EurJOC European Journal of Organic Chemistry

FULL PAPER

DOI: 10.1002/ejoc.201300160

Unified Azoline and Azole Syntheses by Optimized Aza-Wittig Chemistry

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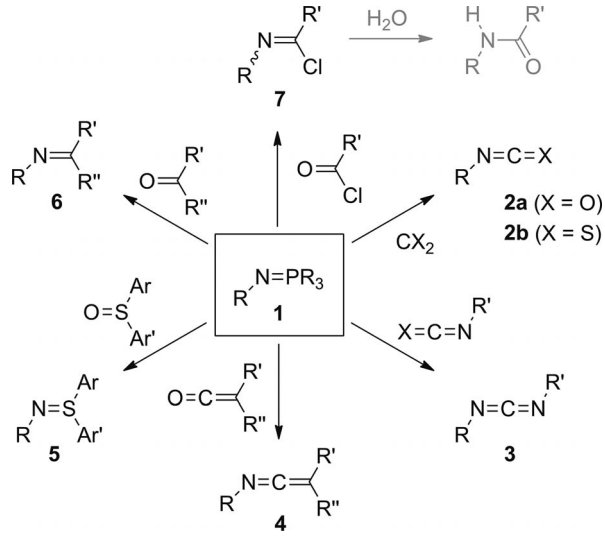
Keywords: Synthetic methods / Wittig reactions / Azides / Cyclization / Heterocycles

Intramolecular aza-Wittig ring closures were applied to synthesize thiazolines, oxazolines, and imidazolines from β-azido thioester, ester, and amide precursors. The cyclization precursors were obtained from amino acid derivatives. Optimized conditions for diazo transfer with a fast rate and racemization suppression, (thio)esterification, and amide coupling reactions are described. The ring closure reaction can be executed with PPh_3 under neutral conditions and was found to be highly chemoselective for five-membered rings. If amide groups were activated with tosyl groups, smooth intramolecular ring closure of iminophosphoranes furnished enantiopure imidazoline products with position-specific tosyl protection. This aza-Wittig-based azoline synthesis was then extended to double azoline ring closures to furnish catenated azoline building blocks common to peptide natural product building blocks and their analogues.

Introduction

Reactions between azides and phosphanes to generate iminophosphoranes were first described by Staudinger and Meyer in 1919. They also used these reactive intermediates to form carbon-nitrogen double bonds from carbonyl compounds.[1–2] Typically, iminophosphoranes are less nucleophilic than the corresponding phosphorus ylides and therefore attracted less attention than their carbon-based analogues described 35 years later by Wittig.[3] This notwithstanding, the aza-Wittig reaction has since developed into a powerful tool for organic synthesis and has been used in a variety of inter- and intramolecular reactions (Scheme 1).[4]

Iminophosphoranes **1** have been converted into isocyanates **2a** and isothiocyanates **2b** by treatment with CO_2 or CS_2, respectively. They can also be used to synthesize carbodiimides **3** by treatment with isocyanates or isothiocyanates.[4] The synthesis of ketimines **4** is possible through transformation of ketenes. Whereas all of these reactions form C=N double bonds, the use of iminophosphoranes **1** to connect nitrogen to other elements has also been described. One example is the formation of sulfimides **5** by treatment of iminophosphoranes **1** with sulfoxides.[5] Most important, however, are the reactions with carbonyl compounds to form imines **6** through formal exchange of C=O for C=NR.



Scheme 1. Examples of reactions of iminophosphoranes (X = O, S).

All these transformations can be regarded as condensation reactions under kinetic control and have been utilized for a wide variety of iminophosphoranes and carbonyl compounds in inter- and intramolecular processes.[4] Recent developments have extended to the application of chiral phosphorus(III) compounds to induce enantioselective desymmetrization,[6] to catalytic use of the phosphorus-containing mediator,[7] and to the direct amination of alcohols through redox coupling.[8] Typically, aza-Wittig reactions are rather inefficient when performed in an intermolecular fashion, but cyclic imine-containing heterocycles can be accessed intramolecularly in a variety of ways. Rate acceleration by supramolecular complex formation has been demonstrated.[9]

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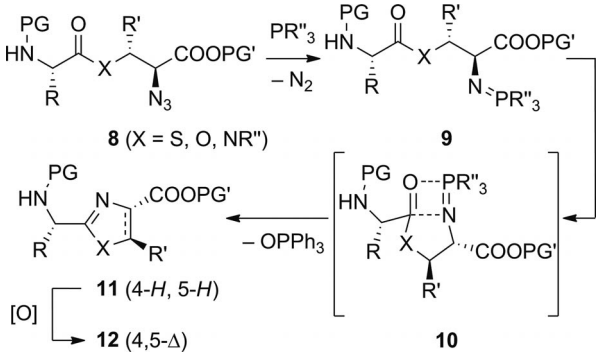
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201300160.

Iminophosphoranes can also be treated with acylating agents R–COX to form amides.[10] Given that the formation of imidoyl chlorides **7** has been observed after reactions between iminophosphoranes and acid chlorides[11] and that imido esters have been isolated from intramolecular acylation attempts,[12] aza-Wittig-type transformations are likely to be involved in these transformations as well.

By analogy to the Wittig reaction, the aza-Wittig reaction is typically assumed to conform to a quasi-concerted [2+2] cycloaddition mechanism, followed by cycloreversion to release phosphane oxide and the imine product. This assumption is supported mostly by theoretical studies[13] and – in one instance – by the isolation of a stable four-membered ring oxazaphosphetidine intermediate.[14] Betaine-type, open-chain intermediates have not yet been found by ^{31}P NMR spectroscopy.

We set out to explore intramolecular aza-Wittig reactions to form azolines from β-azido-substituted thioesters, esters, and amides **8** (Scheme 2). Treatment of these azides with phosphorus(III) reagents should furnish iminophosphoranes **9** after extrusion of nitrogen. These compounds should then undergo aza-Wittig ring closure to afford azolines **11** with release of phosphorus(V) oxide byproducts, in a process favored by the antiparallel arrangement of the C=O and P=N dipoles (**10**). In a follow-up step, the corresponding azoles **12** should be obtainable by oxidation, as desired. Through the employment of the azide group as a latent, preactivated functionality, the ring closure remains redox-neutral, exposes the substrate only to mild P^{III} reagents, and avoids strongly activated reagents such as dehydrating phosphonium(V) salts.[15] Furthermore, chain-like assembly of precursor molecules might be envisioned, because the azido group would preclude O→N or S→N acyl shift reactions.



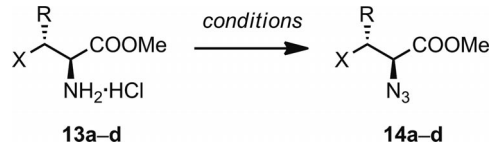
Scheme 2. Conceptual blueprint for azol(in)e synthesis by aza-Wittig reactions (PG = protecting group).

Isolated examples of such aza-Wittig-driven formation of thiazolines and oxazolines have been reported.[16] The synthesis of imidazolines has been reported only for unusually activated systems.[17–18] Thereby, accessible substitution patterns are limited or forcing reaction conditions had to be applied.[18]

Our initial results showed that this synthetic pathway is general and the reactions can be conducted in a highly chemoselective fashion.[19] Mild conditions could typically be applied for aza-Wittig-mediated azole formations. Neither strong acid or base need to be used, and nor do strongly dehydrating conditions or reagentshave to be employed, as are commonly used to synthesize azol(in)es. As a consequence, the aza-Wittig reaction has recently been finding applications in tandem transformations[20] and in the synthesis of complex target molecules.[21] Here we wish to give a full account on the scope and limitations of these transformations when applied to amino acid substrates, which are common elements of many peptide-derived bioactive natural products.

Results and Discussion

Obvious starting materials for amino-acid-derived natural product fragments are amino acid derivatives that can be converted into azides through diazo transfer reactions (Scheme 3).[22] Such reactions often employ electrophilically activated azides such as TfN_3,[23] NfN_3,[24] or $ImSO_2N_3$.[25] These methods vary mainly in the diazo transfer reagent, the base, and the catalyst. However, the synthesis of a chiral azide requires the conversion of the enantiomerically pure amine. When the azide is derived from an amino acid derivative, product racemization can be a serious problem.



Scheme 3. Diazo transfer with amino-acid-derived amines.

In our initial attempts to generate linear azido cyclization precursors for the aza-Wittig ring closures, we applied the procedure described by Wong and co-workers.[23h,23i] With amino-acid-derived substrates, however, the outcomes were somewhat variable, and decreases in *ee* resulted in several cases (Table 1, Entries a–d). Although epimerization might occur at any point in the whole reaction sequence, the resulting α-azido esters **14** are certainly more prone to epimerization than the starting amino esters **13**, because of the increased acidity of their α-protons. The most demanding substrate for the diazo transfer was amine **13d**,[19b] which gave a very low enantiomeric excess of 46% (Entry d).

When using the shelf-stable imidazole-1-sulfonyl azide hydrochloride,[25] we observed the formation of side products resulting from cleavage of sulfonyl azide from the imidazole. These results prompted us to focus on freshly prepared trifluoromethanesulfonyl azide as diazo donor.

We observed that the use of a CH_2Cl_2/DMF mixture instead of the usual aqueous methanol, combined with a higher loading of catalyst, showed better reaction rates, and the products obtained in this way displayed very high enantiomeric excesses (Table 1, Entries e–h) although the yields were slightly reduced. Under these conditions, the metal ions of the catalysts should be less hydrated, which might

Table 1. Comparison of diazo transfer conditions and substrates.

Entry	Compound	X	R	Method[a]	Yield [%]	*ee* [%][b]
a	**14a**	OH	H	A	99	57[b]
b	**14b**	OH	Me	A	52	93[b]
c	**14c**	STr	H	B	71	<42[b]
d	**14d**	NHTs	H	B	84	46[b,c]
e	**14a**	OH	H	C	85	>99[b]
f	**14b**	OH	Me	C	68	>99[b]
g	**14c**	STr	H	D	54	>95[b]
h	**14d**	NHTs	H	D	71	96[b]
i	**14a**	OH	H	E	91	>92[d]
j	**14b**	OH	Me	E	84	>99[c]
k	**14c**	STr	H	E	98	>98[d]
l	**14d**	NHTs	H	E	97	>94[d]

[a] Reagents and conditions. A: TfN_3 (3 equiv.), NEt_3 (3–4 equiv.), $ZnCl_2$ (1 mol-%), H_2O/MeOH/CH_2Cl_2, room temp., 2–14 h. B: TfN_3 (3 equiv.), NEt_3 (1.5 equiv.), $CuSO_4$ (1 mol-%), H_2O/MeOH/CH_2Cl_2, room temp., 2–14 h. C: TfN_3 (3 equiv.), Et*N*i*Pr*$_2$ (2.5 equiv.), $ZnCl_2$ (5 mol-%), CH_2Cl_2/DMF, 0 °C→r.t., 1.5 h. D: TfN_3 (3 equiv.), Et*N*i*Pr*$_2$ (2.5 equiv.), $CuSO_4$ (5 mol-%), CH_2Cl_2/DMF, 0 °C→r.t., 1.5–2 h. E:TfN_3 (3 equiv.), Et_3N (2.5 equiv.), $ZnSO_4$ (2 mol-%), H_2O/MeOH/CH_2Cl_2, 1:5:2, v/v/v, 0 °C, 1 h. [b] Determined by HPLC with chiral modified columns. [c] Determined by ^1H NMR after derivatization. [d] Determined by optical rotation.

explain the enhancement of their activity. We also noticed that free hydroxy groups (Entries a, b, e, f) were tolerated in this transformation as long as $ZnCl_2$ was used[23h] instead of $CuSO_4$ as promoter.

In further experiments we noticed that $ZnSO_4$ displayed a considerably higher catalytic activity for these transformations than $ZnCl_2$. Clean and full conversion was achieved for substrate **13c** in less than one hour (Table 2), without the need to use chromatography. In contrast, use of $CuSO_4$ always led to the formation of side products and required chromatographic purification. The optimized conditions with $ZnSO_4$ were then applied to substrates **13a**–**d**. Gratifyingly, the isolated yields ranged from 84% to 98% and the stereoretention remained high (Table 1, Entries i–l). In an attempt to optimize the reaction times, turnover was monitored for substrate **13d**, for which 95% conversion could be reached after 11.5 min in the presence of 2 mol-% of catalyst, and after 15.5 min if 1 mol-% was used.

Table 2. Comparison of metal salt promoters with amine **13c**.[a]

Entry	Reaction time	Catalyst	Yield [%]
a	3 h	$ZnCl_2$	84
b	1 h	$ZnSO_4$	98
c	3 h	$CuSO_4$	73[b]
d	3 h	–	76[c]

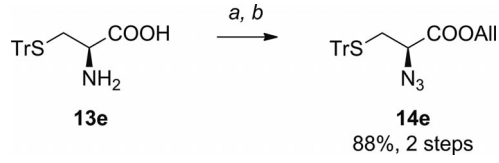
[a] Reagents and conditions: TfN_3 (3 equiv.), Et_3N (2.5 equiv.), catalyst (2 mol-%), H_2O/MeOH/CH_2Cl_2, 1:5:2, v/v/v, 0 °C. [b] After flash chromatography. [c] The reaction was stopped after 3 h.

The reaction rate enhancement due to $ZnSO_4$ in relation to $ZnCl_2$[23h] was rather unexpected. In line with the early literature[23] we found that TfN_3 reacts with primary amines to form azides, but conversion was sluggish and stayed incomplete in the absence of catalyst.

The tendency of these salts to form different complexes in aqueous media might contribute to this effect. $ZnCl_2$ is known to exist in several hydration states, but the chloride ligands stay bound tightly to the metal center.[26,27] In contrast, the sulfate counterion has been found to bind much less tightly to the metal[28] and will thereby render the tetra- or hexacoordinate Zn^{2+} much more Lewis-acidic and hence catalytically active.

Although these findings are certainly of practical value, they are more difficult to interpret in mechanistic terms. We hypothesize that the metal ion assists either adduct formation between amine and sulfonyl azide or the decomposition of the putative intermediate, likely by the chelating ability of the metal ion. However, although some possible mechanisms for the azide transfer have been discussed (see ref.[23h]), there only are few experimental data and considerable disagreement on the actual intermediates involved. The racemization suppression could be a result of increased turnover of activated intermediates. Qualitatively, we observed that prolonged reaction times (>3 h) generally led to decreasing optical purity, suggesting that prolonged exposure of α-azido ester products to the basic medium contributes to the degree of racemization observed.

Free α-amino acids were also found to be suitable substrates for the diazo transfer (Scheme 4). Trityl-protected cysteine **13e** was converted into the azide and protected as its allyl ester with cesium carbonate and allyl bromide to furnish the fully protected cysteine derivative **14e** in 88% yield.

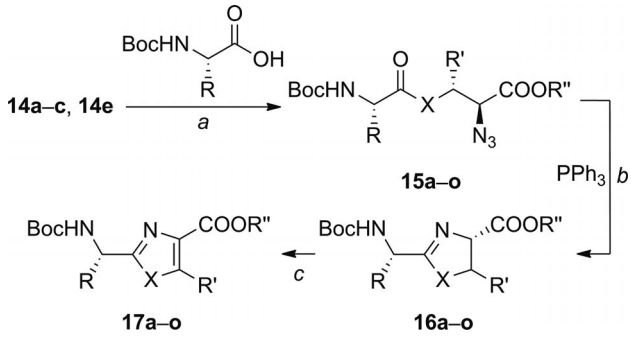


13e **14e**
88%, 2 steps

Scheme 4. Synthesis of an azido allyl ester. Reagents and conditions: a) TfN_3 (3 equiv.), NEt_3 (1.5 equiv.), $ZnSO_4$ (1 mol-%), H_2O/MeOH/CH_2Cl_2 (1:5:2), 0 °C, 30 min; b) Cs_2CO_3 (0.5 equiv.), MeOH, room temp., 10 min, then AllBr (5 equiv.), DMF, room temp., 5 h.

Synthesis of Thiazoles and Oxazoles

Azides **14a**–**c** and **14e** were used as starting materials for the synthesis of thioesters **15a**–**e** and esters **15f**–**o** (Scheme 5, Table 3). We found that the thiols **14c** and **14e** had to be freshly deprotected before being immediately coupled to the acids, because they were prone to oxidation. The protected amino acid was activated in each case with a combination of carbodiimide, HOBt, and Et*N*i*Pr*$_2$. The coupling furnished thioesters **15a**–**e** in good yields except in the case of the proline thioester **15d**, which might be due to its high steric demand. The coupling with alcohols **14a** and **14b** with the aid of DIC and DMAP proceeded with good to excellent yield in all cases to give esters **15f**–**o**.



Scheme 5. Thiazole and oxazole synthesis. For conditions, see Table 3.

Table 3. Overview of thiazole and oxazole synthesis.[a]

Entry	Amino acid	X	R′	R″	Yield [%] 15	16	17	*ee* [%]
a	Ala	S	H	Me	69	98	94	94[b,c]
b	His(Bn)	S	H	Me	74	95	23	98[c]
c	Val	S	H	Me	80	91	85	95[b]
d	Pro	S	H	allyl	54[d]	97	94	99[c]
e	Glu(Cy)	S	H	Me	80[d]	92	86	70[c]
f	Pro	O	H	Me	84	–[f,h]	23[g]	>95
g	Ala	O	H	Me	92	84	62	89–98[b,c]
h	Ala	O	Me	Me	86	78	79	>96[b]
i	Phe	O	H	Me	88	78	78	95[b]
j	Cys(Tr)	O	H	Me	87	97	62	23[c]
k	Glu(Cy)	O	H	Me	99	–[f]	69[g]	>98[c]
l	Tyr(Bn)	O	H	Me	84	62	56	>95
m	Thr(Bn)	O	H	Me	98	18,75[h]	56	>96[b,e]
n	Val	O	H	Me	95	13,48[h]	43	94[c]
o	Gly	O	H	Me	93	–[f]	64[g]	–

[a] Reagents and conditions: a) X = S: i. TFA/CH_2Cl_2 (1:9), Et_3SiH, room temp., 10 min; ii. DIC or EDC, HOBt, EtN*i*Pr_2, protected amino acid, 0.5–16 h, 0→20 °C; X = O: DIC, 1–5 mol-% DMAP, CH_2Cl_2, 0.5–16 h, 0→20 °C; b) PPh_3, THF, –20→40 °C, 2–18 h; c) $BrCCl_3$, DBU, CH_2Cl_2, 0→20 °C, 2–4 h. [b] Determined by ^1H NMR examination of diastereomers after derivatization. [c] Determined by HPLC with chiral modified columns (Daicel AD). [d] EDC, HOBt, NEt_3, CH_2Cl_2, 0 °C. [e] One diastereomer in ^1H NMR. [f] Could not be separated from $OPPh_3$. [g] Yield over two steps. [h] Modified conditions: b) PPh_3, 2,6-lutidine, 80 °C, 4–6 h.

In order to transform the azido (thio)esters into azolines effectively, several conditions for the aza-Wittig transformation were studied. Treatment of substrates **15a–o** with PPh_3 furnished the corresponding iminophosphoranes, which underwent ring closure to yield thiazolines **16a–e** and oxazolines **16f–o**. Azolines **16a–o** could be oxidized to the thiazoles **17a–e** and oxazoles **17f–o** with DBU and $BrCCl_3$.[29] In some cases it was very difficult to separate the oxazolines from the triphenylphosphane oxide formed during the reaction. In these cases the oxazoles were directly generated by oxidation of the crude oxazolines **16f**, **16k**, and **16o**.

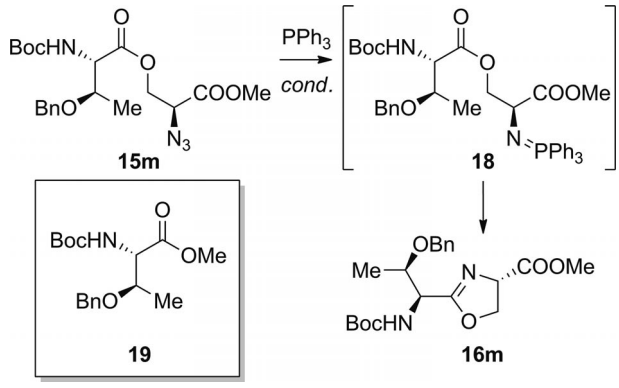
The synthesis of the thiazolines **16a–e** was highly efficient and gave excellent yields without exception (Table 3, Entries a–e). Oxidation to the thiazoles **17a–e** worked equally well, except in the case of the benzyl-protected histidine derivative. In this case interference by the nucleophilic nitrogen might be a reason for the low yield.

Azido esters **15f–o** were found to be less reactive than the thioesters **15a–e**. In the ring closure process, elevated temperatures (>40 °C) had to be employed. Under these conditions most substrates were ring-closed in good yields (Table 3, Entries g–l, o) but β-branched substrates such as proline, threonine, and valine derivatives in particular still gave low yields (Entries f, m, n). The oxidation of the oxazolines proceeded less swiftly than that of the thiazolines.

These data indicated that the cyclization protocol would have to be optimized for sterically demanding esters. The influence of solvent, temperature, and phosphane were therefore studied in detail for the ring closure of the demanding threonine-derived ester **15m**.

Optimization of Solvent

Apart from theoretical calculations,[30] the influence of solvents in aza-Wittig ring closures has not been systematically investigated before. The common solvents for these conversions found in the literature were tested in the ring closure of the sterically congested substrate **15m** (Scheme 6). The results are compiled in Table 4.



Scheme 6. Screening of different conditions for the aza-Wittig ring closure.

Table 4. Optimization of solvent and temperature.

Entry	Solvent	*T* [°C]	*t* [h]	Yield [%]
1	CH_2Cl_2	40	19	–
2	toluene	40	19	9
3	MeOH	40	19	–
4	THF	40/80	19/5	23/42
5	DMF	40/80	19/5	21/44
6	DMSO	80	5	33
7	pyridine	40/80	19/5	37/75
8	2,6-lutidine	80	5	75
9	pyridine/DMF (1:1–9:1)	80	4	38–43

In CH_2Cl_2 and toluene the formation of iminophosphorane **18** was observed (LC-MS, ^{31}P NMR), but the cyclization either did not occur (Entry 1) or was very low-yielding (Entry 2). In MeOH, transesterification of **15m** led to the formation of threonine methyl ester **19** (Entry 3), indicating considerable basicity of the generated iminophosphorane intermediate. Formation of the desired oxazoline

could not be observed. Better results were achieved with polar aprotic solvents such as THF, DMF, and DMSO, especially at elevated temperature (Entries 4–6). The slightly basic solvents pyridine and 2,6-lutidine gave the best results (Entries 7 and 8). Evidence for the importance of a basic, aromatic solvent in this reaction is given by the fact that the yield dropped to 38–43% in mixtures of pyridine and DMF (1:1, 1:3, 1:9; Entry 9). We further noticed that oxazolines derived from sterically unhindered amino acids were prone to hydrolysis, which could be prevented by using pyridine or 2,6-lutidine as solvent. We therefore hypothesize that the slightly basic medium suppresses protonation and consequently improves the reactivity of the iminophosphorane.

Elevated temperatures were also beneficial. Increasing the temperature from 40 °C to 80 °C resulted in doubling of the yields in THF and DMF (Entries 4 and 5) and reduced the reaction times from 19 to 5 h. This effect was even stronger in pyridine, in which the yield rose from 37 to 75%. The conditions with 2,6-lutidine as solvent and a temperature of 80 °C were chosen for studying the phosphane source.

Optimization of Phosphanes

Immediate formation of gas was apparent upon addition of triphenylphosphane to the azides. ^{31}P and ^{13}C NMR experiments with substrate **15m** showed that the azide was quickly transformed into the corresponding iminophosphorane (^{31}P NMR: 10.81 ppm in [D_5]pyridine for iminophosphorane **18**). This iminophosphorane was relatively stable and was slowly consumed over several hours. Interestingly, when we replaced triphenylphosphane by an alkyl phosphane such as PBu_3, PEt_2Ph, or $P(CH_2OH)_3$, only decomposition was observed. With $PEtPh_2$ and $P(C_6H_4SO_3Na)_3$, oxazoline **16m** could be isolated in less than 30% yield. Apparently, stabilized iminophosphoranes derived from triphenylphosphane were more suitable than less stable alkyl-substituted iminophosphoranes. (We attribute this finding to the increased reactivity of an ester or thioester of an amino acid with an α-azido substituent towards nucleophilic attack, relative to an aromatic heterocycle.) Under optimized conditions (PPh_3, 2,6-lutidine, 80 °C, 6 h) the sterically congested oxazolines **16m** and **16n** (Table 2) could be effectively obtained. Threonine-derived **15m** was cyclized in a yield of 75% (before 18%) and the valine-derived **15n** was transformed into **16n** in 48% yield (previously 13%). These conditions were also used for the cyclization of several azido amides to imidazolines.

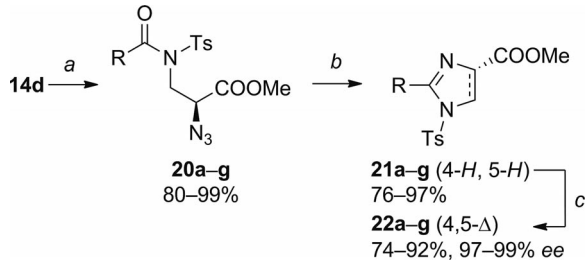
Imidazol(in)e Synthesis and Enantiopurity

Several methods to form chiral imidazol(in)es have been described in the literature,[31] but enantiomerically pure imidazolines with a stereogenic center α to the C-2 position pose considerable challenges to synthesis.[32] We hypothesized that imidazolines might be accessible through aza-Wittig ring closures in a similar fashion to oxazolines and thiazolines. Our data indicated that esters were less reactive than the corresponding thioesters in aza-Wittig ring closure events. Amides should be even less reactive, and had in fact been found to be inert under the conditions described previously. The few examples of amides undergoing aza-Wittig reactions employed highly activated (i.e., electron-poor) substrates or harsh conditions.[17c,17g,18]

To improve the electrophilicity of the amide carbonyl group we introduced a tosyl group onto the amide nitrogen. This group was anticipated to activate the amide oxygen towards undergoing ring closure with an iminophosphorane in the β-position. Secondly, it should serve as a protecting group on the imidazole nitrogen after oxidation to the imidazole. Thirdly, it should allow the N(1) and N(3) positions in the imidazole ring to be distinguished.

In order to explore this strategy, N_α-Boc-L-asparagine was subjected to a diacetoxyiodobenzene-mediated Hofmann degradation[33] and converted into ammonium salt **13d**.[19b] After diazo transfer, azide **14d** was obtained in good yield and high enantiomeric excess (Table 1).

The synthesis of *N*-acyl-sulfonamides **20a**–**g** by acylation of sulfonamide **14d** (Scheme 7) was studied next. Unfortunately, precedence for sulfonamide acylation was found to be rather limited. β-Lactams have been cyclized by use of DCC and 4-pyrrolidinopyridine.[34] Ligation of sulfonyl azides with thioacids[33] can be used to make secondary sulfonamides, and PyBOP has been used to acylate so-called "safety-catch" linkers.[35] However, the use of carbodiimides and 4-aminopyridines was very low-yielding in our hands. Examples of acylation of secondary sulfonamides were even more scarce and seem to require strong activation. In one case, acid anhydrides and Lewis acids have been used for this purpose.[36] We wanted to avoid activation by anhydrides and acid chlorides, firstly because such strong activation often leads to epimerization and secondly because Boc-protected amino acid chlorides tend to form oxazolones.[37]

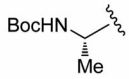
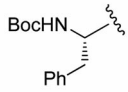
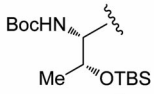
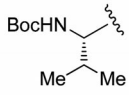
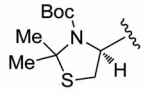
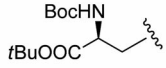
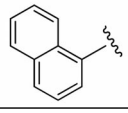


Scheme 7. Imidazoline and imidazole synthesis from azide **14d**. For conditions, see Table 5.

Acid fluorides are more stable than acid chlorides but still highly reactive.[38] Initial experiments with freshly prepared Boc-protected amino acid fluorides[39] gave clean couplings with Boc-alanine and Boc-phenylalanine (Table 5, Entries a and b) without any detectable epimerization. However with sterically hindered amino acids (Entries c, d, and e) yields were lower. After some experimenta-

tion we found that a combination of HATU and solid Cs_2CO_3 in CH_2Cl_2 gave excellent yields and *ee* values in these cases. Surprisingly, cesium carbonate could not be replaced by EtN*i*Pr$_2$ or K_2CO_3; we hypothesize that a soluble sulfonamide cesium salt might be involved. The HATU/Cs_2CO_3 combination proved excellent for all other tested substrates (Entries c–g); only cysteine derivative **20e** showed a measurable amount of a second diastereomer in a ratio of 98:2.

Table 5. Synthesis of imidazoles from azide **14d** and *ee* determination.[a]

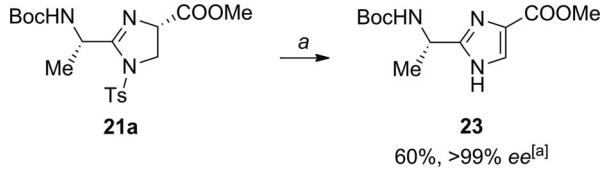
Entry	R	Yield [%]			*ee* [%]
		20	**21**	**22**	
a		97	91	76	> 99[c]
b		80	76	74	> 99[c]
c		85	91	87	> 98[b]
d		85	94	92	> 99[c]
e		85	80	90	96[c]
f		99	91	77	n.d.
g		85	85	82	–

[a] Reagents and conditions. a) Entries a and b: acid fluoride (2 equiv.), EtN*i*Pr$_2$ (2 equiv.), CH_2Cl_2, 0 °C→20 °C, 1–2.5 h; Entries c–g: carboxylic acid (1.1 equiv.), HATU (1.1 equiv.), Cs_2CO_3 (4 equiv.), CH_2Cl_2, 0 °C, 1–4 h. b) Entries a–d, f: PPh_3 (1.5 equiv.), THF, –20 °C→reflux, 2.5–6 h; Entries e and g: PPh_3 (1.5 equiv.), 2,6-lutidine, –20 °C→80 °C, 2–6 h. c) DBU (2 equiv.), $BrCCl_3$ (1.1 equiv.), CH_2Cl_2, room temp., 2.5–6 h. [b] Determined by ^{1}H NMR and HPLC. [c] Determined by HPLC with chiral modified columns.

With the cyclization precursors in hand we proceeded to the critical ring closure step, using the previously optimized conditions (THF, reflux or 2,6-lutidine, 80 °C). Gratifyingly, all substrates were obtained in good to excellent isolated yields. Imidazoline **21a** was prone to hydrolysis of the amidine unit, which occurred upon column chromatography or upon prolonged exposure to $CDCl_3$. Addition of base during chromatography and the use of [D_5]pyridine or [D_6]benzene as NMR solvent suppressed this side reaction. Phenylalanine derivative **21b** also showed hydrolytic ring opening, but to a much lower extent. The oxidation of imidazolines **21a**–**g** under standard conditions[29] with DBU and $BrCCl_3$ performed cleanly in excellent yields.

Importantly, the stereochemical purity of the products was found to be preserved. Among the imidazoles **22a**–**e**, **22c** had an *ee* value of more than 98%, as evidenced by NMR and HPLC analysis. Only cysteine-derived **22e** showed a slightly lower *ee* (96%), which was identical to that of **20e** and hence unaffected by the ring closure/oxidation sequence. Acylated sulfonamide **20g** showed an *ee* = 94%. After ring closure in 2,6-lutidine the *ee* was determined to 82%, indicating a somewhat increased acidity of the hydrogen in the 4-position.

Treatment of imidazoline **21a** with an excess of DBU led to clean formation of the free imidazole **23** (Scheme 8), presumably through elimination of sulfinate. This process was found to be slower than oxidation with $BrCCl_3$ und DBU, with complete conversion being observed after three hours. The elimination could therefore easily be suppressed by adding $BrCCl_3$, which produced the protected imidazole. Surprisingly, no loss of enantiomeric excess could be detected in this transformation.



21a **23**

60%, >99% *ee*[a]

Scheme 8. Imidazoline oxidation by elimination. Reagents and conditions: DBU (15 equiv.), DMF, 0 °C→20 °C, 3 h. [a] Determined by HPLC with chiral modified columns.

Microwave-Assisted Ring Closure

As shown above, the outcomes of the aza-Wittig ring closures were dependent on the solvent and on the reaction temperature. For sterically congested substrates, ring closure with use of conventional heating took several hours. Heating by microwave irradiation was therefore studied for ester **15m** and *N*-acyl-sulfonamide **20e** (Table 6).

Table 6. Microwave assisted aza-Wittig ring closure.

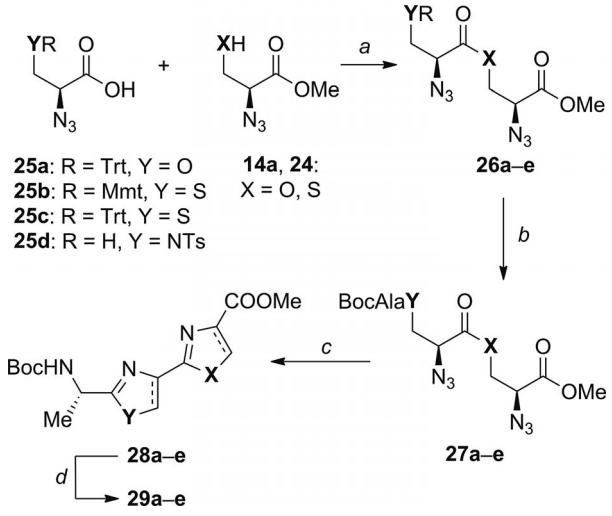
Entry	Azide	Solvent	Microwave, 100 °C		Heating bath, 80 °C	
			Time [h]	Yield[a] [%]	Time [h]	Yield[b] [%]
1	**15m**	DMF	0.5	55	5	44
2	**15m**	2,6-lutidine	0.5	71	5	75
3	**20e**	THF	0.5	63	21	46[c]
4	**20e**	pyridine	0.5	64	6	55
5	**20e**	2,6-lutidine	0.5	75	6	80

[a] Reagents and conditions: PPh_3 (1.5 equiv.), 0 °C→100 °C, microwave (200 W). [b] PPh_3 (1.5 equiv.), 0 °C→80 °C, heating bath. [c] PPh_3 (1.5 equiv.), 0 °C→reflux, heating bath.

Overall, microwave heating for 30 min delivered the azolines in yields comparable to those obtained after 5–6 h conventional heating. The ring closure of **20e** in THF (Entry 3) is remarkable: microwave heating delivered the imidazoline with a yield of 63% after 30 min, whereas cyclization in THF at reflux resulted in an isolated yield of only 46% after 21 h.

