Total Synthesis of *Amaryllidaceae* Pyrrolophenanthridinium Alkaloids via the Ziegler−Ullmann Reaction: Tortuosine, Criasbetaine, and Ungeremine

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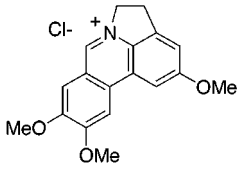
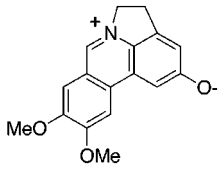
Introduction

In connection with a program in our laboratory directed toward the total synthesis of pyrrolophenanthridinium alkaloids for antitumor screening,[2] we required a short and general approach to the *Narcissus tortuosus* constituent tortuosine, **1**,[3] its structural relative criasbetaine, **2**,[4] from *Crinum asiaticum*, and ungeremine, **3**.[5] Structure−activity relationship (SAR) data for antitumor efficacy within the small class of known *Amaryllidaceae* pyrrolophenanthridinium alkaloids is very limited in scope; however, several encouraging preclinical studies of ungeremine have appeared over the past two decades.[6] Recently, significant efficacy against human ovarian and stomach cancers has been claimed for semisynthetic ungeremine acetate in human clinical trials conducted in the People's Republic of China.[7] The results of limited SAR studies related to the preclinical development of ungeremine have led to the suggestions that C-ring betaine functionality, A-ring oxygenation, and an optimal $O_A-N_B-O_C$ angle, may be important determinants in conferring antitumor properties within the pyrrolophenanthridinium class of alkaloids.[6]

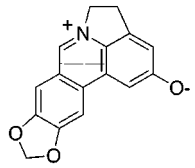


tortuosine chloride, **1**



criasbetaine

2a free base
2b HCl salt
2c CF_3CO_2H salt



ungeremine

3a free base
3b HCl salt
3c CF_3CO_2H salt

Tortuosine and criasbetaine were initially selected as synthetic targets for the current study for the following reasons: (1) No directly comparable biological studies of **1** and **2** have been reported, although the two compounds may provide a relatively subtle SAR probe of the effects of pyrrolophenanthridinium alkaloid C-ring functionality on antitumor efficacy, (2) compounds **1** and **2** have not been previously reported by total synthesis, and (3) the poor availability of these compounds is currently a serious limitation to further study. Tortuosine and criasbetaine have so far been isolated in low yield from their respective natural sources. Compounds **1** and **2** have also been prepared in very limited quantities, for the purpose of structure confirmation, by SeO_2-mediated degradation of stereochemically complex *Amaryllidaceae* alkaloids; however, the required precursor alkaloids for these semisynthetic preparations (galanthine → **1** and methylpseudolycorine → **2**)[3c,4e] are themselves essentially inaccessible. Two previous total syntheses of **3** have been reported; however, neither of the extant approaches is reported to give practical quantities of ungeremine.[8] Interestingly, all of the ungeremine acetate employed in preclinical and human clinical studies in the PRC was apparently obtained via the SeO_2-mediated degradation of lycorine.[6,7]

Results and Discussion

Using a modification of conditions first described by Iwao and Kuraishi, 1-(*tert*-butoxycarbonyl)-5-methoxyindoline, **4**, was lithiated at the C(7) position.[9] The 7-lithio indoline intermediate was subsequently transmetalated with $CuI-P(OEt)_3$ complex. The resulting organocopper

(1) Roche Bioscience Student Intern, 1998.

(2) A preliminary account of the synthesis of tortuosine and criasbetaine has been presented: Stark, L. M.; Lin, X.-F.; Flippin, L. A. *Book of Abstracts*, 217th ACS National Meeting, ORGN-398, 1999, Anaheim, CA.

