Deprotecting Dithiane-Containing Alkaloids

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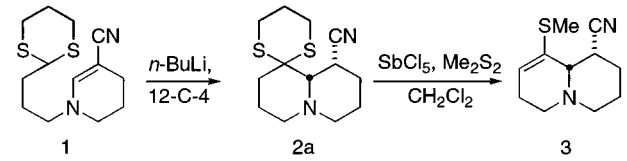
Received May 22, 2001

Dithianes are unparalleled as lynchpin carbanions[1] that directly assemble protected ketones. The unrivaled versatility of dithianes[2] is tempered only by the ultimate unmasking of the dithiane to the corresponding ketone,[3] a seemingly trivial conversion for which numerous reagents have been developed.[4] Dithiane deprotection is particularly challenging for dithiane-containing alkaloids since alkylative, oxidative, and Lewis acidic reagents exhibit similar affinities toward the alkaloid as for the dithiane.[5]

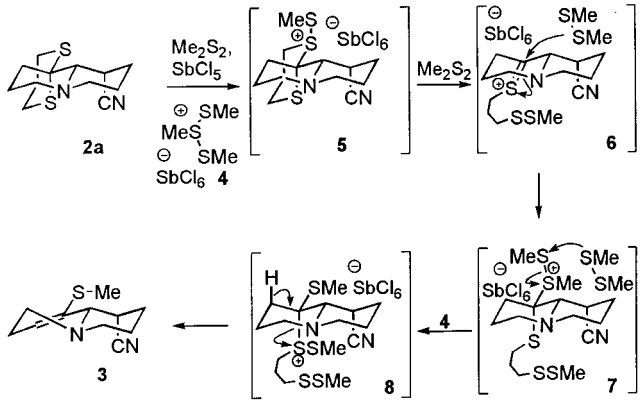
The dithiane-containing quinolizidine **2a** is potentially an excellent alkaloid precursor, being rapidly synthesized by a unique intramolecular conjugate addition reaction.[6] The potential deployment of **2a** in alkaloid syntheses hinges on deprotecting the dithiane in the presence of the tertiary amine. Of the few reagents developed for deprotecting dithiane-containing alkaloids, the combination of $SbCl_5-Me_2S_2$[7] is regarded as being particularly mild[8] and well suited for dithiane-containing amines. Quinolizidine **2a** reacts readily with the $SbCl_5-Me_2S_2$ reagent resulting in a smooth conversion, not to the anticipated ketone, but rather to the vinyl sulfide **3** (Scheme 1)!

The mechanistically challenging formation of vinyl sulfide **3** is surprisingly well precedented.[9] $SbCl_5$ reacts with MeSSMe to generate $SbCl_3$ and the powerful thiomethylating[10] reagent **4**[7] (Scheme 2) that thiomethylates the more accessible equatorial sulfur atom. Dissociation of the resulting sulfonium salt **5** and addition of excess dimethyl disulfide generates **7** that undergoes sequential thiomethyl transfers to afford **8**. Disulfide elimination

Scheme 1



Scheme 2



from **8** cleanly affords **3** (33% yield) accompanied by a polymeric material that presumably arises from self-condensation of intermediate carbocations. Although the dithiane was not hydrolyzed,[11] valuable insight into the precise conditions for hydrolysis was obtained. Specifically, attempts to protect the amine by precomplexing **2a** with $SbCl_3$,[12] or other transition metals, led to poor mass recovery suggesting that **2a** functions as an excellent ligand with a pronounced affinity toward transition metals![13] The inability to hydrolyze[14] or couple the vinyl sulfide **3**[15] further indicated the necessity for deprotecting under aqueous conditions to preferentially intercept the sulfonium intermediate **6**.

