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Synthesis of a Model Compound of Corydendramine A via a Julia Coupling

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Abstract: The synthesis of the tetraenylpiperidine **12**, which has the same core structure as the natural product corydendramine A, has been completed in eight steps starting from 2-piperidinemethanol **3** and *trans,trans*-2,6-nonadienal **6**. The key step of the synthesis was a Julia coupling of sulfone (**10**) with aldehyde (**5**) to form a conjugated triene.

Keywords: Julia coupling, piperidine, triene

INTRODUCTION

In 2000, Lindquist, Shigematsu, and Pannell[1] reported the isolation and structural characterization of the natural products named corydendramine A and B (**1** and **2**, Fig. 1) from the marine hydroid *Corydendrium parasiticum*. *C. parasiticum* does not possess penetrating nematocysts like some other members of the hydroid family. Instead, these lipophilic secondary metabolites serve as fish-feeding deterrents. Other piperidine alkaloids with a similar structural motif, such as prosopinine[2] and micropine,[3] show interesting biological activity: prosopinine has anesthetic, antibiotic, and antihypertensive properties, and micropine has antibiotic properties. Evaluation of corydendramines A and B for

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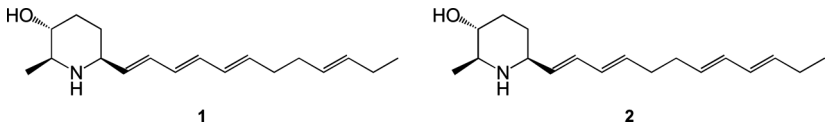


Figure 1. Corydendramines A (**1**) and B (**2**).

similar biological activity would require a large supply, and so a synthetic project was initiated with these compounds as the target.

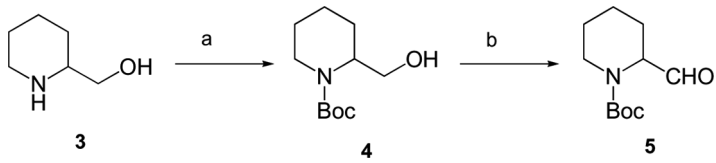
Several other methods of affixing the lipophilic "tail" to the piperidine "head" were attempted without success, including a Negishi-style coupling of a vinylzinc species with a vinyl iodide,[4] and addition of a vinyl boronate to an *N*-acyliminium ion.[5] A reference that showed success in the stereoselective formation of an all-*trans* triene using a Julia coupling[6] led us to adopt that same route in our synthesis.

RESULTS AND DISCUSSION

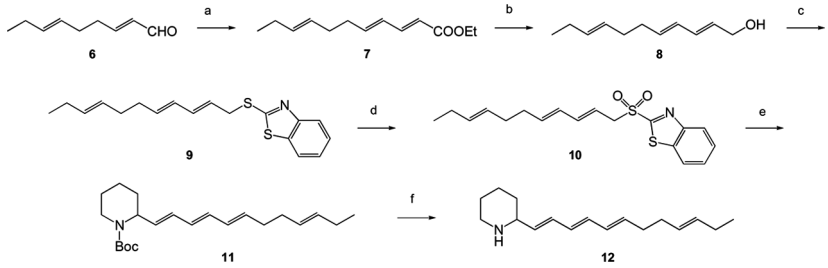
Preparation of the aldehyde coupling partner was achieved in two steps from the commercially available 2-piperidinemethanol (Scheme 1).[7] After protection with a *tert*-butoxycarbamate group, the N-Boc-piperidine-2-methanol **4** was converted to the carbaldehyde **5**[8] by using a Swern oxidation.[9]

The synthesis of the lipophilic tail (Scheme 2) began with *trans, trans*-2,6-nonadienal **6** and use of a Horner–Wadsworth–Emmons[10] reaction to afford the ethyl ester **7**. This ester was subsequently reduced[11] with 2.2 equivalents of diisobutyl aluminum hydride (DIBAL-H) in toluene to afford the alcohol **8** after workup.

