers by chiral HPLC (Diacel Chiracel™ OD-H column, flow rate 1.0 mL/min, 10% *i*-PrOH, 90% hexane, T_r 7.51 (*R*) and 8.35 (*S*) min) provided the enantiomer ratio: 4(*R*)/4(*S*)=96:4 (92%ee).

6.2.2. (*S*)-3-Azido-5-phenylpentanoic acid (11b). General procedure A was followed employing 176 mg of β-lactone **1b** (1.0 mmol). Extractive work-up gave 208 mg (95%) of the title compound. $[\alpha]_D^{25}=-3.0$ (*c* 3.9, CH_2Cl_2). ^1H NMR ($CDCl_3$, 300 MHz) δ 7.35–7.29 (m, 2H), 7.25–7.20 (m, 3H), 3.81 (m, 1H), 2.84 (m, 1H), 2.72 (m, 1H), 2.60 (d, *J*=6.7 Hz, 1H), 1.89 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 177.1, 140.4, 128.5 (2C), 128.3 (2C), 126.2, 58.0, 39.3, 36.0, 32.0. IR (NaCl) 3084, 3059, 3029, 2929, 2855, 2661, 2128, 2098, 1710, 1431, 1257, 749, 699 cm^{-1}. MS (FAB, Na-ethylene glycol): *m/z* 242 $(M+Na)^+$. Anal. calcd for $C_{11}H_{13}N_3O_2$: C, 60.26; H, 5.98; found: C, 60.35; H, 5.99. Conversion of **11b** to the corresponding methyl ester (CH_2N_2, Et_2O) and separation of the enantiomers by chiral HPLC (Diacel Chiracel™ OD-H column, flow rate 1.0 mL/min, 10% *i*-PrOH, 90% hexane, T_r 7.05 (*S*) and 8.44 (*R*) min) provided the enantiomer ratio: 4(*S*)/4(*R*)=96.5:3.5 (93%ee).

6.2.3. (*S*)-3-Azido-5-methylhexanoic acid (11c). General procedure A was followed employing 100 mg of β-lactone **1c** (0.78 mmol). Extractive work-up gave 126 mg (95%) of the title compound. $[\alpha]_D^{25}=+4.2$ (*c* 4.8, CH_2Cl_2). ^1H NMR ($CDCl_3$, 300 MHz) δ 3.86 (m, 1H), 2.56 (d, *J*=7.0 Hz, 2H), 1.81 (m, 1H), 1.55 (ddd, *J*=14.1, 9.5, 5.4 Hz, 1H), 1.33 (ddd, *J*=13.7, 8.7, 4.8 Hz, 1H), 0.98 (d, *J*=6.6 Hz, 3H), 0.97 (d, *J*=6.7 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 177.2, 57.0, 43.3, 40.0, 25.0, 23.0, 21.8; IR (NaCl) 3029, 2954, 2925, 2880, 2870, 2666, 2108, 1710, 1431, 1262 cm^{-1}. MS (CI, methane): *m/z* 172 $(M+H)^+$. HRMS *m/z* cacld for $C_6H_{10}N_1O_2$ $(M-CH_3, N_2)$: 128.0711; found: 128.0713. Conversion of **11c** to the corresponding benzyl ester (BnOH, DCC, DMAP, CH_2Cl_2) and separation of the enantiomers by chiral HPLC (Diacel Chiracel™ OD-H column, flow rate 1.0 mL/min, 3% *i*-PrOH, 97% hexane, T_r 5.45 (*R*) and 5.99 (*S*) min) provided the enantiomer ratio: 4(*S*)/4(*R*)=98.5:1.5 (97%ee).

6.2.4. (*S*)-3-Azidohexanoic acid (11d). General procedure A was followed employing 250 mg of β-lactone **1d** (2.19 mmol). Extractive work-up gave 269 mg (78%) of the title compound. $[\alpha]_D^{25}=+21$ (*c* 4.3, CH_2Cl_2). ^1H NMR ($CDCl_3$, 300 MHz) δ 8.80 (br s, 1H), 3.82 (m, 1H), 2.59 (dd, *J*=16.7, 5.9 Hz, 1H), 2.53 (dd, *J*=16.4, 8.1 Hz, 1H), 1.65–1.37 (m, 4H), 0.98 (t, *J*=7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 177.4, 58.5, 39.2, 36.3, 19.0, 13.5. IR (NaCl) 3049, 2962, 2935, 2875, 2665, 2123, 1715, 1434, 1263 cm^{-1}. MS (CI, isobutane): *m/z* 158 $(M+H)^+$. Anal. calcd for $C_6H_{11}N_3O_2$: C, 45.85; H, 7.05; found: C, 46.19; H, 7.11.

6.2.5. (*S*)-3-Azidoheptanoic acid (11e). General procedure A was followed employing 350 mg of β-lactone **1e** (2.73 mmol). Extractive work-up gave 387 mg (83%) of the title compound. $[\alpha]_D^{25}=+20$ (*c* 4.6, CH_2Cl_2). ^1H NMR ($CDCl_3$, 300 MHz) δ 9.10 (br s, 1H), 3.80 (m, 1H), 2.59 (dd, *J*=16.3, 5.5 Hz, 1H), 2.53 (dd, *J*=16.4, 7.9 Hz, 1H), 1.57 (m, 2H), 1.49–1.30 (m, 4H), 0.94 (t, *J*=7.0 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 177.4, 58.7, 39.3, 33.9, 27.9, 22.2, 13.8. IR (NaCl) 3041, 2958, 2935, 2863, 2669, 2127, 2103, 1715, 1434, 1255 cm^{-1}. MS (CI, isobutane): *m/z* 172 $(M+H)^+$. HRMS *m/z* cacld for $C_6H_{10}N_1O_2$ $(M-CH_3, N_2)^+$: 128.0711; found: 128.0716.

