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Reductive Cyclization of Carbon-Centered Glycine Radicals; A Novel Synthetic Route to Cyclic α-Amino Acids

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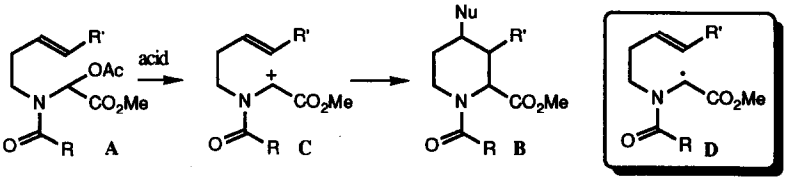
Abstract: Reductive cyclizations (tributyltin hydride, AIBN) of several α-(phenylthio)glycine derivatives with a 3-alkenyl substituent at nitrogen are reported. These reactions proceed via 2-aza-5-alken-1-yl radicals as intermediates which bear electron-withdrawing carbonyl substituents at the radical center and at nitrogen. Such radicals can be considered as relatively stable captodative radicals, but are reactive enough for olefin cyclization. The main products usually arise from 5-*exo* cyclization and are structurally interesting analogues of proline. Varying amounts of pipecolic acid analogues via 6-*endo* cyclization are also obtained in some cases. A similar cyclization of an acetylene is successful, whereas a nitrile fails to cyclize.

INTRODUCTION

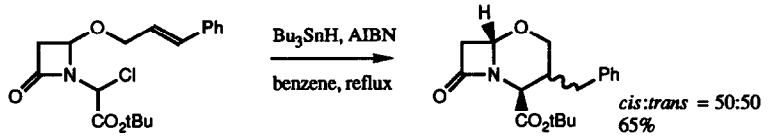
The development of radical cyclization reactions for synthetic purposes is an area of active research since the early eighties.[1] Excellent recent reviews discuss the special advantages of radical versus ionic intermediates.[2] Several successful applications of radical cyclization in natural product synthesis have already been reported.[3] Some years ago our interest in this subject was aroused in connection with our research on olefin cyclization reactions of glycine cation equivalents.[4] We had found that α-alkoxyglycine derivatives **A** bearing a 3-alkenyl substituent on nitrogen cyclize in the presence of acid to give mainly pipecolic acid derivatives **B** via cation **C** as intermediate. We wondered whether the corresponding glycine radical **D** would also undergo olefin cyclization and if so what the scope and the regio- and stereochemistry of this process would be.



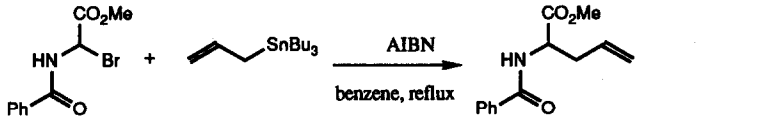
Ample literature precedent exists on the synthesis of nitrogen containing heterocycles via radical cyclization. Thus, 1-aza-,[5] 2-aza-,[6,7] 3-aza-,[8] and 4-aza-5-hexenyl[9] radical ring closures have been reported. Our crucial intermediate **D** can be designated as a 2-aza-5-hexenyl radical with carbonyl substituents at the radical center and at nitrogen. Interestingly, the 2-acyl-2-aza-5-hexenyl radical was one of the first radical types that were extensively studied for application in natural product synthesis, viz. pyrrolizidine alkaloids by Hart and coworkers.[6a-c] Padwa et al. have reported evidence that the presence of an electron-withdrawing substituent at nitrogen is important for successful cyclization of the 2-aza-5-hexenyl radical to monocyclic systems.[6d]

Radical type **D** can be viewed as a captodative radical, because the radical center bears an acceptor (ester

carbonyl) and a donor substituent (carbamate nitrogen). It has been advanced that such radicals are exceptionally stable due to a synergistic effect of both substituents.[10] While this captodative effect is still debated,[11] we questioned whether **D** would be reactive enough for synthetic applications. The work of Bachi and coworkers on the preparation of bicyclic β-lactam systems[7] was highly encouraging in this respect. Despite the alleged radical stability, cyclizations as shown in eq 1 were reported to proceed well. To the best of our knowledge other intramolecular applications of the glycine radical, in particular for the synthesis of monocyclic systems, have not appeared in the literature. Intermolecular reactions of glycine radicals with allylstannanes were published by Baldwin et al.[12] (eq 2) and recently by Hamon et al.[13] The generation and properties of carbon-centered radicals in α-amino acids and peptides have been studied in detail, but synthetic applications, especially with respect to carbon carbon bond formation, have received little attention.[14]



(eq 1)



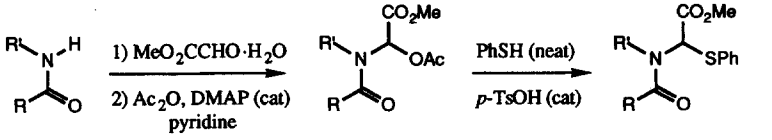
(eq 2)

An important distinction between 2-aza-5-hexenyl cations (iminium ions, e.g. **C**) and 2-aza-5-hexenyl radicals is the regiochemistry of cyclization due to the difference in transition state geometry. Cationic processes mainly lead to 6-membered rings,[15] whereas radical reactions produce mostly 5-membered rings.[1-3] Cyclizations of radical type **D** are thus expected to lead to proline analogues. The study of the synthesis and properties of ring substitution analogues of proline has a long history[16] and is still a topic of high interest.[17] We report herein the details of our investigations on tributyltin hydride mediated cyclizations of radical type **D** and show that this process constitutes a novel access to several proline analogues.[18]

RESULTS

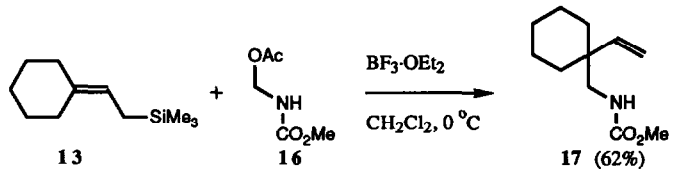
Synthesis of radical cyclization precursors

The phenylthio ethers **1-12** (Table 1) were chosen as starting materials for the radical cyclizations. In addition to nine 2-aza-5-hexenyl systems (**1-9**) we included a 2-aza-6-heptenyl (**10**), a 2-aza-5-hexynyl (**11**) and its corresponding nitrile analogue (**12**). These quite stable *N,S*-acetals were prepared as schematized in eq 3. Treatment of the appropriate *N*-monosubstituted carbamate (or 2-pyrrolidinone in the case of **2**) with methyl glyoxylate in a Dean Stark apparatus, followed by acetylation of the resulting stable hemiacetal provided the acetoxy derivative.[4a] This compound was then subjected to acid catalysed solvolysis in neat thiophenol to give the required radical precursor. The yield of this step varied considerably (usually ca. 60%), but was not optimized. Trisubstituted olefins underwent thiophenol addition to some extent under these conditions, so that the scope of this acidic introduction of the phenylthio function is somewhat limited. Base mediated methods should have broader scope but this was not investigated.

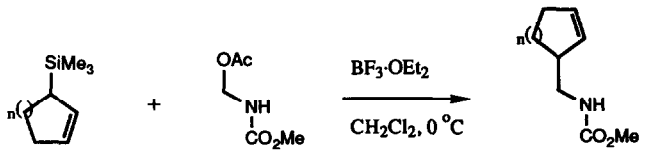


(eq 3)

The radical precursors, purified by using flash chromatography, showed rather complex ^{1}H NMR spectra (often showing two conformers) due to hindered rotation in the carbamate moiety and/or due to the presence of a ca. 1:1 mixture of two stereoisomers (for **2**, **3**, **7**, **8** and **10**). The (broad) singlets of the *N,S*-acetal methine hydrogens were found between 5.15 ppm for **4** and 5.91 and 6.41 ppm (two stereoisomers) for **2**.



13 **16** **17** (62%) (eq 4)



14 n = 1 **16** **18** n = 1 (68%) (eq 5)
15 n = 2 **19** n = 2 (78%)

The starting carbamates leading to radical precursors **1**, **2**, **3**, **5** and **6** have been described before.[4a] The carbamates **17**, **18** and **19** (eq 4, 5) required for the preparation of radical precursors **4**, **7** and **8**, respectively, were obtained through Lewis acid-mediated coupling[4a] of iminium precursor **16** with allylsilanes **13**,[19] **14**[20] and **15**.[20] The carbamates leading to **9** and **12** were prepared from commercially available primary amines. Finally, the carbamates required for **10** and **11** were synthesized from 3-cyclohexene-1-methanol and 3-pentyn-1-ol, respectively, via the corresponding primary amines.

Radical cyclization

The radical cyclizations of precursors **1**-**12** were carried out in toluene solutions at 80-90 °C under nitrogen. The reactions were conducted by slow (6-8 h) addition of a solution of tributyltin hydride (1.4 equiv) and AIBN (0.1 equiv) in toluene. The final concentration of the tributyltin entity was in the 0.02-0.04 M range.

The results of the cyclization reactions are summarized in Table 1. In general, three types of products were obtained, namely the reduction product of the incipient radical and two types of regioisomeric cyclization products, i.e. those resulting from *endo*- and *exo*-cyclization modes. The five-membered ring products could be separated from their six-membered isomers by using flash chromatography, the former always being more polar than the latter. The six-membered ring product could not be separated from the non-cyclized product in three cases (see Table 1). This problem was solved in one case by oxidizing the mixture of **36** and **37** with *m*-chloroperbenzoic acid, so that **36** could be obtained pure by chromatographic removal of the epoxide of **37**.

While the presence of cyclized and/or non-cyclized material was readily inferred from the ^{1}H NMR spectra, the distinction between the *exo*- and *endo*-products was more difficult. Complicating factors were the inseparability of nearly all stereoisomers and broad signals in the ^{1}H NMR spectra due to slow rotation on the NMR time-scale in the carbamate moieties. Nevertheless, the chemical shift of the methine hydrogen at the carbon atom bearing the ester function appeared to be sufficiently diagnostic. Table 2 shows pertinent ^{1}H NMR data of the cyclization products. In a six-membered ring this hydrogen was always found between 4.5 and 5.0 ppm. This low field value is a result of the equatorial orientation of this hydrogen, thus experiencing a deshielding from both methoxycarbonyl groups. The *C*-ester function adopts an axial orientation in order to relieve pseudo-allylic 1,3-strain with the carbamate moiety.[21,22] In a five-membered ring (proline analogue) the pertinent hydrogen was found between 3.8 and 4.5 ppm, thus at higher field than in a six-membered ring. The only exception was of course the cyclization product **38** from **11**, in which the allylic character of the C-2 hydrogen caused a further downfield shift to 4.7 and 4.9 ppm for the two isomers.

Table 1. Cyclization of Radical Precursors **1-12** (Bu_3SnH, AIBN, toluene, 80-90 °C).

