$CDCl_3$) δ 2.48 (s, 3 H), 3.81 (s, 3 H), 6.68 (d, 1 H, J = 2.39 Hz), 6.97 (d, 1 H, J = 3.49 Hz), 6.87–7.47 (dd, 4 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 15.39, 55.32, 114.19, 121.79, 126.00, 126.73, 127.62, 138.41, 141.87, 158.81.

2-(2-Phenylethynyl)-5-(1-propynyl)thiophene (20f):[45] light yellow oil, yield 27 mg (28%); IR (neat, cm^{-1}) 3055 (aromatic CH), 2922 (aliphatic CH), 1597 (aromatic C≡C); ^1H NMR (300 MHz, $CDCl_3$) δ 2.07 (s, 3 H), 6.98 (d, 1 H, J = 3.77 Hz), 7.08 (d, 1 H, J = 3.81 Hz), 7.32–7.51 (m, 5 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 4.72, 72.67, 82.34, 91.30, 93.23, 122.63, 123.18, 125.60, 128.34, 128.49, 130.83, 131.40, 131.55; HREIMS m/z 222.0532 (calcd for $C_{15}H_{10}S$ 222.0503).

2,5-Bis(2-phenylethynyl)thiophene (20g):[45-48] brown oil, yield 91 mg (92%); IR (neat, cm^{-1}) 1598 (aromatic C≡C); ^1H NMR (300 MHz, $CDCl_3$) δ 7.15 (s, 2 H), 7.34–7.53 (m, 10 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 82.25, 94.04, 122.56, 124.64, 128.39, 128.65, 131.45, 131.80; HREIMS m/z 284.0614 (calcd for $C_{20}H_{12}S$ 284.0660).

Acknowledgement is made to the National Institutes Health for support of this research and to the National Science Foundation for financial assisstance towards the purchase of the mass spectrometers and NMR spectrometers.

Registry No. 1, 63543-09-9; 2, 71539-72-5; 3, 495-71-6; 4, 24314-35-0; 5, 2403-62-5; 6, 138695-84-8; 7, 583-05-1; 8, 53842-12-9; 9, 2108-54-5; 10, 22956-51-0; 11, 138695-85-9; 12, 130372-07-5; 13, 127793-62-8; 14, 138695-86-0; 15 (isomer 1), 138695-87-1; 15 (isomer 2), 138695-95-1; 16 (isomer 1), 138695-88-2; 16 (isomer 2), 138695-96-2; 17, 138695-89-3; 18a, 138695-90-6; 18b, 138695-93-9; 19a (isomer 1), 138695-91-7; 19a (isomer 2), 138695-97-3; 19b, 138695-94-0; 20a, 1445-78-9; 20b, 82366-97-0; 20c, 5069-26-1; 20d, 95650-85-4; 20e, 85093-01-2; 20f, 138695-92-8; 20g, 90267-18-8; $(Sn(Bu)_3)_2S$, 4808-30-4; $(Sn(cyclohexyl)_3)_2S$, 13121-76-1; $(Sn(phenyl)_3)_2S$, 77-80-5; methyl vinyl ketone, 78-94-4; divinyl sulfone, 77-77-0; 4-nitrobenzaldehyde, 555-16-8.

Supplementary Material Available: ^1H NMR of 6, 12–17, 18a, 18b, 19b, and 20f (35 pages). Ordering information is given on any current masthead page.

(45) Acetylenic thiophenes 20f and 20g are unstable in light at 22–24 °C.

(46) The thiophene 20g has been previously synthesized but no spectral data were reported.[47,48]

(47) Sanechika, K.; Yamamoto, T.; Yamamoto, A. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 752.

(48) Hudson, J. B.; Towers, G. H. N.; Abramowski, Z.; Hudson, L.; Rossi, R.; Carpita, A.; Neri, D. *Chemosphere* **1989**, *18*, 2317.

Tandem S_N2–Michael Reactions for the Preparation of Simple Five- and Six-Membered-Ring Nitrogen and Sulfur Heterocycles

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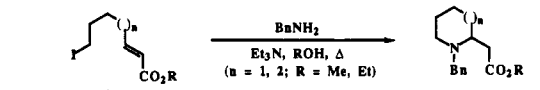
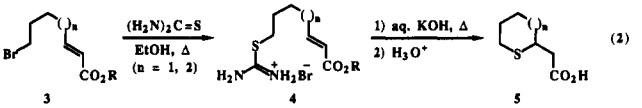
A one-pot tandem S_N2–Michael addition sequence has been developed for the preparation of five-membered- and six-membered-ring nitrogen and sulfur heterocycles from 6- or 7-halo-2-alkenoate esters. Nitrogen-containing rings are prepared by reaction of the ω-halo-2-alkenoate ester with a primary amine in the presence of triethylamine. The sulfur analogues are generated by thiourea displacement of the halide followed by base hydrolysis of the isothiouronium salt. Yields are routinely in the 60–80% range. Experiments are described which elucidate the chronology of the reaction sequences. Ring size and steric hindrance to the initial substitution reaction appear to be the only limitations of the procedure.

As part of our synthetic program aimed at the development of new approaches to functionalized ring systems, we have explored the use of a tandem S_N2–Michael addition route to nitrogen and sulfur heterocycles bearing an acetic acid residue at C-2. Previous studies by Boeckman and co-workers[2] have demonstrated the use of a sequential Gabriel amine synthesis–Michael addition for the preparation of a dihydroisoindole-1-acetic ester precursor to the lycorine alkaloids. In a different context, Vedejs and co-workers[3] have reported the formation of methyl (±)-2*H*-tetrahydrothiopyran-2-acetate from methanolysis of methyl (*E*)-7-(acetylthio)-2-heptenoate. We report here several related procedures which allow for the one-pot synthesis of five- and six-membered-ring nitrogen and sulfur heterocycles by reaction of 6- or 7-halo-2-alkenoate esters with benzylamine (eq 1) or thiourea (eq 2), respectively.



(1)

1 2



(2)

3 4 5

Synthesis of Starting Materials. The heterocyclization substrates used in this study are depicted in Scheme I. Ethyl (*E*)-2-(bromomethyl)cinnamate (6) was prepared by known methods.[4] Ethyl (*E*)-2-(2-bromoethyl)-cinnamate (8) was prepared by Wittig olefination of 2-(2-bromoethyl)benzaldehyde (7)[5] with ethyl (triphenylphosphoranylidene)acetate; treatment of 8 with sodium iodide in acetone afforded 9. Ethyl (*E*)-6-bromo-2-hexenoate (10), ethyl (*E*)-7-bromo-2-heptenoate (12), ethyl

(1) Undergraduate research participant, 1991–1992.

(2) Boeckman, R. K., Jr.; Sabatucci, J. P.; Goldstein, S. W.; Springer, D. M.; Jackson, P. F. *J. Org. Chem.* **1986**, *51*, 3740–3742.

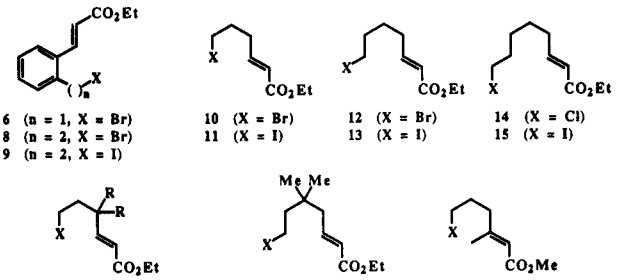
(3) Vedejs, E.; Mullins, M. J.; Renga, J. M.; Singer, S. P. *Tetrahedron Lett.* **1978**, 519–522.

(4) Norcross, B. E.; Lansinger, J. M.; Martin, R. L. *J. Org. Chem.* **1977**, *42*, 369–372.

(5) Reiche, A.; Schmitz, E. *Chem Ber.* **1956**, *89*, 1254–1262.

