A Convenient Synthesis of 8-Substituted Indolizines as Precursors to 5-Substituted Cycl{3.2.2}azine Derivatives

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The synthesis of 8-substituted indolizines is described *via* a two step process in which a 1,4-diketone, containing a *tert*-butyl group, is cyclocondensed with a trialkylsilyl protected pyrrole to provide 5,8-disubstituted indolizines in higher yields than the identical reaction with unprotected pyrrole. Cleavage of the *tert*-butyl group from the indolizine 5-position, by treatment with 85% phosphoric acid, provides 8-substituted indolizines in good yields. Treatment of 8-substituted indolizines with dimethyl acetylenedicarboxylate, in the presence of palladium-on-carbon, provides novel 5-substituted cycl{3.2.2} derivatives.

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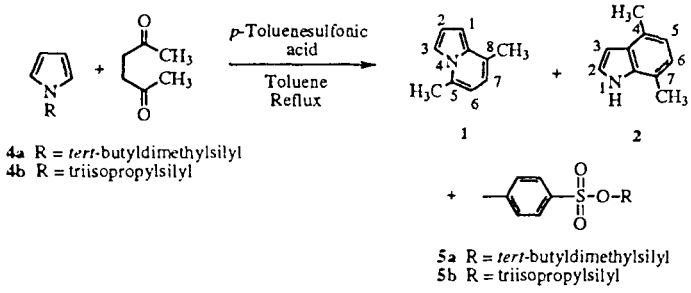
Introduction.

Indolizines are key intermediates for the synthesis of cycl{3.2.2}azine, indolizidine alkaloids, and a new class of aryl substituted indolizidines exhibiting analgesic activity [1-4]. At present, the most general method for the synthesis of indolizines and their related compounds involves the Tschitschibabin reaction employing 2-picoline or its' derivatives with haloketones [5]. However, this method is inconvenient for the synthesis of 1,2,3-unsubstituted indolizines. Recently, Tominaga and co-workers [6] reported the synthesis of 1,2,3-unsubstituted indolizine derivatives in a four step sequence beginning with reaction of nitro ketene dithioacetal, 1,1-bis(methylthio)-2-nitroethylene, with various 1-ethoxycarbonylmethylpyridinium bromides. These indolizine derivatives were allowed to react with dimethyl acetylenedicarboxylate to give the corresponding cycl{3.2.2}azine derivatives. This approach requires multiple steps and relatively exotic starting materials. In this note, we wish to report a simple and efficient approach to 8-substituted indolizines via synthesis of various 5,8-disubstituted indolizines in which a positional protective *tert*-butyl group is removed. Subsequent reaction with dimethyl acetylenedicarboxylate provides 5-substituted cycl{3.2.2}-azines in good yields.

Results and Discussion.

In agreement with previous reports [7,8], we found that the reaction of pyrrole and 2,5-hexanedione, in refluxing toluene with *p*-toluenesulfonic acid monohydrate, resulted in a 17% yield of 5,8-dimethylindolizine **1**, a 29% yield of 4,7-dimethylindole **2**, and <5% yield of the tetramethylcarbazole **3**. However, the identical reaction with 1-(dimethyl-*tert*-butylsilyl)pyrrole **4a** or 1-(triisopropylsilyl)pyrrole **4b** resulted in increased yield and selectivity to **1** (35%), while yield to **2** and **3** were relatively unchanged (Table 1). In-situ desilylation of **4a,b** with concurrent formation of *tert*-butyldimethylsilyl-*p*-toluenesulfonate **5a** and triisopropylsilyl-*p*-toluenesulfonate **5b**, prevented *p*-toluenesulfonic acid regeneration. Thus, near equimolar amounts of *p*-toluenesulfonic acid were required, relative to **4a,b**, to afford complete conversion [9] (Scheme 1).

Scheme 1



To explore the versatility of this method, a variety of symmetrical and unsymmetrical 1,4-diketones were evaluated targeting 5,8-disubstituted indolizines allowing access to novel 5-substituted cycl{3.2.2}azine analogues. 1,4-Diketone synthesis consisted of deprotonating appropriate β-ketoester **6'a-c** with sodium hydride followed by alkylation with 1-chloropinacolone [10]. Decarboethoxylation in dimethylsulfoxide with sodium chloride and water provided 1,4-diketones **6a-c** in good yields Scheme 2 [11]. Cyclocondensation of ketones **6a-c** with **4a,b** provided 5,8-disubstituted indolizines **1a-c** along with indoles **2a-c**. Similar reactions with unprotected pyrrole resulted in lower overall yields to indolizines and indoles in most cases (Table 1). Reactions were monitored for disappearance of **4a,b** *via* gas chromatography. The intermediate product ratios of indolizine to indole were similar to the isolated ratios, and decomposition accounted for the remainder of the pyrrole moiety. Attempts to improve moderate yields with acids of differing strengths were unsuccessful. However, we believe the ease of isolating the indolizine from the indole (R_f = 0.8 *vs.* 0.3) allows preparation of 5,8-disubstituted indolizines in gram quantities.