The alcohol **8** was then transformed into the aromatic sulfide **9** using a Mitsunobu reaction[6] with 2-mercaptobenzothiazole and diisopropyl azodicarboxylate (DIAD). In our first attempt at this reaction, the ^{1}H NMR spectrum of the product after chromatographic purification



Scheme 1. Reagents and conditions: (a) Boc_2O, Et_3N, CH_2Cl_2, rt, 1 h, 84%; and (b) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78°C to 0°C, 2.25 h, 68%.



Scheme 2. Reagents and conditions: (a) $(EtO)_2POCH_2COOEt$, NaH, THF, −30°C to rt, overnight, 83%; (b) DIBAL-H, toluene, 0°C to rt, overnight, 91%; (c) 2-mercaptobenzothiazole, Ph_3P, DIAD, THF, 0°C to rt, overnight, 90%; (d) $(NH_4)_6Mo_7O_{24}$, H_2O_2, EtOH, rt, 8 h, 98%; (e) (i) KHMDS, 18-crown-6, THF, −80°C, 1 h, (ii) **5**, THF, −80°C, 2.5 h, then −80°C to rt, overnight, 98%; and (f) TMSOTf, CH_2Cl_2, 2,6-lutidine, 40%.

indicated the presence of two additional compounds (extra doublets in the 4.0–4.5 ppm region) that were not present in the NMR spectrum of the crude reaction mixture. These extra compounds were likely formed by acid-catalyzed rearrangement of the polyene system during purification with silica gel. To avoid this rearrangement in subsequent runs of this reaction, the silica gel was doped with 1% triethylamine.

Oxidation of the sulfide **9** to the sulfone **10** was completed with fresh hydrogen peroxide and a molybdenum catalyst.[6] In most cases, a sulfoxide side product was present in the crude reaction product, but it could be removed using column chromatography. The key step, the Julia coupling, proceeded in very good yield, with no indication of the presence of other stereoisomers in the ^1H NMR of the coupled product **11** or the ^{13}C NMR of **11** or the deprotected product **12**. Assignment of the ^1H NMR signals to the hydrogen atoms in the molecule (listed in the experimental section) were based on the splitting patterns observed in the spectra and estimated chemical shifts calculated for a triene system. Removal of the Boc group proved problematic: the best yield obtained was only 40% despite attempting a variety of conditions.

EXPERIMENTAL

General

Unless otherwise specified, starting materials were obtained from commercial suppliers and used without purification. Tetrahydrofuran (THF) was distilled over Na/benzophenone, and CH_2Cl_2 and toluene

were distilled over CaH_2. NMR spectra were recorded on a Varian Mercury VX300. Fourier transform–infrared (FT-IR) spectra were recorded on a Mattson Galaxy Series 3000 or a Nicolet 4700 instrument. Electron impact (EI) mass spectra were recorded on an HP 5973 mass selective detector attached to an HP 6890 GC instrument. Electrospray ionization (ESI) mass spectra were recorded on a ThermoFinnigan LCQ-Advantage instrument. Thin-layer chromatography (TLC) was run on aluminum-backed plates of SiO_2 with 0.2 mm thick. All reactions were run under an inert atmosphere of argon, and all glassware was dried in an oven overnight prior to use.

N-Boc-piperidine-2-methanol (4)[9]

