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Solid-Phase Synthesis of Peptide Thioureas and Thiazole-Containing Macrocycles through Ru-Catalyzed Ring-Closing Metathesis

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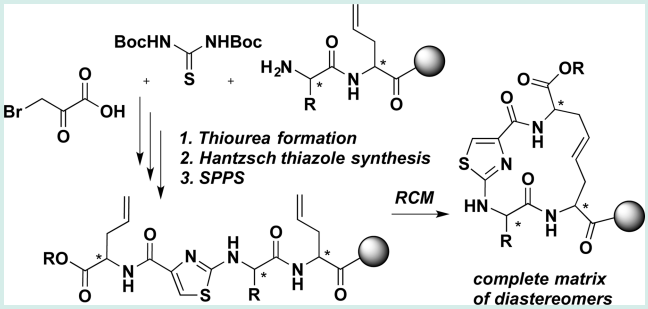
Supporting Information

ABSTRACT: N-Terminally modified α-thiourea peptides can selectively be synthesized on solid support under mild reaction conditions using *N,N′*-di-Boc-thiourea and Mukaiyama's reagent (2-chloro-1-methyl-pyridinium iodide). This N-terminal modification applies to the 20 proteinogenic amino acid residues on three commonly used resins for solid-phase synthesis. Complementary methods for the synthesis of α-guanidino peptides have also been developed. The thiourea products underwent quantitative reactions with α-halo ketones to form thiazoles in excellent purities and yields. When strategically installed between two alkene moieties, said thiazole core was conveniently embedded in peptide macrocycles via Ru-catalyzed ring-closing metathesis reactions. Various 15−17 membered macrocycles were easily accessible in all diastereomeric forms using this methodology. The developed "build/couple/pair" strategy is well suited for the generation of larger and stereochemically complete screening libraries of thiazole-containing peptide macrocycles.



KEYWORDS: *solid-phase synthesis, peptide thioureas, ring-closing metathesis, macrocycles, build/couple/pair*

INTRODUCTION

The thiourea moiety is frequently encountered in biologically active organic compounds, including synthetic drugs, fungicides, and herbicides, which display a range of analgesic, antibacterial,[1] antiviral,[2] and antifungal[3] properties. More recently, thiourea derivatives have been identified as potent inhibitors of enzymatic targets in anticancer chemotherapy, including protein tyrosine kinases,[4] topoisomerases,[5] and human sirtuin type proteins.[6] In addition to being an important pharmacophore for medicinal chemistry, thioureas may also be synthetically versatile building blocks that can be converted into other functional groups or heterocyclic motifs, such as guanidines or thiazoles.[7] The guanidino moiety, being structurally related to thioureas, is present in the side-chain of the amino acid arginine, and embedded in various complex secondary metabolites, such as the tetrodotoxin and ptilomycalin alkaloids.[8] The multifunctional role of the guanidine moiety is often attributed to its superbasic properties, which accommodate π-cation interactions and tight ion-pairings with oxyanions.[9]

Recently, thioureas have found broad utility as versatile organocatalysts presumed to operate via complex hydrogen bonding patterns,[10] enabling the highly enantioselective addition of latent nucleophiles to a broad range of iminium electrophiles. Because of the properties noted above, thioureas have been subject to intense research efforts, and a number of synthetic procedures have been reported to access this compound class.[11−13] In the pursuit of bioactive thioureas and guanidines, the specificity and affinity required for efficient molecular recognition can be fine-tuned by the introduction of stereogenic units.[14] To iteratively map the structural constraints posed by binding domains of proteins and other oligomeric biomolecules, it would be desirable to rapidly access α-thiourea and α-guanidino peptides, preferably through solid-phase synthesis, without resorting to extensive solution-phase synthesis of building blocks. Whereas synthetic methods have been developed for the synthesis of Boc-protected *N*-terminal α-guanidino peptides,[15] the analogous Boc-protected α-thiourea peptides are, to the best of our knowledge, largely unexplored. α-Thiourea peptides would not only be valuable synthetic endpoints for biological investigations, this compound class could also serve as suitable precursors for the solid-phase synthesis of thiazoles, which are frequently encountered in macrocyclic peptides with a plethora of biomedically relevant properties. Synthetic efforts aiming to generate thiazole-containing macrocyclic natural products and their analogs often rely on tedious synthesis of thiazole building blocks, which must be orthogonally protected for routine solid-phase synthesis. In this context, efficient solid-phase synthesis of this motif would be highly valuable for the generation of screening libraries based on new macrocyclic scaffolds. Much attention has recently been drawn to drug discovery based on natural