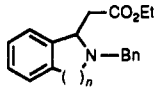
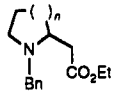
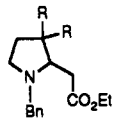
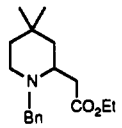
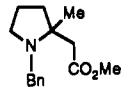
0022-3263/92/1957-1727$03.00/0

Scheme I. Heterocyclization Substrates



6 (n = 1, X = Br)
8 (n = 2, X = Br)
9 (n = 2, X = I)
10 (X = Br)
11 (X = I)
12 (X = Br)
13 (X = I)
14 (X = Cl)
15 (X = I)
19 (X = Br, R,R = Me)
20 (X = I, R,R = Me)
21 (X = Br, R,R = -(CH$_2$)$_5$-)
22 (X = I, R,R = -(CH$_2$)$_5$-)
23 (X = Br)
24 (X = I)
25 (X = Cl)
26 (X = I)

Table I. Formation of Nitrogen Heterocycles by S_N2-Michael Addition

halo ester	nitrogen heterocycle		yield (%)[a]
6, 9		**27** (n = 1) **28c** (n = 2)	69 *b*
11, 13, 15		**29** (n = 1) **30** (n = 2) **31** (n = 3)	63 59 <5
19, 22		**32** (R,R = Me) **33** (R,R = -(CH$_2$)$_5$-)	64 68
24		**34**	66
26		**35**	71

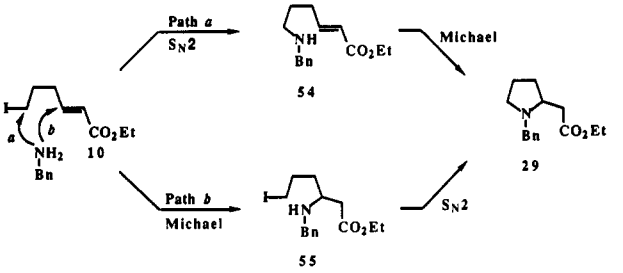
[a] Yields refer to isolated purified products. [b] Use of our conditions resulted in elimination to give ethyl (*E*)-2-vinylcinnamate (**28a**) in 90% yield. The Gabriel approach[2] gave ethyl (±)-1,2,3,4-tetrahydroisoquinoline-1-acetate (**28c**) in 72% yield.

8-chloro-2-octenoate (**14**), and the corresponding iodides (**11**, **13**, and **15**) were prepared by adaptations of established literature procedures.[6] Ethyl (*E*)-6-bromo-4,4-dimethyl-2-hexenoate (**19**), ethyl (*E*)-3-[1-(2-bromoethyl)-cyclohexyl]propenoate (**21**), ethyl (*E*)-7-bromo-5,5-dimethyl-2-heptenoate (**23**), and the corresponding iodides **20**, **22**, and **24** were synthesized from 5-bromo-3,3-dimethyl-1-pentene (**16**),[7] 1-(2-bromoethyl)-1-ethenylcyclohexane (**17**),[7] and 6-bromo-4,4-dimethyl-1-hexene (**18**),[7] respectively, by a sequence involving (1) ozonolysis, (2) Wittig olefination, and (3) halogen exchange. Finally, methyl 6-iodo-3-methyl-2-hexenoate (**26**) was prepared by halogen exchange of the known chloride **25**.[8]

Results and Discussion

The results of our study on the tandem S_N2–Michael addition reaction for the synthesis of nitrogen heterocycles are shown in Table I. Reaction of the ω-iodo-2-alkenoate

Scheme II. Mechanistic Possibilities for the Formation of Nitrogen Heterocycles



with benzylamine in ethanol containing excess triethylamine afforded 60–75% of the five- and six-membered-ring nitrogen heterocycles in one step. The feasibility of the method relies on the fact that the intramolecular ring closure reaction occurs at a faster rate than intermolecular alkylation or Michael addition involving a second molecule of the halide. The reaction was successful for a number of primary amines, but benzylamine offered several advantages. In addition to being more synthetically versatile, the *N*-benzyl group allowed visualization of TLC plates used to monitor the reaction and added a molecular weight contribution similar to that of the iodide being displaced, permitting reactions to be run on a smaller scale. The corresponding bromides were also used for the formation of nitrogen heterocycles, but the reaction was generally much slower.

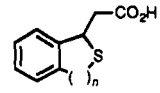
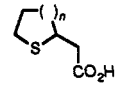
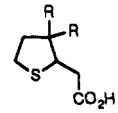
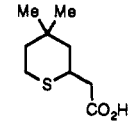
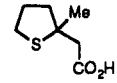
For the preparation of five- and six-membered-ring sulfur heterocycles, the reaction was generally carried out in two stages. The halide was first converted to its isothiouronium salt (i.e. **4**) by reaction with thiourea in refluxing ethanol. Although it was possible to carry out the entire transformation in a single operation, the isothiouronium salts were generally isolated and characterized. Treatment of the salt with 20% aqueous KOH resulted in liberation of the thiolate anion which underwent intramolecular Michael addition to the activated double bond. The acids were easily purified by extraction techniques and isolated essentially pure. An alternative procedure involving reaction of the halide with Na_2S produced a complex mixture of products and could not be used. A summary of our results using thiourea is given in Table II.

Mechanistically, it was of interest to determine the chronology of these processes since one can envision two possible reaction scenarios for each transformation. In the formation of cyclic amines, it is conceivable that S_N2 occurs first followed by Michael addition (path a) but it is also possible that the reverse sequence initiated by Michael addition (path b) is operating (see Scheme II). While a recent report[9] has demonstrated the displacement of an allylic bromide in the presence of a Michael acceptor, it was necessary to explore this process on an unactivated substrate approximating those in the current study. To this end, an ethanol solution of 1-iodohexane and ethyl crotonate was treated with benzylamine and triethylamine using the standard protocol. GC analysis of the reaction mixture indicated that benzylamine and 1-iodohexane were totally consumed after 12 h; ethyl crotonate was also consumed during this time, but to a much lesser extent. These observations suggest that path a more accurately describes the sequence of events.

In the sulfur heterocyclization, isolation of the isothiouronium salt clearly establishes halide displacement as the

(6) Cooke, M. P., Jr.; Widener, R. K. *J. Org. Chem.* **1987**, *52*, 1381–1396.
(7) Beckwith, A. L. J.; Easton, C. J.; Lawrence, T.; Serelis, A. K. *Aust. J. Chem.* **1983**, *36*, 545–556. 1-(2-Bromoethyl)-1-ethenylcyclohexane was prepared from cyclohexylidenemethanol by a synthesis parallel to that described for 5-bromo-3,3-dimethyl-1-pentene.
(8) Balsevich, J. *Can. J. Chem.* **1983**, *61*, 1053–1059.
(9) Barco, A.; Benetti, S.; Casolari, A.; Pollini, G. P.; Spalluto, G. *Tetrahedron Lett.* **1990**, *21*, 3039–3042.

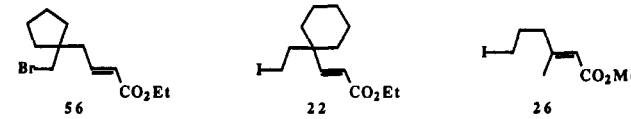
Table II. Formation of Sulfur Heterocycles by S_N2–Michael Addition

halo ester	salt[a]	sulfur heterocycle		yield (%)[b]
6	36		**45** (n = 1)	69
8	37		**46** (n = 2)	73
10	38		**47** (n = 1)	60
12	39		**48** (n = 2)	69
15	40		**49** (n = 3)	<5
19	41		**50** (R,R = Me)	75
21	42		**51** (R,R = –$(CH_2)_5$–)	71
23	43		**52**	78
26	44		**53**	76

[a] Isothiouronium salts were produced in >95% yield. [b] Overall yields of isolated, purified products.

initial reaction of the sequence. The base required for the second stage of the reaction, however, performs three functions: (1) neutralization of the isothiouronium halide salt, (2) hydrolysis of the carboxylic ester, and (3) cleavage of the amidine group to give the thiolate anion which adds in Michael fashion to the α,β-unsaturated acid or ester. While it seemed reasonable that neutralization of the isothiouronium salt occurred first, the chronology of the last two steps was not obvious. To elucidate the train of events leading to ring closure, a control experiment was run where benzylisothiouronium bromide and ethyl cinnamate were simultaneously treated with 20% KOH in 4:1 water/ethanol at room temperature. Under these conditions, TLC analysis indicated that the carboxylic ester was hydrolyzed more rapidly. Benzyl mercaptan was also formed but at a slower rate. This would suggest that some of the final intramolecular Michael reaction involves addition to the monoactivated acrylic acid moiety, a phenomenon having relatively little precedent.[10]

Limitations to the current procedure derived mainly from ring-size effects and steric hindrance at the initial S_N2 reaction site; dehydrohalogenation, observed in the reaction of phenethyl iodide **9**, was not a general problem. While the S_N2–Michael sequence proved equally successful for the formation of five- and six-membered rings, attempts to convert **15** to the seven-membered-ring heterocycles **31** and **49** yielded complex mixtures from which none of the ring-closed products could be isolated. This reflects the increased entropy barrier to approach of remote reactive sites for seven-membered-ring closure. Steric factors also proved to be important. In substrate **56**,[11] where the bromide is essentially neopentyl, the heterocyclization reaction failed and >80% of the starting material was recovered. On the other hand, substrates **22** and **26**, having hindrance at the β-position of the acrylate acceptor moiety, reacted smoothly to give the expected heterocyclic compounds in good yields. Thus, once halide displacement



56 **22** **26**

occurs, the minimal steric demand and greater nucleophilicity[12] of the nitrogen and sulfur donors as well as their proximity to the Michael acceptor allow for efficient ring closure. Finally, these results with hindered substrates further support the assertion that the tandem process is initiated by halide displacement and establish the pivotal role of this reaction in the sequence.