Armed with mechanistic insight the dithiane hydrolysis of **2a** was pursued in aqueous media. Alkaloid **2a** is readily protonated with aqueous acids (TFA,[16] H_2SO_4,[17] $HClO_4$) forming an ammonium salt without perceptible hydrolysis of **2a**. Isolation of the perchlorate salt and exposure to trimethyloxonium tetrafluoroborate resulted in the recovery of only a small amount of unreacted **2a**, despite this procedure successfully cleaving a closely related dithiane-containing alkaloid.[5c] Direct alkylative

(1) Smith, Amos B., III; Pitram, Suresh M. *Org. Lett.* **1999**, *1*, 2001.
(2) (a) Page, P. C. B.; van Niel, M. B.; Prodger, J. C. *Tetrahedron* **1989**, *45*, 7643. (b) Gröbel, B.-T.; Seebach, D. *Synthesis* **1977**, 357.
(3) Difficulties in unmasking dithianes have often emerged during syntheses with complex intermediates necessitating reagent screening and, in some cases, indirect transacetalization followed by hydrolysis. See, for example: Nakatsuka, M.; Ragan, J. A.; Sammakia, T.; Smith, D. B.; Uehling, D. E.; Schreiber, S. L. *J. Am. Chem. Soc.* **1990**, *112*, 5583.
(4) *Protective groups in organic synthesis*, 3rd ed.; Greene, T. W., Wuts, P. G. M., Eds.; John Wiley & Sons: Chichester, 1999.
(5) (a) Forns, P.; Diez, A.; Rubiralta, M. *J. Org. Chem.* **1996**, *61*, 7882. (b) Tang, C. S. F.; Morrow, C. J.; Rapoport, H. *J. Am. Chem. Soc.* **1975**, *97*, 159. (c) Oishi, T.; Takechi, H.; Kamemoto, K.; Ban, Y. *Tetrahedron Lett.* **1974**, 11.
(6) Fleming, F. F.; Hussain, Z.; Weaver, D.; Norman, R. E. *J. Org. Chem.* **1997**, *62*, 1305.
(7) Weiss, R.; Schlierf, C. *Synthesis* **1976**, 323.
(8) Prato, M.; Quintily, U.; Scorrano, G.; Sturaro, A. *Synthesis* **1982**, 679.
(9) Kim, J. K.; Pau, J. K.; Caserio, M. C. *J. Org. Chem.* **1979**, *44*, 1544.
(10) (a) Smallcombe, S. H.; Caserio, M. C. *J. Am. Chem. Soc.* **1971**, *93*, 5826. (b) Helmkamp, G. K.; Cassey, H. N.; Olsen, B. A.; Pettitt, D. J. *J. Org. Chem.* **1965**, *30*, 933.
(11) Similar recalcitrant hydrolyses of vinyl sulfide-containing alkaloids has been noted: Pearson, W. H.; Bergmeier, S. C.; Williams, J. P. *J. Org. Chem.* **1992**, *57*, 3977.
(12) Treatment of **2a** with $SbCl_3$ prior to the addition of **4** causes complete decomposition indicating that complexation between $SbCl_3$ and **2a** is precluded during the formation of **3**.
(13) The use of mercury-based reagents (Corey, E. J.; Erickson, B. W. *J. Org. Chem.* **1971**, *36*, 3553) resulted in poor mass recovery presumably resulting from strong, irreversible complexation[12] with the amine, dithiane, and nitrile groups that make **2a** an excellent metal ligand! Poor mass recovery is observed during the dehydrogenation of quinolizidines with $Hg(OAc)_2$: Kasymov, T. K.; Ishbaev, A. I.; Aslanov, K. A.; Sadykov, A. S. *Chem. Nat. Compd.* **1969**, *5*, 383.
(14) The following reagents were screened. (a) TFA: Grayson, J. I.; Warren, S. *J. Chem. Soc., Perkin Trans. 1* **1977**, 2263 (b) $TiCl_4$: Sato, M.; Takai, K.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.* **1981**, *22*, 1609. (c) HCl: Chou, W.-C.; Fang, J.-M. *J. Org. Chem.* **1996**, *61*, 1473.
(15) Luh, T.-Y.; Ni, Z.-J. *Synthesis* **1990**, 89.
(16) Grayson, J. I.; Warren, S. *J. Chem. Soc., Perkin Trans. 1* **1977**, 2263.
(17) Ho, T.-L.; Ho, H. C.; Wong, C. M. *Can. J. Chem.* **1973**, *51*, 153.

10.1021/jo0157829 CCC: $20.00
Published on Web 08/23/2001

and oxidative hydrolysis (HIO_5[18] or CAN[19]) of **2a** results in poor mass recovery that presumably results from competitive N-alkylation and oxidation.

