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PERHYDROPYRROLO[1,2-*a*]INDOLE SYNTHESIS: DIASTEREOSELECTION IN AN INTRAMOLECULAR CONJUGATE ADDITION OF AN AMINE TO A 1,4-CYCLOHEXADIENONE

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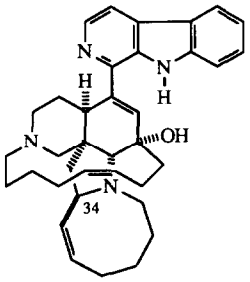
Abstract: *Cyclization of amino-cyclohexadienone* ***4*** *occurs with a high level of diastereoselection to afford perhydroindole* ***13****. The relationship of this observation to controlling the relative stereochemistry between* C_{34} *and other stereogenic centers in the manzamine family of alkaloids is discussed.* © 1997 Elsevier Science Ltd.

Manzamine A (**1**) and related alkaloids have been the focal point of numerous synthetic studies.[1-6] One problem encountered in these studies has been establishment of the relative stereochemistry between C_{34} and stereogenic centers in the cyclohexene substructure of **1**. Previous approaches have not yet addressed this problem,[1] failed to solve the problem,[2-4] or have successfully relied on asymmetric induction by an incipient C_{34} substituent in an intramolecular Diels-Alder reaction.[5-6] Another *potential* solution to this relative stereochemistry problem might involve diastereoselective cyclization of a dienone of type **3** to an enone of type **2**. Although this strategy has not yet been examined within the context of manzamine A, this notion served as the stimulus for the research described herein, an approach to the synthesis of perhydropyrrolo[1,2-*a*]indoles.[7]



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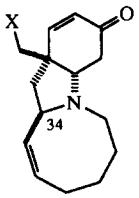

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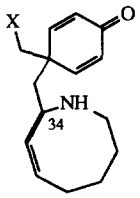

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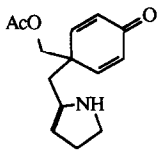
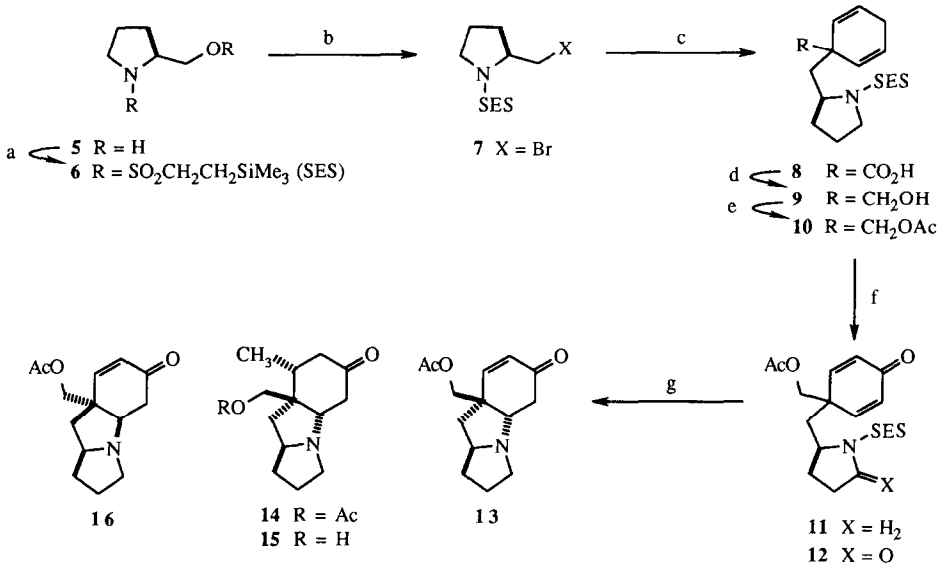


4

As a prelude to examining a cyclization immediately relevant to the manzamine A problem, we have examined amino-dienone **4**, which has proven easier to prepare than substrates of type **3** (*vide infra*). The

preparation of **4** began by treating **5** (L-prolinol) with 2-(trimethylsilyl)ethanesulfonyl chloride[8] and triethylamine in dichloromethane to provide **6** in 71% yield. Treatment of sulfonate **6** with lithium bromide in acetone gave **7** in 64% yield. Alkylation of the dianion of 1,4-dihydrobenzoic acid with **7** in THF-hexane gave **8** in 70% yield.[9-10] The success of this alkylation is notable as β-branched halides with adjacent electron withdrawing groups do not behave well in alkylation reactions except with nucleophiles like cyanide or those derived from β-dicarbonyls. For example, the lithium enolate derived from *N,N*-dimethylisobutyramide gave only a dehydrohalogenation product upon reaction with **7**. Continuing with the synthesis of **4**, carboxylic acid **8** was treated sequentially with triethylamine and ethyl chloroformate in THF, followed by sodium borohydride in water to provide alcohol **9** (86%). Acetylation of **9** gave **10** (81%) and oxidation this cyclohexadiene with PCC gave dienone **11** (66%) along with lactam **12** (5%).[11-12]

