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N-Hydroxypyridine-2(1*H*)-thione Derivatives of Carboxylic Acids as Activated Esters. Part II. Applications in Peptide Synthesis.

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Abstract : The *N*-hydroxypyridine-2(1*H*)-thione derivatives of two urethane-protected α-amino acids readily reacted with free α-amino acid esters or the corresponding benzenesulfenamides to give simple dipeptides in reasonable yields. The benzenesulfenamides are the reagents of choice since they allowed for neutral reaction conditions and exhibited superior reactivity in sterically demanding instances. The atom-economical reaction between a Barton PTOC ester and a benzenesulfenamide afforded products of synthetic and biological value and proceeds in a concerted fashion, thereby maintaining chirality in couplings involving optically active α-amino acid residues. Copyright © 1996 Elsevier Science Ltd

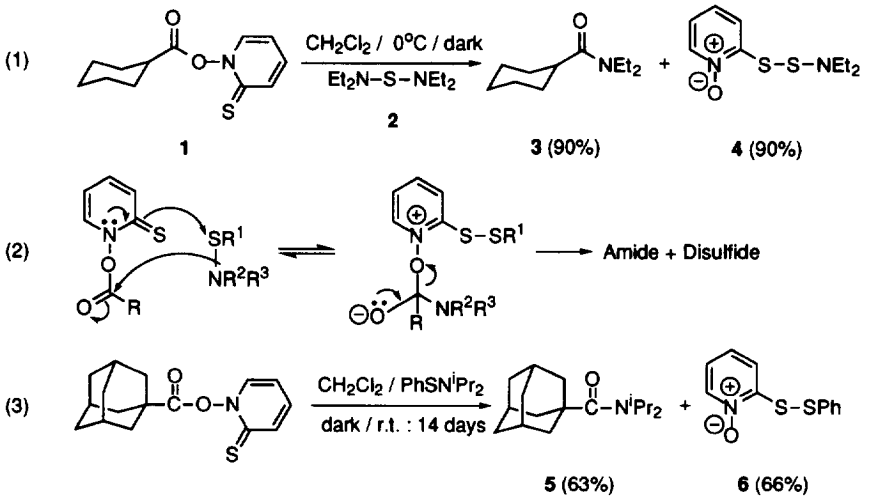
INTRODUCTION

The first synthetic peptide, benzoylglycylglycine, was obtained rather fortuitously in 1881 during Curtius' preparation of hippuric acid[1]. In the century that has since elapsed, time has witnessed the synthesis of peptides and proteins of ever-increasing complexity and biological importance. These range from the relatively simple penicillin antibiotics (which are biosynthetically derived from a dipeptide backbone) to the bovine pancreatic Ribonuclease A[2] (containing 124 amino acid residues). The sheer magnitude of such syntheses has continued to test the limits of chemical synthesis. Nature has, of course, no difficulty in making very large proteins but we, as synthetic chemists, still have far to go. Barring considerations of size, the modern day Organic Chemist is faced with the additional challenge of constructing peptides containing sterically hindered amino acid residues. Both *N*-methylated and α,α-dialkylated amino acid residues possess significant steric bulk which makes their incorporation into peptides difficult[3]. However, peptides containing these hindered residues often are of significant biological importance. Such is the case with *Cyclosporin A* and with the α-helical eicosapeptide *Alamethicin F30*. The former is a cyclic undecapeptide containing no less than seven *N*-methylated amino acid residues. It is the active ingredient of the immunosuppressive drug "Sandimmune" which is used to prevent graft rejection in bone marrow and organ transplants[4]. *Alamethicin F30* contains eight α-aminoisobutyric acid residues. It is an example of a polypeptide antibiotic that forms voltage-dependent ion-conducting pores in lipid-bilayer membranes. These membranes are used in model systems which imitate the electric properties of nerve membranes[5].

In Part I we reported that an acyl derivative of *N*-hydroxypyridine-2(1*H*)-thione (a Barton PTOC ester, where PTOC is the acronym for Pyridine-2-Thione-*N*-OxyCarbonyl) and either an amine (primary or secondary), or the corresponding arenesulfenamide, efficiently reacted under mild conditions to produce both unhindered and sterically congested carboxamides[6]. In this article we expand this chemistry to the synthesis of selected dipeptides containing sterically hindered α-amino acid residues.

RESULTS AND DISCUSSION

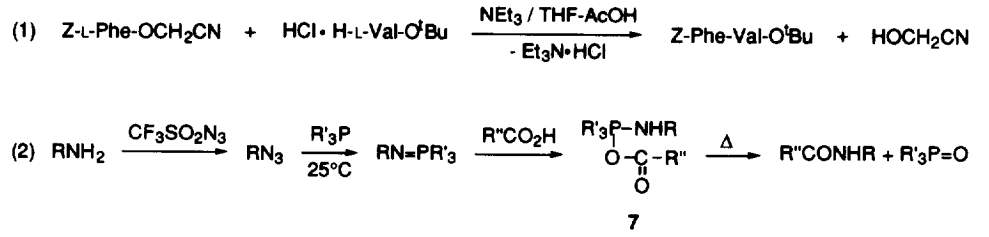
Barton PTOC Esters and Sulfenamides. History has taught that the most elusive of all chemical "skills", serendipity, often can provide us with new reactions. These may accomplish chemical transformations that are completely different from the original design[7]. This was the case when we reacted the Barton PTOC ester **1** with the sulfenamide **2**. Under photolytic conditions, we had hoped that the tetra-substituted hydrazine Et_2N-NEt_2 would be formed. Instead, the carboxamide **3** and the unsymmetrical disulfide **4** were obtained in a smooth, high-yielding transformation (Equation (1) of **Scheme 1**). We considered that this proceeds *via* the concerted process depicted in Equation (2) of **Scheme 1**[6].



SCHEME 1

The fact that the very hindered carboxamide **5** could be prepared in reasonable yield[6] (Equation (3) of **Scheme 1**) drew our attention to the construction of peptides containing sterically congested amino acid residues. Before elaborating on the applications, several features of the reaction between a Barton PTOC ester and a sulfenamide, which are of interest to the peptide chemist, deserve mention. It is common knowledge that the reaction between a carboxylic acid and an amine is an energetically demanding process. This difficulty has been circumvented by transforming the carboxylic acid into any of a myriad of activated derivatives which readily facilitate reaction with the amine at low or normal temperature[8]. On the other hand, activation of the amine is much more difficult to achieve. Rzeszotarska and Tascher[9] achieved *N*-activation of L-valine by protecting the *C*-terminus as the *t*-butyl ester in a study on the racemization of phenylalanine (Equation (1) of **Scheme 2**). However, this activation can, at best, be described as weak since the electron-releasing *t*-butyl group is remote from the amino group. Roberts *et al.*[10] have apparently accomplished *N*-activation by transforming the amino group into an azide which, after activation with a tervalent phosphine *via* the Staudinger reaction, reacts with a

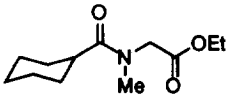
carboxylic acid to produce the peptide bond (Equation (2) of **Scheme 2**). The reaction does, however, require heat (refluxing toluene) to decompose the amino(acyloxy)phosphorane intermediate **7**. It has been suggested that amide bond formation in this instance, too, is the consequence of an activated carboxyl component rather than of the claimed *N*-activation[11].