The stability of **2a** in acid suggested an excellent procedure[20] using bis(trifluoroacetoxy)iodobenzene since the simultaneous formation of trifluoroacetic acid is thought to prevent oxidation of the amine by preferential protonation.[21] Extensive optimization experiments revealed precise conditions for the dithiane hydrolysis while providing mechanistic insight of potentially general relevance for dithiane hydrolyses, particularly dithiane-containing alkaloids. Careful monitoring of the reaction by ^{1}H NMR revealed a rapid initial hydrolysis (<30 min) until approximately 20% conversion, followed by a slower, constant rate of hydrolysis requiring 5 equiv[22] of bis(trifluoroacetoxy)iodobenzene. The dramatic rate changes led to an optimized procedure where bis(trifluoroacetoxy)-iodobenzene is added portionwise to a 1:1 water−acetonitrile solution of the dithiane containing 10 equiv of trifluoroacetic acid, allowing complete hydrolysis in 4 h (85% yield).

Purifying the unmasked ketone proved particularly challenging since the amino ketone **11a** decomposes[23] during silica gel chromatography and coelutes with the dithiane oxidation product 1,2-dithiolane-1,1-dioxide **14**.[24] Isolating spectroscopically pure ketone was achieved through an efficient nonchromatographic purification where the acidic, aqueous reaction mixture is first extracted with hexanes, to remove phenyl iodide, followed by addition of solid K_2CO_3 and ethanethiol to remove the 1,2-dithiolane-1,1-dioxide (**14**). Subsequent extraction with CH_2Cl_2 cleanly provides the ketone **11a** in 85% yield. Presumably, the ethanethiol triggers ring-opening of dithiolane 1,1-dioxide generating a sulfide that is selectively partitioned into the basic aqueous phase.

Identifying 1,2-dithiolane-1,1-dioxide **14** as the ultimate dithiane fragment provides insight into the hydrolysis mechanism (Scheme 3). Presumably protonation and iodination[25] of **2a** results in the transient formation of **9** en route to the sulfonium salt **10** that suffers hydrolysis to generate ketone **11a** and disulfide fragment **12**. Cyclization of **12** leads to dithiolane **13** whose formation is implicated by the spectral identification of the dithiolane dioxide **14**. Oxidation of the dithiolane **13** by bis(trifluoroacetoxy)iodobenzene is presumably faster than oxidation of the protonated quinolizidine **2a**, accounting for the requirement of excess oxidant (Scheme 3).

Scheme 3

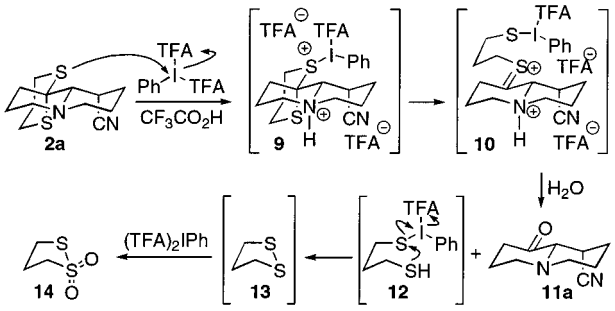
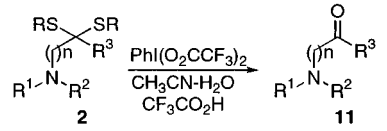
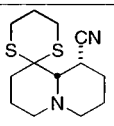
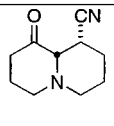
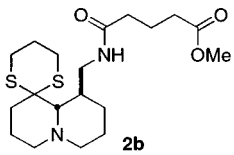
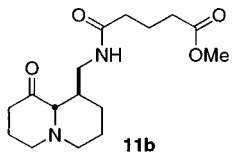
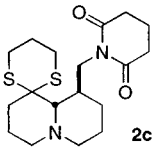
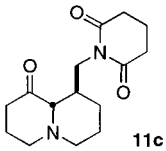
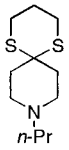
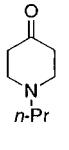
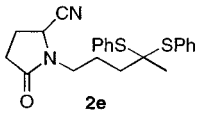
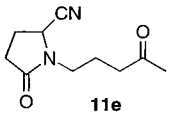


Table 1. Hydrolysis of Dithiane-Containing Alkaloids



Entry	Dithiane	Ketone	Yield
1	 **2a**	 **11a**	85%
2	 **2b**	 **11b**	92%
3	 **2c**	 **11c**	96%
4	 **2d**	 **11d**	71%
5	 **2e**	 **11e**	92%