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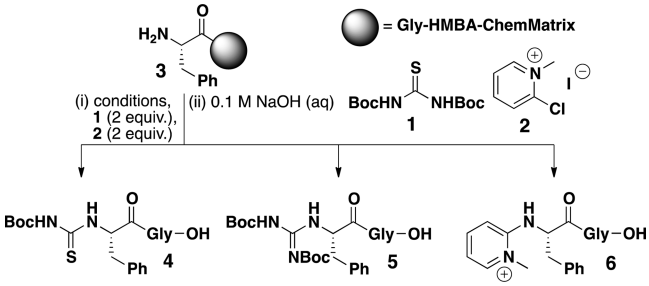
product-like macrocycles, which are underrepresented in screening collections for chemical biology and pharmaceutical research.[16] Macrocyles benefit from being conformationally preorganized so that their binding to protein targets is associated with minimal entropic loss.[17] Along these lines, synthetic macrocycles have successfully been developed to disrupt protein−protein interactions, which belong to the more challenging targets for drug discovery.[18] Efficient methods for the systematic generation of synthetically tractable and structurally novel macrocycles are consequently in high demand, particularly if the synthetic strategy should also facilitate streamlined follow-up stereostructure activity relationship (SSAR) studies.

Herein, we report a truly general approach for the solid-phase synthesis of *N*-teminally modified α-thiourea peptides relying on the activation of *N*,*N*′-di-Boc-thiourea (**1**) with Mukaiyama's reagent (2-chloro-1-methyl-pyridinium iodide, **2**). This method complements the classical Hg(II)-mediated guanylation of primary amines with **2**,[19] and together, the two methods give access to these two classes of *N*-terminally functionalized peptides on solid support, notably from the same peptide substrate and *N*,*N*′-di-Boc-thiourea. We also demonstrate the synthetic usefulness of these α-thioureas by converting them into highly pure thiazoles on solid support. Subsequent incorporation of the thiazole unit into 15−17-membered macrocycles can readily be achieved through carefully optimized Ru-catalyzed ring-closing metathesis reactions. The resulting collection of macrocycles contains up to three stereocenters, which can be independently varied without compromising the event of macrocyclization, thereby pointing toward an efficient "build/couple/pair" strategy for the diversity-oriented synthesis of stereochemically complete macrocyclic compound libraries.[20]

RESULTS AND DISCUSSION

Activation of *N*,*N*′-di-Boc-thiourea (**1**) using $CuSO_4$, $HgCl_2$, or Mukaiyama's reagent for the formation of guanidines is well documented for solution-phase synthesis.[19,21] We recently initiated studies on the solid-phase synthesis of *N*-terminally modified α-guanidino peptides and noted to our surprise the concomitant formation of the corresponding α-thiourea peptides. Following the slow addition (method A) of Mukaiyama's reagent (**2**) in dry DMF to the H-Phe-Gly-HMBA (4-hydroxymethyl-benzoic acid)-functionalized ChemMatrix resin (**3**), swelled in a mixture of **1** and Et_3N in dry DMF, NaOH-mediated release of material from the resin revealed a product mixture consisting of *N*,*N*′-Boc-protected guanidine **4** (37%), *N*-Boc-protected thiourea **5** (52%), and pyridinium derivative **6** (11%) (Table 1, entry 1). In an attempt to suppress the formation of **6**, the reagents (**1**, **2**, and Et_3N) were stirred in dry DMF for 15 min prior to adding the resulting reaction mixture to the resin. Interestingly, this protocol relying on complete "pre-activation" (method B) gave an almost exclusive formation of thiourea product **4** in excellent purity (>95%) (entry 2). The protocol represents a general method for using **1** to form Boc-protected N-terminal α-thiourea peptides under mild conditions,[12,13] and complements existing Fmoc-based protocols toward this compound class.[22] Intrigued by these initial results, we went on to probe whether the selectivity could also be directed toward the exclusive formation of **5** (entry 3−10). However, upon changing the solvent from dry DMF to dry CH_2Cl_2, the reaction outcome was not affected (entries 3 and 4), and changes in the base