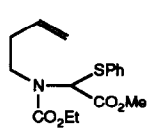
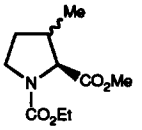
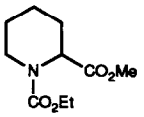
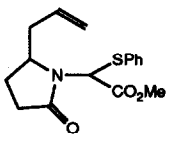
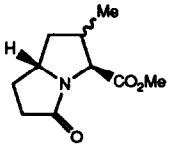
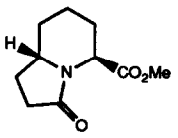
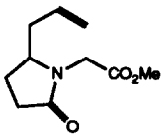
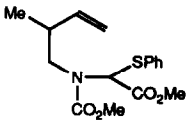
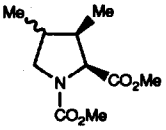
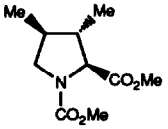
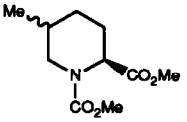
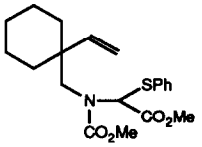
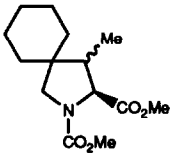
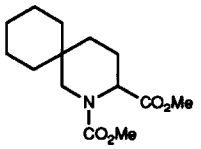
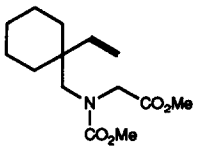
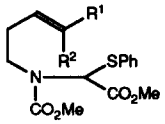
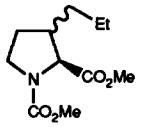
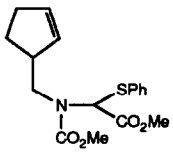
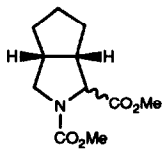
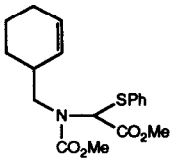
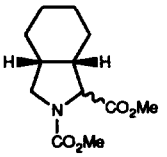
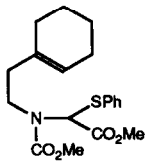
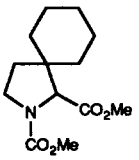
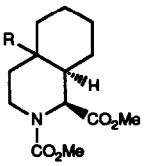
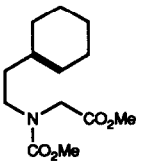
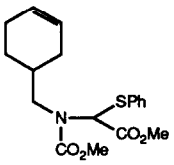
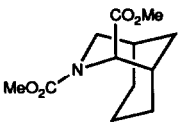
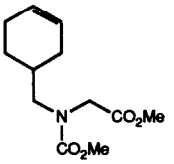
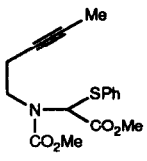
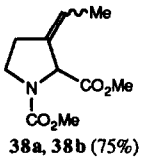
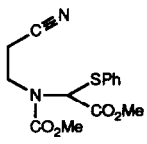
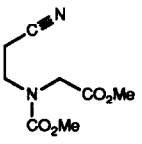
precursor	*exo*-product(s)	*endo*-product(s)	reduced starting material
 **1**	 **20a, 20b** (60%) *cis:trans* = 35:65	 **21** (30%)	
 **2**	 **22a**[a], **22b** (12%) *cis:trans* = 20:80	 **23**[b] (72%)	 **24**[b] (4%)
 **3**	  **25a, 25b** (18%)[c] **25c** (36%)[c]. *cis:trans* = 50:50	 **26a, 26b** (46%) *cis:trans* = 75:25	
 **4**	 **27a, 27b** (41%) *cis:trans* = 29:71	 **28** (36%)	 **29** (3%)
 **5** R^1 = Et, R^2 = H **6** R^1 = H, R^2 = Et	 **30a, 30b** (93%) *cis:trans* = 35:65 **30a, 30b** (91%) *cis:trans* = 30:70		
 **7**	 **31a, 31b** (89%) α:β = 13:87		

Table 1. Continued.

precursor	*exo*-product(s)	*endo*-product(s)	reduced starting material
 **8**	 **32a, 32b** (60%) α:β = 15:85		
 **9**	 **33** (29%)	 **34a**[d] R = ····H (9%) **34b** R = ◀H (52%)	 **35**[d] (7%)
 **10**	 **36**[e] (29%)		 **37**[e] (54%)
 **11**	 **38a, 38b** (75%) Z:E = 59:41		
 **12**			 **39** (100%)

a) The *cis*-relationship between ester and angular hydrogen in **22a** is uncertain. b) Compounds **23** and **24** formed an inseparable mixture. c) Compounds **25a-c** formed an inseparable mixture. d) Compounds **34a** and **35** formed an inseparable mixture. e) Compounds **36** and **37** formed an inseparable mixture; compound **36** was obtained pure after epoxidation of **37** (see text).

The stereochemistry of the proline analogues **20**, **22**, **27**, **30**, **31** and **32**[17d,e] was derived from the relative chemical shifts of the C-2 hydrogens in the *cis*- and *trans*-isomers.[23] In the *cis*-isomers this hydrogen was found at 4.25-4.5 ppm, whereas it resonated at 3.8-4.15 ppm in the *trans*-isomers. A second assignment tool for 3-methylproline esters is the chemical shift of the C-3 methyl group, which in the *cis*-isomers is found at 0.15-0.25 ppm higher field than in the *trans*-isomers.[23] Comparison with literature data on the *N*-acetyl analogue of **20**[23] and the *N*-Boc analogue of **30**[17b] confirmed the assignments of *cis* and *trans* in these cases.

The bicyclic system **22** posed an additional problem. While the *cis/trans* relationships between ester and methyl substituents are certain in both isomers, the orientation of the angular hydrogen in **22a** remains tentative. The structures of the inseparable pyrrolidines **25a**,[16b] **25b** and **25c** (ratio 17:17:66 according to ^{13}C NMR) obtained from precursor **3** could not be fully assigned. The structure of the preponderant isomer was based on the chemical shift of the C-3 methyl hydrogens at 1.13 ppm. All other methyl groups in the mixture of isomers absorbed at higher field (<1.00 ppm). The structures of both isomers of **38** were assigned by using NOE-difference ^1H NMR.

Table 2. Selected ^1H NMR Data for the Radical Cyclization Products.

compound	δ ($NCHCO_2$)[a,b]	pattern	other chemical shifts
20a	4.23, 4.28	d, J = 8.4, 8.5 Hz	0.97 (d, J = 6.9 Hz, CH_3)
20b	3.80, 3.87	d, J = 5.9, 5.7 Hz	1.14 (d, J = 6.8 Hz, CH_3)
21	4.80, 4.91	s	3.90-4.15 (m, H-6_{eq}), 2.80-3.10 (m, H-6_{ax})
22a	4.52	d, J = 8.1 Hz	1.00 (d, J = 7.2 Hz, CH_3)
22b	3.91	d, J = 8.1 Hz	1.25 (d, J = 8.1 Hz, CH_3)
23	4.96	d, J = 4.5 Hz	3.38-3.55 (m, H-8a)
25c	obscured		1.13 (d, J = 6.1 Hz, CH_3)
26a	4.77, 4.93	d, J = 5.2, 5.7 Hz	3.80-4.15 (m, H-6_{eq}), 2.40-2.65 (m, H-6_{ax})
27a	4.33, 4.39	d, J = 9.0, 9.0 Hz	0.84 (d, J = 7.3 Hz, CH_3)
27b	3.84, 3.90	d, J = 10.0, 10.8 Hz	0.98 (d, J = 7.0 Hz, CH_3)
28	4.76, 4.94	d, J = 4.9, 4.9 Hz	3.93, 4.10 (d, J = 13.6 Hz, H-1_{eq}), 2.54, 2.63 (d, J = 13.6 Hz, H-1_{ax})
30a	4.26, 4.33	d, J = 8.2, 8.3 Hz	-
30b	3.89, 3.96	d, J = 5.2, 5.2 Hz	-
31a	4.42, 4.46	bs	-
31b	4.08, 4.15	bs	-
32a	4.31, 4.37	d, J = 7.3, 6.8 Hz	-
32b	4.01, 4.10	d, J = 4.3, 4.7 Hz	-
33	3.99, 4.08	s	-
34a	4.50, 4.67	bs	3.90-4.20 (m, H-3_{eq}), 2.85-3.15 (m, H-3_{ax})
34b	4.60, 4.73	bs	3.85-4.15 (m, H-3_{eq}), 3.25-3.50 (m, H-3_{ax})
36	4.58, 4.72	s	3.87, 3.99 (d, J = 12.9 Hz, H-4_{endo}), 3.25-3.45 (m, H-4_{exo})
38a	4.86, 4.93	s	1.74 (dd, J = 6.9, 2.1 Hz, CH_3), 5.45-5.60 (m, =CH)
38b	4.68, 4.74	s	1.63 (dq, J = 6.9, 1.5 Hz, CH_3), 5.60-5.80 (m, =CH)

a) In $CDCl_3$ at ambient temperature. b) The carbamates showed two signals for this hydrogen due to rotamers.

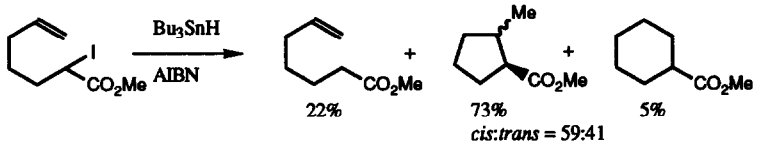
The stereochemical assignment of the piperidines formed is based on a combination of NMR data and mechanistic reasoning (*vide infra*). The *cis*-relationship between the angular hydrogen and the ester function in **23** was proved by using NOE-difference ^1H NMR. The structures of **26a** and **26b** were based on the ^{13}C NMR chemical shift of the C-5 methyl substituent, which was 23.3 ppm in **26a** (equatorial CH_3) and 18.9 ppm in **26b** (axial CH_3).[24] The structures of bicyclic systems **34a** and **34b** were tentatively assigned on the basis of literature analogy[25] and mechanistic considerations.

DISCUSSION

Regiochemistry of the 2-aza-5-hexenyl cyclizations

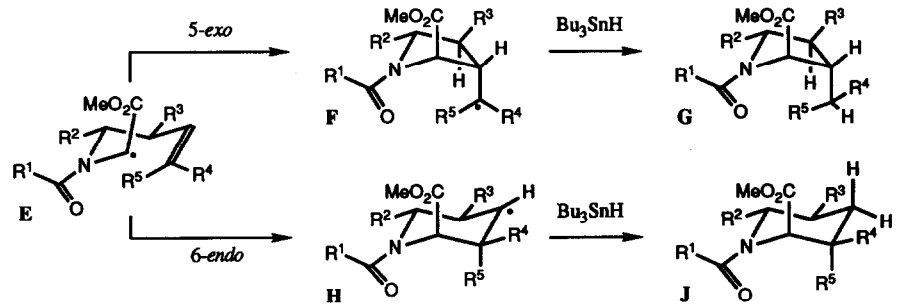
The cyclization of the parent glycine radical generated from **1** proceeds with a 5-*exo*/6-*endo* ratio of 67:33. This ratio is considerably lower than the 98:2 ratio found for the parent 5-hexenyl radical.[26] Curran and Chang reported for the 1-methoxycarbonyl-5-hexenyl radical (eq 6) a 5-*exo*/6-*endo* ratio of 93:7.[27] The further difference in regioselectivity must be ascribed to the presence of the NCO_2Me moiety, which apparently influences the geometry in such a way that the 6-*endo* pathway becomes more competitive. An important factor might be the C-N-C angle of the chain of ca. 120° as opposed to a C-C-C angle of 109° in the all-carbon system.

Furthermore, the conformational freedom of the chain might be somewhat reduced due to remaining orbital overlap between nitrogen and the radical center in the transition state of cyclization.[27] The result of cyclization of pyrrolidone **2** shows the well-known effect of an existing ring on the regioselectivity. The different bond angles imposed by the pyrrolidinone ring lead to a reduction of the 5-*exo*/6-*endo* ratio to 14:86. The groups of Bachi and Hart have reported early examples of this fused ring-effect.[6a-c,7] Introduction of substituents at C-4 of the cyclizing 2-aza-5-hexenyl radical also leads to a lower 5-*exo*/6-*endo* ratio, viz. ca. 54:46 for both the methyl-substituted **3** and the spiro system **4**. Increased steric hindrance for 5-*exo* cyclization probably plays a role here.



(eq 6)

Electronically unbiased 1,2-disubstituted alkenes **5-8** undergo exclusive 5-*exo* cyclization in excellent yields. The geometry of the double bond (*E* in **5** and *Z* in **6**) appears inconsequential for the result, as is the ring size in **7** and **8**. Similar cyclizations as those of **7** and **8** to bicyclic systems have been reported frequently.[28] The trisubstituted olefin **9** cyclizes in a 5-*exo*/6-*endo* ratio of 32:68. Cyclization of the 4-(1-cyclohexenyl)butyl radical, which is the all-carbon analogue of **9** was reported to give a 56:44 ratio of 5-*exo*/6-*endo* cyclization.[25] So, here again the carbamate system shows a moderate shift to 6-*endo* cyclization, compared to the all-carbon system.

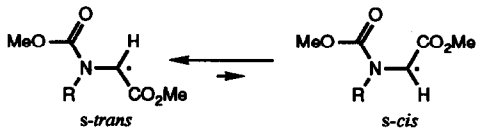


Scheme 1. Stereochemical course of 5-*exo* and 6-*endo* cyclization.