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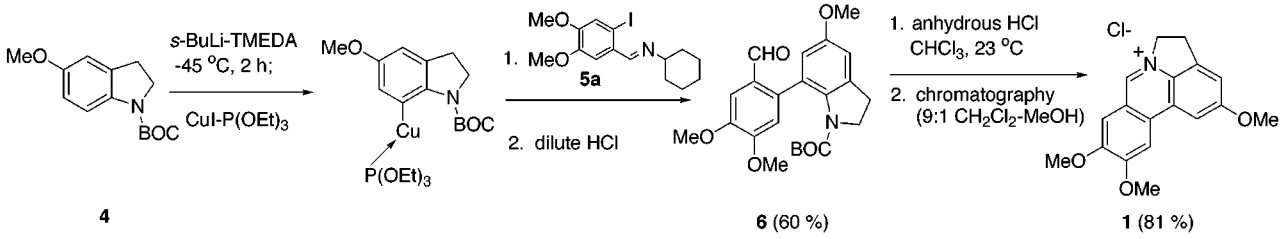
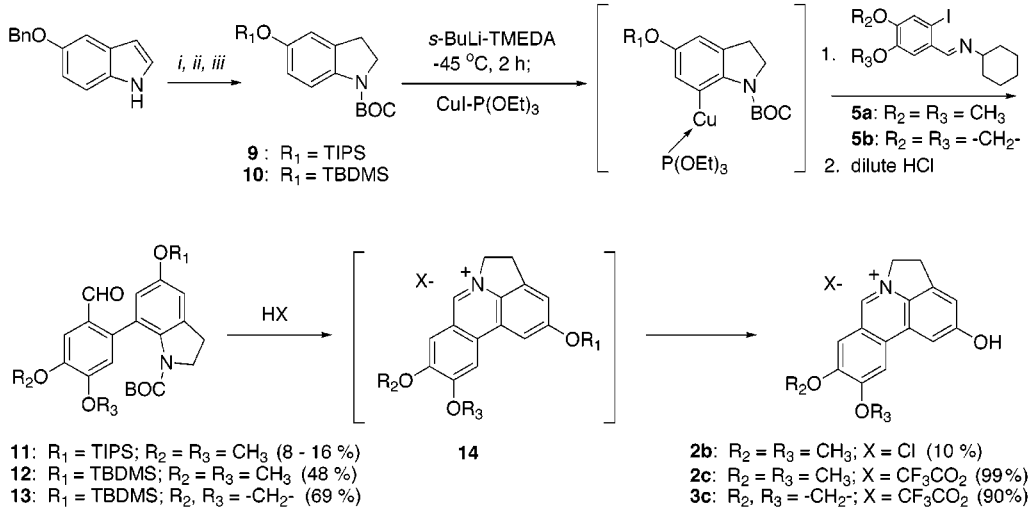
Scheme 1



Scheme 2[a]



[a] (i) $NaCNBH_3$−AcOH; then BOC_2 → **7** (60%); (ii) H_2 (1 atm)/10% Pd−C → **8** (99%); (iii) TIPSCl-imidazole, DMF: **8** → **9** (73%) or TBDMSCl-imidazole, DMF: **8** → **10** (94%).

slurry underwent the Ziegler−Ullmann coupling reaction[10] with 2-iodoaryl imine **5** to give, after mild hydrolytic workup, biarylaldehyde **6** in 60% yield. Removal of the N-*t*-BOC group from **6** with a saturated ether solution of anhydrous HCl also promoted concomitant cyclization and dehydration to afford tortuosine, **1**, in 81% yield (Scheme 1).

We anticipated that a similar approach using a suitable 5-hydroxyindoline synthon would lead to short syntheses of criasbetaine, **2**, and ungeremine, **3**. In the event, commercial 5-benzyloxyindole was reduced with $NaCNBH_3$ to give the corresponding indoline which, without isolation, was protected as a *t*-BOC carbamate, **7**. The O-benzyl group was removed from compound **7** using H_2/Pd−C in ethanol to give 1-(*tert*-butoxycarbonyl)-5-hydroxyindoline, **8**, in 99% yield and the hydroxyl group of compound **8** was efficiently protected either as a triisopropylsilyl (TIPS) ether, **9**, or a *tert*-butyldimethylsilyl (TBDMS) ether, **10**. Initially we investigated the utility of **9** and **10** for the synthesis of criasbetaine. For reasons that are still unclear, the lithiation−transmetalation−Ziegler coupling sequence using TIPS ether **9** afforded biarylaldehyde **11** in very poor yield (8−16%) despite several attempts to optimize it; however, TBDMS ether **10** behaved satisfactorily in the identical metalation−coupling sequence, reliably giving biarylaldehyde **12** in 40−48% yield over several independent trials.

