Xanthate Transfer Addition of a Glycine Radical Equivalent to Alkenes. A Novel Route to α-Amino Acid Derivatives

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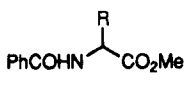
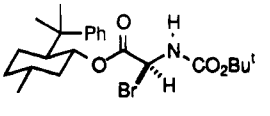
Introduction

The synthesis of α-amino acids continues to attract considerable attention, in particular for the synthesis of novel non-proteinogenic amino acids. Both achiral and chiral anionic and cationic glycine equivalents have been described and utilized in the synthesis of unusual amino acids.[1] In this respect, the use of a glycine radical equivalent has received little attention.

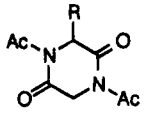
Easton *et al.*[2] described the selective bromination of glycine residues in protected peptides via free radical pathways and explained that the selective reaction of such residues was due to the relative stability of the glycine radical produced by atom transfer reactions "due to non-bonding interactions". Baldwin *et al.*[3] used bromoglycine derivative **1** in reactions with allylstannanes under radical conditions to produce α-alkylated amino acids such as **2**. In addition, the reduction of the bromoglycine derivative **1** with Bu_3SnH or Bu_3SnD to give **3** and **4** was described. In a similar way, the enantioselective synthesis of (*S*)- and (*R*)-2-deuterioglycine was accomplished using the corresponding (−)-8-phenylmenthol ester **5**.[4] Hamon *et al.*[5] reported that the carbon-carbon bond forming radical reactions of **5** with allylstannanes proceed with even higher stereoselectivity.



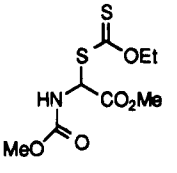
1 R = Br **3** R = H
2 R = allyl **4** R = D



5

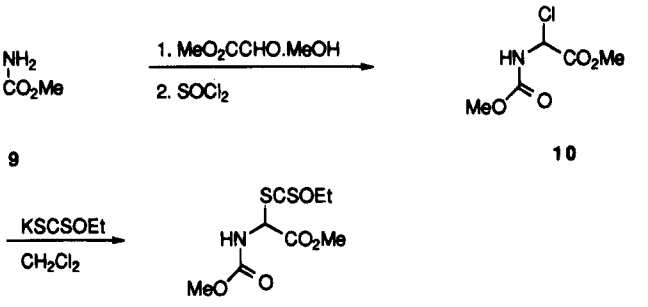


6 R = Br
7 R = H



8

Scheme 1



9 **10** **8**

Although the addition of a glycine radical equivalent to allylstannanes is now well established, the coupling to other types of alkenes poses a problem. Recently, the Bu_3SnH-mediated radical addition of the piperazine-2,5-dione **6** to alkenes was reported.[6] It was shown that quenching of the incipient radical with Bu_3SnH, leading to **7**, is more favorable than coupling with the alkene. The yields of addition products were therefore low.

In this paper we wish to report the efficient addition of a glycine radical equivalent to alkenes by means of xanthate transfer radical addition reactions[7] of xanthate **8**.

Results

Dithiocarbonate **8** was prepared from methyl carbamate (**9**) in three steps (Scheme 1). Addition of **9** to methyl glyoxylate and treatment of the resulting hemiaminal with thionyl chloride gave the sensitive α-chloroglycine **10**.[8] The xanthate group was introduced in a clean substitution reaction with the potassium salt of *O*-ethyl dithiocarbonate[9] to give **8** in 70% yield as a stable, crystalline compound, mp 65–65.5 °C.

The results of the coupling reactions of xanthate **8** with various alkenes are summarized in Table 1. All radical additions of xanthate **8** to alkenes (except entry 4) were performed in a sealed tube at 150–160 °C in benzene (1–2 M) under an argon atmosphere. As a radical initiator, di-*tert*-butyl peroxide (0.3 equiv) was added, which generates methyl radicals at this temperature.[10]

First, the addition of xanthate **8** to methyl acrylate was investigated (entry 1). The use of a slight excess of the acrylate gave the best results, leading to the formation of the glutamic acid derivative **11** in 55% yield, with the xanthate functionality attached to the coupling product. Xanthate **8** was recovered after this reaction in 29% yield. The use of a large excess of acrylate (5 equiv) did not improve the yield but instead gave rise to the formation of substantial amounts of what seemed to be polymeric material. On the other hand, the use of excess xanthate **8** (2.5 equiv) did not lead to **11**; instead, after the reaction

(1) Barrett, G. C., Ed. *Chemistry and Biochemistry of the Amino Acids*; Chapman and Hall: London, 1985. (b) O'Donnell, M. J., Ed. α-*Amino Acid Synthesis*; Tetrahedron Symposia-in-Print number 33; Pergamon: Oxford, 1989; p 5253. (c) Williams, R. M. *Synthesis of Optically Active α-Amino Acids*; Pergamon: Oxford, 1989.

(2) Easton, C. J.; Hay, M. P. *J. Chem. Soc., Chem. Commun.* **1986**, 55.