Scheme 2

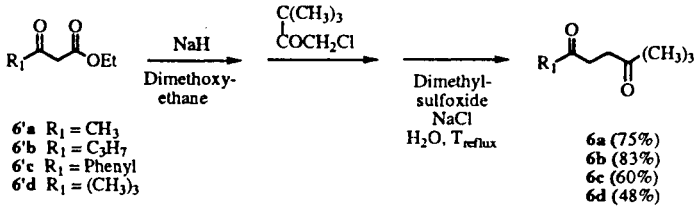
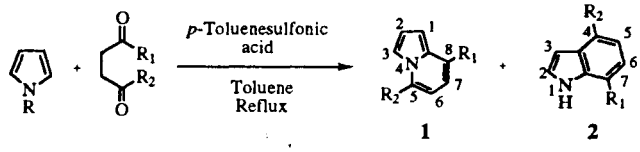


Table 1

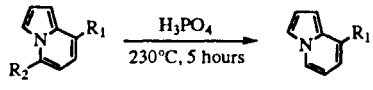


R	R_1	R_2	Isolated Yield (%)	Isolated Yield (%)
H	CH_3	CH_3	**1** (17)	**2** (29)
tert-butyldimethylsilyl	CH_3	CH_3	**1** (35)	**2** (35)
triisopropylsilyl	CH_3	CH_3	**1** (25)	**2** (17)
triisopropylsilyl	CH_3	$C(CH_3)_3$	**1a** (42)	**2a** (32)
H	C_3H_7	$C(CH_3)_3$	**1b** (17)	**2b** (16)
triisopropylsilyl	C_3H_7	$C(CH_3)_3$	**1b** (30)	**2b** (25)
H	Phenyl	$C(CH_3)_3$	**1c** (24)	**2c** (12)
triisopropylsilyl	Phenyl	$C(CH_3)_3$	**1c** (25)	**2c** (21)

With pyrrole or *N*-protected pyrrole, regiospecificity of the substituents in the resulting disubstituted indolizine and indole products were identical as determined by ^1H- and ^{13}C-nmr, implying that electrophilic attack occurs first at the 2-position after in-situ desilylation [3]. In light of numerous reports concerning the directing effect of the triisopropylsilyl and *tert*-butyldimethylsilyl groups to the 3-position in electrophilic substitution reactions [12], it seems probable that initial attack would be expected at the 3-position if the triisopropylsilyl or *tert*-butyldimethylsilyl groups remained intact. Moreover, steric hindrance imparted by the triisopropylsilyl group shows that both *alpha*- and *beta*-positions of the pyrrole nucleus are highly hindered [13]. Evaluation of 1,4-diketones containing the methyl-propyl, methyl-pentyl, and methyl-phenyl acyl substituents resulted in high regiospecific electrophilic attack by the carbonyl bearing the methyl substituent at the two position of the pyrrole moiety with trace amounts of other indolizine/indole isomers [3]. The symmetrical ketone with *tert*-butyl groups **6d** resulted in only trace amounts of cyclocondensed products when allowed to react with **4b** or pyrrole, presumably due to steric demands of the *tert*-butyl group disallowing access to the two position.

Attempts to remove the *tert*-butyl group of **1b** *via* lewis acid catalyzed transalkylation with aluminum trichloride [14] resulted in dimer formation, scrambling of the *tert*-butyl group, and recovery of starting material. Moderation of aluminum trichloride activity with nitroethane [15] provided similar results. Tashiro and co-worker [16] reported removal of the *tert*-butyl group in carbazole and piperidine moieties by treatment with 85% phosphoric acid at elevated temperatures (210-220°). Similarly, we were pleased when treatment of **1a-c** with 85% phosphoric acid at 230° for 5 hours returned 8-substituted indolizines **7a-c** in excellent yields (Table 2).

Table 2

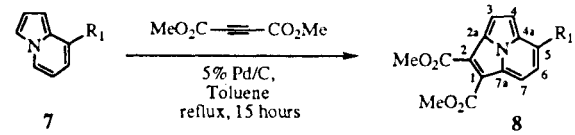


Entry	R_1	R_2	Isolated Yield (%)
1a	CH_3	$C(CH_3)_3$	**7a** (85)
1b	C_3H_7	$C(CH_3)_3$	**7b** (80)
1c	Phenyl	$C(CH_3)_3$	**7c** (75)

Finally, treatment of **7a-c** with 2.5 equivalents of dimethyl acetylenedicarboxylate in refluxing toluene in the presence of 5% palladium-on-carbon provided 5-substituted cycl{3.2.2}azine-1,2-dicarboxylate **8a-c** in good yields (Table 3) [6].

Table 3

Entry	R_1	Isolated Yield (%)
7a	CH_3	**8a** (53)
7b	C_3H_7	**8b** (67)
7c	Phenyl	**8c** (54)



In conclusion, this procedure represents an efficient method for the preparation of novel alkyl and aryl substituted cycl{3.2.2}azine derivatives **8a-c**. The two step synthesis of 8-substituted indolizines **7a-c** from commercially available starting materials, represents a more concise synthesis as compared to the method of Tominaga and co-workers, in which **7a** was prepared in four steps starting with 1-ethoxycarbonylmethyl-3-methylpyridinium bromide and 1,1-bis(methylthio)-2-nitroethylene [6]. An extension of the described 5,8-disubstituted indolizine synthesis including various substituted 1,4-diketones will be published in due course.