Several attempts to prepare criasbetaine hydrochloride by allowing either **11** or **12** to react in $CHCl_3$ saturated with HCl proved inefficient. Removal of the *t*-BOC group and cyclization−dehydration proceeded rapidly from both of these intermediates; however, removal of the silyl group from the intermediate pyrrolophenanthridinium salts, **14**, was very slow, and prolonged exposure to the reaction conditions eventually resulted in the formation of uncharacterized side-products. Using this protocol, yields of isolated criasbetaine hydrochloride, **2b**, never exceeded ca. 10%. In another approach, the TIPS group was first removed from **11** (2 equiv of TBAF, THF, 23 °C, 30 min) to give a phenol followed by treatment with saturated HCl in $CHCl_3$; however, this sequence gave a crude product mixture that appeared by ^1H NMR analysis to suffer extensive *tert*-butyl substitution on the C-ring oxygen atom. Alternately, reaction of crude intermediate **14** (R_1 = TBDMS; $R_2 = R_3 = CH_3$; X = Cl: See Scheme 2) with 2 equiv of TBAF (THF, 23 °C, 16 h) gave <5% yield of criasbetaine along with polar side-products that no longer appeared to contain a C(6)−N(7) double bond (^1H NMR analysis). Finally, it was found that treatment of TBDMS-protected intermediate **12** with refluxing trifluoroacetic acid (neat, 16 h) promoted the desired *t*-BOC removal, cyclization−dehydration, desilylation sequence very cleanly to afford criasbetaine trifluoroacetate, **2c**, in near-quantitative yield. Incorporation of the appropriate A-ring functionality into our optimized approach also provided a new and highly concise synthesis[11] of ungeremine trifluoroacetate, **3c** (Scheme 2).

Synthetic tortuosine chloride, **1**, and criasbetaine hydrochloride, **2b**, were submitted for quantitative as-

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(11) Snieckus synthesis (ref 8a): five linear steps from 5-hydroxyindole, 17% overall yield. Lauk synthesis (ref 8b): eight linear steps from 7-bromo-5-nitroindoline, 2% overall yield. Current method: five linear steps from 5-benzyloxyindole, 35% overall yield.

sessment of growth inhibitory efficacy against 60 human tumor cell lines at the National Cancer Institute.[12] The results of this in vitro study are summarized and contrasted with comparable data provided by the NCI for ungeremine hydrochloride, **3b**, in the Supporting Information. In consonance with their close structural similarity, criasbetaine and ungeremine exhibit somewhat similar (although not identical) potencies and selectivity profiles across the tumor cell-lines in which they were tested in common. Although clear evidence of selectivity against the CNS tumor-cell panel was found for both **2b** and **3b**, neither betaine proved highly potent against any of the cell-lines tested. Tortuosine chloride, **1**, also exhibited general selectivity for the CNS tumor-cell panel; however, this compound displayed relatively high specific potency against the SF-268 glioblastoma CNS cell-line: **Compound number** (pGI_{50}): **2b** (5.4), **3b** (6.0), and **1** (7.8). The unusual selectivity and efficacy of tortuosine chloride against SF-268 cells also compares favorably with the maximum in vitro growth inhibition results reported for ellipticinium-type[13] and protoberberine-type[14] CNS-selective antitumor agents against this cell line.

A convincing mechanistic rationale for tortuosine's remarkable in vitro profile remains to be experimentally determined; however, on the basis of its performance against SF-268 cancer cells, tortuosine chloride has recently been selected for preclinical in vivo antitumor assay at the National Cancer Institute. The results of these investigations will be reported in due course.