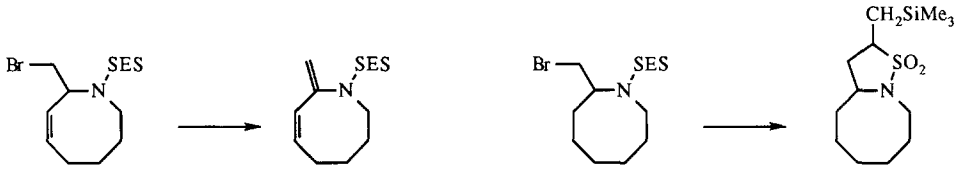


(a) SESCl, Et_3N, CH_2Cl_2 (b) LiBr, acetone (c) 1. 1,4-dihydrobenzoic acid, 2 eq LDA, THF-hexane 2. **7**, -70°C → 25°C (d) 1. $ClCO_2Et$, Et_3N, THF 2. $NaBH_4$, H_2O-THF (e) Ac_2O, Et_3N, 4-DMAP (f) PCC, Celite, PhH (g) CsF, DMF, 75°C, 20h

Generation and cyclization of amino-dienone **4** was accomplished by stirring **11** with three equivalents of cesium fluoride in *N,N*-dimethylformamide at 75 °C for 20 h, providing tricyclic amine **13** in 77%. The structure of **13** was initially assigned on the basis of nOe experiments and firmly established by X-ray crystallographic analysis of **15**, prepared in 55% yield by treatment of **13** with lithium dimethylcuprate followed by hydrolysis of the resulting conjugate adduct **14**.[13] The cyclization of **4** to **13** is related to diastereoselective cyclizations of 1,4-cyclohexadienes described by Wipf and Curran.[14-15] We suggest that the origin of diastereoselectivity in the current

case is related in some way to product stability. For example, **13** is S-shaped whereas the diastereomeric conjugate adduct **16** (not observed) is U-shaped and more sterically conjested. Thus, the observed selectivity is consistent with a thermodynamically controlled (reversible) process or a kinetically controlled reaction with a reasonably well developed transition state.[16]

Attempts to prepare cyclization substrates of type **3**, more relevant to the synthesis of manzamine A (**1**), have thus far met with failure. For example, racemic bromides **17** (mp 93.5-96°C) and **19** (mp 58-60.5°C) were prepared from 2-benzyloxyacetaldehyde and the tetrahydropyranyl ether of 5-hexyn-1-ol using reaction sequences related to those used in the preparation of tetracyclic manzamine A substructures.[2, 17] Attempted alkylation of the dianion of dihydrobenzoic acid with bromide **17**, however, gave dehydrohalogenation product **18** in 83% yield. In addition, treatment of **19** with the same dianion gave a 13% yield of diastereomeric sulfonamides **20**, presumably *via* proton transfer followed by an intramolecular alkylation, and none of the desired alkylation product. Variations of this chemistry designed to provide cyclization substrates of type **3** are still being pursued.



17 **18** **19** **20**

In summary, a reductive alkylation-oxidation-cyclization route to perhydropyrrolo[1,2-*a*]indoles has been developed (**11**→**4**→**13**). Although the reductive alkylation step of this sequence failed when applied to manzamine A itself, this chemisty might serve in general as a route to perhydroindoles from benzoic acid and α-amino acid derivatives.[18]

EXPERIMENTAL

(*S*)-(-)-1-[[2-(Trimethylsilyl)ethyl]sulfonyl]-2-pyrrolidinyl]methyl-2-(trimethylsilyl)ethanesulfonate (6). To 4.03 g (39.8 mmol) of L-prolinol (**5**) and 8.06 g (79.7 mmol) of triethylamine in 50 mL of dry dichloromethane cooled in an ice water bath was added 16.0 g (79.7 mmol) of 2-(trimethylsilyl)ethanesulfonyl chloride dropwise *via* syringe over a 12 min period. The solution was stirred for 5 min, warmed to room temperature and stirred for 3 h. The solution was filtered and the filter cake was washed with 50 mL of dichloromethane. The filtrate was washed sequentially with 50 mL of water and 50 mL of brine, dried ($MgSO_4$) and concentrated *in vacuo* to give 12.1 g (71%) of **6** as a light yellow solid, suitable for use in the following reaction. Chromatography of a sample of **6** over silica gel using ethyl acetate-petroleum ether mixtures as the eluant gave analytically pure **6** as a white solid: mp 62-64°C; $[\alpha]_D$ -30° (c 0.7, $CHCl_3$); IR (CCl_4) 2952, 2897, 1352, 1250, 1177, 1144, 843 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.055 (s, 9H), 0.065 (s, 9H), 1.02-1.08 (m, 4H), 1.96-2.04 (m, 4H), 2.94 (m, 2H), 3.05 (m, 2H), 3.38 (m, 2H), 4.12 (m, 1H), 4.22 (d, J = 4.9 Hz, 2H); ^{13}C

NMR ($CDCl_3$, 75.5 MHz) δ -2.2 (q), -2.1 (q), 9.8 (t), 10.2 (t), 24.7 (t), 28.6 (t) 46.6 (t), 46.8 (t), 48.9 (t), 57.8 (d), 70.8 (t); exact mass calcd. for $C_{14}H_{32}NO_5S_2Si_2$ (M^+-CH_3) *m/z* 414.1250, found *m/z* 414.1261. Anal. calcd. for $C_{15}H_{35}NO_5S_2Si_2$: C, 41.92; H, 8.21. Found C, 42.50; H, 8.14.