EXPERIMENTAL

Melting points were determined on a Thomas Hoover capillary melting point apparatus and are uncorrected. Column chromatography was performed with 63-200 mm silica gel from EM Science. The ^1H and ^{13}C nmr spectra were obtained on a Varian Unity 400 MHz spectrophotometer, and where indicated, a JEOL Model FX90Q, in the specified deuterated solvent at 30°, and are reported in ppm. For samples prepared in deuteriochloroform, the chemical shifts are expressed relative to internal tetramethylsilane. The electron impact mass spectra were determined with a Hewlett-Packard HP-5971A spectrometer. The high resolution mass spectrometry was determined on an VG Autospec spectrometer. Elemental analyses were performed on a Perkin-Elmer 2400 Series II instrument. Gas chromatography was performed on HP-5890 Series II, instrument equipped with an HP-5 Column-30 meter, injector 250°, detector 285°, rate 8°/minute. The ir spectra for solids were recorded using the attenuated total reflectance method (corrected) with a Mattson RS FTIR spectrophotometer. The ir spectra for liquids were recorded with an Applied Systems React IR 1000, Millersville, Md. 1-(Triisopropylsilyl)pyrrole **4b**, 2,5-hexanedione and other common commercial reagents were used as received from Aldrich. 1-(Dimethyl-*tert*-butylsilyl)pyrrole **4a** was prepared via standard procedures defined in the literature [17]. Solvents were purchased anhydrous and used without further drying.

General Procedure for Synthesis of 1,4-Diketones **6a-d**.

To a 100 ml 3-neck flask in a cold water bath was added 70 ml of dimethoxyethane solvent and 2.74 g (68.5 mmoles) sodium hydride as a 60% dispersion in mineral oil. To this, was added 0.90 equivalent of the appropriate β-ketoester **6'a-d** in a dropwise fashion. When the hydrogen evolution ceased, an equimolar amount of 1-chloropinacolone (95%), relative to β-ketoester, was added in a dropwise fashion. The cold water bath was removed and the resulting mixture was refluxed (~90°) for 15 hours. The crude mixture was cautiously quenched with 150 ml dilute sulfuric acid (8%), and extracted with diethyl ether 3 x 60 ml. The resulting crude mixture was concentrated by rotary evaporation and added to a 100 ml 3-neck flask fitted with a condenser. Assuming the crude contained 100% of the alkylated β-ketoester (~60 mmoles), 60 ml of dimethyl sulfoxide, 4.5 equivalents water, and 1.1 equivalents sodium chloride was added to the crude. The contents of the flask were refluxed (~160°) for 20 hours. The resulting solution was quenched with dilute sulfuric acid (8%) and extracted with diethyl ether 4 x 50 ml. The extracts were combined, dried over magnesium sulfate, and rotary evaporated to concentrate. Vacuum distillation provided 1,4-diketone.

6,6-Dimethyl-2,5-heptanedione (**6a**).

This compound was obtained as a colorless liquid (75%), bp 47° (0.3 mm Hg); ir (neat): 1700 cm^{-1}; ^1H nmr (deuteriochloroform, 90 MHz): δ 3.15-2.66 (m, 4H), 2.23 (s, 3H), 1.25 (s, 9H); ms: m/z 156 (M^+), 141, 99, 71, 57.

Anal. Calcd. for $C_9H_{16}O_2$: C, 69.23; H, 10.26. Found: C, 69.12; H, 10.05.

2,2-Dimethyl-3,6-nonanedione (**6b**).

This compound was obtained as a colorless liquid (83%), bp 67° at 0.3 mm Hg; ir (neat): 2964, 1702 (C=O), 1478, 1366, 1058 cm^{-1}; ^1H nmr (deuteriochloroform, 90 MHz): δ 2.98-2.22 (m, 6H), 1.77-1.36 (m, 2H), 1.15 (s, 9H), 0.89 (t, 3H); ms: m/z 184 (M^+), 169, 151, 141, 127, 113, 99, 85, 71, 57.

Anal. Calcd. for $C_{11}H_{20}O_2$: C, 71.74; H, 10.87. Found: C, 71.53; H, 10.92.

1-Phenyl-5,5-dimethyl-1,4-hexanedione (**6c**).

This compound was obtained as a colorless liquid (60%), bp 124° at 0.3 mm Hg; ir (neat): 2968, 2930, 2910, 2872, 1702 (C=O), 1687 (C=O), 1598 cm^{-1}; ^1H nmr (deuteriochloroform, 90 MHz): δ 8.06-7.95 (m, 2H), 7.52-7.44 (m, 3H), 3.27-3.20 (m, 2H), 3.03-2.95 (m, 2H), 1.22 (s, 9H); ms: m/z 203 (M^+-15), 161, 133, 115, 105, 91, 77, 57.

1,4-Di-*tert*-butyl-1,4-butanedione (**6d**).