Synthesis of Fused Azole Dimers

Besides monomeric imidazoles, oxazoles, and thiazoles, the homodimers or mixed dimers of these heterocycles are important substructures in biologically relevant natural products.[40] Such heterocyclic frameworks could be accessible through multiple (parallel) ring closures of linear cyclization precursors. To investigate the feasibility of such transformations the synthesis of bisazides **27a**–**e** (Scheme 9) was envisaged. The bisazides **27a**–**e** were expected to form the corresponding bisiminophosphoranes with 2 equiv. of triphenylphosphane. These could undergo regioselective double ring closures to furnish the dimeric heterocycles **28a**–**e**. Five different heterocyclic dimers were generated by this synthetic strategy. The results are listed in Table 7.



Scheme 9. Multiple aza-Wittig ring closures of bisazides. Reagents and conditions: a) **26a** or **26c**: carboxylic acid (1.3 equiv.), DIC (1.4 equiv.), DMAP (0.1 equiv.), CH_2Cl_2, 0 °C→20 °C; **26b**: carboxylic acid (1.3 equiv.), IPCF (1.3 equiv.), NMM (2.3 equiv.), THF, –20 °C; **26d** or **26e**: carboxylic acid (1.1 equiv.), EDC·HCl (2.2 equiv.), HOBt (2.2 equiv.), CH_2Cl_2/DMF (5:1), 0 °C→20 °C, 2 h. b) **27a**: Et_3SiH (1.05 equiv.), CH_2Cl_2/TFA (10:1), room temp., 10 min; BocAlaOH (1.3 equiv.), DIC (1.4 equiv.), DMAP (0.13 equiv.), CH_2Cl_2/DMF (10:1), 0 °C→20 °C; **27b**: Et_3SiH (1.1 equiv.), CH_2Cl_2/TFA (3:1), room temp., 30 min; BocAlaOH (2 equiv.), DIC (2 equiv.), DMAP (0.2 equiv.), CH_2Cl_2, 0 °C→20 °C, 12 h; **27c**: Et_3SiH (1.1 equiv.), CH_2Cl_2/TFA (2:1), room temp., 1.5 h; BocAlaOH (1.05 equiv.), DIC (1.2 equiv.), Et-N*i*Pr$_2$ (1.2 equiv.), CH_2Cl_2/DMF (10:1), 0 °C→20 °C, 13 h; **27d**: BocAlaF (2 equiv.), EtN*i*Pr$_2$ (1.1 equiv.), CH_2Cl_2, 0 °C, 30 min; **27e**: BocAlaF (1.05 equiv.), EtN*i*Pr$_2$ (1.05 equiv.), CH_2Cl_2, 0 °C, 45 min. c) **28a** or **28b**: PPh_3 (3 equiv.), THF, –20 °C→40 °C; **28c**: PPh_3 (4 equiv.), THF, –20 °C→40 °C; **28d** or **28e**: PPh_3 (3 equiv.), THF, –40 °C→reflux, 6 h. d) **29a** or **29b**: DBU (10 equiv.), $BrCCl_3$ (5 equiv.), CH_2Cl_2, 0 °C→20 °C; **29c**: DBU (12 equiv.), $BrCCl_3$ (6 equiv.), CH_2Cl_2, 0 °C→20 °C; **29d** or **29e**: DBU (10 equiv.), $BrCCl_3$ (5 equiv.), CH_2Cl_2, 0 °C→20 °C, 30 min.

Hydroxyazide **14a** and freshly deprotected mercaptoazide **24** (X = S) were coupled to the acids **25a**–**c** with the aid of carbodiimides or isopropyl chloroformate (IPCF). In the synthesis of **26d** and **26e** the use of base led to decomposition, especially with thioester **26e**. Compounds **26a**–**c** were deprotected with TFA and coupled to Boc-alanine (DIC/DMAP). The bisazides **26d** and **26e** were coupled to BocAlaF. Minimum amounts of base, short reaction times, and rigorous exclusion of water were crucial for this sulfonamide acylation. However, both acylation products were isolated as mixtures of diastereomers (**27d**: 84% *de*, **27e**: 11% *de*), which can be attributed to the highly acidified proton α to the (thio)ester.

Table 7. Multiple ring closures to afford mixed azole-azole dimers (Tr = trityl. Mmt = 4,4′-dimethoxytrityl).

Entry	Y	X	R	Yield [%]		
				26	**27**	**29**
a	O	O	Tr	92	64	27
b	S	S	Mmt	68	51	60
c	S	O	Tr	59	47	64
d	NTs	O	H	61	88	74
e	NTs	S	H	70	51	81

All bisazides were then doubly cyclized with PPh_3 in THF. Only for **27a** was the bisazoline product **28a** isolated (83%); the other azolines **28b**–**e** were all directly oxidized without isolation. The bisthiazoline derived from **27b** was highly prone to autooxidation, whereas cyclization of **27c** led to a mixture of tautomers, presumably enamine isomers. Even though the two intermediates **27d** and **27e** were highly unstable in the presence of base, both underwent clean and regioselective conversion to the corresponding bisazolines. Both intermediates were directly oxidized, because they were prone to acid-catalyzed hydrolysis and, in the case of **27e**, to autooxidation.

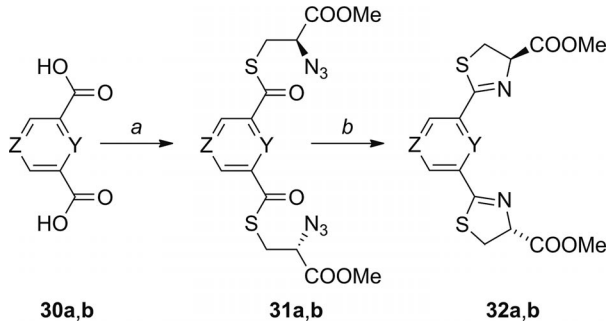
Oxidation to the bisazoles **29a**–**e** proceeded smoothly, except in the case of **29a**, which was found to form slowly and in lower yield. During these experiments we observed that azoline oxidations with DBU and $BrCCl_3$ were highly dependent on the presence of an electron-withdrawing group on the azoline, which might promote deprotonation when DBU is added. We assume that these positions are oxidized first. On the other hand, oxidation was slower for azolines that are only remotely activated. Whereas thiazolines are well known to be oxidized easily (Y = S, Entries b and c) and tosyl imidazolines were also easily oxidized (Y = NTs, Entries d and e), the corresponding oxazolines seem to be more difficult to oxidize without direct activation.

We did not observe the formation of alternative ring closure products; this demonstrates the exceptional selectivity of the aza-Wittig reaction for the formation of five-membered rings. Similar observations were also made during the total syntheses of the halipeptins A and D.[21d] In these cases the formation of a five-membered ring (79–83%) was favored over the alternative aza-Wittig ring closure to a six-membered ring (16–17%).

Ligand Scaffolds

Chiral bisoxazoline or pybox ligands have been successfully used in transition-metal-catalyzed asymmetric transformations,[41] but little is known about the catalytic properties of their sulfur analogues.[42] The bisthiazolinepyridines **32a** and **32b** (Scheme 10, Table 8) were each synthesized

through parallel aza-Wittig ring closures, in two steps from the commercially available bisacids **30a** and **30b** .



Scheme 10. Synthesis of pyridine-fused thiazolines.

Table 8. Synthesis of bisthiazolinepyridine derivatives through multiple aza-Wittig ring closures.[a]

Entry	Y	Z	Yield [%]	
			31	**32**
a	N	CH	31	88
b	CH	N	15	82

[a] Reagents and conditions: a) HOBt, EDC, NEt_3, **24**, CH_2Cl_2, 0 °C→20 °C, 14 h; b) PPh_3, THF, 0 °C→40 °C, 14 h.

In the first step, bisacids **30a** and **30b** were each coupled to thiol **24**. Under unoptimized conditions the bisthioesters were formed in 31% and 15% yields. However, the parallel ring closures of the linear cyclization precursors **31a** and **31b** proceeded cleanly and delivered the desired diastereomerically pure bisthiazolines in high yields. This approach could be used to synthesize a variety of Pybox analogue ligands with high diastereomeric excess.

Summary and Conclusion

We have found that the aza-Wittig reaction can be employed for the synthesis of valuable 1,3-azolines from readily available amino acids. We therefore optimized the synthesis of amino-acid-derived azides with high *ee* values. Importantly, when $ZnSO_4$ was used as a superior catalyst, azide transfers performed cleanly in very high *ee* values even when applied to sensitive amino acid derivatives. The azides have been converted into thioesters, esters, and *N*-acyl-sulfonamides with excellent yields. Whereas thioesters and esters could be synthesized with the aid of carbodiimides, efficient acylation of sulfonamides required acid fluorides or activation with HATU und Cs_2CO_3.

The aza-Wittig syntheses of thiazolines, oxazolines, and imidazolines have been found to be highly advantageous reactions. The investigated thiazolines were formed efficiently even at room temperature, although higher temperatures were necessary to obtain imidazolines and oxazolines in high yields. Sterically congested esters were shown to be the most demanding substrates for these ring closures (Table 3, Entries m and n); they could be obtained in yields of 48% and 75% after optimization of temperature, solvent, and phosphane source. The oxidation of all investigated 1,3-azolines was possible with DBU and $BrCCl_3$, but oxazolines not bearing an electron-withdrawing substituent (e.g., an ester) were sometimes found to be difficult to oxidize (Table 7, Entry 1.)

We have shown that these transformations allow the synthesis of 1,3-azolines and 1,3-azoles with high *ee* values. Double aza-Wittig ring closures showed that five-membered rings are formed with high selectivity. These conditions could be applied to a wide variety of protected amino acids, demonstrating that the transformations tolerate other carbonyl groups, such as esters, amides, and urethanes, as well as protected thiols and alcohols. Reaction times could be shortened by use of microwave irradiation, and the aromatization of a *N*-tosylimidazole was achieved in the absence of the oxidative agent $BrCCl_3$.

This method constitutes an alternative to standard dehydration approaches to azoles, especially in densely functionalized substrates. It allows the retention of stereogenic centers directly attached to the azoline units and does not employ acid or base catalysis. All three types of 1,3-azolines are accessible through the use of similar reaction conditions, and imidazoles can be obtained in a protected form. We hope that these findings will be found useful for late-stage ring formation in total synthesis and for multiple regioselective ring closures.

Experimental Section

Diazo Transfer According to Wong (GP A):[23g,23h] A solution of NaN_3 (6 equiv. per amino group) in H_2O (6 M) was mixed with an equal volume of CH_2Cl_2 and cooled to 0 °C. Tf_2O (6 equiv. per amino group) was added dropwise over 5 min and the reaction mixture was stirred vigorously for 2 h at 0 °C. The biphasic mixture was neutralized with saturated Na_2CO_3 solution and the aqueous layer was extracted twice with the same volume of CH_2Cl_2. The combined organic extracts were washed with saturated Na_2CO_3 solution, and the obtained TfN_3 solution was used without further purification. The substrate and the catalyst (1 mol-% of $CuSO_4$ or $ZnCl_2$) were dissolved in H_2O (same volume as the TfN_3 solution), and base (K_2CO_3 or NEt_3, 3 equiv.) was added. TfN_3 solution was added and the biphasic reaction mixture was diluted to homogeneity with MeOH and stirred until full conversion (monitored by TLC). The organic solvents were evaporated, and the aqueous layer was diluted with H_2O, neutralized with formic acid, and extracted with CH_2Cl_2 (5×). The combined organic extracts were dried with $MgSO_4$ and concentrated in vacuo.

Diazo Transfer Procedure in Nonhydroxylic Solvent (GP B): NaN_3 (6 equiv. per amino group) was suspended in water (to a concentration of 8 M) and an equal volume of CH_2Cl_2 and cooled to –20 °C. Tf_2O (3 equiv. per amino group) was added, and the resulting biphasic solution was stirred at 0 °C for 30 min. Cold satd. $NaHCO_3$ solution (200 vol.-% of the reaction mixture) was added slowly and the layers were separated. The aqueous layer was extracted with cold CH_2Cl_2 (2×, 2.5 times the CH_2Cl_2 volume used), and the combined organic extracts were washed with cold satd. $NaHCO_3$ solution (1× reaction volume). The obtained TfN_3 solution was used without further purification. Substrate and catalyst (0.5 mol-% $CuSO_4$ or $ZnCl_2$) were dissolved in DMF (same volume as the TfN_3/CH_2Cl_2 solution) and cooled to 0 °C. $EtNiPr_2$ (2.5 equiv.) and TfN_3 solution were added, and the mixture was stirred at room

temp. until conversion was complete (monitored by TLC). The CH_2Cl_2 was evaporated at room temp. under reduced pressure. Water was added, and the aqueous layer was extracted four times with Et_2O. The combined organic extracts were dried ($MgSO_4$) and coevaporated in vacuo (room temperature) with toluene until the ether was completely removed.

General Procedure for Diazo Transfer with $ZnSO_4$ (GP C): A solution of NaN_3 (6 mmol) in H_2O (1 mL) was mixed with CH_2Cl_2 (1 mL) and cooled to 0 °C. Tf_2O (3 mmol) was added dropwise, and the reaction mixture was stirred vigorously for 2 h at 0 °C. The biphasic mixture was neutralized with saturated aqueous $NaHCO_3$ solution (1 mL), and the aqueous layer was extracted twice with CH_2Cl_2 (2× 1 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ solution (2× 1 mL), and the resulting TfN_3 solution in CH_2Cl_2 was used directly afterwards without further purification. The hydrochloride salt of the amine substrate (1 mmol) and $ZnSO_4$ (0.02 mmol) were dissolved in MeOH (6.7 mL) and water (1.3 mL). The mixture was cooled to 0 °C, and Et_3N (2.5 mmol) was added slowly, followed by the dropwise addition of the TfN_3 solution prepared as above. The homogeneous mixture was stirred at 0 °C until full conversion was reached (TLC monitoring) and was then quenched by addition of phosphate buffer (pH 3). The pH of the aqueous layer was carefully adjusted to pH 2 by addition of dilute aqueous HCl. The phases were separated, and the aqueous layer was extracted three times with CH_2Cl_2. The combined organic layers were washed with brine, dried with Na_2SO_4 and concentrated in vacuo.

Caution: Although we have never experienced any instability in the course of this work, TfN_3 has been reported to be unstable by others.[43] We recommend taking proper precautions (blast shield) when the reaction mixture or crude reaction product is heated or evaporated. To enhance safety, the TfN_3-containing solutions were not concentrated completely. The mixture either was only partly concentrated and used directly for purification by FCC or was filtered through a short pad of silica before partial concentration. Excess TfN_3 was immediately poured into satd. $NaHCO_3$ solution (pH 9) and stored for 24 h, to ensure complete hydrolysis of the reagent, before the solution was discarded.

General Procedure for the Formation of Thioesters (GP D): The trityl-protected thiol (1.0 equiv.) was dissolved in CH_2Cl_2 (to a concentration of 0.1 M) and treated with TFA (5 vol.-%) and Et_3SiH (1.1 equiv.) at room temp. for 1 h. All volatiles were evaporated, and the residue was dissolved in CH_2Cl_2 (to a concentration of 0.5 M). The carboxylic acid (1.0 equiv.) and HOBt (1.2 equiv.) were dissolved in CH_2Cl_2/DMF (10:1, to a concentration of 0.1 M) and subsequently treated at 0 °C with carbodiimide (DIC or EDC, 1.25 equiv.) and base ($EtNiPr_2$ or Et_3N, 1.2 equiv.). After the mixture had been stirred at 0 °C for 30 min, the freshly prepared thiol solution was added dropwise and the reaction mixture was stirred at 0 °C→room temp. with TLC monitoring. The crude reaction mixture was diluted with EtOAc, (500 vol.-% of the reaction mixture) and washed subsequently with $NaHSO_4$ (1 M) and saturated NaCl solution (200 vol.-% of the reaction mixture each). The organic layer was dried with $MgSO_4$ and concentrated in vacuo.

General Procedure for the Formation of Azido Esters (GP E): The carboxylic acid (4 equiv.) was dissolved in CH_2Cl_2 (to a concentration of 0.2 M) and cooled to 0 °C. A carbodiimide (DCC, DIC, or EDC, 2 equiv.) and DMAP (10 mol-%) were added, and the mixture was stirred at 0 °C for 15 min. The alcohol in CH_2Cl_2 (0.5 M) was added dropwise, and the mixture was stirred at room temp. until full conversion (monitored by TLC). The crude reaction mixture was diluted with EtOAc, and washed with $NaHSO_4$ (1 M) and saturated NaCl solution. The organic layer was dried with $MgSO_4$ and concentrated in vacuo.

General Procedure for the Formation of Azolines through Aza-Wittig Ring Closures (GP F): The azido (thio)ester or *N*-acyltosylamide was dissolved in THF (to a concentration of 0.05 M) and treated dropwise at –20 °C with PPh_3 (1.5 equiv.) in THF (final concentration: 0.03–0.05 M). After 15 min stirring at –20 °C the reaction mixture was warmed to 40 °C and stirred for 6 h, unless stated otherwise. The reaction mixture was allowed to cool to room temp. and the solvent was removed under reduced pressure.

General Procedure for the Formation of Azoles (GP G): The azoline was dissolved in CH_2Cl_2 (to a concentration of 0.05 M) cooled to –10 °C and treated with DBU (2.1 equiv.). After the mixture had been stirred at –10 °C for 10 min, $BrCCl_3$ (1.1 equiv.) was added dropwise, and the reaction mixture was allowed to warm slowly to room temp. until conversion was complete (TLC monitoring). The crude reaction mixture was diluted with EtOAc, (500 vol.-% of the reaction mixture) and washed with $NaHSO_4$ (1 M) and saturated NaCl solution (200 vol.-% of the reaction mixture each). The organic layer was dried with $MgSO_4$ and concentrated in vacuo.

Synthesis of *N*-Acyl-Sulfonamides with DAST (GP H): The acid (2 equiv.) was dissolved in anhydrous CH_2Cl_2 (0.4 M) and cooled to 0 °C. Pyridine (2 equiv.) and DAST (diethylaminosulfur trifluoride, 2.4 equiv.) were added, and the mixture was stirred at 0 °C for 40 min. The organic layer was washed with water, and the combined aqueous layers were washed with CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$) and the solvent was evaporated in vacuo to afford the acid fluoride. Methyl (*S*)-2-azido-3-(tolyl-4′-sulfonylamino)propionate (**14d**, 1 equiv.) was dissolved in anhydrous CH_2Cl_2 (0.8 M) and cooled to 0 °C. $EtNiPr_2$ (2 equiv.) and the freshly prepared acid fluoride (2 equiv.) were added, and the mixture was stirred at room temperature until full conversion was reached (monitored by TLC). Water was added, and the pH of the aqueous layer was adjusted to pH 5 with citric acid (5% in H_2O). The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (1000 vol.-%, 4×). The combined extracts were dried ($MgSO_4$) and concentrated.

Synthesis of *N*-Acyl-Sulfonamides with HATU and Cs_2CO_3 (GP I): The acid (2 equiv.) was dissolved in anhydrous CH_2Cl_2 (to a concentration of 0.2 M), and the mixture was cooled to 0 °C. After addition of HATU (1.1 equiv.) and Cs_2CO_3 (1 equiv.) the mixture was stirred at this temperature for 15 min. More Cs_2CO_3 (3 equiv.) and sulfonamide **14d** (1 equiv.) in anhydrous CH_2Cl_2 (0.3 M) were added, and the mixture was stirred at 0 °C until conversion was complete (TLC monitoring). Water was added, and the pH of the aqueous layer was adjusted to pH 5 with citric acid (5% in H_2O). The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (700 vol.-%, 4×). The combined extracts were dried ($MgSO_4$) and concentrated in vacuo.

Methyl (2*R*,2′*S*)-2-Azido-3-(*N*-Boc-alanylthio)propionate (15a): *N*-Boc-alanine (47 mg, 0.25 mmol) and trityl-thiol **14c** (100 mg, 0.25 mmol) were coupled by **GP D** with DIC (40 μL, 0.30 mmol), HOBt (46 mg, 0.30 mmol), and $EtNiPr_2$ (30 μL, 0.30 mmol). After FCC (5 g, light petroleum/EtOAc, 4:1), thioester **15a** was isolated as a colorless oil (57 mg, 0.17 mmol, 69%). R_f = 0.29 (cyclohexane/EtOAc, 2:1). $[\alpha]_D^{20}$ = –59.3 ($CHCl_3$, c = 1.0). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.00 (d, J = 6.7 Hz, 1 H, NH), 4.40–4.29 (m, 1 H, C*H*CH$_3$), 4.03 (dd, J = 5.6, 7.6 Hz, 1 H, CHN$_3$), 3.76 (s, 3 H, CO_2CH_3), 3.30 (dd, J = 5.4, 14.0 Hz, 1 H, C*H*HCHN$_3$), 3.13 (dd, J = 7.7, 13.9 Hz, 1 H, CH*H*CHN$_3$), 1.41 [s, 9 H, C(CH$_3$)$_3$], 1.33 (d, J = 7.2 Hz, 3 H, CHC*H*$_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 201.2 [C(O)S], 169.2 (CO_2Me), 155.1 (CO_2tBu), 80.7 [*C*(CH$_3$)

$_3$], 61.5 (CHN_3), 56.5 ($CHCH_3$), 53.1 (CO_2CH_3), 30.1 (CH_2S), 28.5 [$C(CH_3)_3$], 18.6 ($CHCH_3$) ppm. IR (KBr): $\tilde{\nu}$ = 3382 (bs), 2980 (bs), 2503 (w), 2118 (s), 1714 (s), 1504 (m), 1454 (m), 1169 (s), 1049 (m), 968 (s), 915 (m), 859 (m), 785 (m), 626 (w), 551 (m) cm^{-1}. LC-MS (ESI): t_R = 9.6 min, C18; calcd. for $C_{12}H_{20}N_4O_5S$ $[M]^+$ 332.1; found 332.6. HRMS (ESI): calcd. for $C_{12}H_{21}N_4O_5S$ $[M + H]^+$ 333.1227; found 333.1230.

Methyl (2*R*,2′*S*)-2-Azido-3-[3-(1-benzyl-1*H*-imidazol-4-yl)-2-(*tert*-butoxycarbonylamino)propanoylthio]propionate (15b): N^{α}-Boc-N^{ε}-benzylhistidine (380 mg, 1.1 mmol) and trityl-thiol **14c** (322 mg, 0.80 mmol) were coupled as described in **GP D** with EDC (211 mg, 1.1 mmol). After chromatography on silica gel (CH_2Cl_2/MeOH 20:1), thioester **15b** was isolated as a colorless oil (287 mg, 0.59 mmol, 74%). R_f = 0.52 (CH_2Cl_2/MeOH 20:1). $[\alpha]_D^{20}$ = –91.2 ($CHCl_3$, c = 1.0). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.41 (s, 1 H, 2′′-H), 7.35–7.05 (m, 5 H, Ph), 6.62 (s, 1 H, 5′′-H), 6.56 (d, J = 7.8 Hz, 1 H, NH), 5.00 (d, J = 2.0 Hz, 2 H, CH_2Ph), 4.57–4.50 (m, 1 H, 2′-H), 3.93–3.83 (m, 1 H, 2-H), 3.75 (s, 3 H, CO_2CH_3), 3.21 (ddd, J = 5.4, 8.5, 13.9 Hz, 1 H, 3-H_a), 3.11 (dt, J = 4.8, 14.8 Hz, 1 H, 3′-H_a), 3.02–2.88 (m, 2 H, 3-H_b, 3′-H_b), 1.43 [s, 9 H, $C(CH_3)_3$] ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 201.6 (COS), 169.2 (CO_2Me), 155.7 (CO_2tBu), 137.4, 137.3 (C-2′′, C-4′′), 136.1, 129.6, 128.5, 127.4 (Ph), 117.5 (C-5′′), 80.3 [$C(CH_3)_3$], 61.5 (C-2), 60.5 (C-2′), 53.0 (CO_2CH_3), 51.0 (CH_2Ph), 30.2, 30.0 (C-3, C-3′), 28.5 [$C(CH_3)_3$] ppm. IR (KBr): $\tilde{\nu}$ = 3338 (bw), 3066 (w), 2979 (m), 2931 (m), 2118 (s), 1747 (s), 1713 (s), 1601 (w), 1497 (s), 1455 (m), 1393 (w), 1367 (m), 1249 (m), 1170 (s), 1079 (w), 1050 (w), 1025 (w), 953 (m), 913 (m), 857 (s), 817 (s), 722 (m), 648 (w) cm^{-1}. LC-MS (ESI): t_R = 7.3 min; calcd. for $C_{22}H_{29}N_6O_5S$ $[M + H]^+$ 489.2; found 488.9. HRMS (ESI): calcd. for $C_{22}H_{29}N_6O_5S$ $[M + H]^+$ 489.1915; found 489.1909.

Methyl (2*R*,2′*S*)-2-Azido-3-(*N*-Boc-valylthio)propionate (15c): *N*-Boc-valine (239 mg, 1.1 mmol) and trityl-thiol **14c** (322 mg, 0.80 mmol) were coupled as described in **GP D** with EDC (211 mg, 1.1 mmol). After chromatography on silica gel (light petroleum/EtOAc, 9:1), thioester **15c** was isolated as a colorless oil (239 mg, 0.64 mmol, 80%). R_f = 0.42 (light petroleum/EtOAc, 4:1). $[\alpha]_D^{20}$ = –44.6 ($CHCl_3$, c = 1.0). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.93 (d, J = 8.9 Hz, 1 H, NH), 4.26 (dd, J = 4.5, 9.2 Hz, 1 H, 2′-H), 4.04 (dd, J = 5.6, 7.6 Hz, 1 H, 2-H), 3.79 (s, 3 H, CO_2CH_3), 3.34 (td, J = 5.6, 13.9 Hz, 1 H, 3-H_a), 3.18 (dd, J = 7.7, 13.9 Hz, 1 H, 3-H_b), 2.33–2.20 (m, 1 H, 3′-H), 1.44 [s, 9 H, $C(CH_3)_3$], 0.97 (d, J = 6.9 Hz, 3 H, 3′-CH_3), 0.85 (d, J = 6.8 Hz, 3 H, 3′-CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 200.5 (COS), 169.2 (CO_2Me), 155.7 (CO_2tBu), 80.7 [$C(CH_3)_3$], 65.7 (C-2′), 61.5 (C-2), 53.2 (CO_2CH_3), 31.1 (C-3′), 30.2 (C-3), 28.5 [$C(CH_3)_3$], 19.6, 17.0 [$CH(CH_3)_2$] ppm. IR (KBr): $\tilde{\nu}$ = 3371 (bw), 2968 (m), 2934 (m), 2119 (s), 1824 (w), 1748 (s), 1713 (s), 1505 (m), 1455 (w), 1438 (w), 1393 (w), 1368 (m), 1307 (w), 1247 (m), 1169 (w), 1079 (w), 1040 (w) cm^{-1}. LC-MS (ESI): t_R = 10.4 min; calcd. for $C_{14}H_{24}N_4O_5S$ $[M]^+$ 360.1; found 360.4. HRMS (ESI): calcd. for $C_{14}H_{25}N_4O_5S$ $[M + H]^+$ 361.1540; found 361.1545.

Allyl (2*R*,2′*S*)-2-Azido-3-(*N*-Boc-prolylthio)propionate (15d): *N*-Boc-proline (50 mg, 0.23 mmol) and allyl (*R*)-2-azido-3-(tritylthio)propionate (**14e**, 101 mg, 0.23 mmol) were coupled as described in **GP D** with EDC (55 mg, 0.30 mmol), HOBt (47 mg, 0.35 mmol), and Et_3N (50 µL, 0.35 mmol). After chromatography on silica gel (light petroleum/EtOAc, 4:1), thioester **15d** was isolated as a colorless oil (48 mg, 0.13 mmol, 54%). R_f = 0.29 (cyclohexane/EtOAc, 2:1). $[\alpha]_D^{20}$ = –70.2 ($CHCl_3$, c = 0.5). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.92 (ddt, J = 5.9, 10.4, 16.3 Hz, 1 H, C*H*=CH_2), 5.36 (d, J = 17.0 Hz, 1 H, CH=C*H*H), 5.28 (d, J = 10.2 Hz, 1 H, CH=CH*H*), 4.67 (d, J = 5.2 Hz, 2 H, CH_2CH=CH_2), 4.50–4.32 (m, 1 H, 2-H), 4.04 (dd, J = 5.4, 7.8 Hz, 1 H, CHN_3), 3.59–3.27 (m, 3 H, 5-H, CH_2CHN_3), 3.25–3.08 (m, 1 H, 5-H), 2.27–2.10 (m, 1 H, 3-H), 2.02–1.84 (m, 3 H, 3-H, 4-H_2), 1.46/ 1.41 [each s, 9 H, $C(CH_3)_3$ – rotamers] ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 201.0 [C(O)S], 168.6 (CO_2All), 154.0 (CO_2tBu), 131.3 (CH=CH_2), 119.8 (CH=CH_2), 81.0 [$C(CH_3)_3$], 67.0 (CH_2CH=CH_2), 66.4/ 66.2 (C-2 – rotamers), 61.6 (CHN_3), 47.2/ 46.9 (CH_2CHN_3), 31.8 (C-3), 30.2/ 29.8 (C-5), 28.6/ 28.5 [$C(CH_3)_3$], 24.4/ 23.6 (C-4) ppm. IR (KBr): $\tilde{\nu}$ = 3418 (bm), 2936 (bm), 2118 (s), 1731 (s), 1714 (s), 1695 (s), 1556 (w), 1538 (w), 1504 (m), 1455 (m), 1370 (w), 1217 (m), 1176 (s), 861 (s), 800 (s), 666 (w) cm^{-1}. LC-MS (ESI): t_R = 10.3 min; calcd. for $C_{16}H_{24}N_4O_5SNa$ $[M + Na]^+$ 407.1; found 407.1. HRMS (ESI): calcd. for $C_{16}H_{25}N_4O_5S$ $[M + H]^+$ 385.1540; found 385.1541.

Methyl (2*R*,2′*S*)-2-Azido-3-(*N*-Boc-ω-cyclohexyl-α-glutamylthio)-propionate (15e): *N*-Boc-ω-cyclohexylglutamine (165 mg, 0.50 mmol) and trityl-thiol **14c** (242 mg, 0.60 mmol) were coupled as described in **GP D** with EDC (124 mg, 0.65 mmol), HOBt (101 mg, 0.75 mmol), and Et_3N (100 µL, 0.75 mmol). After chromatography on silica gel (cyclohexane/EtOAc, 4:1), thioester **15e** was isolated as a colorless oil (188 mg, 0.40 mmol, 80%). R_f = 0.37 (cyclohexane/EtOAc, 2:1). $[\alpha]_D^{20}$ = –26.0 ($CHCl_3$, c = 0.1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.22 (d, J = 7.6 Hz, 1 H, NH), 4.80–4.74 (m, 1 H, Cy), 4.36 (dd, J = 8.5, 12.6 Hz, 1 H, CHN_3), 4.07 (dd, J = 5.6, 7.7 Hz, 1 H, C*H*NHBoc), 3.82 (s, 3 H, CO_2CH_3), 3.36 (ddd, J = 5.5, 10.7, 13.9 Hz, 1 H, C*H*HCHN$_3$), 3.23–3.11 (m, 1 H, CH*H*CHN$_3$), 2.42 (m, 2 H, CH_2CO_2Cy), 2.25–2.12 (m, 1 H, C*H*HCH$_2$CO$_2$Cy), 2.01–1.89 (m, 1 H, CH*H*CH$_2$CO$_2$Cy), 1.88–1.81 (m, 2 H, Cy), 1.74–1.69 (m, 2 H, Cy), 1.61–1.53 (m, 1 H, Cy), 1.45 [s, 9 H, $C(CH_3)_3$], 1.41–1.19 (m, 5 H, Cy) ppm. IR (KBr): $\tilde{\nu}$ = 3418 (bw), 2979 (bm), 2118 (s), 1747 (m), 1732 (m), 1695 (s), 1682 (s), 1556 (w), 1538 (w), 1505 (m), 1455 (m), 1394 (m), 1209 (m), 1170 (s), 1127 (w), 856 (s), 800 (s), 666 (w) cm^{-1}. LC-MS (ESI): t_R = 11.0 min; calcd. for $C_{20}H_{32}N_4O_7S$ $[M]^+$ 472.2; found 472.6.

Methyl (2*S*,2′*S*)-2-Azido-3-(*N*-Boc-prolyloxy)propionate (15f): *N*-Boc-proline (244 mg, 1.1 mmol) and alcohol **14a** (150 mg, 1.0 mmol) were coupled as described in **GP E** with DIC (208 µL, 1.3 mmol). After chromatography on silica gel (light petroleum/EtOAc, 4:1), ester **15f** was isolated as a colorless oil (296 mg, 0.9 mmol, 84%). R_f = 0.23 (light petroleum/EtOAc, 2:1). $[\alpha]_D^{20}$ = –74.2 ($CHCl_3$, c = 1.0). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.43 (2 × dd, J = 3.8, 11.6 Hz, 1 H, C*H*HCHN$_3$ – rotamers), 4.41 (dd, J = 1.6, 4.8 Hz, 1 H, CH*H*CHN$_3$), 4.24 (2 × dd, J = 3.8, 8.6 Hz, 1 H, 2-H – rotamers), 4.08 (q, J = 5.4 Hz, 1 H, CHN_3), 3.78 (s, 3 H, CO_2CH_3), 3.54–3.28 (m, 2 H, 5-H_2), 2.27–2.08 (m, 1 H, 3-H), 1.88 (m, 3 H, 3-H, 4-H_2), 1.41, 1.36 [each s, 9 H, $C(CH_3)_3$ - rotamers] ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.7/ 172.4 (CO_2CH_2 – rotamers), 168.2/ 168.1 (CO_2Me), 154.5/ 153.7 (CO_2tBu), 80.1/ 80.0 [$C(CH_3)_3$], 64.2/ 64.1 (CH_2CHN_3), 60.5/ 60.4 (CHN_3), 59.1/ 58.9 (C-2), 53.2 (CO_2CH_3), 46.7/ 46.4 (C-5), 31.0/ 30.0 (C-3), 28.5/ 28.4 [$C(CH_3)_3$], 24.5/ 23.8 (C-4) ppm. IR (KBr): $\tilde{\nu}$ = 3492 (w), 3370 (w), 2977 (s), 2884 (w), 2521 (w), 2359 (w), 2340 (w), 2112 (s), 1755 (s), 1698 (s), 1478 (m), 1396 (s), 1176 (s), 1088 (m), 970 (m), 919 (m), 888 (m), 773 (m) cm^{-1}. LC-MS (ESI): t_R = 9.7 min, C18; calcd. for $C_{14}H_{22}N_4O_6$ $[M]^+$ 342.2; found 342.6. HRMS (ESI): calcd. for $C_{14}H_{23}N_4O_6$ $[M + H]^+$ 343.1612; found 344.1614.