6.2.6. (*S*)-3-Azido-12-tridecenoic acid (11f). General procedure A was followed employing 50 mg of β-lactone **1f** (0.24 mmol). Extractive work-up gave 52 mg (87%) of the title compound. $[\alpha]_D^{25}=+15$ (*c* 4.1, CH_2Cl_2). ^1H NMR ($CDCl_3$, 300 MHz) δ 10.60 (br s, 1H), 5.82 (dddd, *J*=17.0, 10.2, 6.6, 6.6 Hz, 1H), 5.00 (ddd, *J*=17.0, 3.3, 1.6 Hz, 1H), 4.94 (ddd, *J*=8.9, 2.1, 1.0 Hz, 1H), 3.80 (m, 1H), 2.58 (dd, *J*=16.7, 5.8 Hz, 1H), 2.52 (dd, *J*=16.4, 8.1 Hz, 1H), 2.05 (dt, *J*=8.2, 6.8 Hz, 2H), 1.57 (m, 2H), 1.48–1.25 (m, 12H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 177.2, 139.2, 114.2, 58.9, 39.4, 34.4, 33.8, 29.4 (2C), 29.2, 29.1, 28.9, 25.9. IR (NaCl) 3074, 2925, 2855, 2666, 2103, 1715, 1426, 1262, 908 cm^{-1}.

MS (CI, methane): *m/z* 254 $(M+H)^+$. Anal. calcd for $C_{13}H_{23}N_3O_2$: C, 61.63; H, 9.15; found: C, 62.12; H, 9.30.

6.2.7. (*R*)-3-Azido-3-cyclohexylpropanoic acid (11g). General procedure A was followed employing 200 mg of β-lactone **1g** (1.30 mmol). Extractive work-up gave 238 mg (93%) of the title compound. $[\alpha]_D^{25}=+44$ (*c* 4.9, CH_2Cl_2). ^1H NMR ($CDCl_3$, 300 MHz) δ 10.08 (br s, 1H), 3.65 (m, 1H), 2.58 (dd, *J*=16.3, 3.8 Hz, 1H), 2.45 (dd, *J*=16.4, 9.8 Hz, 1H), 1.79–1.67 (m, 4H), 1.48 (m, 1H), 1.29–1.00 (m, 6H, Cyclohexyl). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 176.0, 64.2, 42.0, 39.4, 36.7, 29.4, 28.2, 26.0, 25.8. IR (NaCl) 3007, 2929, 2853, 2617, 2121, 2085, 1716, 1450, 1271, 999 cm^{-1}. MS (CI, isobutane): *m/z* 198 $(M+H)^+$. HRMS calcd for $C_9H_{15}N_1O_2$ $(M-N_2)^+$: 169.1103; found: 169.1107.

6.2.8. (*S*)-3-Azido-3-(4-nitrophenyl)propanoic acid (11h). General procedure A was followed employing 153 mg of β-lactone **1h** (0.79 mmol). Extractive work-up gave 155 mg (83%) of the title compound. $[\alpha]_D=-139$ (*c* 1.5, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ 8.28 (dt, *J*=1.9, 8.8 Hz, 2H), 7.56 (dt, *J*=2.0, 8.8 Hz, 2H), 5.11 (dd, *J*=5.5, 8.8 Hz, 1H), 2.9 (dd, *J*=8.7, 16.7 Hz, 1H), 2.78 (dd, *J*=5.6, 16.7 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.7, 147.9, 145.2, 127.7, 124.2, 60.9, 40.9. HRMS *m/z* calcd for $C_9H_8N_2O_4$ $(M-N_2)^+$: 208.484; found: 208.490.

6.2.9. Stereochemical proofs for β-azido acids. The absolute configuration of β-azido acids **11b–d** was established by conversion to the corresponding *N*-Boc amino esters **12b–d** ((i) CH_2N_2; (ii) H_2, Boc_2O, Pd–C) and correlation of their optical rotation to those of authentic samples of known configuration: **12b** $[\alpha]_D^{25}=-5.8$ (*c* 1.8, $CHCl_3$) [lit. $[\alpha]_D^{25}=+7.2$ (*R*) (*c* 1.8, $CHCl_3$)];[24a] **12c** $[\alpha]_D^{25}=-25.8$ (*c* 1.47, CH_3OH) [lit. $[\alpha]_D^{25}=-22.8$ (*c* 1.47, CH_3OH)];[24b] **12d** $[\alpha]_D^{25}=-21$ (*c* 1.9, $CHCl_3$) [lit. $[\alpha]_D^{25}=+20.9$ (*R*) (*c* 1.9, $CHCl_3$)].[24a] The configuration of azido acid **11e** was established similarly by conversion to the corresponding *N*-Boc amino acid **12e** ((i) H_2, Pd–C; (ii) Boc_2O, Et_3N): $[\alpha]_D^{25}=-1.0$ (*c* 0.5, DMF) [lit. $[\alpha]_D^{25}=-1.2$ (*c* 0.5, DMF)].[24c] The configuration of the remaining β-azido acids (**11a**,**f**,**g**) was assigned by analogy to these determinations.