This compound was obtained as a colorless liquid (48%), bp 65° at 0.3 mm Hg; ir (neat): 2995, 1710 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform, 90 MHz): δ 2.76 (s, 4H), 1.18 (s, 18H, *tert*-butyl); ^{13}C nmr (deuteriochloroform, 22.5 MHz): δ 214.7, 44.4, 31.0, 27.1; ms: m/z 199 (M^++1), 183, 141, 113, 97, 85, 69, 57.

Anal. Calcd. for $C_{12}H_{22}O_2$: C, 72.73; H, 11.11. Found: C, 72.56; H, 10.98.

General Procedure for Synthesis of Disubstituted Indolizines (**1a-c**) and Indoles **2a-c**.

To a 100 ml 3-neck flask, fitted with a Dean-Stark trap, magnetic stirrer, thermo-watch, and condenser under argon was added 80 ml of toluene plus 20 ml toluene to the Dean-Stark trap. The mixture was refluxed for 30 minutes to remove any water preexisting in the toluene. To approximately 1.0 g of **4a,b** an equimolar amount of the 1,4-diketone, **6a-c**, was added and the mixture sampled for time zero gas chromatography analysis. In the case of pyrrole, 60 mg of *p*-toluenesulfonic acid was added and the solution was allowed to reflux overnight. Regarding **4a,b**, *p*-toluenesulfonic acid in 50-100 mg charges was added intermittently until conversion was complete as determined *via* gas chromatography. The solution was cooled to ambient, 40 ml of ethyl acetate was added, and the solution was quenched with 50 ml of 1% potassium carbonate. The aqueous phase was extracted with 2 x 40 ml of ethyl acetate, the organic phases combined, dried over magnesium sulfate and concentrated by rotary evaporation. Purification was achieved *via* column chromatography, hexane:ethyl acetate (99:1) initially to elute disubstituted indolizines **1a-c**, followed by (95:5) to elute disubstituted indoles **2a-c**.

5,8-Dimethylindolizine (**1**).

This compound was obtained in 40% yield as a pale yellow crystal (hexane), mp 29°, mp 28-30° [7,8]; ^1H nmr (deuteriochloroform, 400 MHz): δ 7.2 (dd, J = 2.6, 1.5 Hz, 1H, H-3), 6.9 (dd, J = 3.9, 2.7 Hz, 1H, H-2), 6.5 (m, 2H, H-1 and H-7), 6.3 (d, J = 6.6 Hz, 1H, H-6), 2.5 (s, 3H), 2.4 (s, 3H); ms: m/z 145 (M^+).

Anal. Calcd. for $C_{10}H_{11}N$: C, 82.76; H, 7.59; N, 9.66. Found: C, 82.89; H, 7.56; N, 9.31.

4,7-Dimethylindole (**2**).

This compound was obtained in 35% yield as a white solid (hexane), mp 99°, mp 99-101° [7,8]; ^1H nmr (deuteriochloroform, 400 MHz): δ 8.0 (broad s, 1H, NH), 7.2 (m, 1H, H-2), 6.9 (d, J = 7.2 Hz, 1H, H-6), 6.8 (d, J = 7.03 Hz, 1H, H-5), 6.6 (m, 1H, H-3), 2.5 (s, 3H), 2.46 (s, 3H); ms: m/z 145 (M^+).

Anal. Calcd. for $C_{10}H_{11}N$: C, 82.76; H, 7.59; N, 9.66. Found: C, 82.78; H, 7.22; N, 9.67.

5-*t*-Butyl-8-methylindolizine (**1a**).

This compound was obtained in 42% yield as a pale yellow solid (diethyl ether), mp 50-52°; ir (condensed phase): 2964, 1481, 1365, 1211, 809, 711 cm^{-1}; ^1H nmr (deuteriochloroform, 400 MHz): δ 7.62 (b, 1H, H-3), 6.82 (dd, 1H, H-2), 6.47 (dd, 2H, J = 7.0, 1.2 Hz, H-7,1), 6.40 (d, 1H, J = 7.0 Hz, H-6), 2.39 (d, 3H, J = 1.2 Hz, 8-CH_3), 1.53 (s, 9H, *tert*-butyl); ^1H nmr (dimethyl sulfoxide-d_6): δ 7.68 (dd, 1H, J = 1.4 Hz, H-3), 6.76 (dd, 1H, J = 2.9 Hz, H-2), 6.49 (dd, 1H, J = 7.0 Hz, H-7), 6.41 (d, 1H, J = 2.9, 1.0 Hz, H-1), 6.40 (d, 1H, J = 7.0 Hz, H-6), 2.31 (t, 3H, J = 1.0 Hz, 8-CH_3), 1.45 (s, 9H, *tert*-butyl); ^{13}C nmr (deuteriochloroform, 100 MHz): δ 142.3, 136.0, 126.2, 116.7, 114.6, 112.4, 107.3, 97.5, 35.2, 28.1, 28.1, 28.1, 18.2; ms: m/z 187 (M^+), 172, 156, 145, 130.

Anal. Calcd. for $C_{13}H_{17}N$: C, 83.35; H, 9.17; N, 7.48. Found: C, 83.73; H, 9.16; N, 7.75.

4-*t*-Butyl-7-methylindole (**2a**).

