Novel Syntheses of Tetrahydropyrroloquinolines: Applications to Alkaloid Synthesis

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Abstract: Two novel routes involving the intramolecular olefin insertion with a zirconium−benzyne complex, followed by a palladium-catalyzed aryl amination, have been developed for the synthesis of tetrahydropyrroloquinolines. In one approach, exemplified in the six-step total synthesis of the South American toad poison dehydrobufotenine (**1**), the tricyclic system was formed via the Pd-catalyzed ring closure of a functionalized tryptamine derivative. In the second, cyclization of an appropriately substituted quinoline yields **13**, an intermediate in the synthesis of damirones A and B, and also makaluvamine C, a topoisomerase II inhibitor exhibiting antitumor properties.

Introduction

The synthesis of indoles bearing substituents at the 3- and 4-positions has been of interest to synthetic chemists for many years due to the large number of biologically active natural products having this substitution pattern.[1] The 1,3,4,5-tetrahydropyrrolo[4,3,2-*de*]quinoline ring system was first recognized as an important feature of natural products when the structure of the toad poison dehydrobufotenine (**1**) was elucidated.[2] Recently, several marine alkaloids[3] based on the tetrahydropyrroloquinoline nucleus have been isolated and characterized. These include the damirones,[4] makaluvamines,[5] and discorhabdines[6] (Figure 1), as well as the batzellines,[7] isobatzellines,[8] and prianosines.[9] These compounds have received considerable attention due to the fact that several exhibit potent *in vitro* cytotoxicity against human tumor cell lines, presumably acting as DNA topoisomerase II inhibitors.[5,10]

The majority of the synthetic work pertaining to these compounds can be divided into two categories on the basis of the strategy employed. In most syntheses, the tricyclic heterocycle has been formed from a preexisting indole. The six-membered ring is then closed by condensation of a tryptamine quinone[11] or cyclization of a 4-aminoindole bearing a two-carbon chain at the 3-position.[12−18] Examples include the syntheses of unsubstituted[12] and 1-methyl-substituted[13] tricyclic systems of *O*-methylnordehydrobufotenine,[14] dehydrobufotenine,[15] damirones A and B,[11a] makaluvamines,[16] batzelline C and isobatzelline C,[17] and discorbhadin C.[11b,16b,c,18]

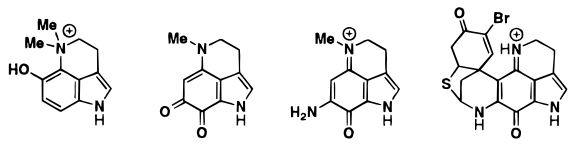

Figure 1.

The second approach has been to start with a quinoline and introduce a nitrogen at the 5-position.[19] Closure of the five-membered ring as a late step gives the tricyclic nucleus. This strategy was used for the syntheses of damirones A and B.[19b]

We report two novel routes to functionalized tetrahydropyrroloquinolines. The first is based on our earlier success in preparing regiochemically pure 3,4-diiodoindolines using the intramolecular insertion reactions of zirconocene-stabilized

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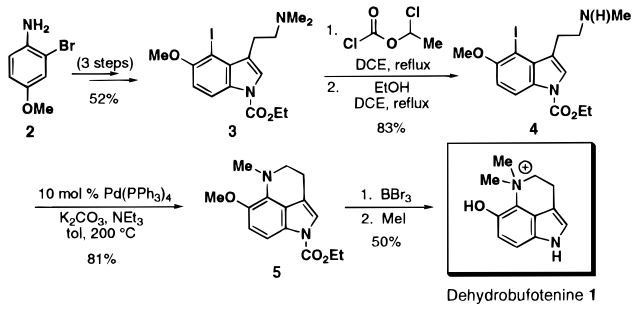
Scheme 1