Methyl (2*S*,2′*S*)-2-Azido-3-(*N*-Boc-alanyloxy)propionate (15g): *N*-Boc-alanine (756 mg, 4.0 mmol) and alcohol **14a** (145 mg, 1.0 mmol) were coupled as described in **GP E** with DCC (413 mg, 2.0 mmol) and DMAP (14 mg, 10 mol-%). After FCC (15 g, light

petroleum/EtOAc, 5:1), ester **15g** was obtained as a colorless oil (290 mg, 0.9 mmol, 92%). R_f = 0.33 (light petroleum/EtOAc, 2:1). $[\alpha]_D^{20}$ = –24.6 ($CHCl_3$, c = 1.0). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.95 (s, 1 H, NH), 4.52 (dd, J = 3.9, 11.6 Hz, 1 H, C*H*HCHN$_3$), 4.40 (dd, J = 5.8, 11.6 Hz, 1 H, CH*H*CHN$_3$), 4.34–4.28 (m, 1 H, CHN$_3$), 4.12 (dd, J = 4.0, 5.7 Hz, 1 H, C*H*CH$_3$), 3.81 (s, 3 H, CO_2CH_3), 1.42 [s, 9 H, C(CH$_3$)$_3$], 1.38 (d, J = 7.2 Hz, 3 H, CHC*H*$_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.0 (*C*O$_2$CH$_2$), 168.2 (CO_2Me), 155.0 (CO_2tBu), 80.0 [*C*(CH$_3$)$_3$], 64.3 (*C*H$_2$CHN$_3$), 60.5 (*C*HCH$_3$), 53.3 (CO_2CH$_3$), 49.4 (CHN$_3$), 28.5 [C(*C*H$_3$)$_3$], 18.6 (CH*C*H$_3$) ppm. IR (KBr): $\tilde{\nu}$ = 3389 cm^{-1} (s), 2979 (s), 2524 (w), 2110 (s), 1745 (s), 1712 (s), 1504 (s), 1454 (m), 1164 (m),1066 (w), 856 (w), 783 (w). LC-MS (ESI): t_R = 9.4 min, C18; calcd. for $C_{12}H_{20}N_4O_6$ [M]$^+$ 316.1; found 316.5.

Methyl (2*S*,3*R*,2′*S*)-2-Azido-3-(*N*-Boc-alanyloxy)butanoate (15h): *N*-Boc-alanine (196 mg, 1.0 mmol) and alcohol **14b** (150 mg, 0.9 mmol) were coupled as described in **GP E** with DIC (190 μL, 1.2 mmol). After FCC (light petroleum/EtOAc, 4:1), ester **15h** was isolated as a colorless oil (267 mg, 0.8 mmol, 86%). R_f = 0.42 (light petroleum/EtOAc, 2:1). $[\alpha]_D^{20}$ = +21.4 ($CHCl_3$, c = 1.0). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.41 (qd, J = 3.7, 6.4 Hz, 1 H, 3-H), 4.91 (s, 1 H, NH), 4.29–4.16 (m, 1 H, CHN$_3$), 3.78 (s, 3 H, CO_2CH_3), 3.74 (d, J = 3.5 Hz, 1 H, 2′-H), 1.42 [s, 9 H, C(CH$_3$)$_3$], 1.36 (d, J = 6.5 Hz, 3 H, 4-H$_3$), 1.34, (d, J = 7.3, 3 H, 3′-H$_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.2 (C-1′), 168.6 (CO_2Me), 155.2 (CO_2tBu), 80.1 [*C*(CH$_3$)$_3$], 71.5 (C-3), 64.7 (C-2′), 53.2 (CO_2CH$_3$), 49.7 (CHN$_3$), 28.5 [C(*C*H$_3$)$_3$], 18.5 (C-3′), 17.2 (C-4) ppm. IR (KBr): $\tilde{\nu}$ = 3385 (m), 2982 (s), 2939 (m), 2114 (s), 1748 (s), 1715 (s), 1505 (m), 1455 (m), 1382 (m), 1248 (m), 1210 (m), 1168 (s), 1067 (w), 892 (m), 857 (m), 798 (m) cm^{-1}. LC-MS (ESI): t_R = 9.6 min, C18; calcd. for $C_{13}H_{22}N_4O_6$ [M]$^+$ 330.2; found 330.4. HRMS (ESI): calcd. for $C_{13}H_{23}N_4O_6$ [M + H]$^+$ 331.1612; found 331.1614.

Methyl (2*S*,2′*S*)-2-Azido-3-(*N*-Boc-phenylalanyloxy)propionate (15i): *N*-Boc-phenylalanine (265 mg, 1.0 mmol) and alcohol **14a** (73 mg, 0.5 mmol) were coupled as described in **GP E** with DCC (108 mg, 0.5 mmol). After chromatography on silica gel (light petroleum/EtOAc, 4:1), ester **15i** was isolated as a colorless oil (173 mg, 0.4 mmol, 88%). R_f = 0.37 (light petroleum/EtOAc, 2:1). $[\alpha]_D^{20}$ = +1.3 ($CHCl_3$, c = 1.0). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.41–7.04 (m, 5 H, Ph), 4.90 (d, J = 7.6 Hz, 1 H, NH), 4.58 (dd, J = 5.8, 12.5 Hz, 1 H, CHN$_3$), 4.44 (dd, J = 4.0, 11.6 Hz, 1 H, C*H*HCHN$_3$), 4.36 (dd, J = 6.1, 11.6 Hz, 1 H, CH*H*CHN$_3$), 4.05 (dd, J = 4.0, 6.0 Hz, 1 H, CHBn), 3.81 (s, 3 H, CO_2CH_3), 3.10 (dd, J = 5.9, 13.8 Hz, 1 H C*H*HPh), 3.03 (dd, J = 6.4, 14.1 Hz, 1 H, CH*H*Ph), 1.39 [s, 9 H, C(CH$_3$)$_3$] ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.6 (*C*O$_2$CH$_2$), 168.1 (CO_2Me), 155.2 (CO_2tBu), 135.9, 129.5, 128.9, 127.4 (Ph), 80.3 [*C*(CH$_3$)$_3$], 64.4 (*C*H$_2$CHN$_3$), 60.5 (CHBn), 54.6 (CHN$_3$), 53.4 (CO_2CH$_3$), 38.4 (CH$_2$Ph), 28.5 [C(*C*H$_3$)$_3$] ppm. IR (KBr): $\tilde{\nu}$ = 3385 (m), 2979 (m), 2111 (s), 1749 (s), 1715 (s), 1504 (m), 1455 (m), 1368 (m), 1247 (m), 1210 (m), 1171 (s), 1059 (w), 957 (m), 858 (s), 798 (s), 701 (m) cm^{-1}. LC-MS (ESI): t_R = 10.3 min, C18; calcd. for $C_{18}H_{24}N_4O_6$ [M]$^+$ 392.2; found 392.5. HRMS (ESI): calcd. for $C_{18}H_{25}N_4O_6$ [M + H]$^+$ 393.1769; found 393.1768.

Methyl (2*S*,2′*R*)- and (2*S*,2′*S*)-2-Azido-3-(*N*-Boc-*S*-trityl-cysteinyloxy)propionate (15j): *S*-Trityl-*N*-Boc-(*R*)-cysteine (510 mg, 1.1 mmol) and alcohol **14a** (73 mg, 0.5 mmol) were coupled as described in **GP E** with DCC (108 mg, 0.6 mmol). After FCC (light petroleum/EtOAc, 4:1), ester **15j** was isolated as a colorless oil (258 mg, 0.4 mmol, 87%, *dr* = 3:2). R_f = 0.19 (light petroleum/EtOAc, 4:1). $[\alpha]_D^{20}$ = –6.5 ($CHCl_3$, c = 1.0). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.44–7.14 (m, 15 H, Tr), 4.93 (d, J = 7.5 Hz, 1 H, NH), 4.43 (dt, J = 3.8, 11.5 Hz, 1 H, C*H*HCHN$_3$), 4.35 (ddd, J = 5.1, 6.4, 11.5 Hz, 1 H, CH*H*CHN$_3$), 4.23 (dd, J = 4.3, 5.9 Hz, 1 H, CHN$_3$), 4.09 (ddd, J = 1.7, 4.6, 8.6 Hz, 1 H, C*H*NHBoc), 3.76/3.73 [2× s (diastereomers 2:1), 3 H, CO_2CH_3], 2.64 (dd, J = 6.5, 11.6 Hz, 1 H, CH*H*STr), 2.55 (ddd, J = 4.8, 11.3, 12.3 Hz, 1 H, C*H*HSTr), 1.41 [s, 9 H, C(CH$_3$)$_3$] ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.5 (CO_2Me), 168.0 (*C*O$_2$CH$_2$), 155.1 (CO_2tBu), 144.4, 129.7, 128.3, 127.1 (Tr), 80.4 [*C*(CH$_3$)$_3$], 64.5 (*C*H$_2$CHN$_3$), 60.5 (CHNHBoc), 53.3 (CO_2CH$_3$), 52.7 (CHN$_3$), 34.1 (CH$_2$STr), 28.5 [C(*C*H$_3$)$_3$] ppm. IR (KBr): $\tilde{\nu}$ = 3413 (w), 3059 (w), 2978 (m), 2930 (w), 2112 (s), 1755 (s), 1715 (s), 1504 (s), 1446 (m), 1368 (m), 1211 (m), 1172 (s), 856 (s), 800 (s), 745 (m), 701 (m), 621 (w) cm^{-1}. LC-MS (ESI): t_R = 11.7 min, C18; calcd. for $C_{31}H_{34}N_4O_6S$ [M]$^+$ 590.2; found 590.1. HRMS (ESI): calcd. for $C_{31}H_{34}N_4O_6SNa$ [M + H]$^+$ 613.2091; found 613.2088.

Methyl (2*S*,2′*S*)-2-Azido-3-(*N*-Boc-ω-cyclohexyl-glutamyloxy)propionate (15k): *N*-Boc-glutamic acid ω-cyclohexyl ester (659 mg, 2 mmol) and alcohol **14a** (73 mg, 0.5 mmol) were coupled as described in **GP E** with DCC (208 mg, 2 mmol). After FCC (light petroleum/EtOAc, 7:1→4:1), ester **15k** was isolated as a colorless oil (227 mg, 0.5 mmol, 99%). R_f = 0.13 (light petroleum/EtOAc, 5:1). $[\alpha]_D^{20}$ = –8.6 ($CHCl_3$, c = 0.5). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.09 (d, J = 7.4 Hz, 1 H, NH), 4.81–4.67 (m, 1 H, Cy), 4.51 (dd, J = 4.1, 11.5 Hz, 1 H, C*H*HCHN$_3$), 4.39 (dd, J = 5.9, 11.6 Hz, 1 H, CH*H*CHN$_3$), 4.32 (dd, J = 7.1, 11.0 Hz, 1 H, CHN$_3$), 4.15 (dd, J = 4.1, 5.8 Hz, 1 H, C*H*NHBoc), 3.81 (s, 3 H, CO_2CH_3), 2.41–2.33 (m, 2 H, C*H*$_2$CO$_2$Cy), 2.22–2.08 (m, 1 H, C*H*HCH$_2$CO$_2$Cy), 2.02–1.89 (m, 1 H, C*H*HCH$_2$CO$_2$Cy), 1.86–1.77 (m, 2 H, Cy), 1.69 (m, 2 H, Cy), 1.51 (m, 1 H, Cy), 1.41 [s, 9 H, C(CH$_3$)$_3$], 1.37–1.19 (m, 5 H, Cy) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.3 (CO_2Cy), 171.9 (CO_2Me), 168.1 (*C*O$_2$CH$_2$), 155.5 (CO_2tBu), 80.4 [*C*(CH$_3$)$_3$], 73.3 (Cy), 64.3 (*C*H$_2$CHN$_3$), 60.5 (CHNHBoc), 53.4 (CO_2CH$_3$), 53.2 (CHN$_3$), 31.8 (Cy), 30.9 (*C*H$_2$CO$_2$Cy), 28.5 [C(*C*H$_3$)$_3$], 27.5 (*C*H$_2$CH$_2$CO$_2$Cy), 25.6, 24.0 (Cy) ppm. IR (KBr): $\tilde{\nu}$ = 3364 (w), 2938 (m), 2862 (w), 2110 (m), 1730 (s), 1539 (m), 1506 (m), 1455 (m), 1393 (m), 1207 (m), 1175 (s), 1057 (w), 860 (s), 799 (s) cm^{-1}. LC-MS (ESI): t_R = 10.9 min, C18; calcd. for $C_{20}H_{32}N_4O_8$ [M]$^+$ 456.2; found 456.6. HRMS (ESI): calcd. for $C_{20}H_{33}N_4O_8$ [M + H]$^+$ 457.2293; found 457.2289.

Methyl (2*S*,2′*S*)-2-Azido-3-(*O*-Benzyl-*N*-Boc-tyrosyloxy)propionate (15l): *O*-Benzyl-*N*-Boc-tyrosine (422 mg, 1.1 mmol) and alcohol **14a** (150 mg, 1.0 mmol) were coupled as described in **GP E** with DIC (208 μL, 1.3 mmol) and DMAP (13 mg, 10 mol-%). After FCC (light petroleum/EtOAc, 4:1), ester **15l** was isolated as a colorless oil (435 mg, 0.9 mmol, 84%). R_f = 0.35 (light petroleum/EtOAc, 2:1). $[\alpha]_D^{20}$ = –6.3 ($CHCl_3$, c = 1.0). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.43–7.26 (m, 5 H, Ph), 7.08–6.99 (m, 2 H, Tyr-Ar), 6.92–6.85 (m, 2 H, Tyr-Ar), 5.02 (s, 2 H, CH$_2$Ph), 4.88 (d, J = 6.2 Hz, 1 H, NH), 4.54 (dd, J = 5.9, 12.7 Hz, 1 H, CHN$_3$), 4.45 (ddd, J = 4.1, 5.2, 11.6 Hz, 1 H, C*H*HCHN$_3$), 4.37 (ddd, J = 2.1, 6.3, 11.6 Hz, 1 H, CH*H*CHN$_3$), 4.15–4.01 (m, 1 H, C*H*NHBoc), 3.81 (s, 3 H, CO_2CH_3), 3.10–2.89 (m, 2 H, Tyr-CH$_2$), 1.40 [s, 9 H, C(CH$_3$)$_3$] ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.6 (*C*O$_2$CH$_2$), 168.1 (CO_2Me), 158.2 (CO_2tBu), 137.2, 130.5, 130.5, 128.8, 128.2, 127.7, 115.3 (Ph, Tyr-Ar), 80.3 [*C*(CH$_3$)$_3$], 70.3 (OCH$_2$Ph), 64.3 (*C*H$_2$CHN$_3$), 60.5 (CHNHBoc), 54.7 (CHN$_3$), 53.4 (CO_2CH$_3$), 37.5 (Tyr-CH$_2$), 28.5 [C(*C*H$_3$)$_3$] ppm. IR (KBr): $\tilde{\nu}$ = 3390 (m), 3033 (m), 2977 (s), 2528 (w), 2112 (s), 1747 (s), 1714 (s), 1611 (m), 1511 (s), 1454 (m), 1367 (s), 1243 (s), 1173 (s), 1021 (m), 823 (m), 739 (m) cm^{-1}. LC-MS (ESI): t_R = 11.0 min, C18; calcd. for $C_{25}H_{30}N_4O_7$ [M]$^+$ 498.2; found 497.8. HRMS (ESI): calcd. for $C_{25}H_{30}N_4O_7Na$ [M + Na]$^+$ 521.2007; found 521.1998.

Methyl (2*S*,2′*S*,3′*S*)-2-Azido-3-(*O*-benzyl-*N*-Boc-threonyloxy)propionate (15m): *O*-Benzyl-*N*-Boc-threonine (2.69 g, 8.8 mmol) and alcohol **14a** (584 mg, 4.0 mmol) were coupled as described in **GP E** with DCC (914 mg, 4.4 mmol) and DMAP (54 mg, 10 mol-%). After FCC (light petroleum/EtOAc, 4:1), ester **15m** was isolated as a colorless oil (1.73 g, 4.0 mmol, 98%). R_f = 0.45 (light petroleum/EtOAc, 2:1). $[\alpha]_D^{20}$ = –18.6 ($CHCl_3$, *c* = 1.0). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38–7.21 (m, 5 H Ph), 5.26 (d, *J* = 9.7 Hz, 1 H, NH), 4.55 (d, *J* = 11.8 Hz, 1 H, CH*H*Ph), 4.42–4.24 (m, 4 H, C*H*HPh, C*H*NHBoc, C*H*$_2$CHN$_3$), 4.17–4.04 (m, 1 H, CHOBn), 3.98 (dd, *J* = 5.0 Hz, 1 H, CHN$_3$), 3.78 (s, 3 H, CO_2CH_3), 1.43 [s, 9 H, C(CH$_3$)$_3$], 1.25 (d, *J* = 6.3 Hz, 3 H, CHC*H*$_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.8 (*C*O$_2$CH$_2$CHN$_3$), 168.0 (*C*O$_2$Me), 156.3 (CO$_2$*t*Bu), 138.1, 128.6, 128.0, 127.9 (Ph), 80.2 [*C*(CH$_3$)$_3$], 74.5 (CHOBn), 71.0 (CH$_2$Ph), 64.4 (*C*H$_2$CHN$_3$), 60.5 (CHN$_3$), 58.5 (CHNHBoc), 53.3 (CO_2CH_3), 28.5 [C(*C*H$_3$)$_3$], 16.4 [CH(*C*H$_3$)] ppm. IR (KBr): $\tilde{\nu}$ = 3444 (w), 2979 (m), 2933 (m), 2111 (s), 1756 (s), 1715 (s), 1505 (s), 1279 (m), 1210 (m), 1165 (s), 1073 (w), 861 (s), 798 (s), 747 (m), 699 (m) cm^{-1}. HPLC: t_R = 11.2 min (method 1). LC-MS (ESI): t_R = 10.6 min, C18; calcd. for $C_{20}H_{29}N_4O_7$ [M + H]$^+$ 437.2; found 436.7. HRMS (ESI): calcd. for $C_{20}H_{29}N_4O_7$ [M + H]$^+$ 437.2031; found 436.2030.

Methyl (2*S*,2′*S*)-2-Azido-3-(*N*-Boc-valyloxy)propionate (15n): *N*-Boc-valine (435 mg, 2.0 mmol) and alcohol **14a** (144 mg, 1.0 mmol) were coupled as described in **GP E** with DIC (343 µL, 2.2 mmol) and DMAP (24 mg, 10 mol-%). After FCC (light petroleum/EtOAc, 4:1), ester **15n** was isolated as a colorless oil (324 mg, 0.9 mmol, 95%). R_f = 0.20 (light petroleum/EtOAc, 4:1). $[\alpha]_D^{20}$ = –17.1 ($CHCl_3$, *c* = 1.0). ^{1}H NMR (400 MHz, [D$_5$]pyridine): δ = 7.21 (d, *J* = 8.4 Hz, 1 H, NH), 3.83–3.80 (m, 2 H, CHN$_3$, C*H*HCHN$_3$), 3.74 (dd, *J* = 6.2, 12.2 Hz, 1 H, CH*H*CHN$_3$), 3.65 (dd, *J* = 5.9, 8.6 Hz, 1 H, C*H*NHBoc), 2.76 (s, 3 H, CO_2CH_3), 1.40 [m, 1 H, C*H*(CH$_3$)$_2$], 0.54 [s, 9 H, C(CH$_3$)$_3$], 0.14/ 0.12 [2× d, *J* = 6.8 Hz, 2×3 H, CH(C*H*$_3$)$_2$] ppm. ^{13}C NMR (100 MHz, [D$_5$]pyridine): δ = 173.0 (*C*O$_2$CH$_2$CHN$_3$), 169.1 (*C*O$_2$CH$_3$), 157.3 (CO$_2$*t*Bu), 79.3 [*C*(CH$_3$)$_3$], 64.7 (CH$_2$), 61.6 (CHN$_3$), 60.6 (CH*i*Pr), 53.3 (CO_2CH_3), 31.6 [*C*H(CH$_3$)$_2$], 28.9 [C(*C*H$_3$)$_3$], 19.8, 18.8 [2× CH(*C*H$_3$)$_2$] ppm. IR (KBr): $\tilde{\nu}$ = 3389 (m), 2969 (s), 2112 (s), 1748 (s), 1714 (s), 1504 (m), 1454 (m), 1367 (w), 1177 (m), 1018 (w), 871 (w), 553 (w) cm^{-1}. LC-MS (ESI): t_R = 10.1 min, C18; calcd. for $C_{14}H_{24}N_4O_6$ [M]$^+$ 344.2; found 344.6. HRMS (FAB): calcd. for $C_{14}H_{24}N_4O_6$ [M + H]$^+$ 344.1774; found 344.1802.

Methyl (2*S*)-2-Azido-3-(*N*-Boc-glycyloxy)propionate (15o): *N*-Boc-glycine (350 mg, 2.0 mmol) and alcohol **14a** (147 mg, 1.0 mmol) were coupled as described in **GP E** with DIC (340 µL, 2.2 mmol) and DMAP (24 mg, 20 mol-%). After FCC (light petroleum/EtOAc, 4:1), ester **15o** was isolated as a colorless oil (286 mg, 0.9 mmol, 93%). R_f = 0.28 (light petroleum/EtOAc, 2:1). $[\alpha]_D^{20}$ = –14.4 ($CHCl_3$, *c* = 1.0). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.01 (s, 1 H, NH), 4.49 (dd, *J* = 4.0, 11.6 Hz, 1 H, C*H*HCHN$_3$), 4.41 (dd, *J* = 6.0, 11.6 Hz, 1 H, CH*H*CHN$_3$), 4.12 (dd, *J* = 4.1, 5.9 Hz, 1 H, CHN$_3$), 3.91 (d, *J* = 5.6 Hz, 2 H, C*H*$_2$NHBoc), 3.79 (s, 3 H, CO_2CH_3), 1.41 [s, 9 H, C(CH$_3$)$_3$] ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.0 (*C*O$_2$CH$_2$), 168.1 (CO$_2$Me), 155.8 (CO$_2$*t*Bu), 80.4 [*C*(CH$_3$)$_3$], 64.3 (*C*H$_2$CHN$_3$), 60.4 (CH$_2$NHBoc), 53.1 (CO_2CH_3), 42.4 (CHN$_3$), 28.4 [C(*C*H$_3$)$_3$] ppm. IR (KBr): $\tilde{\nu}$ = 3401 (s), 2978 (s), 2112 (s), 1747 (s), 1714 (s), 1504 (m), 1454 (m), 1392 (m), 1368 (m), 1162 (s), 1056 (m), 949 (m), 863 (m), 784 (m) cm^{-1}. HPLC: t_R = 7.8 min (method 4). LC-MS (ESI): t_R = 9.1 min, C18; calcd. for $C_{11}H_{18}N_4O_6$ [M]$^+$ 302.1; found 302.4. HRMS (ESI): calcd. for $C_{11}H_{19}N_4O_6$ [M + H]$^+$ 303.1299; found 303.1301.

Methyl (4*R*,1′*S*)-2-[1-(*tert*-Butoxycarbonylamino)ethyl]-4,5-dihydrothiazole-4-carboxylate (16a): Thioester **15a** (55 mg, 0.17 mmol) was cyclized as described in **GP F**. After FCC (cyclohexane/EtOAc, 2:1), ester **16a** was isolated as a colorless resin (47 mg, 0.16 mmol, 98%). R_f = 0.25 (cyclohexane/EtOAc, 1:1). $[\alpha]_D^{20}$ = +31.4 ($CHCl_3$, *c* = 0.5). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.25 (br. s, 1 H, NH), 5.05 (td, *J* = 1.6, 9.3 Hz, 1 H, C*H*CH$_3$), 4.60–4.47 (m, 1 H, 4-H), 3.76 (s, 3 H, CO_2CH_3), 3.61–3.41 (m, 2 H, 5-H$_2$), 1.39 [s, 9 H, C(CH$_3$)$_3$], 1.38 (d, *J* = 4.1 Hz, 3 H, CHC*H*$_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.4 (CO$_2$Me), 171.2 (C=N), 155.0 (CO$_2$*t*Bu), 79.9 [*C*(CH$_3$)$_3$], 78.1 (C-4), 52.9 (CO$_2$*C*H$_3$), 49.4 (*C*HCH$_3$), 35.6 (C-5), 28.5 [C(*C*H$_3$)$_3$], 20.7 (CH*C*H$_3$) ppm. IR (KBr): $\tilde{\nu}$ = 3345 (bw), 2979 (m), 2933 (w), 1799 (w), 1745 (s), 1714 (s), 1622 (m), 1505 (m), 1454 (m), 1393 (w), 1367 (m), 1244 (m), 1203 (m), 1172 (s), 1088 (w), 862 (s), 798 (s) cm^{-1}. LC-MS (ESI): t_R = 8.5 min; calcd. for $C_{12}H_{21}N_2O_4S$ [M + H]$^+$ 289.1; found 288.8. HRMS (ESI): calcd. for $C_{12}H_{21}N_2O_4S$ [M + H]$^+$ 289.1217; found 289.1218.

Methyl (4*R*,1′*S*)-2-[2-(1-Benzyl-1*H*-imidazol-4-yl)-1-(*tert*-butoxycarbonylamino)ethyl]-4,5-dihydrothiazole-4-carboxylate (16b): Thioester **15b** (264 mg, 0.54 mmol) was cyclized as described in **GP F**. After FCC (CH_2Cl_2/MeOH 20:1), thiazoline **16b** was isolated as a colorless resin (228 mg, 0.51 mmol, 95%, *dr* = 3.5:1). R_f = 0.40 (CH_2Cl_2/MeOH 10:1). $[\alpha]_D^{20}$ = –1.7 ($CHCl_3$, *c* = 1.0). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.44 (s, 1 H, 2′′-H), 7.35–7.27 (m, 3 H, Ph), 7.16–7.06 (m, 2 H, Ph), 6.71/ 6.65 [2× s (1:3.5), 1 H, 5′′-H, diastereomers], 6.35/ 6.29 [2× d (1:3.5), *J* = 7.9 Hz, 1 H, NH], 5.05 (d, *J* = 15.3 Hz, 1 H, C*H*HPh), 5.01 (d, *J* = 15.3 Hz, 1 H, CH*H*Ph), 4.95 (t, *J* = 9.3 Hz, 1 H, 4-H), 4.80 (br. s, 1 H, 1′-H), 3.76/ 3.70 [2× s (3.5:1), 3 H, CO_2CH_3], 3.49–3.21 (m, 2 H, 5-H$_2$), 3.15–2.94 (m, 2 H, 2′-H$_2$), 1.41 [s, 9 H, C(CH$_3$)$_3$] ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 179.4/ 178.6 (C-2), 171.3 (CO$_2$Me), 155.5 (CO$_2$*t*Bu), 138.2/ 137.9 (C-4′′), 137.2/ 137.1 (C-2′′), 136.4/ 129.1/ 128.4/ 127.4 (Ph), 117.9/ 117.6 (C-5′′), 79.7 [*C*(CH$_3$)$_3$], 78.8/ 78.6 (C-4), 53.5 (C-1′), 52.8 (CO$_2$*C*H$_3$), 51.0 (CH$_2$Ph), 35.0/ 34.8 (C-5), 32.3 (C-2′), 28.5 [C(*C*H$_3$)$_3$] ppm. IR (KBr): $\tilde{\nu}$ = 2979 (w), 2930 (w), 2360 (s), 2341 (s), 1714 (s), 1616 (w), 1557 (w), 1539 (w), 1497 (s), 1455 (m), 1436 (m), 1393 (w), 1367 (m), 1277 (w), 1234 (m), 1202 (m), 1171 (s), 1046 (w), 1026 (w), 859 (s), 799 (s), 721 (m), 697 (w), 669 (w) cm^{-1}. LC-MS (ESI): t_R = 6.8 min; calcd. for $C_{22}H_{29}N_4O_4S$ [M + H]$^+$ 445.2; found 444.9. HRMS (ESI): calcd. for $C_{22}H_{29}N_4O_4S$ [M + H]$^+$ 445.1904; found 445.1901.

Methyl (4*R*,1′*S*)-2-[1-(*tert*-Butoxycarbonylamino)-2-methylpropyl]-4,5-dihydrothiazole-4-carboxylate (16c): Thioester **15c** (210 mg, 0.58 mmol) was cyclized as described in **GP F**. After FCC (light petroleum/EtOAc, 4:1), thiazoline **16c** was isolated as a colorless resin (167 mg, 0.53 mmol, 91%). R_f = 0.27 (light petroleum/EtOAc, 2:1). $[\alpha]_D^{20}$ = +42.6 ($CHCl_3$, *c* = 0.5). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.20 (d, *J* = 8.3 Hz, 1 H, NH), 5.13 (ddd, *J* = 1.5, 8.1, 9.5 Hz, 1 H, 4-H), 4.51–4.44 (m, 1 H, 1′-H), 3.79 (s, 3 H, CO$_2$Me), 3.62–3.47 (m, 2 H, 5-H$_2$), 2.18 (m, 1 H, 2′-H), 1.44 [s, 9 H, C(CH$_3$)$_3$], 0.99 (d, *J* = 6.8 Hz, 3 H, 2′-CH$_3$), 0.89 (d, *J* = 6.8 Hz, 3 H, 2′-CH$_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.2 (C-2), 171.3 (CO$_2$Me), 155.7 (CO$_2$*t*Bu), 79.9 [*C*(CH$_3$)$_3$], 77.9 (C-4), 58.2 (C-1′), 52.9 (CO$_2$*C*H$_3$), 35.8 (C-5), 32.7 (C-2′), 28.5 [C(*C*H$_3$)$_3$], 19.6, 16.8 [CH(*C*H$_3$)$_2$] ppm. IR (KBr): $\tilde{\nu}$ = 3384 (bw), 2967 (m), 1715 (s), 1620 (m), 1497 (s), 1455 (w), 1392 (w), 1367 (m), 1307 (w), 1234 (m), 1171 (s), 1040 (w), 1012 (w), 929 (s), 875 (s), 798 (s), 665 (w) cm^{-1}. LC-MS (ESI): t_R = 9.5 min; calcd. for $C_{14}H_{24}N_2O_4S$ [M + H]$^+$ 317.2; found 316.8. HRMS (ESI): calcd. for $C_{14}H_{24}N_2O_4S$ [M + H]$^+$ 317.1530; found 317.1531.

Allyl (4*R*,1′*S*)-2-[1-(*tert*-Butoxycarbonyl)pyrrolidin-2-yl]-4,5-dihydrothiazole-4-carboxylate (16d): Thioester **15d** (40 mg, 0.10 mmol)

was cyclized as described in **GP F**. After FCC (light petroleum/EtOAc, 2:1), thiazoline **16d** was isolated as a colorless foam (33 mg, 0.10 mmol, 97%). R_f = 0.29 (cyclohexane/EtOAc, 1:1). $[\alpha]_D^{20}$ = –89.0 ($CHCl_3$, c = 0.5). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.92 (ddt, J = 5.9, 10.4, 17.1 Hz, 1 H, C*H*=CH_2), 5.33 (dq, J = 1.5, 17.2 Hz, 1 H, CH=C*H*H), 5.24 (dd, J = 1.0, 10.4 Hz, 1 H, CH=CH*H*), 5.10 (t, J = 9.0 Hz, 1 H, 4′-H), 4.73–4.61 (m, 3 H, CH_2CH=CH_2, 2-H), 3.62–3.52 (m, 1 H, 5′-H), 3.47 (dd, J = 8.6, 12.5 Hz, 3 H, 5′-H, 5-H_2), 2.29–1.69 (m, 4 H, 3-,4-H_2), 1.44/ 1.40 [each s, 9 H, $C(CH_3)_3$ – rotamers] ppm. IR (KBr): $\tilde{\nu}$ = 3094 (w), 2977 (m), 2930 (m), 2882 (m), 1732 (m), 1697 (s), 1645 (w), 1556 (w), 1505 (m), 1496 (m), 1486 (m), 1455 (m), 1385 (s), 1270 (w), 1228 (m), 1202 (s), 1173 (m), 1110 (m), 919 (s), 871 (s), 797 (s) cm^{-1}. LC-MS (ESI): t_R = 9.3 min; calcd. for $C_{16}H_{24}N_2O_4S$ $[M]^+$ 340.4; found 340.9.

Methyl (4*R*,1′*S*)-2-[1-(*tert*-Butoxycarbonylamino)-3-(cyclohexyloxycarbonyl)propyl]-4,5-dihydrothiazole-4-carboxylate (16e): Thioester **15e** (178 mg, 0.38 mmol) was cyclized as described in **GP F**. After FCC (cyclohexane/EtOAc, 4:1), ester **16e** was isolated as a colorless resin (148 mg, 0.35 mmol, 92%). R_f = 0.48 (cyclohexane/EtOAc, 1:1). $[\alpha]_D^{20}$ = +0.7 ($CHCl_3$, c = 1.0). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.17 (br. s, 1 H, NH), 4.85–4.79 (m, 1 H, 1′-H), 4.74 (dt, J = 4.3, 8.7 Hz, 1 H, Cy), 4.18 (br. s, 1 H, 4-H), 3.76 (s, 3 H, CO_2CH_3), 3.22–2.87 (m, 2 H, 2′-H_2), 2.50–2.34 (m, 2 H, 3′-H_2), 2.16–2.08 (m, 1 H, 5-H_a), 2.01–1.88 (m, 1 H, 5-H_b), 1.84–1.81 (m, 2 H, Cy), 1.70–1.69 (m, 2 H, Cy), 1.50–1.49 (m, 1 H, Cy), 1.42 [s, 9 H, $C(CH_3)_3$], 1.37–1.18 (m, 5 H, Cy) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.9 (CO_2Cy), 171.8 (C=N), 170.4 (CO_2Me), 155.8 (CO_2tBu), 80.4 [$C(CH_3)_3$], 73.4 (Cy), 54.0 (C-4), 53.8 (C-1′), 52.9 (CO_2CH_3), 31.8 (Cy), 31.1 (C-3′), 28.5 [$C(CH_3)_3$], 27.6 (C-5), 26.8 (C-2′), 25.5, 23.9 (Cy) ppm. IR (KBr): $\tilde{\nu}$ = 3361 (bm), 2937 (s), 2859 (m), 1731 (s), 1715 (s), 1615 (w), 1538 (w), 1505 (w), 1454 (m), 1392 (w), 1367 (m), 1176 (m), 1021 (w), 866 (s), 799 (s), 666 (w) cm^{-1}. LC-MS (ESI): t_R = 10.5 min; calcd. for $C_{20}H_{33}N_2O_6S$ $[M + H]^+$ 429.2; found 428.8. HRMS (ESI): calcd. for $C_{20}H_{33}N_2O_6S$ $[M + H]^+$ 429.2054; found 429.2051.