Experimental Section

General. Metalation reactions were performed under an argon atmosphere using oven-dried glassware and freshly purified solvents. Melting points are uncorrected. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) were recorded at room temperature. Column chromatography was performed using 230−400 mesh silica gel.

***tert*-Butyl 5-Methoxy-7-(2-formyl-4,5-dimethoxyphenyl)-2,3-dihydroindole-1-carboxylate (6).** 5-Methoxy-*N*-BOC-indoline, **4**,[9d] (1.62 g; 6.5 mmol) and 2 mL of TMEDA were dissolved in 40 mL of ether at −45 °C (internal thermometer). *sec*-BuLi (10 mL of a 1.3 M solution in cyclohexane) was added dropwise. The reaction mixture was stirred at −45 to −50 °C for 2 h, and CuI−P(EtO)$_3$ complex (4.64 g; 13.0 mmol) was added in one portion. The resulting orange slurry was stirred at −45 °C for 0.5 h, and a solution of imine **5a** (2.43 g; 6.5 mmol) in 5 mL of THF was added in one portion. The reaction mixture was allowed to warm to room temperature (orange slurry → greenish black solution) and stirred overnight. The solution was acidified with dilute aqueous HCl to pH = 4, and the mixture was refluxed for 10 min. The mixture was extracted with ether, the combined ether layers were dried ($MgSO_4$) and concentrated with a rotary evaporator to give a yellow oil. Chromatography of the crude product (3:1 hexanes−EtOAc) gave 1.61 g (60%) of **6**: mp 142.4−143.3 °C; ^{1}H NMR ($CDCl_3$) δ 9.78 (s, 1H), 7.47 (s, 1H), 6.91 (s, 1H), 6.84 (d, J = 2.6 Hz, 1H), 6.64 (d, J = 2.6 Hz, 1H), 4.13−4.04 (m, 2H), 3.958 (s, 3H), 3.955 (s, 3H), 3.80 (s, 3H), 3.07−3.00 (m, 2H), 1.16 (s, 9H); ^{13}C NMR δ 191.7, 157.1, 154.1, 153.2, 148.8, 140.7, 137.1, 135.5, 127.6, 126.2, 116.1, 112.0, 111.2, 108.8, 80.9, 56.6, 56.5, 56.2, 51.1, 30.3, 28.3; LSIMS m/z 414 ((M + H)$^+$, 22%), 314 (42%), 296 (100%). Anal. Calcd for $C_{23}H_{27}NO_6$: C, 66.81; H, 6.58; N, 3.39. Found: C, 66.61; H, 6.60; N, 3.60.

Tortuosine (1). Biarylaldehyde **6** (0.807 g; 1.95 mmol) was dissolved in 5 mL of $CHCl_3$. To this solution was added 16 mL of a satd solution of anhydrous HCl in ether to give a copious yellow precipitate. The precipitate was collected by suction filtration and washed with ether to give 0.675 g of crude solid. The crude material was separated by column chromatography (9:1 CH_2Cl_2−MeOH) to give 0.516 g (80%) of tortuosine chloride, **1**: mp 245−248 °C (dec) (lit. mp 242−243 °C); ^{1}H NMR (DMSO-d_6) δ 9.69 (s, 1H), 8.27 (s, 1H), 8.10 (s, 1H), 7.92 (s, 1H), 7.49 (s, 1H), 5.25 (t, J = 6.5 Hz, 2H), 4.19 (s, 3H), 4.07 (s, 3H), 4.00 (s, 3H), 3.68 (t, J = 6.5 Hz, 2H); ^{13}C NMR (DMSO-d_6) δ 162.4, 157.0, 151.4, 142.3, 138.8, 131.6, 129.5, 124.4, 121.3, 116.7, 110.5, 104.4, 101.9, 57.7, 57.3, 56.6, 27.6; LSIMS m/z 296 (M$^+$, 100%); HR-LSIMS m/z Calcd for $C_{18}H_{18}NO_3$ (M$^+$): 296.1287. Found: 296.1291.