(3) Baldwin, J. E.; Adlington, R. M.; Lowe, C.; O'Neil, I. A.; Sanders, G. L.; Schofield, C. J.; Sweeney, J. B. *J. Chem. Soc., Chem. Commun.* **1988**, 1030.

(4) Hamon, D. P. G.; Razzino, P.; Massy-Westropp, R. A. *J. Chem. Soc., Chem. Commun.* **1991**, 332.

(5) Hamon, D. P. G.; Massy-Westropp, R. A.; Razzino, P. *J. Chem. Soc., Chem. Commun.* **1991**, 722.

(6) Chai, C. L. L.; Page, D. M. *Tetrahedron Lett.* **1993**, *34*, 4373.

(7) For radical sequences involving a xanthate group transfer, see: (a) Delduc, P.; Tailhan, C.; Zard, S. Z. *J. Chem. Soc., Chem. Commun.* **1988**, 308. (b) Mestre, F.; Tailhan, C.; Zard, S. Z. *Heterocycles* **1989**, *28*, 171. (c) Forbes, J. E.; Zard, S. Z. *Tetrahedron Lett.* **1989**, *30*, 4367. (d) Forbes, J. E.; Zard, S. Z. *J. Am. Chem. Soc.* **1990**, *112*, 2034. (e) Forbes, J. E.; Tailhan, C.; Zard, S. Z. *Tetrahedron Lett.* **1990**, *31*, 2565. (f) Boivin, J.; Camara, J.; Zard, S. Z. *J. Am. Chem. Soc.* **1992**, *114*, 7909.

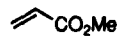
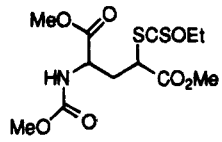
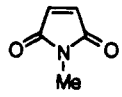
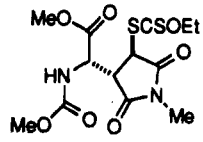
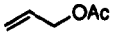
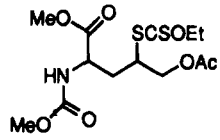
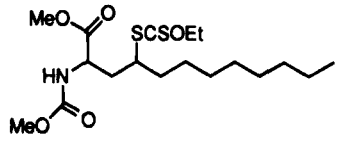
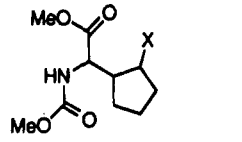
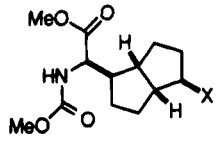
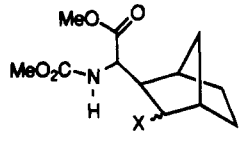
(8) Bernstein, Z.; Ben-Ishai, D. *Tetrahedron* **1977**, *33*, 881.

(9) This method has been applied before in the synthesis of penem derivatives, see: Eur. Pat. Appl. EP 131374 A1, 1985.

(10) Swern, D. In *Comprehensive Organic Chemistry*; Barton, D. H. R., Ollis, W. D., Eds.; Pergamon Press: Oxford, 1979; Vol. 1, p 909.

0022-3263/94/1959-3721$04.50/0

Table 1. Xanthate Transfer Radical Additions of 8 to Alkenes

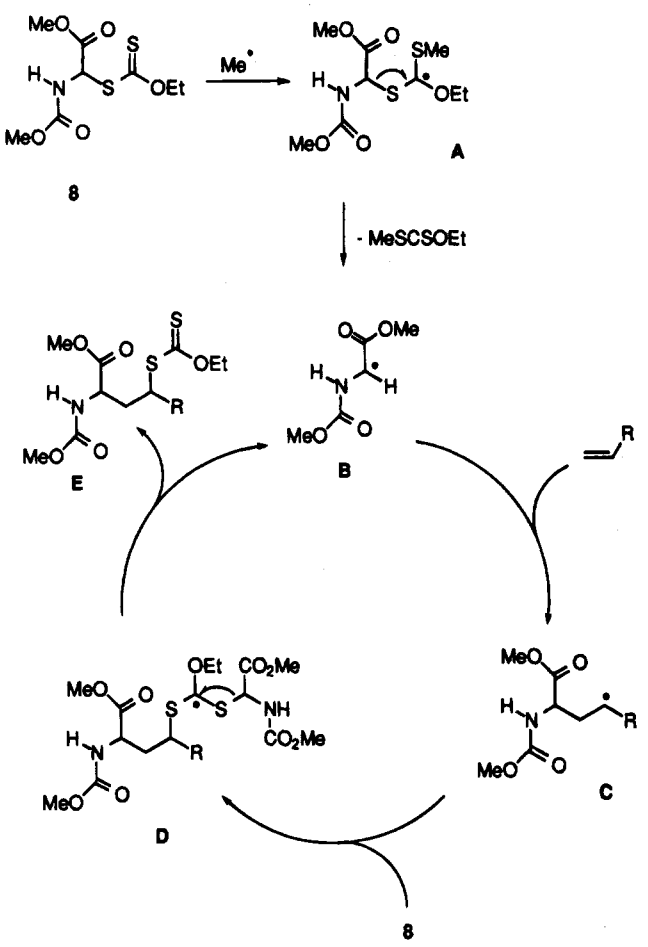
entry	alkene (equiv)		reaction time	products (yield, isomer ratio)		
1		(1.05)	3 h		**11** (55%, 55:45)	**8** (29%)
2		(1.4)	3.5 h		**12** (49%, 55:45)	
3		(1.05) (5)	3.5 h		**13** (25%, 53:47) **13** (41%, 54:46)	**8** (66%) **8** (44%)
4		(10)	1 h		**14** (75%, 53:47)	
5		(40)	2.5 h		Bu_3SnH → **15** X = SCSOEt → **16** X = H (two steps 65%)	
6		(40)	2.5 h		Bu_3SnH → **17** X = SCSOEt (75%, 50:50) → **18** X = H (two steps 73%, 50:50)	
7		(5)	3 h		Bu_3SnH → **19a,b** X = SCSOEt (69%) (X endo/exo = 81:19) → **20** X = H (two steps 61%, 50:50)	