Methyl (*S*)-2-[(*S*)-1-(*tert*-Butoxycarbonylamino)ethyl]-4,5-dihydrooxazole-4-carboxylate (16g): Ester **15g** (100 mg, 0.32 mmol) was cyclized as described in **GP F**. After FCC (cyclohexane/EtOAc, 2:1), oxazoline **16g** was isolated as a colorless oil (72 mg, 0.27 mmol, 84%). R_f = 0.14 (cyclohexane/EtOAc, 1:1). $[\alpha]_D^{20}$ = +46.6 ($CHCl_3$, c = 1.0). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.23 (d, J = 3.2 Hz, 1 H, NH), 4.69 (dd, J = 8.6, 9.9 Hz, 1 H, $CHCO_2$Me), 4.45 (m, 3 H, OCH_2, C*H*CH_3), 3.73 (s, 3 H, CO_2CH_3), 1.37 [s, 9 H, $C(CH_3)_3$], 1.34 (d, J = 7.0 Hz, 3 H, CHC*H*$_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.4 (CO_2Me), 171.2 (C=N), 155.0 (CO_2tBu), 79.8 [$C(CH_3)_3$], 70.3 (OCH_2), 67.9 (*C*HCO_2Me), 52.8 (CO_2CH_3), 44.8 (*C*HCH$_3$), 28.5 [$C(CH_3)_3$], 19.7 (CH*C*H$_3$) ppm. IR (KBr): $\tilde{\nu}$ = 3381 (mb), 2979 (m), 2929 (m), 1746 (s), 1715 (s), 1667 (m), 1505 (m), 1454 (m), 1367 (m), 1245 (m), 1211 (s), 1172 (s), 1057 (w), 958 (s), 862 (s), 798 (s) cm^{-1}. HRMS (ESI): calcd. for $C_{12}H_{21}N_2O_5$ $[M + H]^+$ 273.1445; found 273.1446.

Methyl (4*S*,5*R*,1′*S*)-2-[1-(*tert*-Butoxycarbonylamino)ethyl]-5-methyl-4,5-dihydrooxazole-4-carboxylate (16h): Ester **15h** (108 mg, 0.33 mmol) was cyclized as described in **GP F**. After FCC (light petroleum/EtOAc, 2:1), oxazoline **16h** was isolated as a colorless oil (72 mg, 0.25 mmol, 78%). R_f = 0.17 (light petroleum/EtOAc, 1:1). $[\alpha]_D^{20}$ = +73.8 ($CHCl_3$, c = 1.0). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.25 (br. s, 1 H, NH), 4.83 (dq, J = 6.3, 12.7 Hz, 1 H, OC*H*CH_3), 4.46–4.35 (m, 1 H, BocHNC*H*CH_3), 4.24 (dd, J = 1.5, 7.4 Hz, 1 H, $CHCO_2$Me), 3.76 (s, 3 H, CO_2CH_3), 1.42 [m, 12 H, OCHCH_3, $C(CH_3)_3$], 1.38 (d, J = 7.0 Hz, 3 H, BocHNCHCH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.4 (CO_2Me), 170.4 (C=N), 155.1 (CO_2tBu), 80.0, 79.9 [O*C*HCH$_3$, *C*$(CH_3)_3$], 74.5 (*C*HCO_2Me), 52.8 (CO_2CH_3), 45.1 (*C*HNHBoc), 28.6 [$C(CH_3)_3$], 21.0 (OCH*C*H$_3$), 19.9 (BocHNCH*C*H$_3$) ppm. IR (KBr): $\tilde{\nu}$ = 3384 (mb), 2981 (m), 2932 (m), 1746 (s), 1715 (s), 1661 (m), 1505 (m), 1455 (m), 1367 (m), 1244 (m), 1208 (m), 1174 (s), 1055 (w), 1026 (w), 954 (m), 867 (s), 798 (s) cm^{-1}. HRMS (ESI): calcd. for $C_{13}H_{23}N_2O_5$ $[M + H]^+$ 287.1602; found 287.1602.

Methyl (4*S*,1′*S*)-2-[1-(*tert*-Butoxycarbonylamino)-2-phenylethyl]-4,5-dihydrooxazole-4-carboxylate (16i): Ester **15i** (127 mg, 0.32 mmol) was cyclized as described in **GP F**. After FCC (light petroleum/EtOAc, 5:2), oxazoline **16i** was isolated as a colorless solid (87 mg, 0.25 mmol, 78%). R_f = 0.28 (light petroleum/EtOAc, 1:1), m.p. 73–74 °C. $[\alpha]_D^{20}$ = +75.7 ($CHCl_3$, c = 1.0). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.26–7.05 (m, 5 H, Ph), 5.14 (d, J = 8.0 Hz, 1 H, NH), 4.66 (m, J = 9.8 Hz, 2 H, $CHCO_2$Me, CHBn), 4.53 (dd, J = 8.3, 8.2 Hz, 1 H, OC*H*H), 4.39 (dd, J = 8.7, 10.5 Hz, 1 H, OCH*H*), 3.69 (s, 3 H, CO_2CH_3), 3.09 (dd, J = 5.7, 13.6 Hz, 1 H, C*H*HPh), 2.99 (dd, J = 5.4, 13.6 Hz, 1 H, CH*H*Ph), 1.36 [s, 9 H, $C(CH_3)_3$] ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.0 (CO_2Me), 169.4 (C=N), 155.0 (CO_2tBu), 135.9, 129.5, 128.4, 126.9 (Ph), 79.8 [$C(CH_3)_3$], 70.1 (OCH_2), 67.9 (*C*HCO_2Me), 52.7 (CO_2CH_3), 49.7 (CHBn), 38.9 (CH_2Ph), 28.4 [$C(CH_3)_3$] ppm. IR (KBr): $\tilde{\nu}$ = 3382 (mb), 3030 (w), 2977 (m), 2932 (w), 1746 (s), 1714 (s), 1667 (m), 1505 (s), 1392 (m), 1367 (m), 1337 (w), 1211 (m), 1174 (s), 960 (s), 916 (s), 862 (s), 798 (s), 701 (m) cm^{-1}. HRMS (ESI): calcd. for $C_{18}H_{25}N_2O_5$ $[M + H]^+$ 349.1758; found 349.1759.

Methyl (4*S*,1′*R*)-2-[1-(*tert*-Butoxycarbonylamino)-2-(tritylthio)ethyl]-4,5-dihydrooxazole-4-carboxylate (16j): Ester **15j** (123 mg, 0.21 mmol) was cyclized as described in **GP F**. After FCC (light petroleum/EtOAc, 2:1), **16j** was isolated as a colorless oil (110 mg, 0.20 mmol, 97%, *dr* = 3:2). R_f = 0.15 (light petroleum/EtOAc, 1:1). $[\alpha]_D^{20}$ = +13.4 ($CHCl_3$, c = 0.5). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.47–7.13 (m, 15 H, Tr), 5.12 (d, J = 6.8 Hz, 1 H, NH), 4.76–4.68 (m, 1 H, $CHCO_2$Me), 4.55–4.48 (m, 1 H, OC*H*H), 4.40 (m, 2 H, CH, C*H*NHBoc), 3.74/ 3.73 (2× s, diastereomers 84:16, 3 H, CO_2CH_3), 2.66–2.48 (m, 2 H, CH_2STr), 1.41/ 1.40 (2× s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.2 (CO_2Me), 168.9 (C=N), 154.3 (CO_2tBu), 144.7, 129.8, 128.2, 127.0 (Tr), 80.2 [$C(CH_3)_3$], 70.4 (OCH_2), 68.2 (*C*HCO_2Me), 52.9 (CO_2CH_3), 48.2 (CHNHBoc), 35.2 (CH_2STr), 28.5 [$C(CH_3)_3$] ppm. IR (KBr): $\tilde{\nu}$ = 3405 (wb), 3059 (w), 2977 (w), 2926 (m), 2854 (w), 1747 (s), 1715 (s), 1696 (s), 1505 (m), 1446 (m), 1393 (w), 1368 (w), 1218 (m), 1169 (s), 857 (s), 799 (s), 753 (s), 702 (m) cm^{-1}. LC-MS (ESI): t_R = 11.5 min, C18; calcd. for $C_{31}H_{34}N_2O_5S$ $[M]^+$ 546.2; found 546.2. HRMS (ESI): calcd. for $C_{31}H_{35}N_2O_5S$ $[M + H]^+$ 547.2261; found 547.2258.

Methyl (4*S*,1′*S*)-2-{2-[4-(Benzyloxy)phenyl]-1-(*tert*-butoxycarbonylamino)ethyl}-4,5-dihydrooxazole-4-carboxylate (16l): Ester **15l** (50 mg, 0.10 mmol) was cyclized at 80 °C as described in **GP F** with 2,6-lutidine as solvent. After FCC (light petroleum/EtOAc, 2:1), oxazoline **16l** was isolated as a colorless oil (28 mg, 0.06 mmol, 62%). R_f = 0.17 (light petroleum/EtOAc, 1:1). $[\alpha]_D^{20}$ = +54.6 ($CHCl_3$, c = 1.0). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.44–7.25 (m, 5 H, Ph), 7.07–6.95 (m, 2 H, Ar_{Tyr}), 6.90–6.81 (m, 2 H, Ar_{Tyr}), 5.12 (d, J = 8.1 Hz, 1 H, NH), 5.01 (s, 2 H, OCH_2Ph), 4.69 (m, 2 H, $CHCO_2$Me, C*H*NHBoc), 4.56 (dd, J = 8.1, 8.4 Hz, 1 H, oxazoline-C*H*H), 4.42 (dd, J = 8.7, 10.4 Hz, 1 H, oxazoline-CH*H*), 3.76/ 3.73 (2× s, 3 H, CO_2CH_3), 3.06 (dd, J = 5.6, 13.7 Hz, 1 H, C*H*HNHBoc), 2.97 (dd, J = 5.0, 13.4 Hz, 1 H, CH*H*NHBoc), 1.39 [s, 9 H, $C(CH_3)_3$] ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.1 (CO_2Me), 169.6 (C=N), 158.0 (COBn), 155.1 (CO_2tBu), 137.3 (Ph), 131.1 (Ar_{Tyr}), 130.8, (Ph), 129.0 (Ar_{Tyr}), 128.8, 127.6 (Ph), 114.9

(Ar_{Tyr}), 79.9 [$C(CH_3)_3$], 70.2 (CH_2Ph, oxazoline-CH_2), 68.0 ($CHCO_2Me$), 52.8 (CO_2CH_3), 50.0 (CHNHBoc), 38.2 $CH_2CHNHBoc$, 28.5 [$C(CH_3)_3$] ppm. IR (KBr): $\tilde{\nu}$ = 3392 (mb), 3032 (w), 2976 (m), 2928 (m), 2857 (w), 1745 (s), 1715 (s), 1661 (m), 1505 (s), 1455 (m), 1367 (m), 1242 (m), 1176 (s), 960 (m), 911 (m), 861 (s), 812 (s), 743 (m), 697 (w) cm^{-1}. LC-MS (ESI): t_R = 10.4 min, C18; calcd. for $C_{25}H_{31}N_2O_6$ $[M + H]^+$ 455.2; found 454.9. HRMS (ESI): calcd. for $C_{25}H_{31}N_2O_6$ $[M + H]^+$ 455.2177; found 455.2171.

Methyl (4*S*,1′*S*,2′*R*)-2-[2-(Benzyloxy)-1-(*tert*-butoxycarbonylamino)propyl]-4,5-dihydrooxazole-4-carboxylate (16m): Ester **15m** (50 mg, 0.12 mmol) was cyclized at 80 °C as described in **GP F** with 2,6-lutidine as solvent. After FCC (light petroleum/EtOAc, 3:1), oxazoline **16m** was isolated as a colorless oil (34 mg, 0.09 mmol, 75%). R_f = 0.28 (light petroleum/EtOAc, 1:1). $[\alpha]_D^{20}$ = +51.2 ($CHCl_3$, c = 1.0). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.39–7.19 (m, 5 H, Ph), 5.40 (d, J = 9.5 Hz, 1 H, NH), 4.73 (dd, J = 8.3, 10.1 Hz, 1 H, $CHCO_2Me$), 4.48 (m, 5 H, oxazoline-CH_2, CH_2Ph, C*H*NHBoc), 4.00 (qd, J = 2.1, 6.2 Hz, 1 H, CHOBn), 3.73 (s, 3 H, CO_2CH_3), 1.43 [s, 9 H, $C(CH_3)_3$], 1.23 (d, J = 6.3 Hz, 4 H, $CHCH_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.4 (CO_2Me), 169.2 (C=N), 156.0 (CO_2tBu), 138.3, 128.5, 127.9, 127.8 (Ph), 80.0 [$C(CH_3)_3$], 74.7 ($CHCH_3$), 71.4 (CH_2Ph), 70.2 (OCH_2), 68.2 ($CHCO_2Me$), 53.6 (CHNHBoc), 52.8 (CO_2CH_3), 28.5 [$C(CH_3)_3$], 16.6 ($CHCH_3$) ppm. IR (KBr): $\tilde{\nu}$ = 3445 (w), 3064 (w), 2979 (m), 2933 (w), 1744 (s), 1716 (s), 1667 (m), 1505 (s), 1455 (m) 1368 (m), 1285 (w), 1209 (m), 1173 (s), 1100 (w), 1071 (w), 961 (s), 924 (s), 872 (s), 799 (s), 747 (m), 700 (m) cm^{-1}. LC-MS (ESI): t_R = 10.1 min, C18; calcd. for $C_{20}H_{29}N_2O_6$ $[M + H]^+$ 393.2; found 392.8. HRMS (ESI): calcd. for $C_{20}H_{29}N_2O_6$ $[M + H]^+$ 393.2020; found 393.2015.

Methyl (4*S*,1′*S*)-2-[1-(*tert*-Butoxycarbonylamino)-2-methylpropyl]-4,5-dihydrooxazole-4-carboxylate (16n): Ester **15n** (50 mg, 0.15 mmol) was cyclized at 80 °C as described in **GP F** with 2,6-lutidine as solvent. After FCC (light petroleum/EtOAc, 4:1), oxazoline **16n** was isolated as a colorless oil (21 mg, 0.07 mmol, 48%). R_f = 0.20 (light petroleum/EtOAc, 4:1). $[\alpha]_D^{20}$ = +52.5 ($CHCl_3$, c = 1.0). ^1H NMR (400 MHz, $CDCl_3$): δ = 5.18 (d, J = 8.6 Hz, 1 H, NH), 4.78–4.68 (m, 1 H, $CHCO_2Me$), 4.50 (t, J = 8.2 Hz, 1 H, OC*H*H), 4.46–4.39 (m, 1 H, OCH*H*), 4.32 (dd, J = 4.6, 9.1 Hz, 1 H, CH*i*Pr), 3.75 (s, 3 H, CO_2CH_3), 2.14–2.01 [m, 1 H, $CH(CH_3)_2$], 1.40 [s, 9 H, $C(CH_3)_3$], 0.93/ 0.88 [2× d, J = 6.8 Hz, 2×3 H, $CH(CH_3)_2$] ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.6 (CO_2Me), 170.5 (C=N), 155.7 (CO_2tBu), 79.9 [$C(CH_3)_3$], 70.3 (OCH_2), 67.9 ($CHCO_2Me$), 53.9 (CH*i*Pr), 52.9 (CO_2CH_3), 32.0 [$CH(CH_3)_2$], 28.5 [$C(CH_3)_3$], 19.0, 17.5 [$CH(CH_3)_2$] ppm. IR (KBr): $\tilde{\nu}$ = 3388, 3276 (wb), 2966 (s), 2931 (m), 2876 (w), 1747 (s), 1716 (s), 1661 (m), 1505 (s), 1392 (m), 1368 (m), 1284 (w), 1241 (m), 1206 (m), 1175 (s), 960 (s), 925 (s), 874 (s), 798 (s) cm^{-1}. LC-MS (ESI): t_R = 9.0 min, C18; calcd. for $C_{14}H_{25}N_2O_5$ $[M + H]^+$ 301.2; found 300.9. HRMS (ESI): calcd. for $C_{14}H_{25}N_2O_5$ $[M + H]^+$ 301.1758; found 301.1759.

Methyl (*S*)-2-[1-(*tert*-Butoxycarbonylamino)ethyl]thiazole-4-carboxylate (17a): Thiazoline **16a** (45 mg, 0.16 mmol) was oxidized as described in **GP G**. After FCC (cyclohexane/EtOAc, 2:1), thiazole **17a** was isolated as a colorless solid (42 mg, 0.15 mmol, 94%). R_f = 0.19 (cyclohexane/EtOAc, 2:1), m.p. 97–98 °C. $[\alpha]_D^{20}$ = –35.0 ($CHCl_3$, c = 1.0). ^1H NMR (400 MHz, $CDCl_3$): δ = 8.06 (s, 1 H, 5-H), 5.20 (br. s, 1 H, NH), 5.06 (br. s, 1 H, C*H*CH_3), 3.90 (s, 3 H, CO_2CH_3), 1.58 (d, J = 6.9 Hz, 3 H, $CHCH_3$), 1.40 [s, 9 H, $C(CH_3)_3$] ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.3 (C-2), 162.0 (CO_2Me), 155.1 (CO_2tBu), 147.0 (C-4), 127.6 (C-5), 80.5 [$C(CH_3)_3$], 52.6 (CO_2CH_3), 49.1 ($CHCH_3$), 28.5 [$C(CH_3)_3$], 21.9 ($CHCH_3$) ppm. IR (KBr): $\tilde{\nu}$ = 3354 (bm), 3114 (w), 2980 (m), 2933 (w), 1715 (s), 1567 (w), 1505 (s), 1455 (m), 1393 (w), 1368 (m), 1338 (w), 1294 (w), 1243 (s), 1217 (s), 1171 (s), 1097 (w), 1059 (w), 989 (w), 910 (s), 857 (s), 783 (s), 667 (w), 612 (w) cm^{-1}. HPLC: t_R = 8.0 min (method 5). LC-MS (ESI): t_R = 8.6 min; calcd. for $C_{12}H_{19}N_2O_4S$ $[M + H]^+$ 287.1; found 286.7. HRMS (ESI): calcd. for $C_{12}H_{19}N_2O_4S$ $[M + H]^+$ 287.1060; found 287.1062. $C_{12}H_{18}N_2O_4S$: calcd. C 50.3, H 6.3, N 9.8; found C 50.8, H 6.6, N 9.6.

Methyl (*S*)-2-[2-(1-Benzyl-1*H*-imidazol-4-yl)-1-(*tert*-butoxycarbonylamino)ethyl]thiazole-4-carboxylate (17b): Thiazoline **16b** (59 mg, 0.13 mmol) was oxidized as described in **GP G**. After FCC (CH_2Cl_2/MeOH 20:1), thiazole **17b** was isolated as a colorless solid (14 mg, 0.03 mmol, 23%). R_f = 0.24 (CH_2Cl_2/MeOH 20:1), m.p. 158–159 °C. $[\alpha]_D^{20}$ = –33.6 ($CHCl_3$, c = 0.5). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.92 (s, 1 H, 5-H), 7.40 (s, 1 H, 2′′-H), 7.33–7.25 (m, 3 H, Ph), 6.96 (d, J = 3.5 Hz, 2 H, Ph), 6.90 (d, J = 6.1 Hz, 1 H, NH), 6.42 (s, 1 H, 5′′-H), 5.28 (br. s, 1 H, 1′-H), 4.94 (s, 2 H, CH_2Ph), 3.90 (s, 3 H, CO_2CH_3), 3.29 (br. d, J = 13.1 Hz, 1 H, 2′-H_a), 3.15 (dd, J = 4.3, 14.4 Hz, 1 H, 2′-H_b), 1.42 [s, 9 H, $C(CH_3)_3$] ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.5 (C-2), 162.2 (CO_2Me), 155.7 (CO_2tBu), 147.1 (C-4), 138.0 (C-4′′), 137.2 (C-2′′), 136.2 (Ph), 129.1 (Ph), 128.4 (Ph), 127.2 (Ph, C-5), 117.8 (C-5′′), 80.1 [$C(CH_3)_3$], 53.6 (C-1′), 52.5 (CH_2Ph), 50.9 (CO_2CH_3), 33.0 (C-2′), 28.6 [$C(CH_3)_3$] ppm. IR (KBr): $\tilde{\nu}$ = 3225 (bw), 2924 (s), 2854 (m), 1715 (s), 1504 (m), 1455 (m), 1436 (m), 1393 (w), 1367 (m), 1275 (w), 1242 (s), 1215 (s), 1171 (s), 1119 (m), 1095 (m), 1046 (w), 1027 (w), 858 (s), 813 (s), 722 (s), 697 (m), 650 (w) cm^{-1}. LC-MS (ESI): t_R = 6.7 min; calcd. for $C_{22}H_{27}N_4O_4S$ $[M + H]^+$ 443.2; found 442.9. HRMS (ESI): calcd. for $C_{22}H_{27}N_4O_4S$ $[M + H]^+$ 443.1748; found 443.1745. $C_{22}H_{26}N_4O_4S$: calcd. C 59.7, H 5.9, N 12.7; found C 59.8, H 6.2, N 12.3.

Methyl (*S*)-2-[1-(*tert*-Butoxycarbonylamino)-2-methylpropyl]thiazole-4-carboxylate (17c): Thiazoline **16c** (56 mg, 0.18 mmol) was oxidized as described in **GP G**. After FCC (light petroleum/EtOAc, 4:1), thiazole **17c** was isolated as a colorless solid (47 mg, 0.15 mmol, 85%). R_f = 0.23 (light petroleum/EtOAc, 3:1), m.p. 119–120 °C. $[\alpha]_D^{20}$ = –35.3 ($CHCl_3$, c = 1). ^1H NMR (400 MHz, $CDCl_3$): δ = 8.05 (s, 1 H, 5-H), 5.23 (br. s, 1 H, NH), 4.85 (br. s, 1 H, 1′-H), 3.90 (s, 3 H, CO_2CH_3), 2.40 (m, 1 H, 2′-H), 1.40 [s, 9 H, $C(CH_3)_3$], 0.94 (d, J = 6.8 Hz, 3 H, 2′-CH_3), 0.86 (d, J = 6.9 Hz, 3 H, 2′-CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.7 (C-2), 162.0 (CO_2CH_3), 155.6 (CO_2tBu), 147.2 (C-4), 127.2 (C-5), 80.3 [$C(CH_3)_3$], 58.3 (C-1′), 52.6 (CO_2CH_3), 33.4 (C-2′), 28.5 [$C(CH_3)_3$], 19.6, 17.4 [$CH(CH_3)_2$] ppm. IR (KBr): $\tilde{\nu}$ = 3353 (m), 3119 (w), 2966 (s), 2932 (m), 2876 (w), 1725 (s), 1505 (s), 1435 (w), 1392 (w), 1367 (m), 1346 (w), 1240 (s), 1215 (s), 1170 (s), 1096 (m), 1042 (w), 990 (w), 915 (s), 872 (s), 795 (s), 635 (w) cm^{-1}. LC-MS (ESI): t_R = 9.4 min; calcd. for $C_{14}H_{23}N_2O_4S$ $[M + H]^+$ 315.1; found 314.7. HRMS (ESI): calcd. for $C_{14}H_{23}N_2O_4S$ $[M + H]^+$ 315.1373; found 315.1375. $C_{14}H_{22}N_2O_4S$: calcd. C 53.5, H 7.1, N 8.9; found C 54.0, H 6.7, N 8.8.

Allyl (*S*)-2-[1-(*tert*-Butoxycarbonyl)pyrrolidin-2-yl]thiazole-4-carboxylate (17d): Thiazoline **16d** (24 mg, 0.07 mmol) was oxidized as described in **GP G**. After FCC (light petroleum/EtOAc, 4:1), thiazole **17d** was isolated as a colorless solid (23 mg, 0.07 mmol, 94%). R_f = 0.42 (light petroleum/EtOAc, 1:1), m.p. 92–93 °C. $[\alpha]_D^{20}$ = –94.6 ($CHCl_3$, c = 0.5). ^1H NMR (400 MHz, $CDCl_3$): δ = 8.08 (s, 1 H, 5′-H), 6.03 (ddt, J = 5.7, 11.1, 16.4 Hz, 1 H, C*H*=CH_2), 5.39 (dd, J = 1.2, 17.2 Hz, 1 H, CH=C*H*H), 5.28 (d, J = 10.5 Hz, 1 H, CH=CH*H*), 5.19 (br. s, 1 H, 2-H), 4.84 (d, J =

5.7 Hz, 2 H, CH_2CH=CH$_2$), 3.67–3.36 (m, 2 H, 5-H$_2$), 2.29 (m, 2 H, 3-H$_2$), 1.99–1.83 (m, 2 H, 4-H$_2$), 1.47/ 1.32 [2× s, rotamers, 9 H, C(CH$_3$)$_3$] ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ = 177.3 (C=N), 161.2 (CO$_2$All), 154.4 (CO$_2$*t*Bu), 147.1 (C-4′), 132.2 (*C*H=CH$_2$), 127.3 (C-5′), 119.0 (C=*C*H$_2$), 80.7 [*C*(CH$_3$)$_3$], 66.1 (*C*H$_2$CH=CH$_2$), 59.8 (C-2), 46.9 (C-5), 34.4 (C-3), 28.5 [C(*C*H$_3$)$_3$], 23.4 (C-4) ppm. IR (KBr): $\tilde{\nu}$ = 3102 (w), 2978 (m), 2931 (m), 2883 (m), 1731 (s), 1698 (s), 1575 (w), 1557 (w), 1481 (m), 1455 (m), 1386 (s), 1318 (w), 1228 (s), 1202 (s), 1171 (s), 1110 (m), 1023 (w), 919 (s), 871 (s), 797 (s), 620 (w) cm^{-1}. LC-MS (ESI): t_R = 9.6 min; calcd. for C$_{16}$H$_{23}$N$_2$O$_4$S [M + H]$^+$ 339.1; found 338.9. HRMS (ESI): calcd. for C$_{16}$H$_{23}$N$_2$O$_4$S [M + H]$^+$ 339.1373; found 339.1375.

Methyl (*S*)-2-[1-(*tert*-Butoxycarbonylamino)-3-(cyclohexyloxycarbonyl)propyl]thiazole-4-carboxylate (17e): Thiazoline **16e** (58 mg, 0.14 mmol) was oxidized as described in **GP G**. After FCC (cyclohexane/EtOAc, 3:1), thiazole **17e** was isolated as a colorless solid (50 mg, 0.12 mmol, 86%). R_f = 0.17 (cyclohexane/EtOAc, 3:1), m.p. 110–111 °C. $[\alpha]_D^{20}$ = –22.6 (CHCl$_3$, *c* = 1.0). ^{1}H NMR (400 MHz, CDCl$_3$): δ = 8.07 (s, 1 H, 5-H), 5.48 (br. s, 1 H, NH), 5.01 (br. s, 1 H, 1′-H), 4.72 (td, *J* = 3.9, 9.0 Hz, 1 H, Cy), 3.90 (s, 3 H, CO$_2$Me), 2.48–2.32 (m, 3 H, 3′-H$_2$, 2′-H$_a$), 2.16 (m, 1 H, 2′-H$_b$), 1.87–1.75 (m, 2 H, Cy), 1.68 (m, 2 H, Cy), 1.51 (dd, *J* = 5.0, 7.4 Hz, 1 H, Cy), 1.40 [s, 9 H, C(CH$_3$)$_3$], 1.36–1.16 (m, 5 H, Cy) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ = 173.9 (C-2), 172.7 (CO$_2$Cy), 162.0 (CO$_2$Me), 155.4 (CO$_2$*t*Bu), 147.2 (C-4′), 127.7 (C-5), 80.5 [*C*(CH$_3$)$_3$], 73.4 (Cy), 53.1 (C-1′), 52.6 (CO$_2$*C*H$_3$), 31.8 (Cy), 31.3 (C-3′), 30.6 (C-2′), 28.5 [C(*C*H$_3$)$_3$], 25.5, 24.0 (Cy) ppm. IR (KBr): $\tilde{\nu}$ = 3347 (m), 3118 (w), 2938 (s), 2860 (m), 2357 (w), 2330 (w), 1715 (s), 1574 (w), 1568 (w), 1556 (w), 1505 (s), 1455 (m), 1435 (w), 1418 (w), 1392 (m), 1367 (m), 1336 (m), 1242 (s), 1215 (s), 1174 (s), 1124 (w), 1096 (w), 1042 (w), 1021 (w), 913 (s), 863 (s), 798 (s), 667 (w) cm^{-1}. LC-MS (ESI): t_R = 10.6 min; calcd. for C$_{20}$H$_{31}$N$_2$O$_6$S [M + H]$^+$ 427.2; found 426.8. HRMS (ESI): calcd. for C$_{20}$H$_{31}$N$_2$O$_6$SNa [M + H]$^+$ 427.1897; found 427.1895. C$_{20}$H$_{30}$N$_2$O$_6$S: C 56.3, H 7.1, N 6.6; found C 56.3, H 7.2, N 6.3.

Methyl (*S*)-2-[1-(*tert*-Butoxycarbonyl)pyrrolidin-2-yl]oxazole-4-carboxylate (17f): Ester **16f** (85.5 mg, 0.25 mmol) was cyclized at 80 °C as described in **GP F** with 2,6-lutidine as solvent and subsequently oxidized as described in **GP G**. After FCC (light petroleum/EtOAc, 2:1), oxazole **17f** was isolated as a colorless solid (17 mg, 0.06 mmol, 23%). R_f = 0.26 (light petroleum/EtOAc, 1:1), m.p. 85–86 °C. $[\alpha]_D^{20}$ = –49.8 (CHCl$_3$, *c* = 1.0). ^{1}H NMR (400 MHz, CDCl$_3$): δ = 8.15 (s, 1 H, 5-H), 4.96 (2× br. s, rotamers, 1 H, 2′-CH), 3.90 (s, 3 H, CO$_2$CH$_3$), 3.67–3.39 (m, 2 H, 5′-H$_2$), 2.38–2.21 (m, 1 H, 3′-C*H*H), 2.20–2.00 (m, 2 H, 3′-CH*H*, 4′-C*H*H), 1.99–1.88 (m, 1 H, 4′-CH*H*), 1.35 [2× s (rotamers), 9 H, C(CH$_3$)$_3$] ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ = 166.5 (C=N), 161.9 (CO$_2$Me), 156.2 (CO$_2$*t*Bu), 144.0, 143.5 (C-5), 133.5 (C-4), 80.3 [*C*(CH$_3$)$_3$], 55.1, 54.7 (C-2′), 52.4 (CO$_2$*C*H$_3$), 47.0, 46.7 (C-5′), 32.8, 31.7 (C-3′), 28.4 [C(*C*H$_3$)$_3$], 24.6, 23.9 (C-4′) ppm. IR (KBr): $\tilde{\nu}$ = 2927 (m), 2853 (m), 1747 (s), 1698 (s), 1583 (m), 1455 (w), 1394 (s), 1246 (w), 1164 (m), 1113 (m), 874 (s), 802 (s) cm^{-1}. LC-MS (ESI): t_R = 8.8 min, C18; calcd. for C$_{14}$H$_{20}$N$_2$O$_5$ [M]$^+$ 296.1; found 296.6. HRMS (FAB): calcd. for C$_{14}$H$_{21}$N$_2$O$_5$ [M + H]$^+$ 297.1445; found 297.1446.

Methyl (*S*)-2-[1-(*tert*-Butoxycarbonylamino)ethyl]oxazole-4-carboxylate (17g): Oxazoline **16g** (72 mg, 0.27 mmol) was oxidized as described in **GP G**. After FCC (cyclohexane/EtOAc, 2:1), oxazole **17g** was isolated as a colorless solid (44 mg, 0.16 mmol, 62%). R_f = 0.31 (light petroleum/EtOAc, 1:1), m.p. 99–100 °C. $[\alpha]_D^{20}$ = –44.6 (CHCl$_3$, *c* = 0.9). ^{1}H NMR (400 MHz, MeOD): δ = 8.51 (s, 1 H, oxazole); 4.90 (br. m, 1 H, C*H*CH$_3$), 3.91 (s, 3 H, CO$_2$CH$_3$), 1.55 (d, *J* = 7.0 Hz, 3 H, CHC*H*$_3$), 1.47 [s, 9 H, C(C*H*$_3$)$_3$] ppm. ^{13}C NMR (100 MHz, MeOD): δ = 168.2 (C=N), 163.2 (CO$_2$Me), 157.8 (CO$_2$*t*Bu), 146.3 (C-5), 134.2 (C-4), 81.0 [*C*(CH$_3$)$_3$], 52.8 (CO$_2$*C*H$_3$), 46.2 (*C*HCH$_3$), 29.0 [C(*C*H$_3$)$_3$], 19.5 (CH*C*H$_3$) ppm. IR (KBr): $\tilde{\nu}$ = 3357 (s), 3151 (w), 3113 (m), 2985 (m), 2499 (m), 1720 (s), 1687 (s), 1582 (m), 1528 (s), 1420 (m), 1318 (m), 1247 (w), 1208 (s), 1119 (m), 1066 (w), 996 (m), 944 (m), 928 (w), 869 (m), 810 (m), 778 (s), 603 (w) cm^{-1}. HPLC: t_R = 7.6 min (method 6). HRMS (ESI): calcd. for C$_{12}$H$_{19}$N$_2$O$_5$ [M + H]$^+$ 271.1288; found 271.1285. C$_{12}$H$_{18}$N$_2$O$_5$: C 53.3, H 6.7, N 10.4; found C 53.6, H 7.1, N 10.1.

Methyl (*S*)-2-[1-(*tert*-Butoxycarbonylamino)ethyl]-5-methyloxazole-4-carboxylate (17h): Oxazoline **16h** (69 mg, 0.24 mmol) was oxidized as described in **GP G**. After FCC (cyclohexane/EtOAc, 2:1), oxazole **17h** was isolated as a colorless solid (54 mg, 0.19 mmol, 79%). R_f = 0.33 (light petroleum/EtOAc, 1:1), m.p. 89–90 °C. $[\alpha]_D^{20}$ = –46.2 (CHCl$_3$, *c* = 1.0). ^{1}H NMR (400 MHz, CD$_3$OD): δ = 5.19 (m, 1 H, NH), 4.91 (m, 1 H, C*H*CH$_3$), 3.88 (s, 3 H, CO$_2$CH$_3$), 2.58 (s, 3 H, 5-CH$_3$), 1.50 (d, *J* = 7.0 Hz, 3 H, CHC*H*$_3$), 1.41 [s, 9 H, C(C*H*$_3$)$_3$] ppm. ^{13}C NMR (100 MHz, CD$_3$OD): δ = 163.2 (C=N), 162.8 (CO$_2$Me), 156.7 (C-5), 155.0 (CO$_2$*t*Bu), 127.5 (C-4), 80.2 [*C*(CH$_3$)$_3$], 52.1 (CO$_2$*C*H$_3$), 44.8 (*C*HCH$_3$), 28.5 [C(*C*H$_3$)$_3$], 20.5 (CH*C*H$_3$), 12.2 (C-5-*C*H$_3$) ppm. IR (KBr): $\tilde{\nu}$ = 3356 (s), 2986 (m), 2937 (m), 1718 (s), 1688 (s), 1620 (m), 1525 (s), 1444 (m), 1348 (m), 1248 (m), 1206 (m), 1175 (s), 1100 (s), 1063 (m), 958 (m), 865 (s), 823 (s), 785 (s), 647 (w) cm^{-1}. HPLC: t_R = 9.0 min (method 7). LC-MS (ESI): t_R = 8.7 min, C18; calcd. for C$_{13}$H$_{21}$N$_2$O$_5$S [M + H]$^+$ 285.1; found 284.7. HRMS (FAB): calcd. for C$_{13}$H$_{21}$N$_2$O$_5$ [M + H]$^+$ 285.145; found 285.143.