The optimized bis(trifluoroacetoxy)iodobenzene-mediated hydrolysis and purification effectively unmasks a variety of dithiane-containing alkaloids (Table 1). The efficacy is underscored by the lability of several 3-oxopiperidines that are cleanly obtained with the nonchromatographic purification and yet are unstable to silica gel chromatography (Table 1, entries 1−3). The array of dithianes presented in Table 1 demonstrates that the deprotection is successful with relatively complex quinolizidines, several of which are advanced synthetic inter-

(18) Shi, X.-X.; Khanapure, S. P.; Rokach, J. *Tetrahedron Lett.* **1996**, *37*, 4331.

(19) Ho, T.-L.; Ho, H. C.; Wong, C. M. *J. Chem. Soc., Chem. Commun.* **1972**, 791.

(20) (a) Stork, G.; Zhao, K. *Tetrahedron Lett.* **1989**, *30*, 287. (b) For an analogous procedure with bis(acetoxy)iodobenzene, see: Shi, X.-X.; Wu, Q.-Q. *Synth. Commun.* **2000**, *30*, 4081.

(21) Bis(trifluoroacetoxy)iodobenzene has been used to unmask dithiane-containing alkaloids that, in some contexts, may be enhanced with the modified procedure developed here: (a) Yamada, O.; Ogasawara, K. *Org. Lett.* **2000**, *2*, 2785. (b) Rubiralta, M.; Diez, A.; Reig, I.; Castells, J.; Bettiol, J. L.; Grierson, D. S.; Husson, H. P. *Heterocycles* **1990**, *31*, 173. (c) Micouin, L.; Diez, A.; Castells, J.; López, D.; Rubiralta, M.; Quirion, J.-C.; Husson, H.-P. *Tetrahedron Lett.* **1995**, *36*, 1693. (d) López, I.; Diez, A.; Rubiralta, M. *Tetrahedron* **1996**, *52*, 8581. (e) Forns, P.; Diez, A.; Rubiralta, M.; Solans, X.; Font-Bardia, M. *Tetrahedron* **1996**, *52*, 3563. (f) Reference 5a.

(22) Use of excess periodane was also reported in a related procedure using bis(acetoxy)iodobenzene.[20b]

(23) Although efforts to identify the fate of the amino ketones has been unsuccessful, related indolizidines are known to suffer hydride migration affording iminium ion intermediates that, in this case, could be potentially deleterious: Razavi, H.; Polt, R. *J. Org. Chem.* **2000**, *65*, 5693.

(24) Repetitive chromatography provided a pure sample of **14** that exhibited a ^{1}H NMR spectrum identical to that previously reported: Sheu, C.; Foote, C. S.; Gu, C.-L. *J. Am. Chem. Soc.* **1992**, *114*, 3015.

(25) Moriarty, R. M.; Vaid, R. K. *Synthesis* **1990**, 431.

mediates. The oxidative cleavage accommodates nitrile, α-aminonitrile, amide, imide, lactam, and ester functionality providing the corresponding ketones in 69−97% yield. The dithiane hydrolysis is apparently retarded by proximal electron-withdrawing groups since the nitrile **2a** is hydrolyzed more slowly than **2b** and **2c** and requires a greater excess of the oxidant. Presumably, the strong inductive electron withdrawal from the nitrile decreases the nucleophilicity of the neighboring dithiane group that competes less effectively for the oxidant than the dithiolane **13**.

Dithianes are exceptional reagents whose use in synthesis is tempered only by deprotection to the corresponding ketone. Deprotection of several dithiane-containing alkaloids provides insight into the hydrolysis mechanism with bis(trifluoroacetoxy)iodobenzene that is potentially of general relevance for sensitive dithiane-containing intermediates. The nonchromatographic purification cleanly generates the corresponding ketoamines, providing an ideal dithiane hydrolysis procedure for labile alkaloids.