SCHEME 2

Our method of constructing the peptide bond utilizes the formal activation of the carboxyl terminus of one amino acid residue and the indirect *N*-activation of the other required residue. The carboxylic component is activated by transformation to the corresponding Barton PTOC ester which is readily accessible through a variety of methods[12]. More often than not, Barton PTOC esters are stable, crystalline compounds that, in the solid state, do not (contrary to popular belief) spontaneously decarboxylate when exposed to visible light. A Barton PTOC ester can be considered as the mixed anhydride of a carboxylic and a thiohydroxamic acid[13] and, as such, bear close structural resemblance to the numerous *O*-acyl derivatives of hydroxylamines that have achieved some measure of success in peptide synthesis in recent years[14]. Transforming an amine into an arenesulfenamide[15] does not enhance the nucleophilicity of the nitrogen atom *per se* - a sulfenamide requires, for example, chemical labilization of the S-N bond *via* a tertiary phosphine prior to reaction with a carboxylic acid (to produce a carboxamide)[16]. In our case, activation of the amino component is achieved indirectly through coordination of the thiocarbonyl moiety of the Barton PTOC ester to the *S*-atom of the sulfenamide. This *S*-catenation has a dual effect : the electron density on the *N*-atom of the sulfenamide is inductively increased and this "electron-enriched" *N*-atom is brought in close proximity to the carbonyl moiety of the Barton PTOC ester. The reaction apparently is resistant to the effects of an external nucleophile, proton source or polar additives[6] and we consequently draw the concerted process (proceeding through a seven-membered transition state) depicted in Equation (2) of **Scheme 1** as the mechanism.

As a prelude to the synthesis of dipeptides containing sterically congested residues, we first demonstrated the applicability of our method to two simple sterically hindered amino acids. Sarcosine (*i.e.* *N*-methylglycine) derivative **8** was selected as a mimic for the *N*-methylated case.



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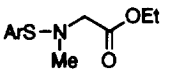

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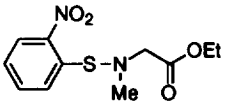

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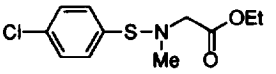

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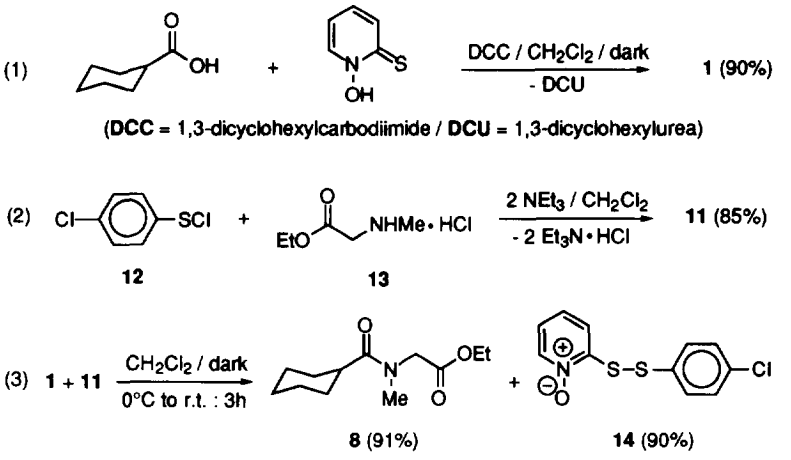
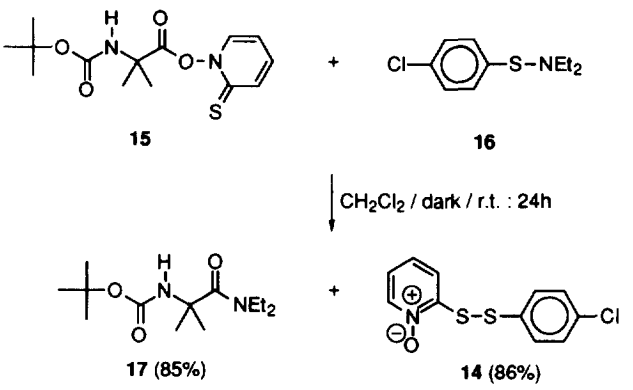
According to the requirements of our reaction, the Barton PTOC ester **1** is the logical chemical equivalent of the acyl cation synthon resulting from disconnection of the carboxamide C-N bond, while the arenesulfenamide **9** would serve as the chemical equivalent of the accompanying amine anion synthon. The activated ester **1** was readily obtained from cyclohexanecarboxylic acid utilizing the DCC-method (Equation (1) of **Scheme 3**), our mainstay for the preparation of Barton PTOC esters. Temptation led us to the *o*-nitrophenylsulfenyl (NPS) group as initial choice for Ar in **9** since NPS-protected α-amino acid esters normally are stable, crystalline compounds[17]. However, the powerfully electron-withdrawing *o*-nitro group imparted sufficient stability to the sulfenamide **10** to render this compound inert towards the Barton PTOC ester **1** at room temperature. The *o*-nitro group was therefore replaced with the less electronegative *p*-chloro atom to give the less stable (and, accordingly, more reactive) sulfenamide **11**. The latter was obtained in 85% yield and > 95% purity (by ^{1}H NMR) through condensation of 4-chlorobenzenesulfenyl chloride **12** and ethyl sarcosinate hydrochloride **13** in the presence of triethylamine as proton scavenger (Equation (2) of **Scheme 3**). Subsequent stoichiometric reaction of the Barton PTOC ester **1** and the 4-chlorobenzenesulfenamide **11** afforded the desired *N*-methylated carboxamide **8** and the unsymmetrical disulfide **14** in yields of 91 and 90%, respectively (Equation (3) of **Scheme 3**). Unsymmetrical disulfides similar to **14** are always produced as by-products of the concerted reaction and are easily separated from the desired carboxamide or peptide *via* chromatography or trituration. Although they need not be isolated, these disulfides are known to act as efficient sulfenylating agents[18] and have recognized antimicrobial properties[19] - *ergo*, they are of both synthetic and biological value. Since the unsymmetrical disulfides absorb intensely under UV-light (275 nm), they are easy to detect and accordingly serve as sentries for the descry of carboxamides or peptides that are not conveniently detectable by, for example, analytical thin-layer chromatography.

The α,α-dialkylated case is illustrated in **Scheme 4**. *t*-Butyloxycarbonyl-protected α-aminoisobutyric acid (Boc-Aib) was first converted in 90% yield to the corresponding Barton PTOC ester **15** using the DCC-method, whilst 4-chlorobenzenesulfenyl chloride **12** was reacted with two molar equivalents of diethylamine to give *N,N*-diethyl-*S*-4-chlorobenzenesulfenamide **16** in quantitative yield. Both **15** and **16** were obtained as non-crystalline compounds of sufficient purity (> 95% by ^{1}H NMR) to be used directly without further attempts at purification. The Boc-Aib Barton PTOC ester **15** and sulfenamide **16** were then reacted in stoichiometric



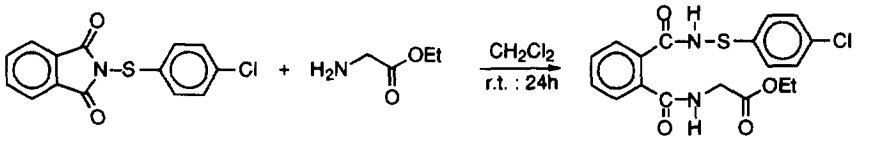
SCHEME 3

amounts at room temperature to afford the sterically hindered α,α-dimethylated carboxamide **17** and the unsymmetrical disulfide **14** in yields of 85 and 86%, respectively.



SCHEME 4

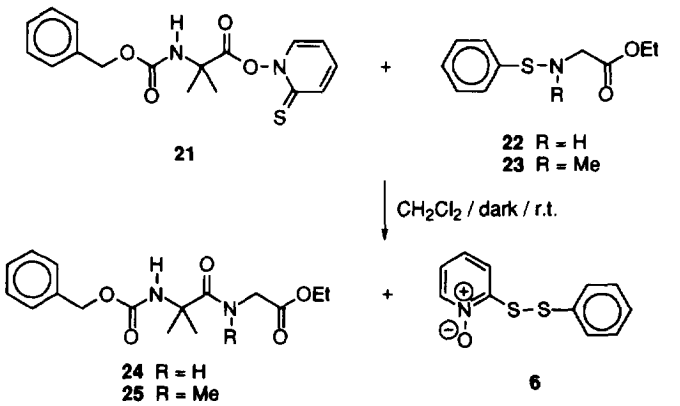
We remark here on the synthesis of arenesulfenamides derived from α-amino acid esters. As an alternative to the most commonly employed sulfenyl chloride method[20], we attempted the preparation of *N*-carboethoxymethyl-4-chlorobenzenesulfenamide by reacting equivalent amounts of *N*-(4-chlorobenzenesulfenyl)-phthalimide **18** and ethyl glycinate **19** in the *absence* of a proton scavenger according to the method of Harpp[21]. As is demonstrated in **Scheme 5**, the ring-opened adduct **20** was obtained as the sole isolated product. We therefore prefer to synthesize the arenesulfenamides derived from α-amino acid esters by the time-tested sulfenyl chloride method, cognizant of the detrimental effect which trace amounts of amine hydrochloride have on the stability and hence the storage lifetime of sulfenamides prepared in this fashion[22].