Methyl (*S*)-2-[1-(*tert*-Butoxycarbonylamino)-2-phenylethyl]oxazole-4-carboxylate (17i): Oxazoline **16i** (43 mg, 0.12 mmol) was oxidized as described in **GP G**. After chromatography on silica gel (light petroleum/EtOAc, 6:1), oxazole **17i** was isolated as a colorless solid (33 mg, 0.10 mmol, 78%). R_f = 0.25 (light petroleum/EtOAc, 4:1), m.p. 119–120 °C. $[\alpha]_D^{20}$ = –11.9 (CHCl$_3$, *c* = 1.0). ^{1}H NMR (400 MHz, CDCl$_3$): δ = 8.10 (s, 1 H, oxazole), 7.24–6.94 (m, 5 H, Ph), 5.19 (m, 2 H, NH, CHBn), 3.88 (s, 3 H, CO$_2$CH$_3$), 3.26–3.11 (m, 2 H, CH$_2$Ph), 1.37 [s, 9 H, C(CH$_3$)$_3$] ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ = 165.1 (C=N), 161.4 (CO$_2$Me), 155.0 (CO$_2$*t*Bu) 144.1 (C-5), 135.8 (Ph), 133.4 (C-4), 129.4, 128.8, 127.5 (Ph), 80.5 [*C*(CH$_3$)$_3$], 52.3 (CO$_2$*C*H$_3$), 50.4 (CHBn), 40.3 (CH$_2$Ph), 28.5 [C(*C*H$_3$)$_3$] ppm. IR (KBr): $\tilde{\nu}$ = 3361 (s), 3063 (w), 2978 (m), 2928 (m), 1732 (s), 1715 (s), 1586 (w), 1520 (m), 1368 (w), 1323 (w), 1330 (m), 1251 (m), 1172 (s), 1109 (m), 964 (m), 936 (m), 893 (s), 871 (s), 768 (m), 702 (m) cm^{-1}. LC-MS (ESI): t_R = 9.7 min, C18; calcd. for C$_{18}$H$_{22}$N$_2$O$_5$ [M]$^+$ 346.2; found 346.6. HRMS (FAB): calcd. for C$_{18}$H$_{23}$N$_2$O$_5$ [M + H]$^+$ 347.161; found 347.164. C$_{18}$H$_{22}$N$_2$O$_5$: C 62.4, H 6.4, N 8.1; found C 62.2, H 6.3, N 8.0.

Methyl (*R*)-2-[1-(*tert*-Butoxycarbonylamino)-2-(tritylthio)ethyl]oxazole-4-carboxylate (17j): Oxazoline **16j** (50 mg, 0.09 mmol) was oxidized as described in **GP G**. After chromatography on silica gel (cyclohexane/EtOAc, 4:1), oxazole **17j** was isolated as a colorless foam (31 mg, 0.06 mmol, 62%). R_f = 0.19 (cyclohexane/EtOAc, 5:1). $[\alpha]_D^{20}$ = –3.9 (CHCl$_3$, *c* = 1.0). ^{1}H NMR (400 MHz, CDCl$_3$): δ = 8.09 (s, 1 H, oxazole), 7.26 (m, 15 H, Tr), 5.14 (d, *J* = 6.8 Hz, 1 H, NH), 4.81 (br. s, 1 H, C*H*NHBoc), 3.88 (s, 3 H, CO$_2$CH$_3$), 2.80–2.65 (m, 2 H, CH$_2$STr), 1.39 [s, 9 H, C(CH$_3$)$_3$] ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ = 164.0 (C=N), 161.6 (CO$_2$Me), 144.5 (C-5), 144.2 (Tr), 133.3 (C-4), 129.8, 128.1, 127.0 (Tr), 80.3 [*C*(CH$_3$)$_3$], 67.2 (CPh$_3$), 52.3 (CO$_2$*C*H$_3$), 48.1 (CHNHBoc), 35.7 (CH$_2$STr), 28.5 [C(*C*H$_3$)$_3$] ppm. IR (KBr): $\tilde{\nu}$ = 3355 (bw), 3161 (w), 3059 (w), 2978 (m), 2928 (m), 2854 (w), 1715 (s), 1583 (w), 1505 (m), 1495 (m), 1445 (w), 1368 (w), 1323 (w), 1247 (m), 1202 (s), 1111 (m),

855 (s), 801 (s), 744 (s), 701 (s), 621 (w) cm^{-1}. LC-MS (ESI): t_R = 11.4 min, C18; calcd. for $C_{31}H_{32}N_2O_5SNa$ $[M + Na]^+$ 567.2; found 567.1. HRMS (FAB): calcd. for $C_{31}H_{33}N_2O_5S$ $[M + H]^+$ 545.211; found 545.214.

Methyl (*S*)-2-[1-(*tert*-Butoxycarbonylamino)-3-(cyclohexyloxycarbonyl)propyl]oxazole-4-carboxylate (17k): Ester **16k** (56 mg, 0.12 mmol) was cyclized as described in **GP F**, in THF at 40 °C, and subsequently oxidized as described in **GP G**. After FCC (light petroleum/EtOAc, 2:1), oxazole **17k** was isolated as a colorless oil (35 mg, 0.09 mmol, 69%). R_f = 0.26 (light petroleum/EtOAc, 2:1). $[\alpha]_D^{20}$ = –18.7 ($CHCl_3$, *c* = 1.0). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.17 (s, 1 H, oxazolyl), 5.30 (d, *J* = 7.5 Hz, 1 H, NH), 4.98 (m, 1 H, C*H*NHBoc), 4.72 (td, *J* = 4.0, 8.9 Hz, 1 H, Cy-CH), 3.90 (s, 3 H, CO_2CH_3), 2.42–2.34 (m, 2 H, CH_2CO_2Cy), 2.33–2.21 (m, 1 H, C*H*HCH_2CO_2Cy), 2.14–2.08 (m, 1 H, CH*H*CH_2CO_2Cy), 1.82 (dd, *J* = 3.0, 7.4 Hz, 2 H, Cy), 1.70 (dd, *J* = 3.4, 9.0 Hz, 2 H, Cy), 1.53 (dd, *J* = 6.6, 10.9 Hz, 1 H, Cy), 1.42 [s, 9 H, $C(CH_3)_3$], 1.37–1.24 (m, 5 H, Cy) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.1 (CO_2Cy), 165.0 (C=N), 161.6 (CO_2Me), 155.4 (CO_2tBu), 144.3 (C-5), 133.5 (C-4), 80.5 [$C(CH_3)_3$], 73.3 (Cy), 52.4 (CO_2CH_3), 48.7 (CHNHBoc), 31.8 (Cy), 30.7 (CH_2CO_2Cy), 29.5 ($CH_2CH_2CO_2Cy$), 28.5 [$C(CH_3)_3$], 25.5, 23.9 (Cy) ppm. IR (KBr): $\tilde{\nu}$ = 3354 (bm), 3162 (w), 2938 (s), 2860 (m), 1727 (s), 1585 (m), 1505 (m), 1454 (m), 1393 (w), 1367 (m), 1324 (m), 1246 (m) 1175 (s), 1112 (m), 1004 (w), 867 (s), 800 (s) cm^{-1}. LC-MS (ESI): t_R = 10.3 min, C18; calcd. for $C_{20}H_{30}N_2O_7$ $[M]^+$ 410.2; found 410.7. HRMS (FAB): calcd. for $C_{20}H_{31}N_2O_7$ $[M + H]^+$ 411.213; found 411.212.

Methyl (*S*)-2-{2-[4-(Benzyloxy)phenyl]-1-(*tert*-butoxycarbonylamino)ethyl}oxazole-4-carboxylate (17l): Oxazoline **16l** (44 mg, 0.10 mmol) was oxidized as described in **GP G**. After FCC (light petroleum/EtOAc, 4:1), oxazole **17l** was isolated as a colorless solid (24 mg, 0.05 mmol, 56%). R_f = 0.45 (light petroleum/EtOAc, 1:1), m.p. 130–131 °C. $[\alpha]_D^{20}$ = –3.8 ($CHCl_3$, *c* = 1.0). ^{1}H NMR (400 MHz, MeOD): δ = 8.10 (s, 1 H, oxazole), 7.42–7.26 (m, 5 H, Ph), 6.92 (d, *J* = 8.3 Hz, 2 H, Ar_{Tyr}), 6.83 (d, *J* = 8.6 Hz, 2 H, Ar_{Tyr}), 5.20 (d, *J* = 7.9 Hz, 1 H, NH), 5.13 (m, 1 H, C*H*NHBoc), 4.99 (s, 2 H, CH_2Ph), 3.89 (s, 3 H, CO_2CH_3), 3.14 (d, *J* = 6.1 Hz, 2 H, $CH_2CHNHBoc$), 1.38 [s, 9 H, $C(CH_3)_3$] ppm. ^{13}C NMR (100 MHz, MeOD): δ = 165.0 (C=N), 161.7 (CO_2Me), 158.1 (COBn), 155.1 (CO_2tBu), 144.0 (C-5), 137.2 (Ph), 133.5 (C-4), 130.5 (Ar_{Tyr}), 128.8 (Ph), 128.1 (Ar_{Tyr}), 128.0 (Ph), 127.6 (Ph), 115.2 (Ar_{Tyr}), 80.4 [$C(CH_3)_3$], 70.2 (CH_2Ph), 52.4 (CO_2CH_3), 50.5 (CHNHBoc), 39.7 ($CH_2CHNHBoc$), 28.5 [$C(CH_3)_3$] ppm. IR (KBr): $\tilde{\nu}$ = 3366 (m), 3160 (w), 3032 (w), 2978 (m), 2930 (m), 1747 (s), 1730 (s), 1715 (s), 1613 (w), 1584 (m), 1506 (s), 1455 (m), 1368 (w), 1318 (w), 1242 (m), 1171 (m), 1111 (m), 861 (s), 802 (s), 739 (m), 697 (w) cm^{-1}. LC-MS (ESI): t_R = 10.5 min, C18; calcd. for $C_{25}H_{28}N_2O_6$ $[M]^+$ 452.2; found 452.5. HRMS (ESI): calcd. for $C_{25}H_{29}N_2O_6$ $[M + H]^+$ 453.2020; found 453.2010.

Methyl (1′*S*,2′*R*)-2-[2-(Benzyloxy)-1-(*tert*-butoxycarbonylamino)propyl]oxazole-4-carboxylate (17m): Oxazoline **16m** (29 mg, 0.08 mmol) was oxidized as described in **GP G**. After FCC (light petroleum/EtOAc, 3:1), oxazole **17m** was isolated as a colorless oil (16 mg, 0.042 mmol, 56%). R_f = 0.45 (light petroleum/EtOAc, 1:1). $[\alpha]_D^{20}$ = –17.0 ($CHCl_3$, *c* = 0.5). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.11 (s, 1 H, 5-H), 7.28–7.18 (m, 3 H, Ph), 7.15–7.03 (m, 2 H, Ph), 5.52 (d, *J* = 9.3 Hz, 1 H, NH), 4.94 (d, *J* = 9.3 Hz, 1 H, C*H*NHBoc), 4.48 (d, *J* = 11.8 Hz, 1 H, C*H*HPh), 4.29 (d, *J* = 11.8 Hz, 1 H, CH*H*Ph), 4.08 (m, 1 H, CHOBn), 3.90 (s, 3 H, CO_2CH_3), 1.43 [s, 9 H, $C(CH_3)_3$], 1.25 (d, *J* = 6.3 Hz, 3 H, CHC*H*$_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.3 (C=N), 161.8 (CO_2Me), 156.0 (CO_2tBu), 144.1 (C-5), 138.0 (Ph), 133.6 (C-4), 128.5, 128.0, 127.9 (Ph), 80.4 [$C(CH_3)_3$], 75.5 (CHOBn), 71.3 (CH_2Ph), 54.0 (CHNHBoc), 52.4 (CO_2CH_3), 28.5 [$C(CH_3)_3$], 16.4 (CHCH_3) ppm. IR (KBr): $\tilde{\nu}$ = 3441 (w), 3162 (w), 2979 (m), 2927 (m), 1716 (s), 1586 (w), 1504 (m), 1455 (w), 1368 (w), 1325 (w), 1232 (m), 1205 (m), 1172 (s), 1111 (m), 1028 (w), 868 (s), 800 (s), 700 (w) cm^{-1}. LC-MS (ESI): t_R = 10.2 min, C18; calcd. for $C_{20}H_{26}N_2O_6$ $[M]^+$ 390.2; found 390.6. HRMS (ESI): calcd. for $C_{20}H_{27}N_2O_6$ $[M + H]^+$ 391.1864; found 391.1866.

Methyl (*S*)-2-[1-(*tert*-Butoxycarbonylamino)-2-methylpropyl]oxazole-4-carboxylate (17n): Oxazoline **16n** (15 mg, 0.05 mmol) was oxidized as described in **GP G**. After FCC (light petroleum/EtOAc, 3:1), oxazole **17n** was isolated as a colorless oil (6 mg, 0.02 mmol, 43%). R_f = 0.26 (light petroleum/EtOAc, 2:1). $[\alpha]_D^{20}$ = –30.2 ($CHCl_3$, *c* = 0.5). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.16 (s, 1 H, 5-H), 5.27 (d, *J* = 8.7 Hz, 1 H, NH), 4.77 (dd, *J* = 6.4, 8.8 Hz, 1 H, CH*i*Pr), 3.89 (s, 3 H, CO_2CH_3), 2.17 [dq, *J* = 6.5, 12.9 Hz, 1 H, C*H*$(CH_3)_2$], 1.41 [s, 9 H, $C(CH_3)_3$], 0.91 [d, *J* = 7.3 Hz, 3 H, CH(CH_3)$_2$], 0.89 [d, *J* = 6.8 Hz, 3 H, CH(CH_3)$_2$] ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.4 (C=N), 161.8 (CO_2Me), 155.6 (CO_2tBu), 144.0 (C-5), 133.4 (C-4), 80.3 [$C(CH_3)_3$], 54.5 (CH*i*Pr), 52.4 (CO_2CH_3), 33.2 [$CH(CH_3)_2$], 28.5 [$C(CH_3)_3$], 18.9/ 18.2 [$CH(CH_3)_2$] ppm. IR (KBr): $\tilde{\nu}$ = 3354 (w), 3155 (w), 2970 (m), 1790 (s), 1747 (s), 1715 (s), 1584 (w), 1539 (w), 1531 (w), 1505 (m), 1471 (w), 1392 (w), 1368 (m), 1324 (w), 1236 (m), 1203 (m), 1172 (s), 1110 (m), 875 (s), 800 (s), 666 (w) cm^{-1}. LC-MS (ESI): t_R = 9.3 min, C18; calcd. for $C_{14}H_{22}N_2O_5$ $[M]^+$ 298.2; found 298.6. HRMS (ESI): calcd. for $C_{14}H_{23}N_2O_5$ $[M + H]^+$ 299.1602; found 299.1601.

Methyl 2-[(*tert*-Butoxycarbonylamino)methyl]oxazole-4-carboxylate (17o): Ester **16o** (48 mg, 0.16 mmol) was cyclized as described in **GP F**, in THF at 40 °C, and subsequently oxidized as described in **GP G**. After FCC (light petroleum/EtOAc, 2:1), oxazole **17o** was isolated as a colorless solid (26 mg, 0.10 mmol, 64%). R_f = 0.24 (light petroleum/EtOAc, 1:1), m.p. 72–73 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.15 (s, 1 H, oxazole), 5.24 (s, 1 H, NH), 4.45 (d, *J* = 5.7 Hz, 2 H, CH_2NHBoc), 3.87 (s, 3 H, CO_2CH_3), 1.41 [s, 9 H, $C(CH_3)_3$] ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.5 (C=N), 161.6 (CO_2Me), 155.6 (CO_2tBu), 144.4 (C-5), 133.5 (C-4), 80.5 [$C(CH_3)_3$], 52.4 (CO_2CH_3), 38.1 (CH_2NHBoc), 28.5 [$C(CH_3)_3$] ppm. IR (KBr): $\tilde{\nu}$ = 3363 (bm), 3161 (w), 2980 (m), 1715 (s), 1589 (m), 1505 (m), 1455 (m), 1437 (w), 1393 (w), 1368 (m), 1323 (m), 1277 (m), 1248 (m), 1207 (m), 1173 (s), 1111 (m), 1053 (w), 1002 (w), 906 (s), 862 (s), 806 (s), 666 (w) cm^{-1}. LC-MS (ESI): t_R = 8.0 min, C18; calcd. for $C_{11}H_{16}N_2O_5$ $[M]^+$ 256.1; found 256.6. HRMS (ESI): calcd. for $C_{11}H_{17}N_2O_5$ $[M + H]^+$ 257.1132; found 257.1133.

Methyl (*S*)-2-Azido-3-{[(*S*)-2-*tert*-butoxycarbonylaminopropionyl]-(tolyl-4′-sulfonyl)amino}propionate (20a): (*S*)-*N*-Boc-alanine (4.42 g, 23.4 mmol) was activated as described in **GP H** and coupled to 2-azido-3-(tolyl-4′-sulfonylamino)propionic acid methyl ester **14d** (3.50 g, 11.7 mmol). The crude product was purified by FCC (750 g silica, light petroleum/EtOAc, 8:2) to yield *N*-acyl-sulfonamide **20a** (5.30 g, 11.3 mmol, 97%) as a colorless oil. R_f = 0.57 (light petroleum/EtOAc, 1:1). $[\alpha]_D^{20}$ = –56.5 (*c* = 2.0 in $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.92 (d, *J* = 7.9 Hz, 2 H, SO_2CCH), 7.34 (d, *J* = 8.1 Hz, 2 H, CH_3CCH), 5.23–5.09 (m, 1 H, 2′-H), 4.98 (d, *J* = 8.1 Hz, 1 H, N*H*), 4.36 (dd, *J* = 5.6, 14.8 Hz, 1 H, 2-H), 4.21 (dd, *J* = 5.6, 14.8 Hz, 1 H, 3-H_a), 3.95 (dd, *J* = 8.6, 14.8 Hz, 1 H, 3-H_b), 3.79 (s, 3 H, $COOCH_3$), 2.42 (s, 3 H, $ArCH_3$), 1.40–1.35 [m, 12 H, $CHCH_3$, $C(CH_3)_3$] ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 175.6 (C-1′), 168.8 (C-1), 155.2 [$COC(CH_3)_3$], 145.6 (CH_3CCH), 135.6 ($CHCSO_2$), 130.2 (CH_3CCH), 128.2 ($CHCSO_2$), 80.2 [$C(CH_3)_3$], 60.7 (C-2), 53.2 ($COOCH_3$), 49.9 (C-

2′), 46.4 (C-3), 28.4 [C(*C*H$_3$)$_3$], 21.8 (ArCH$_3$), 19.6 (*C*H$_3$CH) ppm. IR (KBr): $\tilde{\nu}$ = 2981 (m), 2118 (s), 1749 (m), 1703 (s), 1505 (m), 1363 (m), 1166 (s) cm^{-1}. HPLC: t_R = 9.7 min (method 2). LC-MS (ESI): t_R = 10.4 min, C18; calcd. for $C_{19}H_{28}N_5O_7S$ [M + H]$^+$ 470.2; found 469.6. HRMS (ESI): calcd. for $C_{19}H_{28}N_5O_7S$ [M + H]$^+$ 470.1704; found 470.1699.

Methyl (*S*)-2-Azido-3-{[(*S*)-*N*-*tert*-butoxycarbonylphenylalanyl]-(tolyl-4′-sulfonyl)amino}propionate (20b): (*S*)-*N*-Boc-phenylalanine (534 mg, 2.01 mmol) was activated as described in **GP H** and coupled to azide **14d** (200 mg, 0.67 mmol). Workup and FCC (60 g, *n*-hexane/EtOAc, 41:8) gave **20b** (293 mg, 0.54 mmol, 80%) as a colorless oil. R_f = 0.62 (light petroleum/EtOAc, 3:2). $[\alpha]_D^{20}$ = –64.1 (*c* = 2.0 in CHCl$_3$). ^{1}H NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 7.93 (d, *J* = 8.1 Hz, 2 H, SO$_2$CC*H*), 7.33 (d, *J* = 8.2 Hz, 2 H, CH$_3$CC*H*), 7.31–7.19 (m, 5 H, 3′′-H, 4′′-H, 2′′-H), 5.44–5.30 (m, 1 H, 2′-H), 4.97 (d, *J* = 8.9 Hz, 1 H, N*H*), 4.38 (dd, *J* = 5.3, 8.2 Hz, 2-H), 4.11 (dd, *J* = 5.2, 15.0 Hz, 1 H, 3-H$_a$), 3.95 (dd, *J* = 8.8, 14.9 Hz, 1 H, 3-H$_b$), 3.81 (s, 3 H, COOCH$_3$), 3.28 (dd, *J* = 4.8, 13.9 Hz, 1 H, 3′-H$_a$), 2.74 (dd, *J* = 8.8, 13.6 Hz, 1 H, 3′-H$_b$), 2.42 (s, 3 H, ArCH$_3$), 1.30 [s, 9 H, C(C*H*$_3$)$_3$] ppm. ^{13}C NMR (100 MHz, CDCl$_3$, 25 °C): δ = 174.1 (C-1′), 168.8 (C-1), 155.1 [*C*OC(CH$_3$)$_3$], 145.5 (CH$_3$*C*CH), 136.0 (C-1′′), 135.6 (CH*C*SO$_2$), 130.1 (CH$_3$C*C*H), 129.5 (C-2′′), 128.7 (C-3′′), 128.3 (*C*HCSO$_2$), 127.2 (C-4′′), 80.1 [*C*(CH$_3$)$_3$], 60.5 (C-3), 55.1 (C-2′), 53.2 (COO*C*H$_3$), 46.3 (C-2), 39.6 (C-3′), 28.3 [C(*C*H$_3$)$_3$], 21.2 (ArCH$_3$) ppm. IR (KBr): $\tilde{\nu}$ = 2981 (m), 2119 (s), 1749 (m), 1703 (s), 1499 (m), 1365 (s), 1167 (s) cm^{-1}. HPLC: t_R = 10.7 min (method 2). LC-MS (ESI): t_R = 11.1 min, C18; calcd. for $C_{25}H_{32}N_5O_7S$ [M + H]$^+$ 546.2; found 545.5. HRMS (ESI): calcd. for $C_{25}H_{32}N_5O_7S$ [M + H]$^+$ 546.2017; found 546.2012.

Methyl (*S*)-2-Azido-3-{[(2*S*,3*R*)-2-*tert*-butoxycarbonylamino-3-(*tert*-butyldimethylsilyloxy)butyryl](tolyl-4′-sulfonyl)amino}propionate (20c): (2*S*,3*R*)-*N*-Boc-*O*-TBS-threonine (246 mg, 0.74 mmol) was coupled to azide **14d** (200 mg, 0.67 mmol) as described in **GP I**. The crude product was purified by FCC (100 g, light petroleum/EtOAc, 4:1) to yield **20c** (352 mg, 0.57 mmol, 86%) as a colorless oil. R_f = 0.73 (light petroleum/EtOAc, 3:2). $[\alpha]_D^{20}$ = –28.1 (*c* = 5.0 in CHCl$_3$). ^{1}H NMR (400 MHz, CDCl$_3$, 25 °C): δ = 7.96 (d, *J* = 8.3 Hz, 2 H, C*H*CSO$_2$), 7.35 (d, *J* = 8.0 Hz, 2 H, CH$_3$CC*H*), 5.32 (d, *J* = 9.3 Hz, 1 H, N*H*), 5.15 (d, *J* = 10.0 Hz, 1 H, 2′-H), 4.38–4.28 (m, 1 H, 3′-H), 4.25 (dd, *J* = 4.0, 9.7 Hz, 1 H, 2-H), 4.08 (dd, *J* = 3.9, 14.7 Hz, 1 H, 3-H$_a$), 3.91 (dd, *J* = 9.8, 14.7 Hz, 1 H, 3-H$_b$), 3.79 (s, 3 H, COOCH$_3$), 2.43 (s, 3 H, ArCH$_3$), 1.42 [s, 9 H, OC(C*H*$_3$)$_3$], 1.23 (d, *J* = 6.2 Hz, 3 H, 4′-H), 0.87 [s, 9 H, SiC(C*H*$_3$)$_3$], 0.07 (s, 3 H, SiC*H*$_{3a}$), 0.03 (s, 3 H, SiC*H*$_{3b}$) ppm. ^{13}C NMR (100 MHz, CDCl$_3$, 25 °C): δ = 173.0 (C-1′), 168.9 (*C*OOCH$_3$), 156.3 [*C*OC(CH$_3$)$_3$], 145.5 (CH*C*SO$_2$), 135.8 (CH$_3$*C*CH), 130.2 (CH$_3$C*C*H), 128.2 (*C*HCSO$_2$), 80.1 [O*C*(CH$_3$)$_3$], 69.5 (C-3′), 60.0 (C-2), 59.4 (C-2′), 53.2 (COO*C*H$_3$), 46.9 (C-3), 28.5 [OC(*C*H$_3$)$_3$], 26.0 [SiC(*C*H$_3$)$_3$], 21.9 (ArCH$_3$), 21.4 (C-4′), 18.2 [Si*C*(CH$_3$)$_3$], –4.0 (SiCH$_{3a}$), –4.8 (SiCH$_{3b}$) ppm. IR (KBr): $\tilde{\nu}$ = 2954 (m), 2862 (w), 2121 (s), 1750 (m), 1708 (s), 1489 (m), 1367 (s), 1167 (s), 833 (w) cm^{-1}. HPLC: t_R = 12.8 min (method 2). LC-MS (ESI): t_R = 12.5 min, C18; calcd. for $C_{26}H_{44}N_5O_8SSi$ [M + H]$^+$ 614.3; found 613.7. HRMS (ESI): calcd. for $C_{26}H_{44}N_5O_8SSi$ [M + H]$^+$ 614.2674; found 614.2672.

Methyl (*S*)-2-Azido-3-{[(*S*)-2-*tert*-butoxycarbonylamino-3-methylbutyryl](tolyl-4′-sulfonyl)amino}propionate (20d): (*S*)-*N*-Boc-valine (120 mg, 0.55 mmol) was coupled to azide **14d** (150 mg, 0.50 mmol) as described in **GP I**. The crude product was purified by chromatography (50 g silica, cyclohexane/EtOAc, 4:1) to yield **20d** (213 mg, 0.43 mmol, 86%) as a colorless oil. R_f = 0.57 (light petroleum/EtOAc, 3:2). $[\alpha]_D^{20}$ = –96.7 (*c* = 2.0 in CHCl$_3$). ^{1}H NMR (400 MHz, CDCl$_3$, 25 °C): δ = 7.90 (d, *J* = 8.1 Hz, 2 H, SO$_2$CC*H*), 7.31 (d, *J* = 8.2 Hz, 2 H, CH$_3$CC*H*), 5.15 (br. s, 1 H, 2′-H), 4.96 (d, *J* = 9.6 Hz, 1 H, N*H*), 4.34 (dd, *J* = 4.8, 7.9 Hz, 1 H, 2-H), 4.14 (dd, *J* = 5.0, 14.7 Hz, 1 H, 3-H$_a$), 3.94 (dd, *J* = 8.2, 13.9 Hz, 1 H, 3-H$_b$), 3.79 (s, 3 H, COOCH$_3$), 2.40 (s, 3 H, ArCH$_3$), 2.15 (dd, *J* = 6.4, 11.8 Hz, 1 H, 3′-H), 1.38 [s, 9 H, C(C*H*$_3$)$_3$], 0.99 (d, *J* = 6.7 Hz, 3 H, 4′-H$_a$), 0.81 (d, *J* = 6.9 Hz, 3 H, 4′-H$_b$) ppm. ^{13}C NMR (100 MHz, CDCl$_3$, 25 °C): δ = 174.4 (C-1′), 168.7 (C-1), 155.7 [*C*OC(CH$_3$)$_3$], 145.5 (CH$_3$*C*CH), 135.8 (CH*C*SO$_2$), 130.1 (CH$_3$C*C*H), 128.2 (*C*HCSO$_2$), 80.0 [*C*(CH$_3$)$_3$], 60.5 (C-2), 58.3 (C-2′), 53.1 (COO*C*H$_3$), 46.4 (C-3), 32.0 (C-3′), 28.3 [C(*C*H$_3$)$_3$], 21.7 (ArCH$_3$), 19.8 (C-4′$_a$), 16.4 (C-4′$_b$) ppm. IR (KBr): $\tilde{\nu}$ = 2973 (m), 2120 (s), 1750 (m), 1701 (s), 1502 (m), 1366 (s), 1167 (s), 815 (w) cm^{-1}. HPLC: t_R = 10.6 min (method 2). LC-MS (ESI): t_R = 10.8 min, C18; calcd. for $C_{21}H_{32}N_5O_7S$ [M + H]$^+$ 498.2; found 497.5. HRMS (ESI): calcd. for $C_{21}H_{32}N_5O_7S$ [M + H]$^+$ 498.2017; found 498.2006.

***tert*-Butyl (*R*)-4-[(*S*)-2-(Azido-2-methoxycarbonylethyl)(tolyl-4′-sulfonyl)aminocarbonyl]-2,2-dimethylthiazolidine-3-carboxylate (20e):** (*R*)-3-(*tert*-Butoxycarbonyl)-2,2-dimethylthiazolidine-4-carboxylic acid (194 mg, 0.74 mmol) was coupled to azide **14d** (200 mg, 0.67 mmol) as described in **GP I**. The crude product was purified by FCC (70 g silica, cyclohexane/EtOAc, 21:4) to yield *N*-acyl-sulfonamide **20e** (326 mg, 0.60 mmol, 90%) as a colorless oil. R_f = 0.34 (light petroleum/EtOAc, 4:1). $[\alpha]_D^{20}$ = –63.5 (*c* = 4.0 in CHCl$_3$). ^{1}H NMR (400 MHz, CDCl$_3$, 25 °C): δ = 7.92 (d, *J* = 6.2 Hz, 2 H, SO$_2$CC*H*)*, 7.80 (br. s, 2 H, SO$_2$CC*H*)*, 7.32 (d, *J* = 7.7 Hz, 2 H, CH$_3$CC*H*), 5.71 (br. s, 1 H, 4′-H)*, 5.56 (br. s, 1 H, 4′-H)*, 4.30 (dd, *J* = 5.8, 8.3 Hz, 1 H, 2-H), 4.13 (dd, *J* = 4.5, 13.9 Hz, 1 H, 3-H$_a$), 3.76 (s, 3 H, COOCH$_3$), 3.66 (dd, *J* = 8.2, 13.4 Hz, 1 H, 3-H$_b$), 3.43 (dd, *J* = 7.1, 11.3 Hz, 1 H, 5′-H$_a$), 3.14 (d, *J* = 11.5 Hz, 1 H, 5′-H$_b$), 2.40/ 2.31 (s each, 3 H, ArCH$_3$)*, 1.80 [s, 3 H, C(C*H*$_3$)$_{2a}$], 1.73 [s, 3 H, C(C*H*$_3$)$_{2b}$], 1.39/ 1.26 [s each, 9 H, C(C*H*$_3$)$_3$]* ppm. * Rotamers. ^{13}C NMR (100 MHz, CDCl$_3$, 25 °C): δ = 171.7 (O*C*NSO$_2$), 168.8 (C-1), 152.8 [*C*OC(CH$_3$)$_3$], 145.3 (CH$_3$*C*CH), 135.3 (CH*C*SO$_2$), 130.1 (CH$_3$C*C*H), 128.0 (*C*HCSO$_2$), 81.0 [*C*(CH$_3$)$_3$], 70.5 (C-2′), 67.9 (C-4′), 60.2 (C-2), 53.2 (COOCH$_3$), 46.6 (C-3), 31.2 (C-5′), 30.8 [C(*C*H$_3$)$_{2a}$], 28.6 [C(*C*H$_3$)$_{2b}$], 28.4 [C(*C*H$_3$)$_3$], 21.7 (ArCH$_3$) ppm. IR (KBr): $\tilde{\nu}$ = 2979 (m), 2117 (s), 1749 (m), 1682 (s), 1361 (s), 1170 (s), 820 (w) cm^{-1}. HPLC: t_R = 11.3 min (method 2) B, 1 mL min^{-1}. LC-MS (ESI): t_R = 11.5 min, C18; calcd. for $C_{22}H_{32}N_5O_7S_2$ [M + H]$^+$ 542.2; found 541.6. HRMS (ESI): calcd. for $C_{22}H_{32}N_5O_7S_2$ [M + H]$^+$ 542.1731; found 542.1738.

***tert*-Butyl (*S*)-4-{[(*S*)-2-Azido-2-methoxycarbonylethyl](tolyl-4′-sulfonyl)amino}-2-*tert*-butoxycarbonylamino-4-oxobutyrate (20f):** 1-*tert*-Butyl (*S*)-2-(*tert*-butoxycarbonylamino)succinate (216 mg, 0.74 mmol) was coupled to azide **14d** (90 mg, 0.67 mmol) as described in **GP I**. The crude product was purified by FCC (60 g silica, cyclohexane/EtOAc, 7:3) to yield *N*-acyl-sulfonamide **20f** (384 mg, 0.67 mmol, 100%) as a colorless oil. R_f = 0.56 (light petroleum/EtOAc, 3:2). $[\alpha]_D^{20}$ = –5.0 (*c* = 1.0 in CHCl$_3$). ^{1}H NMR (400 MHz, CDCl$_3$, 25 °C): δ = 7.80 (d, *J* = 8.4 Hz, 2 H, SO$_2$CC*H*), 7.35 (d, *J* = 8.1 Hz, 2 H, CH$_3$CC*H*), 5.41 (d, *J* = 8.3 Hz, 1 H, N*H*), 4.37 (m, 2 H, 2-H, 2′-H), 4.15 (dd, *J* = 5.7, 14.7 Hz, 2 H, 1-H$_a$), 4.08 (dd, *J* = 8.7, 14.7 Hz, 1 H, 1-H$_b$), 3.82 (s, 3 H, COOCH$_3$), 3.35 (dd, *J* = 4.1, 18.0 Hz, 1 H, 3′-H$_a$), 3.19 (dd, *J* = 4.0, 18.0 Hz, 1 H, 3′-H$_b$), 2.43 (s, 3 H, ArCH$_3$), 1.39 [s, 9 H, C(C*H*$_3$)$_{3a}$], 1.33 [s, 9 H, C(C*H*$_3$)$_{3b}$] ppm. ^{13}C NMR (100 MHz, CDCl$_3$, 25 °C): δ = 171.6 (O*C*NSO$_2$), 169.8 (C-1′), 168.9 (*C*OOCH$_3$), 155.7 [O*C*(O)NH], 145.7 (CH$_3$*C*CH), 136.1 (CH*C*SO$_2$), 130.3 (CH$_3$C*C*H), 128.0 (*C*HCSO$_2$), 82.3 [*C*$_a$(CH$_3$)$_3$], 80.0 [*C*$_b$(CH$_3$)$_3$],

60.7 (C-2), 53.2 (COO*C*H$_3$), 50.5 (C-2′), 46.5 (C-1), 39.6 (C-3′), 28.5 [C(*C*$_a$H$_3$)$_3$], 27.9 [C(*C*$_b$H$_3$)$_3$], 21.8 (ArCH$_3$) ppm. IR (KBr): $\tilde{\nu}$ = 2971 (m), 2119 (s), 1744 (s), 1707 (s), 1498 (m), 1364 (s), 1163 (s) cm^{-1}. HPLC: t_R = 10.8 min (method 2). LC-MS (ESI): t_R = 11.1 min, C18; calcd. for $C_{24}H_{36}N_5O_9S$ [M + H]$^+$ 570.2; found 569.5. HRMS (ESI): calcd. for $C_{24}H_{36}N_5O_9S$ [M + H]$^+$ 570.2222; found 570.2228.