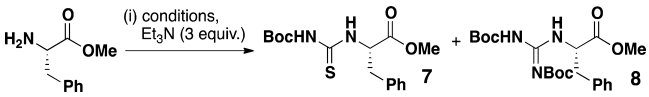
Table 1. Reaction Conditions for the Solid-Phase Synthesis of Thiourea Peptides



				product distribution (%)[b]		
entry	base	solvent	method[a]	4	5	6
1	Et_3N (3 equiv)	DMF	A	52	37	11
2	Et_3N (3 equiv)	DMF	B	>95	<5	<5
3	Et_3N (3 equiv)	CH_2Cl_2	A	62	33	<5
4	Et_3N (3 equiv)	CH_2Cl_2	B	>95	<5	<5
5[c]	Et_3N (3 equiv)	DMF	A	67	25	8
6[c]	Et_3N (3 equiv)	DMF	B	72	14	14
7	Et_3N (20 equiv)	DMF	A	60	35	<5
8	Et_3N (20 equiv)	DMF	B	51	20	29
9	DBU (3 equiv)[d]	DMF	A	<5	<5	30
10	DBU (3 equiv)[e]	DMF	B	<5	<5	18

[a]Method A: Slow addition of **2** to a solution of **3**, **1** and the base. Method B: A mixture of **1**, **2**, and Et_3N in DMF was allowed to react for 15 min before being added to the resin (preactivation). [b]The product distribution was determined by RP-HPLC (215 nm). [c]1.2 equiv. of **1** and **2** were used. [d]Only 34% conversion was observed (HPLC). [e]Only 18% conversion was observed (HPLC).

Table 2. Solution-Phase Synthesis of Phenylalanine-Derived Thiourea and Guanidine Derivatives



		product yield (%)[a]	
entry	conditions	7	8
1	**1** (2 equiv), **2** (2 equiv), DMF[b]	<1	54
2	**1** (1.2 equiv), **2** (1.2 equiv), DMF[b]	8	84
3	**1** (2 equiv), **2** (2 equiv), CH_2Cl_2[c]	63	0
4	**1** (1.2 equiv), **2** (1.2 equiv), CH_2Cl_2[c]	48	1

[a]The product yields were determined by RP-HPLC (215 nm). [b]Dropwise addition of **2** to a solution of H-Phe-OH, **1** and Et_3N. [c]A mixture of **1**, **2**, and Et_3N was allowed to react for 15 min before being added to H-Phe-OMe in CH_2Cl_2 as solvent.

concentration did not give any improvement with respect to the formation of **5** (entries 5−8). By choosing a stronger base, such as DBU (1,8-diazabicyclo[5.4.0]undec-7-ene), **6** became the sole product in mixtures containing substantial amounts of unconverted starting material (entries 9−10).

Surprised by these results, we set out to test selected conditions from Table 1 (entries 1, 4, and 5) for the solution-phase reactivity of L-phenylalanine methyl ester (Table 2).

Interestingly, slow addition of **1** resulted in the selective formation of guanidine derivative **8** (entry 1), and by further lowering the amounts of **1** and **2** to near-stoichiometric amounts, the desired product **8** was obtained in excellent yield (entry 2, 84%), contrary to the corresponding transformation

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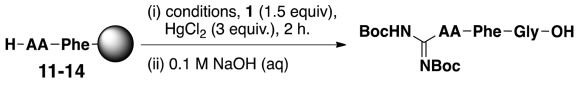
Table 3. Solid-Phase Synthesis of α-Guanidino Peptides Using $HgCl_2$ and Mukaiyama's Reagent