Experimental Section[26]

(±)-(1*S*)-9-Methylthio-1,2,3,6,7,9a-hexahydroquinolizinecarbonitrile (3). $SbCl_5$ (0.21 mL, 1.67 mmol) was added to a room-temperature CH_2Cl_2 solution (15 mL) of Me_2S_2 (0.15 mL, 1.70 mmol). After 5 min, the mixture was cooled to −78 °C and a CH_2Cl_2 solution (2 mL) of **2a**[6] (172 mg, 0.83 mmol) was added over 5 min. The cooling bath was removed, and after 3 h at ambient temperature aqueous NaOH (5%, 20 mL) was added. The aqueous phase was extracted with CH_2Cl_2 (4 × 20 mL), the extracts were dried ($MgSO_4$) and concentrated, and the resultant crude material was purified by radial chromatography (1 mm plate, 1:19−3:10 EtOAc/hexanes) to afford 49.2 mg (33%) of **3** as a colorless oil: IR (film) 3040, 2238, 1630 cm^{-1}; ^1H NMR (CS_2)[27] δ 1.84−1.96 (m, 4H), 2.21−3.24 (m, 7H), 2.57 (s, 3H), 3.50−3.52 (m, 1H), 5.90 (d, J = 6.2 Hz, 1H); ^{13}C NMR (CS_2) δ 15.9, 22.9, 27.1, 28.7, 32.2, 51.4, 56.2, 65.2, 117.9, 122.5, 133.2; MS *m/e* 209 (M + H).

General Hydrolysis Procedure. Solid [bis(trifluoroacetoxy)-iodo]benzene (1 equiv) was added to a room-temperature CH_3CN/H_2O solution (1:1) of the dithiane (1 equiv) and trifluoroacetic acid (10 equiv). After 0.5 h, additional solid [bis-(trifluoroacetoxy)iodo]benzene (1.5−2.3 equiv) was added with the reaction being terminated 2.5 h later. The resultant mixture was extracted with hexane (3 × ∼15 mL), the aqueous phase was neutralized with solid K_2CO_3 (until basic to litmus paper), and then neat EtSH (1 mL) was added following by stirring for 5 min. The resulting solution was diluted with saturated, aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$) and concentrated to afford spectroscopically pure ketone.

(±)-(1*S*)-9-Oxo-1,2,3,6,7,8,9a-heptahydroquinolizinecarbonitrile (11a). The general procedure was employed with a CH_3CN/H_2O solution (30 mL, 1:1) of **2a** (200 mg, 0.75 mmol), trifluoroacetic acid (830 mg, 7.3 mmol), and [bis(trifluoroacetoxy)iodo]benzene (316 mg, 0.73 mmol; 722 mg, 1.68 mmol; 316 mg, 0.73 mmol) added initially and at 0.5 and 2.5 h intervals, respectively, to provide 113.7 mg (85%) of **11a**: IR (film) 2758, 2249, 1719 cm^{-1}; ^1H NMR δ 1.53 (tt, J = 13.3, 4.2 Hz, 2H), 1.59−1.69 (m, 2H), 1.91−2.75 (m, 7H), 2.98−3.01 (m, 2H), 3.34−3.35 (m, 1H); ^{13}C NMR δ 21.9, 23.0, 27.1, 28.2, 38.7, 53.9, 56.2, 71.3, 120.0, 203.7.

(±)-Methyl 4-[*N*-[((1*S*)-9-Oxo-1,2,3,6,7,8,9a-heptahydroquinolizinyl)methyl]carbamoyl]butanoate (11b). The general procedure was employed with a CH_3CN/H_2O solution (10 mL, 1:1) of **2b** (150.8 mg, 0.38 mmol), trifluoroacetic acid (430 mg, 3.8 mmol), and [bis(trifluoroacetoxy)iodo]benzene (160.4 mg, 0.37 mmol; 245.1 mg, 0.57 mmol) added initially and at 0.5 h, respectively, to provide 107.6 mg (92%) of **11b** as an oil: IR (film) 3307, 1726, 1649 cm^{-1}; ^1H NMR δ 1.05−1.10 (m, 1H), 1.51−2.69 (m, 13H), 2.78−3.08 (m, 4H), 3.32−3.45 (m, 2H), 3.67 (s, 3H), 3.68−3.95 (m, 2H), 5.99 (s, 1H); ^{13}C NMR δ 20.9, 23.9, 24.9, 25.5, 28.5, 33.2, 35.5, 40.3, 42.8, 51.5, 54.8, 55.5, 73.0, 172.2, 173.6, 208.3.