only starting material **8** was isolated in 77% yield. Similar results were obtained in the addition of **8** to *N*-methylmaleimide (entry 2), which, in the presence of 1.4 equiv of alkene, gave the *trans*-substituted pyrrolidinedione **12** in 49% yield as a 55:45 mixture of diastereomers.

The addition of the glycine radical equivalent **8** to allyl acetate proved more difficult (entry 3). When 1.05 equiv of allyl acetate was used, the coupled product **12** was isolated in only 25% yield, along with 66% of starting material **8**. However, the use of excess alkene now led to a significant increase in the yield of the desired coupling product. In the presence of 5 equiv of allyl acetate, addition took place to give 41% yield of **13** along with 44% of starting material **8**. With these results in hand, the addition of **8** to 1-decene (entry 4) was performed with 10 equiv of alkene to afford α-amino ester **14** in 75% isolated yield. This reaction was performed in *tert*-butylbenzene at 150–160 °C in ordinary glasware, as the relatively high boiling point of 1-decene (166–173 °C) did not require sealed tube conditions. Next, we investigated the addition of xanthate **8** to cyclopentene (entry 5). In the presence of 40 equiv of cyclopentene, xanthate **15** was formed as a mixture of four diastereomers. After removal of the xanthate group with Bu_3SnH, *N,O*-protected cyclopentylglycine **16** was isolated in 65% yield as a single product.

Reaction of **8** with *cis,cis*-1,5-cyclooctadiene (entry 6) gave a tandem radical reaction: first addition to one of the double bonds, followed by 5-*exo* cyclization. In this way, xanthate **17** was isolated as a 1:1 mixture of diastereomers in 75% yield. After removal of the xanthate group with Bu_3SnH, *N,O*-protected octahydropentaleneglycine **18** was obtained in 73% yield (two steps), again as a 1:1 mixture of diastereomers. The *exo* orientation of the glycine group and the *cis*-fusion of the two carbocycles in **18** was derived from the clear NOE effects for NCH and the angular hydrogen atoms. The exo-orientation of the xanthate group in **17** remains tentative and is based on mechanistic reasoning. As a final experiment, the xanthate transfer radical addition of **8** to norbornene was investigated (entry 7). In the presence of 5 equiv of

Scheme 2



norbornene, the coupled product **19** was formed in 69% yield as an 81:19 mixture of endo and exo isomers, with respect to the xanthate group. Both **19a** and **19b** were obtained as ca. 1:1 mixtures of diastereomers. The stereochemistry of the endo product **19a** was derived from the clear NOE effects for NCH with both the adjacent bridgehead hydrogen atom and CHS. For **19b**, CHS showed vicinal coupling constants of 8.1 and 8.7 Hz, while in **19a** broad singlets were found. After removal of the xanthate group, *N,O*-protected 2-norbornylglycine **20** was isolated in 61% yield over two steps.

Discussion

From the results of the coupling reactions of glycine radical equivalent **8** to alkenes as presented above, it appears that in the case of unbiased alkenes (entries 3–7), the yield of coupled product may be improved by using a large excess of alkene, while lower yields are obtained when an excess of acrylate or maleimide is used (entries 1–2). These results may be explained as follows. Scheme 2 shows the chain reaction of the coupling of xanthate **8** to alkenes. The reaction is initiated with the addition of a methyl radical to the thiocarbonyl group of xanthate **8**, to yield radical **A** which is stabilized by three heteroatoms. Homolytic cleavage of the glycine C–S bond gives methyl xanthate and the captodatively-stabilized[11,12] glycine radical **B**. Reaction with an alkene gives radical **C**. Addition of this radical to xanthate **8** provides radical **D**, which will break the glycine C–S bond to give the xanthate transfer addition product **E** and another glycine radical equivalent **B**.