Stereochemistry of the 2-aza-5-hexenyl cyclizations

The stereochemical course of the 2-aza-5-hexenyl cyclizations (precursors **1-8**) shows a small to moderate preference for the *trans*-products in all cases. This result is in agreement with the rules advanced by Beckwith and coworkers,[25,29] if one assumes as the most favorable situation a quasi-axial orientation for the ester substitutent in a chair-like transition state of cyclization. This quasi-axial orientation of the ester function corresponds with an s-*trans* conformation about the •C-N bond of the glycine radical (eq 7).[14] Scheme 1 shows the most favorable radical conformation **E**, leading to both 5-*exo* and 6-*endo* cyclization, which explains the stereochemistry of the major 5- and 6-membered ring products **G** and **J**, respectively, from precursors **1-9**. The transition state structures leading to the minor *cis*-3-substituted proline analogues may contain either a boat-like arrangement or an s-*cis* radical •C-N bond conformation (eq 7). Further research is needed to resolve this point. Nevertheless, our results nicely accommodate the Beckwith rules with the key difference that due to the pseudo-allylic 1,3-strain caused by the *N*-carbonyl function the ester group assumes an axial orientation. The

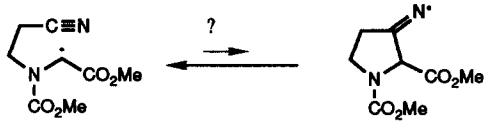
corresponding cyclizations to the oxygen heterocycles (O instead of NCOR) mainly give *cis*-products as expected.[30]



(eq 7)

Other cyclizations

The cyclization of the 2-aza-6-heptenyl radical from **10** is expected to be much slower than the previous cyclizations.[31] This is borne out by experiment as besides the expected 6-*exo* cyclization product **36** the premature reduction product **37** is the major product. The cyclization of the 2-aza-5-hexynyl radical, generated from **11** leads exclusively to the 5-*exo* product **38** as expected from literature precedent.[32] Finally, the nitrile **12** does not lead to a cyclization product after radical generation, but instead the starting radical is quantitatively reduced. Perhaps cyclization of the incipient radical to the iminyl radical is so slow that only premature reduction occurs. Alternatively there could be a highly unfavorable equilibrium (eq 8). Nitriles are known to be not as reactive as alkenes and alkynes in radical cyclizations.[33]



(eq 8)

Conclusions

Cyclizations of 1,2-di(methoxycarbonyl)-2-aza-5-hexenyl radicals proceed with a somewhat lower 5-*exo*/6-*endo* ratio than the corresponding 5-hexenyl radicals. The preference for five-membered ring formation, however, is still considerable. Thus, despite the captodative character of these glycine derived radicals, tin hydride mediated olefin cyclization is a synthetically useful route to various new proline analogues. The preparative relevance of glycine radicals has recently been further enhanced by applying the atom transfer cyclization method, details of which will be reported in due course.[34]

EXPERIMENTAL

General information. Tributyltin hydride was purchased from Aldrich and AIBN from Fluka. Toluene was distilled from sodium and stored on sodium wire. For further general information see ref 4a. **General procedures A-G** are described in ref 4a. **General procedure H.** (eq 3) is as follows: To a solution of the acetoxy compound in thiophenol was added TsOH monohydrate (ca. 0.1 equiv) and the reaction mixture was stirred for 18-24 h at rt. The reaction mixture was taken up in CH_2Cl_2 and washed with cold (0 °C) aq 1 N NaOH (50 mL on 1 mL of thiophenol). The aq layer was washed (2 ×) with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed.

[*N*-(3-Butenyl)-*N*-(ethoxycarbonyl)amino](phenylthio)acetic acid methyl ester (1). According to procedure H, acetoxy[*N*-(3-butenyl)-*N*-(ethoxycarbonyl)amino]acetic acid methyl ester[4a] (279 mg, 1.02 mmol) was stirred in 2 mL of thiophenol with TsOH monohydrate (18 mg, 0.095 mmol) to give **1** (178 mg, 0.549 mmol, 54%) as a colorless oil. R_f 0.51 (EtOAc/hexanes: 1/4). IR 1740 (C=O), 1690 (NC=O). ^{1}H NMR (200 MHz) 0.95-1.30 (bm, 3 H, CH_2CH_3), 2.15-2.50 (m, 2 H), 3.10-3.40 (m, 1 H, NCH), 3.40-3.60 (m, 1 H, NCH), 3.79 (s, 3 H, OCH_3), 3.75-4.20 (bm, 2 H, OCH_2), 4.95-5.15 (m, 2 H, $=CH_2$), 5.60-5.85 (m, 1 H, -CH=), 5.96 (bs) and 6.28 (bs, two rotamers, 1 H, NCHS), 7.25-7.35 (m, 3 H) and 7.45-7.55 (m, 2 H, SC_6H_5).

2-Oxo-α-(phenylthio)-5-(2-propenyl)-pyrrolidineacetic acid methyl ester (2). According to procedure H, α-

acetoxy-2-oxo-5-(2-propenyl)-pyrrolidineacetic acid methyl ester[4a] (362 mg, 1.42 mmol) was stirred in 4 mL of thiophenol with TsOH monohydrate (15 mg, 0.075 mmol) to give **2** (129 mg, 0.424 mmol, 30%) as a colorless oil. R_f 0.35 (EtOAc/hexanes: 1/6). IR 1740 (C=O), 1685 (NC=O). ^{1}H NMR (250 MHz, mixture of diastereoisomers) 1.55-2.50 (m, 5 H), 2.55-2.70 and 2.80-2.95 (m, 1 H), 3.60-3.75 and 3.85-4.00 (m, 1 H, NC*H*CH_2), 3.77 (s, 3 H, OCH_3), 5.00-5.15 (m, 2 H, =CH_2), 5.55-5.80 (m, 1 H, -CH=), 5.91 and 6.41 (s, 1 H, NCHS), 7.15-7.40 (m, 3 H) and 7.50-7.60 (m, 2 H, SC_6H_5).

[*N*-(2-Methyl-3-butenyl)-*N*-(methoxycarbonyl)amino](phenylthio)acetic acid dimethyl ester (3). According to procedure H, acetoxy[*N*-(2-methyl-3-butenyl)-*N*-(methoxycarbonyl)amino]acetic acid dimethyl ester[4a] (301.1 mg, 1.103 mmol) was treated in 4 mL of thiophenol with TsOH monohydrate (25 mg, 0.13 mmol) to give **3** (253.0 mg, 0.760 mmol, 69%) as a colorless oil. R_f 0.45 (EtOAc/hexanes: 1/4). IR 1740 (C=O), 1700 (NC=O). ^{1}H NMR (200 MHz, mixture of diastereoisomers) 0.93 (d) and 0.96 (d, J = 6.6 Hz, 3 H, C*H*$_3$CH), 2.45 (quintet, J = 7.2 Hz, 1 H, CH_3CH), 3.00-3.75 (m, 5 H, OCH_3 + NCH_2), 3.76 (s, 3 H, OCH_3), 4.85-5.00 (m, 2 H, =CH_2), 5.50-5.80 (m, 1 H, -CH=), 5.84 (bs, 1 H, NCHS), 7.25-7.35 (m, 3 H) and 7.40-7.55 (m, 2 H, SC_6H_5).

[*N*-((1-Vinyl-1-cyclohexyl)methyl)-*N*-(methoxycarbonyl)amino](phenylthio)acetic acid methyl ester (4). According to general procedure A, methyl *N*-(acetoxymethyl)carbamate **16** (465 mg, 3.16 mmol) was treated with (2-(trimethylsilyl)ethylidene)cyclohexane **13**[19] (699 mg, 3.84 mmol) and BF_3•OEt_2 (0.8 mL, 6.50 mmol) in 10 mL of CH_2Cl_2 to give methyl *N*-((1-vinyl-1-cyclohexyl)methyl)carbamate **17** (384 mg, 1.95 mmol, 62%) as a colorless oil. R_f 0.38 (EtOAc/hexanes: 1/5). IR 3440 (NH), 1710 (NC=O). ^{1}H NMR (250 MHz) 1.10-1.60 (m, 10H), 2.95-3.05 (m, 2 H, CH_2N), 3.63 (s, 3 H, OCH_3), 4.60 (bs, 1 H, NH), 4.95-5.05 (m) and 5.10-5.20 (m, two rotamers, 2 H, =CH_2), 5.40-5.60 (m, 1 H, -CH=). According to general procedure F, **17** (370 mg, 1.88 mmol) was treated with methyl glyoxylate hydrate (1.2 g, 13.6 mmol) in 20 mL benzene to give [*N*-((1-vinyl-1-cyclohexyl)methyl)-*N*-(methoxycarbonyl)amino](hydroxy)acetic acid methyl ester (337 mg, 1.18 mmol, 63%) as a colorless oil. R_f 0.32 (EtOAc/hexanes: 1/2). IR 3530 (OH), 1750 (C=O), 1685 (NC=O). ^{1}H NMR (250 MHz, mixture of diastereoisomers) 1.10-1.75 (m, 10 H), 3.10-3.40 (m, 2 H, CH_2N), 3.66 (s, 3 H, OCH_3), 3.77 (s, 3 H, OCH_3), 4.20 (bs, 1 H, OH), 4.85 (bs, 1 H, NCHO), 5.00-5.30 (m, 2 H, =CH_2), 5.60-5.75 (m, 1 H, -CH=). According to general procedure G, the glyoxylate adduct (323 mg, 1.13 mmol) was treated with acetic anhydride (1.25 mL, 1.16 mmol) in 10 mL pyridine to give acetoxy[*N*-((1-vinyl-1-cyclohexyl)methyl)-*N*-(methoxycarbonyl)amino]acetic acid methyl ester (304 mg, 0.932 mmol, 83%) as a colorless oil. R_f 0.48 (EtOAc/hexanes: 1/4). IR 1740 and 1705 (3 × C=O). ^{1}H NMR (200 MHz, mixture of diastereoisomers) 1.10-1.75 (m, 10 H), 2.16 (s, 3 H, C=OCH_3), 3.00-3.15 (m, 1 H, CHN), 3.35-3.55 (m, 1 H, CHN), 3.70 (s, 3 H, OCH_3), 3.77 (s, 3 H, OCH_3), 5.00-5.25 (m, 2 H, =CH_2), 5.55-5.75 (m, 1 H, -CH=) 6.15 (bs, 1 H, NCHO). According to procedure H, the acetoxy compound (259 mg, 0.791 mmol) was stirred in 4 mL of thiophenol with TsOH monohydrate (15 mg, 0.075 mmol) to give **4** (218 mg, 0.576 mmol, 73%) as a colorless oil. R_f 0.35 (EtOAc/hexanes: 1/6). IR 1740 (C=O), 1700 (NC=O). ^{1}H NMR (200 MHz) 1.10-1.70 (m, 10 H), 2.50-2.75 (m, 1 H, CHN), 3.20-3.60 (m, 1 H, CHN), 3.68 (s, 3 H, OCH_3), 3.80 (s, 3 H, OCH_3), 4.70-5.00 (m, 2 H, =CH_2), 5.15 (s, 1 H, NCHS), 5.50-5.70 (m, 1 H, -CH=), 7.20-7.40 (m, 3 H) and 7.45-7.60 (m, 2 H, SC_6H_5).

[*N*-((*E*)-3-Hexenyl)-*N*-(methoxycarbonyl)amino](phenylthio)acetic acid methyl ester (5). According to procedure H, acetoxy[*N*-((*E*)-3-hexenyl)-*N*-(methoxycarbonyl)amino]acetic acid methyl ester[4a] (343 mg, 1.20 mmol) was stirred in 3 mL of thiophenol with TsOH monohydrate (25 mg, 0.13 mmol) to give **5** (125 mg, 0.371 mmol, 31%) as a colorless oil. R_f 0.60 (EtOAc/hexanes: 1/2). IR 1740 (C=O), 1695 (NC=O). ^{1}H NMR (200 MHz) 0.95 (t, J = 7.5 Hz, 3 H, CH_3), 1.98 (quintet, J = 7.2 Hz, 2 H, CH_2CH_3), 2.15-2.45 (m, 2 H, NCH_2CH_2), 3.15-3.85 (m, 8 H, 2 × OCH_3 + CH_2N), 5.20-5.60 (m, 2 H, CH=CH), 5.99 (bs) and 6.24 (bs, two rotamers, 1 H, NCHS), 7.20-7.35 (m, 3 H) and 7.45-7.55 (m, 2 H, SC_6H_5).

[*N*-((*Z*)-3-Hexenyl)-*N*-(methoxycarbonyl)amino](phenylthio)acetic acid methyl ester (6). According to procedure H, acetoxy[*N*-((*Z*)-3-hexenyl)-*N*-(methoxycarbonyl)amino]acetic acid methyl ester[4a] (849 mg, 2.96 mmol) was stirred in 3 mL of thiophenol with TsOH monohydrate (25 mg, 0.13 mmol) to give **6** (464 mg, 1.38 mmol, 47%) as a colorless oil. R_f 0.63 (EtOAc/hexanes: 1/2). IR 1740 (C=O), 1700 (NC=O). ^{1}H NMR (200 MHz) 0.95 (t, J = 7.4 Hz, 3 H, CH_2CH_3), 1.90-2.45 (m, 4 H), 3.10-3.55 (m, 5 H, CH_2N + OCH_3), 3.79 (s, 3 H, OCH_3), 5.25-5.55 (m, 2 H, CH=CH), 5.99 (bs) and 6.25 (bs, two rotamers, 1 H, NCHS), 7.20-7.35 (m, 3 H) and 7.45-7.55 (m, 2 H, SC_6H_5).