6.3. General procedure B: S_N2 addition of *o*-nitrobenzenesulfonamide, mono sodium salt to β-lactone 1

To a 50°C suspension of 700 mg of *o*-nitrobenzenesulfonamide, mono sodium salt (3.13 mmols, 2.0 equiv.) and 200 mg of activated powdered 4 Å molecular seives in 5.2 mL of anhydrous DMSO (0.3 M in lactone) was added 200 mg of β-lactone **1** (1.56 mmols) via syringe. The resulting suspension was stirred until all the lactone had been consumed as monitored by TLC (~5 h). After cooling the reaction mixture to ambient temperature, 5 mL of 1 M aqueous HCl was added and the resulting mixture was extracted with ethyl acetate (3×5 mL). The combined organic extracts were washed with water (2×5 mL) and brine (2×5 mL). The organic layer was separated, dried (Na_2SO_4), and concentrated in vacuo to afford a yellow solid. The solid was triturated with chloroform and the insoluble material (*o*-nitrobenzenesulfonamide) removed by filtration. The filtrate was concentrated in vacuo to afford the crude β-sulfonamido acid. The crude acid was dissolved in ethyl acetate and an ethereal solution of CH_2N_2 was added until a yellow color persisted. Glacial acetic acid was added to decolorize the reaction mixture and the volatiles were evaporated in vacuo to afford the β-sulfonamido ester **15** as a yellow oil that was purified by silica gel chromatography (hexanes/ethyl acetate).

6.3.1. (*S*)-4-Benzyloxy-3-(*o*-nitrobenzenesulfonamido)-butanoic acid, methy ester (15a). General procedure B was followed employing 200 mg of β-lactone **1a** (1.04 mmol). Extractive work-up gave 272 mg (64%) of the title compound. $[\alpha]_D^{25}=+72$ (*c* 4.5, $CHCl_3$). ^1H NMR ($CDCl_3$, 300 MHz) δ 8.13 (m, 1H), 7.79 (m, 1H), 7.67 (m, 2H), 7.34–7.28 (m, 3H), 7.16 (m, 2H), 6.10 (d, *J*=8.0 Hz, 1H), 4.33 (s, 2H), 4.02 (m, 1H), 3.60 (s, 3H), 3.50 (dd, *J*=9.8, 5.4 Hz, 1H), 3.42 (dd, *J*=9.5, 5.0 Hz, 1H), 2.71 (dd, *J*=16.4, 5.6 Hz, 1H), 2.64 (dd, *J*=16.5, 6.6 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.0, 147.4, 137.1, 134.4, 133.3, 132.7, 130.5, 128.2 (2C), 127.7 (2C), 127.6, 125.2, 73.0, 70.7, 51.7, 51.2, 36.6. IR (NaCl) 3335, 3089, 3061, 3030, 2950, 2867, 1735, 1541, 1366, 1164, 1121, 851, 784, 741, 697, 653 cm^{-1}. MS (EI, 70 eV): *m/z* 287 $(M-CH_2OBn)^+$, 222 $[M-SO_2(C_6H_4NO_2)]^+$. HRMS *m/z* calcd for $C_{10}H_{11}N_2O_6S$ $[M-CH_2OBn]^+$: 287.0338; found: 287.0331.

6.3.2. (*S*)-3-(*o*-Nitrobenzenesulfonamido)-5-phenylpentanoic acid, methy ester (15b). General procedure B was followed employing 200 mg of β-lactone **1b** (1.14 mmol). Extractive work-up gave 322 mg (72%) of the title compound. $[\alpha]_D^{25}=-4.6$ (*c* 8.2, $CHCl_3$). ^1H NMR ($CDCl_3$, 300 MHz) δ 8.11 (m, 1H), 7.88 (m, 1H), 7.74 (m, 2H), 7.29–7.11 (m, 3H), 7.08 (m, 2H), 5.93 (d, *J*=8.6 Hz, 1H), 3.85 (m, 1H), 3.61 (s, 3H), 2.73–2.47 (m, 2H), 2.57 (dd, *J*=16.3, 5.0 Hz, 1H), 2.51 (dd, *J*=16.3, 5.5 Hz, 1H), 1.94–1.85 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.0, 147.4, 140.5, 134.4, 133.5, 132.8, 130.3, 128.2 (2C), 128.1 (2C), 125.9, 125.0, 51.6, 51.2, 38.9, 36.2, 31.7. IR (NaCl) 3335, 3089, 3061, 3026, 2946, 2859, 1727, 1541, 1358, 1168, 848, 784, 741, 695, 653 cm^{-1}. MS (EI, 70 eV): *m/z* 287 $(M-CH_2Bn)^+$, 206 $[M-SO_2(C_6H_4NO_2)]^+$. Anal. calcd for $C_{18}H_{20}N_2O_6S$: C, 55.09; H, 5.14; found: C, 55.07; H, 5.34. The enantiomeric purity of the β-sufonamido ester **15b** was determined by the integration of the methyl ester portion (CO_2Me) of the crude (*S*)-α-methoxyphenylacetamides which provided the diastereomer ratio: 3(*S*)/3(*R*)>96.5:3.5. (93% de). ^1H NMR ($CDCl_3$, 500 MHz) [$-CO_2Me$] δ 3.70 (major), 3.59 (minor). The diastereomeric (*S*)-α-methoxyphenylacetamides were prepared from **15b** by sulfonamide deprotection (PhSH, K_2CO_3, DMF) followed by coupling the derived β-amino ester with (*S*)-α-methoxyphenylacetic acid (DCC, 5 mol% DMAP).