(*S*)-(-)-2-(Bromomethyl)-1-[[2-(trimethylsilyl)ethyl]sulfonyl]pyrrolidine (7). To a solution of 11.33 g (27.4 mmol) of sulfonate **6** in 140 mL of acetone was added 19.0 g (0.22 mol) of anhydrous lithium bromide. The solution was diluted with 50 mL of acetone and stirred under reflux for 42 h. The solution was diluted with 1.0 L of diethyl ether and washed with 400 mL of water. The aqueous phase was extracted with two 200 mL portions of diethyl ether and the combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. The residual yellow oil was chromatographed over 250 g of silica gel (eluted with ethyl acetate-hexane, 1:3) to give 5.77 g (64%) of bromide **7** as a white solid: mp 60-62°C; $[\alpha]_D$ -49.4° (c 0.35, $CHCl_3$); IR (CCl_4) 2954, 1334, 1251, 1142 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.05 (s, 9H), 1.03 (m, 2H), 1.97-2.11 (m, 4H), 2.91 (m, 2H), 3.37-3.46 (m, 3H), 3.60 (dd, *J* = 10.1, 3.1 Hz, 1H), 4.12 (m, 1H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ -2.1 (q), 10.0 (t), 24.6 (t), 30.4 (t) 36.3 (t), 47.3 (t), 49.4 (t), 59.6 (d); exact mass calcd. for $C_{10}H_{22}NO_2SSi^{79}Br$ *m/z* 327.0325, found *m/z* 327.0321; exact mass calcd. for $C_{10}H_{22}NO_2SSi^{81}Br$ *m/z* 329.0305, found *m/z* 327.0311. Anal. calcd. for $C_{10}H_{22}NO_2SSi$: C, 36.58; H, 6.75. Found: C, 37.16; H, 6.66.

(-)-1-[[(*S*)-1-[[2-(Trimethylsilyl)ethyl]sulfonyl]-2-pyrrolidinyl]methyl]-2,5-cyclohexadiene-1-carboxylic acid (8). To 17.5 mL (21.88 mmol) of a 1.25 M solution of lithium diisopropylamide mono(tetrahydrofuran) in cyclohexane, in 20 mL of dry tetrahydrofuran cooled to -10°C, was added dropwise a solution of 1.38 g (11.2 mmol) of 1,4-dihydrobenzoic acid in 15 mL of tetrahydrofuran over a 30 min period. To the resulting orange-brown solution (color characteristic of the dianion), was added dropwise 3.58 g (10.95 mmol) of bromide **7** in 20 mL of tetrahydrofuran. The solution was allowed to warm to room temperature where it was stirred for 3 h. The reaction mixture was then poured into 50 mL of water and concentrated *in vacuo*. The aqueous layer was extracted with two 50-mL portions of ether and brought to pH 1 with 7 mL of 20% aqueous hydrochloric acid. The mixture was extracted with four 100-mL portions of ether, and the combined organic extracts were washed with 50 mL of 10% aqueous sodium thiosulfite, 100 mL of brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was chromatographed over 175 g of silica gel (eluted with ethyl acetate-petroleum ether, 1:5 to ethyl acetate-petroleum ether, 1:1) to give 2.84 g (70%) of acid **8** as a white solid: mp 128-130°C; $[\alpha]_D$ -6.8° (c 0.44, $CHCl_3$); IR (CCl_4) 1697 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.05 (s, 9H), 1.03 (m, 2H), 1.73 (m, 1H), 1.79-2.00 (m, 3H), 1.87 (dd, *J* = 13.7, 10.4 Hz, 1H), 2.30 (dd, *J* = 13.7, 2.7 Hz, 1H), 2.67 (br d, *J* = 1.5 Hz, 2H), 2.85 (m, 2H), 3.22 (dt, *J* = 10.1, 6.2 Hz, 1H), 3.38 (dt, *J* = 10.1, 6.8 Hz, 1H), 3.89 (m, 1H), 5.74 (dq, *J* = 10.2, 2.0 Hz, 1H), 5.83 (dq, *J* = 10.0, 2.0 Hz, 1H), 5.88-5.95 (dtd, *J* = 10.2, 4.8, 1.6 Hz, 1H), 5.95-6.02 (dtd, *J* = 10.2, 4.7, 1.5 Hz, 1H), the COOH was not recorded; ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ -2.1 (q), 9.9 (t), 24.8 (t), 25.8 (t), 32.9 (t), 44.9 (t),46.7 (s), 47.1 (t), 47.9 (t), 56.8 (d), 126.2 (d), 126.4 (d), 126.7 (d), 126.8 (d), 179.8 (s); exact mass calcd. for $C_{16}H_{26}NO_4SSi$ (M^+-CH_3) *m/z* 356.1353, found *m/z* 356.1363. Anal. calcd. for $C_{17}H_{29}NO_4SSi$: C, 54.95; H, 7.87. Found: C, 54.84; H, 7.85.

(*S*)-(-)-2-[[1-(Hydroxymethyl)-2,5-cyclohexadien-1-yl]methyl]-1-[[2-(trimethylsilyl)ethyl]sulfonyl]pyrrolidine (9). To 1.93 g (5.2 mmol) of carboxylic acid **8** in 30 mL of dry tetrahydrofuran in a