Triethylamine (23.34 mL, 156.42 mmol) was added to a solution of 2-piperidinemethanol (5.00 g, 43.45 mmol) in dichloromethane (150 mL) dropwise, and the solution was stirred for an hour upon complete addition. Then a solution of di-*tert*-butyl dicarbonate (Boc_2O, 11.38 g, 52.14 mmol) in dichloromethane (20 mL) was added dropwise to the solution, and it was stirred for an additional hour upon complete addition. The reaction was poured into 50 mL water. The organic phase was extracted with water, and the aqueous phases were extracted with dichloromethane (2×20 mL). The combined organic phases were washed with brine, dried over $MgSO_4$, and filtered, and the solvent was removed in vacuo. The crude product was purified via column chromatography using silica gel and hexanes/EtOAc (1:1) to afford alcohol **4** (7.865 g, 84%) as a white solid. Several peaks in the ^1H NMR experienced broadening as a result of the presence of rotamers associated with the carbamate. Mp 75–77°C (lit. Mp 74–78°C).[12] ^1H NMR (300 MHz, $CDCl_3$) δ: 4.29 (1H, m), 3.94 (1H, 2x br s), 3.81 (1H, dd, $J = 10.8$, 9.1 Hz, C**H**$_2$OH), 3.61 (1H, dd, $J = 10.5$, 5.9 Hz, C**H**$_2$OH), 2.87 (1H, apparent br t), 2.12 (1H, br s), 1.53–1.73 (6H, m), 1.46 (9H, s, ^{t}Bu). ^{13}C NMR (75 MHz, $CDCl_3$): 156.6, 80.0, 61.9, 52.7, 40.1, 28.6, 25.5, 25.4, 19.8. IR (film): 3418, 2934, 1668 cm^{-1}. M/S (EI) m/z: 215 (M^+), 184, 142, 128 (100%), 84, 57.

N-Boc-piperidine-2-carbaldehyde (5)[9]

DMSO (7.15 mL, 101.6 mmol) was added dropwise to a solution of freshly distilled oxalyl chloride (4.56 mL, 50.8 mmol) in dichloromethane (100 mL) at −78°C, and the solution was stirred for 45 min. A solution of the alcohol **4** (7.29 g, 33.9 mmol) in dichloromethane (20 mL) was added

dropwise, and the solution was stirred for 1 h at −78°C. Triethylamine (38.22 mL, 254.0 mmol) was added to the solution, which was warmed to 0°C upon complete addition of the base and was allowed to stir an additional 30 min. The reaction was poured into 50 mL water, the layers were separated, and the aqueous phase was extracted with dichloromethane (4 × 20 mL). The combined organic phases were washed with 1% HCl (10 mL), water, saturated sodium bicarbonate, and brine. The organic phase was then dried over $MgSO_4$ and filtered, and the solvent was removed in vacuo. The crude product was purified via column chromatography using silica gel and EtOAc/hexanes (20/80) to afford the aldehyde **5** (4.8992 g, 68%) as a colorless oil. Several peaks in the ^{1}H NMR experienced broadening as a result of the presence of rotamers associated with the carbamate. Pairs of peaks from rotameric carbons in the ^{13}C NMR spectrum are enclosed within parentheses. ^{1}H NMR (300 MHz, $CDCl_3$): 9.58 (1H, s, CHO), 4.54 (1H, apparent br d), 3.92 (1H, apparent br d), 2.90 (1H, br s), 2.15 (1H, apparent br d), 1.58–1.73 (5H, m), 1.46 (9H, s, ^{t}Bu). ^{13}C NMR (75 MHz, $CDCl_3$): 201.6, 158.0, 80.6, 77.5, (61.6, 60.8), (43.3, 42.1), 28.5, (24.9, 23.8), 21.1. IR (thin film): 2940, 1734, 1693, 1405, 1164 cm^{-1}.

Ethyl (2*E*,4*E*,8*E*)-Undeca-2,4,8-trienoate (7)