When 1 equiv of alkene was used, the addition of **8** to methyl acrylate led to the formation of the coupled product **11** in 55% yield (entry 1), while addition of allyl acetate gave **13** in only 25% yield. Apparently, the addition of glycine radical **B** to an electron-poor, activated alkene is more favorable than to an unbiased alkene. The use of excess acrylate did not improve yields, probably as a result of competition between the addition of radical **C** to either xanthate **8** or to the reactive alkene. Addition of **C** to the alkene leads to the undesired formation of telomers. In the case of unbiased alkenes such as allyl acetate, the use of excess alkene gave better yields. Apparently, the addition of **C** to unbiased alkenes is not competitive with the addition of **C** to xanthate **8**. The stereoselectivity for the radical additions of **8** to alkenes with respect to the glycine stereocenter was low, with the expected formation of ca. 1:1 mixtures of diastereomers in all cases. The addition of **8** to *N*-methylmaleimide was completely *trans*-selective, as may be expected from steric interactions in this system. This selectivity was also found in related xanthate transfer additions to this olefin.[7a,b] The tandem addition–cyclization reaction of **8** to *cis,cis*-1,5-cyclooctadiene gave the selective formation of the exo product **18**. This result is in accordance with the stereoselectivity of the radical addition of acetaldehyde to this diene.[13] The addition of glycine radical equivalent **8** to norbornene was exo-specific to give **20**. This selectivity in the addition of carbon-centered radicals to this alkene has been reported before.[14] The preferred formation of **19a** with an unfavorable *endo* orientation of the xanthate group is probably a result of a strong steric factor caused by the *exo*-glycine substituent, working against syn addition.[15]

In conclusion, we have shown that glycine radical equivalent **B** adds efficiently to alkenes under xanthate transfer conditions. This method nicely exploits the inherent stability of this captodative radical and gives access to various *N,O*-protected α-amino acids. Intramolecular versions of this method for the preparation of cyclic α-amino acids will be reported in due course.

Experimental Section

General Information. Experimental techniques and analytical measurements were applied as previously described.[16] IR spectral data are reported in cm^{-1}. NMR chemical shifts are reported in ppm, with $CDCl_3$ as a solvent. Benzene was distilled from sodium and stored on sodium wire. Chloro((methoxycarbonyl)amino)acetic acid methyl ester was prepared according to a literature procedure.[8]

((Ethoxy(thiocarbonyl))sulfanyl((methoxycarbonyl)amino)acetic Acid Methyl Ester (8). To a solution of chloro((methoxycarbonyl)amino)acetic acid methyl ester (4.40 g, 24.2 mmol) in CH_2Cl_2 (48 mL) was added potassium *O*-ethyl dithiocarbonate (4.08 g, 25.5 mmol), and the resulting suspension was

(11) Viehe, H. G.; Janousek, Z.; Merényi, R. *Acc. Chem. Res.* **1985**, *18*, 148.

(12) For a recent paper on the captodative radical stabilization of glycine radicals, see: Schulze, R.; Beckhaus, H.-D.; Rüchardt, C. *Chem. Ber.* **1993**, *126*, 1031.

(13) Dowbenko, R. *J. Am. Chem. Soc.* **1964**, *86*, 946.

(14) (a) Reusch, W. *J. Org. Chem.* **1962**, *27*, 1882. (b) Osborn, C. L.; Van Auken, T. V.; Trecker, D. J. *J. Am. Chem. Soc.* **1968**, *90*, 5806. (c) Traynham, J. G.; Lane, A. G.; Bhacca, N. S. *J. Org. Chem.* **1969**, *34*, 1302. (d) Byers, J. H.; Lane, G. C. *J. Org. Chem.* **1993**, *58*, 3355.

(15) This steric factor is even stronger in the radical addition of $BrCCl_3$ to norbornene, leading to the exclusive formation of the *trans*-substituted addition product, see ref 14c.

(16) Udding, J. H.; Fraanje, J.; Goubitz, K.; Hiemstra, H.; Speckamp, W. N.; Kaptein, B.; Schoemaker, H. E.; Kamphuis, J. *Tetrahedron: Asymmetry* **1993**, *4*, 425.

stirred for 20 min. Flash chromatography afforded **8** (4.529 g, 16.9 mmol, 70%) as a yellow oil, R_f 0.40 (EtOAc/hexane 1:2). Crystallization from pentane gave white needles, mp 65–65.5 °C: IR ($CHCl_3$) 3430, 2990, 2955, 1730, 1500, 1435; ^1H NMR (250 MHz) 1.40 (t, J = 7.1 Hz, 3H), 3.70 (s, 3H), 3.79 (s, 3H), 4.64 (q, J = 7.2 Hz, 2H), 5.87 (d, J = 9.0 Hz, 1H), 6.15 (d, J = 8.3 Hz, 1H); ^{13}C NMR (63 MHz) 13.45, 52.71, 53.42, 60.00, 70.43, 155.09, 167.61, 209.99. Anal. Calcd for $C_8H_{13}NO_5S_2$: C, 35.95; H, 4.90; N, 5.24. Found: C, 35.93; H, 4.96; N, 5.27.

General Procedure for the Radical Addition Reactions of 8 to Alkenes. To a solution of **8** in benzene in a resealable Pyrex tube were added the required alkene and di-*tert*-butyl peroxide (DTBP, 0.3 equiv), and argon was bubbled through the solution for 15 min. The tube was placed in an oil bath and heated at 150–155 °C. After cooling, the mixture was directly brought onto a silica column and subjected to flash chromatography.