flame dried flask was added 0.91 g (1.25 mL, 8.97 mmol) of triethylamine at -10°C *via* syringe. The solution was stirred 10 min and 0.85 g (0.75 mL, 7.9 mmol) of neat ethyl chloroformate was added dropwise. The solution was stirred at -10°C for 30 min and 0.78 g (21.0 mmol) of sodium borohydride in 6 mL of water was added *via* an additional funnel (gas formation was observed). The reaction mixture was stirred for 3 h and was acidified with 4 mL of 20% aqueous hydrochloric acid. The solvent was removed *in vacuo* and the residue was extracted with four 20-mL portions of ether. The combined organic extracts were washed with 10 mL of water, 20 mL of brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was chromatographed over 125 g of silica gel (eluted sequentially with ethyl acetate-petroleum ether, 1:6, 1:2, and 1:1) to give 1.59 g (86%) of alcohol **9** as a colorless oil: $[\alpha]_D$ -9.3° (c 0.9, $CHCl_3$); IR (neat) 3516 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.03 (s, 9H), 0.99 (m, 2H), 1.41 (dd, *J* = 13.6, 10.6 Hz, 1H), 1.70-2.00 (m, 5H), 1.93 (dd, *J* = 13.5, 2.2 Hz, 1H), 2.64 (ddd, *J* = 6.6, 3.3, 1.5 Hz, 2H), 2.83 (m, 2H), 3.21-3.35 (m, 2H), 3.32 (s, 2H), 3.83 (m, 1H), 5.43 (dq, *J* = 10.1, 2.1 Hz, 1H), 5.49 (dq, *J* = 10.1, 2.1 Hz, 1H), 5.90 (dtd, *J* = 10.1, 3.9, 1.6 Hz, 1H), 5.95 (dtd, *J* = 10.1, 3.9, 1.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ -2.1 (q), 9.9 (t), 24.8 (t), 26.4 (t), 33.1 (t), 42.3 (s), 43.6 (t), 46.4 (t), 48.1 (t), 57.5 (d), 70.2 (t), 126.8 (d), 127.6 (d), 128.0 (d), 130.5 (d); exact mass calcd. for $C_{17}H_{31}NO_3SSi$ *m/z* 357.179, found *m/z* 357.189.

(*S*)-(-)-2-[[1-(Hydroxymethyl)-2,5-cyclohexadien-1-yl]methyl]-1-[[2-(trimethylsilyl)ethyl]sulfonyl]pyrrolidine acetate (ester) (10). To a mixture of 1.51 g (4.23 mmol) of alcohol **9**, 1.30 g (1.80 mL, 12.9 mmol) of triethylamine and 50 mg (0.4 mmol) of 4-*N*,*N*-(dimethylamino)pyridine in 10 mL of dry dichloromethane was added 1.30 g (1.20 mL, 12.7 mmol) of acetic anhydride dropwise. The solution was stirred for 5 h at room temperature and partitioned between 100 mL of ether and 50 mL of saturated aqueous sodium bicarbonate. The aqueous layer was extracted with two 50-mL portions of ether and the combined organic extracts were washed with 40 mL of brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residual yellow oil was chromatographed over 80 g of silica gel (eluted with ethyl acetate-hexane, 1:6 and then ethyl acetate-hexane, 1:2) to give 1.50 g (81%) of acetate **10** as a colorless oil: IR (neat) 1743, 1668 cm^{-1}; $[\alpha]_D$ -3.15° (c 0.68, $CHCl_3$); ^1H NMR ($CDCl_3$, 250 MHz) δ 0.03 (s, 9H), 1.00 (m, 2H), 1.49 (dd, *J* = 13.5, 10.7 Hz, 1H), 1.67-1.98 (m, 4H), 2.01 (s, 3H), 2.02 (dd, *J* = 13.3, 2.2 Hz, 1H), 2.62 (br s, 2H), 2.81 (m, 2H), 3.20 (dt, *J* = 10.0, 6.3 Hz, 1H), 3.32 (dt, *J* = 10.0, 6.8 Hz, 1H), 3.78 (m, 1H), 3.84 (ABq, *J* = 10.6 Hz, 2H), 5.42 (dq, *J* = 10.1, 1.9 Hz, 1H), 5.53 (dq, *J* = 10.1, 1.9 Hz, 1H), 5.82 (dm, *J* = 10.0 Hz, 1H), 5.97 (dm, *J* = 10.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ -2.1 (q), 9.9 (t), 20.7 (q), 24.8 (t), 26.2 (t), 33.1 (t), 39.9 (s), 43.6 (t), 46.2 (t), 48.1 (t), 57.6 (d), 71.1 (t), 126.0 (d), 126.5 (d), 128.6 (d), 129.7 (d), 170.6 (s); exact mass calcd. for $C_{18}H_{30}NO_4SSi$ (M^+-CH_3) *m/z* 384.1674, found *m/z* 384.1698.

(*S*)-(+)-2-[[1-(Hydroxymethyl)-4-oxo-2,5-cyclohexadien-1-yl]methyl]-1-[[2-(trimethylsilyl)ethyl]sulfonyl]pyrrolidine acetate (ester) (11) and (*S*)-(-)-5-[[1-(Hydroxymethyl)-4-oxo-2,5-cyclohexadien-1-yl]methyl]-1-[[2-(trimethylsilyl)ethyl]sulfonyl]-2-pyrrolidinone acetate (ester) (12). To 1.50 g (3.76 mmol) of diene **10** and 4.25 g of Celite in 70 mL of dry benzene cooled in an ice-water bath was added 4.25 g (11.3 mmol) of pyridinium dichromate in one portion, followed by the addition of 1.13 g (1.25 mL, 11.3 mmol) of 90% *tert*-butyl hydroperoxide *via* syringe. The resulting mixture was stirred for 15 min in the cooling bath and 4 h at room temperature (timing is important!). The reaction mixture was diluted