18 **19** **20** (62%)

SCHEME 5

The viability of our method as appropriate for the synthesis of hindered peptides was ultimately proven by the synthesis of dipeptides **24** and **25** as illustrated in **Scheme 6** and **Table 1**. The Barton PTOC ester **21** of benzyloxycarbonyl-protected α-aminoisobutyric acid (Z-Aib) was prepared in 90% yield using the DCC-method and is a crystalline, light-yellow solid. The benzenesulfenamides proved to be the most powerful of the amine carriers[6], hence ethyl glycinate and ethyl sarcosinate were condensed with benzenesulfenyl chloride in the presence of triethylamine to give the benzenesulfenamides **22** and **23** in yields of 91 and 99% respectively. Both **22** and **23** are oils and were used directly without attempts at purification since ^{1}H NMR indicated purity of > 95% in each case. As indicated in **Table 1**, Z-Aib Barton PTOC ester **21** smoothly reacted with both **22** and **23** to give the dipeptides **24** (Z-Aib-Gly-OEt) and **25** (Z-Aib-Sar-OEt) together with excellent yields of the unsymmetrical disulfide **6**. The dipeptide **24** was previously synthesized by Frérot *et al.*[23] using coupling reagents of the puissant BOP family, *viz.* BOP (92% yield), PyBOP® (87%), BroP (89%) and PyBroP (87%). These couplings employed Z-Aib, ethyl glycinate hydrochloride, diisopropylethylamine as proton scavenger and, of course, the coupling reagent. After one hour at room temperature, acid-base work-up and column chromatography afforded **24** in the indicated yields. In the case of BOP and BroP, HMPA was formed as a carcinogenic by-product. From entry 1 in **Table 1**, it is clear that the result obtained with the Barton PTOC ester - benzenesulfenamide couple **21**-**22** compares very favorably. The synthesis of **24** was achieved in superior yield (95%) after comparable reaction time (one hour) at room temperature and required only column chromatography to separate **24** from the environmentally "friendly" unsymmetrical disulfide **6**.



21 **22** R = H, **23** R = Me

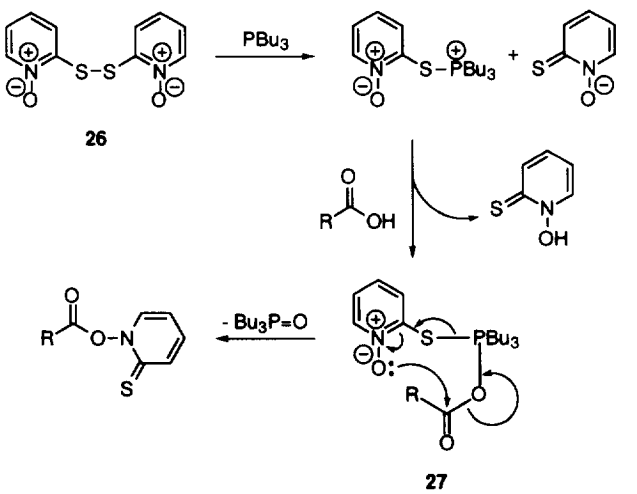
24 R = H, **25** R = Me **6**

SCHEME 6

TABLE 1. Reaction of Z-Aib Barton PTOC Ester **21** with α-Amino Acid Ester Benzenesulfenamides **22** and **23**.

Entry	Sulfenamide	Dipeptide	Time (h)	% Isolated Yield	
				Dipeptide	**6**
1	**22**	**24**	1	95	97
2	**23**	**25**	12	92	99

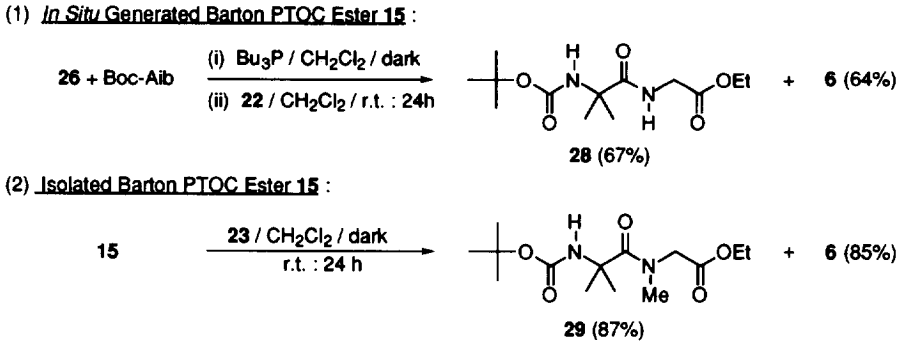
We also studied the formation of dipeptides utilizing Barton PTOC esters generated *in situ* by reaction of the appropriate carboxylic acid with 2,2'-dithiodipyridine-1,1'-dioxide **26** and tri-*n*-butylphosphine[12a], a system which bears close resemblance to Mukaiyama's method of peptide formation *via* oxidation-reduction condensation[24]. The mechanism drawn in **Scheme 7** provides an alternative to that previously proposed[12a]. In the original mechanism, the Barton PTOC ester results from an intermolecular attack of the *N*-hydroxypyridine-2(1*H*)-thione anion on an intermediate acyloxyphosphonium salt, whereas the mechanism depicted in **Scheme 7** is based on the formation of the intermediate acyloxyphosphorane **27** which with facility collapses in an intramolecular fashion (*via* a seven-membered transition state) to liberate the desired Barton PTOC ester and tri-*n*-butylphosphine oxide. The stability of the latter provides the thermodynamic impetus for this reaction.



SCHEME 7

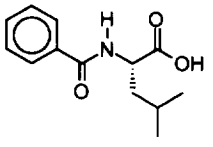
As illustrated in **Scheme 8**, the use of an *in situ* generated Barton PTOC ester is only slightly inferior to the use of the isolated congener. In Equation (1) the *in situ* generated Boc-Aib Barton PTOC ester **15** reacted with benzenesulfenamide **22** to produce the moderately hindered dipeptide **28** (Boc-Aib-Gly-OEt) in modest yield (67%), whilst in Equation (2) the isolated Boc-Aib Barton PTOC ester **15** reacted with benzenesulfenamide **23**

to produce the severely hindered dipeptide **29** (Boc-Aib-Sar-OEt) in satisfactory yield (87% - this figure is diminished to 78% if the isolated yield - 90% - of **15** is taken into account).



SCHEME 8

In order to gauge whether the reaction between an optically active Barton PTOC ester and a sulfenamide preserves optical integrity the Young test[25], which is known to be supersensitive for detecting racemization[26], was applied. Synthesis of the Barton PTOC ester of benzoyl-L-leucine **30** by the DCC-method was hampered by the facile formation of racemic 4-isobutyl-2-phenyloxazolone **31**.