2-((Ethoxy(thiocarbonyl))sulfanyl)-4-((methoxycarbonyl)amino)pentanedioic Acid Dimethyl Ester (11). A mixture of **8** (86.5 mg, 0.324 mmol), methyl acrylate (0.031 mL, 0.34 mmol, freshly distilled), and DTBP (14 mg, 0.1 mmol) in benzene (0.32 mL) was heated in a sealed tube at 150–155 °C for 3 h. Flash chromatography afforded two fractions. The first consisted of **8** (25 mg, 0.094 mmol, 29%). The second fraction consisted of a 55:45 mixture of diastereomers of **11** (63 mg, 0.178 mmol, 55%) as a colorless oil: R_f 0.35 (EtOAc/hexane 1:1); IR ($CHCl_3$) 3430, 2990, 2950, 1730, 1510, 1435; ^1H NMR (200 MHz) 1.41 (t, J = 7.0 Hz, 3H), 2.12–2.28 (m), 2.40 (t, J = 7.0 Hz) and 2.50–2.75 (m, 2H), 3.67 (s), 3.68 (s), 3.72 (s), 3.74 (s) and 3.75 (s, 9H), 4.47–4.54 (m, 2H), 4.62 (q, J = 7.1 Hz) and 4.63 (q, J = 7.1 Hz, 2H), 5.33 (d, J = 8.5 Hz, 0.55H), 5.42 (d, J = 8.5 Hz, 0.45H); ^{13}C NMR (63 MHz, most carbons show two peaks because of diastereomers) 13.59, 13.62, 33.98, 34.33, 48.39, 48.64, 52.26, 52.47, 52.64, 52.87, 52.95, 70.68, 70.77, 156.36, 170.37, 170.64, 171.62, 210.80, 211.15; HRMS calcd for $C_{12}H_{19}NO_7S_2$ 353.0603, found 353.0609.

(4-((Ethoxy(thiocarbonyl))sulfanyl)-1-methyl-2,5-dioxopyrrolidin-3-yl))(methoxycarbonyl)amino)acetic Acid Methyl Ester (12). A mixture of **8** (60.5 mg, 0.226 mmol), *N*-methylmaleimide (35.2 mg, 0.317 mmol), and DTBP (10 mg, 0.07 mmol) in benzene (0.23 mL) was heated in a sealed tube at 150–155 °C for 3.5 h. Flash chromatography afforded **12** (41.6 mg, 0.110 mmol, 49%) as a colorless oil: R_f 0.35 (EtOAc/hexane 1:1); IR ($CHCl_3$) 3420, 2990, 2950, 1785, 1710, 1510, 1435; ^1H NMR (400 MHz) 1.37 (t, J = 7.1 Hz) and 1.38 (t, J = 7.1 Hz, 3H), 3.03 (s) and 3.05 (s, 3H), 3.47 (dd, J = 3.3, 6.7 Hz, 0.55H), 3.69 (s) and 3.70 (s, 3H), 3.76 (s) and 3.83 (s, 3H), 3.83–3.89 (m, 0.45H), 4.26 (d, J = 6.5 Hz, 0.45H), 4.53 (d, J = 6.5 Hz, 0.55H), 4.61 (q, J = 7.1 Hz) and 4.62 (q, J = 7.1 Hz, 2H), 4.85 (dd, J = 3.0, 8.2 Hz, 0.45H), 5.01 (dd, J = 3.1, 9.0 Hz, 0.55H), 5.51 (d, J = 8.8 Hz, 0.45H), 5.96 (d, J = 8.8 Hz, 0.55H); ^{13}C NMR (63 MHz, most carbons show two peaks because of diastereomers) 13.57, 25.48, 25.57, 47.68, 48.15, 50.02, 50.28, 52.47, 52.77, 52.97, 53.16, 53.30, 70.88, 71.17, 156.15, 169.49, 170.23, 172.16, 172.30, 173.87, 175.07, 209.57, 209.65; HRMS calcd for $C_{13}H_{18}N_2O_7S_2$ 378.0555, found 378.0523.

