Fused-Ring Nitrogen and Sulfur Heterocycles by a Tandem S_N2-Michael Addition Reaction

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A tandem S_N2-Michael addition reaction has been developed for the synthesis of *cis*- and *trans*-fused nitrogen and sulfur heterocycles from the *cis* and *trans* isomers of ethyl (±)-(2*E*)-3-[2-(iodomethyl)cyclohexyl]-2-propenoate. Octahydro-1*H*-isoindole-1-acetic acid and octahydrobenzo[*c*]thiophene-1-acetic acid derivatives have been prepared and their stereochemistries elucidated using NMR and X-ray crystallographic methods. Cyclization substrates for both the *cis*- and the *trans*-fused rings are readily available in four steps from known compounds. Yields for the cyclization range from 80-85% and stereochemical selectivities with respect to the side chain vary from 12.5-16:1 for the *cis*-fused structures to 6-7.5:1 for the *trans*-fused structures. Steric interactions in the transition states for ring closure are proposed to rationalize the observed preferences.

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Introduction.

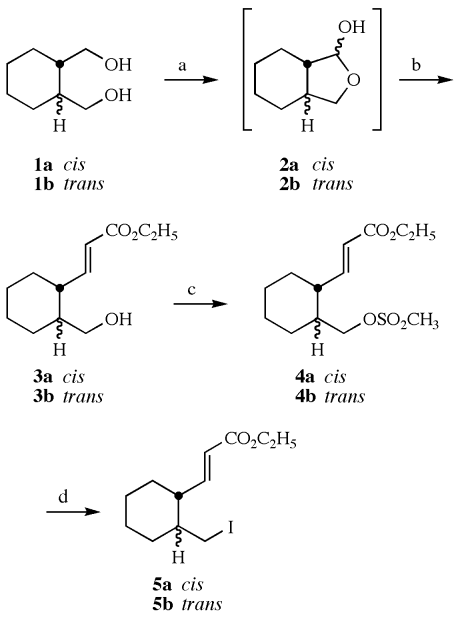
A previous report from this laboratory described a tandem S_N2-Michael addition reaction for the synthesis of monocyclic 5- and 6-membered nitrogen and sulfur heterocycles [1]. While some of these simple ring systems have valuable biological activity [2-4] there are many other active compounds that incorporate fused-ring heterocycles [5]. Thus, we wished to explore this heterocylization procedure for the synthesis of more complex targets. The viability of the S_N2-Michael sequence to prepare fused-ring structures hinges on the degree of selectivity one can achieve in the Michael cyclization step. In the current study, we have employed this strategy to synthesize octahydro-1*H*-isoindole-1-acetic acid and octahydrobenzo[*c*]-thiophene-1-acetic acid derivatives. Elucidation of the product stereochemistries indicates that the ring closures proceed with good to excellent selectivity.

Results and Discussion.

The synthesis of our cyclization substrates started from the known *cis* [6] and *trans* [7] isomers of 2-hydroxymethylcyclohexylmethanol (**1a** and **1b**, respectively, Scheme 1). Selective oxidation [8] of **1a** using *o*-iodoxybenzoic acid (IBX) [9] in dimethyl sulfoxide gave lactol **2a** [9]. Wittig olefination [10] of **2a** with (carbethoxymethylene)triphenylphosphorane in benzene then yielded hydroxy acrylate ester **3a**. Finally, alcohol **3a** was converted *via* its mesylate **4a** [11] into iodide **5a** [1] that served as the *cis*-fused heterocycle precursor. A similar sequence was used to prepare the *trans*-fused heterocycle precursor **5b**.

The results of our cyclization studies are summarized in Schemes 2 and 3. Nitrogen heterocycles were prepared in one step by refluxing each iodo acrylate **5** with 1.1 equivalent of benzylamine in ethanol containing 1.1 equivalent of triethylamine [1]. The sulfur heterocycles were prepared in two steps by: 1) reacting each isomer of **5** with 1.0 equivalent of thiourea in refluxing ethanol to give the corresponding isothiuronium salt **10** and 2) heating each salt in 10% aqueous potassium hydroxide [1,12]. Both cyclizations proceed *via* a favorable 5-*exo*-*trig* transition state [13]. The formation of the nitrogen heterocycles was found to be relatively selective yielding a 16:1 mixture of **6**:**7** from **5a** and a 6:1 mixture of **8**:**9** from **5b**. These product mixtures were readily separated by preparative thin layer chromatography. The sulfur ring systems were formed with similar selectivities giving a 12.5:1 ratio of **11**:**12** from **5a** and a 7.5:1 ratio of **13**:**14** from **5b**. The