with 100 mL of ethyl acetate and filtered through a pad of Celite which was rinsed with two 100-mL portions of ethyl acetate. The combined filtrates were washed with 50 mL of water, two 50-mL portions of brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was chromatographed over 75 g of silica gel (eluted gradually with ethyl acetate-petroleum ether, 1:4 to 1:1) to give 1.023 g (66%) of pure dienone **11** as a pale yellow oil: $[\alpha]_D$ +10.1° (c 3.1, $CHCl_3$); IR (neat) 1746, 1667, 1628 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 0.01 (s, 9H), 0.94 (dd, *J* = 17.9, 1.2 Hz, 1H), 0.94 (dd, *J* = 6.5, 2.3 Hz, 1H), 1.50 (m, 1H), 1.71-1.91 (m, 3H), 1.79 (dd, *J* = 13.5, 10.7 Hz, 1H), 1.96 (s, 3H), 2.38 (dd, *J* = 13.6, 1.9 Hz, 1H), 2.77 (m, 2H), 3.23 (t, *J* = 6.3 Hz, 2H), 3.50 (m, 1H), 4.07 (ABq, *J* = 10.8 Hz, 2H), 6.33 (dd, *J* = 10.1, 1.8 Hz, 1H), 6.40 (dd, *J* = 10.1, 1.9 Hz, 1H), 6.77 (dd, *J* = 10.1, 3.0 Hz, 1H), 6.90 (dd, *J* = 10.1, 3.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ -2.1 (q), 9.9 (t), 20.5 (q), 25.0 (t), 33.7 (t), 42.9 (t), 45.5 (s), 45.8 (t), 48.1 (t), 56.7 (d), 67.8 (t), 131.1 (d), 131.6 (d), 150.5 (d), 150.7 (d), 170.2 (s), 185.6 (s); exact mass calcd. for $C_{19}H_{31}NO_5SSi$ *m/z* 413.1693, found *m/z* 413.1695. Continued elution with ethyl acetate-petroleum ether, 2:1 gave 125 mg (8%) of impure acylsulfonamide **12**. This material was chromatographed over 5 g of silica gel (eluted with ethyl acetate-petroleum ether, 1:2) to give 80 mg (5%) of pure **12**: $[\alpha]_D$ -12.6° (c 2.55, $CHCl_3$); IR (neat) 1738, 1730, 1667, 1628 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 0.05 (s, 9H), 0.85 (td, *J* = 13.5, 4.8 Hz, 1H), 1.00 (td, *J* = 13.5, 4.8 Hz, 1H), 1.76 (m, 1H), 2.01 (s, 3H), 2.04 (dd, *J* = 15.8, 12.9 Hz, 1H), 2.30 (m, 1H), 2.40 (dd, *J* = 17.7, 2.3 Hz, 1H), 2.44 (m, 1H), 2.63 (ddd, *J* = 17.7, 11.1, 8.9 Hz, 1H), 3.24-3.48 (td, *J* = 14.0, 4.6 Hz, 2H), 3.96 (m, 1H), 4.12 (ABq, *J* = 10.8 Hz, 2H), 6.39 (dd, *J* = 10.1, 1.6 Hz, 1H), 6.48 (dd, *J* = 10.2, 1.2 Hz, 1H), 6.81 (dd, *J* = 10.1, 3.0 Hz, 1H), 6.95 (dd, *J* = 10.1, 3.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ -2.1 (q), 9.6 (t), 20.5 (q), 26.2 (t), 30.2 (t), 40.5 (t), 45.1 (s), 50.3 (t), 56.6 (d), 67.7 (t), 131.6 (d), 132.1 (d), 149.5 (d), 149.6 (d), 170.2 (s), 173.8 (s), 185.6 (s); exact mass calcd. for $C_{19}H_{29}NO_6SSi$ *m/z* 427.1486, found *m/z* 427.1580.

(+)-(4a*S*,8a*S*,9a*S*)-1,2,3,4a,5,8a,9,9a-Octahydro-8a-(hydroxymethyl)-6*H*-pyrrolo[1,2-*a*]indol-6-one acetate (ester) (13). To a mixture of 1.10 g (2.66 mmol) of dienone **11** in 40 mL of dry tetrahydrofuran was added 1.27 g (8.35 mmol) of cesium fluoride. The reaction was stirred and heated at 75°C for 20 h. At this stage, TLC analysis indicated some starting material was left. Thus, 500 mg (3.3 mmol) of cesium fluoride was added and the reaction mixture was then heated at 75-80°C for 20h. The mixture was cooled to room temperature, diluted with 40 mL of dichloromethane:methanol (1:1), and the solid residue was removed by filtration. The filtrate was concentrated *in vacuo*, and the residual *N,N*-dimethylformamide was removed under high vacuum (40°C at 1 mm Hg). The residue was diluted with 100 mL of ether, filtered, and concentrated *in vacuo*. The residual yellow oil was chromatographed over 13 g of silica gel (eluted with ethyl acetate-hexane, 1:2) to give 41 mg of a 4:5 mixture of starting material and enone **13**. Continued elution with ethyl acetate-hexane (1:1) followed by straight ethyl acetate gave 505 mg (77%) of pure tricycle **13** as a pale yellow oil (free base): $[\alpha]_D$ +101.3° (c 1.2, $CHCl_3$); IR (neat) 1744, 1682 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.44 (m, 1H), 1.54 (dd, *J* = 12.6, 9.6 Hz, 1H), 1.69-1.91 (m, 3H), 2.03 (s, 3H), 2.06 (dd, *J* = 12.6, 6.8 Hz, 1H), 2.50-2.64 (m, 3H), 2.92 (dt, *J* = 10.6, 6.4 Hz, 1H), 3.01 (dd, *J* = 5.0, 2.9 Hz, 1H), 3.45 (dq, *J* = 9.6, 6.7 Hz, 1H), 4.15 (ABq, *J* = 11.2 Hz, 2H), 6.05 (d, *J* = 10.2 Hz, 1H), 6.51 (dd, *J* = 10.1, 2.0 Hz, 1H); ^1H NMR (C_6D_6, 300 MHz) δ 0.95 (dd, *J* = 12.2, 10.1 Hz, 1H), 0.98 (m, 1H), 1.36-1.51 (m, 4H), 1.56 (s, 3H), 2.14 (dt, *J* = 10.4, 6.2 Hz, 1H), 2.34 (dd, *J* = 16.9, 3.6 Hz, 1H), 2.49 (m, 1H), 2.52 (dd, *J* = 10.5, 1.7 Hz, 1H), 2.67 (dt, *J* = 10.2, 6.1 Hz, 1H), 3.15 (dq, *J*