5-Acetoxy-4-((ethoxy(thiocarbonyl))sulfanyl)-2-((methoxycarbonyl)amino)pentanoic Acid Methyl Ester (13). A mixture of **8** (88.6 mg, 0.331 mmol), allyl acetate (0.18 mL, 1.66 mmol), and DTBP (14.5 mg, 0.10 mmol) in benzene (0.33 mL) was heated in a sealed tube at 150–155 °C for 3.5 h. Flash chromatography gave two fractions. The first fraction consisted of **8** (39 mg, 0.16 mmol, 44%). The second fraction consisted of a 54:46 mixture of diastereomers of **13** (50.1 mg, 0.136 mmol, 41%) as a yellowish oil: R_f 0.40 (EtOAc/hexane 1:1); IR ($CHCl_3$) 3430, 2990, 2950, 1730, 1505, 1435, 1360, 1230; ^1H NMR (400 MHz) 1.41 (t, J = 7.1 Hz) and 1.42 (t, J = 7.1 Hz, 3H), 2.07 (s, 3H), 2.07–2.23 (m) and 2.30–2.37 (m, 2H), 3.67 (s) and 3.70 (s, 3H), 3.74 (s) and 3.75 (s, 3H), 4.03–4.11 (m, 1H), 4.21–4.39 (m, 2H), 4.49–4.61 (m, 1H), 4.63 (q, J = 7.1 Hz) and 4.64 (q, J = 7.1 Hz, 2H), 5.26 (J = 7.9 Hz, 0.54H), 5.43 (d, J = 7.7 Hz, 0.46H); ^{13}C NMR (63 MHz, most carbons show two peaks because of diastereomers) 13.67, 20.66, 20.70, 33.54, 33.85, 45.65, 46.09, 51.85, 52.01, 52.46, 52.61, 52.65, 64.82, 65.50, 70.39, 156.29, 170.42, 170.45, 171.91, 172.09, 212.19; HRMS calcd for $C_{13}H_{21}NO_7S_2$ 367.0759, found 367.0748.

In a similar way, **8** (88.9 mg, 0.333 mmol) was reacted with allyl acetate (0.038 mL, 0.35 mmol) and DTBP (15 mg, 0.10 mmol) in 0.33 mL of benzene for 3.5 h to give **13** (30 mg, 0.082 mmol, 25%) as a 53:47 mixture of diastereomers and recovered starting material **8** (59 mg, 0.22 mmol, 66%).

4-((Ethoxy(thiocarbonyl))sulfanyl)-2-((methoxycarbonyl)amino)dodecanoic Acid Methyl Ester (14). To a solution of **8** (150 mg, 0.561 mmol) in *tert*-butylbenzene (0.28 mL) were added 1-decene (1.06 mL, 5.6 mmol) and DTBP (25 mg, 0.17 mmol). The mixture was heated at 150–155 °C on an oil bath under a dry nitrogen atmosphere for 1 h. Flash chromatography afforded two fractions. The first fraction consisted of one diastereomer of **14** (11 mg, 0.027 mmol, 5%) as a colorless oil: R_f 0.30 (EtOAc/hexane 1:4); IR ($CHCl_3$) 3420, 2950, 2920, 2850, 1725, 1505, 1435; ^1H NMR (400 MHz) 0.87 (t, J = 7.0 Hz, 3H), 1.25 (br s, 12H), 1.42 (t, J = 7.1 Hz, 3H), 1.56–1.65 (m, 1H), 1.71–1.81 (m, 1H), 2.06–2.19 (m, 2H), 3.64–3.85 (m, 1H, CHS), 3.70 (s, 3H), 3.73 (s, 3H), 4.44 (dt, J = 4.8, 8.4 Hz, 1H), 4.63 (q, J = 7.1 Hz, 2H), 5.42 (d, J = 8.0 Hz, 1H); ^{13}C NMR (63 MHz) 13.77, 14.06, 22.64, 26.65, 29.19, 29.35 (two carbons), 31.83, 32.82, 37.50, 47.40, 52.04, 52.44, 52.50, 69.95, 156.62, 172.41, 214.35; HRMS calcd for $C_{18}H_{33}NO_5S_2$ 407.1800, found 407.1813. The second fraction consisted of a 1:1 mixture of diastereomers of **14** (160 mg, 0.393 mmol, 70%) as a light yellow oil: R_f 0.30 and 0.25 (EtOAc/hexane 1:4); IR ($CHCl_3$) 3420, 2950, 2920, 2850, 1725, 1505, 1435. Spectroscopic data derived from this mixture for the second diastereomer of **14**: ^1H NMR (400 MHz, characteristic signals) 3.67 (s, 3H), 3.75 (s, 3H), 3.78–3.86 (m, 1H), 5.22 (d, J = 7.1 Hz, 1H); ^{13}C NMR (100 MHz, characteristic signals) 34.28, 37.00, 47.87; HRMS calcd for $C_{18}H_{33}NO_5S_2$ 407.1800, found 407.1775.

(2-((Ethoxy(thiocarbonyl))sulfanyl)cyclopentyl)((methoxycarbonyl)amino)acetic Acid Methyl Ester (15) and Cyclopentyl((methoxycarbonyl)amino)acetic Acid Methyl Ester (16). A mixture of **8** (102.7 mg, 0.384 mmol), cyclopentene (1.35 mL, 15.4 mmol, freshly distilled), and DTBP (17 mg, 0.12 mmol) in benzene (0.19 mL) was heated in a sealed tube at 150–155 °C for 2.5 h. Flash chromatography (EtOAc/hexane 1:4) afforded a mixture of diastereomers of **15** (95.2 mg), containing some starting material (**8**). This mixture was taken up in benzene (6 mL) and AIBN (5 mg, 0.03 mmol) and Bu_3SnH (0.323 mL, 1.2 mmol) were added. After the mixture was heated at reflux for 0.5 h, the DBU workup procedure[17] was applied. Flash chromatography afforded **16** (54 mg, 0.251 mmol, 65%) as a yellowish oil: IR ($CHCl_3$) 3440, 2950, 2860, 1720, 1505, 1445, 1435, 1355, 1335; ^1H NMR (400 MHz) 1.25–1.41 (m, 2H), 1.50–1.80 (m, 6H), 2.15–2.25 (m, 1H), 3.66 (s, 3H), 3.71 (s, 3H), 4.27 (t, J = 7.9 Hz, 1H), 5.22 (d, J = 7.9 Hz, 1H); ^{13}C NMR (100 MHz) 24.97, 25.22, 28.21, 28.84, 42.57, 52.07, 52.28, 56.94, 156.77, 173.06; HRMS calcd for $C_{10}H_{17}NO_4$ 215.1157, found 215.1158.