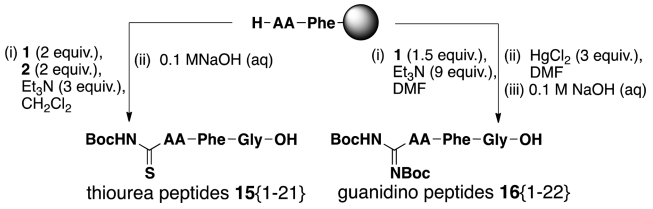


11: AA = Trp(Boc) **12**: AA = Lys(Boc) **13**: AA = Ser(*t*-Bu) **14**: AA = His(Trt)

		conversion (%)[a]			
entry	conditions	11	12	13	14
1[b]	Et_3N (3 equiv), DMF	51[c]	7	76[c]	0
2	Et_3N (3 equiv), DMF	61	27	0[d]	44
3	Et_3N (3 equiv), DMF, 16 h	41	74	29	69
4	Et_3N (3 equiv), DMF, 45 °C	0	65	0[d]	44
5	DBU (3 equiv), DMF,	33	76	56	69
6	Et_3N (3 equiv), CH_2Cl_2	0	0	0	0
7	Et_3N (9 equiv), DMF[e]	73[f]	>95	>95	>95

[a]Conversion was determined by RP-HPLC (215 nm). [b]1.5 equiv $HgCl_2$ used. [c]Thiourea formation was observed for **11** (29%) for **13** (45%). [d]Complete cleavage of *t*-Bu ether. [e]**1** and Et_3N added to the resin. $HgCl_2$ (DMF) added after 5 min. [f]Full conversion could be achieved by washing of the resin followed by a second treatment with HgO, **1** and base in DMF.

Table 4. Synthesis of *N*-Boc-thiourea and *N,N′*-di-Boc-guanidino Peptides



	product (purity %)[a]			product (purity %)[a]	
AA	thiourea	guanidine	AA	thiourea	guanidine
Gly	**15**{*1*}, >95	**16**{*1*}, >95	Thr(*t*-Bu)	**15**{*12*}, >95	**16**{*12*}, 91
Ala	**15**{*2*}, >95	**16**{*2*}, >95	Asn(Trt)	**15**{*13*}, >95	**16**{*13*}, 91
Val	**15**{*3*}, >95	**16**{*3*}, 80	Gln(Trt)	**15**{*14*}, >95	**16**{*14*}, 86
Leu	**15**{*4*}, >95	**16**{*4*}, 91	Cys(Trt)	*c*	**16**{*15*}, >95
Ile	**15**{*5*}, >95	**16**{*5*}, >95	Cys(S-*t*-Bu)	**15**{*15*}, >95	**16**{*16*}, 90
Met	**15**{*6*}, >95	**16**{*6*}, 85	Arg(Pbf)	**15**{*16*}, >95	**16**{*17*}, 81
Phe[a]	**15**{*7*}, >95	**16**{*7*}, 82	His(Trt)	**15**{*17*}, >95	**16**{*18*}, >95
Pro	**15**{*8*}, >95	**16**{*8*}, 92	His(Boc)	**15**{*18*}, 86	**16**{*19*}, 80
Tyr(*t*-Bu)	**15**{*9*}, >95	**16**{*9*}, 91	Lys(Boc)	**15**{*19*}, >95	**16**{*20*}, >95
Trp(Boc)	**15**{*10*}, >95	**16**{*10*}, >95	Asp(O-*t*-Bu)	**15**{*20*}, 79	**16**{*21*}, 84
Ser(*t*-Bu)	**15**{*11*}, >95	**16**{*11*}, >95	Glu(O-*t*-Bu)	**15**{*21*}, 92	**16**{*22*}, 89

[a]Purity was determined by RP-HPLC (215 nm). [a]The formation of **15**{*7*} and **16**{*7*} works equally well on Tentagel and $PEGA_{800}$ resins (>95% purity for **15**{*7*}; and 70−75% purity for **16**{*7*}). [c]β-Elimination was observed upon cleavage from the solid support.

on solid support. On the other hand, the preactivation protocol resulted in the selective formation of thiourea derivative **7** (entry 3) in good yield (63%), which could not be optimized by adjusting reagent stoichiometries.