= 9.9, 6.4 Hz, 1H), 3.78 (ABq, *J* = 11.2 Hz, 2H), 5.87 (dd, *J* = 10.2, 1.8 Hz, 1H), 6.01 (d, *J* = 10.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 20.45 (q), 25.4 (t), 32.5 (t), 40.0 (t), 42.4 (t), 49.3 (s), 53.0 (t), 62.1 (d), 67.0 (d), 67.3 (t), 130.5 (d), 149.3 (d), 170.1 (s), 197.6 (s); exact mass calcd. for $C_{14}H_{19}NO_3$ (free base) *m/z* 249.1366, found *m/z* 249.1344.

The free base **13** was dissolved in 2 mL of $CDCl_3$ saturated with gaseous hydrochloric acid and then concentrated *in vacuo* to afford the corresponding hydrochloride salt of **13** as a pale yellow solid: $[\alpha]_D$ +113.1° (c 1.5, $CHCl_3$); IR (KBr Pellet) 3445, 1754, 1679 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) d 1.63 (m, 1H), 1.77 (dd, *J* = 12.7, 10.5 Hz, 1H), 1.89-2.00 (m, 3H), 2.02 (s, 3H), 2.17 (dd, *J* = 12.7, 6.9 Hz, 1H), 2.70 (dd, *J* = 17.85, 4.0 Hz, 1H), 2.80 (dd, *J* = 18.0, 1.7 Hz, 1H), 2.89 (m, 1H), 3.21 (m, 1H), 3.40 (br s, 1H), 3.75 (m, 1H), 4.22 (ABq, *J* = 11.3 Hz, 2H), 6.17 (d, *J* = 10.2 Hz, 1H), 6.50 (dd, *J* = 10.1, 1.9 Hz, 1H); The free base and the hydrochloric salt have the same ^{1}H NMR spectrum in C_6D_6; exact mass calcd. for $C_{14}H_{19}NO_3$ (HCl salt) *m/z* 249.1366, found *m/z* 249.1364

(-)-(4a*S*,8*S*,8a*S*,9a*S*)-Decahydro-8a-(hydroxymethyl)-8-methyl-6*H*-pyrrolo-[1,2-*a*]indol-6-one acetate (ester) (14) and (-)-(4a*S*,8*S*,8aS,9a*S*)-Decahydro-8a-(hydroxymethyl)-8-methyl-6*H*-pyrrolo [1,2-*a*]indol-6-one (15). To a suspension of 46 mg (0.24 mmol) of copper (I) iodide in 1 mL of dry diethyl ether cooled in an ice-water bath was added dropwise 0.28 mL of a 1.4 M solution of ethereal methyl lithium. The resulting gray mixture was cooled in an dry ice-acetone bath and stirred for 30 min, during which time it became bright yellow. To this mixture was added dropwise, *via* syringe, a solution of 23 mg (0.092 mmol) of tricyclic enone **13** in 1.5 mL of dry ether. The resulting yellow mixture was stirred for 4 h between -70°C and 5°C, and then quenched with a few drops of methanol. The resulting yellow slurry slowly turned white and was partitioned between 10 mL of dichloromethane and 5 mL of saturated aqueous sodium bicarbonate. The aqueous layer was extracted with 10 mL of dichloromethane, and the combined organic extracts were dried ($NaSO_4$-Na_2CO_3, 1:1) and concentrated *in vacuo*. The residue was chromatographed over 1 g of silica gel (eluted with ethyl acetate-hexane, 1:2) to give 11 mg (45%) of acetate **14** as a pale yellow oil (free base): $[\alpha]_D$ -74.5° (c 0.48, $CHCl_3$); IR (neat) 1741, 1714 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.95 (d, *J* = 6.7 Hz, 3H), 1.36 (dd, *J* = 13.8, 5.0 Hz, 1H), 1.43 (m, 1H), 1.70 (m, 1H), 1.89 (m, 2H), 2.07 (s, 3H), 2.09 (m, 1H), 2.15 (dd, *J* = 17.7, 3.4 Hz, 1H), 2.19 (dd, *J* = 13.8, 7.4 Hz, 1H), 2.36 (dd, *J* = 17.7, 13.7 Hz, 1H), 2.42 (dd, *J* = 16.5, 3.3 Hz, 1H), 2.48 (dd, *J* = 16.5, 2.7 Hz, 1H), 2.67 (ddd, *J* = 11.9, 6.8, 3.2 Hz, 1H), 2.86 (dt, *J* = 11.5, 7.2 Hz, 1H), 2.94 (t, *J* = 3.0 Hz, 1H), 3.40 (m, 1H), 4.08 (ABq, *J* = 11.1 Hz, 2H); ^{1}H NMR (C_6D_6, 500 MHz) δ 0.55 (d, *J* = 6.8 Hz, 3H), 0.88 (dd, *J* = 13.7, 5.3 Hz, 1H), 1.04 (m, 1H), 1.34 (m, 1H), 1.44-1.55 (m, 2H), 1.62 (s, 3H), 1.66 (m, 1H), 1.74 (dd, *J* = 13.7, 7.5 Hz, 1H), 2.00 (dd, *J* = 17.5, 3.6 Hz, 1H), 2.21 (dd, *J* = 16.5, 2.6 Hz, 1H), 2.26 (dd, *J* = 17.5, 13.9 Hz, 1H), 2.30 (ddd, *J* = 12.0, 6.9, 5.3 Hz, 1H), 2.39 (dd, *J* = 16.4, 3.4 Hz, 1H), 2.57 (t, *J* = 3.0 Hz, 1H), 2.65 (dt, *J* = 11.4, 7.2 Hz, 1H), 3.07 (m, 1H), 3.80 (ABq, *J* = 11.1 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 15.5 (q), 20.75 (q), 24.7 (t), 29.6 (d), 32.2 (t), 33.95 (t), 42.2 (t), 43.3 (t), 48.7 (s), 52.1 (t), 64.0 (d), 67.0 (d), 69.95 (t), 170.8 (s), 212.0 (s); exact mass calcd. for $C_{15}H_{23}NO_3$ *m/z* 265.1679, found *m/z* 265.1674. Continued elution with ethyl acetate provided 4 mg (13%) of alcohol **15** as a white solid: mp 144-145.5°C; $[\alpha]_D$ -60° (c 0.07, $CHCl_3$); IR (KBr Pellet) 3446, 1717 cm^{-1}; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 0.95 (d, *J* = 6.3 Hz, 3H), 1.30