Solid sodium hydride (900 mg, 22 mmol) was washed with hexanes (3 × 10 mL). THF (40 mL), was then added to the hydride and the solution was cooled to −30°C. Triethyl phosphonoacetate (4.36 mL, 22 mmol) was added dropwise, and the solution was stirred for 30 min. The silvery solution became clear upon completion of the reaction. (2*E*,6*E*)-Nonadienal **6** (2.0 mL, 12.6 mmol) was added dropwise to the clear solution, stirred for 30 min at −30°C, allowed to warm to 10°C overnight, and then brought to room temperature and stirred for 1 h. The reaction was poured into a separatory funnel with saturated ammonium chloride and diethyl ether. The layers were separated, and the aqueous phase was extracted with diethyl ether (3 × 15 mL). The combined organic phases were washed with 10% sodium carbonate (2 × 10 mL) and brine (2 × 10 mL), dried over $MgSO_4$, and filtered, and the solvent was removed in vacuo. The crude product was purified via column chromatography on silica gel using EtOAc–hexanes (15/85) to afford the ester **7** (2.1908 g, 83%) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): 7.26 (1H, dd, J = 15.5, 10.0 Hz, H3), 6.07–6.23 (2H, m, H4 and H5), 5.79 (1H, d, J = 15.2 Hz, H2), 5.50 (1H, dt, J = 15.2, 6.0 Hz, H8 or H9), 5.37 (1H, dt, J = 15.2, 6.3, 1.3 Hz, H8 or H9), 4.21 (2H, q, J = 7.1 Hz, Et), 2.24 (2H, q, J = 6.2 Hz, H6 or H7), 2.13 (2H, q, J = 6.9 Hz, H6 or H7), 2.01

(2H, quin t, $J = 7.0$, 1.2 Hz, H10), 1.30 (3H, t, $J = 7.2$ Hz, Et), 0.97 (3H, t, $J = 7.5$ Hz, H11). ^{13}C NMR (75 MHz, $CDCl_3$): 167.5, 145.2, 144.2, 133.3, 128.8, 127.9, 119.5, 60.4, 33.2, 31.9, 25.8, 14.5, 14.1. IR (film): 1715, 1643, 1617 cm^{-1}. MS (EI) m/z: 208 (M^+), 140, 69 (100%), 67.

(2*E*,4*E*,8*E*)-Undeca-2,4,8-trien-1-ol (8)

DIBAL-H (1 M in hexanes, 20.0 mL, 20 mmol) was added dropwise to a solution of ethyl undeca-2,4,8-trienoate **7** (2.0355 g, 9.77 mmol) in toluene (40 mL) at 0°C. The solution was warmed to room temperature and allowed to stir overnight. The solution was again cooled to 0°C, and HCl (6 M, 3.5 mL, 21.0 mmol) was added dropwise to the solution. The reaction was warmed to room temperature and stirred for 2 h, whereupon it was poured into brine (20 mL), diethyl ether (30 mL), and solid sodium chloride (10 g). The layers were separated, and the aqueous phase was washed with diethyl ether (3×15 mL). The combined organic phases were washed with brine, dried over $MgSO_4$, and filtered, and the solvent was removed in vacuo. The crude product was flushed with ethyl acetate through a small column consisting of a layer of silica gel on top of a layer of Celite, and the solvent was again removed in vacuo. The product was kept under high vacuum for 2 h to completely remove traces of isobutyl alcohol, producing the pure alcohol **8** (1.4785 g, 91%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): 6.23 (1H, dd, $J = 14.9$, 10.0 Hz, H3), 6.06 (1H, dd, $J = 15.0$, 10.5 Hz, H4), 5.75 (1H, dq, $J = 14.9$, 5.9 Hz, H2 or H5), 5.71 (1H, dq, $J = 14.9$, 5.9 Hz, H2 or H5), 5.48 (1H, dt, $J = 15.5$, 5.7 Hz, H8 or H9), 5.38 (1H, dt, $J = 15.2$, 5.6 Hz, H8 or H9), 4.17 (2H, d, $J = 5.9$ Hz, H1), 1.95–2.20 (6H, m, H6, H7, and H10), 1.46 (1H, br s, OH), 0.97 (3H, t, $J = 7.3$ Hz, H11). ^{13}C NMR (75 MHz, $CDCl_3$): 135.3, 132.9, 132.3, 129.8, 129.7, 128.4, 63.8, 32.9, 32.4, 25.8, 14.2. IR (film): 3347, 2962, 1660, 1441 cm^{-1}. MS (EI) (m/z): 166 (M^+), 122, 79 (100%), 69, 67.