Scheme 1. Proposed Mechanism for the Selective Formation of Boc-Protected Thioureas

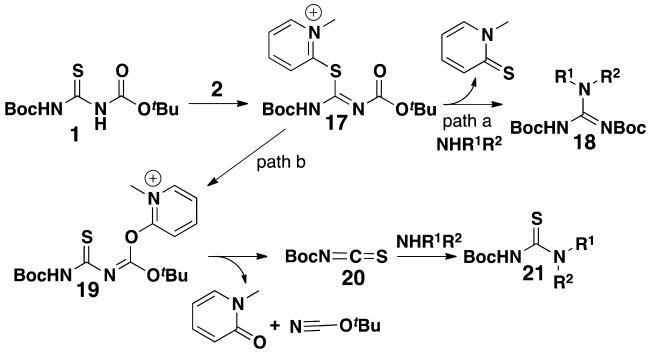
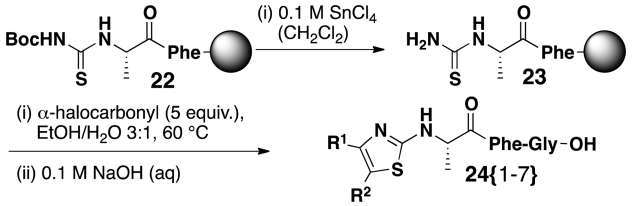


Table 5. Synthesis of Thiazole-Functionalized Peptides



entry	α-halocarbonyl	product (R^1, R^2)	purity[a] (%)
1	$PhCOCH_2Cl$	**24**{*1*} (Ph. H)	>95
2	4-$HOC_6H_4COCH_2Cl$	**24**{*2*} (4-HOC_6H_4, H)	90
3	$(CH_3O)_2CHCH_2Br$	**24**{*3*} (H, H)	87
4	$PhCOCH_2Br$	**24**{*1*} (Ph, H)	92
5	4-$BrC_6H_2COCH_2Br$	**24**{*4*} (4-BrC_6H_4, H)	87
6	$EtCOCH_2Br$	**24**{*5*} (Et, H)	93
7	$(EtO)_2CHCHBrCH_3$	**24**{*6*} (H, Me)	84
8	$(HO_2C)COCH_2Br$	**24**{*7*} (CO_2H, H)	88

[a]Purity was determined by RP-HPLC (215 nm).

As only poor results were obtained for the formation of guanidine **5** with Mukaiyama's reagent as activator of **1** (Table 1), a complementary protocol for the solid-phase synthesis of **5** was desirable. Several different activators, such as 1*H*-pyrazole-1-carboxamidine hydrochloride (**9**)[23] and its Boc-protected analogue (**10**),[24] were screened along with *N*-iodosuccinimide[25] and Cu-mediated activation of **1**.[19] Low conversion of the starting material as well as bad selectivity was generally observed using these conditions (except for $CuCl_2$, Table S1, Supporting Information). The observed selectivity for **5** using $CuCl_2$ prompted us to explore the stronger activating potentials of HgO, $HgCl_2$, and $Hg(CF_3COO)_2$. Both HgO and $HgCl_2$ were found to give the guanidine product in high purity. Studies using HgO as the activation reagent was found to give **5** as the sole product (Table S2, Supporting Information). However, this reaction was incomplete for most of the 20 proteinogenic amino acids.

It was evident from these results that the guanylation of α-amino acids using HgO as activator greatly depends on the steric environment of the *N*-terminus. The activation reagent was changed to $HgCl_2$, and four HMBA-linked test-substrates Trp(Boc)-Phe-Gly (**11**), Lys(Boc)-Phe-Gly (**12**), Ser(*t*-Bu)-Phe-Gly (**13**), and His(Trt)-Phe-Gly (**14**) were readily converted to the corresponding α-guanidino peptides (Table 3). The conditions identified above (Table S2 Supporting Information, entry 5) were used as a starting point for optimizing the Hg-activated guanylation reaction (Table 3,