Methyl (*S*)-2-Azido-3-[(naphth-1-ylcarbonyl)(tolyl-4′-sulfonyl)-amino]propionate (20g): 1-Naphthoic acid (16 mg, 0.09 mmol) was coupled to azide **14d** (25 mg, 0.08 mmol) as described in **GP I**. The crude product was purified by FCC (8 g silica, cyclohexane/EtOAc, 17:8) to yield *N*-acyl-sulfonamide **20g** (32 mg, 0.07 mmol, 85%) as a colorless oil. R_f = 0.64 (light petroleum/EtOAc, 6:4). $[\alpha]_D^{20}$ = –18.0 (c = 1.0 in CHCl$_3$). ^{1}H NMR (400 MHz, CDCl$_3$, 25 °C): δ = 7.90 (d, J = 8.1 Hz, 1 H, 8′-H), 7.79 (d, J = 8.1 Hz, 1 H, 2′-H), 7.57–7.41 (m, 6 H, 5′-H, 6′-H, C*H*CSO$_2$, 7′-H, 3′-H), 7.36 (ddd, J = 1.3, 6.9, 8.3 Hz, 1 H, 4′-H), 7.05 (d, J = 8.6 Hz, 2 H, CH$_3$CC*H*), 4.52 (dd, J = 5.1, 8.9 Hz, 1 H, 2-H), 4.42 (dd, J = 5.1, 14.6 Hz, 1 H, 3-H$_a$), 4.26 (dd, J = 8.9, 14.6 Hz, 1 H, 3-H$_b$), 3.81 (s, 3 H, COOCH$_3$), 2.29 (s, 3 H, ArCH$_3$) ppm. ^{13}C NMR (100 MHz, CDCl$_3$, 25 °C): δ = 170.6 (O*C*NSO$_2$), 168.8 (*C*OOCH$_3$), 145.3 (CH*C*SO$_2$), 135.4 (CH$_3$*C*CH), 133.3 (C-1′), 131.8 (C-4a′), 131.3 (C-8′), 130.0 (C-8a′), 129.6 (CH$_3$C*C*H), 128.6 (*C*HCSO$_2$), 128.5 (C-2′), 127.4 (C-6′), 126.9 (C-5′), 126.5 (C-7′), 124.6 (C-4′), 124.5 (C-3′), 61.0 (C-2), 53.3 (COO*C*H$_3$), 46.8 (C-3), 21.7 (ArCH$_3$) ppm. IR (KBr): $\tilde{\nu}$ = 2120 (s), 1747 (m), 1689 (m), 1358 (m), 1288 (w), 1171 (m) cm^{-1}. HPLC: t_R = 11.6 min (method 2). LC-MS (ESI): t_R = 10.7 min, C18; calcd. for $C_{22}H_{21}N_4O_5S$ [M + H]$^+$ 453.1; found 452.6. HRMS (ESI): calcd. for $C_{22}H_{21}N_4O_5S$ [M + H]$^+$ 453.1223; found 453.1227; HPLC with chiral modified columns: t_R = 24.9 min [Chiralpak IA, A: isohexane, B: CH_2Cl_2/EtOH 100:4; 10 to 50% (50 min) B, 0.5 mL min^{-1}].

Methyl (*S*)-2-[(*S*)-1-*tert*-Butoxycarbonylaminoethyl]-1-(tolyl-4′-sulfonyl)-4,5-dihydroimidazole-4-carboxylate (21a): *N*-Acyl-sulfonamide **20a** (567 mg, 1.21 mmol) was cyclized in THF at reflux for 2.5 h as described in **GP F**. The acid-labile crude product was typically oxidized without further purification. For analytical purposes the crude product was purified by chromatography (110 g silica, *n*-hexane/EtOAc, 3:2 +0.5% NEt$_3$) to yield imidazoline **21a** (460 mg, 1.08 mmol, 89%) as a colorless oil. R_f = 0.49 (light petroleum/EtOAc, 2:3). $[\alpha]_D^{20}$ = +176.7 (c = 2.0 in toluene). ^{1}H NMR (400 MHz, [D$_6$]benzene, 25 °C): δ = 8.00 (d, J = 8.1 Hz, 2 H, C*H*CSO$_2$), 6.87 (d, J = 8.1 Hz, 2 H, CH$_3$CC*H*), 5.80–5.63 (m, 1 H, CH$_3$C*H*), 5.35 (d, J = 9.2 Hz, 1 H, N*H*), 4,12–3.94 (m, 2 H, 4-H, 5-H$_a$), 3.36–3.29 (m, 1 H, 5-H$_b$), 3.24 (s, 3 H, COOCH$_3$), 1.86 (s, 3 H, ArCH$_3$), 1.45–1.38 [m, 12 H, C*H*$_3$CH, C(C*H*$_3$)$_3$] ppm. ^{13}C NMR (100 MHz, [D$_6$]benzene, 25 °C): δ = 170.9 (*C*OOCH$_3$), 165.3 (C-2), 155.8 [*C*OC(CH$_3$)$_3$], 144.9 (CH$_3$*C*CH), 135.4 (CH*C*SO$_2$), 130.6 (CH$_3$C*C*H), 128.7 (*C*HCSO$_2$), 79.5 [*C*(CH$_3$)$_3$], 66.1 (C-4), 52.3 (COO*C*H$_3$), 51.6 (C-5), 46.7 (CH$_3$*C*H), 28.8 [C(*C*H$_3$)$_3$], 21.6 (*C*H$_3$CH), 21.5 (ArCH$_3$) ppm. IR (KBr): $\tilde{\nu}$ = 2981 (m), 1753 (m), 1702 (s), 1643 (m), 1364 (s), 1165 (s), 816 (w) cm^{-1}. HPLC: t_R = 14.3 min (method 2). LC-MS (ESI): t_R = 10.0 min, C18; calcd. for $C_{19}H_{28}N_3O_6S$ [M + H]$^+$ 426.2; found 425.8. HRMS (ESI): calcd. for $C_{19}H_{28}N_3O_6S$ [M + H]$^+$ 426.1693; found 426.1690.

Methyl (*S*)-2-[(*S*)-1-*tert*-Butoxycarbonylamino-2-phenylethyl]-1-(tolyl-4′-sulfonyl)-4,5-dihydroimidazole-4-carboxylate (21b): Acylated sulfonamide **20b** (32 mg, 0.059 mmol) was cyclized in THF at reflux as described in **GP F**. The crude product was purified by FCC (6 g silica, light petroleum/EtOAc, 14:11) to yield imidazoline **21b** (22 mg, 0.044 mmol, 75%) as a colorless oil. R_f = 0.42 (light petroleum/EtOAc, 2:3). $[\alpha]_D^{20}$ = +109.8 (c = 3.0 in CHCl$_3$). ^{1}H NMR (400 MHz, CDCl$_3$, 25 °C): δ = 7.90 (d, J = 8.1 Hz, 2 H, C*H*CSO$_2$), 7.33 (d, J = 8.0 Hz, 2 H, CH$_3$CC*H*), 7.30–7.17 (m, 5 H, 3′′-H, 4′′-H, 2′′-H), 5.62 (dd, J = 8.5, 12.2 Hz, 1 H, 1′-H), 5.20 (d, J = 9.5 Hz, 1 H, N*H*), 4.44 (dd, J = 7.6, 10.4 Hz, 1 H, 4-H), 4.19 (dd, J = 7.3, 10.3 Hz, 1 H, 5-H$_a$), 3.80–3.64 (m, 4 H, 5-H$_b$, COOCH$_3$), 3.36 (dd, J = 4.4, 13.8 Hz, 1 H, 2′-H$_a$), 2.94 (dd, J = 7.7, 13.7 Hz, 1 H, 2′-H$_b$), 2.43 (s, 3 H, ArCH$_3$), 1.36 [s, 9 H, C(C*H*$_3$)$_3$] ppm. ^{13}C NMR (100 MHz, CDCl$_3$, 25 °C): δ = 170.3 (*C*OOCH$_3$), 162.7 (C-2), 155.0 [*C*OC(CH$_3$)$_3$], 145.3 (CH$_3$*C*CH), 136.3 (C-1′′), 134.3 (CH*C*SO$_2$), 130.4 (CH$_3$C*C*H), 130.0 (C-2′′), 128.4 (C-3′′), 127.9 (*C*HCSO$_2$), 126.9 (C-4′′), 79.7 [*C*(CH$_3$)$_3$], 65.7 (C-4), 53.0 (COO*C*H$_3$), 50.7 (C-5), 50.4 (C-1′), 40.8 (C-2′), 28.4 [C(*C*H$_3$)$_3$], 21.8 (ArCH$_3$) ppm. IR (KBr): $\tilde{\nu}$ = 2977 (m), 1746 (m), 1712 (s), 1638 (m), 1499 (m), 1364 (s), 1167 (s) cm^{-1}. HPLC: t_R = 11.7 min (method 2). LC-MS (ESI): t_R = 10.9 min, C18; calcd. for $C_{25}H_{32}N_3O_6S$ [M + H]$^+$ 502.2; found 501.9. HRMS for $C_{25}H_{32}N_3O_6S$ [M + H]$^+$ 502.2000; found 502.2006.

Methyl (*S*)-2-[(1*R*,2*R*)-1-*tert*-Butoxycarbonylamino-2-(*tert*-butyldimethylsilyloxy)propyl]-1-(tolyl-4′-sulfonyl)-4,5-dihydroimidazole-4-carboxylate (21c): *N*-Acyl-sulfonamide **20c** (54 mg, 0.09 mmol) was cyclized in THF at reflux as described in **GP F**. The crude product was purified by FCC (10 g silica, light petroleum/EtOAc, 39:11) to yield imidazoline **21c** (45 mg, 0.08 mmol, 91%) as a colorless oil. R_f = 0.11 (light petroleum/EtOAc, 3:2). $[\alpha]_D^{20}$ = +100.8 (c = 1.0 in CHCl$_3$). ^{1}H NMR (400 MHz, CDCl$_3$, 25 °C): δ = 7.93 (d, J = 8.3 Hz, 2 H, C*H*CSO$_2$), 7.34 (d, J = 8.0 Hz, 2 H, CH$_3$CC*H*), 5.39 (d, J = 10.1 Hz, 1 H, N*H*), 5.29–5.23 (m, 1 H, 1′-H), 4.45–4.37 (m, 1 H, 2′-H), 4.37–4.28 (m, 1 H, 5-H$_a$), 4.13 (dd, J = 9.6, 10.9 Hz, 1 H, 5-H$_b$), 3.77–3.70 (m, 4 H, 4-H, COOCH$_3$), 2.43 (s, 3 H, ArCH$_3$), 1.47 [s, 9 H, OC(C*H*$_3$)$_3$], 1.29 (d, J = 5.3 Hz, 3 H, 3′-H), 0.85 [s, 9 H, SiC(C*H*$_3$)$_3$], 0.04 (s, 3 H, SiC*H*$_{3a}$), –0.02 (s, 3 H, SiC*H*$_{3b}$) ppm. ^{13}C NMR (100 MHz, CDCl$_3$, 25 °C): δ = 170.2 (*C*OOCH$_3$), 161.6 (C-2), 156.2 [*C*OC(CH$_3$)$_3$], 145.2 (CH$_3$*C*CH), 134.4 (CH*C*SO$_2$), 130.4 (CH$_3$C*C*H), 128.0 (*C*HCSO$_2$), 79.8 [O*C*(CH$_3$)$_3$], 69.2 (C-2′), 66.5 (C-4), 55.4 (C-1′), 52.9 (COO*C*H$_3$), 50.4 (C-5), 28.6 [OC(*C*H$_3$)$_3$], 26.0 [SiC(*C*H$_3$)$_3$], 21.8 (ArCH$_3$), 21.3 (C-3′), 18.1 [Si*C*(CH$_3$)$_3$], –4.3 (Si*C*H$_{3a}$), –4.9 (Si*C*H$_{3b}$) ppm. IR (KBr): $\tilde{\nu}$ = 2932 (m), 2862 (w), 1748 (m), 1715 (s), 1495 (m), 1365 (m), 1166 (s), 833 (m) cm^{-1}. HPLC: t_R = 12.5 min (method 2). LC-MS (ESI): t_R = 12.3 min, C18; calcd. for $C_{26}H_{44}N_3O_7SSi$ [M + H]$^+$ 570.3; found 569.9. HRMS (ESI): calcd. for $C_{26}H_{44}N_3O_7SSi$ [M + H]$^+$ 570.2664; found 570.2656.

Methyl (*S*)-2-[(*S*)-1-*tert*-Butoxycarbonylamino-2-methylpropyl]-1-(tolyl-4′-sulfonyl)-4,5-dihydroimidazole-4-carboxylate (21d): *N*-Acyl-sulfonamide **20d** (25 mg, 0.050 mmol) was cyclized in THF at reflux as described in **GP F**. The crude product was purified by FCC (5 g silica, light petroleum/EtOAc, 18:7) to yield imidazoline **21d** (21 mg, 0.046 mmol, 92%) as a colorless solid. R_f = 0.62 (light petroleum/EtOAc, 2:3). $[\alpha]_D^{20}$ = +161.3 (c = 2.0 in CHCl$_3$). ^{1}H NMR (400 MHz, CDCl$_3$, 25 °C): δ = 7.92 (d, J = 8.2 Hz, 2 H, SO$_2$CC*H*), 7.33 (d, J = 8.1 Hz, 2 H, CH$_3$CC*H*), 5.34 (dd, J = 3.4, 10.2 Hz, 1 H, 1′-H), 5.21 (d, J = 10.1 Hz, 1 H, N*H*), 4.46 (ddd, J = 1.3, 6.7, 10.9 Hz, 1 H, 4-H), 4.10 (dd, J = 6.8, 10.3 Hz, 1 H, 5-H$_a$), 3.74 (s, 3 H, COOCH$_3$), 3.71–3.63 (m, 1 H, 5-H$_b$), 2.42 (s, 3 H, ArCH$_3$), 2.34–2.21 (m, 1 H, 2′-H), 1.44 [s, 9 H, C(C*H*$_3$)$_3$], 1.06 (d, J = 6.8 Hz, 3 H, 3′-H$_a$), 0.87 (d, J = 6.9 Hz, 3 H, 3′-H$_b$) ppm. ^{13}C NMR (100 MHz, CDCl$_3$, 25 °C): δ = 170.9 (*C*OOCH$_3$), 163.6 (C-2), 155.8 [*C*OC(CH$_3$)$_3$], 145.2 (CH$_3$*C*CH), 134.0 (CH*C*SO$_2$), 130.4 (CH$_3$C*C*H), 128.1 (*C*HCSO$_2$), 79.7 [O*C*(CH$_3$)$_3$], 65.5 (C-4), 53.6 (C-1′), 52.9 (COO*C*H$_3$), 51.0 (C-5), 32.8 (C-2′), 28.5 [OC(*C*H$_3$)$_3$], 21.8 (ArCH$_3$), 19.9 (C-3′$_a$), 16.0 (C-3′$_b$) ppm. IR (KBr): $\tilde{\nu}$ = 2973 (m), 1753 (m), 1698 (s), 1644 (m), 1534 (m), 1367 (m), 1167 (s) cm^{-1}. HPLC: t_R = 11.5 min (method 2). LC-MS (ESI):

t_R = 10.8 min, C18; calcd. for $C_{21}H_{32}N_3O_6S$ $[M + H]^+$ 454.2; found 453.9. HRMS (ESI): calcd. for $C_{21}H_{32}N_3O_6S$ $[M + H]^+$ 454.2006; found 454.2000.

***tert*-Butyl (*R*)-4-[(*S*)-4-Methoxycarbonyl-1-(tolyl-4′-sulfonyl)-4,5-dihydroimidazol-2-yl]-2,2-dimethylthiazolidine-3-carboxylate (21e):** *N*-Acyl-sulfonamide **20e** (22 mg, 0.041 mmol) was cyclized in 2,6-lutidine at 80 °C as described in **GP F**. The crude product was purified by FCC (5 g silica, light petroleum/EtOAc, 19:6) to yield imidazoline **21e** (16 mg, 0.033 mmol, 80%) as a colorless solid. R_f = 0.30 (light petroleum/EtOAc, 7:3), m.p. 115–116 °C. $[\alpha]_D^{20}$ = +59.1 (c = 1.0 in $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.96 (d, J = 5.6 Hz, 2 H, SO_2CCH)*, 7.77 (br. s, 2 H, SO_2CCH)*, 7.35 (d, J = 8.1 Hz, 2 H, CH_3CCH), 5.87, 5.57 (each br. s, 1 H, 4′-H)*, 4.61–4.38 (m, 1 H, 4-H)*, 4.11–3.95, 3.89–3.77 (each m, 2 H, 5-H)*, 3.71 (s, 3 H, $COOCH_3$), 3.63–3.51 (m, 2 H, 5-H)*, 3.51–3.35 (m, 1 H, 5′-H_a)*, 3.24–3.02 (m, 1 H, 5′-H_b)*, 2.43 (s, 3 H, $ArCH_3$), 1.91–1.81 [m, 3 H, $C(CH_3)_{2a}$]*, 1.78 [s, 3 H, $C(CH_3)_{2b}$], 1.47, 1.35 [each s, 9 H, $C(CH_3)_3$]* ppm. * Rotamers. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 170.8 ($COOCH_3$), 160.0 (C-2), 152.9 [$COC(CH_3)_3$], 144.9 (CH_3CCH), 134.1 ($CHCSO_2$), 130.3 (CH_3CCH), 128.2 ($CHCSO_2$), 80.7 [$OC(CH_3)_3$], 72.0 (C-2′)*, 70.5 (C-2′)*, 66.2 (C-4), 63.7 (C-4′)*, 62.6 (C-4′)*, 52.7 ($COOCH_3$), 50.9 (C-5), 31.9 (C-5′), 31.6 [$C(CH_3)_{2b}$], 28.7 [$C(CH_3)_3$], 28.3 [$C(CH_3)_{2a}$], 21.8 ($ArCH_3$) ppm. * Rotamers. IR (KBr): $\tilde{\nu}$ = 2977 (w), 1745 (m), 1692 (m), 1641 (w), 1358 (s), 1098 (s), 811 (w) cm^{-1}. HPLC: t_R = 12.4 min (method 2). LC-MS (ESI): t_R = 11.2 min, C18; calcd. for $C_{22}H_{32}N_3O_6S_2$ $[M + H]^+$ 498.2; found 497.9. HRMS (ESI): calcd. for $C_{22}H_{32}N_3O_6S_2$ $[M + H]^+$ 498.1727; found 498.1720.

Methyl (*S*)-2-[(*S*)-2-*tert*-Butoxycarbonyl-2-*tert*-butoxycarbonylaminoethyl]-1-(tolyl-4′-sulfonyl)-4,5-dihydroimidazole-4-carboxylate (21f): *N*-Acyl-sulfonamide **20f** (335 mg, 0.59 mmol) was cyclized in THF at reflux as described in **GP F**. The crude product was purified by FCC (50 g silica, light petroleum/EtOAc, 31:19) to yield imidazoline **21f** (282 mg, 0.54 mmol, 91%) as a colorless oil. R_f = 0.49 (light petroleum/EtOAc, 1:1). $[\alpha]_D^{20}$ = +42.8 (c = 1.0 in $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.74 (d, J = 8.3 Hz, 2 H, SO_2CCH), 7.35 (d, J = 8.0 Hz, 2 H, CH_3CCH), 5.77 (d, J = 9.2 Hz, 1 H, NH), 4.63–4.54 (m, 1 H, 1′-H), 4.54–4.46 (m, 1 H, 4-H), 4.00–3.85 (m, 2 H, 5-H), 3.70 (s, 3 H, $COOCH_3$), 3.39 (dd, J = 4.1, 17.6 Hz, 1 H, 2′-H_a), 2.99 (dd, J = 3.8, 17.1 Hz, 1 H, 2′-H_b), 2.44 (s, 3 H, $ArCH_3$), 1.43 [s, 9 H, $C(CH_3)_{3a}$], 1.39 [s, 9 H, $C(CH_3)_{3b}$] ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 171.0 ($COOCH_3$), 170.1 [$OC(O)CH$], 159.3 (C-2), 155.9 [$OC(O)NH$], 145.3 (CH_3CCH), 135.1 ($CHCSO_2$), 130.4 (CH_3CCH), 127.5 ($CHCSO_2$), 81.9 [$C_a(CH_3)_3$], 79.7 [$C_b(CH_3)_3$], 65.3 (C-4), 52.9 ($COOCH_3$), 51.3 (C-1′), 50.6 (C-5), 32.4 (C-2′), 28.6 [$C(C_aH_3)_3$], 28.1 [$C(C_bH_3)_3$], 21.8 ($ArCH_3$) ppm. IR (KBr): $\tilde{\nu}$ = 2980 (m), 1743 (s), 1717 (s), 1499 (m), 1364 (m), 1163 (s), 814 (w) cm^{-1}. HPLC: t_R = 10.2 min (method 2). LC-MS (ESI): t_R = 10.8 min, C18; calcd. for $C_{24}H_{36}N_3O_8S$ $[M + H]^+$ 526.2; found 525.9. HRMS (ESI): calcd. for $C_{24}H_{36}N_3O_8S$ $[M + H]^+$ 526.2218; found 526.2210. $C_{24}H_{35}N_3O_8S$: C 54.8, H 6.7, N 8.0; found C 54.6, H 6.5, N 7.9.

Methyl (*S*)-2-(Naphthalen-1-yl)-1-(tolyl-4′-sulfonyl)-4,5-dihydroimidazole-4-carboxylate (21g): *N*-Acyl-sulfonamide **20g** (177 mg, 0.39 mmol) was cyclized in 2,6-lutidine at 80 °C as described in **GP F**. The crude product was purified by FCC (30 g silica, light petroleum/EtOAc, 13:12) to yield imidazoline **21g** (136 mg, 0.33 mmol, 85%) as a colorless oil. R_f = 0.34 (light petroleum/EtOAc, 1:1). $[\alpha]_D^{20}$ = +43.2 (c = 4.0 in $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.92 (d, J = 8.2 Hz, 1 H, 4′-H), 7.79 (d, J = 8.5 Hz, 2 H, 5′-H, 8′-H), 7.62 (dd, J = 1.0, 7.1 Hz, 1 H, 3′-H), 7.47 (dd, J = 7.2, 8.2 Hz, 1 H, 2′-H), 7.43 (ddd, J = 1.1, 6.9, 8.1 Hz, 1 H, 7′-H), 7.34 (ddd, J = 1.2, 6.9, 8.3 Hz, 1 H, 6′-H), 7.19 (d, J = 8.3 Hz, 2 H, $CHCSO_2$), 6.95 (d, J = 8.1 Hz, 2 H, CH_3CCH), 4.88 (dd, J = 7.6, 10.6 Hz, 1 H, 4-H), 4.49–4.27 (m, 2 H, 5-H), 3.75 (s, 3 H, $COOCH_3$), 2.26 (s, 3 H, $ArCH_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 171.0 ($COOCH_3$), 159.6 (C-2), 144.7 (CH_3CCH), 134.6 ($CHCSO_2$), 133.2 (C-1′), 131.4 (C-4a′), 131.1 (C-4′), 129.5 (CH_3CCH), 128.9 (C-3′), 128.2 (C-5′), 127.7 ($CHCSO_2$), 126.9 (C-6′), 126.5 (C-8a′), 126.0 (C-7′), 125.1 (C-8′), 124.4 (C-2′), 66.7 (C-4), 52.9 ($COOCH_3$), 50.9 (C-5), 21.5 ($ArCH_3$) ppm. IR (KBr): $\tilde{\nu}$ = 2962 (m), 1743 (s), 1631 (m), 1360 (m), 1171 (s), 806 (m) cm^{-1}. HPLC: t_R = 9.1 min (method 2). LC-MS (ESI): t_R = 10.0 min, C18; calcd. for $C_{22}H_{21}N_2O_4S$ $[M + H]^+$ 409.1; found 409.0. HRMS (ESI): calcd. for $C_{22}H_{21}N_2O_4S$ $[M + H]^+$ 409.1217; found 409.1210; HPLC with chiral modified columns: t_R = 38.3 min [Chiralpak IA, A: isohexane, B: CH_2Cl_2/EtOH 100:4; 20% (70 min) B, 0.5 mL min^{-1}].

Methyl 2-[(*S*)-1-*tert*-Butoxycarbonylaminoethyl]-1-(tolyl-4′-sulfonyl)imidazole-4-carboxylate (22a): Crude imidazoline **21a** (386 mg, 0.91 mmol) was oxidized with DBU (407 μL, 2.72 mmol) and $BrCCl_3$ (134 μL, 1.36 mmol) as described in **GP G**. The crude product was purified by FCC (90 g silica, light petroleum/EtOAc, 17:8) to yield imidazole **22a** (266 mg, 0.63 mmol, 76%) as a colorless solid (69% over two steps). R_f = 0.58 (light petroleum/EtOAc, 2:3), m.p. 141–142 °C. $[\alpha]_D^{20}$ = –44.8 (c = 4.0 in $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.91–7.97 (m, 3 H, $CHCSO_2$, 5-H), 7.35 (d, J = 8.1 Hz, 2 H, CH_3CCH), 5.44–5.54 (m, 1 H, CH_3CH), 5.40 (d, J = 9.5 Hz, 1 H, NH), 3.86 (s, 3 H, $COOCH_3$), 2.42 (s, 3 H, $ArCH_3$), 1.45 (d, J = 6.6 Hz, 3 H, CH_3CH), 1.38 [s, 9 H, $C(CH_3)_3$] ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 162.3 ($COOCH_3$), 154.8 (C-2), 152.1 [$COC(CH_3)_3$], 147.0 (CH_3CCH), 134.3 (C-4), 132.7 ($CHCSO_2$), 130.7 (CH_3CCH), 128.2 ($CHCSO_2$), 124.8 (C-5), 79.8 [$C(CH_3)_3$], 52.3 ($COOCH_3$), 44.2 (CH_3CH), 28.5 [$C(CH_3)_3$], 22.8 (CH_3CH), 21.9 ($ArCH_3$) ppm. IR (KBr): $\tilde{\nu}$ = 3337 (m), 2984 (m), 1713 (s), 1558 (m), 1386 (m), 1163 (s), 813 (m) cm^{-1}. HPLC: t_R = 10.5 min (method 2). LC-MS (ESI): t_R = 10.2 min, C18; calcd. for $C_{19}H_{26}N_3O_6S$ $[M + H]^+$ 424.2; found 423.8. HRMS (ESI): calcd. for $C_{19}H_{26}N_3O_6S$ $[M + H]^+$ 424.1534; found 424.1537. $C_{19}H_{25}N_3O_6S$: C 53.9, H 6.0, N 9.9; found C 53.6, H 6.0, N 10.0.

Methyl 2-[(*S*)-1-*tert*-Butoxycarbonylamino-2-phenylethyl]-1-(tolyl-4′-sulfonyl)imidazole-4-carboxylate (22b): Imidazoline **21b** (117 mg, 0.23 mmol) was oxidized as described in **GP G**. The crude product was purified by FCC (40 g silica, light petroleum/EtOAc, 18:7) to yield imidazole **22b** (86 mg, 0.17 mmol, 74%) as a colorless oil. R_f = 0.64 (light petroleum/EtOAc, 1:1). $[\alpha]_D^{20}$ = –71.3 (c = 2.0 in $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.94 (s, 1 H, 5-H), 7.92 (d, J = 8.1 Hz, 2 H, $CHCSO_2$), 7.29 (d, J = 8.2 Hz, 2 H, CH_3CCH), 7.25–7.13 (m, 5 H, 3′′-H, 4′′-H, 2′′-H), 5.78–5.68 (m, 1 H, 1′-H), 5.33 (d, J = 9.8 Hz, 1 H, NH), 3.88 (s, 3 H, $COOCH_3$), 3.27 (dd, J = 5.6, 13.5 Hz, 1 H, 2′-H_a), 2.97 (dd, J = 8.9, 13.4 Hz, 1 H, 2′-H_b), 2.39 (s, 3 H, $ArCH_3$), 1.28 [s, 9 H, $C(CH_3)_3$] ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 162.3 ($COOCH_3$), 154.7 [$COC(CH_3)_3$], 150.8 (C-2), 147.0 (CH_3CCH), 136.7 (C-1′′), 134.3 ($CHCSO_2$), 132.8 (C-4), 130.7 (CH_3CCH), 129.7 (C-2′′), 128.5 (C-3′′), 128.2 ($CHCSO_2$), 126.9 (C-4′′), 124.7 (C-5), 79.7 [$C(CH_3)_3$], 52.4 ($COOCH_3$), 49.4 (C-1′), 43.0 (C-2′), 28.3 [$C(CH_3)_3$], 21.9 ($ArCH_3$) ppm. IR (KBr): $\tilde{\nu}$ = 1711 (s), 1497 (m), 1384 (m), 1162 (s), 813 (w), 760 (w), 701 (w) cm^{-1}. HPLC: t_R = 11.9 min (method 2). LC-MS (ESI): t_R = 11.0 min, C18; calcd. for $C_{25}H_{30}N_3O_6S$ $[M + H]^+$ 500.2; found 499.7. HRMS (ESI): calcd. for $C_{25}H_{30}N_3O_6S$ $[M + H]^+$ 500.1844; found 500.1850.

Methyl 2-[(1*R*,2*R*)-1-*tert*-Butoxycarbonylamino-2-(*tert*-butyldimethylsilanyloxy)propyl]-1-(tolyl-4′-sulfonyl)imidazole-4-carb-

oxylate (22c): Imidazoline **21c** (255 mg, 0.43 mmol) was oxidized as described in **GP G**. The crude product was purified by FCC (55 g silica, light petroleum/EtOAc, 21:4) to yield imidazole **22c** (213 mg, 0.38 mmol, 88%) as a colorless oil. R_f = 0.56 (light petroleum/EtOAc, 3:2). $[\alpha]_D^{20}$ = –34.5 (c = 4.0 in $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.97 (d, J = 8.4 Hz, 2 H, CHCSO$_2$), 7.93 (s, 1 H, 5-H), 7.33 (d, J = 8.1 Hz, 2 H, CH$_3$CCH), 5.58 (d, J = 10.1 Hz, 1 H, NH), 5.42 (dd, J = 3.6, 10.1 Hz, 1 H, 1′-H), 4.21–4.07 (m, 1 H, 2′-H), 3.83 (s, 3 H, COOCH$_3$), 2.40 (s, 3 H, ArCH$_3$), 1.39 [s, 9 H, OC(CH_3)$_3$], 1.20 (d, J = 6.1 Hz, 3 H, 3′-H), 0.80 [s, 9 H, SiC(CH_3)$_3$], –0.12 (s, 3 H, SiCH_{3a}), –0.21 (s, 3 H, SiCH_{3b}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 162.3 (COOCH$_3$), 155.7 [COC(CH$_3$)$_3$], 149.9 (C-2), 147.0 (CH$_3C$CH), 134.6 (CHCSO$_2$), 133.1 (C-4), 130.7 (CH$_3C$CH), 128.2 (CHCSO$_2$), 125.1 (C-5), 79.6 [OC(CH$_3$)$_3$], 71.3 (C-2′), 53.8 (C-1′), 52.2 (COOCH$_3$), 28.5 [OC(CH$_3$)$_3$], 25.9 [SiC(CH$_3$)$_3$], 21.9 (ArCH$_3$), 21.0 (C-3′), 18.1 [SiC(CH$_3$)$_3$], –4.8 (SiCH$_{3a}$), –5.1 (SiCH$_{3b}$) ppm. IR (KBr): $\tilde{\nu}$ = 2954 (m), 2858 (m), 1745 (m), 1714 (s), 1500 (m), 1383 (m), 1160 (s), 838 (m) cm^{-1}. HPLC: t_R = 14.6 min (method 2). LC-MS (ESI): t_R = 12.5 min, C18; calcd. for $C_{26}H_{42}N_3O_7SSi$ [M + H]$^+$ 568.3; found 567.9. HRMS (ESI): calcd. for $C_{26}H_{42}N_3O_7SSi$ [M + H]$^+$ 568.2507; found 568.2508.

Methyl 2-[(*S*)-1-*tert*-Butoxycarbonylamino-2-methylpropyl]-1-(tolyl-4′-sulfonyl)imidazole-4-carboxylate (22d): Imidazoline **21d** (260 mg, 0.52 mmol) was oxidized as described in **GP G**. The crude product was purified by FCC (45 g silica, light petroleum/EtOAc, 19:6) to yield imidazole **22d** (217 mg, 0.48 mmol, 92%) as a colorless oil. R_f = 0.53 (light petroleum/EtOAc, 16:9). $[\alpha]_D^{20}$ = –54.9 (c = 6.0 in $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.94 (d, J = 8.3 Hz, 2 H, SO$_2$CCH), 7.91 (s, 1 H, 5-H), 7.30–7.25 (m, 2 H, CH$_3$CCH), 5.36–5.19 (m, 2 H, NH, 1′-H), 3.80 (s, 3 H, COOCH$_3$), 2.34 (s, 3 H, ArCH$_3$), 2.16–1.98 (m, 1 H, 2′-H), 1.33 [s, 9 H, C(CH_3)$_3$], 0.92 (d, J = 6.8 Hz, 3 H, 3′-H$_a$), 0.82 (d, J = 6.7 Hz, 3 H, 3′-H$_b$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 162.2 (COOCH$_3$), 155.2 [COC(CH$_3$)$_3$], 151.1 (C-2), 146.8 (CH$_3C$CH), 134.4 (CHCSO$_2$), 132.7 (C-4), 130.6 (CH$_3C$CH), 128.2 (CHCSO$_2$), 124.5 (C-5), 79.4 [OC(CH$_3$)$_3$], 52.6 (C-1′), 52.2 (COOCH$_3$), 35.2 (C-2′), 28.3 [OC(CH$_3$)$_3$], 21.8 (ArCH$_3$), 19.4 (C-3′$_a$), 17.7 (C-3′$_b$) ppm. IR (KBr): $\tilde{\nu}$ = 2968 (m), 1713 (s), 1501 (m), 1382 (m), 1165 (s), 815 (w) cm^{-1}. HPLC: t_R = 11.8 min (method 2). LC-MS (ESI): t_R = 11.0 min, C18; calcd. for $C_{21}H_{30}N_3O_6S$ [M + H]$^+$ 452.2; found 451.8. HRMS (ESI): calcd. for $C_{21}H_{30}N_3O_6S$ [M + H]$^+$ 452.1850; found 452.1842.