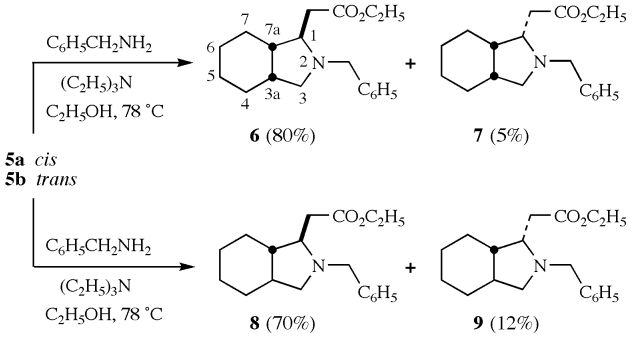
Scheme 1[a]



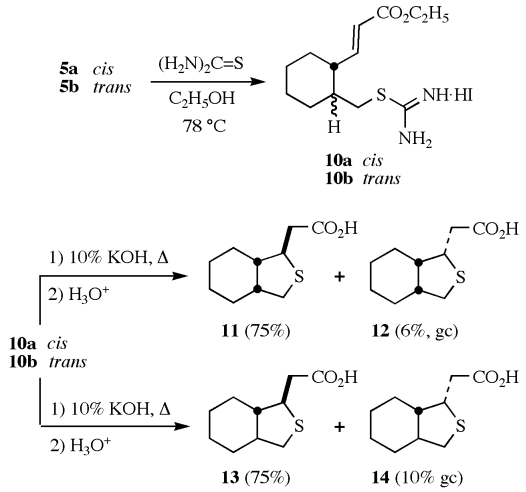
[a] Key: (a) *o*-iodoxybenzoic acid, aqueous dimethyl sulfoxide; (b) $Ph_3P{=}CHCO_2C_2H_5$, benzene, 80 °C, 47-48% for two steps; (c) CH_3SO_2Cl, $(C_2H_5)_3N$, dichloromethane, 0 °C, 94-96%; (d) NaI, acetone, 56 °C, 82-84%.

major products from the sulfur heterocyclizations were purified by crystallization.

Scheme 2



Scheme 3

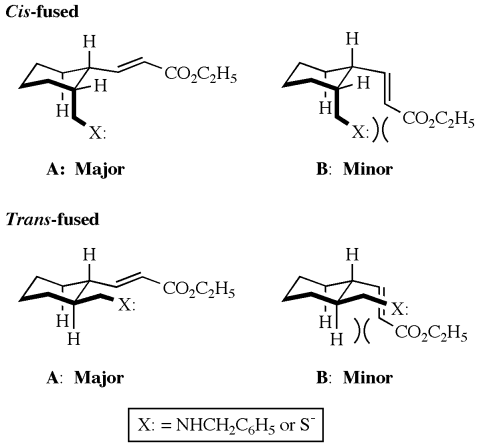


Structural assignments for the products were derived from COSY-45 [14] and NOESY [15] spectra of **6**-**9**, **11** and **13** and X-ray crystallographic analysis of **11**. Proton signals were initially assigned from the COSY-45 spectrum. In the NOESY spectrum of **6**, correlation of the side chain methylene protons with the protons on C7a and C3a established that the C1 acetic acid residue is *cis* to both bridgehead hydrogens; the minor isomer **7** lacked these interactions, but a correlation was observed between the *cis*-oriented protons on C1 and C7a. A similar study of **8** indicated that the acetic acid side chain is *cis* to the adjacent C7a hydrogen but *trans* to the C3a hydrogen. In **9**, a correlation between the protons on C1 and C7a confirmed that the side chain was *trans* to the C7a bridgehead hydrogen. Finally, correlations were also noted between the bridgehead protons in the *cis*-fused products **6** and **7**, but not in the *trans*-fused products **8** and **9**. The NOESY results for **11** and **13** paralleled those observed for the nitrogen heterocycles. A single crystal X-ray structure of **11** confirmed the assignment for the *cis*-fused octahydrobenzo[*c*]thiophene derivative.