The S_N2–Michael reaction constitutes an efficient approach to the construction of five- and six-membered ring heterocycle-substituted acetic acid derivatives. The ease and efficiency of the process make it a valuable addition to the limited synthetic methodology currently available for the preparation of these systems. Further efforts are underway to expand the number of accessible heterocycles using this approach,[13] to induce asymmetry in the products, and to apply this technology to the synthesis of biologically active natural and unnatural compounds.

Experimental Section

All solvents and reagents were used as received from the vendors. All reactions were run under dry N_2. Reactions were monitored by one of the following methods: (1) TLC on hard layer silica gel GF plates (Analtech) with UV or phosphomolybdic acid detection or (2) capillary GC (Varian 3400) with FI detection on an SE-30 column (6-m × 0.25-mm i.d., 0.25-μm film thickness) programmed between 40 and 150 °C. Preparative separations were performed using one of the following methods: (1) PTLC on 20-cm × 20-cm silica gel GF (2000-μm thickness) plates (An-

(10) Bergman, E. D.; Ginsberg, D.; Pappo, R. *Org. React.* **1959**, *10*, 179–555.

(11) Compound **56** was prepared using the following sequence of reactions: (1) alkylation of the anion from ethyl cyclopentanecarboxylate (LDA, THF–HMPA, –78 °C, 78%) with allyl bromide, (2) reduction of the ester ($LiAlH_4$, THF, 80%), (3) conversion to the bromide (MsCl, Et_3N, CH_2Cl_2; LiBr, Et_2O–HMPA, 87%), (4) ozonolysis of the allylic double bond (O_3, MeOH; then Me_2S, 87%), and (5) Wittig olefination ($Ph_3P{=}CHCO_2Et$, PhH, Δ, 72%). Conversion to the iodide by halogen exchange was not possible in this compound.

(12) (a) Isaacs, N. S. *Physical Organic Chemistry*; Longman-Wiley: New York, 1987; pp 242–246. (b) Carey, F. A.; Sundberg, R. J. *Advanced Organic Chemistry, Pt. A*, 3rd ed.; Plenum: New York, 1990; pp 284–289. (c) March, J. *Advanced Organic Chemistry*, 3rd ed.; Wiley: New York, 1985; pp 304–310.

(13) Studies on the formation and stereochemistry of fused ring systems generated by this method will be the subject of a future publication, Bunce, R. A.; Peeples, C. J. Unpublished results.

altech), (2) flash chromatography[14] on silica gel (Grace, grade 62, 60–200 mesh) mixed with Sylvania 2282 phosphor slurry packed into Vycor columns (band elution monitored by hand-held UV lamp) or (3), flash vacuum chromatography[15] on a 10-cm × 10-cm plug of silica gel (60–200 mesh). Melting points are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were measured at 300 and 75 MHz, respectively. MS (EI/DP) and HRMS (EI/DP) were obtained at 70 eV. MS (FAB, actually LSIMS) were obtained in a thioglycerol matrix using Cs at 35 keV.

Ethyl (*E*)-2-(bromomethyl)cinnamate (**6**) was prepared by the method of Norcross and co-workers.[4] Ethyl (*E*)-6-bromo-2-hexenoate (**10**),[16] ethyl (*E*)-7-bromo-2-heptenoate (**12**),[17] and ethyl (*E*)-8-chloro-2-octenoate (**14**) were prepared from 4-bromo-1-butanol,[16] 5-bromo-1-pentanol,[18] and commercial 6-chloro-1-hexanol by adaptations of known methods.[6] The physical and spectral data for the previously unreported **14** were as follows: bp 90–95 °C (0.5 mmHg); IR (thin film) 1728, 1660 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.96 (dt, 1 H, J = 15.6, 6.8 Hz), 5.83 (d, 1 H, J = 15.6 Hz), 4.18 (q, 2 H, J = 7.1 Hz), 3.54 (t, 2 H, J = 6.5 Hz), 2.22 (m, 2 H), 1.80 (m, 2 H), 1.50 (m, 4 H), 1.29 (t, 3 H, J = 7.1 Hz); ^{13}C NMR ($CDCl_3$) δ 166.5, 148.6, 121.5, 60.1, 44.7, 32.2, 31.6, 27.2, 26.3, 14.2; HRMS m/e for $C_{10}H_{17}{}^{35}ClO_2$ calcd 204.0917, found 204.0916; m/e for $C_{10}H_{17}{}^{37}ClO_2$ calcd 206.0887, found 206.0886.

Anal. Calcd for $C_{10}H_{17}ClO_2$: C, 58.62; H, 8.30. Found: C, 58.56; H, 8.29.

Ethyl (*E*)-2-(2-Bromoethyl)cinnamate (8). A 250-mL benzene solution of 8.26 g (38.8 mmol) of 2-(2-bromoethyl)-benzaldehyde (**7**)[5] was treated with 13.5 g (38.8 mmol) of ethyl (triphenylphosphoranylidene)acetate, refluxed for 6 h, and concentrated to give a tan semisolid mass. The product was purified by flash vacuum chromatography[15] using 15% ether in hexane. Concentration of the eluent afforded the crude bromo ester as a light yellow oil which was purified by flash chromatography[14] on an 80-cm × 2.5-cm silica gel column eluted with 4% ether in hexane. The first and major band yielded 7.46 g (26.4 mmol, 68%) of **8** as a colorless oil: IR (thin film) 3050, 1710, 1630 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.95 (d, 1 H, J = 15.6 Hz), 7.58 (m, 1 H), 7.29 (m, 3 H), 6.39 (d, 1 H, J = 15.6 Hz), 4.28 (q, 2 H, J = 7.2 Hz), 3.51 (t, 2 H, J = 7.5 Hz), 3.31 (t, 2 H, J = 7.5), 1.35 (t, 3 H, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 166.7, 141.1, 138.2, 133.3, 130.6, 130.2, 127.7, 127.0, 120.7, 60.7, 36.5, 32.1, 14.4; HRMS m/e for $C_{13}H_{15}{}^{79}BrO_2$ calcd 282.0255, found 282.0249; m/e for $C_{13}H_{15}{}^{81}BrO_2$ calcd 284.0235, found 284.0237.

Anal. Calcd for $C_{13}H_{15}BrO_2$: C, 55.12; H, 5.30. Found: C, 55.08; H, 5.29.

Ethyl (*E*)-6-Bromo-4,4-dimethyl-2-hexenoate (19), Ethyl (*E*)-3-[1-(2-Bromoethyl)cyclohexyl]propenoate (21), and Ethyl (*E*)-7-Bromo-5,5-dimethyl-2-heptenoate (23). Solutions containing 100 mmol of 5-bromo-3,3-dimethyl-1-pentene (**16**),[7] 1-(2-bromoethyl)-1-ethenylcyclohexane (**17**),[7] or 6-bromo-4,4-dimethyl-1-hexene (**18**)[7] in 500 mL of CH_2Cl_2 were cooled to −78 °C and treated with ozone until TLC indicated complete consumption of starting material. The reactions were quenched at −78 °C with 6.60 g (7.80 mL, 106 mmol) of dimethyl sulfide, warmed to 20 °C, and stirred for 4–6 h. The solvent was removed in vacuo, and the resulting oil was diluted with ether, washed with water and saturated aqueous NaCl, dried (Na_2SO_4), and concentrated in vacuo. The crude bromo aldehydes were used without further purification.