(1*R,3a*R**,4*R**,6a*R**)-(4-((Ethoxy(thiocarbonyl))sulfanyl))octahydropentalen-1-yl)((methoxycarbonyl)amino)acetic Acid Methyl Ester (17) and (1*R**,3a*R**,6a*R**)-(Octahydropentalen-1-yl)((methoxycarbonyl)amino)acetic Acid Methyl Ester (18).** A mixture of **8** (137.2 mg, 0.5132 mmol), *cis,cis*-1,5-cyclooctadiene (2.5 mL, 20.5 mmol, freshly distilled), and DTBP (22.5 mg, 0.154 mmol) in benzene (0.26 mL) was heated in a sealed tube at 150–155 °C for 2.5 h. Flash chromatography afforded **17** as a 50:50 mixture of diastereomers (0.145 mg, 0.386 mmol, 75%): R_f 0.50 (EtOAc/hexane 1:2); ^1H NMR (200 MHz) 1.23–1.47 (m, 3H), 1.39 (t, J = 7.1 Hz, 3H), 1.64–2.53 (m, 8H), 3.60–3.74 (m, 1H), 3.65 (s, 3H), 3.71 (s, 3H), 4.31 (t, J = 6.0 Hz) and 4.36 (t, J = 6.0 Hz, 1H), 4.60 (q, J = 7.1 Hz, 2H), 5.27 (d, J = 9.1 Hz) and 5.34 (d, J = 9.1 Hz, 1H). This mixture was taken up in benzene (7.7 mL), and AIBN (6.4 mg, 0.04 mmol) and Bu_3SnH (0.534 mL, 1.54 mmol) were added. After the solution was heated at reflux for 0.5 h, the DBU workup procedure[17] was applied. Flash chromatography afforded **18** (96 mg, 0.376 mmol, 73%) as a 50:50 mixture of diastereomers: R_f 0.30 (EtOAc/hexane 1:2); IR ($CHCl_3$) 3440, 3950, 2860, 1720, 1510, 1445, 1435, 1340; ^1H NMR (400 MHz) 1.01–1.10 (m, 1H), 1.17–1.35 (m, 3H), 1.44–1.89 (m, 7H), 2.12–2.21 (m, 1H), 2.39–2.43 (m, 1H), 3.65 (s, 3H), 3.70 (s) and 3.71 (s, 3H), 4.29 (t, J = 8.5 Hz, 0.5H), 4.32 (t, J = 8.5 Hz, 0.5H), 5.20 (d, J = 8.4 Hz, 0.5H), 5.27 (d, J = 8.4 Hz, 0.5H); ^{13}C NMR (100 MHz, most carbons show two peaks because of diastereomers) 25.21, 25.75, 30.26, 31.28, 32.35, 32.69, 32.78, 33.14, 33.16, 33.27, 43.44, 43.80, 45.13, 45.32, 50.29, 50.33, 51.95, 52.10, 52.28, 56.42, 56.54, 156.69, 156.80, 172.98, 173.14; HRMS calcd for $C_{13}H_{21}NO_4$ 255.1470, found 255.1463.