***tert*-Butyl (*R*)-4-[4-Methoxycarbonyl-1-(tolyl-4′-sulfonyl)imidazol-2-yl]-2,2-dimethylthiazolidine-3-carboxylate (22e):** Imidazoline **21e** (166 mg, 0.33 mmol) was oxidized as described in **GP G**. The crude product was purified by FCC (35 g silica, light petroleum/EtOAc, 39:11) to yield imidazole **22e** (149 mg, 0.30 mmol, 91%) as a colorless oil. R_f = 0.49 (light petroleum/EtOAc, 7:3). $[\alpha]_D^{20}$ = –60.4 (c = 2.0 in $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 8.06–7.81 (m, 3 H, 5-H, SO$_2$CCH), 7.37 (d, J = 8.0 Hz, 2 H, CH$_3$CCH), 5.83 (br. s, 1 H, 4′-H), 3.81 (s, 3 H, COOCH$_3$), 3.38 (br. s, 1 H, 5′-H$_a$), 2.86 (br. s, 1 H, 5′-H$_b$), 2.44 (s, 3 H, ArCH$_3$), 2.02 [s, 3 H, C(CH_3)$_{2a}$], 1.81 [s, 3 H, C(CH_3)$_{2b}$], 1.57–0.87 [m, 9 H, C(CH_3)$_3$]* ppm. * Rotamers. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 162.5 (COOCH$_3$), 150.0 [COC(CH$_3$)$_3$, C-2], 147.0 (CHCCH$_3$), 134.6 (CHCSO$_2$), 132.7 (C-4), 130.7 (CH$_3C$CH), 128.1 (CHCSO$_2$), 125.1 (C-5), 80.6 [OC(CH$_3$)$_3$], 71.8 (C-2′), 61.2 (C-4), 52.0 (COOCH$_3$), 33.3 (C-5), 29.8 [C(CH$_3$)$_{2b}$], 28.4 [C(CH$_3$)$_{2a}$, C(CH$_3$)$_3$], 22.0 (ArCH$_3$) ppm. IR (KBr): $\tilde{\nu}$ = 2978 (m), 1743 (m), 1702 (m), 1354 (s), 1161 (s), 1088 (m), 816 (w) cm^{-1}. HPLC: t_R = 12.3 min (method 2). LC-MS (ESI): t_R = 11.3 min, C18; calcd. for $C_{22}H_{30}N_3O_6S_2$ [M + H]$^+$ 496.2; found 495.9. HRMS (ESI): calcd. for $C_{22}H_{30}N_3O_6S_2$ [M + H]$^+$ 496.1571; found 496.1563.

Methyl 2-[(*S*)-2-*tert*-Butoxycarbonyl-2-*tert*-butoxycarbonylaminoethyl]-1-(tolyl-4′-sulfonyl)imidazole-4-carboxylate (22f): Imidazoline **21f** (189 mg, 0.36 mmol) was oxidized as described in **GP G**. The crude product was purified by FCC (45 g silica, light petroleum/EtOAc, 33:17) to yield imidazole **22f** (146 mg, 0.28 mmol, 77%) as a colorless oil. R_f = 0.67 (light petroleum/EtOAc, 3:2). $[\alpha]_D^{20}$ = +16.0 (c = 2.0 in $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.98 (s, 1 H, 5-H), 7.80 (d, J = 8.3 Hz, 2 H, SO$_2$CCH), 7.35 (d, J = 8.1 Hz, 2 H, CH$_3$CCH), 5.55 (d, J = 8.8 Hz, 1 H, NH), 4.68–4.53 (m, 1 H, 1′-H), 3.80 (s, 3 H, COOCH$_3$), 3.34 (dd, J = 6.6, 16.1 Hz, 1 H, 2′-H$_a$), 3.26 (dd, J = 4.8, 16.0 Hz, 1 H, 2′-H$_b$), 2.40 (s, 3 H, ArCH$_3$), 1.35 [s, 18 H, C(CH_3)$_{3a}$, C(CH_3)$_{3b}$] ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 169.8 [OC(O)CH], 162.1 (COOCH$_3$), 155.4 [OC(O)NH], 147.1 (CH$_3C$CH), 146.4 (C-2), 134.2 (CHCSO$_2$), 132.3 (C-4), 130.7 (CH$_3C$CH), 127.9 (CHCSO$_2$), 125.2 (C-5), 82.2 [C_a(CH$_3$)$_3$], 79.7 [C_b(CH$_3$)$_3$], 52.2 (C-1′), 52.0 (COOCH$_3$), 31.5 (C-2′), 28.4 [C(C_aH$_3$)$_3$], 27.9 [C(C_bH$_3$)$_3$], 21.9 (ArCH$_3$) ppm. IR (KBr): $\tilde{\nu}$ = 2980 (m), 1739 (s), 1713 (s), 1499 (m), 1370 (m), 1158 (s), 813 (m) cm^{-1}. HPLC: t_R = 11.7 min (method 2). LC-MS (ESI): t_R = 10.8 min, C18; calcd. for $C_{24}H_{34}N_3O_8S$ [M + H]$^+$ 524.2; found 523.9. HRMS (ESI): calcd. for $C_{24}H_{34}N_3O_8S$ [M + H]$^+$ 524.2061; found 524.2055. $C_{24}H_{33}N_3O_8S$: C 55.1, H 6.4, N 8.0; found C 55.1, H 6.9, N 7.7.

Methyl 2-(Naphthalen-1-yl)-1-(tolyl-4′-sulfonyl)imidazole-4-carboxylate (22g): Imidazoline **21g** (92 mg, 0.23 mmol) was oxidized as described in **GP G**. The crude product was purified by FCC (30 g silica, light petroleum/EtOAc, 33:17) to yield imidazole **22g** (76 mg, 0.19 mmol, 82%) as a colorless solid. R_f = 0.62 (light petroleum/EtOAc, 1:1), m.p. 157–159 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 8.43 (s, 1 H, 5-H), 8.00–7.88 (m, 1 H, 4′-H), 7.76 (d, J = 8.2 Hz, 1 H, 8′-H), 7.54–7.42 (m, 2 H, 3′-H, 2′-H), 7.34 (ddd, J = 1.1, 6.8, 8.1 Hz, 1 H, 7′-H), 7.07 (ddd, J = 1.3, 6.8, 8.3 Hz, 1 H, 6′-H), 6.89 (d, J = 8.5 Hz, 2 H, CHCSO$_2$), 6.85 (dd, J = 0.8, 8.5 Hz, 1 H, 5′-H), 6.74 (d, J = 8.0 Hz, 2 H, CH$_3$CCH), 3.92 (s, 3 H, COOCH$_3$), 2.13 (s, 3 H, ArCH$_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 162.6 (COOCH$_3$), 146.5 (CH$_3C$CH), 146.4 (C-2), 132.9 (C-4a′), 132.7 (CHCSO$_2$), 132.7 (C-1′), 132.4 (C-4), 130.9 (C-4′), 130.4 (C-3′), 129.6 (CH$_3C$CH), 128.1 (CHCSO$_2$), 128.0 (C-8′), 126.7 (C-6′), 125.9 (C-7′), 125.7 (C-8a′), 125.4 (C-5), 125.0 (C-5′), 124.4 (C-2′), 52.3 (COOCH$_3$), 21.6 (ArCH$_3$) ppm. IR (KBr): $\tilde{\nu}$ = 2949 (w), 1740 (s), 1595 (w), 1530 (w), 1381 (m), 1176 (s), 803 (m), 777 (m) cm^{-1}. HPLC: t_R = 10.9 min (method 2). LC-MS (ESI): t_R = 10.4 min, C18; calcd. for $C_{22}H_{19}N_2O_4S$ [M + H]$^+$ 407.1; found 407.0. HRMS (ESI): calcd. for $C_{22}H_{19}N_2O_4S$ [M + H]$^+$ 407.1060; found 407.1055.

Methyl 2-[(*S*)-1-*tert*-Butoxycarbonylaminoethyl]imidazole-4-carboxylate (23): Methyl (*S*)-2-[(*S*)-1-*tert*-butoxycarbonylaminoethyl]-1-(tolyl-4′-sulfonyl)-4,5-dihydroimidazole-4-carboxylate (**21a**, 192 mg, 0.45 mmol) was dissolved in anhydrous DMF (5.4 mL). DBU (1 mL, 6.76 mmol) was added at 0 °C and the mixture was stirred at room temperature for 3 h. EtOAc, (20 mL) and water (30 mL) were added and the pH of the aqueous layer was adjusted to pH 3–4 with $NaHSO_4$ solution (1 M). The layers were separated and the aqueous layer was extracted with EtOAc, (2 × 20 mL). The pH of the aqueous layer was adjusted to pH 9 with satd. $NaHCO_3$ solution and the layer was extracted with EtOAc, (3 × 20 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. The crude product was purified by FCC (35 g silica, light petroleum/EtOAc, 3:7) to yield imidazole **23** (74 mg, 0.27 mmol, 60%) as a colorless oil. R_f = 0.25 (light petroleum/EtOAc, 3:7).

$[\alpha]_D^{20}$ = –69.8 ($CHCl_3$, c = 2.0). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.61 (s, 1 H, 5-H), 5.80 (d, J = 7.8 Hz, 1 H, N*H*), 4.97–4.83 (m, 1 H, C*H*CH_3), 3.81 (s, 3 H, $COOCH_3$), 1.55 (d, J = 7.0 Hz, 3 H, CH*C*H_3), 1.36 [s, 9 H, C(*C*H_3)$_3$] ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 163.0 (*C*$OOCH_3$), 156.2 [*C*$OC(CH_3)_3$], 152.1 (C-2), 129.7 (C-4), 125.9 (C-5), 80.3 [*C*$(CH_3)_3$], 51.8 ($COOCH_3$), 44.9 (CH_3CH), 28.4 [C(*C*H_3)$_3$], 19.9 (*C*H_3CH) ppm. IR (KBr): $\tilde{\nu}$ = 2981 (m), 1714 (s), 1525 (m), 1250 (m), 1165 (s) cm^{-1}. HPLC: t_R = 5.9 min (method 2). LC-MS (ESI): t_R = 4.9 min, C18; calcd. for $C_{12}H_{20}N_3O_4$ [M + H]$^+$ 270.1; found 269.7 min, C18. HRMS (ESI): calcd. for $C_{12}H_{20}N_3O_4$ [M + H]$^+$ 270.1448; found 270.1483.

(*S*)-2-Azido-3-(trityloxy)propionic Acid (25a): *O*-Trityl-serine (1.04 g, 3.0 mmol) was converted as described in **GP A** with $CuSO_4$ as catalyst and Et_3N as base. After FCC (light petroleum/EtOAc/AcOH, 20:20:0.1), azide **25a** was isolated as a colorless solid (0.81 g, 2.2 mmol, 72%). R_f = 0.17 (light petroleum/EtOAc/AcOH, 20:20:0.1), m.p. 121–122 °C (dec. > 126 °C). $[\alpha]_D^{20}$ = –18.6 ($CHCl_3$, c = 1.0). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.94 (br. s, 1 H, CO_2H), 7.42–7.22 (m, 15 H, Tr), 4.16 (dd, J = 2.9, 4.1 Hz, 1 H, CHN_3), 3.45 (dd, J = 4.3, 9.6 Hz, 1 H, C*H*HOTr), 3.29 (dd, J = 2.9, 9.7 Hz, 1 H, C*H*HOTr) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.8 (CO_2H), 143.0, 128.5, 128.0, 127.3 (Tr), 87.6 (CPh_3), 63.9 (CH_2OTr), 61.5 (CHN_3) ppm. IR (KBr): $\tilde{\nu}$ = 3391 (s), 3559 (bs), 2881 (m), 2111 (s), 1757 (m), 1731 (s), 1632 (m), 1490 (m), 1447 (m), 1223 (s), 1092 (m), 1011 (m), 904 (m), 707 (s), 632 (m) cm^{-1}. HPLC: t_R = 9.8 min (method 8). HRMS (ESI): calcd. for $C_{22}H_{18}N_3O_3$ [M – H]$^-$ 372.1354; found 372.1340.

(*R*)-2-Azido-3-[(4-methoxyphenyl)diphenylmethylthio]propionic Acid (25b): *S*-Methoxytrityl-cysteine (3.94 g, 10 mmol) was converted into the corresponding azide as described in **GP A** with $CuSO_4$ as catalyst and Et_3N as base. After FCC (2×, light petroleum/EtOAc/AcOH, 20:20:0.1), azide **25b** was isolated as a slightly yellow oil (4.15 g, 9.9 mmol, 99%). R_f = 0.23 (light petroleum/EtOAc/HCOOH, 50:50:0.1). $[\alpha]_D^{20}$ = –51.2 ($CHCl_3$, c = 0.5). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.72 (s, 1 H, CO_2H), 7.51–7.14 (m, 12 H, Mmt), 6.81 (d, J = 9.0 Hz, 2 H, Mmt), 3.77 (s, 3 H, OCH_3), 3.22 (dd, J = 5.7, 8.2 Hz, 1 H, CHN_3), 2.71 (dd, J = 5.7, 13.5 Hz, 1 H, C*H*HSMmt), 2.58 (dd, J = 8.2, 13.5 Hz, 1 H, CH*H*SMmt) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.9 (CO_2H), 158.5, 144.6, 136.4, 130.9, 129.6, 128.3, 127.1, 113.6 (Mmt), 67.1 (CHN_3), 55.5 (OCH_3), 33.3 (CH_2SMmt) ppm. IR (KBr): $\tilde{\nu}$ = 3055 (ws), 2115 (s), 1727 (s), 1605 (m), 1506 (s), 1444 (m), 1250 (s), 1181 (s), 1081 (w), 1034 (m), 823 (m), 743 (m), 700 (s), 621 (w), 581 (m) cm^{-1}.

(*R*)-2-Azido-3-(tritylthio)propionic Acid (25c): *S*-Trityl-cysteine (0.73 g, 2.0 mmol) was converted into the corresponding azide as described in **GP A** with $CuSO_4$ as catalyst and K_2CO_3 (0.41 g, 3 mmol) as base. After FCC (light petroleum/EtOAc/AcOH, 20:20:0.1), azide **25c** was isolated as a colorless oil (0.73 g, 1.9 mmol, 94%). R_f = 0.20 (light petroleum/EtOAc/HCOOH, 50:50:0.1). $[\alpha]_D^{20}$ = –15.2 ($CHCl_3$, c = 0.5). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.43 (d, J = 7.6 Hz, 6 H, Tr), 7.33–7.19 (m, 9 H, Tr), 3.14 (t, J = 6.3 Hz, 1 H, CHN_3), 2.71 (dd, J = 5.2, 13.5 Hz, 1 H, C*H*HSTr), 2.59 (dd, J = 7.9, 13.3 Hz, 1 H, CH*H*STr) ppm; not detected: CO_2H; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.3 (CO_2H), 144.3, 129.7, 128.4, 127.2 (Tr), 67.7 (CHN_3), 33.3 (CH_2STr) ppm. IR (KBr): $\tilde{\nu}$ = 3062 (ws), 2361 (m), 2118 (s), 1958 (w), 1719 (s), 1595 (w), 1489 (m), 1445 (m), 1241 (m), 1080 (w), 1034 (w), 890 (m), 743 (s), 698 (s) cm^{-1}. HRMS (ESI): calcd. for $C_{22}H_{18}N_3O_2S$ ([M – H]$^-$) 388.1125; found 388.1125.

(*S*)-2-Azido-3-(tolyl-4′-sulfonylamino)propionic Acid (25d): (*S*)-2-(*tert*-Butoxycarbonylamino)-3-(tolyl-4′-sulfonylamino)propionic acid (4.86 g, 13.57 mmol) was dissolved in HCl in dioxane (4 N, 30 mL) and stirred at room temperature for 4 h. All volatiles were removed in vacuo, and the obtained crude ammonium salt (3.96 g, 13.43 mmol, 99%) was converted into the azide as described in **GP B**. The crude product was purified by FCC (400 g silica, CH_2Cl_2/MeOH 99:1 +0.5% HCOOH) to yield acid **25d** (2.72 g, 9.57 mmol, 71%) as a light yellow oil. R_f = 0.21 ($CHCl_3$/MeOH/HCOOH 184:16:1). $[\alpha]_D^{20}$ = –54.0 (c = 2.0 in MeOH). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 8.87 (br. s, 1 H, COOH), 7.74 (d, J = 8.2 Hz, 2 H, SO_2CCH), 7.31 (d, J = 8.0 Hz, 2 H, CH_3CCH), 5.62 (t, J = 6.1 Hz, 1 H, SO_2NH), 4.20 (t, J = 5.7 Hz, 1 H, CH_2CH), 3.41–3.18 (m, 2 H, CH_2), 2.42 (s, 3 H, $ArCH_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 172.5 (COOH), 144.4 (CSO_2), 136.4 (CH_3CCH), 130.2 ($CHCSO_2$), 127.2 (CH_3CCH), 61.3 (CH_2CH), 43.8 (CH_2), 21.7 ($ArCH_3$) ppm. IR (KBr): $\tilde{\nu}$ = 2118 (s), 1742 (m), 1327 (m), 1159 (s), 814 (w) cm^{-1}. HPLC: t_R = 8.0 min (method 9). HRMS (ESI): calcd. for $C_{10}H_{13}N_4O_4S$ [M + H]$^+$ 285.0652; found 285.0654.

Methyl (2*S*,2′*S*)-2-Azido-3-[2-azido-3-(trityloxy)propanoyloxy]-propionate (26a): Carboxylic acid **25a** (280 mg, 0.75 mmol) and alcohol **14a** (83 mg, 0.57 mmol) were coupled with DIC as described in **GP E**. After FCC (light petroleum/EtOAc, 7:1), bisazide **26a** was isolated as a colorless oil (264 mg, 0.53 mmol, 92%). R_f = 0.23 (light petroleum/EtOAc, 4:1). $[\alpha]_D^{20}$ = –25.6 ($CHCl_3$, c = 1.0). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.45–7.21 (m, 15 H, Tr), 4.50 (dd, J = 6.2, 11.6 Hz, 1 H, 3-H), 4.43 (dd, J = 3.8, 11.6 Hz, 1 H, 3-H), 4.07 (dd, J = 3.8, 6.3 Hz, 1 H, 2-H), 3.87 (dd, J = 3.8, 4.8 Hz, 1 H, 2′-H), 3.79 (s, 3 H, CO_2CH_3), 3.56 (m, 2 H, 3′-H_2) ppm. IR (KBr): $\tilde{\nu}$ = 3375 (bm), 3059 (m), 2973 (m), 2108 (s), 1748 (s), 1712 (m), 1617 (m), 1492 (m), 1449 (m), 1388 (w), 1242 (s), 1179 (s), 1092 (m), 1033 (w), 901 (w), 763 (m), 707 (s), 634 (w) cm^{-1}. LC-MS (ESI): t_R = 11.2 min; calcd. for $C_{26}H_{24}N_6O_5Na$ [M + Na]$^+$ 523.2; found 523.3. HRMS (ESI): calcd. for $C_{26}H_{24}N_6O_5Na$ [M + Na]$^+$ 523.1700; found 523.1695.

Methyl (2*R*,2′*S*)-2-Azido-3-{2-azido-3-[(4-methoxyphenyl)-diphenylmethylthio]propanoylthio}propionate (26b): Trityl thioether **14c** (605 mg, 1.5 mmol) was treated at room temp. with Et_3SiH (0.26 mL, 1.65 mmol) in CH_2Cl_2/TFA (10 mL, 20:1) for 30 min. The reaction mixture was diluted with toluene (10 mL) and the solvent was removed in vacuo. Carboxylic acid **25b** (818 mg, 1.95 mmol) was dissolved in THF (15 mL) and cooled to –20 °C. NMM (0.38 mL, 3.50 mmol), isopropyl chloroformate (0.25 mL, 1.95 mmol), and the crude thiol **24** in THF (3 mL) were added dropwise. The reaction mixture was stirred for 2 h at –20 °C, filtered through a sinter plate, and diluted with EtOAc, (150 mL). The organic layer was washed twice with citric acid (5%) and saturated NaCl solution, dried with $MgSO_4$, and concentrated in vacuo. After FCC (light petroleum/EtOAc, 9:1), bisazide **26b** was isolated as a colorless oil (574 mg, 1.02 mmol, 68%). R_f = 0.42 (light petroleum/EtOAc, 2:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.47–7.15 (m, 13 H, Mmt), 6.88–6.76 (m, 2 H, Mmt), 4.02 (dt, J = 5.3, 7.8 Hz, 1 H, 2-H), 3.78 (s, 3 H, CO_2CH_3), 3.77 (s, 3 H, Mmt-OCH_3), 3.30 (dd, J = 5.5, 13.9 Hz, 1 H, 3-H_a), 3.16–3.03 (m, 2 H, 3-H_b, 2′-H), 2.73 (dd, J = 5.1, 13.8 Hz, 1 H, 3′-H_a), 2.61 (dd, J = 8.8, 13.8 Hz, 1 H, 3′-H_b) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 196.1 (C-1′), 168.9 (C-1), 158.5, 144.6, 136.3, 130.9, 129.6, 128.3, 127.1, 113.6, 68.3 (Mmt), 67.3 (C-2), 61.1 (C-2′), 55.4 (Mmt-OCH_3), 53.2 (CO_2CH_3), 34.4 (C-3), 30.4 (C-3′) ppm. IR (KBr): $\tilde{\nu}$ = 3354 (bw), 3056 (m), 2954 (m), 2837 (m), 2493 (bw), 2115 (s), 1747 (s), 1694 (s), 1651 (w), 1605 (m), 1556 (w), 1506 (s), 1443 (m), 1251 (m), 1081 (m), 1033 (s), 823 (s), 743 (s), 701 (s), 622 (m), 581 (m), 544 (w) cm^{-1}. HPLC: t_R = 12.8 min (method 11). MS (ESI): calcd. for $C_{27}H_{26}N_6O_4S_2Na$ [M + Na]$^+$ 585.1; found 585.2.

Methyl (2*S*,2′*R*)-2-Azido-3-[2-azido-3-(tritylthio)propanoyloxy]-propionate (26c): Methyl ester **14c** (450 mg, 1.12 mmol) was dissolved in THF (6 mL), cooled to 0 °C, treated with LiOH (1 M, 2.2 mL), and stirred for 20 min at room temp. The reaction mixture was acidified with citric acid (10%) and the organic solvent was evaporated. The aqueous residue was extracted with EtOAc, (3× 25 mL). The combined organic layers were washed with saturated NaCl solution, dried with Na_2SO_4, and concentrated in vacuo. The crude carboxylic acid **25c** (which was also available by diazo transfer on the free acid; see above) was coupled with alcohol **14a** (161 mg, 1.1 mmol) as described in **GP E** with DIC (0.22 mL, 1.45 mmol). After FCC (light petroleum/EtOAc, 5:1), bisazide **26c** was isolated as a colorless oil (339 mg, 0.66 mmol, 59%). R_f = 0.43 (light petroleum/EtOAc, 2:1). $[\alpha]_D^{20}$ = –22.8 ($CHCl_3$, c = 0.5). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.45–7.20 (m, 15 H, Tr), 4.47–4.34 (m, 2 H, 3-H_2), 4.16–4.05 (m, 1 H, 2-H), 3.74 (2× s, 3 H, CO_2CH_3), 3.16–3.01 (m, 1 H, 2′-H), 2.71 (dd, J = 6.1, 13.6 Hz, 1 H, 3′-H), 2.56 (ddd, J = 2.4, 8.1, 13.6 Hz, 1 H, 3′-H) ppm. IR (KBr): $\tilde{\nu}$ = 3060 (m), 3031 (m), 2957 (w), 2113 (s), 1749 (s), 1595 (w), 1490 (m), 1445 (m), 1211 (s), 1179 (s), 1080 (w), 1034 (w), 855 (s), 800 (s), 747 (m), 702 (m), 676 (w), 620 (w) cm^{-1}. MS (MALDI): calcd. for $C_{26}H_{24}N_6O_4SNa$ [M + Na]$^+$ 539.1; found 539.6.

(*S*)-2-Azido-2-(methoxycarbonyl)ethyl (*S*)-2-Azido-3-(tolyl-4′-sulfonylamino)propionate (26d): (*S*)-2-Azido-3-(tolyl-4′-sulfonylamino)propionic acid (**25d**, 1.21 g, 4.26 mmol) and HOBt (1.15 g, 8.5 mmol) were dissolved in anhydrous CH_2Cl_2 (15 mL) and DMF (4 mL) and cooled to 0 °C. EDC×HCl (1.64 g, 8.5 mmol) was added, and the mixture was stirred for 15 min. Methyl (*S*)-2-azido-3-hydroxypropionate (**14a**, 560 mg, 3.86 mmol), dissolved in anhydrous CH_2Cl_2, was added (5 mL). The mixture was stirred for 2 h at room temp., and the solvent was evaporated in vacuo The crude product was dissolved in ethyl acetate (100 mL) and washed with $NaHSO_4$ solution (1 M, 200 mL). The aqueous layer was extracted with ethyl acetate (3× 100 mL), and the combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. FCC (400 g silica, light petroleum/EtOAc, 33:17) yielded ester **26d** (956 mg, 2.35 mmol, 61%) as a light yellow oil. R_f = 0.41 (light petroleum/EtOAc, 31:19). $[\alpha]_D^{20}$ = –57.9 (c = 2.0 in $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 7.75 (d, J = 8.3 Hz, 2 H, SO_2CCH), 7.32 (d, J = 8.0 Hz, 2 H, CH_3CCH), 5.11 (t, J = 6.7 Hz, 1 H, NH), 4.56 (dd, J = 4.0, 11.5 Hz, 1 H, 3′-H_a), 4.47 (dd, J = 5.8, 11.5 Hz, 1 H, 3′-H_b), 4.23 (dd, J = 4.0, 5.7 Hz, 1 H, 2′-H), 4.18 (dd, J = 5.6, 6.3 Hz, 1 H, 2-H), 3.85 (s, 3 H, $COOCH_3$), 3.31 (ddd, J = 5.5, 6.7, 13.7 Hz, 1 H, 3-H_a), 3.27–3.19 (m, 1 H, 3-H_b), 2.43 (s, 3 H, $ArCH_3$) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 168.1 (*C*OOMe), 167.9 (C-1), 144.2 (CH_3CCH), 136.8 ($CHCSO_2$), 130.1 (CH_3CCH), 127.2 ($CHCSO_2$), 64.9 (C-3′), 61.5 (C-2), 60.3 (C-2′), 53.6 ($COOCH_3$), 43.9 (C-3), 21.7 ($ArCH_3$) ppm. IR (KBr): $\tilde{\nu}$ = 2958 (w), 2110 (s), 1745 (s), 1157 (s), 814 (m) cm^{-1}. HPLC: t_R = 10.4 min (method 3). LC-MS (ESI): t_R = 9.2 min, C18; calcd. for $C_{14}H_{18}N_7O_6S$ [M + H]$^+$ 412.1; found 411.9. HRMS (ESI): calcd. for $C_{14}H_{18}N_7O_6S$ [M + H]$^+$ 412.1032; found 412.1034.

Methyl (*R*)-2-Azido-3-[(*S*)-2-azido-3-(tolyl-4′-sulfonylamino)-propionylsulfanyl]propionate (26e): (*S*)-2-Azido-3-(tolyl-4′-sulfonylamino)propionic acid (**25d**, 457 mg, 1.61 mmol) and HOBt (435 mg, 3.22 mmol) were dissolved in anhydrous CH_2Cl_2 (5 mL) and DMF (1.5 mL) and cooled to 0 °C. EDC×HCl (614 mg, 3.22 mmol) was added and the mixture was stirred for 15 min. Freshly deprotected methyl (*R*)-2-azido-3-mercaptopropionate (**24**, 233 mg, 1.45 mmol; see **GP D**) in anhydrous CH_2Cl_2 (2.5 mL) was added, and the mixture was stirred for 2 h. The solvents were evaporated, and the crude product was dissolved in EtOAc, (25 mL) and washed with phosphate buffer (pH 7, 50 mL). The aqueous layer was extracted with ethyl acetate (3× 25 mL), and the combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. FCC (150 g silica, light petroleum/EtOAc, 33:17) yielded thioester **26e** (435 mg, 1.02 mmol, 70%) as a yellow oil. R_f = 0.09 (light petroleum/EtOAc, 4:1). $[\alpha]_D^{20}$ = –61.0 (c = 3.0 in $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 7.75 (d, J = 8.3 Hz, 2 H, SO_2CCH), 7.32 (d, J = 8.0 Hz, 2 H, CH_3CCH), 5.13 (t, J = 6.1 Hz, 1 H, NH), 4.20 (dd, J = 5.1, 7.1 Hz, 1 H, 2-H), 4.16–4.05 (m, 1 H, 2′-H), 3.82 (m, 3 H, $COOCH_3$), 3.45–3.34 (m, 2 H, 3-H_a, 3′-H_a), 3.23–3.15 (m, 2 H, 3′-H_b, 3-H_b), 2.43 (s, 3 H, $ArCH_3$) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 196.1 (C-1), 169.0 (*C*OOMe), 144.2 (CH_3CCH), 136.7 ($CHCSO_2$), 130.1 (CH_3CCH), 127.3 ($CHCSO_2$), 68.6 (C-2), 61.0 (C-2′), 53.4 ($COOCH_3$), 44.7 (C-3), 30.4 (C-3′), 21.7 ($ArCH_3$) ppm. IR (KBr): $\tilde{\nu}$ = 2956 (w), 2926 (w), 2110 (s), 1743 (m), 1685 (m), 1328 (m), 1157 (s), 814 (m) cm^{-1}. HPLC: t_R = 11.0 min (method 3). LC-MS (ESI): t_R = 9.7 min, C18; calcd. for $C_{14}H_{18}N_7O_5S_2$ [M + H]$^+$ 428.1; found 427.9. HRMS (ESI): calcd. for $C_{14}H_{18}N_7O_5S_2$ [M + H]$^+$ 428.0805; found 428.0805.

Methyl (2*S*,2′*S*,2′′*S*)-2-Azido-3-[2-azido-3-(*N*-Boc-alanyloxy)-propanoyloxy]propionate (27a): Trityl ether **26a** (125 mg, 0.25 mmol) was treated at room temp. with Et_3SiH (0.04 mL, 0.26 mmol) in CH_2Cl_2/TFA (5.5 mL, 10:1) for 10 min. The reaction mixture was carefully neutralized by dropwise addition of saturated $NaHCO_3$ solution and diluted with H_2O (10 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2× 15 mL). The combined organic extracts were dried with $MgSO_4$ and concentrated in vacuo. The crude alcohol was coupled with *N*-Boc-alanine (61 mg, 0.33 mmol) as described in **GP E** with DIC (60 μL, 0.35 mmol). After FCC (light petroleum/EtOAc, 2:1), triester **27a** was isolated as a colorless oil (75 mg, 0.18 mmol, 70%). R_f = 0.19 (light petroleum/EtOAc, 2:1). $[\alpha]_D^{20}$ = –30.0 ($CHCl_3$, c = 0.1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.98 (d, J = 4.7 Hz, 1 H, NH), 4.61–4.39 (m, 4 H, 3′-H_2, 3-H_2), 4.32 (br. s, 1 H, 2′-H), 4.21 (ddd, J = 4.2, 5.8, 10.0 Hz, 1 H, 2-H), 4.14 (dd, J = 4.7, 9.3 Hz, 1 H, 2′′-H), 3.83 (s, 3 H, CO_2CH_3), 1.42 [s, 9 H, $CO_2C(CH_3)_3$], 1.38 (d, J = 7.2 Hz, 3 H, 3′′-H_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.9 (C-1′′), 168.0, 167.2 (C-1′, C-1), 155.3 (CO_2tBu), 80.3 [$C(CH_3)_3$], 65.0, 64.2 (C-3′, C-3), 60.4, 60.3 (C-2′, C-2), 53.5 (CO_2CH_3), 49.4 (C-2′′), 28.5 [$C(CH_3)_3$], 18.5 (C-3′′) ppm. IR (KBr): $\tilde{\nu}$ = 3363 (bw), 2979 (m), 2112 (s), 1748 (s), 1714 (s), 1566 (w), 1505 (m), 1455 (m), 1368 (m), 1245 (m), 1167 (s), 1069 (m), 797 (w), 555 (w) cm^{-1}. LC-MS (ESI): t_R = 8.9 min; calcd. for $C_{15}H_{23}N_7O_8$ [M]$^+$ 429.2; found 428.8. HRMS (ESI): calcd. for $C_{15}H_{24}N_7O_8$ [M + H]$^+$ 430.1681; found 430.1681.

Methyl (2*R*,2′*S*,2′′*S*)-2-Azido-3-[2-azido-3-(*N*-Boc-alanylthio)-propanoylthio]propionate (27b): Methoxytrityl thioether **26b** (48 mg, 0.09 mmol) was treated with Et_3SiH (20 μL, 0.10 mmol) in CH_2Cl_2/TFA (4.0 mL, 3:1) for 30 min at room temp. The reaction mixture was diluted with toluene (10 mL) and concentrated in vacuo. The crude thiol was coupled to *N*-Boc-alanine (34 mg, 0.18 mmol) as described in **GP D** with DIC (30 μL, 0.18 mmol). After FCC (light petroleum/EtOAc, 4:1), bisthioester **27b** was isolated as a colorless oil (34 mg, 0.07 mmol, 82%) and directly subjected to the next step owing to its high lability. R_f = 0.16 (light petroleum/EtOAc, 4:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.93 (br. s, 1 H, NH), 4.43–4.33 (m, 1 H, 2′-H), 4.18–4.06 (m, 2 H, 2-H, 6-H), 3.82 (s, 3 H,CO_2CH_3), 3.48–3.35 (m, 2 H, 3′-H_2), 3.28–3.06 (m, 2 H, 3-H_2), 1.44 [s, 9 H, $CO_2C(CH_3)_3$], 1.37 (d, J = 7.2 Hz, 3 H, 3′-H_3) ppm. IR (KBr): $\tilde{\nu}$ = 3377 (bm), 2979 (m), 2924 (m), 2118 (s), 1695 (s), 1505 (m), 1454 (m), 1368 (m), 1247 (s), 1170 (s), 1018 (w), 970 (m), 885 (w), 858 (w) cm^{-1}. MS (MALDI-TOF): calcd. for $C_{15}H_{23}N_7O_6S_2Na$ [M + Na]$^+$ 484.1; found 484.6.