The bromo aldehydes were converted to the bromo esters by treatment with 34.8 g (100 mmol) of ethyl (triphenylphosphoranyldiene)acetate as described for the preparation of **8**. Flash vacuum chromatography[15] using 15% ether in hexane followed by vacuum distillation or flash chromatography[14] afforded the following:

Ethyl (*E*)-6-bromo-4,4-dimethyl-2-hexenoate (19): 17.0 g (68.3 mmol, 68%); bp 78–80 °C (0.5 mmHg); IR (thin film) 1725, 1655, 1391, 1371 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.88 (d, 1 H, J = 15.6 Hz), 5.75 (d, 1 H, J = 15.6 Hz), 4.20 (q, 2 H, J = 7.2 Hz), 3.27 (m, 2 H), 2.00 (m, 2 H), 1.30 (t, 3 H, J = 7.2), 1.10 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 166.5, 155.7, 118.8, 60.3, 45.3, 37.7, 28.2, 26.1 (2), 14.2; HRMS m/e for $C_{10}H_{17}{}^{79}BrO_2$ calcd 248.0411, found 248.0416; m/e for $C_{10}H_{17}{}^{81}BrO_2$ calcd 250.0391, found 250.0397.

Anal. Calcd for $C_{10}H_{17}BrO_2$: C, 48.19; H, 6.83. Found: C, 48.44; H, 6.86.

Ethyl (*E*)-3-[1-(2-bromoethyl)cyclohexyl]propenoate (21): 18.0 g (62.2 mmol, 62%); band 3, eluted with 4% ether in hexane; IR (thin film) 1715, 1640 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.77 (d, 1 H, J = 16.2 Hz), 5.76 (d, 1 H, J = 16.2 Hz), 4.19 (q, 2 H, J = 7.2 Hz), 3.23 (m, 2 H), 1.98 (m, 2 H), 1.59 (m, 2 H), 1.41 (m, 8 H), 1.29 (t, 3 H, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 166.6, 154.8, 120.8, 60.4, 43.9, 41.3, 35.2, 28.1, 26.0, 22.0, 14.3; HRMS m/e for $C_{13}H_{21}{}^{79}BrO_2$ calcd 288.0725, found, 288.0728; m/e for $C_{13}H_{21}{}^{81}BrO_2$ calcd 290.0704; found 290.0698.

Anal. Calcd for $C_{13}H_{21}BrO_2$: C, 53.98; H, 7.27. Found: C, 53.78; H, 7.25.

Ethyl (*E*)-7-bromo-5,5-dimethyl-2-heptenoate (23): 18.5 g (70.2 mmol, 70%); bp 91–93 °C (0.5 mmHg); IR (thin film) 1725, 1656, 1391, 1370 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.94 (dt, 1 H, J = 15.6, 7.8 Hz), 5.83 (dd, 1 H, J = 15.6, 1.2 Hz), 4.20 (q, 2 H, J = 7.2 Hz), 3.38 (m, 2 H), 2.12 (dd, 2 H, J = 7.8, 1.2 Hz), 1.86 (m, 2 H), 1.30 (t, 3 H, J = 7.2 Hz), 0.96 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 166.1, 145.0, 124.0, 60.2, 45.4, 44.6, 35.1, 28.5, 26.5 (2), 14.2; HRMS m/e for $C_{11}H_{19}{}^{79}BrO_2$ calcd 262.0568, found 262.0563; m/e for $C_{11}H_{19}{}^{81}BrO_2$: calcd 264.0548, found 264.0544.

Anal. Calcd for $C_{11}H_{19}BrO_2$: C, 50.19; H, 7.22. Found: C, 50.31; H, 7.24.

General Procedure for Preparing Iodo Esters from Chloro and Bromo Esters. The iodides were prepared by reacting the chloro or bromo esters with 5 equiv of NaI in refluxing acetone for 12–24 h. The crude reaction mixtures were cooled, concentrated in vacuo, diluted with water, and extracted (2×) with ether. The ether extracts were washed with water, 5% aqueous $Na_2S_2O_3$, and saturated aqueous NaCl, dried ($MgSO_4$), and concentrated in vacuo to afford the iodo esters. The following compounds were pure by NMR analysis and were used without further purification:

Ethyl (*E*)-2-(2-iodoethyl)cinnamate (9): 3.02 g (9.20 mmol, 92%) from 2.83 g (10 mmol) of bromide **8**; IR (thin film) 3050, 1710, 1635, 1600 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.91 (d, 1 H, J = 15.9 Hz), 7.56 (m, 1 H), 7.31 (m, 2 H), 7.21 (m, 1 H), 6.38 (d, 1 H, J = 15.9 Hz), 4.27 (q, 2 H, J = 7.2 Hz), 3.28 (m, 4 H), 1.34 (t, 3 H, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 166.7, 141.1, 139.9, 133.0, 130.2 (2), 127.6, 127.0, 120.6, 60.7, 37.5, 14.4, 4.5; HRMS m/e for $C_{13}H_{15}IO_2$ calcd 330.0117, found 330.0116.

Ethyl (*E*)-6-iodo-2-hexenoate (11): 7.55 g (28.2 mmol, 99%) from 6.30 g (28.5 mmol) of bromide **10**; IR (thin film) 1728, 1661 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.89 (dt, 1 H, J = 15.6, 6.8 Hz), 5.88 (d, 1 H, J = 15.6 Hz), 4.18 (q, 2 H, J = 7.2 Hz), 3.19 (t, 2 H, J = 6.9 Hz), 2.33 (q, 2 H, J = 6.9 Hz), 1.98 (quintet, 2 H, J = 6.9 Hz), 1.28 (t, 3 H, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 167.0, 146.4, 122.5, 60.2, 32.6, 31.3, 14.2, 5.4; MS (FAB) m/e 269 (M^+ + 1).

Ethyl (*E*)-7-iodo-2-heptenoate (13): 7.97 g (28.2 mmol, 99%) from 6.70 g (28.5 mmol) of bromide **12**; IR (thin film) 1728, 1660 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.94 (dt, 1 H, J = 15.6, 6.9 Hz), 5.83 (d, 1 H, J = 15.6 Hz), 4.19 (q, 1 H, J = 7.1 Hz), 3.19 (t, 2 H, J = 6.9 Hz), 2.23 (m, 2 H), 1.85 (m, 2 H), 1.60 (m, 2 H), 1.29 (t, 3 H, J = 7.1 Hz); ^{13}C NMR ($CDCl_3$) δ 166.4, 148.0, 121.8, 60.2, 32.7, 30.9, 28.8, 14.2, 6.1; MS (FAB) m/e 283 (M^+ + 1).

Ethyl (*E*)-8-iodo-2-octenoate (15): 7.22 g (24.4 mmol, 98%) from 5.13 g (25.0 mmol) of chloride **14**; IR (thin film) 1728, 1661 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.94 (dt, 1 H, J = 15.6, 6.9 Hz), 5.82 (d, 1 H, J = 15.6 Hz), 4.18 (q, 2 H, J = 7.1 Hz), 3.19 (t, 2 H, J = 7.0 Hz), 2.22 (m, 2 H), 1.82 (m, 2 H), 1.46 (m, 4 H), 1.29 (t, 3 H, J = 7.1 Hz); ^{13}C NMR ($CDCl_3$) δ 166.5, 148.6, 121.5, 60.1, 33.1, 31.8, 29.9, 26.9, 14.2, 6.6; MS (FAB) m/e 297 (M^+ + 1).

Ethyl (*E*)-6-iodo-4,4-dimethyl-2-hexenoate (20): 1.75 g (5.91 mmol, 98.5%) from 1.49 g (6.00 mmol) of bromide **19**; IR (thin film) 1725, 1650, 1395, 1372, 950 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.80

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(d, 1 H, J = 15.9 Hz), 5.68 (d, 1 H, J = 15.9 Hz), 4.15 (q, 2 H, J = 7.2 Hz), 2.96 (m, 2 H), 1.97 (m, 2 H), 1.23 (t, 3 H, J = 7.2 Hz), 1.01 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 166.6, 155.6, 118.9, 60.3, 47.0, 39.2, 25.8 (2), 14.2, 0.9; MS (FAB) m/e 297 (M^+ + 1).

Ethyl (*E*)-3-[1-(2-iodoethyl)cyclohexyl]propenoate (22): 1.92 g (5.71 mmol, 95%) from 1.73 g (6.00 mmol) of bromide **21**; IR (thin film) 1718, 1648 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.77 (d, 1 H, J = 16.2 Hz), 5.76 (d, 1 H, J = 16.2 Hz), 4.19 (q, 2 H, J = 7.2 Hz), 2.94 (m, 2 H), 1.95 (m, 2 H), 1.57 (m, 2 H), 1.39 (m, 8 H), 1.23 (t, 3 H, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 166.6, 154.8, 120.8, 60.4, 43.8, 41.2, 35.1, 26.0, 22.0, 14.3, 0.9; MS (FAB) m/e 337 (M^+ + 1).