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(3-((Ethoxy(thiocarbonyl))sulfanyl)bicyclo[2.2.1]hept-2-yl)((methoxycarbonyl)amino)acetic Acid Methyl Ester (19). A mixture of **8** (87.3 mg, 0.3265 mmol), norbornene (154 mg, 1.63 mmol), and DTBP (14 mg, 0.10 mmol) in benzene (0.33 mL) was heated in a sealed tube at 150–155 °C for 3 h. Flash chromatography afforded two fractions. The first fraction consisted of a 42:58 mixture of diastereomers of **(1*R**,2*S**,3*S**,4*S**)-(3-((ethoxy(thiocarbonyl))sulfanyl))bicyclo[2.2.1]hept-2-yl)-((methoxycarbonyl)amino)acetic acid methyl ester (19a)** (42 mg, 0.12 mmol, 37%): R_f 0.50 (EtOAc/hexane 1:2); IR ($CHCl_3$) 3430, 2950, 2870, 1720, 1505, 1450, 1435, 1235, 1050; ^{1}H NMR (400 MHz) 1.11–1.18 (m, 1H), 1.33–1.70 (m, 6H), 1.39 (t, J = 7.1 Hz) and 1.40 (t, J = 7.1 Hz, 3H), 2.27 (br s, 1H), 2.63 (bs, 1H), 3.64 (s), 3.66 (s), 3.72 (s) and 3.74 (s, 6H), 3.76 (br s, 0.58H), 3.87 (br s, 0.42H), 4.21 (t, J = 8.7 Hz, 0.42H), 4.30 (t, J = 8.3 Hz, 0.58H), 4.61 (q, J = 7.2 Hz) and 4.62 (q, J = 7.2 Hz, 2H), 5.26 (d, J = 7.8 Hz) and 5.29 (d, J = 7.8 Hz, 1H); ^{13}C NMR (63 MHz, most carbons show two peaks because of diastereomers) 13.72, 23.13, 23.28, 29.81, 29.93, 36.46, 36.64, 38.84, 39.46, 40.69, 40.79, 49.87, 50.43, 52.30, 52.35, 52.41, 53.33, 53.43, 56.24, 56.78, 69.65, 69.74, 156.49, 156.67, 171.78, 213.53, 213.91; HRMS calcd for $C_{15}H_{23}NO_5S_2$ 361.1018, found 361.1020. The second fraction consisted of a 50:10:20:20 mixture of diastereomers of **19** (38.1 mg, 0.105 mmol, 32%), with **19a/19b** = 60:40: R_f 0.50 and 0.45 (EtOAc/hexane 1:2). Spectroscopic data derived from this mixture for **(1*R**,2*S**,3*R**,4*S**)-(3-((ethoxy(thiocarbonyl)sulfanyl))-bicyclo[2.2.1]hept-2-yl)((methoxycarbonyl)amino)acetic acid methyl ester (19b)**: ^{1}H NMR (400 MHz, characteristic signals) 2.22 (d, J = 12.9 Hz, major isomer), 2.38–2.42 (m) and 2.50 (t, J = 6.8 Hz, 2H), 3.98 (d, J = 8.1 Hz) and 4.04 (dd, J = 1.6, 8.7 Hz, 1H), 4.24–4.29 (m) and 4.35–4.40 (m, 1H), 4.95 (d, J = 9.9 Hz, 0.5H), 5.16 (d, J = 6.8 Hz, 0.5H); ^{13}C NMR (50 MHz, characteristic signals, most carbons show two peaks because of diastereomers) 28.12, 28.51, 29.66, 30.40, 35.97, 36.18, 37.88, 39.66, 44.63, 44.91, 47.79, 49.18, 56.40, 56.60.

(1*R,2*S**,4*S**)-(Bicyclo[2.2.1]hept-2-yl)((methoxycarbonyl)amino)acetic Acid Methyl Ester (20).** A mixture of **8** (100 mg, 0.374 mmol), norbornene (176 mg, 1.87 mmol), and DTBP (16.4 mg, 0.11 mmol) in benzene (0.37 mL) was heated in a sealed tube at 150–155 °C for 3 h. Flash chromatograpyh afforded a 75:25 mixture of **19a** and **19b** (86 mg, 0.24 mmol, 64%). Both were present as approximately 1:1 mixtures of their diastereomers, R_f 0.50 and 0.45 (EtOAc/hexane 1:2). The mixture was taken up in benzene (4.8 mL) and AIBN (4 mg, 0.024 mmol) and Bu_3SnH (0.256 mL, 0.95 mmol) were added. After the mixture was heated at reflux for 0.5 h, the DBU workup procedure[17] was applied. Flash chromatography afforded **20** (55.2 mg, 0.23 mmol, 61% from **8**) as a 50:50 mixture of diastereomers: R_f 0.35 (EtOAc/hexane 1:2); IR ($CHCl_3$) 3430, 2950, 2870, 1720, 1505, 1450, 1435; ^{1}H NMR (400 MHz) 1.10–1.14 (m, 3H), 1.25–1.38 (m, 3H), 1.41–1.56 (m, 2H), 1.65–1.79 (m, 1H), 2.13 (s, 0.5H), 2.19 (s, 0.5H), 2.24 (s, 1H), 3.65 (s) and 3.66 (s, 3H), 3.70 (s) and 3.73 (s, 3H), 3.99 (t, J = 9.3 Hz) and 4.01 (t, J = 9.2 Hz, 1H), 5.09 (d, J = 7.7 Hz, 0.5H), 5.18 (d, J = 8.1 Hz, 0.5H); ^{13}C NMR (100 MHz, most carbons show two peaks because of diastereomers) 28.39, 28.49, 29.88, 29.99, 33.82, 34.52, 35.72, 35.87, 36.40, 36.49, 38.36, 38.69, 45.16, 45.36, 52.04, 52.31, 52.56, 57.56, 57.99, 156.58, 156.77, 172.98, 173.16; HRMS calcd for $C_{12}H_{19}NO_4$ 241.1314, found 241.1331.

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Supplementary Material Available: Copies of ^{1}H and/or ^{13}C NMR spectra for all new compounds, i.e. **8**, **11–14**, **16–20** (23 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of this journal, and can be ordered from the ACS; see any current masthead page for ordering information.