Several earlier reports suggested that closure of *cis* substrate **5a** would favor the all-*cis* product (side chain *cis* to the *cis*-oriented bridgehead hydrogens) [16]; formation of the *trans*-fused system from **5b**, however, had no precedent. Previous syntheses of 6,5-fused carbocyclic systems using the Michael reaction involved closure of a cyclohexanone enolate on a side chain acceptor to form two new stereocenters α and β to the carbonyl. The reaction protocols for these cyclizations varied depending on the structure of the substrate but were invariably carried out under equilibrating conditions that led to the thermodynamic products. In each case, the all-*cis* 6,5-fused bicyclic structure was produced as the major product. This stereochemical outcome was attributed primarily to steric effects in the transition state [16a].

In the current work, the stereochemistry of the ring junction is set prior to the ring closure and cyclization creates only one new stereocenter at C1. Again, the reaction conditions should favor the thermodynamic products and steric factors should control the selectivity (Scheme 4). In the transition state leading to the *cis*-fused product **6**, rotamer **A** would be preferred since it minimizes the 1,3-diaxial-like interaction between the Michael donor (CH_2-X:) and the acrylate acceptor found in rotamer **B**. Additionally, the cyclization of **B** forces the side chain into the molecular cavity created by the *cis*-fused rings and results in eclipsing of the side chain methylene with C7 of the octahydroisoindole. Thus, product **6** predominates over **7**. In the transition state leading to the *trans*-fused product **8**, a similar rotamer preference applies, though the steric differentiation is less pronounced. Furthermore, eclipsing of the side chain with C7 is still present, but the two groups are not as close. Thus, the preference for product **8** over **9** is significantly reduced.

Scheme 4



In summary, we have applied the S_N2-Michael addition reaction to the preparation of *cis* and *trans* 6,5-fused nitrogen and sulfur heterocycles. The reactions are efficient and proceed with useful selectivities. The stereochemical results are easily rationalized by analysis of steric effects in the transition state. We are continuing to explore this process for the preparation of other polycyclic ring systems.

EXPERIMENTAL

All solvents were distilled prior to use; other reagents were used as received from the vendors. All reactions were run under dry nitrogen in oven-dried glassware. Reactions were monitored by one of the following methods: 1) thin layer chromatography on hard layer silica gel GF plates (Analtech) using ultraviolet or phosphomolybdic acid detection or 2) capillary gas chromatography (SE-30 column, 6 m x 0.25 mm i.d., 0.25 μm film thickness) with flame ionization detection programmed between 50-300°. Preparative separations were performed using one of the following methods: 1) preparative thin layer chromatography on 20 cm x 20 cm silica gel GF plates (Analtech) or 2) flash chromatography [17] on silica gel (Grace, grade 62, 60-200 mesh) containing ultraviolet-active phosphor (Sorbent Technologies no. 5). In each case, band elution was monitored using a hand-held ultraviolet lamp. Melting points were uncorrected. Ir spectra were run as thin films on sodium chloride disks and were referenced to polystyrene. Unless otherwise noted, ^{1}H nmr and ^{13}C nmr spectra were measured in deuteriochloroform at 300 MHz and 75 MHz, respectively, and were referenced to internal tetramethylsilane; coupling constants (J) have been given in Hz. COSY-45 and NOESY spectra were recorded at 400 MHz. Unless otherwise specified, high resolution mass spectra (direct probe/electron impact) were obtained at 70 electron volts.

Representative Procedure for the Oxidation-Wittig Olefination Sequence: Ethyl (±)-(2*E*)-3-[(1*R**,2*R**)-2-(Hydroxymethyl)-cyclohexyl]-2-propenoate (**3a**).

The procedure of Corey and Palani [8] was adapted. To a stirred mixture of 3.60 g (12.9 mmoles) of *o*-iodoxybenzoic acid (IBX) [9] in 2 mL of dimethyl sulfoxide was added 1.50 g (10.4 mmoles) of **1a**. The white paste was stirred at 23° for 2 hours, then quenched with 5 mL of water. The mixture was filtered through Celite and the filter cake was washed with water and dichloromethane. The layers were separated and the aqueous phase was extracted with dichloromethane (two times). The combined organic extracts were dried (magnesium sulfate), and concentrated under vacuum to afford 1.20 g (8.45 mmoles, 81%) of **2a** as a colorless oil; the product from 4 runs was combined and used without further purification. The spectral data matched those reported previously [8].