6.3.3. (*S*)-5-Methyl-3-(*o*-nitrobenzenesulfonamido)hexanoic acid, methy ester (15c). General procedure B was followed employing 200 mg of β-lactone **1c** (1.56 mmol). Extractive work-up gave 381 mg (74%) of the title compound. $[\alpha]_D^{25}=-15$ (*c* 8.4, $CHCl_3$). ^1H NMR ($CDCl_3$, 300 MHz) δ 8.18 (m, 1H), 7.89 (m, 1H), 7.75 (m, 2H), 5.78 (d, *J*=8.4 Hz, 1H), 3.89 (m, 1H), 3.62 (s, 3H), 2.55 (dd,

J=16.2, 4.9 Hz, 1H), 2.48 (dd, J=16.2, 5.6 Hz, 1H), 1.58 (m, 1H), 1.50 (m, 1H), 1.30 (m, 1H), 0.85 (d, J=6.5 Hz, 3H), 0.77 (d, J=6.4 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.2, 147.5, 134.7, 133.5, 132.9, 130.3, 125.2, 51.6, 49.9, 43.8, 39.4, 24.3, 22.6, 21.4. IR (NaCl) 3331, 3093, 2958, 2867, 1735, 1537, 1362, 1160, 851, 780, 741, 653 cm^{-1}. MS (EI, 70 eV): m/z 344 (M)$^+$, 287 (M$-CH_2CHMe_2$)$^+$, 186 [$SO_2(C_6H_4NO_2)$]$^+$. HRMS m/z calcd for $C_{14}H_{20}N_2O_6S$ (M$-CH_2OBn$)$^+$: 344.1042; found: 344.1037. The enantiomeric purity of the β-sufonamido ester **15c** was determined by the integration of the methyl ester portion (CO_2Me) of the crude (*S*)-α-methoxyphenylacetamides which provided the diastereomer ratio: 3(*S*)/3(*R*)>97.5:2.5. (95% de). ^{1}H NMR ($CDCl_3$, 500 MHz) [$-CO_2Me$] δ 3.70 (major), 3.57 (minor). The diastereomeric (*S*)-α-methoxyphenylacetamides were prepared from **15c** by sulfonamide deprotection (PhSH, K_2CO_3, DMF) followed by coupling the derived β-amino ester with (*S*)-α-methoxyphenylacetic acid (DCC, 5 mol% DMAP).

6.3.4. (*S*)-3-(*o*-Nitrobenzenesulfonamido)-12-tridecenoic acid, methy ester (15d). General procedure B was followed employing 200 mg of β-lactone **1f** (0.95 mmol). Extractive work-up gave 337 mg (83%) of the title compound. $[\alpha]_D^{25}$=+4.4 (*c* 3.9, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.17 (m, 1H), 7.88 (m, 1H), 7.75 (m, 2H), 5.81 (dddd, J=16.9, 10.3, 6.7, 6.7 Hz, 1H), 5.78 (d, J=8.2 Hz, 1H), 5.00 (m, 1H,), 4.94 (m, 1H), 3.80 (m, 1H), 3.61 (s, 3H), 2.57 (dd, J=16.2, 5.2 Hz, 1H), 2.49 (dd, J=16.3, 6.1 Hz, 1H), 2.03 (m, 2H), 1.54 (m, 2H), 1.37–1.15 (m, 12H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.2, 147.5, 138.9, 134.7, 133.4, 132.8, 130.3, 125.1, 114.0, 51.7, 51.6, 39.2, 34.6, 33.8, 29.1 (2C), 28.8, 28.7, 28.6, 25.5. IR (NaCl) 3331, 3073, 2927, 2855, 1735, 1541, 1358, 1168, 784, 741 cm^{-1}. MS (EI, 70 eV): m/z 353 (M$-MeO_2CCH_2$)$^+$, 287 (M$-(CH_2)_8$-$CHCH_2$)$^+$, 186 [$SO_2(C_6H_4NO_2)$]$^+$. HRMS m/z cacld for $C_{10}H_{11}N_2O_6S$ (M$-(CH_2)_8CHCH_2$)$^+$: 287.0338; found: 287.0330.

6.3.5. (*R*)-3-Cyclohexyl-3-(*o*-nitrobenzenesulfonamido)-propionic acid, methy ester (15e). General procedure B was followed employing 308 mg of β-lactone **1g** (2.0 mmol). Extractive work-up gave 309 mg (43%) of the title compound. $[\alpha]_D^{25}$=−33 (*c* 1.9, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.15 (m, 1H), 7.87 (m, 1H), 7.74 (m, 2H), 5.77 (d, J=8.8 Hz, 1H), 3.66 (m, 1H), 3.56 (s, 3H), 2.54 (dd, J=16.2, 6.0 Hz, 1H), 2.54 (dd, J=16.1, 5.4 Hz, 1H), 1.84–1.48 (m, 6H), 1.27–1.03 (m, 3H), 0.99–0.84 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.5, 147.5, 134.9, 133.3, 132.8, 130.4, 125.1, 60.3, 56.6, 51.7, 41.4, 36.6, 29.2, 28.8, 25.9, 25.8. IR (NaCl) 3331, 3097, 2927, 2852, 1731, 1541, 1442, 1358, 1164, 852, 784, 733, 657 cm^{-1}. MS (EI, 70 eV): m/z 297 (M$-MeO_2CCH_2$)$^+$, 287 (M$-C_6H_{11}$)$^+$, 186 [$SO_2(C_6H_4NO_2)$]$^+$. HRMS m/z cacld for $C_{10}H_{11}N_2O_6S$ (M$-C_6H_{11}$): 287.0338; found: 287.0326. Anal. calcd for $C_{16}H_{22}N_2O_6S$: C, 51.88; H, 5.99; found: C, 51.86; H, 6.05. The enantiomeric purity of the β-sulfonamido ester **15e** was determined by the integration of the methyl ester portion (CO_2Me) of the crude (*S*)-α-methoxyphenylacetamides which provided the diastereomer ratio: 3(*R*)/3(*S*)>98:2 (>95% de). ^{1}H NMR ($CDCl_3$, 500 MHz) [$-CO_2Me$] δ 3.70 (major), 3.52 (minor). The diastereomeric (*S*)-α-methoxyphenylacetamides were prepared from **15e** by sulfonamide deprotection (PhSH, K_2CO_3, DMF) followed by coupling the derived β-amino ester with (*S*)-α-methoxyphenylacetic acid (DCC, 5 mol% DMAP).