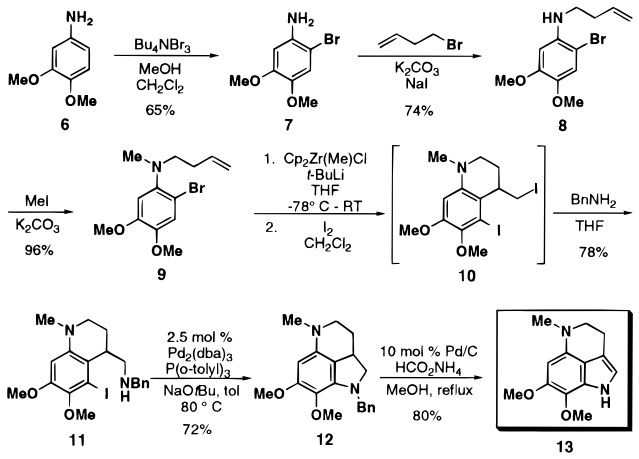
benzyne complexes.[20] The second involves construction of a functionalized tetrahydroquinoline, followed by Pd-catalyzed ring closure to afford the tricyclic ring system.

Results and Discussion

To demonstrate the utility of the first approach, we undertook the total synthesis of the toad poison dehydrobufotenine (**1**). The tryptamine derivative **3**[20d] could be selectively demethylated with ACE−Cl to afford **4** (Scheme 1).[21] Treatment of **4** with $Pd(PPh_3)_4$, K_2CO_3, and NEt_3 gave the desired tricyclic intermediate **5** in good yield.[22] The unusually high temperatures required for this cyclization were necessitated by incompatibility of our optimal conditions for the intramolecular Pd-catalyzed aryl amination; the use of NaO*t*Bu as the base led to the cleavage of the carbamate, and no cyclization product was observed.[22b] Cleavage of both the carbamate and the *O*-methyl groups with BBr_3[23] followed by *in situ* quaternization by addition of excess MeI and $KHCO_3$ produces **1** as its iodide salt.[24] In this manner, **1** was synthesized in six steps in 17% overall yield from **2**. This represents only the second synthesis of dehydrobufotenine (**1**).[15]

Our second approach to tetrahydropyrroloquinolines uses zirconocene−benzyne chemistry to construct the six-membered ring followed by palladium-catalyzed formation of the tricyclic system. To test the utility of this approach, we undertook the synthesis of **13**, an intermediate in previous total syntheses of makaluvamine C[16a] and damirones A and B.[19b] Bromination of 4-aminoveratrole (**6**) with Bu_4NBr_3 gave **7** in 65% yield (Scheme 2). Monoalkylation with 4-bromo-1-butene yielded **8**, and followed by methylation gave **9** in 72% yield. Treatment of **9** with 2 equiv of *t*BuLi in the presence of $Cp_2Zr(Me)Cl$, followed by addition of I_2 gave the 4,5-diiodotetrahydroquinoline **10** which was treated with excess benzylamine at room temperature to yield the tetrahydroquinoline **11** in 78% yield from **9**.[25] Reaction of **11** with $Pd_2(dba)_3$, P(*o*-tolyl)$_3$, and NaO*t*Bu at 80 °C cleanly afforded the tricyclic heterocycle **12** which was treated with 10 mol % Pd/C in the presence of

Scheme 2



ammonium formate, giving **13**.[26] Since **13** was an intermediate in previous total syntheses of makaluvamine C and of damirones A and B, this work contributes to their formal synthesis.

In summary, we have developed two novel approaches to the construction of tetrahydropyrroloquinoline ring systems, and have used them for the total syntheses of dehydrobufotenine, makaluvamine C, and damirones A and B. A study of the scope of these processes as well as their application to natural product synthesis is currently underway in our laboratories.