This compound was obtained 32% yield as a white solid (diethyl ether), mp 82-84°; ir (chloroform): 3490 (NH), 2980, 1210, 760 cm^{-1}; ^1H nmr (deuteriochloroform, 400 MHz): δ 8.07 (broad s, 1H, NH), 7.22 (dd, 1H, J = 2.7 Hz, H-2), 7.01-6.95 (m, 2H, J = 7.8, 0.4 Hz, H-6,5), 6.83 (dd, 1H, J = 2.2 Hz, H-3), 2.49 (d, 3H, J = 0.6 Hz, 7-CH_3), 1.53 (s, 9H, *tert*-butyl); ms: m/z 187 (M^+), 172, 157, 144, 132, 117.

Anal. Calcd. for $C_{13}H_{17}N$: C, 83.35; H, 9.17; N, 7.48. Found: C, 83.83; H, 9.00; N, 7.64.

5-*t*-Butyl-8-propylindolizine (**1b**).

This compound was obtained in 30% yield as a colorless liquid; ir (neat): 2958, 2931, 2871, 1623, 1465, 1366, 1260, 1210, 1102, 804, 697 cm^{-1}; ^1H nmr (deuteriochloroform, 400 MHz): δ 7.65 (d, 1H, J = 2.2 Hz, H-3), 6.85 (m, 1H, H-2), 6.54 (s, 1H, H-1), 6.53 (d, 1H, J = 7 Hz, H-7), 6.45 (d, 1H, J = 7 Hz, H-6), 2.78 (t, 2H, J = 7.4 Hz, CH_2), 1.86-1.77 (m, 2H, J = 7.4 Hz, CH_2), 1.56 (s, 9H, *t*-butyl), 1.05 (t, 3H, J = 7.4 Hz, CH_3); ^{13}C nmr (deuteriochloroform, 100 MHz): δ 142.2, 135.5, 130.6, 115.6, 114.3, 112.2, 107.2, 97.3, 35.1, 34.5, 28.1, 28.1, 28.1, 22.1, 14.4; ms: m/z 215 (M^+), 200, 173, 158.

Anal. Calcd. for $C_{15}H_{21}N$: C, 83.65; H, 9.85; N, 6.51. Found: C, 83.74 H, 9.55; N, 6.62.

4-*t*-Butyl-7-propylindole (**2b**).

This compound was obtained in 25% yield as a light brown oil; ir (neat): 3419 (NH), 2954, 2931, 2869, 1503, 1360, 812, 729 cm^{-1}; ^1H nmr (deuteriochloroform, 400 MHz): δ 8.1 (broad s, 1H, NH), 7.2 (dd, 1H, J = 3.1 Hz, H-2), 6.98 (d, 1H, J = 7.6 Hz, H-5), 6.95 (d, 1H, J = 7.6 Hz, H-6), 6.8 (dd, 1H, J = 3.3 Hz, H-3), 2.78 (t, 2H, J = 7.4 Hz, CH_2), 1.83-1.74 (m, 2H, J = 7.4 Hz, CH_2), 1.51 (s, 9H, *t*-butyl), 1.03 (t, 3H, J = 7.4 Hz, CH_3); ms: m/z 215 (M^+), 200, 171, 158, 130.

Anal. Calcd. for $C_{15}H_{21}N$: C, 83.65; H, 9.85; N, 6.51. Found: C, 83.94 H, 9.81; N, 6.57.

5-*t*-Butyl-8-phenylindolizine (**1c**).

This compound was obtained in 26% yield as a pale yellow solid (hexane), mp 92-94°; ^1H nmr (deuteriochloroform, 400 MHz): δ 7.69 (m, 1H), 7.66-7.64 (m, 2H), 7.46-7.41 (m, 2H), 7.39-7.34 (m, 1H), 6.85-6.83 (m, 1H), 6.66 (d, 1H, J = 7.2 Hz), 6.62-6.61 (m, 1H), 6.56 (d, 1H, J = 7.2 Hz), 1.58 (s, 9H); ^{13}C nmr (deuteriochloroform, 100 MHz): δ 129.1, 125.4, 120.0, 117.0, 114.4, 114.3, 113.4, 102.8, 100.4, 98.6, 93.3, 85.1, 21.1, 13.7; ms: m/z 249 (M^+), 234, 218, 207.

Anal. Calcd. for $C_{18}H_{19}N$: C, 86.70; H, 7.68; N, 5.62. Found: C, 86.87 H, 7.80; N, 5.64.

4-*t*-Butyl-7-phenylindole (**2c**).

This compound was obtained in 25% yield as a light brown oil; ^1H nmr (deuteriochloroform, 400 MHz): δ 8.39 (broad s, 1H, NH), 7.62-7.59 (m, 2H), 7.50-7.45 (m, 2H), 7.36 (tt, 1H, J = 1.4 and 7.4 Hz), 7.19-7.16 (m, 1H), 7.14 (s, 2H), 6.85-6.84 (m, 1H), 1.56 (s, 9H); ^{13}C nmr (deuteriochloroform, 100 MHz): δ 142.6, 139.3, 134.4, 129.1, 128.3, 127.2, 125.5, 123.9, 122.9, 121.8, 116.4, 104.4, 35.7, 30.7; ms: m/z 249 (M^+), 234, 218, 204, 193.