[*N*-((2-Cyclopenten-1-yl)methyl)-*N*-(methoxycarbonyl)amino](phenylthio)acetic acid methyl ester (7). According to general procedure A, methyl *N*-(acetoxymethyl)carbamate **16** (968 mg, 6.58 mmol) was treated with 3-

trimethylsilylcyclopentene **14**[20] (1.33 mL, 7.90 mmol) and BF_3•OEt_2 (1.5 mL, 12.2 mmol) in 10 mL of CH_2Cl_2 to give methyl *N*-(2-cyclopenten-1-ylmethyl)carbamate **18** (693 mg, 4.47 mmol, 68%) as a colorless oil. R_f 0.45 (EtOAc/hexanes: 1/4). IR 3460 (NH), 1705 (NC=O). ^{1}H NMR (250 MHz) 1.40-1.55 (m, 1 H), 1.90-2.05 (m, 1 H), 2.20-2.40 (m, 2 H), 2.75-2.95 (m, 1 H), 3.00-3.20 (m, 2 H), 3.63 (s, 3 H, OCH_3), 4.71 (bs, 1 H, NH), 5.50-5.60 (m, 1 H, -CH=), 5.70-5.80 (m, 1 H, -CH=). According to general procedure F, **18** (690 mg, 4.45 mmol) was treated with methyl glyoxylate hydrate (2.3 g, 26 mmol) in 15 mL of benzene to give [*N*-((2-cyclopenten-1-yl)methyl)-*N*-(methoxycarbonyl)amino](hydroxy)acetic acid methyl ester (541 mg, 2.23 mmol, 50%) as a colorless oil. R_f 0.28 (EtOAc/hexanes: 1/2). IR 3530 (OH), 1745 (C=O), 1690 (NC=O). ^{1}H NMR (250 MHz, mixture of diastereoisomers) 1.40-1.55 (m, 1 H), 1.90-2.05 (m, 1 H), 2.20-2.40 (m, 2 H), 2.90-3.05 (m, 1 H), 3.15-3.35 (m, 2 H), 3.68 (s, 3 H, OCH_3), 3.78 (s, 3 H, OCH_3), 4.21 (bs, 1 H, OH), 5.03 (bs, 1 H, C*H*OH), 5.60-5.80 (m, 2 H, CH=CH). According to general procedure G, the glyoxylate adduct (482 mg, 1.98 mmol) was treated with acetic anhydride (0.22 mL, 2.40 mmol) in 15 mL pyridine to give acetoxy[*N*-((2-cyclopenten-1-yl)methyl)-*N*-(methoxycarbonyl)amino]acetic acid methyl ester (545 mg, 1.91 mmol, 96%) as colorless oil. R_f 0.43 (EtOAc/hexanes: 1/2). IR 1740 and 1710 (3 × C=O). ^{1}H NMR (250 MHz, mixture of diastereoisomers) 1.35-1.55 (m, 1 H), 1.85-2.05 (m, 1 H), 2.14 (s, 3 H, C=OCH_3), 2.15-2.40 (m, 2 H), 2.90-3.05 (m, 1 H), 3.05-3.15 (m, 1 H, CHN), 3.35-3.50 (m, 1 H, CHN), 3.72 (s, 3 H, OCH_3), 3.76 (s, 3 H, OCH_3), 5.55-5.80 (m, 2 H, CH=CH), 6.33 (bs) and 6.39 (bs, 1 H, NCHO). According to procedure H, the acetoxy compound (498 mg, 1.75 mmol) was stirred in 4 mL of thiophenol with TsOH monohydrate (20 mg, 0.10 mmol) to give **7** (359 mg, 1.07 mmol, 61%) as a colorless oil. R_f 0.40 (EtOAc/hexanes: 1/4). IR 1745 (C=O), 1700 (NC=O). ^{1}H NMR (250 MHz, mixture of diastereoisomers) 1.30-1.55 (m, 1 H), 1.85-2.00 (m, 1 H), 2.10-2.40 (m, 2 H), 2.80-3.15 (m, 2 H), 3.35-3.70 (m, 4 H, NCH + OCH_3), 3.77 (s, 3 H, OCH_3), 5.50-5.70 (m, 2 H, CH=CH), 5.83 (bs, 1 H, NCHS), 7.20-7.30 (m, 3 H) and 7.40-7.50 (m, 2 H, SC_6H_5).

[*N*-((2-Cyclohexen-1-yl)methyl)-*N*-(methoxycarbonyl)amino](phenylthio)acetic acid methyl ester (8). According to general procedure A, methyl *N*-(acetoxymethyl)carbamate **16** (2.16 g, 14.7 mmol) was treated with 3-trimethylsilylcyclohexene **15**[20] (2.70 g, 17.5 mmol) and BF_3•OEt_2 (2.50 mL, 20.3 mmol) in 35 mL of CH_2Cl_2 to give methyl *N*-((2-cyclohexen-1-yl)methyl)carbamate **19** (1.94 g, 11.5 mmol, 78%) as a colorless oil. R_f 0.45 (EtOAc/hexanes: 1/4). IR 3300 (NH), 1730 (NC=O). ^{1}H NMR (200 MHz) 1.15-1.85 (m, 4 H), 1.85-2.05 (m, 2 H), 2.15-2.40 (m, 1 H), 2.95-3.30 (m, 2 H, CH_2N), 3.65 (s, 3 H, OCH_3), 4.81 (bs, 1 H, NH), 5.51 (dd, J = 10.1, 1.9 Hz, 1 H, =C*H*CH), 5.70-5.85 (m, 1 H, CH_2CH=). According to general procedure F, **19** (1.05 g, 6.21 mmol) was treated with methyl glyoxylate hydrate (5.3 g, 61.2 mmol) in 80 mL of benzene to give [*N*-((2-cyclohexen-1-yl)methyl)-*N*-(methoxycarbonyl)amino](hydroxy)acetic acid methyl ester (1.08 g, 4.20 mmol, 68%) as a colorless oil. R_f 0.38 (EtOAc/hexanes: 1/2). IR 3530 (OH), 1745 (C=O), 1690 (NC=O). ^{1}H NMR (200 MHz, mixture of diastereoisomers) 1.20-1.90 (m, 4 H), 1.90-2.10 (m, 2 H), 2.35-2.55 (m, 1 H), 3.15-3.40 (m, 2 H, NCH_2), 3.71 (s, 3 H, OCH_3), 3.81 (s, 3 H, OCH_3), 4.10 (bs, 1 H, OH), 4.85-5.20 (m, 1 H, NCHO), 5.50-5.65 (m, 1 H, =C*H*CH), 5.70-5.85 (m, 1 H, CH_2CH=). According to general procedure G, the glyoxylate adduct (1.05 g, 4.09 mmol) was treated with acetic anhydride (0.55 mL, 5.83 mmol) in 10 mL of pyridine to give acetoxy[*N*-((2-cyclohexen-1-yl)methyl)-*N*-(methoxycarbonyl)amino]acetic acid methyl ester (1.00 g, 3.34 mmol, 82%) as colorless oil. R_f 0.34 (EtOAc/hexanes: 1/4). IR 1750, 1715 (3 × C=O). ^{1}H NMR (200 MHz, mixture of diastereoisomers) 1.20-1.90 (m, 4 H), 1.90-2.05 (m, 2 H), 2.17 (s, 3 H, C=OCH_3), 2.30-2.55 (m, 1 H), 3.05-3.20 (m, 1 H, NCH), 3.35-3.50 (m, 1 H, NCH), 3.74 (s, 3 H, OCH_3), 3.79 (s, 3 H, OCH_3), 5.45-5.60 (m, 1 H, =C*H*CH), 5.70-5.85 (m, 1 H, CH_2CH=), 6.25-6.40 (m, 1 H, NCHO). According to procedure H, the acetoxy compound (0.524 g, 1.75 mmol) was stirred in 8 mL of thiophenol with TsOH monohydrate (24 mg, 0.12 mmol) to give **8** (596 mg, 1.71 mmol, 98%) as a colorless oil. R_f 0.43 (EtOAc/hexanes: 1/4). IR 1740 (C=O), 1700 (NC=O). ^{1}H NMR (200 MHz, mixture of diastereoisomers) 1.20-1.80 (m, 4 H), 1.90-2.05 (m, 2 H), 2.20-2.45 (m, 1 H), 2.95-3.75 (m, 5 H, CH_2N + OCH_3), 3.79 (s, 3 H, OCH_3), 5.40-5.60 (m, 1 H, =C*H*CH), 5.65-5.90 (m, 2 H, CH_2CH= + NCHS), 7.25-7.35 (m, 3 H) and 7.45-7.60 (m, 2 H, C_6H_5S).

[*N*-(2-(1-Cyclohexen-1-yl)ethyl)-*N*-(methoxycarbonyl)amino](phenylthio)acetic acid methyl ester (9). According to general procedure E, 2-(1-cyclohexen-1-yl)ethylamine (Aldrich, 10 mL, 71.7 mmol) was treated with Et_3N (11.0 mL, 78.9 mmol) and methyl chloroformate (6.7 mL, 86.7 mmol) in 100 mL of CH_2Cl_2 to give methyl *N*-(2-(1-cyclohexen-1-yl)ethyl)carbamate (13.0 g, 71.0 mmol, 99%) as a light yellow oil. IR 3450 (NH), 1710 (NC=O). ^{1}H NMR (200 MHz) 1.50-1.70 (m, 4 H), 1.80-2.20 (m, 6 H), 3.24 (bq, J = 6.2 Hz, 2 H, CH_2N), 3.65 (s, 3 H, OCH_3), 4.66 (bs, 1 H, NH), 5.45 (bs, 1 H, -CH=). According to general procedure F, methyl *N*-(2-(1-cyclohexen-1-yl)ethyl)carbamate (1.6 g, 8.7 mmol) was treated with methyl

glyoxylate hydrate (5.1 g, 58 mmol) in 70 mL of benzene to give [*N*-(2-(1-cyclohexen-1-yl)ethyl)-*N*-(methoxycarbonyl)amino]-(hydroxy)acetic acid methyl ester (2.26 g, 8.34 mmol, 96%) as a colorless oil. R_f 0.45 (EtOAc/hexanes: 1/2). IR 3530 (OH), 1745 (C=O), 1700 (NC=O). ^{1}H NMR (200 MHz) 1.50-1.70 (m, 4 H), 1.58 (bs, 1 H, OH), 1.90-2.10 (m, 4 H), 2.20-2.40 (m, 2 H), 3.35 (t, J = 4.0 Hz, 2 H, CH_2N), 3.72 (s, 3 H, OCH_3), 3.81 (s, 3 H, OCH_3), 5.22 (bs, 1 H, NCHO), 5.45 (bs, 1 H, -CH=). According to general procedure G, the glyoxylate adduct (1.91 g, 7.05 mmol) was treated with acetic anhydride (0.80 mL, 8.3 mmol) and DMAP (40 mg, 0.33 mmol) in 20 mL of pyridine to give acetoxy[*N*-(2-(1-cyclohexen-1-yl)ethyl)-*N*-(methoxycarbonyl)amino]acetic acid methyl ester (1.98 g, 3.63 mmol, 90%) as a colorless oil. R_f 0.40 (EtOAc/hexanes: 1/2). IR 1740 and 1710 (3 × C=O). ^{1}H NMR (200 MHz) 1.45-1.70 (m, 4 H), 1.90-2.05 (m, 4 H), 2.17 (s, 3 H, C=OCH_3), 2.10-2.30 (m, 2 H), 3.15-3.35 (m, 1 H, NC*H*CH_2), 3.35-3.55 (m, 1 H, NC*H*CH_2), 3.75 (s, 3 H, OCH_3), 3.79 (s, 3 H, OCH_3), 5.44 (bs, 1 H, -CH=), 6.50 (bs, NCHO). According to procedure H, the acetoxy compound (304 mg, 0.973 mmol) was stirred in 4 mL of thiophenol with TsOH monohydrate (25 mg, 0.13 mmol) to give **9** (226 mg, 0.623 mmol, 64%) as a colorless oil. R_f 0.67 (EtOAc/hexanes: 1/4). IR 1740 (C=O), 1700 (NC=O). ^{1}H NMR (200 MHz) 1.30-2.30 (m, 10 H), 3.15-3.75 (m, 5 H, CH_2N + OCH_3), 3.79 (s, 3 H, OCH_3), 5.42 (bs, 1 H, -CH=), 5.99 and 6.25 (bs, two rotamers, 1 H, NCHS), 7.15-7.40 (3 H) and 7.40-7.60 (m, 2 H, C_6H_5S).