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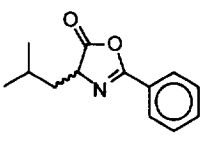

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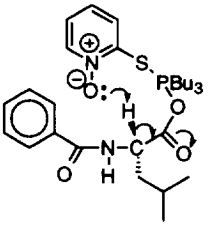

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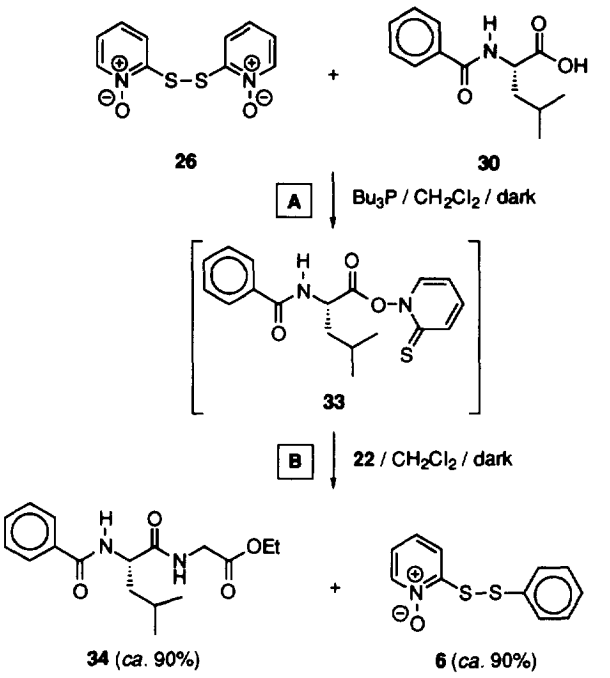
Since the DCC-method also performed poorly according to the original report of Williams and Young[25], we re-visited our method involving the use of 2,2'-dithiodipyridine-1,1'-dioxide **26**, tri-*n*-butylphosphine and an appropriate carboxylic acid[12a,12b]. In our original work, complete racemization was observed when both the formation of the Barton PTOC ester and subsequent coupling with ethyl glycinate (the Young test) were performed at 0°C. This racemization may either be the result of an intramolecular proton abstraction in the intermediate acyloxyphosphorane **32** or it may be due to the oxazolone **31**[27] which itself may result from cyclization of either **27** or the Barton PTOC ester **33**. In order to curb this racemization, the Barton PTOC ester **33** was generated *in situ* at low temperature under careful kinetic control, whilst subsequent reaction with the required sulfenamide **22** was similarly conducted (**Scheme 9** and **Table 2**). Under the conditions stipulated in entry 3 of **Table 2**, racemization at *all* stages of the transformation was thus virtually eliminated since benzoyl-L-leucylglycine ethyl ester **34** was obtained (after mild acid-base work-up and flash column chromatography over

silica gel) with $[\alpha]_D^{22}$ -32.5° (*c* 3.1, EtOH). According to Williams and Young, this α-value corresponds to an L-isomer content (excluding L-isomer present as racemate and hence, enantiomeric excess) of 96%[25].



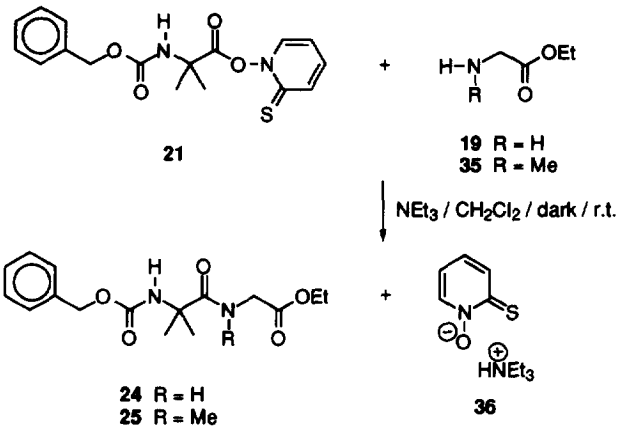
SCHEME 9

TABLE 2. Effect of Reaction Conditions on the Racemization Observed in the Classical Young Test with Benzenesulfenamide **22**.

Entry	Reaction Conditions		$[\alpha]_D^{22}$	% ee[25]
	A	**B**	(*c* 3.1, EtOH)	
1	0°C, then r.t. for 30 min.	0°C, then r.t. for 30 min.	-10.3°	30
2	-78°C for 90 min.	-78 ↦ -20°C for 6h.	-29.5°	88
3	-95† ↦ -78°C for 90 min.	-78 ↦ -20°C for 12h.	-32.5°	96

†Obtained using a MeOH - N_2(l) bath.

Barton PTOC Esters and Free Amines. Barton PTOC esters readily reacted with unhindered primary and secondary amines to produce the corresponding carboxamides[6]. The reaction was successfully applied to the



SCHEME 10

TABLE 3. Reaction of Z-Aib Barton PTOC Ester **21** with Free α-Amino Acid Esters **19** and **35**.

Entry	Ester	Dipeptide	Time (h)	% Isolated Yield of Dipeptide
1	**19**	**24**	12	96
2	**35**	**25**	12	90

synthesis of dipeptides **24** and **25** (**Scheme 10** and **Table 3**), **28** and **29** (**Scheme 11**) and was shown to preserve optical integrity (**Scheme 12** and **Table 4**), albeit to a lesser extent than was the case with the corresponding sulfenamides (*cf.* **Scheme 9** and **Table 2**).

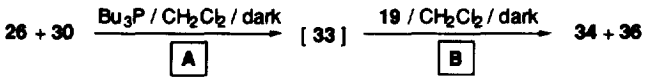
(1) Free Amine and Barton PTOC Ester 15 Generated *In Situ* :

26 + Boc-Aib $\xrightarrow[\text{(ii) } \mathbf{19} / CH_2Cl_2 / \text{r.t.} : 24h]{\text{(i) } Bu_3P / CH_2Cl_2 / \text{dark}}$ **28** (67%) + **36**

(2) Free Amine and Isolated Barton PTOC Ester 15 :

15 + **35** $\xrightarrow[\text{reflux} : 48h]{\mathbf{23} / CH_2Cl_2 / \text{dark}}$ **29** (81%) + **36**

SCHEME 11



SCHEME 12

TABLE 4. Effect of Reaction Conditions on the Racemization Observed in the Classical Young Test with Free α-Amino Acid Ester **19**.

Entry	Reaction Conditions		% Isolated Yield	$[\alpha]_D^{22}$	% ee[25]
	A	B	of **34**	(*c* 3.1, EtOH)	
1[12a]	0°C, then r.t. for 30 min.	0°C, then r.t. for 30 min.	90	0	0
2	-78°C for 90 min.	-78 ↦ -20°C for 6h.	92	-28.4°	86
3	-95† ↦ -78°C for 90 min.	-78 ↦ -20°C for 12h.	94	-30.6°	90

†Obtained using a MeOH-N_2(l) bath

But for an extra synthetic step (conversion of the α-amino acid ester to the required benzenesulfenamide), the use of a benzenesulfenamide offered two major advantages over the corresponding free amine in the context of our reaction. In the first, the benzenesulfenamides appeared to be more reactive towards Barton PTOC esters than were the corresponding free amines in cases where the desired peptide bond was flanked by sterically congested amino acid residues. This was born out by the fact that the formation of dipeptide **29** from the Barton PTOC ester **15** and the benzenesulfenamide **23** required 24h at room temperature (Equation (2) of **Scheme 8**), while the reaction with the corresponding free amine **35** demanded 48h in refluxing dichloromethane (Equation (2) of **Scheme 11**). The second major advantage was mildness of reaction. The free α-amino acid esters were used with a tertiary amine base as proton scavenger (*cf.* **Scheme 10**) whereas couplings with the corresponding benzenesulfenamides were performed under essentially neutral conditions[28] (*cf.* **Scheme 6**). The latter is an important feature of the concerted reaction. Peptide chemists are painfully aware of the fact that tertiary amines are far from innocuous and, more often than not, they are the culprits in side reactions (racemization, cyclization and *O*-acylation, *inter alia*) catalyzed by proton abstraction[29]. Tertiary amine bases are, therefore, to be avoided whenever possible. However, the vast majority of coupling methods still employ these proton scavengers[30].

In conclusion, we have shown that Barton PTOC esters readily reacted with free α-amino acid esters or the corresponding benzenesulfenamides to produce dipeptides in satisfactory yield. The benzenesulfenamides functioned as activated α-amino acid esters and were the reagents of choice in sterically demanding instances.

Although only marginally, the benzenesulfenamides preserved optical integrity to a greater extent than did the corresponding free amines and facilitated reaction under mild, neutral conditions. The reaction between a Barton PTOC ester and a benzenesulfenamide is *zeitgeist* in that it adheres to a principle of ever-increasing popularity, that of atom-economy[31] : all the atoms in the reactants are expressed in the products, both of which are of synthetic and biological value. As such, the concerted reaction between a Barton PTOC ester and an arenesulfenamide should provide yet another addition to the peptide chemist's arsenal of coupling techniques.