1-(*tert*-Butoxycarbonyl)-5-(benzyloxy)indoline (7). To a solution of 5-(benzyloxy)indole (15.0 g; 67 mmol) in 200 mL of acetic acid was added sodium cyanoborohydride (12.7 g; 202 mmol), and the reaction mixture was stirred for 30 min at 23 °C. The reaction mixture was cooled with an ice bath, made basic with aqueous NaOH, and extracted with ether to give 14.3 g of a yellow oil. The crude oil was combined with di-*tert*-butyl dicarbonate (18.3 g; 84 mmol) in 200 mL of THF, and the reaction mixture was allowed to stir overnight at room temperature. The reaction mixture was concentrated with a rotary evaporator, and the crude product was recrystallized from ether−pentane to afford 13.1 g (60%) of **7**: mp 89.3−90.2 °C; ^{1}H NMR ($CDCl_3$) δ 7.8−7.65 (br m, 1H), 7.45−7.25 (m, 5H), 6.8−6.7 (m, 2H), 5.02 (s, 2H), 3.96 (br t, J = 8.6 Hz, 2H), 3.05 (t, J = 8.6 Hz, 2H), 1.55 (br s, 9H); ^{13}C NMR ($CDCl_3$) δ 154.8, 152.6, 137.6, 136.9 (br), 132.7 (br), 128.6, 127.9, 127.5, 80.6 (br), 71.0, 47.9, 28.6, 27.6. Anal. Calcd for $C_{20}H_{23}NO_3$: C, 73.82; H, 7.12, N, 4.30. Found: C, 73.93; H, 7.09; N, 4.56.

1-(*tert*-Butoxycarbonyl)-5-(*tert*-butyldimethylsilyloxy)-indoline (10). BOC-protected indoline **7** (5.77 g; 17.7 mmol) and 10% Pd−C were mixed in 100 mL of absolute ethanol, and the mixture was stirred under 1 atm of hydrogen overnight. The reaction mixture was filtered through Celite and concentrated under vacuum to give 3.75 g (90%) of highly pure 1-(*tert*-butoxycarbonyl)-5-hydroxyindoline, **8**.[15] The BOC-protected hydroxyindoline (3.75 g; 15.9 mmol), *tert*-butyldimethylsilyl chloride (5.28 g; 35.0 mmol), and imidazole (2.71 g; 39.8 mmol) were mixed in dry DMF, and the reaction mixture was stirred at 23 °C overnight. After an extractive (ether) workup, column chromatography (99:1 hexanes−EtOAc) afforded 5.22 g (94%) of **10**: mp 58.4−59.5 °C; ^{1}H NMR ($CDCl_3$) δ 7.75−7.6 (br m, 1H), 6.64 (br d, J = 0.8 Hz, 1H), 6.61 (br d, J = 0.8 Hz, 1H), 3.95 (br t, J = 8.7 Hz, 2H), 3.02 (t, J = 8.7 Hz, 2H), 1.55 (br s, 9H), 0.97 (s, 9H), 0.16 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 152.6; 150.9; 118.4; 116.8; 115.0, 47.7, 28.5, 27.5, 25.7, 18.2, −4.5; EIMS m/z 349 (M$^+$, 13%), 294 (22%), 293 (100%); HR-EIMS Calcd for $C_{19}H_{31}NO_3Si$: 349.2073. Found: 349.2073.

1-(*tert*-Butoxycarbonyl)-5-(triisopropylsilyloxy)indoline (9). Protection of compound **8** using the general procedure with TIPSCl gave 73% of **9** as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 7.75−7.6 (br m, 1H), 6.7−6.6 (br m, 2H), 3.95 (br t, J = 8.3 Hz, 2H), 3.05 (t, J = 8.3 Hz, 2H), 1.55 (br s, 9H), 1.3−1.15 (m, 3H), 1.09 (d, J = 6.8 Hz, 18 H); ^{13}C NMR ($CDCl_3$) δ 152.5, 151.4, 136.5 (br s), 132.2 (br s), 118.0, 116.5, 114.9, 80.4 (br s), 47.7, 28.5, 27.3, 17.9, 12.6. HR-EIMS Calcd for $C_{22}H_{37}NO_3Si$: 391.2543. Found: 391.2542.