(dd, J = 13.6, 5.0 Hz, 1H), 1.41 (m, 1H), 1.60-1.96 (m, 4H), 2.10 (dd, J = 13.4, 7.5 Hz, 1H), 2.20 (m, 2H), 2.32 (dd, J = 18.6, 14.8 Hz, 1H), 2.40 (dd, J = 16.6, 3.6 Hz, 1H), 2.54 (dd, J = 16.4, 2.6 Hz, 1H), 2.67 (ddd, J = 11.6, 7.0, 5.3 Hz, 1H), 2.85 (dt, J = 11.5, 7.0 Hz, 1H), 3.01 (br t, J = 3.0 Hz, 1H), 3.37 (br dt, J = 12.4,7.2 Hz, 1H), 3.61 (ABq, J = 10.6 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 15.6 (q), 24.7 (t), 28.9 (d), 32.2 (t), 33.5 (t), 42.6 (t), 43.6 (t), 50.55 (s), 52.3 (t), 64.2 (d), 66.9 (d), 68.55 (t), 212.7 (s); exact mass calcd. for $C_{13}H_{21}NO_2$ *m/z* 224.1652, found *m/z* 224.1604. Anal. Calcd. for $C_{13}H_{21}NO_2$: C, 69.61; H, 9.89. Found: C, 69.23; H, 9.49. Hydrolysis of **14** using lithium hydroxide in methanol/tetrahydrofuran/water (2:2:1) provided additional **15** as a white solid: mp 144-146°C.

1,2,5,6,7,8-Hexahydro-2-methylene-1-[[2-(trimethylsilyl)ethyl]sulfonyl]azocine (18). To 208 mg (2.06 mmol) of diisopropylamine in 1.5 mL of dry tetrahydrofuran cooled in a dry ice-acetone bath was added dropwise 693 μL (1.73 mmol) of 2.5 M *n*-butyllithium in hexanes. The solution was stirred for 40 min, allowed to warm to -10°C, and 102 mg (0.83 mmol) of 1,4-dihydrobenzoic acid in 1.1 mL of dry tetrahydrofuran was added in one portion. The resulting orange-brown solution was stirred for 30 min followed by dropwise addition *via* syringe of 303 mg (0.83 mmol) of bromide **17** in 1.7 mL of tetrahydrofuran over a 2 min period. The solution was allowed to warm to room temperature and was stirred for 3.5 h followed by addition of 4.0 mL of water. The solution was concentrated *in vacuo* and the residual aqueous suspension was extracted with two 5 mL portions of diethyl ether. The combined extracts were concentrated to give 196 mg (83%) of pure **18** as a light yellow oil: ^{1}H NMR ($CDCl_3$, 250 MHz) δ 0.00 (s, 9H), 0.97-1.08 (m, 2H), 1.55-1.72 (m, 4H), 2.52-2.65 (m, 2H), 2.94-3.05 (m, 2H), 3.52-3.58 (m, 2H), 5.10 (s, 1H), 5.24 (s, 1H), 5.59-5.72 (m, 1H), 6.20 (d, J = 13.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ -2.1, 10.1, 22.9, 23.9, 24.8, 48.7, 50.8, 116.9, 130.6, 130.86, 144.5; exact mass calcd. for $C_{13}H_{25}NO_2SSi$ *m/z* 289.1533, found *m/z* 289.1545.