Anal. Calcd. for $C_{18}H_{19}N$: C, 86.70; H, 7.68; N, 5.62. Found: C, 86.63 H, 7.80; N, 5.61.

8-Methylindolizine (**7a**).

To **1a** (350 mg, 1.87 mmoles) was added 5.8 g of 85% phosphoric acid in a 25 ml sealable teflon screwcap vial. The entire flask was submersed in an oil bath preheated to 230°. After 5 hours the contents were cooled and cautiously poured into 150 ml of 1% potassium carbonate. The neutralized material was extracted 3 x 60 ml with diethyl ether and dried over magnesium sulfate. Filtration and rotary evaporation followed by column chromatography (99:1, hexane:ethyl acetate) provided **7a** (205 mg, 85%) as a colorless oil; ir (neat): 3103, 3042, 2937, 2918, 2853, 1478, 1355, 1305, 1077, 1019. 745, 691 cm^{-1}; ^1H nmr (deuteriochloroform, 400 MHz): δ 7.82 (d, 1H, J = 6.8 Hz, 5-H), 7.32 (dd, 1H, J = 1.6 Hz, 3-H), 6.8 (dd, 1H, J = 2.5, 3.9 Hz, 2-H), 6.48-6.40 (m, 3H, 1,6,7-H), 2.42 (s, 3H, 8-CH_3); reported ^1H nmr (deuteriochloroform) [6]: δ 7.73-7.47 (m, 1H, 5-H), 7.20-7.10 (m, 1H, 3-H), 6.68 (dd, 1H, J = 2.0,4.0 Hz, 2-H), 6.47-6.07 (m, 3H, 1,6,7-H), 2.33 (s, 3H, 8-CH_3); ^{13}C nmr (deuteriochloroform, 100 MHz): δ 133.9 (C9), 128.3 (C5), 123.2 (C8), 116.0 (C7), 113.0 (C2), 110.3 (C3), 104.1 (C6), 97.3 (C1), 18.1 (C10); ms: m/z 131 (M^+), 130 (M^+-1), 116, 115, 103, 77.

8-Propylindolizine (**7b**).

To **1b** (800 mg, 3.68 mmoles) was added 12.5 g of 85% phosphoric acid in a 25 ml sealable teflon screwcap glass vial. The entire flask was submersed in an oil bath preheated to 230°. After 5 hours, the contents were cooled and cautiously poured into 1% potassium carbonate. The neutralized material was extracted 3 x 60 ml with diethyl ether and dried over magnesium sulfate. Filtration and rotary evaporation followed by column chromatography (100%, pentane) provided **7b** (554 mg, 80%) as a yellow oil; ir (neat): 3103, 3042, 2957, 2930, 2868, 1629, 1455, 1363, 1305, 1081, 745 cm^{-1}; ^1H nmr (deuteriochloroform, 400 MHz): δ 7.78 (d, 1H, J = 6.8 Hz, H-5), 7.23 (dd, 1H, J = 2.7, 1.4 Hz, H-2), 6.75 (dd, 1H, J = 2.7, 1.2 Hz, H-3), 6.46-6.38 (m, 3H, H-1,6,7), 2.72 (t, 2H, J = 7.4 hz, CH_2), 1.77 (m, 2H, J = 7.4 Hz, CH_2), 1.0 (t, 3H, J = 7.4 Hz, CH_3); ^{13}C nmr (deuteriochloroform, 100 MHz): δ 133.5 (C9), 132.7 (C5), 123.2 (C8), 115.0 (C7), 112.9 (C2), 112.7 (C3), 110.3 (C6), 97.2 (C1), 34.5 (C10), 21.9 (C11), 14.2 (C12); ms: m/z 159 (M^+), 144, 131, 117, 103, 89, 77, 63, 51.

Anal. Calcd. for $C_{11}H_{13}N$: C, 82.97; H, 8.23; N, 8.80. Found: C, 82.88; H, 8.28; N, 8.70.

8-Phenylindolizine (**7c**).

To **1c** (250 mg, 1.00 mmole) was added 6.2 g of 85% phosphoric acid in a 25 ml sealable teflon screwcap glass vial. The entire flask

was submersed in an oil bath preheated to 230°. After 5 hours, the contents were cooled and cautiously poured into 1% potassium carbonate. The neutralized material was extracted 3 x 60 ml with diethyl ether and dried over magnesium sulfate. Filtration and rotary evaporation followed by column chromatography (100%, pentane) provided **7c** (148 mg, 80%) as a yellow oil; ^{1}H nmr (deuteriochloroform, 400 MHz): δ 7.88-7.86 (dt, 1H, J = 1.0 and 5.9 Hz), 7.68 (m, 1H), 7.66 (m, 1H), 7.46-7.42 (m, 2H), 7.39-7.34 (m, 2H), 6.80-6.78 (m, 1H), 6.64-6.62 (dd, 1H, J = 1.0 and 6.8 Hz), 6.55-6.50 (m, 2H); ^{13}C nmr (deuteriochloroform, 100 MHz): δ 139.2, 133.0, 132.1, 128.5, 128.2, 127.8, 124.3, 116.4, 113.6, 113.1, 110.5, 99.2; ms: m/z 193 (M^+), 178, 165, 152, 139, 126, 115, 95, 84.