Methyl (2*S*,2′*R*,2′′*S*)-2-Azido-3-[2-azido-3-(*N*-Boc-alanylthio)-propanoyloxy]propionate (27c): Trityl thioether **26c** (300 mg, 0.58 mmol) was treated at room temp. with Et_3SiH (0.10 mL, 0.64 mmol) in CH_2Cl_2/TFA (9 mL, 2:1) for 1.5 h. The reaction mixture was diluted with toluene (10 mL) and the solvent was removed in vacuo. The crude thiol was coupled with *N*-Boc-alanine (115 mg, 0.61 mmol) as described in **GP D** with DIC (0.11 mL, 0.70 mmol), HOBt (107 mg, 0.70 mmol), and EtN*i*Pr$_2$ (0.12 mL, 0.70 mmol). After FCC (light petroleum/EtOAc, 5:1), thioester **27c** was isolated as a colorless oil (188 mg, 0.42 mmol, 73%). R_f = 0.30 (light petroleum/EtOAc, 2:1). $[\alpha]_D^{20}$ = –35.6 ($CHCl_3$, *c* = 0.5). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.93 (br. s, 1 H, NH), 4.54 (dt, *J* = 3.7, 11.5 Hz, 1 H, 3-H$_a$), 4.47 (ddd, *J* = 2.3, 5.9, 11.6 Hz, 1 H, 3-H$_b$), 4.41–4.32 (m, 1 H, 2′′-H), 4.20 (ddd, *J* = 4.1, 5.9, 7.3 Hz, 1 H, 2-H), 4.08 (dd, *J* = 6.0, 7.1 Hz, 1 H, 2′-H), 3.83 (s, 3 H, CO_2CH_3), 3.32 (m, 1 H, 3′-H$_a$), 3.17 (m, 1 H, 3′-H$_b$), 1.44 [s, 9 H, $CO_2C(CH_3)_3$], 1.36 (d, *J* = 7.3 Hz, 3 H, 3′′-H$_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 201.6 (C-1′′), 168.2, 168.1 (C-1′, C-1), 155.1 (CO_2tBu), 80.8 [$C(CH_3)_3$], 65.0 (C-3), 61.4 (C-2′), 60.3 (C-2), 56.6 (C-2′′), 53.5 (CO_2CH_3), 30.1 (C-3′), 28.5 [$C(CH_3)_3$], 18.6 (C-3′′) ppm. IR (KBr): $\tilde{\nu}$ = 3386 (bm), 2980 (m), 2115 (s), 1750 (s), 1714 (s), 1506 (m), 1454 (m), 1369 (w), 1245 (s), 1168 (s), 1051 (w), 962 (s), 914 (s), 856 (s) cm^{-1}. LC-MS (ESI): t_R = 10.0 min; calcd. for $C_{15}H_{23}N_7O_7S$ [M]$^+$ 445.1; found 445.6. HRMS (ESI): calcd. for $C_{15}H_{24}N_7O_7S$ [M + H]$^+$ 446.1452; found 446.1453.

(*S*)-2-Azido-2-(methoxycarbonyl)ethyl (*S*)-2-Azido-3-{[(*S*)-2-(*tert*-butoxycarbonylamino)propionyl](tolyl-4′-sulfonyl)amino}propionate (27d): Bisazide **26d** (451 mg, 1.10 mmol) was dissolved in anhydrous CH_2Cl_2 (2.4 mL) and cooled to 0 °C. (*S*)-*N*-Boc-alanyl fluoride (419 mg, 2.19 mmol; see **GP H**) in anhydrous CH_2Cl_2 (2.4 mL) and EtN*i*Pr$_2$ (199 µL, 1.21 mmol) were added and the mixture was stirred at 0 °C. After 45 min, toluene (2 mL) and formic acid (122 µL, 3.23 mmol) were added and the volatiles were removed in vacuo. The crude product was purified by FCC (135 g silica, light petroleum/EtOAc, 37:13) to give *N*-acyl-sulfonamide **27d** (560 mg, 0.96 mmol, 88%), together with a second diastereomer (*dr* = 92:8), as a light yellow oil. R_f = 0.26 (light petroleum/EtOAc, 37:13). $[\alpha]_D^{20}$ = –61.4 (*c* = 1.0 in $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C, major isomer): δ = 7.92 (d, *J* = 7.5 Hz, 2 H, SO_2CCH), 7.34 (d, *J* = 8.1 Hz, 2 H, CH_3CCH), 5.21–5.11 (m, 1 H, 2′′-H), 4.98 (d, *J* = 7.6 Hz, 1 H, NH), 4.56 (dd, *J* = 4.0, 11.5 Hz, 1 H, 3′-H$_a$), 4.50 (dd, *J* = 5.9, 11.5 Hz, 1 H, 3′-H$_b$), 4.39 (dd, *J* = 5.5, 7.8 Hz, 1 H, 2-H), 4.27–4.17 (m, 2 H, 2′-H, 3-H$_a$), 4.01 (dd, *J* = 8.4, 14.9 Hz, 1 H, 3-H$_b$), 3.84 (s, 3 H, $COOCH_3$), 2.43 (s, 3 H, $ArCH_3$), 1.37 [m, 12 H, $C(CH_3)_3$, $CHCH_3$] ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 175.7 (C-1′′), 168.0 (*C*OOMe), 167.8 (C-1), 155.2 [*C*OC(CH$_3$)$_3$], 145.6 (CH_3CCH), 135.7 ($CHCSO_2$), 130.2 (CH_3CCH), 128.2 ($CHCSO_2$), 80.2 [$C(CH_3)_3$], 65.0 (C-3′), 60.7 (C-2), 60.3 (C-2′), 53.4 ($COOCH_3$), 50.0 (C-2′′), 46.3 (C-3), 28.4 [$C(CH_3)_3$], 21.8 ($ArCH_3$), 19.6 (CH_3CH) ppm. IR (KBr): $\tilde{\nu}$ = 2979 (w), 2112 (m), 1749 (m), 1699 (m), 1363 (m), 1160 (s), 814 (w) cm^{-1}. HPLC: major diastereomer: t_R = 12.7 min, minor diastereomer: t_R = 13.0 min, (method 3). LC-MS (ESI): t_R = 10.4 min, C18; calcd. for $C_{22}H_{31}N_8O_9S$ [M + H]$^+$ 583.2; found 582.6. HRMS (ESI): calcd. for $C_{22}H_{31}N_8O_9S$ [M + H]$^+$ 583.1929; found 583.1927.

Methyl (*R*)-2-Azido-3-((*S*)-2-azido-3-{[(*S*)-2-(*tert*-butoxycarbonylamino)propionyl](tolyl-4′-sulfonyl)amino}propionylsulfanyl)-propionate (27e): Bisazide **26e** (218 mg, 0.51 mmol) was dissolved in anhydrous CH_2Cl_2 (1 mL) and cooled to –20 °C. (*S*)-*N*-Boc-alanyl fluoride (102 mg, 0.54 mmol; see **GP H**) in anhydrous CH_2Cl_2 (1.2 mL) and EtN*i*Pr$_2$ (88 µL, 0.54 mmol) was added and the mixture was stirred at 0 °C. After 45 min, toluene (1 mL) and formic acid (40 µL, 1.02 mmol) were added and the volatiles were removed in vacuo. The crude product was purified by FCC (35 g silica, light petroleum/EtOAc, 19:6) to give bis-azide **27e** (155 mg, 0.26 mmol, 51%) together with a second diastereomer (*dr*: 56:44) as a light yellow oil. R_f = 0.21 (major diastereomer), 0.19 (minor diastereomer), (light petroleum/EtOAc, 19:6). $[\alpha]_D^{20}$ = –69.4 (*c* = 1.0 in $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.94 (d, *J* = 8.1 Hz, 2 H, SO_2CCH), 7.35 (d, *J* = 8.2 Hz, 2 H, CH_3CCH), 5.27–5.13 (m, 1 H, 2′′-H), 4.97 (d, *J* = 7.8 Hz, 1 H, NH), 4.51 (dd, *J* = 5.2, 8.8 Hz, 1 H, 2-H), 4.20 (dd, *J* = 5.3, 14.8 Hz, 1 H, 3-H$_a$), 4.13 (dd, *J* = 5.6, 7.7 Hz, 1 H, 2′-H), 3.91 (dd, *J* = 8.6, 14.7 Hz, 1 H, 3-H$_b$), 3.84 (s, 3 H, $COOCH_3$), 3.40 (dd, *J* = 5.6, 13.9 Hz, 1 H, 3′-H$_a$), 3.18 (dd, *J* = 7.7, 13.9 Hz, 1 H, 3′-H$_b$), 2.43 (s, 3 H, $ArCH_3$), 1.46–1.32 [m, 12 H, $C(CH_3)_3$, $CHCH_3$] ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 195.7 (C-1), 175.6 (C-1′′), 169.1 (*C*OOMe), 155.3 [*C*OC(CH$_3$)$_3$], 145.7 (CH_3CCH), 135.5 ($CHCSO_2$), 130.3 (CH_3CCH), 128.3 ($CHCSO_2$), 80.3 [$C(CH_3)_3$], 67.7 (C-2), 61.1 (C-2′), 53.3 ($COOCH_3$), 50.2 (C-2′′), 47.1 (C-3), 30.4 (C-3′), 28.4 [$C(CH_3)_3$], 21.9 ($ArCH_3$), 19.6 (CH_3CH) ppm. IR (KBr): $\tilde{\nu}$ = 2961 (w), 2927 (w), 2115 (s), 1746 (m), 1693 (s), 1364 (m), 1161 (s), 814 (m) cm^{-1}. HPLC: major diastereomer t_R = 12.0 min, minor diastereomer: t_R = 12.2 (method 3). LC-MS (ESI): t_R = 10.6 min, C18; calcd. for $C_{22}H_{31}N_8O_8S_2$ [M + H]$^+$ 599.2; found 598.7. HRMS (ESI): calcd. for $C_{22}H_{31}N_8O_8S_2$ [M + H]$^+$ 599.1701; found 599.1698.

Methyl (4*S*,4′*S*,1′′*S*)-2′-[1-(*tert*-Butoxycarbonylamino)ethyl]-4,4′,5′-tetrahydro-2,4′-bisoxazole-4-carboxylate (28a): Bisazide **27a** (63 mg, 0.15 mmol) was cyclized as described in **GP F**. After double purification on silica gel (1. CH_2Cl_2/MeOH 25:1, 2. CH_2Cl_2/MeOH 40:1), the bisoxazoline **28a** was isolated as a colorless resin (42 mg, 0.12 mmol, 83%). R_f = 0.41 (CH_2Cl_2/MeOH 20:1). $[\alpha]_D^{20}$ = –8.0 ($CHCl_3$, *c* = 0.1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.20 (br. s, 1 H, NH), 4.91–4.71 (m, 2 H, 4-H, 4′-H), 4.61–4.38 (m, 5 H, 5-H$_2$, 5′-H$_2$, 1′′-H), 3.75 (s, 3 H, CO_2CH_3), 1.40 [s, 9 H, $CO_2C(CH_3)_3$], 1.37 (d, *J* = 7.0 Hz, 3 H, 2′′-H$_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.1 (CO_2Me), 168.6, 168.4 (C-2, C-2′), 155.1 (CO_2tBu), 80.0 [$C(CH_3)_3$], 71.0, 70.4 (C-5,C-5′), 68.2, 63.5 (C-4,C-4′), 52.3 (CO_2CH_3), 45.0 (C-1′′), 28.5 [$C(CH_3)_3$], 19.7 (C-2′′) ppm. IR (KBr): $\tilde{\nu}$ = 3057 (m), 3021 (w), 2923 (w), 2357 (m), 2340 (m), 1979 (w), 1906 (w), 1842 (w), 1732 (m), 1715 (m), 1696 (w), 1682 (w), 1590 (w), 1574 (w), 1505 (m), 1486 (m), 1437 (s), 1394 (w), 1372 (w), 1334 (w), 1309 (w), 1193 (s), 1120 (s), 1070 (w), 1027 (w), 997 (w), 857 (s), 800 (s), 755 (s), 722 (s), 696 (s) cm^{-1}. LC-MS (ESI): t_R = 7.9 min; calcd. for $C_{15}H_{23}N_3O_6$ [M]$^+$ 341.2; found 341.5.

Methyl (*S*)-2′-[1-(*tert*-Butoxycarbonylamino)ethyl]-2,4′-bioxazole-4-carboxylate (29a): Bisoxazoline **28a** (17 mg, 0.05 mmol) was oxidized as described in **GP G**. After FCC (light petroleum/EtOAc, 2:1), bisoxazole **29a** was isolated as a colorless solid (6 mg, 0.02 mmol, 33%). R_f = 0.19 (light petroleum/EtOAc, 1:1), m.p. 184–185 °C. $[\alpha]_D^{20}$ = –35.3 ($CHCl_3$, *c* = 0.6). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.28, 8.27 (2× s, 2×1 H, 5-H, 5′-H), 5.18 (br. s, 1 H, NH), 5.02 (br. s, 1 H, 1′′-H), 3.92 (s, 3 H, CO_2CH_3), 1.56 (d, *J* = 6.9 Hz, 3 H, 2′′-H$_3$), 1.43 [s, 9 H, $CO_2C(CH_3)_3$] ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.7 (C-2′), 166.6 (C-2), 161.5 (CO_2Me), 153.6 (CO_2tBu) 143.9 (C-5), 139.8 (C-5′), 128.7 (C-4), 110.0 (C-4′), 80.5 [$C(CH_3)_3$], 52.5 (CO_2CH_3), 45.0 (C-1′′), 28.5 [$C(CH_3)_3$], 20.4 (C-2′′) ppm. IR (KBr): $\tilde{\nu}$ = 3327 (m), 3141 (w), 3111 (w), 2963 (w), 2852 (w), 1726 (s), 1688 (s), 1635 (w), 1574 (m), 1539 (m), 1505 (w), 1393 (w), 1368 (w), 1325 (m), 1272 (w), 1204 (m), 1178 (m), 1114 (w), 1099 (m), 1070 (w), 1031 (w), 867 (s), 799 (s) cm^{-1}. LC-MS (ESI): t_R = 8.5 min; calcd. for $C_{30}H_{38}N_6O_{12}$ [M + M]$^+$ (dimer) 674.3; found 674.6. HRMS (ESI): calcd. for $C_{15}H_{20}N_3O_6$ [M + H]$^+$ 338.1347; found 338.1350.

Methyl (*S*)-2′-[1-(*tert*-Butoxycarbonylamino)ethyl]-2,4′-bithiazole-4-carboxylate (29b): Bisazide **27b** (40 mg, 0.09 mmol) was cyclized as described in **GP F** and subsequently oxidized as described in **GP G**. After FCC (cyclohexane/EtOAc, 3:1), bithiazole **29b** was isolated as a colorless solid (19 mg, 0.05 mmol, 60%). R_f = 0.27 (light petroleum/EtOAc, 2:1), m.p. 168–169 °C. $[\alpha]_D^{20}$ = –25.6 ($CHCl_3$, c = 1.0). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.15 (s, 1 H, 5-H), 8.03 (s, 1 H, 5′-H), 5.16 (br. s, 1 H, NH), 5.08 (br. s, 1 H, 1′′-H), 3.94 (s, 3 H, CO_2CH_3), 1.61 (d, J = 6.8 Hz, 3 H, 1′′-CH_3), 1.43 [s, 9 H, $CO_2C(CH_3)_3$] ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.9 (C-2′), 163.7 (C-2), 162.1 (CO_2Me), 155.1 (CO_2tBu), 148.3 (C-5), 147.7 (C-4′), 128.2 (C-4), 117.3 (C-5′), 80.5 [*C*(CH_3)$_3$], 52.7 (CO_2CH_3), 49.0 (C-1′′), 28.5 [C(*C*H_3)$_3$], 21.9 (1′′-CH_3) ppm. IR (KBr): $\tilde{\nu}$ = 3386 (m), 3329 (m), 3122 (w), 2985 (m), 2935 (w), 1720 (s), 1687 (s), 1502 (m), 1449 (m), 1392 (w), 1368 (w), 1329 (w), 1285 (m), 1242 (s), 1169 (s), 1088 (w), 1060 (w), 1022 (w), 994 (m), 923 (m), 862 (s), 810 (s), 668 (w) cm^{-1}. HPLC: t_R = 10.3 min (method 11). LC-MS (ESI): t_R = 8.7 min; calcd. for $C_{15}H_{19}N_3O_4S_2Na$ [M + Na]$^+$ 392.1; found 391.9. HRMS (ESI): calcd. for $C_{15}H_{20}N_3O_4S_2$ [M + H]$^+$ 370.0895; found 370.0929.

Methyl 2-{2-[(*S*)-1-(*tert*-Butoxycarbonylamino)ethyl]thiazol-4-yl}oxazole-4-carboxylate (29c): Bisazide **27c** (22 mg, 0.05 mmol) was cyclized as described in **GP F** and subsequently oxidized as described in **GP G**. After FCC (cyclohexane/EtOAc, 3:1), bisazole **29c** was isolated as a colorless solid (11 mg, 0.03 mmol, 64%). R_f = 0.25 (light petroleum/EtOAc, 1:1), m.p. 176–177 °C. $[\alpha]_D^{20}$ = –41.9 ($CHCl_3$, c = 1.0). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.27 (s, 1 H, 5-H), 8.06 (s, 1 H, 5′-H), 5.20 (br. s, 1 H, NH), 5.12 (br. s, 1 H, 1′′-H), 3.93 (s, 3 H, CO_2CH_3), 1.63 (d, J = 6.8 Hz, 3 H, 1′′-CH_3), 1.43 [s, 9 H, $CO_2C(CH_3)_3$] ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.8 (C-2′), 161.6 (CO_2Me), 158.0 (C-2), 155.0 (CO_2tBu), 143.9 (C-5), 142.7 (C-4′), 134.5 (C-4), 121.4 (C-5′), 80.4 [*C*(CH_3)$_3$], 52.3 (CO_2CH_3), 48.9 (C-1′′), 28.4 [C(*C*H_3)$_3$], 21.8 (1′′-CH_3) ppm. IR (KBr): $\tilde{\nu}$ = 3363 (s), 3129 (m), 2985 (m), 2929 (m), 2853 (w), 1725 (s), 1688 (s), 1593 (w), 1571 (m), 1515 (s), 1476 (w), 1440 (m), 1390 (w), 1368 (w), 1337 (w), 1322 (m), 1300 (m), 1252 (m), 1224 (m), 1172 (s), 1115 (m), 1062 (w), 1003 (w), 991 (w), 951 (s), 930 (m), 891 (m), 862 (s), 841 (s), 806 (s), 793 (s), 733 (m), 695 (w), 669 (w) cm^{-1}. HPLC: t_R = 10.8 min (method 12). LC-MS (ESI): t_R = 7.8 min; calcd. for $C_{15}H_{19}N_3O_5S$ [M]$^+$ 353.1; found 353.4. HRMS (ESI): calcd. for $C_{15}H_{20}N_3O_5S$ [M + H]$^+$ 354.1118; found 354.1120.

Methyl 2-{2-[(*S*)-1-(*tert*-Butoxycarbonylamino)ethyl]-1-(tolyl-4′-sulfonyl)imidazol-4-yl}oxazole-4-carboxylate (29d): Bisazide **27d** (195 mg, 0.33 mmol) was cyclized with triphenylphosphane (263 mg, 1.00 mmol) in THF as described in **GP F** and subsequently oxidized with DBU (500 μL, 3.34 mmol) and $BrCCl_3$ (164 μL, 1.67 mmol) as described in **GP G**. The crude product was purified by FCC (70 g silica, light petroleum/EtOAc, 27:23) to give bis-azole **29d** (121 mg, 0.25 mmol, 76%) as a colorless oil. R_f = 0.41 (light petroleum/EtOAc, 3:7). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 8.23 (s, 1 H, 5-H), 8.04 (s, 1 H, 5′-H), 7.96 (d, J = 7.7 Hz, 2 H, SO_2CCH), 7.35 (d, J = 8.5 Hz, 2 H, CH_3CCH), 5.60–5.49 (m, 1 H, C*H*CH_3), 5.41 (d, J = 9.5 Hz, 1 H, N*H*), 3.92 (s, 3 H, $COOCH_3$), 2.42 (s, 3 H, $ArCH_3$), 1.50 (d, J = 6.7 Hz, 3 H, CHCH_3), 1.40 [s, 9 H, C(CH_3)$_3$] ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 161.6 (*C*OOMe), 157.1 (C-2), 154.8 [*C*OC(CH$_3$)$_3$], 152.6 (C-2′), 147.1 (CH_3CCH), 143.7 (C-5), 134.5 (C-4), 134.4 ($CHCSO_2$), 130.8 (CH_3CCH), 129.5 (C-4′), 128.2 ($CHCSO_2$), 120.4 (C-5′), 79.9 [*C*(CH_3)$_3$], 52.5 ($COOCH_3$), 44.3 (*C*HCH_3), 28.5 [C(*C*H$_3$)$_3$], 22.9 (CH*C*H$_3$), 22.0 ($ArCH_3$) ppm. IR (KBr): $\tilde{\nu}$ = 2979 (w), 1747 (m), 1706 (s), 1498 (m), 1170 (s), 815 (w) cm^{-1}. HPLC: t_R = 11.7 min (method 3). LC-MS (ESI): t_R = 10.2 min, C18; calcd. for $C_{22}H_{27}N_4O_7S$ [M + H]$^+$ 491.2; found 490.8. HRMS (ESI): calcd. for $C_{22}H_{27}N_4O_7S$ [M + H]$^+$ 491.1595; found 491.1590.

Methyl 2-{2-[(*S*)-1-(*tert*-Butoxycarbonylamino)ethyl]-1-(tolyl-4′-sulfonyl)imidazol-4-yl}thiazole-4-carboxylate (29e): *N*-Acyl-sulfonamide **27e** (100 mg, 0.17 mmol) was cyclized with triphenylphosphane (131 mg, 0.50 mmol) as described in **GP F** and subsequently oxidized with DBU (250 μL, 1.67 mmol) and $BrCCl_3$ (82 μL, 0.84 mmol) as described in **GP G**. The crude product was purified by FCC (55 g silica, light petroleum/EtOAc, 3:2) to give bis-azole **29e** (69 mg, 0.14 mmol, 81%) as a colorless oil. R_f = 0.56 (light petroleum/EtOAc, 2:3). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 8.12 (s, 1 H, 5-H), 8.05 (s, 1 H, 5′-H), 7.94 (d, J = 7.8 Hz, 2 H, SO_2CCH), 7.33 (d, J = 8.3 Hz, 3 H, CH_3CCH), 5.58–5.45 (m, 1 H, C*H*CH_3), 5.32 (d, J = 8.1 Hz, 1 H, N*H*), 3.95 (s, 3 H, $COOCH_3$), 2.40 (s, 3 H, $ArCH_3$), 1.51 (d, J = 6.7 Hz, 4 H, CHCH_3), 1.41 [s, 9 H, C(CH_3)$_3$] ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 162.6 (C-2), 162.0 (*C*OOMe), 154.8 [*C*OC(CH$_3$)$_3$], 151.6 (C-2′), 147.7 (C-4), 146.8 (CH_3CCH), 135.2 (C-2′), 134.6 ($CHCSO_2$), 130.7 (CH_3CCH), 128.1 ($CHCSO_2$), 127.6 (C-5), 117.0 (C-5′), 79.9 [*C*(CH_3)$_3$], 52.7 ($COOCH_3$), 44.4 (*C*HCH_3), 28.5 [C(*C*H$_3$)$_3$], 22.9 (CH*C*H$_3$), 21.9 ($ArCH_3$) ppm. IR (KBr): $\tilde{\nu}$ = 2977 (w), 1708 (s), 1496 (m), 1171 (s), 1084 (s), 814 (w) cm^{-1}. HPLC: t_R = 12.7 min (method 3). LC-MS (ESI): t_R = 10.6 min, C18; calcd. for $C_{22}H_{27}N_4O_6S_2$ [M + H]$^+$ 507.1; found 506.8. HRMS (ESI): calcd. for $C_{22}H_{27}N_4O_6S_2$ [M + H]$^+$ 507.1367; found 507.1361.

(2′*R*,2′′*R*)-*S*^{2},*S*^{6}-Bis[2-azido-2-(methoxycarbonyl)ethyl] Pyridine-2,6-dicarbothioate (31a): Trityl thioether **14c** (403 mg, 1.0 mmol) was treated at room temp. with Et_3SiH (0.18 mL, 1.1 mmol) in CH_2Cl_2/TFA (5.5 mL, 10:1) for 10 min. Toluene (10 mL) was added and the solvents were removed in vacuo. The crude thiol was dissolved in CH_2Cl_2 (3 mL) and coupled with pyridine-2,6-dicarboxylic acid (**30a**, 84 mg, 0.5 mmol) as described in **GP D** with EDC (240 mg, 1.25 mmol), HOBt (203 mg, 1.50 mmol), and Et_3N (0.2 mL, 1.50 mmol). After FCC (light petroleum/EtOAc, 2:1), bisazide **31a** was isolated as a colorless oil (70 mg, 0.15 mmol, 31%). R_f = 0.44 (light petroleum/EtOAc, 1:1). $[\alpha]_D^{20}$ = –20.0 ($CHCl_3$, c = 0.5). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.17 (dd, J = 0.6, 7.7 Hz, 2 H, 3-H, 5-H), 8.06 (dd, J = 7.0, 8.4 Hz, 1 H, 4-H), 4.21 (dd, J = 5.4, 8.2 Hz, 2 H, 2′-H), 3.86 (s, 6 H, CO_2CH_3), 3.58 (ddd, J = 0.6, 5.4, 14.0 Hz, 2 H, 1′-H_a), 3.33 (ddd, J = 1.1, 8.2, 14.0 Hz, 2 H, 1′-H_b) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 191.9 (COS), 169.4 (CO_2Me), 150.8 (C-2, C-6), 139.3 (C-4), 124.6 (C-3, C-5), 61.7 (C-2′), 53.3 (CO_2CH_3), 30.2 (C-1′) ppm. IR (KBr): $\tilde{\nu}$ = 3330 (bw), 3084 (w), 3007 (w), 2957 (m), 2925 (w), 2852 (w), 2498 (bw), 2119 (s), 1746 (s), 1674 (s), 1582 (w), 1505 (w), 1437 (m), 1404 (w), 1273 (s), 1209 (s), 1176 (s), 1079 (w), 1014 (w), 999 (w), 913 (s), 827 (s), 777 (m), 739 (m), 646 (m), 624 (w) cm^{-1}. LC-MS (ESI): t_R = 9.5 min; calcd. for $C_{15}H_{16}N_7O_6S_2$ [M + H]$^+$ 454.1; found 453.8. HRMS (ESI): calcd. for $C_{15}H_{16}N_7O_6S_2$ [M + H]$^+$ 454.0598; found 454.0594.

(2′*R*,2′′*R*)-*S*^{3},*S*^{5}-Bis[2-azido-2-(methoxycarbonyl)ethyl] Pyridine-3,5-dicarbothioate (31b): Trityl thioether **14c** (403 mg, 1.0 mmol) was treated at room temp. with Et_3SiH (0.18 mL, 1.1 mmol) in CH_2Cl_2/TFA (5.5 mL, 10:1) for 10 min. The reaction mixture was diluted with toluene (10 mL) and the solvent was removed in vacuo. The crude thiol was dissolved in CH_2Cl_2 (3 mL) and coupled with pyridine-3,5-dicarboxylic acid (**30b**, 84 mg, 0.5 mmol) as described in **GP D** with EDC (240 mg, 1.25 mmol), HOBt (203 mg, 1.50 mmol), and Et_3N (0.2 mL, 1.50 mmol). After FCC (light petroleum/EtOAc, 2:1), bisazide **31b** was isolated as a colorless oil (33 mg, 0.07 mmol, 15%). R_f = 0.40 (light petroleum/EtOAc, 1:1). $[\alpha]_D^{20}$ = –18.8 ($CHCl_3$, c = 0.5). ^{1}H NMR (400 MHz, $CDCl_3$): δ =

9.33 (d, J = 2.2 Hz, 2 H, 2-H, 6-H), 8.69 (d, J = 2.2 Hz, 1 H, 4-H), 4.25 (dd, J = 5.4, 7.6 Hz, 2 H, 2′-H), 3.87 (s, 6 H, CO_2CH_3), 3.66 (dd, J = 5.4, 14.0 Hz, 2 H, 1′-H_a), 3.43 (dd, J = 7.6, 14.0 Hz, 2 H, 1′-H_b) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 188.5 (COS), 169.1 (CO_2Me), 152.5 (C-2, C-6), 133.5 (C-4), 132.2 (C-3, C-5), 61.4 (C-2′), 53.4 (CO_2CH_3), 30.5 (C-1′) ppm. IR (KBr): $\tilde{\nu}$ = 3006 (w), 2956 (w), 2924 (w), 2853 (w), 2498 (bw), 2119 (s), 1746 (s), 1673 (s), 1588 (w), 1505 (w), 1437 (m), 1211 (m), 1172 (s), 1146 (m), 1015 (w), 894 (s), 800 (s), 750 (m), 699 (m) cm^{-1}. LC-MS (ESI): t_R = 9.2 min; calcd. for $C_{15}H_{16}N_7O_6S_2$ [M + H]$^+$ 454.1; found 453.9. HRMS (ESI): calcd. for $C_{15}H_{16}N_7O_6S_2$ [M + H]$^+$ 454.0598; found 454.0592.

(4′*R*,4′′*R*)-2,6-Bis(4-methoxycarbonyl-4,5-dihydrothiazol-2-yl)-pyridine (32a): Bisazide **31a** (51 mg, 0.11 mmol) was cyclized as described in **GP F**. After FCC (light petroleum/EtOAc, 1:1), bisthiazoline **32a** was isolated as a colorless solid (36 mg, 0.10 mmol, 88%). R_f = 0.57 (CH_2Cl_2/MeOH 20:1). $[\alpha]_D^{20}$ = +7.4 ($CHCl_3$, c = 1.0). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.22 (d, J = 7.8 Hz, 2 H, 3-H, 5-H), 7.85 (t, J = 7.8 Hz, 1 H, 4-H), 5.36 (td, J = 1.4, 9.5 Hz, 2 H, 4′-H), 3.82 (s, 6 H, CO_2CH_3), 3.61 (qd, J = 9.6, 11.4 Hz, 4 H, 5′-H_2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.0 (C-2′), 171.0 (CO_2Me), 149.9 (C-2, C-6), 137.2 (C-4), 123.6 (C-3, C-5), 79.0 (C-4′), 52.8 (CO_2CH_3), 34.2 (C-5′) ppm. IR (KBr): $\tilde{\nu}$ = 3004 (w), 2954 (m), 2926 (m), 2852 (w), 1740 (s), 1601 (m), 1568 (m), 1505 (w), 1455 (m), 1436 (m), 1316 (m), 1272 (m), 1229 (s), 1202 (s), 1177 (s), 1136 (w), 1053 (w), 996 (w), 935 (s), 823 (s), 797 (s), 742 (m), 723 (w), 695 (w), 646 (w) cm^{-1}. HPLC: t_R = 9.9 min (method 13). LC-MS (ESI): t_R = 8.8 min; calcd. for $C_{15}H_{16}N_3O_4S$ [M + H]$^+$ 366.1; found 366.0. HRMS (ESI): calcd. for $C_{15}H_{16}N_3O_4S_2$ [M + H]$^+$ 366.0577; found 366.0580.

(4′*R*,4′′*R*)-3,5-Bis(4-methoxycarbonyl-4,5-dihydrothiazol-2-yl)-pyridine (32b): Bisazide **31b** (24 mg, 0.05 mmol) was cyclized as described in **GP F**. After FCC (light petroleum/EtOAc, 1:1), bisthiazoline **32b** (16 mg, 0.04 mmol, 82%) was isolated as a colorless solid. R_f = 0.46 (CH_2Cl_2/MeOH 20:1). $[\alpha]_D^{20}$ = +1.0 ($CHCl_3$, c = 1.0). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.13 (d, J = 1.8 Hz, 2 H, 2-H, 6-H), 8.54 (t, J = 3.3 Hz, 1 H, 4-H), 5.31 (t, J = 9.2 Hz, 2 H, 4′-H), 3.85 (s, 6 H, CO_2CH_3), 3.75 (m, 4 H, 5′-H_2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.8 (CO_2Me), 167.7 (C-2′), 151.8 (C-2, C-3, C-5, C-6), 135.2 (C-4), 78.5 (C-4′), 52.9 (CO_2CH_3), 35.8 (C-5′) ppm. IR (KBr): $\tilde{\nu}$ = 3000 (w), 2954 (m), 2924 (m), 2854 (m), 1743 (s), 1603 (m), 1505 (w), 1485 (w), 1437 (m), 1344 (m), 1272 (m), 1203 (s), 1177 (s), 1120 (w), 1052 (m), 1024 (m), 928 (s), 905 (s), 858 (s), 798 (s), 751 (m), 722 (m), 699 (m) cm^{-1}. HPLC: t_R = 8.8 min (method 13). LC-MS (ESI): t_R = 8.4 min; calcd. for $C_{15}H_{16}N_3O_4S$ [M + H]$^+$ 366.1; found 366.0. HRMS (ESI): calcd. for $C_{15}H_{16}N_3O_4S_2$ [M + H]$^+$ 366.0577; found 366.0578.

Supporting Information (see footnote on the first page of this article): Additional experimental procedures, HPLC traces for *ee* determinations (Figure S1–S4), ^{1}H and ^{13}C NMR spectra of all relevant intermediates and final products.

Acknowledgments

Support by the Deutsche Forschungsgemeinschaft (DFG) (AR493-1, -2) is acknowledged. Dr. S. D. Harkal is thanked for initial contributions to the project.

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Received: January 29, 2013
Published Online: ■

EurJOC European Journal of Organic Chemistry

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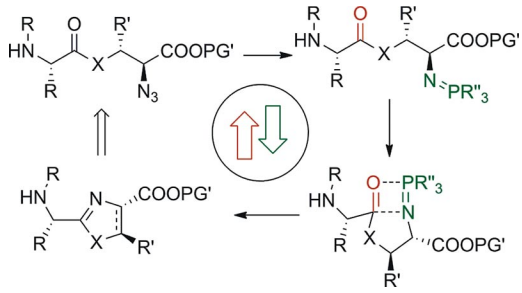

Intramolecular aza-Wittig ring closures have been developed to synthesize thiazolines, oxazolines, and imidazolines from β-azido thioester, ester, and amide precursors. Optimized conditions for diazo transfer with $ZnSO_4$ as catalyst are described. General aza-Wittig-based azoline synthesis for single and double azoline ring closures have been studied in depth and optimized.

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Unified Azoline and Azole Syntheses by Optimized Aza-Wittig Chemistry

Keywords: Synthetic methods / Wittig reactions / Azides / Cyclization / Heterocycles