[*N*-((3-Cyclohexen-1-yl)methyl)-*N*-(methoxycarbonyl)amino](phenylthio)acetic acid methyl ester (10). According to general procedure B, 3-cyclohexene-1-methanol (Aldrich, 10.0 mL, 85.7 mmol) was treated with Et_3N (12.0 mL, 86.1 mmol) and mesyl chloride (7.0 mL, 90.4 mmol) in 120 mL of CH_2Cl_2 to give 3-cyclohexene-1-methanol methanesulfonate (16.3 g, 85.7 mmol, 100 %) as a light yellow oil. IR 1350 and 1175 (SO_3). ^{1}H NMR (200 MHz) 1.25-1.50 (m, 1 H), 1.65-2.30 (m, 6 H), 2.99 (s, 3 H, SO_2CH_3), 4.09 (d, J = 6.3 Hz, 2 H, CH_2O), 5.55-5.80 (m, 2 H, CH=CH). According to general procedure C, 3-cyclohexene-1-methanol methanesulfonate (16.3 g, 85.7 mmol) was treated with NaN_3 (45.0 g, 692 mmol) in 200 mL of DMF to give 4-(azidomethyl)-1-cyclohexene (11.5 g, 84.0 mmol, 98%) as a light yellow oil. IR 2090 (N_3). ^{1}H NMR (200 MHz) 1.20-1.45 (m, 1 H), 1.65 -2.25 (m, 6 H), 3.21 (d, J = 6.4 Hz, 2 H, CH_2N_3), 5.55-5.75 (m, 2 H, CH=CH). According to general procedure D, 4-(azidomethyl)-1-cyclohexene (11.5 g, 84.0 mmol) was treated with triphenylphospine (22.6 g, 86.3 mmol) and water (4.7 mL, 261 mmol) in 250 mL of THF to give 3-cyclohexene-1-methanamine (6.82 g, 61.4 mmol, 73%) as a colorless liquid, bp 90-92 ^{o}C/20 mmHg. IR 3380 (s) and 3200 (b, NH_2). ^{1}H NMR (250 MHz) 1.15-1.30 (m, 1 H), 1.62 (bs, 2 H, NH_2), 1.50-2.20 (m, 6 H), 2.59 (d, J = 6.2 Hz, 2 H, CH_2N), 5.55-5.70 (m, 2 H, CH=CH). According to general procedure E, 3-cyclohexene-1-methanamine (6.8 g, 61.3 mmol) was treated with Et_3N (9.4 mL, 67.4 mmol) and methyl chloroformate (5.2 mL, 67.3 mmol) in 80 mL of CH_2Cl_2 to give methyl *N*-[(3-cyclohexen-1-yl)methyl]carbamate (10.1 g, 59.8 mmol, 97%) as a colorless oil. IR 3460 (NH), 1720 (C=O). ^{1}H NMR (200 MHz) 1.15-1.40 (m, 1 H), 1.60-1.85 (m, 3 H), 1.95-2.20 (m, 3 H), 3.00-3.20 (m, 2 H, CH_2N), 3.66 (s, 3 H, OCH_3), 4.76 (bs, 1 H, NH), 5.55-5.75 (m, 2 H, CH=CH). According to general procedure F, methyl *N*-[(3-cyclohexen-1-yl)methyl]carbamate (1.22 g, 7.22 mmol) was treated with methyl glyoxylate hydrate (4.8 g, 55 mmol) in 70 mL of benzene to give [*N*-((3-cyclohexen-1-yl)methyl)-*N*-(methoxycarbonyl)amino](hydroxy)acetic acid methyl ester (1.09 g, 4.24 mmol, 59%) as a colorless oil. R_f 0.45 (EtOAc/hexanes: 1/2). IR 3550 (OH), 1750 (C=O), 1695 (NC=O). ^{1}H NMR (250 MHz, mixture of diastereoisomers) 1.15-1.35 (m, 1 H), 1.55-2.20 (m, 6 H), 3.27 (d, J = 7.2 Hz, 2 H, CH_2N), 3.69 (s, 3 H, OCH_3), 3.79 (s, 3 H, OCH_3), 4.20 (bs, 1 H, OH), 4.99 (bs, 1 H, NCHO), 5.55-5.75 (m, 2 H, CH=CH). According to general procedure G, the glyoxylate adduct (0.876 g, 3.41 mmol) was treated with acetic anhydride (0.40 mL, 4.2 mmol) and DMAP (40 mg, 0.33 mmol) in 10 mL of pyridine to give acetoxy[*N*-((3-cyclohexen-1-yl)methyl)-*N*-(methoxycarbonyl)amino]acetic acid methyl ester (0.920 g, 3.08 mmol, 90%) as a colorless oil. R_f 0.53 (EtOAc/hexanes: 1/4). IR 1745 and 1710 (3 × C=O). ^{1}H NMR (200 MHz, mixture of diastereoisomers) 1.10-1.35 (m, 1 H), 1.55-2.10 (m, 6 H), 2.15 (s, 3 H, C=OCH_3), 3.00-3.15 (m, 1 H, CHN), 3.30-3.45 (m, 1 H, CHN), 3.73 (s, 3 H, OCH_3), 3.77 (s, 3 H, OCH_3), 5.55-5.75 (m, 2 H, CH=CH), 6.36 (bs, 1 H, NCHO). According to procedure H, the acetoxy compound (333 mg, 1.11 mmol) was stirred in 4 mL of thiophenol with TsOH monohydrate (30 mg, 0.16 mmol) to give **10** (301 mg, 0.861 mmol, 77%) as a colorless oil. R_f 0.66 (EtOAc/hexanes: 1/4). IR 1740 (C=O), 1700 (NC=O). ^{1}H NMR (250 MHz, mixture of diastereoisomers) 1.10-1.30 (m, 1 H), 1.50-2.10 (m, 6 H), 2.95-3.20 (m, 1 H, CHN), 3.20-3.75 (m, 4 H, OCH_3 + NCH), 3.77 (s, 3 H, OCH_3), 5.50-5.70 (m, 2 H, CH=CH), 5.78 (bs, 1 H, NCHS), 7.15-7.35 (m, 3 H) and 7.35-7.55 (m, 2 H, SC_6H_5).

[*N*-(3-Pentynyl)-*N*-(methoxycarbonyl)amino](phenylthio)acetic acid methyl ester (11). According to general procedure B, 3-pentyn-1-ol (Aldrich, 15.3 g, 182 mmol) was treated with Et_3N (27 mL, 194 mmol) and mesyl chloride (15 mL, 194

mmol) in 150 mL of CH_2Cl_2 to give 3-pentyn-1-ol methanesulfonate (29.7 g, 183 mmol, quantitative yield) as a light yellow oil. IR 1355 and 1175 (SO_3). ^1H NMR (200 MHz) 1.75 (t, J = 2.5 Hz, 3 H, $\equiv CCH_3$), 2.56 (tq, J = 6.8, 2.5 Hz, 2 H, $CH_2C\equiv$), 3.02 (s, 3 H, SO_3CH_3), 4.23 (t, J = 6.8 Hz, 2 H, CH_2O). According to general procedure C, 3-pentyn-1-ol methanesulfonate (29.6 g, 183 mmol) was treated with NaN_3 (90 g, 1.38 mol) in 300 mL of DMF to give crude 5-azido-2-pentyne (19.8 g, 182 mmol, 99%) which was used in the next step. IR 2100 (N_3). ^1H NMR (200 MHz) 1.76 (t, J = 2.5 Hz, 3 H, $\equiv CCH_3$), 2.39 (tq, J = 6.8, 2.5 Hz, 2 H, $CH_2C\equiv$), 3.22 (t, J = 6.8 Hz, 2 H, CH_2N_3). According to general procedure D, crude 5-azido-2-pentyne was treated with triphenylphospine (49 g, 187 mmol) and water (10 mL, 0.56 mol) in 500 mL of THF to give the crude 3-pentyn-1-amine (5.3 g, 63.9 mmol) which was used in the next step. IR 3380 (s) and 3200 (b, NH_2). ^1H NMR (200 MHz) 1.74 (t, J = 2.5 Hz, 3 H, $\equiv CCH_3$), 2.20-2.35 (m, 2 H, $CH_2C\equiv$), 2.58 (t, J = 7.4 Hz, 2 H, CH_2N), 3.40 (bs, 2 H, NH_2). According to general procedure E, crude 3-pentyn-1-amine was treated with Et_3N (9.8 mL, 70 mmol) and methyl chloroformate (5.9 mL, 76 mmol) in 125 mL of CH_2Cl_2 to give methyl *N*-(3-pentynyl)carbamate (3.48 g, 24.7 mmol, 14% calculated on alcohol) as a colorless oil. R_f 0.33 (EtOAc/hexanes: 1/4). IR 3460 (NH), 1720 (C=O). ^1H NMR (200 MHz) 1.76 (t, J = 2.5 Hz, 3 H, $\equiv CCH_3$), 2.20-2.35 (m, 2 H, $CH_2C\equiv$), 3.25 (q, J = 6.3 Hz, 2 H, CH_2N), 3.65 (s, 3 H, OCH_3), 5.05 (bs, 1 H, NH). According to general procedure F, methyl *N*-(3-pentynyl)carbamate (1.11 g, 7.87 mmol) was treated with methyl glyoxylate hydrate (4.5 g, 52 mmol) in 70 mL of benzene to give hydroxy[*N*-(3-pentynyl)-*N*-(methoxycarbonyl)amino]acetic acid methyl ester (1.14 g, 4.96 mmol, 63%) as a colorless oil. R_f 0.50 (EtOAc/hexanes: 1/4). IR 3530 (OH), 1740 (C=O), 1705 (NC=O). ^1H NMR (200 MHz) 1.77 (t, J = 2.5 Hz, 3 H, $\equiv CCH_3$), 2.20-2.50 (m, 2 H, $CH_2C\equiv$), 3.15-3.60 (m, 2 H, CH_2N), 3.73 (s, 3 H, OCH_3), 3.81 (s, 3 H, OCH_3), 5.30 (bs, 1 H, NCHO). According to general procedure G, the glyoxylate adduct (1.10 g, 4.80 mmol) was treated with acetic anhydride (0.55 mL, 5.83 mmol) and DMAP (30 mg, 0.25 mmol) in 15 mL of pyridine to give acetoxy[*N*-(3-pentynyl)-*N*-(methoxycarbonyl)amino]acetic acid methyl ester (0.624 g, 2.30 mmol, 48%) as a light yellow oil. R_f 0.28 (EtOAc/hexanes: 1/4). IR 1750 and 1715 (3 × C=O). ^1H NMR (200 MHz) 1.74 (t, J = 2.5 Hz, 3 H, $\equiv CCH_3$), 2.14 (s, 3 H, $C=OCH_3$), 2.25-2.50 (m, 2 H, $CH_2C\equiv$), 3.20-3.40 (m, 1 H, NCH), 3.45-3.65 (m, 1 H, NCH), 3.74 (bs, 3 H, OCH_3), 3.77 (s, 3 H, OCH_3), 6.53 (bs, 1 H, NCHO). According to procedure H, the acetoxy compound (351 mg, 1.29 mmol) was stirred in 5 mL of thiophenol with TsOH monohydrate (25 mg, 0.13 mmol) to give **11** (302 mg, 0.950 mmol, 73%) as a colorless oil. R_f 0.43 (EtOAc/hexanes: 1/4). IR 1740 (C=O), 1700 (NC=O). ^1H NMR (200 MHz) 1.76 (t, J = 2.5 Hz, 3 H, $\equiv CCH_3$), 2.25-2.50 (m, 2 H, $CH_2C\equiv$), 3.20-3.75 (m, 5 H, CH_2N and OCH_3), 3.79 (s, 3 H, OCH_3), 6.00 and 6.25 (bs, two rotamers, 1 H, NCHS), 7.20-7.40 and 7.40-7.55 (m, 5 H, SC_6H_5).