A solution of 4.80 g (33.8 mmoles) of **2a** and 17.4 g (50.0 mmoles) of (carbethoxymethylene)triphenylphosphorane in 125 mL of benzene was stirred and heated under reflux for 16 hours. The mixture was cooled to 25° and concentrated under vacuum to afford a brown semisolid mass. The residue was layered onto a 20 cm x 12 cm plug of silica gel in a sintered glass frit and 2 L of 75:25 hexane:ether was poured through under aspirator vacuum. Concentration of the filtrate afforded an viscous yellow oil that was purified by flash chromatography on an 80 cm x 2.5 cm column eluted with increasing concentrations of ether in hexane. Compound **3a** (3.44 g, 16.2 mmoles, 48%) was isolated from band 3 as a colorless oil; ir: 3425, 1723, 1652 cm^{-1}; ^{1}H nmr: δ 7.16 (dd, 1H, J = 15.5, 9.1), 5.88 (d, 1H, J = 15.5), 4.19 (q, 2H, J = 7.1), 3.45 (d, 2H, J = 7.3), 2.67 (m, 1H), 1.84 (m, 1H), 1.73 (m, 1H), 1.70-1.43 (complex, 6H), 1.38 (m, 2H), 1.29 (t, 3H, J = 7.1); ^{13}C nmr: δ 166.7, 149.7, 121.6, 64.4, 60.1, 42.3, 39.1, 30.1, 24.9, 24.6, 22.1, 14.0; hrms: m/z Calcd. for $C_{12}H_{20}O_3$: 212.1412; Found: 212.1418.

Anal. Calcd. for $C_{12}H_{20}O_3$: C, 67.92; H, 9.43. Found: C, 67.77; H, 9.40.

Ethyl (±)-(2*E*)-3-[(1*R**,2*S**)-2-(Hydroxymethyl)cyclohexyl]-2-propenoate (**3b**).

This compound (3.38 g, 16.0 mmoles, 47%) was isolated as a colorless oil; ir: 3422, 1723, 1652 cm^{-1}; ^{1}H nmr: δ 6.81 (dd, 1H, J = 15.6, 9.5), 5.79 (d, 1H, J = 15.6), 4.15 (q, 2H, J = 7.1), 3.58 (dd, 1H, J = 10.9, 3.8), 3.42 (dd, 1H, J = 10.9, 6.2), 2.04 (m, 1H), 1.95-1.50 (complex, 6H), 1.43-1.25 (complex, 4H), 1.29 (t, 3H, J = 7.1); ^{13}C nmr: δ 166.8, 153.0, 120.8, 66.1, 60.3, 43.9, 43.2, 32.4, 28.8, 25.6, 25.4, 14.3; hrms: m/z Calcd. for $C_{12}H_{20}O_3$: 212.1412; Found: 212.1415.

Anal. Calcd. for $C_{12}H_{20}O_3$: C, 67.92; H, 9.43. Found: C, 67.84; H, 9.38.

Representative Procedure for Methanesulfonate Ester Preparation: Ethyl (±)-(2*E*)-3-{(1*R**,2*R**)-2-[(Methanesulfonyloxy)-methyl]cyclohexane}-2-propenoate (**4a**).

This compound was prepared from **3a** using the general procedure of Crossland and Servis [11]. Compound **4a** (2.41 g, 8.31 mmoles, 96%) was isolated as a light yellow oil and used directly in the next reaction; ir: 1720, 1655, 1360, 1181 cm^{-1}; ^{1}H nmr: δ 7.10 (dd, 1H, J = 15.5, 9.1), 5.89 (d, 1H, J = 15.5), 4.20 (q, 2H, J = 7.1), 3.99 (m, 2H), 2.99 (s, 3H), 2.69 (m, 1H), 2.10 (m, 1H), 1.76 (m, 1H), 1.65 (m, 2H), 1.57 (m, 3H), 1.41 (m, 2H), 1.30 (t, 3H, J = 7.1); ^{13}C nmr: δ 166.2, 147.7, 122.8, 71.4, 60.3, 39.4, 38.8, 37.1, 29.9, 24.6, 24.2, 21.7, 14.1; ms (chemical ionization, isobutane): m/z 291 (M^++1, 39).