Ethyl (*E*)-7-iodo-5,5-dimethyl-2-heptenoate (24): 1.76 g (5.67 mmol, 95%) from 1.58 g (6.00 mmol) of bromide **23**; IR (thin film) 1725, 1652, 1395, 1372 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.87 (dt, 1 H, J = 15.6, 7.8 Hz), 5.76 (dd, 1 H, J = 15.6, 1.2 Hz), 4.12 (q, 2 H, J = 7.2 Hz), 3.07 (m, 2 H), 2.03 (dd, 2 H, J = 7.8, 1.2 Hz), 1.85 (m, 2 H), 1.23 (t, 3 H, J = 7.2 Hz), 0.86 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 166.1, 145.0, 123.9, 60.2, 47.2, 44.3, 36.5, 26.1 (2), 14.2, 0.9; MS (FAB) m/e 311 (M^+ + 1).

Methyl (*E*)-6-iodo-3-methyl-2-hexenoate (26): 1.53 g (5.70 mmol, 95%) from 1.06 g (6.00 mmol) of chloride **25**;[8] the spectral data matched those reported previously.[19]

General Procedure for the Closure of 1-(Phenylmethyl)-2-pyrrolidineacetic and 1-(Phenylmethyl)-2-piperidineacetic Esters. A mixture of 5.6 mmol of the halo ester, 600 mg (5.6 mmol) of benzylamine, and 620 mg (6.2 mmol) of triethylamine in 15 mL of alcohol (MeOH or EtOH depending on the ester group of the halo ester) was refluxed with stirring for 36 h. The mixture was cooled and concentrated in vacuo to yield a light yellow oily residue which was diluted with 20 mL of water and extracted with ether (2×). The combined organic extracts were washed with water, 5% aqueous $Na_2S_2O_3$, and saturated aqueous NaCl, dried ($MgSO_4$), and concentrated under vacuum to afford a light yellow oil which was separated by silica gel column chromatography, eluting with increasing concentrations of ether in hexane. The following compounds were prepared.

Ethyl (±)-2-(phenylmethyl)-2,3-dihydro-1*H*-isoindole-1-acetate (27): band 3, eluted with 9% ether in hexane; oil; 1.14 g (3.86 mmol, 69%) from **6**; IR (thin film) 1740, 1600, 1500, 750, 702 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.39–7.10 (cplx, 9 H), 4.49 (t, 1 H, J = 5.9 Hz), 4.21–4.05 (cplx, 4 H), 3.64 (d, 2 H, J = 13.2 Hz), 2.81 (m, 2 H), 1.24 (t, 3 H, J = 7.1 Hz); ^{13}C NMR ($CDCl_3$) δ 172.0, 142.4, 139.3, 128.6, 128.3, 127.1, 127.0, 126.8, 122.2, 65.5, 60.4, 58.4, 58.0, 40.4, 14.1; HRMS m/e for $C_{19}H_{21}NO_2$ calcd 295.1572, found 295.1569.

Anal. Calcd for $C_{19}H_{21}NO_2$: C, 77.18; H, 7.16. Found: C, 76.94; H, 7.15.

Ethyl (±)-1-(phenylmethyl)-2-pyrrolidineacetate (29): band 3, eluted with 15% ether in hexane; oil; 872 mg (3.53 mmol, 63%) from **11**; IR (thin film) 3090, 3070, 3035, 1740, 740, 705 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.26 (m, 5 H), 4.13 (q, 2 H, J = 7.2 Hz), 3.97 (d, 1 H, J = 13.0 Hz), 3.26 (d, 1 H, J = 13.0 Hz), 2.89 (m, 2 H), 2.66 (m, 1 H), 2.34 (m, 1 H), 2.18 (m, 1 H), 2.05 (m, 1 H), 1.67 (m, 3 H), 1.24 (t, 3 H, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 172.3, 139.4, 128.7, 128.1, 126.7, 60.7, 60.1, 58.6, 53.8, 39.8, 30.8, 22.1, 14.2; MS m/e 247 (M^+).

Anal. Calcd for $C_{15}H_{21}NO_2$: C, 72.78; H, 8.56. Found: C, 72.59; H, 8.53.

Ethyl (±)-1-(phenylmethyl)-2-piperidineacetate (30): band 3, eluted with 14% ether in hexane; oil; 891 mg (3.41 mmol, 61%) from **13**; IR (thin film) 3090, 3070, 3035, 1740, 740, 705 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.26 (m, 5 H); 4.12 (q, 2 H, J = 7.2 Hz), 3.80 (d, 1 H, J = 13.5 Hz), 3.35 (d, 1 H, J = 13.5 Hz), 2.97 (m, 1 H), 2.72 (dd, 1 H, J = 14.7, 4.8 Hz), 2.62 (m, 1 H), 2.45 (dd, 1 H, J = 14.7, 8.0 Hz), 2.17 (m, 1 H), 1.74 (m, 1 H), 1.61 (m, 1 H), 1.47 (m, 4 H), 1.24 (t, 3 H, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 172.8, 139.5, 128.6, 128.1, 126.7, 60.3, 58.5, 57.5, 50.1, 36.2, 30.9, 25.1, 22.2, 14.2; MS m/e 261 (M^+).

Anal. Calcd for $C_{16}H_{23}NO_2$: C, 73.45; H, 8.87. Found: C, 73.18; H, 8.85.

Ethyl (±)-1-(phenylmethyl)-3,3-dimethyl-2-pyrrolidineacetate (32): band 3, eluted with 12% ether in hexane; oil; 1.01 g (3.67 mmol, 65.5%) from **20**; IR (thin film) 3090, 3065, 3030, 1740, 1375, 740, 702 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.27 (m, 5 H), 4.10 (m, 2 H), 3.95 (d, 1 H, J = 13.2 Hz), 3.31 (d, 1 H, J = 13.2 Hz), 2.82 (m, 1 H), 2.76 (m, 2 H), 2.39 (d, 2 H, J = 6.3 Hz), 2.21 (q, 1 H, J = 8.1 Hz), 1.53 (m, 2 H), 1.23 (t, 3 H, J = 6.9 Hz), 1.01 (s, 3 H), 0.97 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 173.1, 140.0, 128.3, 128.0, 126.5, 69.5, 60.1, 59.2, 51.0, 40.4, 38.8, 36.4, 27.9, 24.1, 14.1; MS (FAB) m/e 276 (M^+ + 1).

Anal. Calcd for $C_{17}H_{25}NO_2$: C, 74.12; H, 9.16. Found: C, 74.07; H, 9.25.

Ethyl (±)-2-(phenylmethyl)-2-azaspiro[4.5]decane-1-acetate (33): band 3, eluted with 14% ether in hexane; oil; 1.20 g (3.80 mmol, 68%) from **22**; IR (thin film) 3090, 3065, 1735, 740, 701 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.27 (m, 5 H), 4.14 (q, 2 H, J = 7.2 Hz), 3.98 (d, 1 H, J = 13.2 Hz), 3.32 (d, 1 H, J = 13.2 Hz), 2.82 (m, 2 H), 2.49 (dd, 1 H, J = 15.3, 5.1 Hz), 2.39 (dd, 1 H, J = 15.3, 9.3 Hz), 2.21 (dd, 1 H, J = 9.3, 5.1 Hz), 1.53 (m, 5 H), 1.28 (m, 7 H), 1.26 (t, 3 H, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 173.5, 140.2, 128.5, 128.1, 126.6, 70.4, 60.3, 59.9, 51.3, 44.5, 36.4 (2), 33.7, 33.1, 26.4, 23.3, 22.9, 14.2; HRMS m/e for $C_{20}H_{29}NO_2$ calcd 315.2198, found 315.2196.

Anal. Calcd for $C_{20}H_{29}NO_2$: C, 76.14; H, 9.27. Found: C, 76.44; H, 9.39.