[*N*-(2-Cyanoethyl)-*N*-(methoxycarbonyl)amino](phenylthio)acetic acid methyl ester (12). A solution of 3-aminopropionitrile fumarate[35] (Aldrich, 10.0 g, 78.05 mmol) in 100 mL of water was adjusted to pH 10 with sodium hydroxide, a solution of methyl chloroformate (6.10 mL, 79.0 mmol) in 25 mL of ether was added, and the two-phase mixture was stirred vigorously for 4 h, with addition of dilute NaOH as needed to maintain pH 10. An additional 100 mL of ether was added, the ether layer was removed, and the aq phase was again washed with 100 mL of ether, after which the combined ether layers were washed with water (50 mL) and saturated aq NaCl (50 mL). The organic layer was dried ($MgSO_4$) and concentrated *in vacuo* to give methyl *N*-(2-cyanoethyl)carbamate (1.87 g, 14.6 mmol, 19%) as a colorless oil. IR 3460 (NH), 2250 (C≡N), 1720 (NC=O). ^1H NMR (200 MHz) 2.62 (t, J = 6.2 Hz, 2 H, CH_2CN), 3.45 (q, J = 6.2 Hz, 2 H, NCH_2), 3.70 (s, 3 H, OCH_3), 5.22 (bs, 1 H, NH). According to general procedure F, methyl *N*-(2-cyanoethyl)carbamate (1.38 g, 10.8 mmol) was treated with methyl glyoxylate hydrate (5.0 g, 57 mmol) in 70 mL of benzene to give [*N*-(2-cyanoethyl)-*N*-(methoxycarbonyl)amino](hydroxy)acetic acid methyl ester (1.75 g, 8.10 mmol, 75%) as a colorless oil. R_f 0.45 (EtOAc/hexanes: 1/2). IR 3510 (OH), 2250 (C≡N), 1745 (C=O), 1705 (NC=O). ^1H NMR (200 MHz) 2.69 (bt, J = 6.9 Hz, 2 H, CH_2CN), 3.35-3.60 (m, 1 H, CHN), 3.65-3.85 (m, 1 H, CHN), 3.76 (s, 3 H, OCH_3), 3.83 (s, 3 H, OCH_3), 4.35 (bs, 1 H, OH), 5.45 (bs) and 5.55 (bs, 1 H, NCHO). According to general procedure G, the glyoxylate adduct (1.73 g, 8.01 mmol) was treated with acetic anhydride (0.80 mL, 8.3 mmol) and DMAP (35 mg, 0.29 mmol) in 20 mL of pyridine to give acetoxy[*N*-(2-cyanoethyl)-*N*-(methoxycarbonyl)amino]acetic acid methyl ester (1.99 g, 7.71 mmol, 96%) as a colorless oil. R_f 0.50 (EtOAc/hexanes: 1/4). IR 2250 (C≡N), 1750 and 1720 (3 × C=O). ^1H NMR (200 MHz) 2.16 (s, 3 H, $OCOCH_3$), 2.68 (bs, 2 H, CH_2CN), 3.40-3.60 (m, 1 H, CHN), 3.60-3.80 (m, 1 H, CHN), 3.79 (s, 3 H, OCH_3), 6.61 (bs, 1 H, NCHO). According to procedure H, the acetoxy compound (685 mg, 2.65 mmol) was stirred in 5 mL of thiophenol with TsOH monohydrate (300 mg, 1.56 mmol) to give **12** (186.2 mg, 0.605 mmol, 23%) as a colorless oil. R_f 0.72 (EtOAc/hexanes: 1/4). IR 2240 (C≡N), 1740 (C=O), 1705 (NC=O). ^1H NMR (200 MHz) 2.60-2.85 (m, 2 H, CH_2CN), 3.35-3.80 (m, 5 H, OCH_3 + CH_2N),

3.82 (bs, 3 H, OCH_3), 6.09 (bs) and 6.38 (bs, 1 H, NCHS), 7.25-7.40 (m, 3 H) and 7.40 (m, 2 H, SC_6H_5).

Cyclization of 1. To a solution of phenylthio precursor **1** (148 mg, 0.458 mmol) in 10 mL of toluene at 80-90 °C under a nitrogen atmosphere was added a solution of tributyltin hydride (0.20 mL, 0.74 mmol) and AIBN (10 mg, 0.06 mmol) in 10 mL of toluene over a period of 8 h. The resulting solution was cooled to rt and stirred for 18 h. The solvent was removed *in vacuo* and the residue was chromatographed to give two fractions. The first fraction consisted of **1,2-piperidinedicarboxylic acid 1-ethyl, 2-methyl ester (21)** (29.5 mg, 0.137 mmol, 30%) as a colorless oil. R_f 0.25 (EtOAc/hexanes: 1/4). IR 1735 (C=O), 1680 (NC=O). ^{1}H NMR (200 MHz) 1.10-1.75 (m, 9H), 2.10-2.30 (m, 1 H, H^{3eq}), 2.80-3.10 (m, 1 H, H^{6ax}), 3.72 (s, 3 H, OCH_3), 3.90-4.15 (m, 1 H, H^{6eq}), 4.13 (q, J = 7.1 Hz, 2 H, CH_2O), 4.80 (bs) and 4.91 (bs, 1 H, two rotamers, H^{2eq}). ^{13}C NMR (50 MHz) 14.6 (CH_3), 20.7, 24.7, 26.7, 41.6 (C-6), 52.1 (OCH_3), 54.1 and 54.4 (C-2), 61.5 (OCH_2), 156.2 (b, NC=O), 172.2 (C=O). The second fraction consisted of a 35:65 mixture of ***rel*-(2*R*,3*S*)-3-methyl-1,2-pyrrolidinedicarboxylic acid 1-ethyl, 2-methyl ester (20a)** and ***rel*-(2*R*,3*R*)-3-methyl-1,2-pyrrolidinedicarboxylic acid 1-ethyl, 2-methyl ester (20b)** (58.9 mg, 0.274 mmol, 60%) as a colorless oil. R_f 0.20 (EtOAc/hexanes: 1/4). IR 1740 (C=O), 1680 (NC=O). ^{1}H NMR (200 MHz) 0.97 (d, J = 6.9 Hz, 3 H, CH_3, **20a**), 1.14 (d, J = 6.8 Hz, 3 H, CH_3, **20b**), 1.10-1.30 (m, 3 H, OCH_2CH_3), 1.45-2.15 (m, 2 H, 2 × H^4), 2.25-2.60 (m, 1 H, H^3), 3.25-3.75 (m, 2 H, 2 × H^5), 3.68 (s) and 3.70 (s) and 3.72 (s, 6 H, 2 × OCH_3), 3.80 (d, J = 5.9 Hz) and 3.87 (d, J = 5.7 Hz, two rotamers, 1 H, H^2, **20b**), 4.23 (d, J = 8.4 Hz) and 4.28 (d, J = 8.5 Hz, two rotamers, 1 H, H^2, **20a**). ^{13}C NMR (63 MHz) **20a**: 14.7 (CH_2CH_3), 18.4 ($CHCH_3$), 31.0 and 31.9 (C-4), 36.2 and 37.1 (C-3), 45.9 and 46.2 (C-5), 51.9 (OCH_3), 52.0 (OCH_3), 61.2 (OCH_2), 63.0 and 63.1 (C-2), 154.5 (NC=O), 172.0 (C=O). **20b**: 14.6 (CH_2CH_3), 18.4 ($CHCH_3$), 31.8 and 32.4 (C-4), 38.3 and 39.4 (C-3), 45.6 and 46.0 (C-5), 51.4 (OCH_3), 51.9 (OCH_3), 61.1 (OCH_2), 65.8 and 65.9 (C-2), 155.0 (NC=O), 172.9 and 173.0 (C=O).

Cyclization of 2. To a solution of thiophenoxy precursor **2** (129 mg, 0.424 mmol) in 10 mL of toluene at 80-90 °C under a nitrogen atmosphere was added a solution of tributyltin hydride (0.16 mL, 0.595 mmol) and AIBN (10 mg, 0.062 mmol) in 15 mL of benzene over a period of 6 h. The resulting solution was cooled to rt and stirred for 18 h. The solvent was removed *in vacuo* and the residue was chromatographed to give two fractions. The first fraction consisted of ***rel*-(5*R*,8a*R*)-octahydro-3-oxo-indolizine-5-carboxylic acid methyl ester (23)** (63.4 mg, 0.322 mmol, 76%) as a colorless oil. This fraction was contaminated with 4% of the reduced starting material **24**. R_f 0.55 (EtOAc). IR 1730 (C=O), 1675 (NC=O). ^{1}H NMR (200 MHz) 1.00-2.05 (m, 7 H), 2.05-2.50 (m, 3 H), 3.55-3.80 (m, 1 H, H^{8a}), 3.70 (s, 3 H, OCH_3), 4.80 (d, J = 5.7 Hz, 1 H, H^5). ^{1}H NMR (C_6D_6, 250 MHz, NOE experiment) 0.47-0.67 (m, 1 H, H^{8ax}), 0.85-1.05 (m, 1 H, H^1), 1.05-1.35 (m, 4 H, H^{6ax} + H^{7ax} + H^{7eq} + H^{8eq}), 1.47-1.63 (m, 1 H, H^1), 1.87-1.98 (m, 1 H, H^{6eq}), 2.00-2.10 (m, 2 H, 2 × H^2), 3.23 (s, 3 H, OCH_3), 3.38-3.55 (m, 1 H, H^{8a}), 4.96 (d, J = 4.5 Hz, 1 H, H^{5eq}). ^{13}C NMR (50 MHz) 20.5, 26.0, 26.1, 30.1, 32.7, 51.0 (C-5), 52.2 (OCH_3), 54.7 (C-8a), 171.2 (C=O), 174.6 (C-3). Accurate mass 197.1032 (calcd for $C_{10}H_{15}NO_3$ 197.1052). The second fraction consisted of a 20:80 mixture of ***rel*-(5*R*,6*S*,7a*S*)-6-methyl-hexahydro-3-oxo-1*H*-pyrrolizine-5-carboxylic acid methyl ester (22a)** and ***rel*-(5*R*,6*R*,7a*S*)-6-methyl-hexahydro-3-oxo-1*H*-pyrrolizine-5-carboxylic acid methyl ester (22b)** (10 mg, 0.051 mmol, 12%) as a colorless oil. R_f 0.41 (EtOAc). ^{1}H NMR (200 MHz) **22a**: characteristic signals 1.00 (d, J = 7.2 Hz, 3 H, CH_3), 4.52 (d, J = 7.7 Hz, 1 H, H^5); **22b**: characteristic signals 1.25 (d, J = 6.7 Hz, 3 H, CH_3), 3.91 (d, J = 8.1 Hz, 1 H, H^5). Accurate mass 197.1045 (calcd for $C_{10}H_{15}NO_3$ 197.1052).