(±)-1-[((1*S*)-9-Oxo-1,2,3,6,7,8,9a-heptahydroquinolizinyl)methyl]piperidine-2,6-dione (11c). The general procedure was employed with a CH_3CN/H_2O solution (10 mL, 1:1) of **2c** (50.3 mg, 0.136 mmol), trifluoroacetic acid (160 mg, 1.40 mmol), and [bis(trifluoroacetoxy)iodo]benzene (57.6 mg, 0.13 mmol; 86 mg, 0.20 mmol) added initially and at 0.5 h, respectively, to provide 39.7 mg (96%) of **11c** as an oil: IR (film) 1724, 1674; ^1H NMR δ 1.00 (ddd, J = 25, 12, 5 Hz, 1H), 1.48−2.08 (m, 6H), 2.19 (td, J = 11, 4 Hz, 2H), 2.25−2.71 (m, 9H), 2.81−2.96 (m, 2H), 3.65 (dd, J = 13.5, 4.5 Hz, 1H), 3.79 (dd, J = 13.5, 7.7 Hz, 1H); ^{13}C NMR δ 16.8, 23.7, 26.4, 27.4, 32.1, 32.7, 40.5, 43.0, 55.4, 55.5, 73.7, 173.2, 207.4.

9-Aza-9-propyl-1,5-dithiaspiro[5.5]undecane (2d). Neat 1,3-propanedithiol (650 mg, 6.0 mmol) and ethereal $BF_3{\cdot}OEt_2$ (0.3 mL) were added to a room-temperature CH_2Cl_2 solution (10 mL) of **11d** (282 mg, 2 mmol). After 16 h, ice-cold aqueous NaOH (5% v/v, 30 mL) was added, the aqueous phase was extracted with EtOAc (3 × ∼30 mL), and the combined organic extracts were dried ($MgSO_4$). Concentration of the resulting crude material and purification by radial chromatography (hexane/EtOAc 95:5−70:30) provided 298 mg (65%) of **11d** as an oil: IR (film) 2809, 2772 cm^{-1}; ^1H NMR δ 0.89 (t, J = 7 Hz, 3H), 1.43−1.56 (m, 2H), 1.95−2.03 (m, 2H), 2.10−2.14 (m, 4H), 2.29−2.35 (m, 2H), 2.53−2.57 (m, 4H), 2.79−2.83 (m, 4H); ^{13}C NMR δ 11.9. 20.0, 25.7, 25.9, 37.4, 48.3, 49.0, 60.4,

1-Propylpiperidin-4-one (11d). The general procedure was employed with a CH_3CN/H_2O solution (15 mL, 9:1) of **2d** (144 mg, 0.64 mmol), trifluoroacetic acid (732 mg, 6.4 mmol), and [bis-(trifluoroacetoxy)iodo]benzene (412 mg, 0.96 mmol) to provide, after radial chromatography (60:40−20:80 hexane/EtOAc), 63.7 mg (71%) of **20** that exhibited spectral data identical to that of a commercial sample.

5-Oxo-1-(4-oxopentyl)pyrrolidine-2-carbonitrile (11e). The general procedure was employed with a CH_3CN/H_2O solution (10 mL, 9:1) of **2e** (57.1 mg, 0.14 mmol) and [bis(trifluoroacetoxy)iodo]benzene (61.9 mg, 0.14 mmol; 92.9 mg, 0.22 mmol) added initially and at 0.5 h, respectively, to provide, after filtration through silica gel (1:9 hexane/EtOAc) 26.6 mg (92%) of **11e** as an oil: IR (film) 2244, 1709 cm^{-1}; ^1H NMR δ 1.70−1.97 (m, 2H), 2.11 (s, 3H), 2.28−2.58 (m, 6H), 3.12 (dt, J = 14, 6 Hz, 1H), 3.63−3.73 (m, 1H), 4.51−4.55 (m, 1H); ^{13}C NMR δ 20.5, 23.4, 28.9, 29.9, 40.5, 41.2, 47.8, 117.6, 174.0, 207.8.

Acknowledgment. Financial support from the Johnson and Johnson Focused Giving Program is gratefully acknowledged.

Supporting Information Available: ^1H NMR and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0157829

(26) For general experimental procedures see ref 6. Bis(trifluoroacetoxy)iodobenzene from Aldrich was used without purification.

(27) The ^1H and ^{13}C NMR spectra in CS_2 were referenced to the proton and carbon residual signals of the external reference C_6D_6.