Dimethyl 5-Methylcycl[3.2.2]azine-1,2-dicarboxylate (**8a**).

To 50 ml 3-neck flask, fitted with a condenser and stir bar, was added **7a** (25 mg, 0.18 mmole), 20 ml toluene, 49 mg 5% palladium-on-carbon (0.13 equivalent), and 53 mg (2.0 equivalents) of dimethyl acetylenedicarboxylate. The solution was allowed to reflux for 16 hours, while monitoring disappearance of starting material by thin layer chromatography. The resulting mixture was filtered, concentrated via rotary evaporation, and isolated *via* thin layer chromatography by eluting 2 times with hexane:ethyl acetate (70:30) to deliver yellow prisms (25.6 mg, 53%), mp 95-96° (diethyl ether); (mp 93°) [6]; ^{1}H nmr (deuteriochloroform, 400 MHz): δ 8.32 (d, 1H, J = 8.4 Hz, 7-H), 7.72-7.65 (m, 2H, 4 and 6-H), 7.44 (d, 1H, J = 4.8 Hz, 3-H), 4.06 (s, 3H, OCH_3), 4.02 (s, 3H, OCH_3), 2.86 (s, 3H, 5-CH_3); Reported ^{1}H nmr (deuteriochloroform) [6]: δ 8.32 (d, 1H, J = 8.4 Hz, 7-H), 7.73-7.63 (m, 2H, 4 and 6-H), 7.44 (d, 1H, J = 4.6 Hz, 3-H), 4.06 (s, 3H, OCH_3), 4.02 (s, 3H, OCH_3), 2.87 (s, 3H, 5- CH_3); ms: m/z 272 (M^++1), 271 (M^+), 240, 210, 182, 154, 153, 126, 104.

Dimethyl 5-Propylcycl[3.2.2]azine-1,2-dicarboxylate (**8b**).

To 50 ml 3-neck flask, fitted with a condenser and stir bar, was added **7b** (35 mg, 0.22 mmole), 20 ml toluene, 66 mg 5% palladium-on-carbon (0.14 equivalent), and 80 mg (2.0 equivalents) of dimethyl acetylenedicarboxylate. The solution was allowed to reflux for 15 hours, while monitoring disappearance of starting material via thin layer chromatography. The resulting mixture was filtered, concentrated *via* rotary evaporation, and isolated *via* thin layer chromatography by eluting 2 times with hexane:ethyl acetate (70:30) to deliver a yellow oil (44.3 mg, 67%); ir (neat): 2953, 2872, 1722 (broad), 1490, 1436, 1301, 1270, 1204, 1131, 1050, 776, 710 cm^{-1}; ^{1}H nmr (deuteriochloroform, 400 MHz): δ 8.37 (d, 1H, J = 8.2 Hz, 7-H), 7.72 (d, 1H, J = 8.4 Hz, H-6), 7.69 (d, 1H, J = 4.9 Hz, H-4), 7.45 (d, 1H, J = 4.9 Hz, H-3), 4.06 (s, 3H, OCH_3), 4.03 (s, 3H, OCH_3), 3.15 (t, 2H, J = 7.4 Hz, $CH_2CH_2CH_3$), 1.88 (m, 2H, $CH_2CH_2CH_3$), 1.00 (t, 3H, J = 7.2 Hz, $CH_2CH_2CH_3$); ^{13}C nmr (deuteriochloroform, 100 MHz): δ 164.7 (C=O), 164.4 (C=O), 131.7 (C-5), 131.2 (C-4'), 129.8, 128.8, 128.4 (C-7'), 127.7 (C-2'), 126.3 (C-6), 119.4 (C-4), 117.7 (C-7), 114.5 (C-3), 52.4 (OCH_3), 51.7 (OCH_3), 34.0 ($CH_2CH_2CH_3$), 25.0 ($CH_2CH_2CH_3$), 14.0 ($CH_2CH_2CH_3$); ms: m/z 299 (M^+), 268, 239, 212, 196, 181, 153, 139, 126.

Anal. Calcd. for $C_{17}H_{17}NO_4$: C, 68.21; H, 5.73; N, 4.68. Found: C, 67.95; H, 5.95; N, 4.60.

Dimethyl 5-Phenylcycl[3.2.2]azine-1,2-dicarboxylate (**8c**).