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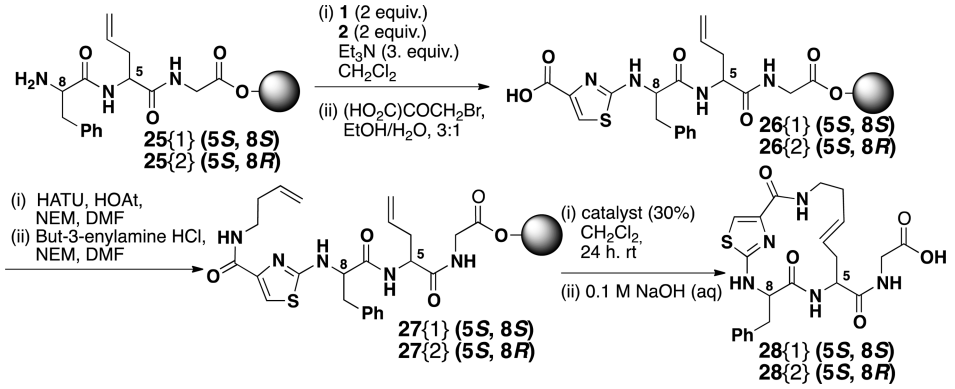
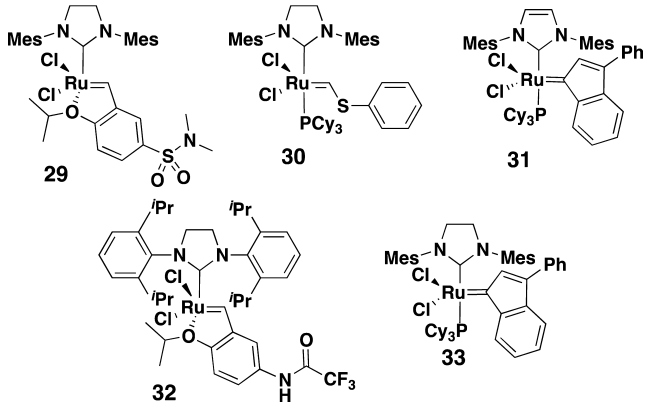
Table 6. Synthesis of Thiazole-Functionalized Peptides



entry	catalyst	conversion of 27{1} (%)[a]	conversion of 27{2} (%)[a]
1	Grubbs 1st	48	22
2	Hoveyda–Grubbs 1st	16	0
3	Grubbs 2nd	>95	88
4	Hoveyda–Grubbs 2nd	90	67
5	**29**	94	93
6	**30**	15	3
7	**31**	22	8
8	**32**	>95	74
9	**33**	61	41

[a]Purity was determined by RP-HPLC (215 nm).



entry 1). When all the reagents were added together, low conversion and formation of the thiourea product were observed. However, thiourea formation could be completely avoided by using a 2-fold excess of $HgCl_2$ over **1** (entry 2). Prolonging the reaction time, or heating to 45 °C, gave minor improvements in the conversion of most substrates (entries 3 and 4). The application of a stronger base only had a minor influence on the outcome (entry 5), but a change in solvent to CH_2Cl_2 completely shut down the reaction (entry 6). Full conversion of **11**–**14** was effectively achieved by treating the resin with **1** and Et_3N in DMF before adding $HgCl_2$.

Formation of Thiourea and Guanidino Peptides. With optimized conditions in hand for both the formation of α-thiourea peptides (Table 1, entry 4) and α-guanidino peptides (Table 3, entry 7), we set out to test the protocol against the 20 proteinogenic α-amino acid residues (protected at their side-chains). Rewardingly, all reactions produced the corresponding α-thiourea peptides in excellent purity irrespective of the steric bulk and functional groups of the side-chains (Table 4). For the mercury-activated guanylation of the 20 proteinogenic α-amino acids good to excellent purity was observed (Table 4). For more sterically hindered amino acids (Leu, Ile, Trp(Boc), Asn(Trt), and Arg(Pbf)), the reaction was repeated once to achieve full conversion. Notably, no oxidation of the methionine residue was observed in either of the two protocols.

On the basis of the above results, we propose a mechanism for the observed reactions where the presumed *S*-arylated intermediate **17** may react directly with an amine to give the guanidine product **18** (path a). Considering the exclusive formation of thiourea derivatives under the preactivation reaction conditions, we speculate if intermediate **17** is converted into the *O*-arylated intermediate **19** (path b) and not into the generally accepted di-Boc-carbodiimide intermediate. Reaction of the amine with either **19** (or the plausible Boc-isothiocyanate intermediate **20**) leads to the thiourea product **21**.