EXPERIMENTAL SECTION

General : The general experimental details have been outlined elsewhere[6]. Specific rotations (α-values) were measured on a Jasco DIP-360 digital polarimeter at 22°C in absolute ethanol using the sodium D-line. Fast Atom Bombardment (FAB) High Resolution Mass Spectrometry (HRMS) was performed by the Mass Spectrometry Applications Laboratory of Texas A&M University.

General Procedure for the Preparation of Barton PTOC Esters via the DCC-method : A solution of the required carboxylic acid (5.00 mmol, 1.0 eq.) in anhydrous dichloromethane (25 mL) was added dropwise over a period of 25 minutes to a stirred solution of *N*-hydroxypyridine-2(1*H*)-thione[32] (5.00 mmol, 1.0 eq.) and 1,3-dicyclohexylcarbodiimide (5.10 mmol, 1.02 eq.) in anhydrous dichloromethane (25 mL) at 0°C in the dark (aluminum foil) under an argon atmosphere. The resulting light-yellow mixture was slowly (2h) warmed to ambient temperature and stirred until TLC (hexanes : acetone = 7 : 3 v/v) indicated complete consumption of the thiohydroxamic acid. The mixture was filtered through a short pad (*ca.* 10 cm.) of silica gel (pre-packed with neat dichloromethane) to remove insoluble 1,3-dicyclohexylurea. The filtrate was concentrated under aspirator-vacuum (30 mmHg) at 25°C to give the crude Barton PTOC ester.

N-(cyclohexylcarbonyloxy)-pyridine-2(1*H*)-thione **1** was prepared from commercially available cyclohexanecarboxylic acid and was obtained as colorless needles (91%) after crystallization from dichloromethane / hexanes at -20°C; m.p. 110-112°C (decomposition with evolution of CO_2, lit.[33] : 110°C); IR (KBr) : ν_{max} 2917, 1768, 1589, 1400, 1064 cm^{-1}; ^1H NMR ($CDCl_3$) : δ 7.65 (d, 1H, J = 8.4 Hz), 7.58 (d, 1H, J = 7.0 Hz), 7.21 (t, 1H, J = 8.4 Hz), 6.65 (t, 1H, J = 7.0 Hz), 2.75 (tt, 1H, J = 3.5 and 11.1 Hz), 2.35-1.20 (m, 10H); ^{13}C NMR ($CDCl_3$) : δ 175.5, 170.9, 137.6, 137.1, 133.4, 112.5, 40.8, 28.5, 25.2, 24.9.

Boc-Aib Barton PTOC Ester **15** was prepared from Boc-Aib[3] and was obtained as a dark-green oil. This oil was taken up in ether (50 mL) and successively washed with ice-cold 5% m/v aqueous $NaHCO_3$ (4 x 25 mL) and brine (25 mL). The ethereal layer was dried over $MgSO_4$, filtered and again concentrated under aspirator-vacuum to give **15** in 90% yield as a light-yellow foam that could not be crystallized; IR (neat) : ν_{max} 3286, 2930, 1784, 1694, 1521 cm^{-1}; ^1H NMR ($CDCl_3$) : δ 7.72-7.58 (m, 2H), 7.30-7.14 (m, 1H), 6.73-6.59 (m, 1H), 1.70 (s, 6H), 1.46 (s, 9H); ^{13}C NMR ($CDCl_3$) : δ 175.5, 170.0, 154.7, 137.8, 136.9, 133.5, 112.9, 80.3, 55.6, 28.1, 25.4.

Z-Aib Barton PTOC Ester **21** was prepared from Z-Aib[34] and was obtained as colorless needles (90%) after a single crystallization from dichloromethane / hexanes at -20°C; m.p. 91-93°C (decomposition with evolution of CO_2); IR (KBr) : ν_{max} 3245, 2944, 1806, 1694, 1506 cm^{-1}; ^1H NMR ($CDCl_3$) : δ 7.62 (dd, 1H, J = 1.3 and 8.8 Hz), 7.40-7.28 (m, 6H), 7.20-7.09 (m, 1H), 6.59-6.42 (m, 1H), 5.57-5.40 (br. s, 1H), 5.12 (s, 2H), 1.73 (s, 6H); ^{13}C NMR ($CDCl_3$) : δ 175.7, 169.5, 155.3, 138.0, 137.1, 136.0, 133.5, 128.5, 128.2, 127.9, 112.8, 67.1, 56.2, 25.5; Anal. Calc. for $C_{17}H_{18}N_2O_4S$: C 58.95, H 5.24, N 8.09, S 9.26. Found : C 58.86, H 5.25, N 8.09, S 9.17.

General Procedure for the Synthesis of α-Amino Acid Ester Sulfenamides via the Sulfenyl Chloride Method : A solution of the appropriate arenesulfenyl chloride (5.00 mmol, 1.0 eq.) in anhydrous ether (25 mL) was added dropwise over a period of 25 minutes to a stirred solution of the required α-amino acid ester (5.00 mmol, 1.0 eq.) and triethylamine (5.50 mmol, 1.1 eq.) in anhydrous ether (25 mL) at 0°C under an argon atmosphere. The resulting snow-white suspension was stirred at 0°C for 1h and filtered through Celite® 545. The precipitate was washed with anhydrous ether (100 mL) and the combined filtrates were concentrated under aspirator-vacuum at 30°C to give the desired arenesulfenamide as a colorless oil which was > 95% pure by ^1H NMR. The arenesulfenamide was used directly without further purification.

N-carboethoxymethyl-*N*-methyl-*S*-4-chlorobenzenesulfenamide **11** was obtained in 85% yield from 4-chlorobenzenesulfenyl chloride **12**[35], ethyl sarcosinate hydrochloride **13**[36] and 2.2 molar equivalents of triethylamine; IR (neat) : ν_{max} 2986, 1735, 1470, 1195, 1009 cm^{-1}; ^1H NMR ($CDCl_3$) : δ 7.28 (s, 4H), 4.22 (q, 2H, J = 7.2 Hz), 3.74 (s, 2H), 2.94 (s, 3H), 1.29 (t, 3H, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$) : δ 170.4, 138.1, 131.7, 128.9, 126.4, 61.5, 60.9, 46.7, 14.2; GC-MS (m/z, %) : 259, 260, 261 (M^+, 35, 5.0, 13), 186, 187, 188 (B^+, 100, 11, 38), 143, 144, 145 (77, 11, 29), 108 (31).

N,N-diethyl-*S*-4-chlorobenzenesulfenamide **16** was obtained in quantitative yield from 4-chlorobenzenesulfenyl chloride **12** and 2.2 molar equivalents of diethylamine; IR (neat) : ν_{max} 2967, 1468, 1374, 1006, 678 cm^{-1}; ^1H NMR ($CDCl_3$) : δ 7.24 (s, 4H), 2.98 (q, 4H, J = 7.1 Hz), 1.16 (t, 6H, J = 7.1 Hz); ^{13}C NMR ($CDCl_3$) : δ 140.1, 130.8, 128.6, 125.9, 52.2, 13.6; GC-MS (m/z, %) : 215, 216, 217 (M^+, 62, 8.6, 24), 200, 201, 202 (84, 10, 31), 143, 144, 145 (B^+, 100, 13, 38), 108 (33).

N-carboethoxymethylbenzenesulfenamide **22** was obtained in 91% yield from benzenesulfenyl chloride[35] and ethyl glycinate **19**[36]; IR (neat) : ν_{max} 3336, 2982, 1723, 1473, 1204 cm^{-1}; ^1H NMR ($CDCl_3$) : δ 7.34-7.28 (m, 4H), 7.20-7.09 (m, 1H), 4.19 (q, 2H, J = 7.1 Hz), 3.72 (d, 2H, J = 6.1 Hz), 3.46-3.32 (br. s, 1H), 1.26 (t, 3H, J = 7.1 Hz); ^{13}C NMR ($CDCl_3$) : δ 171.6, 140.8, 128.8, 125.8, 124.0, 61.1, 53.6, 14.1; GC-MS (m/z, %) : 211 (M^+, 82), 138 (B^+), 109 (84).