To 50 ml 3-neck flask, fitted with a condenser and stir bar, was added **7c** (52 mg, 0.27 mmol), 20 ml toluene, 92 mg 5% palladium-on-carbon (0.16 equivalent), and 102 mg (2.0 equivalents) of dimethyl acetylenedicarboxylate. The solution was allowed to reflux for 17 hours, while monitoring disappearance of starting material via thin layer chromatography. The resulting mixture was filtered, concentrated via rotary evaporation, and isolated via thin layer chromatography by eluting 2 times with hexane:ethyl acetate (70:30) to deliver a yellow prisms (49 mg, 54%) mp 123-125° (diethyl ether); ir (neat): 2953, 2872, 1722 (broad), 1490, 1436, 1301, 1270, 1204, 1131, 1050, 776, 710 cm^{-1}; ^{1}H nmr (deuteriochloroform, 400 MHz): δ 8.50 (d, 1H, J = 8.4 Hz), 8.02 (d, 1H, J = 8.2 Hz), 7.84-7.82 (m, 2H), 7.77 (d, 1H, J = 4.7 Hz), 7.60-7.56 (m, 3H), 7.52-7.48 (m, 1H), 4.08 (s, 3H), 4.05 (s, 3H); ^{13}C nmr (deuteriochloroform, 100 MHz): δ 164.5 (C=O), 164.2 (C=O), 137.1, 130.5, 129.7, 129.5, 129.2, 129.0, 128.6, 128.0, 125.2, 121.4, 120.7, 118.0, 115.9, 112.8, 52.5, 51.8; ms, m/z: 333 (M^+), 302, 272, 259, 244, 216. High resolution ms: m/z (M^+) calcd 333.100, obsd 333.099.

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REFERENCES AND NOTES

[1a] R. J. Windgassen, W. H. Saunders Jr., and V. Boekelheide, *J. Am. Chem. Soc.*, **81**, 1459 (1959); [b] V. Boekelheide and A. Miller, *J. Org. Chem.*, **26**, 431 (1961); [c] A. Galbraith, T. Small, R. A. Barnes, and V. Boekelheide, *J. Am. Chem. Soc.*, **83**, 453 (1961); [d] M. DePompei, and W. W. Paudler, *J. Org. Chem.*, **41**, 1661 (1975).

[2] E. T. Borrows, D. O. Holland, and J. Kenyon, *J. Chem. Soc.*, 1083 (1946).

[3] J. O. Smith, Approaches to Gephyrotoxin Alkaloids and Cycl{3.2.2}azine Analogues, Ph.D. Thesis, Illinois Institute of Technology, 1996.

[4] W. H. Pearson and B. M. Gallagher, *Tetrahedron*, **52**, 12039 (1996).

[5] A. E. Tschitschibabin, *Ber.*, **60**, 1607 (1927).

[6] Y. Tominaga, Y. Shiroshita, T. Kurokawa, H. Gotou, Y. Matsuda, and A. Hosomi, *J. Heterocyclic Chem.*, **26**, 477 (1989).

[7] L. K. Dalton and T. Teitei, *Aust. J. Chem.*, **21**, 2053 (1968).

[8] C. O. Bender and R. Bonnett, *J. Chem. Soc. (C)*, 3036 (1968).

[9a] To exemplify the stability of **4b** in the reaction mixture, its' treatment with *p*-toluenesulfonic acid (0.50 equivalent) over a 24 hours period in refluxing toluene, resulted in 98% isolated yield of **5b**, and quantitative recovery of unreacted **4b** based on *p*-toluenesulfonic acid added. Likewise, treatment of **4a** gave **5a** (70%), and near quantitative recovery of unreacted **4a**. Corey and co-workers [18] have reported the use of similar compounds, such as **5a,b** as silylating agents for tertiary or hindered secondary alcohols. Specifically, triisopropylsilyl triflate and *tert*-butyldimethylsilyl triflate. Indeed, the reaction of **5b**, benzyl alcohol, 2,6-lutidine in dichloromethane at molar ratios of {1.1:1:2} resulted in silylation of the alcohol at room temperature. Also, the reaction of **5a**, *tert*-butyl alcohol, and 2,6-lutidine in dichloromethane at molar ratios of {1.3:1:2.2} resulted in silylation of the alcohol at room temperature [3]; [b] Reactions were primarily evaluated utilizing the triisopropylsilyl protecting group when improved stoichiometric accountability of **4b**, with respect to formation of triisopropylsilyl tosylate **5b**, was observed in comparison to reactions run with the *tert*-butyldimethylsilyl group.

[10] O. Dann, H. Distler, and H. Merkel, *Chem. Ber.*, **85**, 457 (1952).

[11] A. P. Krapcho, E. G. E. Jahngen, and A. J. Lovey, *Tetrahedron Letters*, **13**, 1091 (1974).

[12a] G. Simchen and M. W. Majchrzak, *Tetrahedron Letters*, **26**, 5035 (1985); [b] J. Muchowski, and D. R. Solas, *Tetrahedron Letters*, **24**, 3455 (1983); [c] H. J. Anderson and C. E. Loader, *Synthesis*, 353 (1985).

[13] B. L. Bray, P. H. Mathies, R. Naef, D. R. Solas, T. T. Tidwell, D. R. Artis, and J. M. Muchowski, *J. Org. Chem.*, **55**, 6317 (1990).

[14] M. Tashiro, T. Yamato, and G. Fukata, *J. Org. Chem.*, **43**, 1413 (1978).
[15] L. Schmerling, *Ind. Eng. Chem.*, **40**, 2072 (1948).
[16] M. Tashiro, *Synthesis*, 921 (1979).
[17] D. Dhanak and C. B. Reese, *J. Chem. Soc., Perkin Trans. 1*, 2181 (1986).
[18] E. J. Corey, H. Cho, C. Rucker, and D. H. Hua, *Teterahedron Letters*, **22**, 3455 (1981).