Cyclization of 3. To a solution of phenylthio precursor **3** (181 mg, 0.561 mmol) in 15 mL of toluene at 80-90 °C under a nitrogen atmosphere was added a solution of tributyltin hydride (0.23 mL, 0.86 mmol) and AIBN (15 mg, 0.093 mmol) in 25 mL of toluene over a period of 5 h. The resulting solution was cooled to rt and stirred for 18 h. The solvent was removed *in vacuo* and the residue was chromatographed to give two fractions. The first fraction consisted of a 75:25 mixture of ***rel*-(2*R*,5*R*)-5-methyl-1,2-piperidinedicarboxylic acid dimethyl ester (26a)** and ***rel*-(2*R*,5*S*)-5-methyl-1,2-piperidinedicarboxylic acid dimethyl ester (26b)** (55.3mg, 0.257mmol, 46%) as a colorless oil. R_f 0.38 (EtOAc/hexanes: 1/4). IR 1680 (C=O), 1735 (NC=O). ^{1}H NMR (200 MHz) 0.86 (d, J = 6.4 Hz, 3 H, CH_3, **26a**), 0.87 (d, J = 6.3 Hz, 3 H, CH_3, **26b**), 1.40-1.75 (m, 3 H), 2.15-2.30 (m, 1 H, H^{3eq}), 2.40-2.65 (m, 1 H, H^{6ax}), 3.68 (s) and 3.72 (s, 6 H, 2 × OCH_3), 3.80-4.15 (m, 1 H, H^{6eq}), 4.77 (d, J = 5.2 Hz) and 4.93 (d, J = 5.7 Hz, two rotamers, 1 H, H^{2eq}). ^{13}C NMR (50 MHz) 18.9 (CH_3, **26b**), 23.3 (CH_3, **26a**), 26.6 and 26.8, 29.3 and 29.4, 30.3 and 30.4 (C-5), 48.2 and 48.4 (C-6), 52.0 (OCH_3), 52.6 (OCH_3), 53.5 and 53.8 (C-2), 156.0 (b, NC=O), 171.9 (C=O). Accurate mass 215.1153 (calcd for $C_{10}H_{17}NO_4$ 215.1158). The second fraction consisted of a 17:17:66 mixture of

***rel*-(2*R*,3*S*,4*S*)-3,4-dimethyl-1,2-pyrrolidinedicarboxylic acid dimethyl ester (25a)**, ***rel*-(2*R*,3*S*,4*R*)-3,4-dimethyl-1,2-pyrrolidinedicarboxylic acid dimethyl ester (25b)** and ***rel*-(2*R*,3*R*,4*S*)-3,4-dimethyl-1,2-pyrrolidinedicarboxylic acid dimethyl ester (25c)** (65.6 mg, 0.305 mmol, 54%) as a colorless oil. R_f 0.25 (EtOAc/hexanes: 1/4). IR 1690 (C=O), 1740 (NC=O). ^{1}H NMR (200 MHz) 0.80-1.05 (m, 3 × 4-CH_3 (**25a** + **25b** + **25c**) + 2 × 3-CH_3 (**25a** + **25b**)), 1.13 (d, J = 6.1 Hz, 3-CH_3, **25c**), 1.60-2.40 (m, H^3 and H^4), 2.80-3.20 (m, 2 × H^5), 3.55-3.85 (m, 2 × OCH_3), 3.75-4.00 (m, H^2, **25c**), 4.20-4.35 (m, H^2, **25a** + **25b**). ^{13}C NMR (50 MHz, selected signals) 34.2 and 35.1 (C-4, **25a** or **25b**), 37.2 and 38.1 (C-4, **25a** or **25b**), 39.9 and 40.6 (C-4, **25c**), 41.1 and 42.1 (C-3, **25a** or **25b**), 42.9 and 43.8 (C-3, **25a** or **25b**), 45.8 and 46.9 (C-3, **25c**), 52.0 and 52.3 (C-5, **25a** or **25b**), 53.3 and 53.7 (C-5, **25a** or **25b**), 53.5 and 53.7 (C-5, **25c**), 63.8 and 64.0 (C-2, **25a** or **25b**), 65.5 and 65.7 (C-2, **25a** or **25b**), 66.4 and 66.6 (C-2, **25c**). Accurate mass 215.1132 (calcd for $C_{10}H_{17}NO_4$ 215.1158).

Cyclization of 4. To a solution of phenylthio precursor **4** (171 mg, 0.454 mmol) in 13 mL of toluene at 80-90 °C under a nitrogen atmosphere was added a solution of tributyltin hydride (0.18 mL, 0.681 mmol) and AIBN (10 mg, 0.062 mmol) in 18 mL of toluene over a period of 6 h. The resulting solution was cooled to rt and stirred for 18 h. The solvent was removed *in vacuo* and the residue was chromatographed to give two fractions. The first fraction consisted of **2-azaspiro[5.5]undecane-2,3-dicarboxylic acid dimethyl ester (28)** (43.9 mg, 0.163 mmol, 36%) as a colorless oil. R_f 0.45 (EtOAc/hexanes: 1/4). IR 1735 (C=O), 1685 (NC=O). ^{1}H NMR (200 MHz) 0.95-1.60 (m, 12 H), 1.75-2.10 (m, 2 H), 2.54 (d) and 2.63 (d, J = 13.6 Hz, two rotamers, 1 H, H^{1ax}), 3.69 (s, 3 H, OCH_3), 3.72 (s, 3 H, OCH_3), 3.93 (d) and 4.10 (d, J = 13.6 Hz, two rotamers, 1 H, H^{1eq}), 4.76 (bd, J = 4.9 Hz) and 4.94 (bd, J = 4.9 Hz, two rotamers, 1 H, H^{3eq}). ^{13}C NMR (50 MHz) 21.2, 21.4, 21.5, 21.8, 26.4, 30.6, 32.1 and 32.2, 37.7 and 37.8 (C-1), 49.7 and 49.8 (C-6), 52.0 (OCH_3), 52.7 (OCH_3), 54.0 and 54.2 (C-3), 157.5 (b, NC=O), 171.9 (C=O). Accurate mass 269.1611 (calcd for $C_{14}H_{23}NO_4$ 269.1627). The second fraction consisted of a 29:71 mixture of ***rel*-(3*R*,4*S*)-4-methyl-2-azaspiro[4.5]decane-2,3-dicarboxylic acid dimethyl ester (27a)** and ***rel*-(3*R*,4*R*)-4-methyl-2-azaspiro[4.5]decane-2,3-dicarboxylic acid dimethyl ester (27b)** (49.7 mg, 0.185 mmol, 41%) as a colorless oil. R_f 0.38 (EtOAc/hexanes: 1/4). IR 1740 (C=O), 1690 (NC=O). ^{1}H NMR (200 MHz) 0.84 (d, J = 7.3 Hz, 3 H, CH_3, **27a**), 0.98 (d, J = 7.0 Hz, 3 H, CH_3, **27b**), 0.95-2.45 (m, 11 H), 2.90-3.60 (m, 2 H, 2 × H^1), 3.62 and 3.67 and 3.70 and 3.73 (s, 6 H, 2 × OCH_3), 3.84 (d, J = 10.0 Hz) and 3.90 (d, J = 10.8 Hz, two rotamers, 1 H, H^3, **27b**), 4.33 (d, J = 9.0 Hz) and 4.39 (d, J = 9.0 Hz, two rotamers, 1 H, H^3, **27a**). Accurate mass 269.1619 (calcd for $C_{14}H_{23}NO_4$ 269.1627).

Cyclization of 5. To a solution of phenylthio precursor **5** (103 mg, 0.306 mmol) in 10 mL of toluene at 80-90 °C under a nitrogen atmosphere was added a solution of tributyltin hydride (0.13 mL, 0.48 mmol) and AIBN (15 mg, 0.093 mmol) in 5 mL of toluene over a period of 6 h. The resulting solution was cooled to rt and stirred for 18 h. The solvent was removed *in vacuo* and the residue was chromatographed to give an inseparable 35:65 mixture of ***rel*-(2*R*,3*S*)-3-propyl-1,2-pyrrolidinedicarboxylic acid dimethyl ester (30a)** and ***rel*-(2*R*,3*R*)-3-propyl-1,2-pyrrolidinedicarboxylic acid dimethyl ester (30b)** (65.2 mg, 0.285 mmol, 93%) as a colorless oil. R_f 0.35 (EtOAc/hexanes: 1/4). IR 1740 (C=O), 1685 (NC=O). ^{1}H NMR (250 MHz) 0.85-0.95 (m, 3 H, CH_3), 1.05-1.80 (m, 5 H), 1.90-2.40 (m, 2 H), 3.25-3.70 (m, 2 H, 2 × H^5), 3.63 (s) and 3.68 (s) and 3.95 (s) and 3.97 (s, 6 H, 2 × OCH_3), 3.89 (d, J = 5.2 Hz) and 3.96 (d, J = 5.2 Hz, two rotamers, 1 H, H^2 **30b**), 4.26 (d, J = 8.2 Hz) and 4.33 (d, J = 8.3 Hz, two rotamers, 1 H, H^2 **30a**). ^{13}C NMR (50 MHz) **30a**: 13.8 (CH_3), 21.0, 28.6 and 29.6 (C-4), 31.9 and 32.0, 41.7 and 42.6 (C-3), 45.6 and 46.1 (C-5), 51.9 (OCH_3), 52.2 (OCH_3), 62.1 and 62.4 (C-2), 154.8 (NC=O), 171.9 (C=O). **30b**: 13.7 (CH_3), 20.5, 29.3 and 30.2 (C-4), 35.3 and 35.4, 43.1 and 44.2 (C-3), 45.4 and 45.9 (C-5), 51.4 (OCH_3), 52.2 (OCH_3), 64.1 and 64.4 (C-2), 155.2 (NC=O), 173.0 (C=O). Accurate mass 229.1320 (calcd for $C_{11}H_{19}NO_4$ 229.1314).

Cyclization of 6. To a solution of phenylthio precursor **6** (444 mg, 1.32 mmol) in 22 mL of toluene at 80-90 °C under a nitrogen atmosphere was added a solution of tributyltin hydride (0.50 mL, 1.86 mmol) and AIBN (21 mg, 0.13 mmol) in 40 mL of toluene over a period of 7 h. The resulting solution was cooled to rt and stirred for 18 h. The solvent was removed *in vacuo* and the residue was chromatographed to give a inseparable 30:70 mixture of **30a** and **30b** (275 mg, 1.20 mmol, 91%) as a colorless oil.

Cyclization of 7. To a solution of phenylthio precursor **7** (338 mg, 1.01 mmol) in 25 mL of toluene at 80-90 °C under a nitrogen atmosphere was added a solution of tributyltin hydride (0.40 mL, 1.51 mmol) and AIBN (10 mg, 0.062 mmol) in 45 mL of toluene over a period of 5 h. The resulting solution was cooled to rt and stirred for 18 h. The solvent was removed *in vacuo* and the residue was chromatographed to give two fractions. The first fraction consisted of ***rel*-(1*R*,3a*R*,6a*S*)-octahydro-**

cyclopenta[*c*]pyrrole-1,2-dicarboxylic acid dimethyl ester (31b) (44.6 mg, 0.196 mmol, 19%) as a colouless oil. R_f 0.28 (EtOAc/hexanes: 1/4). IR 1740 (C=O), 1680 (NC=O). ^{1}H NMR (200 MHz) 1.30-2.10 (m, 6H), 2.55-2.80 (m, 2 H, H^{3a} and H^{6a}), 3.20-3.40 (m, 1 H, H^3), 3.55-3.75 (m, 1 H, H^3), 3.64 (s) and 3.68 (s) and 3.71 (s, 6 H, 2 × OCH_3), 4.08 (bs) and 4.15 (bs, two rotamers, 1 H, H^1). ^{13}C NMR (50 MHz) 25.5 (C-5), 32.3, 32.8 and 33.0, 41.4 and 42.5, 48.0 and 49.2, 52.0 (OCH_3), 52.5 (OCH_3), 52.6 and 53.1 (C-3), 65.4 and 65.7 (C-1), 155.0 (b, NC=O), 173.1 (C=O). Accurate mass 227.1153 (calcd for $C_{11}H_{17}NO_4$ 227.1158). The second fraction was an 83:17 mixture of ***rel*-(1*R*,3a*S*,6a*R*)-octahydro-cyclopenta[*c*]pyrrole-1,2-dicarboxylic acid dimethyl ester (31a)** and **31b** (160.7 mg, 0.708 mmol, 70%) as a colorless oil. R_f 0.25 (EtOAc/hexanes: 1/4). ^{1}H NMR (200 MHz) **31a**: characteristic signals 2.75-2.95 (m, 1 H, H^3), 3.01 (d) and 3.05 (d, J = 8.5 Hz, two rotamers, H^3), 4.42 (bs) and 4.46 (bs, two rotamers, 1 H, H^1). ^{13}C NMR (50 MHz) 26.1 (CH_2), 27.9 (CH_2), 29.5 (CH_2), 51.5 (OCH_3), 62.5 (C-1). Accurate mass 227.1170 (calcd for $C_{11}H_{17}NO_4$ 227.1158).