N-carboethoxymethyl-*N*-methylbenzenesulfenamide **23** was obtained in 99% yield from benzenesulfenyl chloride and ethyl sarcosinate **35**[36]; IR (neat) : ν_{max} 2982, 1740, 1437, 1195, 1100 cm^{-1}; ^1H NMR ($CDCl_3$) : δ 7.38-7.27 (m, 4H), 7.23-7.12 (m, 1H), 4.21 (q, 2H, J = 7.2 Hz), 3.75 (s, 2H), 2.94 (s, 3H), 1.28 (t, 3H, J =

7.2 Hz); ^{13}C NMR ($CDCl_3$) : δ 170.5, 139.1, 128.7, 126.1, 125.5, 61.6, 60.8, 46.6, 14.2; GC-MS (m/z, %) : 225 (M^+, 44), 152 (B^+), 109 (66).

General Procedure for the Reaction Between Barton PTOC Esters and

A -- *Free α-Amino Acid Esters* : A solution of the α-amino acid ester (1.20 mmol, 1.2 eq.) in anhydrous dichloromethane (2.5 mL) was added dropwise over a period of 5 minutes to a stirred solution of the required Barton PTOC ester (1.00 mmol, 1.0 eq.) and triethylamine (1.20 mmol, 1.2 eq.) in anhydrous dichloromethane (2.5 mL) at ambient temperature in the dark (aluminum foil) under an argon atmosphere. The mixture was stirred until TLC (hexanes : acetone = 7 : 3 v/v) indicated complete consumption of the Barton PTOC ester. The volatiles were removed under aspirator-vacuum at 30°C. The residue was taken up in ethyl acetate (20 mL) and successively washed with 5% m/v aqueous $KHSO_4$ (3 x 5 mL), brine (5 mL), 5% m/v aqueous $NaHCO_3$ (3 x 5 mL) and again with brine (5 mL). The organic phase was dried over Na_2SO_4, filtered, concentrated and flash-chromatographed to give the analytically pure dipeptide.

B -- *Arenesulfenamides Derived From α-Amino Acid Esters* : A solution of the arenesulfenamide (1.05 mmol, 1.05 eq.) in anhydrous dichloromethane (2.5 mL) was added dropwise over a period of 5 minutes to a stirred solution of the required Barton PTOC ester (1.00 mmol, 1.0 eq.) in anhydrous dichloromethane (2.5 mL) at ambient temperature in the dark (aluminum foil) under an argon atmosphere. The mixture was stirred until TLC (hexanes : acetone = 7 / 3 v/v) indicated complete consumption of the Barton PTOC ester. The volatiles were removed under aspirator-vacuum at 30°C and the residue was flash-chromatographed over silica gel to give both the dipeptide and the unsymmetrical disulfide in an analytically pure state.

Model Reactions

Scheme 3 (Equation (3)) : Application of the general procedure **B** to Barton PTOC ester **1** and arenesulfenamide **11** gave *N*-carboethoxymethyl-*N*-methylcyclohexanecarboxamide **8** (207 mg, 0.91 mmol, 91%, R_f 0.43) as a colorless oil and 2-(4'-chlorophenyldithio)-pyridine-*N*-oxide **14** (243 mg, 0.90 mmol, 90%, R_f 0.10) as a colorless, crystalline solid after flash column chromatography (hexanes : acetone = 8 : 2 v/v).

For **8** - IR (neat) : ν_{max} 2942, 1741, 1632, 1450, 1406, 1199, 1142, 1105, 1034 cm^{-1}; ^1H NMR[37] ($CDCl_3$) : δ 4.31-4.11 (m, Sar-O$\underline{CH_2}CH_3$), 4.11-4.05 (m, Sar-CH_2), 3.11 and 2.96 (2 x s in a ratio of 3 : 1, Sar-NMe), 2.66-2.46 and 2.39-2.22 (2 x m in a ratio of 3 : 1, cyclohexyl methine), 1.89-1.16 (m, cyclohexyl methylenes and Sar-OCH$_2\underline{CH_3}$); ^{13}C NMR ($CDCl_3$) : δ 176.6 (CO_{amide}), 169.4 (CO_{ester}), 61.5 and 60.9 (Sar-O$\underline{CH_2}CH_3$), 51.5 and 49.5 (Sar-CH_2), 40.6 and 40.4 (cyclohexyl methine), 36.3 and 34.9 (Sar-NMe), 29.3, 28.9 and 25.7 (cyclohexyl methylenes), 14.1 (Sar-OCH$_2\underline{CH_3}$); GC-MS (m/z, %) : 227 (M^+, 23), 154 (21), 118 (39), 83 (B^+), 55 (59); Anal. Calc. for $C_{12}H_{21}NO_3$: C 63.41, H 9.31, N 6.16. Found : C 63.16, H 9.18, N 6.12.

For **14** - M.p. 131-133°C (dec.; lit.[19] : 133.5-137.5°C); IR (KBr) : ν_{max} 3064, 1453, 1247, 1083, 808 cm^{-1}; ^1H NMR ($CDCl_3$) : δ 8.25 (d, 1H, *J* = 6.3 Hz), 7.73 (dd, 1H, *J* = 1.4 and 8.2 Hz), 7.48-7.10 (m, 6H); ^{13}C NMR ($CDCl_3$) : δ 150.6, 138.4, 133.6, 132.7, 129.3, 128.9, 126.3, 122.1, 121.5; GC-MS (m/z, %) : 278, 279, 280 (M^+, 29, 4.4, 13), 220, 221, 222 (B^+, 100, 14, 10), 156 (63).

Scheme 4 : Application of the general procedure **B** to Boc-Aib Barton PTOC ester **15** and arenesulfenamide **16** gave the unsymmetrical disulfide **14** (232 mg, 0.86 mmol, 86%) as before (*vide supra*) and Boc-Aib-NEt_2 **17** (219 mg, 0.85 mmol, 85%, R_f 0.37) after flash column chromatography (acetone : hexanes = 7 : 3 v/v). Recrystallization from ether afforded an analytically pure sample of **17** as colorless needles, m.p. 113-115°C; IR (KBr) : ν_{max} 3345, 2976, 1706, 1614, 1161 cm^{-1}; ^1H NMR (C_6D_6; spectrum referenced to residual solvent peak at δ 7.15 ppm) : δ 5.76-5.48 (br. s, 1H), 3.44-3.00 (m, 4H), 1.47 (s, 6H), 1.41 (s, 9H), 1.10-0.70 (br. s, 6H); ^{13}C NMR (C_6D_6) : δ 171.9, 154.1, 78.5, 56.6, 41.6, 28.5, 25.9, 13.4; GC-MS (m/z, %) : 258 (M^+, 0.4), 158 (36), 102 (78), 58 (B^+); Anal. Calc. for $C_{13}H_{26}N_2O_3$: C 60.44, H 10.14, N 10.84. Found : C 60.53, H 10.08, N 10.91.

Attempted Preparation of N-carboethoxymethyl-4-chlorobenzenesulfenamide via Phthalimide Derivative ***18*** :

(i) *N*-(4-chlorobenzenesulfenyl)-phthalimide **18** : A solution of 4-chlorobenzenesulfenyl chloride **12** (2.44 g, 13.60 mmol, 1.0 eq.) in anhydrous *N,N*-dimethylformamide (5 mL) was added dropwise over a period of 5 minutes to a stirred solution of phthalimide (2.02 g, 13.60 mmol, 1.0 eq.) and triethylamine (2.3 mL, 16.32 mmol, 1.2 eq.) in anhydrous *N,N*-dimethylformamide (10 mL) at ambient temperature under an argon atmosphere[38]. The resulting light-yellow mixture was stirred at ambient temperature for 1h and diluted with ice-cold water (100 mL). The precipitate was filtered off, collected and recrystallized from absolute ethanol to give **18** (3.21 g, 11.06 mmol, 81%) as small, colorless crystals, m.p. 171-173°C (lit.[39] : 174°C); IR (KBr) : ν_{max} 1728, 1705, 1340, 1272, 1044 cm^{-1}; ^1H NMR ($CDCl_3$) : δ 8.00-7.87 (m, 2H), 7.86-7.73 (m, 2H), 7.57 (d, 2H, *J* = 8.3 Hz), 7.30 (d, 2H, *J* = 8.3 Hz); ^{13}C NMR ($CDCl_3$) : δ 167.5, 135.8, 134.8, 133.3, 132.8, 131.8, 129.5, 124.1.