6.3.6. Stereochemical proofs for β-sulfonamido acids. The absolute configuration of β-sulfonamido acids **15b** and **15c** was established by conversion to the corresponding *N*-Boc amino methyl esters **12b** and **12c** ((i) CH_2N_2; (ii) PhSH, K_2CO_3, DMF; (iii) Boc_2O, Et_3N), respectively, and correlation of their optical rotation to those of authentic samples of known configuration: **12b** $[\alpha]_D^{25}$=−6.4 (*c* 1.8, $CHCl_3$) [lit. $[\alpha]_D^{25}$=+7.2 (*R*) (*c* 1.8, $CHCl_3$)];[24a] **12c** $[\alpha]_D^{25}$=−28.7 (*c* 1.47, CH_3OH) [lit. $[\alpha]_D^{25}$=−22.8 (*c* 1.47, CH_3OH)];[24b] The configuration of the remaining β-sulfonamido acids (**15a**,**d**,**e**) was assigned by analogy to these determinations.

6.4. General procedure C: β-peptide coupling reactions

To 0.2 M solution of azido acid **11** (4.9 mmol) in CH_2Cl_2 was added oxalyl chloride (1.2 equiv., 5.9 mmol) and DMF (0.03 equiv., 0.15 mmol). The resulting solution was stirred 2 h at ambient temperature whereupon the volatile reaction components were evaporated in vacuo to afford the acid chloride **17** as a yellow oil.

In a separate flask, a suspension of 10% Pd–C (0.49 mmol) and ethyl acetate (0.3 M in **16**) was stirred under hydrogen gas (1 atm via balloon) for 1 h. A 1.2 M solution of azido ester **16** (4.9 mmol) in ethyl acetate was then added and the reaction stirred 2 h under 1 atm of H_2. The reaction mixture was filtered through celite and the filtrate was evaporated to afford the amino ester **17** as a yellow oil. This oil was dissolved into CH_2Cl_2 (14 mL) containing diisopropylethylamine (1.2 equiv., 5.9 mmol) and a 1 M CH_2Cl_2 solution of the acid chloride (prepared above) was added and the resulting solution was stirred 15 min at ambient temperature. The reaction was quenched by adding 1N aqueous $NaHCO_3$ and the resulting mixture was extracted with diethyl ether (2×). The combined organic portions were washed with brine and dried ($MgSO_4$), and the crude product mixture was purified by silica gel chromatography (hexanes/ethyl acetate) to provide the coupling product.

6.4.1. (3*R*)-3-((3*R*)-3-Azido-5-methylhexanoylamino)-5-phenylpentanoic acid, methyl ester (20a). General procedure C was followed using 861 mg of azido acid *ent*-**11c** (5.0 mmol) and 1.173 g of azido ester *ent*-**16b** (from *ent*-**11b**, 5.0 mmol) to afford 1.341 g of dipeptide **20a** (74%) as a colorless oil. $[\alpha]_D$=+16 (*c* 2.7, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44–7.39 (m, 2H), 7.34–7.29 (m, 3H), 6.48 (d, J=9.0, 1H), 4.52–4.41 (m, 1H), 4.10–4.01 (m, 1H), 3.81 (s, 3H), 2.85–2.76 (m, 2H), 2.71 (t, J=5.2 Hz, 2H), 2.50 (dd, J=4.6, 11.5 Hz, 1H), 2.40 (dd, J=8.7, 14.6 Hz, 1H), 2.06–1.88 (m, 3H), 1.69–1.61 (m, 1H), 1.49–1.37 (m, 1H), 1.10 (d, J=3.5 Hz, 3H), 1.08 (d, J=3.6 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.5, 169.6, 141.5, 128.8, 128.6, 126.4, 58.3, 53.7, 52.0, 46.3, 43.8, 42.6, 38.5, 35.9, 33.0, 32.0, 25.3, 23.3, 22.1. IR (NaCl) 3291, 2951, 2107, 1747, 1644, 1549, 1259, 1200, 697 cm^{-1}. HRMS calcd for $C_{19}H_{28}N_4O_3$: 360.2161; found 360.2150.

6.4.2. (3*R*)-3-((3*S*)-3-Azido-5-phenylpentanoylamino)-3-cyclohexylpropionic acid, methyl ester (20b). General procedure C was followed using 1.1 g of azido acid **11b** (4.9 mmol) and 1.0 g of azido ester **16g** (from **11g**, 4.9 mmol) to afford 1.6 g of dipeptide **20a** (83%) as a colorless solid. $[\alpha]_D=-27$ (*c* 1.8, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ 7.38–7.26 (m, 5H), 6.33 (d, *J*=9.4 Hz, 1H), 4.20–4.11 (m, 1H), 4.01–3.93 (m, 1H), 3.77 (s, 3H), 2.94–2.39 (m, 6H), 2.00–1.56 (m, 8H), 1.34–0.98 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.5, 168.9, 140.7, 128.5, 128.3, 126.1, 59.2, 51.7, 50.6, 42.0, 40.7, 36.3, 35.8, 32.2, 29.6, 29.2, 26.1, 25.8. HRMS calcd for $C_{21}H_{30}N_4O_3$: 386.2318; found 386.2327.