Experimental Section

All reactions involving organometallic reagents were conducted under an atmosphere of purified argon using standard Schlenk techniques or under nitrogen in a Vacuum Atmospheres Co. drybox. All organic reactions were performed under an atmosphere of argon or nitrogen. Nuclear magnetic resonance (NMR) spectra were recorded on a Varian XL-300 or VXR-500 or a Bruker AC250 FT spectrometer. Infrared (IR) spectra were recorded on a Perkin-Elmer Series 1600 FT spectrometer. Gas chromatography analyses were performed on a Hewlett-Packard Model 5890 GC with a 3392A integrator and FID detector using a 25 m capillary column with cross-linked SE-30 as a stationary phase. Electron impact mass spectra and high-resolution mass determinations (HRMS) were recorded on a Finnegan MAT System 8200. Tetrahydrofuran, benzene, diethyl ether, and hexane were dried and deoxygenated by continuous refluxing over sodium/benzophenone ketyl under nitrogen or argon followed by distillation. Methylene chloride was dried by refluxing over CaH_2 under nitrogen followed by distillation. Acetonitrile was stored over activated 3 Å molecular sieves prior to use. Anhydrous *N*,*N*-dimethylformamide (DMF) was purchased from Aldrich Chemical Co. and was used without further purification. Cp_2ZrCl_2 was purchased from Boulder Scientific Inc., Mead, Co. All other reagents either were prepared according to published procedures or were available from commercial sources and used without further purification. Unless otherwise stated, preparative flash chromatography was performed on E.M. Science Kieselgel 60 (230−400 mesh). Yields refer to isolated yields of compounds estimated to be ≥95% pure (unless otherwise noted) as determined by ^{1}H NMR and either capillary GC or combustion analysis. All reported yields are representative. Elemental analyses were performed by E & R Microanalytical Laboratory, Inc., Corona, NY.

4. 1-Chloroethyl chloroformate (0.54 mL, 5 mmol) was added dropwise to a solution of **3** (0.35 g, 0.84 mmol) in dichloroethane (6 mL) at 0 °C. The solution was stirred at 0 °C for 10 min and then heated to reflux. After 12 h, the solution was cooled to room temperature (RT), and the solvent was removed using a rotary evaporator to yield a red-white precipitate. The precipitate was dissolved in dichloroethane (6 mL), and then EtOH (6 mL) was added dropwise. The red solution was heated to reflux for 12 h and cooled to RT, and the solvent was removed using a rotary evaporator. The residue was partitioned between Et_2O (15 mL) and 1 N NaOH solution

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(15 mL). The organic layer was washed with water (10 mL) and brine (10 mL), dried over $MgSO_4$, and filtered, and the solvents were removed via rotary evaporation. The product was purified by flash chromatography (2:6:2 hexane/ethyl acetate/NEt_3) to give 0.28 g (82%) of a white solid: mp 208−210.5 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.18 (d, J = 8.5 Hz, 1H), 7.49 (s, 1H), 6.90 (d, J = 8.8 Hz, 1H), 4.45 (q, J = 7.1 Hz, 2H), 3.92 (s, 3H), 3.17 (t, J = 7.1 Hz, 2H), 2.96 (t, J = 7.1 Hz, 2H), 2.49 (s, 3H), 1.45 (t, J = 7.1 Hz, 3H), 1.17 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 154.2, 150.1, 132.3, 131.7, 125.7, 120.2, 115.6, 108.8, 77.2, 63.1, 57.5, 52.4, 36.4, 26.4, 14.3; IR (KBr, cm^{-1}) 3239, 2934, 2784, 1733, 1411, 1252, 1128. Anal. Calcd for $C_{15}H_{19}N_2O_3I$: C, 44.79; H, 4.76. Found: C, 44.69; H, 4.91.