Deprotection of *N*-Boc-thiourea derivatives is hampered by the instability of the thiocarbonyl moiety toward aqueous acid. Previously reported deprotection reagents, such as TMSOTf/2,6-lutidine,[26] gave products of low purity. Rewardingly, we discovered that dilute stannic chloride (0.1 M in CH_2Cl_2, 2 × 30 min) cleanly removed the Boc moiety from the *N*-Boc-

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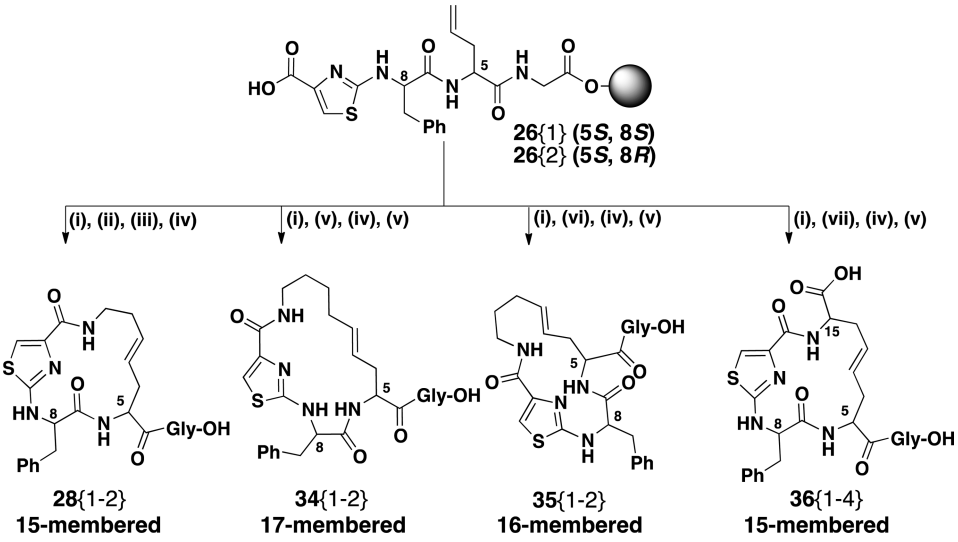
Table 7. Synthesis of Peptide-Based Macrocycles via RCM-Cyclization[c]



entry	product	conversion (%)[a]	purity (%)[b]	E/Z ratio
1	**28**{*1*} (5*S*,8*S*)	>95	71	9:1
2	**28**{*2*} (5*S*,8*R*)	>95	74	>20:1
3	**34**{*1*} (5*S*,5*S*)	>95	51	>20:1
4	**34**{*2*} (5*S*,8*R*)	>95	65	>20:1
5	**35**{*1*} (5*S*,8*S*)	>95	69	3:1
6	**35**{*2*} (5*S*,8*R*)	86	71	9:1
7	**36**{*1*} (5*S*,8*S*,15*S*)	>95	76	9:1
8	**36**{*2*} (5*S*,8*R*,15*S*)	>95	86	2:1
9	**36**{*3*} (5*S*,8*S*,15*R*)	>95	86	>20:1
10	**36**{*4*} (5*S*,8*R*,15*R*)	85	77	9:1

[a]Conversion of diene to macrocyclic alkene as analyzed by RP-HPLC (215 nm). [b]Purity was determined by RP-HPLC (215 nm). [c]Reaction conditions: (i) HATU, HOAt, NEM, DMF; (ii) but-3-enylamine, NEM, DMF; (iii) 30 mol % **29**, CH_2Cl_2; (iv) 0.1 M NaOH (aq); (v) 0.1 M HCl (aq); (vi) pent-4-enylamine, NEM, DMF; (vii) L-H-Gly(allyl)-OMe for the synthesis of **36**{*1*} (5*S*, 8*S*, 15*S*) and **36**{*2*} (5*S*, 8*R*, 15*S*) NEM, DMF; or D-H-Gly(allyl)-OMe for the synthesis of **36**{*3*} (5*S*, 8*S*, 15*R*) and **36**{*4*} (5*S*, 8*R*, 15*R*), NEM, DMF.

thiourea amino acid residues listed in Table 3. The only exception identified was Trp(Boc) residue, which required more forcing conditions (0.25 M $SnCl_4$ in EtOAc, 3 × 2 h).[27] Deprotection of the *N*,*N*′-di-Boc guanidines can also be mediated with TFA but higher purity was typically observed when using the stannic chloride protocol, except for Cys(*S*-*t*-Bu) and His(Boc) guanidine.[28] In general, *t*-Bu ethers, esters, and carbamates (Boc) were cleaved with stannic chloride, whereas trityl, Pbf (2,2,4,6,7-pentamethyldihydrobenzo-furan-5-sulfonyl), and *t*-Bu disulfides remained largely untouched, which renders the $SnCl_4$-deprotection protocol well-suited for the synthesis of thiourea and guanidine peptides with protected side chains.