6.4.3. (3*S*)-3-[(3*S*)-3-Azido-3-(4-nitrophenyl)propionylamino]-5-phenylpentanoic acid, methyl ester (20c). General procedure C was followed using 153 mg of azido acid **11h** (0.65 mmol) and 151 mg of azido ester **16b** (from **11b**, 0.65 mmol) to afford 226 mg of dipeptide **20c** (82%) as a colorless solid. $[\alpha]_D=-95$ (*c* 3.0, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ 8.28 (d, *J*=8.7 Hz, 2H), 7.60 (d, *J*=8.7 Hz, 2H), 7.37–7.32 (m, 2H), 7.27–7.23 (m, 3H), 6.54 (d, *J*=9.0 Hz, 1H), 5.29 (dd, *J*=5.5, 8.6 Hz, 1H), 4.37 (m, 1H), 3.69 (s, 3H), 2.78–2.55 (m, 6H), 2.00–1.89 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.9, 167.8, 147.5, 146.1, 140.9, 128.3, 128.1, 127.5, 125.9, 123.9, 61.5, 51.5, 45.9, 43.4, 38.0, 35.4, 32.3. HRMS calcd for $C_{21}H_{23}N_5O_5$: 425.1699; found: 425.1704.

6.4.4. (3*S*)-3-((3*S*)-3-Azido-4-benzyloxybutyrylamino)-5-phenylpentanoic acid, methyl ester (20d). General procedure C was followed using 282 mg of azido acid *ent*-**11a** (1.3 mmol) and 303 mg of azido ester **16b** (from **11b**, 1.3 mmol) to afford 410 mg of dipeptide **20d** (74%) as a colorless oil after column chromatography. $[\alpha]_D=-9.1$ (*c* 2.2, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ 7.43–7.27 (m, 9H), 6.33 (d, *J*=8.9 Hz, 1H), 4.66 (s, 2H), 4.42–4.38 (m, 1H), 4.19–4.14 (m, 1H), 3.76 (s, 3H), 3.73–3.62 (m, 2H), 2.81–2.68 (m, 2H), 2.63 (t, *J*=4.2 Hz, 2H), 2.50 (dd, *J*=4.9, 18.2 Hz, 1H), 2.38 (dd, *J*=8.6, 14.7 Hz, 1H), 2.07–1.85 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.3, 169.0, 141.3, 137.7, 128.6, 128.5, 128.0, 127.7, 126.2, 73.5, 72.1, 58.4, 51.9, 46.1, 38.5, 38.4, 35.9, 32.7. IR (thin film) 3299, 3063, 2950, 2861, 2127, 1736, 1549, 1496, 1268, 1202, 750, 699 cm^{-1}. HRMS calcd for $C_{23}H_{28}N_4O_4$: 424.2111; found: 424.2121.

6.4.5. (3*R*)-3-[(3*R*)-3-((3*R*)-3-Azido-5-methylhexanoylamino)-5-methylhexanoylamino]-5-phenyl-pentanoic acid, methyl ester (21). General procedure C was followed using 494 mg of azido acid *ent*-**11c** (2.9 mmol) and 1.04 g of dipeptide **20a** (2.9 mmol) to afford 1.1 g of tripeptide **21** (74%) as a colorless solid after column chromatography. $[\alpha]_D=+33$ (*c* 2.4, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ 7.38–7.22 (m, 5H), 7.02 (d, *J*=8.9 Hz, 1H), 6.38 (d, *J*=9.0 Hz, 1H), 4.41–4.35 (m, 2H), 4.11–4.08 (m, 1H), 3.76 (s, 3H), 2.77–2.35 (m, 8H), 1.95–1.70 (m, 4H), 1.62–1.53 (m, 2H), 1.44–1.35 (m, 2H); 1.03–0.98 (m, 12H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.2, 171.0, 169.3, 141.2, 128.6, 128.4, 126.2, 58.03, 51.9, 46.2, 44.9, 43.6, 43.0, 42.5, 40.3, 38.6, 35.7, 32.7, 25.3, 25.1, 23.2, 22.9, 22.3, 21.9. HRMS calcd for $C_{26}H_{41}N_5O_4$: 487.3159; found: 487.3168.