5. $Pd(PPh_3)_4$ (92 mg, 0.08 mmol) was added to a mixture of **4** (0.32 g, 0.80 mmol), NEt_3 (4 mL), and K_2CO_3 (0.33 g, 2.4 mmol) in toluene (10 mL). The yellow mixture was heated to 200 °C for 15 h, cooled to RT, and poured into a separatory funnel containing Et_2O (15 mL) and water (15 mL). The organic layer was washed with water (10 mL) and brine (10 mL), dried over $MgSO_4$, and filtered, and the solvents were removed using a rotary evaporator. The product was purified by flash chromatography (4:1 hexane/ethyl acetate) to give 0.18 g (82%) of a white powder: mp 71.1−72.8 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.42 (br s, 1H), 7.16 (s, 1H), 6.90 (d, J = 8.9 Hz, 1H), 4.45 (q, J = 7.5 Hz, 2H), 3.87 (s, 3H), 3.27 (t, J = 6.6 Hz, 2H), 3.09 (s, 3H), 2.85 (t, J = 6.5 Hz, 2H), 1.44 (t, J = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 151.5, 144.0, 131.2, 129.4, 123.3, 117.4, 116.0, 113.0, 107.1, 62.7, 57.6, 52.7, 41.1, 20.0, 14.4; IR ($CDCl_3$, cm^{-1}) 3129, 2951, 1726, 1408, 1258, 1080. Anal. Calcd for $C_{15}H_{18}N_2O_3$: C, 65.68; H, 6.61. Found: C, 65.75; H, 6.56.

Dehydrobufotenine (1).[15] A solution of 1 M BBr_3 in CH_2Cl_2 (1 mL, 1 mmol) was added dropwise to a flask containing **5** (46 mg, 0.17 mmol) in CH_2Cl_2 (10 mL) at −78 °C. The solution was warmed to RT overnight, and then the solvent was removed *in vacuo*. CH_2Cl_2 (10 mL) and $KHCO_3$ (0.14 g, 1.0 mmol) were added, and then the mixture was cooled to 0 °C and MeOH (5 mL) was added dropwise. After 0.5 h at 0 °C, the mixture was warmed to RT and stirred for 1 h. The solvent was removed *in vacuo*, and the residue was dissolved in MeOH (5 mL). Methyl iodide (16 μL, 0.26 mmol) was added, and the mixture was stirred at RT until TLC (10% MeOH/MeCN) showed no remaining starting material. The solvent was removed using a rotary evaporator, and the residue was extracted with CH_2Cl_2. The organic phase was concentrated to give a gray solid. Slow recrystallization from MeOH gave 28 mg (50%) of a gray-white solid: mp 241.0−243.8 °C; ^{1}H NMR (CD_3OD, 300 MHz) δ 7.09 (d, J = 8.3 Hz, 1H), 6.90 (s, 1H), 6.62 (d, J = 8.3 Hz, 1H), 3.9 (t, J = 5.4 Hz, 2H), 3.7 (s, 6H), 3.24 (t, J = 5.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 161.4, 134.2, 130.4, 122.6, 120.0, 114.8, 104.1, 102.8, 69.5, 53.7, 20.2. Anal. Calcd for $C_{12}H_{15}N_2OI$: C, 43.65; H, 4.58. Found: C, 43.97; H, 4.46.

2-Bromo-4,5-dimethoxyaniline (7).[27] Bu_4NBr_3 (36 g, 75 mmol) was added to a solution of 4-aminoveratrole (10 g, 65 mmol) in CH_2Cl_2 (265 mL) and MeOH (130 mL). After 20 min at RT, the solution was poured into a separatory funnel containing Et_2O (300 mL) and saturated Na_2SO_3 solution (300 mL). The organic layer was washed with water (200 mL), dried over $MgSO_4$, and filtered, and the solvents were removed using a rotary evaporator. The product was purified by flash chromatography (10:1 and then 4:1 hexane/ethyl acetate) to give 10.7 g (67%) of a purple oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.92 (s, 3H), 6.38 (s, 1H), 3.83−3.76 (br s, 2H), 3.81 (s, 3H), 3.78 (s, 3H).