Ethyl (±)-(2*E*)-3-{(1*R**,2*S**)-2-[(Methanesulfonyloxy)-methyl]cyclohexane}-2-propenoate (**4b**).

This compound (2.38 g, 8.20 mmoles, 94%) was isolated as a light yellow oil and used directly in the next step; ir: 1714, 1659, 1360, 1182 cm^{-1}; ^{1}H nmr: δ 6.77 (dd, 1H, J = 15.6, 9.6), 5.85 (d, 1H, J = 15.6), 4.16 (q, 2H, J = 7.1), 4.12 (dd, 1H, J = 9.6, 3.7), 3.99 (dd, 1H, J = 9.6, 6.2), 2.98 (s, 3H), 2.04 (m, 1H), 1.94 (m, 1H), 1.87-1.55 (complex, 4H), 1.39-1.19 (complex, 4H), 1.29 (t, 3H, J = 7.1); ^{13}C nmr: δ 166.2, 150.9, 121.6, 72.6, 60.2, 42.7, 40.7, 36.9, 32.1, 28.4, 25.0, 24.9, 14.1; ms (chemical ionization, isobutane): m/z 291 (M^++1, 100).

Representative Procedure for Iodide Formation: Ethyl (±)-(2*E*)-3-[(1*R**,2*R**)-2-(Iodomethyl)cyclohexyl]-2-propenoate (**5a**).

A solution of 0.68 g (2.34 mmoles) of **4a** and 1.74 g (11.6 mmoles) of sodium iodide in 25 mL of acetone was stirred and heated under reflux for 14 hours. The reaction was cooled and concentrated under vacuum to afford an orange solid. This residue was dissolved in 30 mL of water and extracted with ether (two times). The combined ether extracts were washed with water, 5% sodium thiosulfate and saturated sodium chloride, then dried (magnesium sulfate), and concentrated to afford 0.62 g (1.92 mmoles, 82%) of **5a**

as a yellow oil. This product was used without further purification; ir: 1727, 1652 cm^{-1}; ^1H nmr: δ 7.02 (dd, 1H, J = 15.6, 9.3), 5.98 (d, 1H, J = 15.6), 4.19 (q, 2H, J = 7.1), 3.08 (dd, 1H, J = 9.8, 7.3), 2.93 (dd, 1H, J = 9.8, 8.0), 2.88 (m, 1H), 1.91 (m, 1H), 1.78-1.55 (complex, 4H), 1.52-1.26 (complex, 4H), 1.30 (t, 3H, J = 7.1); ^{13}C nmr: δ 166.4, 147.5, 123.0, 60.3, 42.7, 41.3, 30.4, 28.8, 24.9, 21.6, 14.2, 11.4; ms (chemical ionization, isobutane): m/z 323 (M^++1, 68).

Ethyl (±)-(2*E*)-3-[(1*R**,2*S**)-2-(Iodomethyl)cyclohexyl]-2-propenoate (**5b**).

This compound (0.63 g, 1.96 mmoles, 84%) was isolated as a yellow oil; ir: 1727, 1652 cm^{-1}; ^1H nmr: δ 6.70 (dd, 1H, J = 15.6, 9.6), 5.94 (d, 1H, J = 15.6), 4.19 (q, 2H, J = 7.1), 3.28 (dd, 1H, J = 9.9, 2.6), 3.06 (dd, 1H, J = 9.9, 6.0), 2.03 (m, 1H), 1.96-1.52 (complex, 5H), 1.40-1.18 (complex, 4H), 1.30 (t, 3H, J = 7.1); ^{13}C nmr: δ 166.5, 151.2, 121.8, 60.3, 45.9, 41.3, 32.2, 31.9, 25.4, 25.2, 16.1, 13.2; ms (chemical ionization, isobutane): m/z 323 (M^++1, 100).

Representative Procedure for the Tandem S_N2-Michael Synthesis of *Cis*-Fused Octahydro-1*H*-isoindole-1-acetates.