***tert*-Butyl 5-(*tert*-Butyldimethylsilyloxy)-7-(2-formyl-4,5-dimethoxyphenyl)-2,3-dihydroindole-1-carboxylate (12).** Indoline **10** (1.00 g; 2.9 mmol) and 0.86 mL of TMEDA were dissolved in 15 mL of dry THF. At −40 °C (internal thermometer) *sec*-Buli (4.4 mL of a 1.3 M solution in cyclohexane) was added dropwise to the reaction mixture. The mixture was allowed to stir for 2 h at −40 to −50 °C, and CuI−P(OEt)$_3$

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complex (2.04 g; 5.72 mmol) was added in one portion to give a clear orange solution. The solution was stirred for 0.5 h at −40 °C, and a solution of imine **5a**[10] (1.07 g; 2.9 mmol) in 5 mL of THF was added in one portion. The reaction mixture was allowed to warm to room temperature over about 1 h, and the resulting green-black solution was allowed to stir at room-temperature overnight. The reaction mixture was quenched with aqueous ammonium chloride and extracted with ether. The ether layer was acidified to pH = 4 with aqueous HCl, refluxed for 5 min, washed with satd NaCl, dried ($MgSO_4$), and concentrated under vacuum to give a yellow, viscous oil. Chromatographic purification of the crude product (85:15 hexane EtOAc) gave 0.72 g (48%) of **12**: mp 119.8−121.5 °C; ^{1}H NMR ($CDCl_3$) δ 9.78 (s, 1H), 7.47 (s, 1H), 6.88 (s, 1H), 6.75 (d, J = 2.5 Hz, 1H), 6.58 (d, J = 2.5 Hz, 1H), 4.11−4.04 (m, 2H), 3.953 (s, 3H), 3.951 (s, 3H), 3.00 (t, J = 7.7 Hz, 2H), 1.16 (s, 9H), 0.98 (s, 9H), 0.20 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 191.5, 153.8, 153.0, 152.6, 148.4, 140.6, 136.7, 135.6, 127.2, 126.0, 122.1, 116.7, 111.6, 108.5, 80.7, 60.5, 56.34, 56.29, 50.9, 29.9, 29.1, 25.8, 18.4, −4.2; EIMS m/z 513 (M^+, 26%), 413 (57%), 396 (100%); HR-LSIMS Calcd for $C_{28}H_{39}NO_6Si$: 513.2547. Found: 513.2545.

***tert*-Butyl 5-(*tert*-Butyldimethylsilyloxy)-7-(2-formyl-4,5-(methylenedioxy)phenyl)-2,3-dihydroindole-1-carboxylate (13).** Indoline **10** (1.05 g; 3.0 mmol) and 0.9 mL of TMEDA were dissolved in 15 mL of THF at −40 °C. *sec*-BuLi (4.4 mL of a 1.3 M solution in cyclohexane) was added to the reaction mixture over 5 min. The reaction mixture was maintained between −40 to −50 °C for 2 h, and CuI−$P(OEt)_3$ complex (2.14 g; 6.0 mmol) was added in one portion to give a clear orange solution. The reaction mixture was stirred for 0.5 h at −40 °C, and a solution of imine **5b**[10] (1.07 g; 3.0 mmol) in 5 mL of THF was added in one portion. The reaction mixture was allowed to warm to room temperature, stirred overnight, and worked up as above to give a crude oil. Flash chromatography of the crude material (9:1 hexanes−EtOAc) afforded 1.20 g (80%) of **13**. Recrystallization of the chromatographed product from hexane gave 1.04 g (69%) of analytically pure **13**: mp 152.3−153.3 °C; ^{1}H NMR (DMSO-d_6) δ 9.62 (s, 1H), 7.26 (s, 1H), 6.92 (s, 1H), 6.86 (d, J = 2.3 Hz, 1H), 6.51 (d, J = 2.3 Hz, 1H), 6.16 (d, J = 9.7 Hz, 2H), 4.05−3.90 (m, 2H), 3.05−2.95 (m, 2H), 1.13 (s, 9H), 0.95 (s, 9H), 0.18 (s, 6H); ^{13}C NMR (DMSO-d_6) δ 190.2, 152.3, 152.0, 147.3, 142.2, 137.4, 135.5, 127.2, 126.9, 121.4, 116.9, 109.6, 105.3, 102.5, 80.1, 50.8, 29.5, 27.9, 25.9, 18.3, −4.2. Anal. Calcd for $C_{27}H_{35}NO_6Si$: C, 65.16; H, 7.09; N, 2.81. Found: C, 65.21; H, 7.15; N, 2.92.