Cyclization of 8. To a solution of phenylthio precursor **8** (580 mg, 1.66 mmol) in 30 mL of toluene at 80-90 °C under a nitrogen atmosphere was added a solution of tributyltin hydride (0.63 mL, 2.28 mmol) and AIBN (11 mg, 0.068 mmol) in 45 mL of toluene over a period of 6 h. The resulting solution was cooled to rt and stirred for 18 h. The solvent was removed *in vacuo* and the residue was chromatographed to give a 15:85 mixture of ***rel*-(1*R*,3a*R*,7a*S*)-octahydro-1*H*-isoindole-1,2-dicarboxylic acid dimethyl ester (32a)** and ***rel*-(1*R*,3a*S*,7a*R*)-octahydro-1*H*-isoindole-1,2-dicarboxylic acid dimethyl ester (32b)** (240 mg, 0.997 mmol, 60%) as a colorless oil. R_f 0.35 (EtOAc/hexanes: 1/4). IR 1745 (C=O), 1690 (NC=O). ^{1}H NMR (200 MHz) 1.10-1.80 (m, 8 H), 2.15-2.50 (m, 2 H, H^{3a} + H^{7a}), 3.15-3.65 (m, 2 H, 2 × H^3), 3.65 (s) and 3.70 (s) and 3.72 (s, 6 H, 2 × OCH_3), 4.01 (d, J = 4.3 Hz) and 4.10 (d, J = 4.7 Hz, two rotamers, 1 H, H^1, **32b**), 4.31 (d, J = 7.3 Hz) and 4.37 (d, J = 6.8 Hz, two rotamers, 1 H, H^1, **32a**). ^{13}C NMR (50 MHz) **32a**: 21.1, 23.1, 23.8, 24.5, 36.4 and 37.1 (C-3a), 39.8 and 40.8 (C-7a), 48.4 and 48.8 (C-3), 51.7 (OCH_3), 52.3 (OCH_3), 63.4 and 63.7 (C-1), 155.5 (NC=O), 170.1 and 170.6 (C=O); **32b**: 22.0 and 22.1, 22.7 and 22.8, 25.1 and 25.3, 26.0 and 26.2, 35.1 and 36.1 (C-3a), 42.1 and 43.2 (C-7a), 49.5 and 49.8 (C-3), 51.9 (OCH_3), 52.3 (OCH_3), 63.1 and 63.2 (C-1), 155.3 and 155.8 (NC=O), 172.8 (C=O). Accurate mass 241.1320 (calcd for $C_{12}H_{19}NO_4$ 241.1314).

Cyclization of 9. To a solution of phenylthio precursor **9** (218 mg, 0.599 mmol) in 15 mL of toluene at 80-90 °C under a nitrogen atmosphere was added a solution of tributyltin hydride (0.23 mL, 0.86 mmol) and AIBN (15 mg, 0.093 mmol) in 25 mL of toluene over a period of 6 h. The resulting solution was cooled to rt and stirred for 18 h. The solvent was removed *in vacuo* and the residue was chromatographed to give three fractions. The first fraction consisted of ***rel*-(1*R*,4a*R*,8a*S*)-octahydro-1*H*-isoquinoline-1,2-dicarboxylic acid dimethyl ester (34b)** (79.4 mg, 0.311 mmol, 52%) as a colorless oil. R_f 0.49 (EtOAc/hexanes: 1/4). IR 1740 (C=O), 1685 (NC=O). ^{1}H NMR (250 MHz) 0.80 -1.80 (m, 12 H), 3.25-3.50 (m, 1 H, H^{3ax}), 3.65 (s, 6 H, 2 × OCH_3), 3.85-4.15 (m, 1 H, H^{3eq}), 4.60 (bs) and 4.73 (bs, 1 H, H^{1eq}). ^{13}C NMR (50 MHz) 25.7, 26.2, 29.0, 32.4 (b), 33.5, 34.6 (C-4a), 41.1 (C-3), 42.9 (C-8a), 51.2 (OCH_3), 52.6 (OCH_3), 57.7 (b, C-1), 156.0 (b, NC=O), 171.5 (b, C=O). MS (EI, 70 eV) 255 (M^+, <1), 196 (M^+ - CO_2Me, 100). The second fraction consisted of **2-azaspiro[4.5]decane-1,2-dicarboxylic acid dimethyl ester (33)** (44.3 mg, 0.713 mmol, 29%) as a colorless oil. R_f 0.37 (EtOAc/hexanes: 1/4). IR 1730 (C=OO), 1685 (NC=O). ^{1}H NMR (200 MHz) 1.00-2.00 (m, 12 H), 3.25-3.75 (m, 8 H, 2 × OCH_3 and CH_2N), 3.99 (s) and 4.08 (s, two rotamers, H^1). ^{13}C NMR (50 MHz) 22.5, 22.9, 25.6 and 25.8, 33.0 and 33.1, 33.6 and 33.8, 35.3 and 35.4, 44.3 and 44.8, 45.4 and 46.5, 51.6 and 51.8 (OCH_3), 52.5 and 52.6 (OCH_3), 68.1 and 68.3 (C-1), 155.8 (b, NC=O)), 172.2 and 172.4 (C=O). Accurate mass 255.1468 (calcd for $C_{13}H_{21}NO_4$ 255.1471). The third fraction consisted of a 56:44 inseparable mixture of ***rel*-(1*R*,4a*R*,8a*S*)-octahydro-1*H*-isoquinoline-1,2-dicarboxylic acid dimethyl ester (34a)** and ***N*-(2-(1-cyclohexen-1-yl)ethyl)-*N*-(methoxycarbonyl)-glycine methyl ester (35)** (24.4 mg, 0.0958 mmol, 16%) as a colorless oil. R_f 0.41 (EtOAc/hexanes: 1/4). ^{1}H NMR (200 MHz) **34a**: characteristic signals 2.85-3.15 (m, 1 H, H^{3ax}), 3.90-4.20 (m, 1 H, H^{3eq}), 4.50 (bs) and 4.67 (bs, 1 H, H^1). **35**: characteristic signals 3.20-3.40 (m, 2 H, NCH_2), 4.25 and 4.28 (s, 2 H, NCH_2CO_2), 5.42 (bs, 1 H, =CH).

Cyclization of 10. To a solution of phenylthio precursor **10** (280 mg, 0.800 mmol) in 20 mL of toluene at 80-90 °C under a nitrogen atmosphere was added a solution of tributyltin hydride (0.30 mL, 1.12 mmol) and AIBN (21 mg, 0.13 mmol) in 30 mL of toluene over a period of 6 h. The resulting solution was cooled to rt and stirred for 18 h. The solvent was removed *in vacuo* and the residue was chromatographed to give an inseparable 35:65 mixture of ***rel*-(1*R*,2*R*,5*S*)-3-azabicyclo[3.3.1]nonane-**

2,3-dicarboxylic acid dimethyl ester (36) and ***N*-(2-(1-cyclohexen-1-yl)ethyl)-*N*-(methoxycarbonyl)glycine methyl ester (37)** (160 mg, 0.664 mmol, 83%) as a colorless oil. ^{1}H NMR (200 MHz) **37**: characteristic signals 3.95 (s) and 4.01 (s, 2 H, NCH_2CO_2), 5.55-5.75 (m, 2 H, CH=CH). Compound **36** was obtained pure as follows. To a stirred solution of the 35:65 mixture of **36** and **37** (108 mg, 0.446 mmol) in 5 mL of CH_2Cl_2 under a nitrogen atmosphere at 0 °C, was added MCPBA (tech. 85%, 70 mg, 0.34 mmol).[36] The reaction mixture was allowed to warm up to rt over a 1 h period and stirred subsequently for 18 h. Dichloromethane (25 mL) was added to the reaction mixture and washed with aq Na_2CO_3. The water layer was extracted (2 ×) with 10 mL of CH_2Cl_2. The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed to give two fractions. The first fraction consisted of **36** (29 mg, 0.12 mmol, 27%) as a colorless oil. R_f 0.36 (EtOAc/hexanes: 1/4). IR 1730 (C=O), 1680 (NC=O). ^{1}H NMR (200 MHz) 1.40-1.95 (m, 9 H), 2.30-2.45 (m, 1 H, H^1), 3.25-3.45 (m, 1 H, H^{4ax}), 3.68 (s) and 3.71 (s) and 3.73 (s, 6 H, rotamers, 2 × OCH_3), 3.87 (d) and 3.99 (d, J = 12.9 Hz, two rotamers, H^{4eq}), 4.58 (s) and 4.72 (s, 1 H, two rotamers, H^2). ^{13}C NMR (50 MHz) 19.9, 27.0 and 27.1 (C-5), 28.6 and 28.7 (C-1), 29.8 and 30.0, 31.3 and 31.4, 31.6 and 31.8, 47.5 (C-4), 52.0 and 52.1 (OCH_3), 52.7 (OCH_3), 60.0 and 60.2 (C-2), 156.4 and 157.1 (NC=O), 172.8 and 172.9 (C=O). Accurate mass 241.1313 (calcd for $C_{12}H_{19}NO_4$ 241.1314). The second fraction consisted of ***N*-[(7-oxabicyclo[4.1.0]heptan-3-yl)methyl]-*N*-(methoxycarbonyl)glycine methyl ester** (*cis*:*trans* = 50:50, 72.3 mg, 0.281 mmol, 63%) as a colorless oil. R_f 0.15 (EtOAc/hexanes: 1/4). IR 1750 (C=O), 1695 (NC=O). ^{1}H NMR (200 MHz, mixture of diastereoisomers) 0.80-2.25 (m, 7 H), 3.05-3.25 (m, 4 H, CH_2N + 2 × CHO), 3.67 and 3.71 and 3.73 (s, 6 H, 2 × OCH_3), 3.90 and 3.96 (s, two rotamers) 3.92 and 3.97 (s, two rotamers, NCH_2CO_2Me). Accurate mass 257.1275 (calcd for $C_{12}H_{19}NO_5$ 257.1287).

Cyclization of 11. To a solution of phenylthio precursor **11** (279 mg, 0.870 mmol) in 15 mL of toluene at 80-90 °C under a nitrogen atmosphere was added a solution of tributyltin hydride (0.33 mL, 1.22 mmol) and AIBN (15 mg, 0.093 mmol) in 30 mL of toluene over a period of 6 h. The resulting solution was cooled to rt and stirred for 18 h. The solvent was removed *in vacuo* and the residue was chromatographed to give a 59:41 mixture of **(*Z*)-3-ethylidene-1,2-pyrrolidinedicarboxylic acid dimethyl ester (38a)** and **(*E*)-3-ethylidene-1,2-pyrrolidinedicarboxylic acid dimethyl ester (38b)** (139 mg, 0.653 mmol, 75%) as a colorless oil. R_f 0.23 (EtOAc/hexanes: 1/4). IR 1740 (C=O), 1700 (NC=O). ^{1}H NMR (200 MHz, NOE mult) 1.63 (dq, J = 6.9, 1.5 Hz, 3 H, =CHCH_3, **38b**), 1.74 (dd, J = 6.9, 2.1 Hz, 3 H, =CHCH_3, **38a**), 2.30-2.75 (m, 2 H, 2 × H^4), 3.20-3.50 (m, 1 H, H^5), 3.55-3.75 (m, 7 H, 2 × OCH_3 + H^5), 4.68 (bs) and 4.74 (bs, two rotamers, 1 H, H^2, **38b**), 4.86 (bs) and 4.93 (bs, two rotamers, 1 H, H^2, **38a**), 5.45-5.60 (m, 1 H, =CH-, **38a**), 5.60-5.80 (m, 1 H, =CH-, **38b**). ^{13}C NMR (50 MHz) **38a**: 14.5 (CH_3), 30.1 and 31.1 (C-4), 45.0 and 45.3 (C-5), 52.0 (OCH_3), 52.4 (OCH_3), 60.0 and 60.3 (C-2), 121.1 (=CH), 134.3 and 135.1 (C-3), 154.8 (NC=O), 170.9 (C=O). **38b**: 14.3 (CH_3), 26.0 and 26.9 (C-4), 45.3 and 45.8 (C-5), 52.1 (OCH_3), 52.4 (OCH_3), 62.9 and 63.2 (C-2), 119.8 (=CH), 134.9 and 135.8 (C-3), 155.3 (NC=O), 171.5 (C=O). Accurate mass 213.0982 (calcd for $C_{10}H_{15}NO_4$ 213.1001).

Cyclization of 12. To a solution of phenylthio precursor **12** (164 mg, 0.533 mmol) in 7 mL of toluene at 80-90 °C under a nitrogen atmosphere was added a solution of tributyltin hydride (0.2 mL, 6.3 mmol) and AIBN (8 mg, 0.05 mmol) in 10 mL of toluene over a period of 7 h. The resulting solution was cooled to rt and stirred for 18 h. The solvent was removed *in vacuo* and the residue was taken up in 20 mL of CH_2Cl_2 and washed with HOAc/H_2O (1:10). The organic layer was dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed to give ***N*-(2-cyanoethyl)-*N*-(methoxycarbonyl)-glycine methyl ester (39)** (105.5 mg, 0.533 mmol, 100%) as a colorless oil. R_f 0.59 (EtOAc/hexanes: 1/4). IR 2240 (C≡N), 1750 (C=O), 1705 (NC=O). ^{1}H NMR (250 MHz) 2.64 (t, J = 6.9 Hz) and 2.69 (t, J = 6.7 Hz, two rotamers, 2 H, $CH_2C{\equiv}N$), 3.58 (t, J = 6.7 Hz, 2 H, CH_2N), 3.69 (s) and 3.74 (s) and 3.75 (s, 6 H, 2 × OCH_3), 4.08 (s) and 4.09 (s, two rotamers, 2 H, NCH_2CO_2).

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