Ethyl (±)-1-(phenylmethyl)-4,4-dimethyl-2-piperidineacetate (34): band 3, eluted with 12% ether in hexane; oil; 1.06 g (3.69 mmol, 66%) from **24**; IR (thin film) 3090, 3065, 3030, 1740, 1390, 1372, 740, 700 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.27 (m, 5 H), 4.13 (m, 2 H), 4.07 (d, 1 H, J = 13.5 Hz), 3.13 (d, 1 H, J = 13.5 Hz), 2.88 (m, 1 H), 2.71 (dd, 1 H, J = 15.1, 5.0 Hz), 2.60 (dt, 1 H, J = 11.1, 3.5 Hz), 2.31 (dd, 1 H, J = 15.1, 6.9 Hz), 2.16 (dt, 1 H, J = 12.4, 2.7 Hz), 1.39 (m, 3 H), 1.23 (t, 3 H, J = 6.9 Hz), 1.19 (m, 1 H), 0.94 (s, 3 H), 0.92 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 172.3, 139.5, 128.6, 126.6, 60.2, 57.7, 54.8, 48.7, 45.3, 40.5, 37.7, 32.6, 29.2, 24.1, 14.1; MS (FAB) m/e 290 (M^+ + 1).

Anal. Calcd for $C_{18}H_{27}NO_2$: C, 74.69; H, 9.40. Found: C, 74.89; H, 9.51.

Methyl (±)-(phenylmethyl)-2-methyl-2-pyrrolidineacetate (35): band 3, eluted with 12% ether in hexane; oil; 0.99 g (3.99 mmol, 71%) from **26**; IR (thin film) 3080, 3060, 3025, 1735, 1602, 1595, 1375, 730, 700 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.28 (m, 5 H), 3.68 (d, 1 H, J = 12.9 Hz), 3.66 (s, 3 H), 3.44 (d, 1 H, J = 12.9 Hz), 2.66 (m, 1 H), 2.49 (m, 1 H), 2.48 (s, 2 H), 2.18 (m, 1 H), 1.71 (m, 3 H), 1.16 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 172.5, 140.4, 128.3, 128.1, 126.5, 61.9, 52.7, 51.3, 50.5, 42.2, 37.1, 20.8, 20.6; HRMS m/e for $C_{15}H_{21}NO_2$ calcd 247.1572, found 247.1566.

Anal. Calcd for $C_{15}H_{21}NO_2$: C, 72.79; H, 8.56. Found: C, 73.01; H, 8.57.

Ethyl (*E*)-2-Vinylcinnamate (28a). Treatment of 1.00 g (3.03 mmol) ethyl (*E*)-2-(2-iodoethyl)cinnamate (**9**) under the heterocyclization conditions described above afforded 552 mg (2.73 mmol, 90%) of **28a** as a colorless oil following PTLC using 10% ether in hexane: IR (thin film) 1710, 1635, 1600 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.04 (d, 1 H, J = 16.2 Hz), 7.50 (m, 2 H), 7.32 (m, 2 H), 7.07 (m, 1 H), 6.35 (d, 1 H, J = 16.2 Hz), 5.63 (m, 1 H), 5.42 (m, 1 H), 4.27 (q, 2 H, J = 7.2 Hz), 1.34 (t, 3 H, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 166.8, 142.3, 138.0, 134.2, 132.5, 130.0, 127.9, 127.0 (2), 120.3, 118.0, 60.5, 14.4; HRMS m/e for $C_{13}H_{14}O_2$ calcd 202.0988, found 202.0974.

Ethyl (*E*)-2-(2-Phthalimidoethyl)cinnamate (28b). The general procedure of Baker and Sifniades[20] was used. To a stirred solution of 1.41 g (5.00 mmol) of ethyl (*E*)-2-(2-bromoethyl)-cinnamate (**8**) in 15 mL of dry DMF was added 1.02 g (5.5 mmol) of potassium phthalimide in small portions while maintaining the reaction temperature below 50 °C. The reaction mixture was stirred at 25 °C for 24 h, and 50 mL of $CHCl_3$ was added. The layers were separated, and the $CHCl_3$ layer was washed with water and saturated aqueous NaCl, dried (Na_2SO_4), and concentrated in vacuo to afford a light yellow solid. The crude product was recrystallized from MeOH to yield 1.53 g (4.4 mmol, 88%) of **28b** as a white solid: mp 112–113 °C; IR ($CHCl_3$) 1775, 1725, 1710, 1635 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.10 (d, 1 H, J = 15.6 Hz), 7.79 (m, 2 H), 7.68 (m, 2 H), 7.54 (m, 1 H), 7.24 (m, 3 H), 6.29 (d, 1 H, J = 15.6 Hz), 4.25 (q, 2 H, J = 7.2 Hz), 3.88 (t, 2 H, J = 7.8

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Hz), 3.12 (t, 2 H, J = 7.8 Hz), 1.35 (t, 3 H, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 168.0, 166.6, 141.3, 137.6, 133.9, 133.7, 132.0, 130.5, 130.2, 127.4, 126.7, 123.2, 120.3, 60.5, 38.8, 32.0, 14.3; HRMS m/e for $C_{21}H_{19}NO_4$ calcd 349.1314, found 349.1319.

Anal. Calcd for $C_{21}H_{19}NO_4$: C, 72.12; H, 5.48. Found: C, 72.06; H, 5.47.

Ethyl (±)-1,2,3,4-Tetrahydroisoquinoline-1-acetate (28c). The general procedure of Boeckman and co-workers[2] was followed. A solution of 1.00 g (2.87 mmol) of **28b** and 129 mg (0.125 mL, 4.02 mmol) of hydrazine hydrate in 10 mL of absolute EtOH was refluxed with stirring for 6 h, cooled, and concentrated in vacuo. The resulting yellow solid was dissolved in ether and washed with 1 M aqueous NaOH and saturated aqueous NaCl, dried ($MgSO_4$), and concentrated in vacuo to yield a yellow oil which was purified by flash chromatography[14] on an 80 cm × 2.5 cm silica gel column eluted with increasing concentrations of ether in hexane. The first and major band, eluted with 70:30 hexane/ether, yielded 453 mg (2.07 mmol, 72%) of **28c**[21] as a colorless oil after concentration: IR (thin film) 3340, 1725 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.12 (m, 4 H), 4.48 (m, 1 H), 4.18 (q, 2 H, J = 6.9 Hz), 3.21 (m, 1 H), 3.03 (m, 1 H), 2.81 (m, 4 H), 2.64 (bs, 1 H), 1.26 (t, 3 H, J = 6.9 Hz); ^{13}C NMR ($CDCl_3$) δ 172.3, 137.4, 135.4, 129.5, 126.4, 126.0, 125.9, 60.6, 52.7, 41.3, 40.7, 29.7, 14.2; MS m/e 219 (M^+).

Anal. Calcd for $C_{13}H_{17}NO_2$: C, 71.14; H, 7.81. Found: C, 71.22; H, 7.83.

General Procedure for Preparing Isothiouronium Salts from Bromides and Iodides. The general procedure of Speziale[22] was used. A mixture of 380 mg (5.00 mmol) of thiourea and 5.00 mmol of the halide in 5 mL of EtOH was refluxed with stirring for 24 h. The resulting mixture was cooled and concentrated in vacuo to yield the isothiouronium salt as a clear light yellow oil which was used without further purification. Salts which crystallized were filtered, washed with ether, and dried. The following compounds were prepared:

Isothiouronium salt 36 from ethyl (*E*)-2-(bromomethyl)cinnamate (6): 1.54 g (4.45 mmol, 99%); oil; IR ($CHCl_3$) 3400–2500, 1700, 1665, 1645 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 9.30 (bs, 2 H), 9.13 (bs, 2 H), 7.95 (d, 1 H, J = 15.8 Hz), 7.86 (m, 1 H), 7.57 (m, 1 H), 7.44 (m, 2 H), 6.65 (d, 1 H, J = 15.8 Hz), 4.75 (s, 2 H), 4.22 (q, 2 H, J = 7.1 Hz), 1.28 (t, 3 H, J = 7.1 Hz); ^{13}C NMR (DMSO-d_6) δ 168.6, 166.4, 140.2, 133.3 (2), 130.9, 130.6, 129.1, 127.5, 120.7, 60.3, 32.3, 14.2; MS (FAB) m/e 265 (M^+ – Br).

Isothiouronium salt 37 from ethyl (*E*)-2-(2-bromoethyl)cinnamate (8): 1.49 g (4.15 mmol, 92%); mp 173–174 °C; IR ($CHCl_3$) 3720–2910, 1715, 1645, 1630 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 9.11 (bs, 4 H), 7.86 (d, 1 H, J = 15.6 Hz), 7.73 (m, 1 H), 7.33 (m, 3 H), 6.51 (d, 1 H, J = 15.6 Hz), 4.18 (q, 2 H, J = 7.2 Hz), 3.43 (t, 2 H, J = 6.9 Hz), 3.07 (t, 2 H, J = 6.9 Hz), 1.24 (t, 3 H, J = 7.2 Hz); ^{13}C NMR (DMSO-d_6) δ 169.6, 166.1, 140.9, 138.1, 132.8, 130.4, 130.3, 127.5, 127.0, 120.2, 60.2, 31.3, 30.9, 14.3; MS (FAB) m/e 279 (M^+ – Br).