A solution of 356 mg (1.11 mmoles) of **5a**, 132 mg (0.13 mL, 1.23 mmoles) of benzylamine and 111 mg (0.15 mL, 1.23 mmoles) of triethylamine in 5 mL of ethanol was stirred and heated under reflux for 120 hours. The mixture was cooled to 25° and concentrated to afford a dark brown residue that was diluted with 20 mL of water and extracted with ether (two times). The combined ether extracts were washed with water, 5% sodium thiosulfate and saturated sodium chloride, then dried (magnesium sulfate), and concentrated to yield a brown oil that was purified on two 20 cm x 20 cm silica gel preparative thin layer chromatography plates. Elution with 99:1 hexane:ether (two times), 95:5 hexane:ether (two times), 90:10 hexane:ether (two times) and 85:15 hexane:ether (two times) showed four bands. Bands 3 and 4 contained products **7** and **6**, respectively.

Ethyl (±)-(1*S**,3a*R**,7a*S**)-2-Benzyl-2,3,3a,4,5,6,7,7a-octahydro-1*H*-isoindole-1-acetate (**7**).

This compound (18 mg, 0.06 mmoles, 5%) was isolated as a light yellow oil; ir: 1730 cm^{-1}; ^1H nmr: δ 7.26 (m, 5H), 4.13 (q, 2H, J = 7.2), 3.92 (d, 1H, J = 13.8), 3.41 (d, 1H, J = 13.8), 3.21 (m, 1H), 2.92 (m, 1H), 2.49 (m, 2H), 2.31 (m, 2H), 2.02 (m, 1H), 1.71 (m, 1H), 1.63-1.12 (complex, 7H), 1.25 (t, 3H, J = 7.2); ^{13}C nmr: δ 172.9, 140.7, 128.3, 128.1, 126.6, 65.3, 60.2, 58.7, 54.8, 41.0, 35.4, 35.4, 25.5, 24.8, 22.9, 20.9, 14.2; hrms: m/z Calcd. for $C_{19}H_{27}NO_2$: 301.2036; Found: 301.2036.

Anal. Calcd. for $C_{19}H_{27}NO_2$: C, 75.75; H, 8.97; N, 4.65. Found: C, 75.67; H, 9.08; N, 4.74.

Ethyl (±)-(1*R**,3a*R**,7a*S**)-2-Benzyl-2,3,3a,4,5,6,7,7a-octahydro-1*H*-isoindole-1-acetate (**6**).

This compound (268 mg, 0.89 mmoles, 80%) was isolated as a light yellow oil; ir: 1735 cm^{-1}; ^1H nmr: δ 7.26 (m, 5H), 4.12 (q, 2H, J = 7.2), 4.02 (d, 1H, J = 13.2), 3.59 (d, 1H, J = 13.2), 2.98 (m, 1H), 2.80 (m, 1H), 2.45 (m, 2H), 2.30 (m, 2H), 1.82 (m, 1H), 1.58 (m, 4H), 1.35 (m, 4H), 1.25 (t, 3H, J = 7.2); ^{13}C nmr: δ 172.7, 140.2, 128.6, 128.1, 126.7, 66.7, 60.6, 60.2, 56.0, 43.7, 41.3, 35.8, 28.4, 25.7, 24.6, 22.5, 14.3; hrms: m/z Calcd. for $C_{19}H_{27}NO_2$: 301.2036; Found: 301.2035.

Anal. Calcd. for $C_{19}H_{27}NO_2$: C, 75.75; H, 8.97; N, 4.65. Found: C, 75.64; H, 9.07; N, 4.77.

Representative Procedure for the Tandem S_N2-Michael Synthesis of *Trans*-Fused Octahydro-1*H*-isoindole-1-acetates.

Compound **5b** (360 mg, 1.12 mmoles) was reacted in the same manner to give a mixture of **8** and **9**. Preparative thin layer chromatography showed four bands. Bands 3 and 4 contained products **9** and **8**, respectively.

Ethyl (±)-(1*S**,3a*S**,7a*S**)-2-Benzyl-2,3,3a,4,5,6,7,7a-octahydro-1*H*-isoindole-1-acetate (**9**).