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References

1. Pommier, A.; Pons, J.-M. *Synthesis* **1993**, 441.
2. For a discussion of β-lactones as surrogates for prototypical aldol adducts, see: (a) Nelson, S. G.; Peelen, T. J.; Wan, Z. *J. Am. Chem. Soc.* **1999**, *121*, 9742. (b) Nelson, S. G.; Wan, Z.; Peelen, T. J.; Spencer, K. L. *Tetrahedron Lett.* **1999**, *40*, 6535–6540. (c) Nelson, S. G.; Wan, Z. *Org. Lett.* **2000**, *2*, 1883.
3. The S_N2 ring opening pathway provides entry to a variety of versatile synthesis building blocks including β-amino acids and β-thiocarboxylic acids. Nitrogen nucleophiles: (a) Arnold, L. D.; Kalantar, T. H.; Vederas, J. C. *J. Am. Chem. Soc.* **1985**, *107*, 7105. (b) Griesbeck, A.; Seebach, D. *Helv. Chim. Acta* **1987**, *70*, 1326. (c) Arnold, L. D.; May, R. G.; Vederas, J. C. *J. Am. Chem. Soc.* **1988**, *110*, 2237. (d) Castagnani, R.; De Angelis, F.; De Fusco, E.; Giannessi, F.; Misiti, D.; Meloni, D.; Tinti, M. O. *J. Org. Chem.* **1995**, *60*, 8318. (e) Bernabei, I.; Castagnani, R.; De Angelis, F.; De Fusco, E.; Giannessi, F.; Misiti, D.; Muck, S.; Scafetta, N.; Tinti, M. O. *Chem. Eur. J.* **1996**, *2*, 826. Sulfur nucleophiles: (f) Griesbeck, A.; Seebach, D. *Helv. Chim. Acta* **1987**, *70*, 1326. (g) Tempkin, O.; Blacklock, T. J.; Burke, J. A.; Anastasia, M. *Tetrahedron: Asymmetry* **1996**, *7*, 2721.
4. For the ring opening of β-lactones with carbon nucleophiles, see: (a) Sato, T.; Kawara, T.; Kawashima, M.; Fujisawa, T. *Chem. Lett.* **1980**, 571. (b) Sato, T.; Kawara, T.; Nishizawa, A.; Fujisawa, T. *Tetrahedron Lett.* **1980**, *21*, 3377. (c) Fujisawa, T.; Sato, T.; Kawara, T.; Ohashi, K. *Tetrahedron Lett.* **1981**, *22*, 4823. (d) Sato, T.; Naruse, K.; Fujisawa, T. *Tetrahedron Lett.* **1982**, *23*, 3587. (e) Sato, T.; Itoh, T.; Hattori, C.; Fujisawa, T. *Chem. Lett.* **1983**, 1391. (f) Kawashima, M.; Sato, T.; Fujisawa, T. *Tetrahedron* **1989**, *45*, 403.
5. For a preliminary account of this work, see: Nelson, S. G.; Spencer, K. L. *Angew. Chem., Int. Ed. Engl.* **2000**, *39*, 1323.
6. For reviews of conjugate enone additions, see: (a) Rossiter, B. E.; Swingle, N. M. *Chem. Rev.* **1992**, *92*, 771. (b) Sibi, M. P.; Manyem, S. *Tetrahedron* **2000**, *56*, 8033. (c) Krause, N.; Hoffman-Röder, A. *Synthesis* **2001**, 171.
7. For selected recent examples: (a) Sikorski, W. H.; Reich, H. J. *J. Am. Chem. Soc.* **2001**, *123*, 6527. (b) Lee, P. H.; Ahn, H.; Lee, K.; Sung, S.-Y.; Kim, S. *Tetrahedron Lett.* **2001**, *42*, 37. (c) Reich, H. J.; Sikorski, W. H. *J. Org. Chem.* **1999**, *64*, 14. (d) Strzalko, T.; Seyden-Penne, J.; Wartski, L.; Corset, J.; Castella-Ventura, M.; Froment, F. *J. Org. Chem.* **1998**, *63*, 3295.
8. For reviews: (a) Pearson, R. G. *Chemical Hardness*; Wiley–VCH: New York, 1997. (b) Pearson, R. G. *J. Chem. Ed.* **1987**, *64*, 561. (c) Ho, T. *Tetrahedron* **1985**, *41*, 1.
9. For the 'hard/soft' classification of specific Lewis bases, see: (a) Pearson, R. G. *J. Am. Chem. Soc.* **1963**, *85*, 3533. (b) Pearson, R. G. *Science* **1966**, *151*, 172. (c) Pearson, R. G.;