Isothiouronium salt 38 from ethyl (*E*)-6-bromo-2-hexenoate (10): 1.47 g (4.95 mmol, 99%); oil; IR (thin film) 3650–2400, 1720, 1660, 1640 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 9.17 (bs, 2 H), 9.05 (bs, 2 H), 6.92 (dt, 1 H, J = 15.6, 6.9 Hz), 5.93 (d, 1 H, J = 15.6 Hz), 4.12 (q, 2 H, J = 7.2 Hz), 3.22 (m, 2 H), 2.33 (m, 2 H), 1.78 (m, 2 H), 1.23 (t, 3 H, J = 7.2 Hz); ^{13}C NMR (DMSO-d_6) δ 169.8, 166.0, 148.1, 121.4, 60.0, 30.2, 29.6, 26.9, 14.4; MS (FAB) m/e 217 (M^+ – Br).

Isothiouronium salt 39 from ethyl (*E*)-7-bromo-2-heptenoate (12): 1.54 g (4.95 mmol, 99%); oil; IR (thin film) 3450–2740, 1720, 1640, 1610 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 9.12 (bs, 2 H), 9.01 (bs, 2 H), 6.88 (dt, 1 H, J = 15.9, 6.9 Hz), 5.88 (d, 1 H, J = 15.9 Hz), 4.11 (q, 2 H, J = 6.9 Hz), 3.20 (m, 2 H), 2.25 (m, 2 H), 1.57 (m, 4 H), 1.21 (t, 3 H, J = 6.9 Hz), ^{13}C NMR ($CDCl_3$) δ 169.9, 165.6, 148.9, 121.3, 59.7, 30.6, 29.8, 27.9, 26.1, 14.4; MS (FAB) m/e 231 (M^+ – Br).

Isothiouronium salt 41 from ethyl (*E*)-6-bromo-4,4-dimethyl-2-hexenoate (19): 1.59 g (4.92 mmol, 98%); oil; IR (thin film) 3700–2300, 1710, 1650 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 9.16 (bs, 2 H), 9.04 (bs, 2 H), 6.83 (d, 1 H, J = 15.8 Hz), 5.73 (d, 1 H, J = 15.8 Hz), 4.09 (q, 2 H, J = 7.2 Hz), 3.03 (m, 2 H), 1.66 (m, 2 H), 1.19 (t, 3 H, J = 7.2 Hz), 1.05 (s, 6 H); ^{13}C NMR (DMSO-d_6) δ 169.8, 165.8, 156.1, 118.5, 59.8, 39.3, 36.7, 36.4, 26.4, 25.7, 14.1; MS (FAB) m/e 245 (M^+ – Br).

Isothiouronium salt 42 from ethyl (*E*)-3-[1-(2-bromoethyl)cyclohexyl]propenoate (21): 1.75 g (4.80 mmol, 96%); oil; IR (thin film) 3610–2820, 1735, 1660 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 9.08 (bs, 4 H), 6.74 (d, 1 H, J = 16.2 Hz), 5.81 (d, 1 H, J = 16.2 Hz), 4.12 (q, 2 H, J = 7.2 Hz), 2.96 (m, 2 H), 1.66 (m, 3 H), 1.39 (m, 9 H), 1.22 (t, 3 H, J = 7.2 Hz); ^{13}C NMR (DMSO-d_6) δ 169.7, 165.7, 154.6, 120.7, 59.9, 55.9, 34.2, 25.7, 25.4, 21.6, 18.5, 14.1; MS (FAB) m/e 285 (M^+ – Br).

Isothiouronium salt 43 from ethyl (*E*)-7-bromo-5,5-dimethyl-2-heptenoate (23): 1.67 g (4.94 mmol, 100%); oil; IR (thin film) 3700–2300, 1720, 1650, 1391, 1371 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 9.11 (bs, 2 H), 9.05 (bs, 2 H), 6.81 (dt, 1 H, J = 15.6, 7.8 Hz), 5.89 (d, 1 H, J = 15.6 Hz), 4.08 (q, 2 H, J = 7.2 Hz), 3.16 (m, 2 H), 2.15 (d, 2 H, J = 7.8 Hz), 1.45 (m, 2 H), 1.18 (t, 3 H, J = 7.2 Hz), 0.88 (s, 6 H); ^{13}C NMR (DMSO-d_6) δ 169.9, 165.3, 145.7, 123.5, 59.7, 43.1, 39.3, 34.0, 26.3, 26.2, 18.4, 14.1; MS (FAB) m/e 259 (M^+ – Br).

Isothiouronium salt 44 from methyl (*E*)-6-iodo-3-methyl-2-hexenoate (26): 1.67 g (4.88 mmol, 98%); oil; IR (thin film) 3700–2450, 1715, 1660 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 8.97 (bs, 4 H), 5.70 (s, 1 H), 3.62 (s, 3 H), 3.18 (t, 2 H, J = 7.2 Hz), 2.29 (t, 2 H, J = 7.2 Hz), 2.12 (s, 3 H), 1.79 (quintet, 2 H, J = 7.2 Hz); ^{13}C NMR (DMSO-d_6) δ 169.6, 166.0, 158.7, 115.4, 50.7, 38.4, 29.6, 26.4, 18.3; MS (FAB) m/e 217 (M^+ – I).

General Procedure for Conversion of Isothiouronium Salts to Sulfur Heterocycles. The basic procedure of Speziale was used.[22] To a mixture of 3.25 g (58.0 mmol) of KOH in 13 mL of water was added 4.50 mmol of the isothiouronium salt, and the mixture was refluxed with stirring for 8 h. The reaction was cooled to 0–5 °C and was quenched by cautious dropwise addition of a solution of 50% aqueous H_2SO_4 until acidic to Congo red indicator. The mixture was extracted with ether (2×), and the combined organic layers were washed with water and saturated aqueous NaCl, dried (Na_2SO_4), and concentrated in vacuo. Analytical samples of solid products were obtained by recrystallization from the indicated solvents. The following compounds were prepared:

(±)-1,3-Dihydrobenzo[*c*]thiophene-1-acetic acid (45): 602 mg (3.11 mmol, 69%) from **36**; mp 106–107 °C (hexane–ether); IR ($CHCl_3$) 3300–2720, 1715 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 10.50–9.00 (bs, 1 H), 7.22 (m, 4 H), 5.01 (dd, 1 H, J = 9.6, 4.4 Hz), 4.33 (d, 1 H, J = 14.0 Hz), 4.18 (d, 1 H, J = 14.0 Hz), 3.12 (dd, 1 H, J = 16.8, 4.4 Hz), 2.86 (dd, 1 H, J = 16.8, 9.6 Hz); ^{13}C NMR ($CDCl_3$) δ 177.5, 142.3, 140.3, 127.4, 127.0, 125.0, 124.0, 48.9 48.9, 44.1, 36.7; HRMS m/e for $C_{10}H_{10}O_2S$ calcd 194.0396, found 194.0401.

Anal. Calcd for $C_{10}H_{10}O_2S$: C, 61.84; H, 5.19. Found: C, 61.76; H, 5.28.

(±)-3,4-Dihydro-1*H*-2-benzothiopyran-1-acetic acid (46): 684 mg (3.29 mmol, 73%) from **37**; mp 108–109 °C (hexane–ether); IR ($CHCl_3$) 3690–2800, 1725 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 10.82–9.90 (bs, 1 H), 7.20 (m, 4 H), 4.37 (m, 1 H), 3.05 (m, 2 H), 2.98 (m, 3 H), 2.84 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 177.3, 136.7, 136.4, 129.9, 127.3, 127.2, 126.6, 43.4, 37.0, 30.6, 24.1; HRMS m/e for $C_{11}H_{12}O_2S$ calcd 208.0553, found 208.0549.

Anal. Calcd for $C_{11}H_{12}O_2S$: C, 62.44; H, 5.81. Found: C, 62.33; H, 5.80.