This compound (40 mg, 0.13 mmoles, 12%) was isolated as a light yellow oil; ir: 1725 cm^{-1}; ^1H nmr: δ 7.25 (m, 5H), 4.11 (q, 2H, J = 7.2), 4.04 (d, 1H, J = 12.9), 3.61 (d, 1H, J = 12.9), 3.45 (m, 1H), 2.91 (m, 1H), 2.32 (m, 2H), 1.97 (m, 1H), 1.87-1.46 (complex, 6H), 1.27-0.98 (complex, 4H), 1.25 (t, 3H, J = 7.2); ^{13}C nmr: δ 173.0, 140.1, 128.8, 128.1, 126.7, 62.5, 61.0, 60.2, 59.4, 47.5, 42.1, 39.0, 29.5, 26.6, 26.2, 25.7, 14.2; hrms: m/z Calcd. for $C_{19}H_{27}NO_2$: 301.2036; Found: 301.2033.

Anal. Calcd. for $C_{19}H_{27}NO_2$: C, 75.75; H, 8.97; N, 4.65. Found: C, 75.61; H, 9.01; N, 4.68.

Ethyl (±)-(1*R**,3a*S**,7a*S**)-2-Benzyl-2,3,3a,4,5,6,7,7a-octahydro-1*H*-isoindole-1-acetate (**8**).

This compound (236 mg, 0.78 mmoles, 70%) was isolated as a light yellow oil; ir: 1730 cm^{-1}; ^1H nmr: δ 7.27 (m, 5H), 4.13 (q, 2H, J = 7.2), 3.96 (d, 1H, J = 13.8), 3.51 (d, 1H, J = 13.8), 2.84 (m, 1H), 2.60 (m, 2H), 2.50 (m, 2H), 1.84-1.72 (complex, 4H), 1.46 (m, 1H), 1.29 (m, 1H), 1.24 (t, 3H, J = 7.2), 1.22 (m, 1H), 1.08 (m, 3H); ^{13}C nmr: δ 172.8, 140.7, 128.5, 128.2, 126.6, 66.5, 60.2, 59.8, 57.3, 51.0, 43.0, 39.1, 29.3, 28.7, 25.9, 25.8, 14.2; hrms: m/z Calcd. for $C_{19}H_{27}NO_2$: 301.2036; Found: 301.2034.

Anal. Calcd. for $C_{19}H_{27}NO_2$: C, 75.75; H, 8.97; N, 4.65. Found: C, 75.50; H, 9.05; N, 4.73.

Representative Procedure for the Preparation of Isothiuronium Salt **10a** from **5a**.

The procedure of Speziale [12] was used. A solution of 660 mg (2.05 mmoles) of **5a** and 156 mg (2.05 mmoles) of thiourea in 5 mL of ethanol was refluxed with stirring for 120 hours. The resulting mixture was cooled and concentrated to yield 800 mg (2.01 mmoles, 98%) of **10a** as a tan solid that was used without further purification; ir: 3540-2850, 1720, 1660, 1620 cm^{-1}; ^1H nmr (deuteriodimethyl sulfoxide): δ 9.07 (br s, 4H), 7.02 (dd, 1H, J = 15.6, 7.2), 5.93 (d, 1H, J = 15.6), 4.13 (q, 2H, J = 7.1), 3.00 (m, 2H), 2.71 (m, 1H), 1.84 (m, 1H), 1.62 (m, 4H), 1.37 (m, 4H), 1.22 (t, 3H, J = 7.1); ^{13}C nmr (deuteriodimethyl sulfoxide): δ 169.8, 165.5, 148.4, 122.5, 60.0, 40.1, 33.1, 29.1, 27.0 (2), 23.7, 21.7, 14.2; ms (fast atom bombardment, thioglycerol): m/z 271 (M^+-I).

Isothiuronium Salt **10b** from **5b**.

This salt (790 mg, 1.99 mmoles, 97%) was obtained as a light brown oil and was used without further purification; ir: 3650-2720, 1730, 1655, 1645 cm^{-1}; ^1H nmr (deuteriodimethyl sulfoxide): δ 9.03 (br s, 4H), 6.75 (dd, 1H, J = 15.6, 6.9), 5.89 (d, 1H, J = 15.6), 4.11 (q, 2H, J = 7.1), 3.19 (m, 1H), 2.94 (m, 1H), 2.07 (m, 1H), 1.85 (m, 1H), 1.64 (m, 4H), 1.22 (t, 3H, J = 7.1), 1.17 (m, 3H), 1.10 (m, 1H); ^{13}C nmr (deuteriodimethyl sulfoxide): δ 170.0, 165.6, 151.5, 121.6, 59.8, 45.0, 39.7, 35.5, 31.7, 29.8, 24.9, 24.7, 14.2; ms (fast atom bombardment, thioglycerol): m/z 271 (M^+-I).