Criasbetaine Trifluoroacetate (2c). Biarylaldehyde **12** (0.335 g; 0.65 mmol) was refluxed in 5 mL of trifluoroacetic acid for 16 h. The reaction mixture was concentrated with a rotary evaporator, and the residue was triturated with ether. The crude residue was purified by column chromatography (85:15 CH_2Cl_2−MeOH) to afford 0.265 g (99%) of criasbetaine trifluoroacetate monohydrate **2c**: mp 238−240 °C; ^{1}H NMR (DMSO-d_6) δ 10.95 (s, 1H), 9.56 (s, 1H), 8.14 (s, 1H), 7.98 (s, 1H), 7.90 (s, 1H), 7.40 (s, 1H), 5.21 (t, J = 6.8 Hz, 2H), 4.16 (s, 3H), 4.01 (s, 3H), 3.68 (t, J = 6.8 Hz, 2H); ^{13}C NMR (DMSO-d_6) δ 161.1, 156.8, 151.4, 141.5, 139.0, 130.8, 129.1, 124.8, 121.3, 116.6, 110.5, 104.3, 104.2, 57.3, 56.5, 56.1, 27.7; ^{19}F NMR (DMSO-d_6 solution; external reference: CCl_3F) δ −73.91; LSIMS m/z 282 ($M + H)^+$, 100%); HR-LSIMS Calcd for $C_{17}H_{16}NO_3$ ($M + H)^+$: 282.1130. Found: 282.1130. Anal. Calcd for $C_{17}H_{15}NO_3 + CF_3CO_2H + H_2O$: C, 55.21; H, 4.39; N, 3.39. Found: C, 54.94; H, 3.86; N, 3.52.

Ungeremine Trifluoroacetate (3c). Biarylaldehyde **13** (0.200 g; 0.4 mmol) was added to 5 mL of trifluoroacetic acid, and the solution was refluxed for 14 h. The reaction mixture was concentrated with a rotary evaporator, and the residue was triturated with ether to give 137 mg of a green powder. Recrystallization of the crude solid from methanol gave pale yellow crystalline **3c** (100 mg; 66% yield): mp >250 °C; ^{1}H NMR (DMSO-d_6) δ 11.08 (br s, 1H), 9.54 (s, 1H), 8.25 (s, 1H), 7.86 (s, 1H), 7.79 (d, J = 1 Hz, 1H), 7.38 (d, J = 1 Hz, 1H), 6.44 (s, 2H), 5.19 (br t, J = 6.5 Hz, 2H), 3.67 (br t, J = 6.5 Hz, 2H); ^{13}C NMR (DMSO-d_6) δ 161.3, 155.7, 150.3, 141.6, 139.0, 131.5, 130.9, 125.1, 122.7, 117.1, 107.5, 104.3, 104.0, 101.8, 56.1, 27.7; ^{19}F NMR (DMSO-d_6 solution; external reference: CCl_3F) δ −73.93. Anal. Calcd for $C_{18}H_{12}F_3NO_5$: C, 57.00; H, 3.19; N, 3.69. Found: C, 56.77; H, 3.11; N, 3.83.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra of all new compounds and comprehensive screening results for **1**, **2b**, and **3b** in the NCI human tumor cell-line panel. This material is available free of charge via the Internet at http://pubs.acs.org.

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