(±)-2-Tetrahydrothiopheneacetic acid (47): 446 mg (3.06 mmol, 68%) from **38**; bp 72–76 °C (0.5 mmHg); IR (thin film) 3700–2200, 1712 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 10.35 (bs, 1 H), 3.71 (quint, 1 H, J = 6.9 Hz), 2.89 (m, 2 H), 2.66 (m, 2 H), 2.18 (m, 1 H), 2.03 (m, 2 H), 1.65 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 178.0, 43.3, 42.0, 36.7, 32.5, 30.0; HRMS m/e for $C_6H_{10}O_2S$ calcd 146.0396, found 146.0396.

Anal. Calcd for $C_6H_{10}O_2S$: C, 49.31; H, 6.85. Found: C, 49.63; H, 6.88.

(±)-2*H*-Tetrahydrothiopyran-2-acetic acid (48): 498 mg (3.11 mmol, 69%) from **39**; mp 73–74 °C (hexane–ether); IR ($CHCl_3$) 3400–2780, 1710 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 9.73 (bs, 1 H), 3.15 (m, 1 H), 2.69 (m, 2 H), 2.53 (m, 2 H), 2.07 (m, 1 H), 1.90 (m, 2 H), 1.62 (m, 1 H), 1.46 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 177.2, 40.5, 37.6, 33.8, 28.9, 26.7, 25.4; HRMS m/e for $C_7H_{12}O_2S$ calcd

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160.0553, found 160.0549.

Anal. Calcd for $C_7H_{12}O_2S$: C, 52.50; H, 7.50. Found: C, 52.77; H, 7.56.

(±)-3,3-Dimethyl-2-tetrahydrothiopheneacetic acid (50): 587 mg (3.37 mmol, 75%) from **41**; mp 55–56 °C (hexane–ether); IR ($CHCl_3$) 3500–2300, 1715, 1390, 1370 cm^{-1}; ^1H NMR ($CDCl_3$) δ 11.10 (bs, 1 H), 3.33 (dd, 1 H, J = 10.8, 3.7 Hz), 2.81 (m, 2 H), 2.75 (dd, 1 H, J = 16.5, 3.7 Hz), 2.43 (dd, 1 H, J = 16.5, 10.8 Hz), 1.83 (m, 2 H), 1.11 (s, 3 H), 0.96 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 178.7, 51.8, 44.3, 44.1, 237.4, 28.7, 26.0, 20.9; HRMS m/e for $C_8H_{14}O_2S$ calcd 174.0714, found 174.0709.

Anal. Calcd for $C_8H_{14}O_2S$: C, 55.14; H, 8.09. Found: C, 55.84; H, 8.09.

(±)-2-Thiaspiro[4.5]decane-1-acetic acid (51): 683 mg (3.20 mmol, 71%) from **42**; mp 101–102 °C (hexane–ether); IR (thin film) 3520–2880, 1725 cm^{-1}; ^1H NMR ($CDCl_3$) δ 12.40–11.60 (bs, 1 H), 3.36 (dd, 1 H, J = 11.4, 3.6 Hz), 2.81 (m, 2 H), 2.76 (dd, 1 H, J = 15.9, 3.6 Hz), 2.40 (dd, 1 H, J = 15.9, 11.4 Hz), 1.93 (m, 1 H), 1.77 (m, 1 H), 1.57–1.25 (cplx, 10 H); ^{13}C NMR ($CDCl_3$) δ 178.5, 64.0, 50.8, 47.8, 38.0, 34.9, 30.6, 28.2, 26.4, 23.3, 23.1; HRMS m/e for $C_{11}H_{18}O_2S$ calcd 214.1022, found 214.1006.

Anal. Calcd for $C_{11}H_{18}O_2S$: C, 61.65; H, 8.47. Found: C, 61.84; H, 8.35.

(±)-4,4-Dimethyl-2*H*-tetrahydrothiopyran-2-acetic acid (52): 662 mg (3.52 mmol, 78%) from **43**; mp 96–97 °C (hexane–ether); IR ($CHCl_3$) 3500–2100, 1720, 1395, 1375 cm^{-1}; ^1H NMR ($CDCl_3$) δ 11.35 (bs, 1 H), 3.31 (m, 1 H), 2.91 (dt, 1 H, J = 13.5, 2.7 Hz), 2.44 (m, 3 H), 1.66 (m, 2 H), 1.44 (dt, 1 H, J = 13.2, 3.9 Hz), 1.24 (t, 1 H, J = 12.6 Hz), 0.93 (s, 3 H), 0.91 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 177.7, 46.8, 40.9, 39.0, 33.7, 33,3, 30.6, 25.4, 23.7; HRMS m/e for $C_9H_{16}O_2S$ calcd 188.0871, found 188.0870.

Anal. Calcd for $C_9H_{16}O_2S$: C, 57.42; H, 8.56. Found: C, 57.35; H, 8.64.

(±)-2-Methyl-2*H*-tetrahydrothiopheneacetic acid (53): 576 mg (3.60 mmol, 80%) from **45**; mp 33–34 °C (pentane–ether); IR ($CHCl_3$) 3700–2200, 1710, 1376 cm^{-1}; ^1H NMR ($CDCl_3$) δ 11.28–10.92 (bs, 1 H), 2.96 (m, 2 H), 2.76 (s, 2 H), 2.11 (m, 2 H), 2.03 (m, 1 H), 1.95 (m, 1 H), 1.56 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 177.2, 53.7, 48.0, 44.0, 33.3, 29.6, 29.5; HRMS m/e for $C_7H_{12}O_2S$ calcd 160.0558, found 160.0557.

Anal. Calcd for $C_7H_{12}O_2S$: C, 52.43; H, 7.55. Found: C, 52.58; H, 7.64.

Reaction Chronology Studies. A. Nitrogen Heterocycles. A 5-mL EtOH solution of 0.57 g (0.62 mL, 5.00 mmol) of ethyl crotonate, 0.54 g (0.55 mL, 5.00 mmol) of benzylamine, 1.06 g (0.74 mL, 5.00 mmol) of 1-iodohexane, and 0.56 g (0.77 mL, 5.50 mmol) of triethylamine was heated at reflux according to the standard heterocyclization procedure. The reaction was monitored by GC analysis of 0.15-μL aliquots removed from the reaction at 30-min intervals during the first 3 h and at 1-h intervals thereafter. After 12 h, all of the benzylamine and 1-iodohexane had been consumed. A significant amount (ca. 75%) of the ethyl crotonate remained unreacted after this time.

B. Sulfur Heterocycles. A mixture of 1.24 g (5.00 mmol) of benzylisothiouronium bromide and 0.88 g (5.00 mmol) of ethyl cinnamate was stirred at 23 °C with 20% KOH in 4:1 water/EtOH. The reaction was monitored by TLC at 15-min intervals for disappearance of the reactants. After 40 min, the ethyl cinnamate had been completely consumed. Benzyl mercaptan and its cinnamate addition product were formed to only a minor extent during this period.

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Supplementary Material Available: High-field ^1H NMR and ^{13}C NMR spectra for **9, 11, 13, 15, 20, 22, 24, 28a, 36, 37, 38, 39, 41, 42, 43,** and **44** (32 pages). Ordering information is given on any current masthead page.

Silyl Group-Transfer-Mediated Serial Michael Additions

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Three protocols have been developed for achieving ordered, multiple (serial) Michael reactions initiated by silyl enol ethers or silyl ketene acetals. Anion (fluoride or *m*-chlorobenzoate) catalysis was most effective for reactions of silyl ketene acetal **2** with bis diesters, as in the highly selective formation of **3**. Lewis acid (ZnI_2) catalysis was more general than anion catalysis and afforded stereochemically complementary products with lower selectivity. The use of $SnCl_2$–trityl chloride was effective in reactions of both silyl ketene acetals and silyl enol ethers with bis enones. Very high stereoselectivity was generally observed in the formation of cyclopentanes. The products of serial Michael reactions of bis enones could be regiospecifically cyclized to bicyclic enones. Overall, it was found that the serial Michael reactions initiated by silyl enolates can be used to form efficiently and selectively complex cyclics from simple acyclic precursors.

Introduction

Ordered sequences of Michael reactions, in which each intermediate Michael addition initiates a specific subsequent addition, are a potentially powerful tool for the synthesis of cyclics and polycyclics. The utility of these "serial Michael additions" has been exemplified by the use of sequential inter- and intramolecular Michael reactions in the total syntheses of 3-desmethylaflavinine[2] and dihydronepatolactone,[3] "double Michael" reactions as Diels–Alder equivalents in several syntheses,[4] and the sequencing of up to three intermolecular Michael reactions by Posner.[5] In principle, large and varied arrays of

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