8. A mixture of **7** (9.9 g, 42.7 mmol), sodium iodide (19.4 g, 129 mmol), K_2CO_3 (17.8 g, 129 mmol), and 4-bromo-1-butene (6.5 mL, 64 mmol) in DMF (150 mL) was heated to 100 °C for 10 h, cooled to RT, and poured into a separatory funnel containing Et_2O (200 mL) and water (200 mL). The organic layer was washed with water (2 × 100 mL) and brine (100 mL), dried over $MgSO_4$, and filtered, and the solvents were removed using a rotary evaporator. The product was purified by flash chromatography (10:1 and then 4:1 hexane/ethyl acetate) to give 9.0 g (74%) of a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.97 (s, 1H), 6.28 (s, 1H), 5.82 (m, 1H), 5.17 (m, 2H), 4.00 (br s, 1H), 3.86 (s, 3H), 3.79 (s, 3H), 3.20 (q, J = 6.1 Hz, 2H), 2.42 (q, J = 5.9 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 149.2, 140.6, 139.4, 134.9, 116.9, 116.4, 98.4, 96.9, 56.5, 55.6, 43.2, 33.1; IR (film, cm^{-1}) 3395, 2931, 1515, 1211; HRMS (EI) for $C_{12}H_{16}N_1O_2Br$, calcd 285.03644, found 285.03667.

9. A mixture of **8** (2.5 g, 8.74 mmol), K_2CO_3 (3.62 g, 26.2 mmol), and methyl iodide (1.62 mL, 26.2 mmol) in DMF (30 mL) was heated to 100 °C for 2 h, cooled to RT, and poured into a separatory funnel containing Et_2O (75 mL) and water (75 mL). The organic layer was washed with water (2 × 50 mL) and brine (50 mL), dried over $MgSO_4$, and filtered, and the solvents were removed using a rotary evaporator to give 2.45 g (94%) of a pale yellow oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.04 (s, 1H), 6.70 (s, 1H), 5.82 (m, 1H), 5.02 (m, 2H), 3.86 (s, 3H), 3.84 (s, 3H), 2.99 (t, J = 7.8 Hz, 2H), 2.72 (s, 3H), 2.27 (q, J = 7.8 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 148.7, 144.9, 144.2, 136.3, 116.4, 115.8, 110.9, 106.5, 56.4, 56.2, 42.1, 32.1; IR (film, cm^{-1}) 3075, 2935, 2839, 1504, 1213, 1034; HRMS (EI) for $C_{13}H_{18}N_1O_2Br$, calcd 299.05209, found 299.05272.

11. A solution of 1.7 M *t*BuLi (1.56 mL, 2.66 mmol) was added dropwise to a Schlenk flask containing **9** (0.4 g, 1.33 mmol) and Cp_2-Zr(Me)Cl (0.36 g, 1.33 mmol) in THF (7 mL) at −78 °C. The solution was stirred at −78 °C for 3 h and then warmed to RT. After 10 h, the THF was removed *in vacuo* to give an orange foam, which was dissolved in CH_2Cl_2 (7 mL). The solution was cooled to 0 °C, and a solution of iodine (1 g, 3.99 mmol) in THF (1 mL) and CH_2Cl_2 (7 mL) was quickly added. The purple solution was stirred at 0 °C for 3 h and then warmed to RT. After 3 h, the solution was poured into a separatory funnel containing Et_2O (25 mL) and saturated Na_2SO_3 solution (25 mL). The organic layer was dried over $MgSO_4$ and filtered, and the solvents were removed using a rotary evaporator to give an orange oil. Note: the diiodide compound should not be heated since it is thermally unstable. The oil was dissolved in THF (1 mL) and cooled to 0 °C, and benzylamine (15 mL) was added. The solution was allowed to warm to RT overnight, and then the excess benzyl amine was removed via Kugelrohr distillation. Flash chromatography (2:1 hexane/ethyl acetate with 5% NEt_3) of the remaining residue gave 0.47 g (78%) of an orange oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.33−7.19 (m, 5H), 6.12 (s, 1H), 3.87 (d, J = 13.8 Hz, 1H), 3.79 (s, 3H), 3.77 (d, J = 13.8 Hz, 1H), 3.69 (s, 3H), 3.20 (dt, J = 4.0, 11.7 Hz, 1H), 3.10−3.00 (m, 2H), 2.85 (s, 3H), 2.82 (dd, J = 2.9, 9.3 Hz, 1H), 2.44 (dd, J = 10.6, 13.2 Hz, 1H), 2.19 (m, 1H), 1.79 (m, 1H), 1.39 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 151.3, 143.5, 140.8, 139.3, 128.3, 128.0, 126.8, 117.9, 101.7, 96.8, 60.4, 56.0, 53.8, 51.8, 46.4, 41.2, 39.1, 23.2; IR (film cm^{-1}) 3332, 2926, 1592, 1494, 1262, 1018; HRMS (EI) for $C_{20}H_{25}N_2O_2I$, calcd 452.09608, found 452.09573.