(ii) Adduct **20** : A solution of ethyl glycinate **19** (108 mg, 1.05 mmol, 1.05 eq.) in anhydrous dichloromethane (5 mL) was added dropwise over a period of 5 minutes to a stirred solution of **18** (290 mg, 1.00 mmol, 1.0 eq.) in anhydrous dichloromethane (5 mL) at ambient temperature under an argon atmosphere. The solution was stirred at ambient temperature for 24h and the solvent was evaporated under aspirator-vacuum at 30°C. The residue was triturated with pentane (50 mL) and chilled in a refrigerator at -20°C for 1h. The precipitate was filtered off and successively washed with ether (3 x 25 mL) and ice-cold absolute ethanol (3 x 25 mL). The precipitate was collected and recrystallized from boiling absolute ethanol to give **20** (244 mg, 0.62 mmol, 62%) as colorless needles, m.p. 145-147°C (dec.); IR (KBr) : ν_{max} 3369, 3221, 1714, 1643, 1413, 1216 cm^{-1}; ^1H NMR (DMSO; spectrum referenced to residual solvent peak at δ 2.49 ppm) : δ 10.12-10.00 (br. s, 1H), 8.95-8.55 (m, 1H), 7.58 (s, 4H), 7.37 (s, 4H), 4.11 (q, 2H, *J* = 7.1 Hz), 3.96 (d, 2H, *J* = 5.3 Hz), 1.20 (t, 3H, *J* = 7.1 Hz); ^{13}C NMR (DMSO) : δ 170.3, 169.7, 167.6, 139.0, 135.8, 135.1, 130.0, 128.7, 128.0,

127.8, 124.9, 60.5, 41.2, 14.1; Anal. Calc. for $C_{18}H_{17}ClN_2O_4S$: C 55.03, H 4.36, N 7.13, S 8.16. Found : C 54.95, H 4.40, N 7.05, S 8.05.

Dipeptides **24** and **25**

Dipeptides **24** and **25** were synthesized in yields of 95 and 92% respectively by reacting Z-Aib Barton PTOC ester **21** with arenesulfenamides **22** and **23** according to the general procedure **B**. Flash column chromatography (hexanes : acetone = 7 : 3 v/v) afforded **24** (R_f 0.32) and **25** (R_f 0.21) together with the unsymmetrical disulfide **6** (R_f 0.11) in yields of 97 and 99% respectively (*cf.* **Scheme 6**). Dipeptides **24** and **25** were also prepared by reacting **21** with the free α-amino acid esters **19** and **35** according to the general procedure **A** (*cf.* **Scheme 10**).

Z-Aib-Gly-OEt **24**[23] was obtained as a colorless oil; IR (neat) : ν_{max} 3343, 2986, 1737, 1660, 1524 cm^{-1}; ^1H NMR ($CDCl_3$) : δ 7.34 (s, 5H), 7.02-6.76 (br. s, 1H), 5.53 (s, 1H), 5.09 (s, 2H), 4.19 (q, 2H, J = 7.1 Hz), 3.99 (d, 2H, J = 4.8 Hz), 1.54 (s, 6H), 1.27 (t, 3H, J = 7.1 Hz); ^{13}C NMR ($CDCl_3$) : δ 174.6, 169.8, 155.0, 136.1, 128.4, 128.1, 128.0, 66.7, 61.3, 56.8, 41.5, 25.4, 14.0; Exact Mass (FAB^+ - HRMS) Calc. for $C_{16}H_{23}N_2O_5$ [$(M+H)^+$] : 323.1607. Found : 323.1622.

Z-Aib-Sar-OEt **25** was obtained as a colorless oil; IR (neat) : ν_{max} 3303, 2985, 1721, 1629, 1520 cm^{-1}; ^1H NMR ($CDCl_3$) : δ 7.34 (s, 5H), 5.72-5.52 (br. s, 1H), 5.09 (s, 2H), 4.17 (q, 2H, J = 7.2 Hz), ~ 4.25-3.95 (br. s, 2H), 3.30-2.95 (br. s, 3H), 1.59 (s, 6H), 1.26 (t, 3H, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$) : δ 173.1, 169.3, 154.2, 136.4, 128.4, 128.1, 66.5, 61.1, 56.8, 51.9, 37.5, 25.3, 14.1; Anal Calc. for $C_{17}H_{24}N_2O_5$: C 60.70, H 7.19, N 8.33. Found : C 60.59, H 7.23, N 8.23.

2-(Phenyldithio)-pyridine-*N*-oxide **6** was obtained as a colorless, crystalline solid on standing in a refrigerator at -20°C, m.p. 79-81°C (dec.; lit.[19] : 82.1-82.2°C); IR (neat) : ν_{max} 2925, 1462, 1248, 1135, 686 cm^{-1}; ^1H NMR ($CDCl_3$) : δ 8.24 (d, 1H, J = 6.1 Hz), 7.78 (dd, 1H, J = 1.9 and 8.2 Hz), 7.49 (dd, 1H, J = 1.6 and 8.1 Hz), 7.38-7.19 (m, 4H), 7.19-7.08 (m, 1H); ^{13}C NMR ($CDCl_3$) : δ 151.3, 138.5, 134.3, 129.3, 127.7, 127.6, 126.3, 121.9, 121.8.

In Situ Generated *vs.* Isolated Barton PTOC Ester **15**

(i) Use of the *In Situ* Generated Barton PTOC Ester **15** : A solution of tri-*n*-butylphosphine (282 μL, 1.10 mmol, 1.1 eq.) in anhydrous dichloromethane (2.5 mL) was added dropwise over a period of 5 minutes to a stirred solution of Boc-Aib (203 mg, 1.00 mmol, 1.0 eq.) and **26**[18] (277 mg, 1.10 mmol, 1.1 eq.) in anhydrous dichloromethane (15 mL) at 0°C in the dark (aluminum foil) under an argon atmosphere. The yellow mixture was stirred at ambient temperature for 30 minutes and a solution of either the benzenesulfenamide **22** (*cf.* Equation (1) of **Scheme 8**; 211 mg, 1.00 mmol, 1.0 eq.) or the corresponding free α-amino acid ester **19** (*cf.* Equation (1) of **Scheme 11**; 103 mg, 1.00 mmol, 1.0 eq.) in anhydrous dichloromethane (2.5 mL) was added

dropwise over a period of 5 minutes in the dark under an argon atmosphere. The mixture was stirred until TLC (hexanes : acetone = 7 : 3 v/v) indicated complete consumption of the Barton PTOC ester **15**. The volatiles were removed under aspirator-vacuum at 30°C, the residue was taken up in ethyl acetate (20 mL) and successively washed with 5% m/v aqueous $KHSO_4$ (3 x 5 mL), brine (5 mL), 5% m/v aqueous $NaHCO_3$ (3 x 5 mL) and again with brine (5 mL). The organic layer was dried over Na_2SO_4, filtered, concentrated and flash-chromatographed (hexanes : acetone = 7 : 3 v/v) to give the dipeptide Boc-Aib-Gly-OEt **28** (193 mg, 0.67 mmol, 67%, R_f 0.31) and, in the case of the benzenesulfenamide **22**, the unsymmetrical disulfide **6** (151 mg, 0.64 mmol, 64%, R_f 0.17) as before (*vide supra*). The dipeptide **28** was obtained as a colorless, crystalline solid, m.p. 100-101°C; IR (KBr) : ν_{max} 3351, 3311, 2987, 1755, 1683, 1662, 1520, 1191, 1194 cm^{-1}; ^1H NMR ($CDCl_3$) : δ 7.06-6.87 (br. s, 1H), 5.03 (s, 1H), 4.21 (q, 2H, *J* = 7.2 Hz), 4.03 (d, 2H, *J* = 5.1 Hz), 1.51 (s, 6H), 1.44 (s, 9H), 1.28 (t, 3H, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$) : δ 174.9, 169.5, 154.7, 80.2, 61.3, 56.7, 41.6, 28.3, 25.6, 14.1; Anal Calc. for $C_{13}H_{24}N_2O_5$: C 54.15, H 8.39, N 9.72. Found : C 54.25, H 8.37, N 9.80.