Octahydro-2-[(trimethylsilyl)methyl]-2*H*-isothiazolo[2,3-*a*]azocine 1,1-dioxide (20). To 177 mg (1.74 mmol) of diisopropylamine in 0.5 mL of tetrahydrofuran cooled in a dry ice-ethylene glycol bath was added dropwise *via* syringe 587 μL (1.47 mmol) of 2.5 M *n*-butyllithium in hexanes over a 1.5 min period. The solution was stirred for 30 min and 87 mg (0.70 mmol) of 1,4-dihydrobenzoic acid in 0.5 mL of tetrahydrofuran was added dropwise *via* syringe over a 3 min period. The orange-brown solution was stirred for 30 min followed by dropwise addition of 258 mg (0.70 mmol) of bromide **19** in 1.0 mL of tetrahydrofuran over a 3 min period. The solution was stirred at -15°C for 9 h and 3.0 mL of water was added. The solution was allowed to warm to room temperature, 10 mL of water was added, and the mixture was extracted with two 6-mL portions of dichloromethane. The combined extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The residual oil was chromatographed over 12 g of silica gel (eluted with ethyl acetate-hexane, 5:1) to give 184 mg (71%) of recovered bromide **19** and 27 mg (13%) of **20** as a mixture of diastereomers: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.09 (s, 9H, $Si(CH_3)_3$), 0.80 (m, 1H, $SiCH_2$), 1.25 (m, 1H, $SiCH_2$), 1.40-1.90 (m, 12H), 2.04 (m, 0.67H, CH of one diastereomer), 2.30 (m, 0.33 H, CH of other diastereomer), 2.80 (m, 1H), 3.0 (m, 0.33H), 3.25 (m, 1.67H), 3.70 (m, 1H); ^{13}C NMR ($CDCl_3$, 75.5 MHz), δ -1.1 (q), 14.4 (t), 15.0 (t), 23.2 (t), 23.3 (t), 24.0 (t), 24.4 (t), 26.7 (t), 26.9 (t), 27.6 (t), 28.5 (t), 32.4 (t), 33.8 (t), 34.1 (t), 34.2 (t), 44.4 (t), 44.9 (t), 53.0 (d), 55.1 (d), 56.8 (d), 58.0 (d); exact mass calcd. for $C_{13}H_{27}NO_2SSi$ *m/z* 289.1533, found *m/z* 289.1545. The starting 1,4-dihydrobenzoic acid was recovered from the aqueous phase by acidification and extraction with dichloromethane.

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10. Alkylation of the dianion of 1,4-dihydrobenzoic acid with the iodide corresponding to **7** gave a 45% yield of **8**. Treatment of the same dianion with the *N*-Cbz analog of **7**, followed by diazomethane, gave the methyl ester of the *N*-Cbz analog of **8** in 66% yield. Reductive alkylation of benzoic acid with the *N*-Cbz analog of **7** using lithium in ammonia gave the N-Cbz analog of **8** in 58% yield as a white solid (mp 149-150°C).
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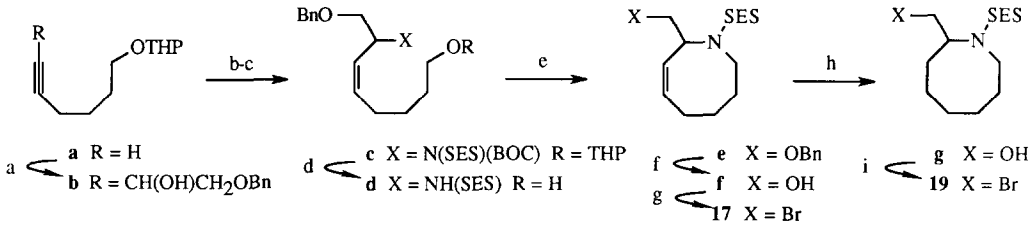
17. The preparation of **18** and **20** is described below. A notable feature is use of the Mitsunobu reaction to close the 8-membered ring.



(a) 1. *n*-BuLi, THF, -78°C 2. $PhCH_2OCH_2CHO$ (60%) (b) Ph_3P, NH(SES)(BOC), DEAD, 0°C→rt, 24 h (80%)
(c) 5% $Pd/BaSO_4$, H_2, pyridine, rt (89%) (d) 1. TFA-CH_2Cl_2 (1:1), 0°C, 3 h 2. K_2CO_3, MeOH, rt, 16 h (95%)
(e) Bu_3P, THF, DEAD, 0°C→25°C, 35 h (59%) (f) BCl_3•Me_2S (2 eq), CH_2Cl_2, -78°C→rt, 20 h (83%)
(g) 1. MsCl, Et_3N, CH_2Cl_2, 0°C→rt, 22 h (91%) 2. LiBr (8 eq), acetone, Δ, 72 h (90%) (h) 5% $Pd(OH)_2/C$, H_2 (1 atm), EtOH, rt, 18 h (98%) (i) Same as g with yields of 80% and 85%.

For step b see: Campbell, J. A.; Hart, D. J. *J. Org. Chem.* **1993**, *58*, 2900. For step f see: Congreve, M. S.; Davison, E. C.; Fuhry, M. A. M.; Holmes, A. B.; Payne, A. N.; Robinson, R. A.; Ward, S. E. *Synlett* **1993**, 663.
18. This paper is dedicated to Professor Samuel Danishefsky on the occasion of receipt of the Tetrahedron Prize.

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