Songstad, J. *J. Am. Chem. Soc.* **1967**, *89*, 1827. (d) Pearson, R. G. *J. Am. Chem. Soc.* **1988**, *110*, 7684 and references therein.
10. Chattaraj, P. K.; Lee, H.; Parr, R. G. *J. Am. Chem. Soc.* **1991**, *113*, 1855.
11. Calter, M. A.; Guo, X. *J. Org. Chem.* **1998**, *63*, 5308.
12. For a review: Weinreb, S. M.; Folmer, J. J. *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. E., Ed.; Wiley: New York, 1995; Vol. 3, p 2083.
13. Garigipati, S. G.; Tschaen, D. M.; Weinreb, S. M. *J. Am. Chem. Soc.* **1985**, *107*, 7790.
14. For the conversion of morpholine amides to ketones, see: Martín, R.; Romea, P.; Tey, C.; Urpí, F.; Vilarrasa, J. *Synlett* **1997**, 1414.
15. Juaristi, E. *Enantioselective Synthesis of β-Amino Acids*; Wiley–VCH: New York, 1997.
16. For reviews of β-peptide synthesis and structure, see: (a) Hintermann, T.; Seebach, D. *Chimia* **1997**, *50*, 244. (b) Seebach, D.; Matthews, J. L. *J. Chem. Soc., Chem. Commun.* **2015**, 1997. (c) Koert, U. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1836. (d) Gellman, S. H. *Acc. Chem. Res.* **1998**, *31*, 173.
17. Asymmetric β-amino acid synthesis employing optically active starting materials or chiral auxiliaries: (a) Ref. 15. (b) Juaristi, E.; Quintana, D.; Escalante, J. *Aldrichim. Acta* **1994**, *27*, 3. (c) Cole, D. C. *Tetrahedron* **1994**, *50*, 9517. (d) Cardillo, G.; Tomasini, C. *Chem. Soc. Rev.* **1996**, 117. See also: (e) Enders, D.; Bettray, W.; Raabe, G.; Runsink, J. *Synthesis* **1994**, 1322. (f) Enders, D.; Wahl, H.; Bettray, W. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 455–457. (g) Podlech, J.; Seebach, D. *Liebigs Ann.* **1995**, 1217. (h) Guibourdenche, C.; Podlech, J.; Seebach, D. *Liebigs Ann.* **1996**, 1121. and references therein. (i) Farras, J.; Ginesta, X.; Sutton, P. W.; Taltavull, J.; Egeler, F.; Romea, P.; Urpi, F.; Vilarrasa, J. *Tetrahedron* **2001**, *57*, 7665.
18. Recent catalytic asymmetric synthesis of β-amino acid derivatives: (a) Falborg, L.; Jørgensen, K. A. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2823. (b) Kobayashi, S.; Ishitani, H.; Ueno, M. *J. Am. Chem. Soc.* **1998**, *120*, 431. (c) Sibi, M. P.; Shay, J. J.; Liu, M.; Jasperse, C. P. *J. Am. Chem. Soc.* **1998**, *120*, 6615. (d) Zhou, F.; Detty, M. R.; Lachicotte, R. J. *Tetrahedron Lett.* **1999**, *40*, 585. (e) Meyers, J. K.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1999**, *121*, 8959. (f) Guerin, D. J.; Miller, S. J. *J. Am. Chem. Soc.* **2002**, *124*, 2134.
19. (a) Arnold, L. D.; Kalantar, T. H.; Vederas, J. C. *J. Am. Chem. Soc.* **1985**, *107*, 7105. (b) Griesbeck, A.; Seebach, D. *Helv. Chim. Acta* **1987**, *70*, 1326. (c) Arnold, L. D.; May, R. G.; Vederas, J. C. *J. Am. Chem. Soc.* **1988**, *110*, 2237. (d) Castagnani, R.; De Angelis, F.; De Fusco, E.; Giannessi, F.; Misiti, D.; Meloni, D.; Tinti, M. O. *J. Org. Chem.* **1995**, *60*, 8318. (e) Bernabei, I.; Castagnani, R.; De Angelis, F.; De Fusco, E.; Giannessi, F.; Misiti, D.; Muck, S.; Scafetta, N.; Tinti, M. O. *Chem. Eur. J.* **1996**, *2*, 826.
20. For an alternative approach to β-amino acid derivatives derived from β-lactones, see: Yang, H. W.; Romo, D. *J. Org. Chem.* **1999**, *64*, 7657.
21. For recent developments in asymmetric β-lactone synthesis, see: Yang, H. W.; Romo, D. *Tetrahedron* **1999**, *55*, 6403.
22. β-Lactones possessing α-branched substituents are not obtained in sufficiently high enantioselectivities from the catalyzed AAC reactions to be generally useful. Lactone **1g** was readily prepared from the enzyme-mediated resolution of the racemic β-lactone derived from the achiral AAC reaction, see: (a) Nelson, S. G.; Spencer, K. L. *J. Org. Chem.* **2000**, *65*, 1227. (b) Koichi, Y.; Suginaka, K.; Yamamoto, Y. *J. Chem. Soc., Perkin Trans. 1* **1995**, 1645.
23. To verify that lactone ring opening was proceeding with rigorous inversion of stereochemistry, the enantiomeric purities of azides **11a–c** were determined by chiral HPLC (Chiralcel OD-H column) of the methyl esters derived from **11a** and **11b**, and the benzyl ester derived from **11c**. See Section 6 for full procedural details.
24. (a) Compounds **12b** and **12d**: Alcón, M.; Canas, M.; Poch, M.; Moyano, A.; Pericás, M. A.; Riera, A. *Tetrahedron Lett.* **1994**, *35*, 1589. (b) Compound **12c**: Gordon, E. M.; Godfrey, J. D.; Delaney, N. G.; Asaad, M. M.; Von Langen, D.; Cushman, D. W. *J. Med. Chem.* **1988**, *31*, 2199. (c) Compound **12e**: Mendre, C.; Rodriguez, M.; Laur, J.; Aumelas, A.; Martinez, J. *Tetrahedron* **1988**, *44*, 4415.
25. For the synthesis of β-lactones via lactonization of β-hydroxy carboxylate derivatives, see Ref. 21 and references therein.
26. Acidic work-up of the dimethylsulfoxide reaction solutions should remove any remaining azide reagent by conversion to the sulfoximine, see: Johnson, C. R.; Rogers, P. E. *J. Org. Chem.* **1973**, *38*, 1793.
27. The potassium and magnesium halide carbamate salts were unstable toward decomposition during the course of the reaction.
28. (a) Fukuyama, T.; Jow, C.-K.; Cheung, M. *Tetrahedron Lett.* **1995**, *36*, 6373. (b) Wipf, P.; Henninger, T. C. *J. Org. Chem.* **1997**, *62*, 1586. (c) Miller, S. C.; Scanlan, T. S. *J. Am. Chem. Soc.* **1997**, *119*, 2301.
29. Seebach, D.; Abele, S.; Gademann, K.; Jaun, B. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 1595. and references therein.
30. Barchi, Jr. J. J.; Huang, X.; Appella, D. H.; Christianson, L. A.; Durell, S. R.; Gellman, S. H. *J. Am. Chem. Soc.* **2000**, *122*, 2711. and references therein.
31. (a) Hamura, Y.; Schneider, J. P.; Degrado, W. F. *J. Am. Chem. Soc.* **1999**, *121*, 12200. (b) Porter, E. A.; Wang, X.; Lee, H.-S.; Weisblum, B.; Gellman, S. H. *Nature* **2000**, *404*, 565.
32. Grademann, K.; Ernst, M.; Hoyer, D.; Seebach, D. *Angew. Chem. Int. Ed. Engl.* **1999**, *38*, 1223.