12. A mixture of **11** (0.4 g, 0.88 mmol), $Pd_2(dba)_3$ (20 mg, 0.022 mmol), P(*o*-tolyl)$_3$ (28 mg, 0.088 mmol), and NaO*t*Bu (0.34 g, 3.52 mmol) in toluene (5 mL) was heated to 80 °C for 20 h, cooled to RT, and poured into a separatory funnel containing Et_2O (20 mL) and water (20 mL). The organic layer was washed with water (15 mL) and brine (15 mL), dried over $MgSO_4$, and filtered, and the solvents were removed using a rotary evaporator. The product was purified by flash chromatography (10:1 hexane/ethyl acetate) to give 0.21 g (72%) of a yellow oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.44−7.26 (m, 5H), 5.75 (s, 1H), 5.14 (d, J = 14.5 Hz, 1H), 4.01 (d, J = 14.4 Hz, 1H), 3.87 (s, 3H), 3.73 (s, 3H), 3.43 (t, J = 8.1 Hz, 1H), 3.22−3.14 (m, 3H), 2.90 (s, 3H), 2.68 (dd, J = 8.5, 11.9 Hz, 1H), 2.07 (m, 1H), 1.70 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 154.7, 142.9, 139.4, 139.3, 128.4, 128.2, 127.2, 126.8, 108.4, 87.3, 62.2, 61.1, 56.3, 54.5, 51.0, 37.8, 35.4, 27.0; IR (film, cm^{-1}) 2934, 2822, 1622, 1504, 1256, 1101; HRMS (EI) for $C_{20}H_{24}N_2O_2$, calcd 324.18378, found 324.18341.

13. [16a,19b] A mixture of **12** (0.12 g, 0.37 mmol), 5 mol % Pd/C by weight (79 mg, 0.037 mmol), and ammonium formate (0.23 g, 3.7 mmol) in MeOH (6 mL) was heated to reflux for 17 h, cooled to RT, and filtered through Celite. The MeOH was removed via rotary evaporation, and the residue was dissolved in CH_2Cl_2 (10 mL). The organic phase was washed with water (5 mL), dried over $MgSO_4$, and filtered, and the solvents were removed using a rotary evaporator. The product was purified by flash chromatography (4:1 hexane/ethyl acetate) to give 69 mg (80%) of an amorphous solid: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.97 (br s, 1H), 6.64 (s, 1H), 6.01 (s, 1H), 3.94 (s, 3H), 3.92 (s, 3H), 3.26 (t, J = 5.7 Hz, 2H), 3.04 (t, J = 5.7 Hz, 2H), 2.94 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 149.2, 139.2, 127.8, 114.7, 114.4, 111.0, 89.3, 61.0, 58.2, 52.8, 38.2, 23.4; IR (film, cm^{-1}) 3345, 2932, 1621, 1520.

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