(ii) Use of the Isolated Barton PTOC Ester **15** : Application of the general procedure **B** to the Barton PTOC ester **15** and the arenesulfenamide **23** (*cf.* Equation (2) of **Scheme 8**) or application of the general procedure **A** to the Barton PTOC ester **15** and the free α-amino acid ester **35** (*cf.* Equation (2) of **Scheme 11**) afforded the dipeptide Boc-Aib-Sar-OEt **29** in the indicated yields. The dipeptide **29** was obtained as a colorless oil; IR (neat) : ν_{max} 3307, 2966, 1773, 1681, 1629, 1446, 1383, 1166, 1096 cm^{-1}; ^1H NMR ($CDCl_3$) : δ 5.24-4.88 (br. s, 1H), 4.19 (q, 2H, *J* = 7.1 Hz), ~ 4.30-3.98 (br. s, 2H), 3.42-3.08 (br. s, 3H), 1.54 (s, 6H), 1.43 (s, 9H), 1.27 (t, 3H, *J* = 7.1 Hz); ^{13}C NMR ($CDCl_3$) : δ 173.3, 169.3, 153.8, 79.5, 60.9, 56.5, 51.7, 37.3, 28.1, 25.6, 14.0; Anal Calc. for $C_{14}H_{26}N_2O_5$: C 55.61, H 8.67, N 9.26. Found : C 55.51, H 8.62, N 9.17.

Racemization

(i) Benzoyl-L-leucine **30**[25]: A solution of freshly distilled benzoyl chloride (12.3 mL, 0.105 mol, 1.05 eq.) in 2.0 M NaOH (60 mL, 0.120 mol, 1.1 eq.) was added dropwise over a period of 30 minutes to a stirred solution of commercially available L-leucine (13.25 g, 0.100 mol, 1.0 eq.) in 2.0 M NaOH (50 mL, 0.100 mol, 1.0 eq.) at 0°C. The mixture was stirred at 0°C for 15 minutes and extracted with ether (4 x 50 mL). The organic extracts were discarded and the aqueous layer was acidified with 2.0 M HCl to pH 3 and re-extracted with ether (4 x 50 mL). These ether extracts were combined and dried over Na_2SO_4, filtered and concentrated under aspirator-vacuum at 30°C. The residual oil was taken up in anhydrous ether (250 mL) and cyclohexylamine (12.1 mL, 0.105 mol, 1.05 eq.) was added dropwise over a period of 15 minutes and under vigorous stirring. The resulting snow-white mixture was stirred for an additional 30 minutes and filtered. The precipitate was collected and recrystallized from 2-propanol to give benzoyl-L-leucine cyclohexylammonium salt (29.00 g, 0.087 mol, 87%) as colorless needles, m.p. 148-150°C and $[\alpha]_D^{22}$ +14.4° (*c* 4.25, EtOH; lit.[25] : m.p. 145-146°C and $[\alpha]_D^{19}$ +14.4° for *c* 4.25, EtOH). 2.0 M HCl (100 mL, 0.200 mol, excess) was subsequently added dropwise over a period of 30 minutes to a stirred suspension of the cyclohexylammonium salt (12.30 g, 0.037 mol, 1.0 eq.) in ethyl acetate (100 mL) at ambient temperature. The two phases were separated and the

aqueous layer was extracted with ethyl acetate (4 x 50 mL). The ethyl acetate layers were combined and dried over Na_2SO_4, filtered and concentrated under aspirator-vacuum at 30°C. The remaining oil was taken up in chloroform (50 mL) and treated with petroleum ether (b.p. 40-60°C) until a slight turbidity persisted. The volatiles were once again removed *in vacuo* and the remaining white solid was recrystallized from chloroform / petroleum ether to give benzoyl-L-leucine **30** (8.36 g, 0.036 mol, 96%) as small, colorless crystals, m.p. 70-72°C (lit.[25] : 106°C[40]); $[\alpha]_D^{22}$ -6.9° (*c* 2.6, EtOH; lit.[25] : $[\alpha]_D^{23}$ -6.9° for *c* 2.6, EtOH); IR (KBr) : ν_{max} 3334, 2957, 1713, 1612, 1542 cm^{-1}; ^1H NMR ($CDCl_3$) : δ 10.65-10.30 (br. s, 1H), 7.78 (d, 2H, *J* = 6.9 Hz), 7.56-7.33 (m, 3H), 6.80 (d, 1H, *J* = 8.3 Hz), 4.90-4.75 (m, 1H), 1.90-1.60 (m, 3H), 0.97 (d, 6H, *J* 5.1 Hz); ^{13}C NMR ($CDCl_3$) : δ 176.9, 168.0, 133.5, 131.9, 128.6, 127.2, 51.3, 41.2, 25.0, 22.8, 21.9.

(ii) Benzoyl-L-leucylglycine Ethyl Ester **34** : A solution of tri-*n*-butylphosphine (566 µL, 2.20 mmol, 1.1 eq.) in anhydrous dichloromethane (2.5 mL) was added dropwise over a period of 5 minutes to a stirred solution of benzoyl-L-leucine **30** (471 mg, 2.00 mmol, 1.0 eq.) and **26** (556 mg, 2.20 mmol, 1.1 eq.) in dichloromethane (25 mL) at -95°C (MeOH / liquid-N_2) in the dark (aluminum foil) under an argon atmosphere. The yellow solution was slowly (90 minutes) warmed to -78°C and a solution of either the benzenesulfenamide **22** (*cf.* **Scheme 9**; 506 mg, 2.40 mmol, 1.2 eq.) or the corresponding free α-amino acid ester **19** (*cf.* **Scheme 12**; 248 mg, 2.40 mmol, 1.2 eq.) in anhydrous dichloromethane (2.5 mL) was added dropwise over a period of 5 minutes in the dark under an argon atmosphere. The mixture was slowly (12h) warmed to -20°C. The volatiles were removed under aspirator-vacuum at 20°C, the residue was taken up in ethyl acetate (20 mL) and successively washed with 5% m/v aqueous $KHSO_4$ (3 x 5 mL), brine (5 mL), 5% m/v aqueous $NaHCO_3$ (3 x 5 mL) and again with brine (5 mL). The organic layer was dried over Na_2SO_4, filtered, concentrated and flash-chromatographed (hexanes : acetone = 7 : 3 v/v) over silica gel to give **34** (R_f 0.26) as a colorless, crystalline solid and, in the case of the benzenesulfenamide **22**, the unsymmetrical disulfide **6** (R_f 0.17) as before (*vide supra*). For **34** : m.p. 141-143°C (lit.[25] : 141-144°C); $[\alpha]_D^{22}$ -32.5° (*c* 3.1 in EtOH; 96% ee[25]); IR (KBr) : ν_{max} 3275, 2958, 1749, 1627, 1538, 1193 cm^{-1}; ^1H NMR ($CDCl_3$) : δ 7.81 (d, 2H, *J* = 6.7 Hz), 7.55-7.33 (m, 3H), 7.32-7.04 (m, 2H), 4.90-4.73 (m, 1H), 4.17 (q, 2H, *J* = 7.1 Hz), 4.07-3.83 (m, 2H), 1.86-1.60 (m, 1H), 1.24 (t, 3H, *J* = 7.1 Hz), 0.94 (d, 6H, *J* = 3.4 Hz); ^{13}C NMR ($CDCl_3$) : δ 172.6, 169.5, 167.4, 133.7, 131.7, 128.5, 127.1, 61.4, 51.9, 41.3, 41.1, 24.8, 22.8, 22.1, 14.0.

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