Representative Procedure for the Synthesis of Sulfur Heterocycles: (±)-(1*R**,3a*R**,7a*S**)-1,3,3a,4,5,6,7,7a-Octahydrobenzo[*c*]thiophene-1-acetic Acid (**11**).

The procedure of Speziale [12] was modified. A mixture of 800 mg (2.01 mmoles) of **10a** and 10.0 mL of 10% aqueous potassium hydroxide was stirred and heated under reflux for 8 hours. The mixture was cooled to 0-5° and cautiously acidified by dropwise addition of 9 *M* sulfuric acid to pH 2. The resulting mixture was extracted with ether (two times) and the combined organic layers were washed with water and saturated sodium chloride, then dried (sodium sulfate), and concentrated. Compound **11** (300 mg, 1.50 mmoles, 75%) was obtained as colorless needles from ether-hexane, mp 83-84°; ir: 3580-2870, 1725 cm^{-1}; ^1H nmr: δ 11.20-10.40 (br s, 1H), 3.48 (m, 1H), 2.90 (m, 1H), 2.75 (m, 2H), 2.56 (m, 1H), 2.40 (m, 1H), 1.92 (m, 1H), 1.57 (m, 6H), 1.37 (m, 2H); ^{13}C nmr: δ 177.5, 48.2, 46.3, 42.2, 42.1, 34.8, 26.5, 26.1, 23.2, 23.0; hrms: m/z Calcd. for $C_{10}H_{16}SO_2$: 200.0866; Found: 200.0869.

Anal. Calcd. for $C_{10}H_{16}O_2S$: C, 60.00; H, 8.00. Found: C, 60.28; H, 8.05.

Minor product **12** (6% by gas chromatography) could not be isolated completely free of compound **11**.

(±)-(1*R**,3a*S**,7a*S**)-1,3,3a,4,5,6,7,7a-Octahydrobenzo[*c*]thiophene-1-acetic Acid (**13**).

This compound (299 mg, 1.50 mmoles, 75%) was obtained as colorless needles from ether-hexane, mp 131-132°; ir: 3294-2340, 1700 cm^{-1}; ^1H nmr: δ 8.20 (br s, 1H), 3.29 (td, 1H, J = 9.8, 3.7), 2.89 (m, 2H), 2.55 (dd, 1H, J = 9.9, 7.7), 2.50 (dd, 1H, J = 13.1, 9.9), 1.94 (m, 2H), 1.79 (tm, 2H, J = 9.1), 1.59 (m, 1H), 1.23-0.97 (complex, 5H); ^{13}C nmr: δ 177.8, 53.0, 48.6, 48.3, 39.9, 36.6, 31.8, 30.0, 25.5, 25.4; hrms: m/z Calcd. for $C_{10}H_{16}SO_2$: 200.0866; Found: 200.0865.

Anal. Calcd. for $C_{10}H_{16}O_2S$: C, 60.00; H, 8.00. Found: C, 60.23; H, 8.02.

Minor product **14** (10% by gas chromatography) could not be isolated completely free of compound **13**.

Experimental X-ray Data for **11**.

Intensity data were measured on a Brucker P4 diffractometer with MoK_α radiation (λ = 0.71073 Å) at room temperature [18]. All non-hydrogen positions were determined using the SHELXS [19] structure solution program and refined by full matrix least squares methods on the basis of F^2 using the SHELXL97 [20] refinement program. Hydrogen atoms were placed in calculated positions using idealized geometry and constrained to those positions during final refinements. $C_{10}H_{16}O_2S$, formula weight: 200.29, a = 7.164(3) Å, b = 13.375(4) Å, c = 21.708(8) Å, β = 91.24(4)˚, V = 2135.5(13) $Å^3$, Z = 8, monoclinic space group $P2_1/a$, density(calculated) = 1.246 Mg/m^3, 2361 unique reflections, R = 0.0658.

Structural and atomic parameters have been deposited with the Cambridge Crystallographic Data Center as deposition no. 177360. Copies may be obtained from the Director, Cambridge Crystallographic Data Center, 12 Union Road, Cambridge CB2 1EZ.

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