Formation of Thiazole-Containing Macrocycles. To further demonstrate the synthetic usefulness of these solid-supported thiourea derivatives, a small collection of thiazoles was synthesized from a selection of α-halo ketones via the Hantzsch thiazole synthesis.[29] Along these lines, the *N*-Boc protected thiourea tripeptide (**22**) was deprotected using the stannic chloride protocol, followed by addition of the ketone in EtOH/H_2O. Heating the reaction to 60 °C for 16 h gave the seven thiazole derivatives (**24**{*1*−*7*}) in excellent purity (Table 5).

The reaction between peptide-based thioureas and bromo-pyruvic acid (Table 5, entry 8) leads to carboxylated thiazoles, which readily undergo amide-forming reactions through on-resin activation. We therefore further investigated a strategy for the synthesis of novel peptide macrocycles. By incorporating an allylglycine residue near the C-terminal of the peptide, upstream of the thiourea and thiazole formation steps, a series of macrocycles was synthesized through ring closing metathesis (RCM) reactions with alkene moieties introduced on the carboxy-functionalized thiazoles.[30] Initial RCM experiments were performed on the two diastereomeric forms, **27**{*1*} and **27**{*2*}, of a solid-supported but-3-enylamine derivative.

The ring-closing was performed by exposing the peptide to 30 mol % catalyst in dry degassed CH_2Cl_2 to a final concentration of 0.02 M for 24 h.[31]

A total of nine ruthenium-alkylidene catalysts were tested (Table 6), with the Grubbs second and Hoveyda Grubbs second generation catalysts, **29** and **32**, giving the highest conversions (67% → 95%).[32] Both diastereomeric macrocyles were found to be synthetically tractable, where diene (5*S*, 8*S*)-diastereomer **27**{*1*} cyclized considerably faster than diene (5*S*, 8*R*)-diastereomer **27**{*2*}. The conversion could be further increased by repeating the reaction on the resin once. The Grubbs second generation catalyst and **29** were found to be equally effective for the RCM of **27**. Catalyst **29** was chosen for the subsequent RCM reactions, merely because of its lower price than the Grubbs second generation catalyst. With a working protocol for the formation of stereoisomeric thiazole-containing peptide macrocycles, we set out to synthesize a library of 15-, 16- and 17-membered macrocycles with up to three stereocenters in the ring. A total of 10 out of the 20

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possible stereoisomers were successfully synthesized. Stereochemical diversity was conveniently introduced by using enantiopure phenylalanine and allylglycine derivatives. Rewardingly, all diastereomeric dienes underwent cyclization. Most notably, all 4 diastereomers of the 15-membered macrocycle **36** were smoothly formed following this protocol. In total, ten macrocycles were formed with full stereochemical control (Table 7) in excellent product yields and purities.[33]

CONCLUSION

In summary, we have developed a method for the mild and selective formation of *N*-terminally modified α-thiourea peptides using *N,N′*-di-Boc-thiourea and Mukaiyama's reagent on solid support. A complementary method for the solid-phase synthesis of the structurally similar α-guanidino peptides was also developed, thereby enabling a general and preferential access to two biologically interesting motifs with Mukaiyama's reagent. These *N*-terminal modifications proved compatible with the 20 proteinogenic α-amino acid residues and three commonly used supports for solid-phase synthesis. The products could be selectively deprotected using stannic chloride and form thiazoles by reaction with α-halo ketones. Such thiazole-containing peptides with properly positioned alkene moieties served as excellent substrates for solid-phase RCM reactions to form stereochemically diverse 15−17-membered macrocycles with full stereochemical control of up to three embedded stereocenters. The developed protocol is well suited for the generation of stereochemically complete screening libraries of thiazole-containing peptide macrocycles. We foresee that such "build/couple/pair" libraries will be particularly well suited for the study of stereostructure−activity relationships upon biological screening.

ASSOCIATED CONTENT

Supporting Information

Synthetic details and experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(33) The main impurity in macrocycles **28**{*1*−*2*} and **34**{*1*−*2*}−**36**{*1*−*4*} stems from unconverted **26**{*1*−*2*} (typical 5−10%).