2-[(2*E*,4*E*,8*E*)-Undeca-2,4,8-trienylsulfanyl]-benzothiazole (9)

(2*E*,4*E*,8*E*)-Undeca-2,4,8-trien-1-ol **8** (1.134 g, 6.82 mmol) was added to a solution of 2-mercaptobenzothiazole (1.71 g, 10.23 mmol) in THF (20 mL) at room temperature. In a separate flask, triphenylphosphine (3.13 g, 120 mmol) was dissolved in THF (80 mL) and was cooled to 0°C. DIAD (2.23 mL, 11.2 mmol) was added dropwise to the triphenylphosphine solution. The solution turned from colorless to opaque white before complete addition. Then the alcohol/benzothiazole solution was

transferred into the triphenylphosphine/DIAD solution dropwise via syringe. The reaction was allowed to warm to room temperature and stirred overnight. The solvent was removed in vacuo, and the residue was purified by column chromatography using silica gel and EtOAc/Et_3N/hexanes (10/1/89), affording the sulfide **9** (1.95 g, 90%) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): 7.86 (1H, ddd, $J = 8.2$, 1.1, 0.6 Hz, Ar), 7.76 (1H, ddd, $J = 7.9$, 1.2, 0.6 Hz, Ar), 7.43 (1H, ddd, $J = 8.5$, 7.3, 1.3 Hz, Ar), 7.30 (1H, ddd, $J = 8.2$, 7.6, 1.1 Hz, Ar), 6.33 (1H, dd, $J = 14.7$, 10.0 Hz, H3), 6.04 (1H, dd, $J = 15.2$, 10.2 Hz, H4), 5.76 (1H, dt, $J = 15.0$, 7.5 Hz, H2), 5.72 (1H, dt, $J = 15.5$, 6.4 Hz, H5), 5.48 (1H, dt, $J = 15.5$, 6.4 Hz, H8 or H9), 5.38 (1H, dt, $J = 15.5$, 5.7 Hz, H8 or H9), 4.04 (2H, d, $J = 7.3$ Hz, H1), 1.94–2.19 (6H, m, H6, H7, H10), 0.96 (3H, t, $J = 7.5$ Hz, H11). ^{13}C NMR (75 MHz, $CDCl_3$): 166.7, 153.4, 135.7, 135.5, 135.2, 132.9, 129.5, 128.4, 126.2, 124.5, 124.4, 121.7, 121.2, 35.1, 33.0, 32.4, 25.8, 14.1. IR (film): 3020, 2960, 1460, 1427, 1309, 1238, 991 cm^{-1}.

2-[(2*E*,4*E*,8*E*)-Undeca-2,4,8-triene-1-sulfonyl]-benzothiazole (10)

Ammonium molybdate tetrahydrate (764 mg, 0.618 mmol) was added to a solution of hydrogen peroxide (30% aq., 1.89 mL, 61.8 mmol), and the mixture was stirred for 10 min. In a separate flask with a stir bar, the sulfide **9** (1.95 g, 6.18 mmol) was dissolved in absolute ethanol (25 mL). The peroxide solution was transferred into the sulfide solution dropwise with a pipet, and the color changed from clear yellow to an opaque yellow. The reaction was stirred for 8 h and was then poured into water (30 mL) and ether (20 mL). The aqueous phase was washed with ether (2×20 mL). The combined organic phases were washed with 20 mL each of 10% thiosulfate, saturated sodium bicarbonate, and brine, then dried over $MgSO_4$, filtered, and concentrated in vacuo. The product was purified via column chromatography on silica gel using EtOAc/Et_3N/hexanes (20/2/78) to afford the sulfone **10** (2.10 g, 98%) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): 8.24 (1H, ddd, $J = 8.5$, 1.5, 0.8 Hz, Ar), 8.01 (1H, ddd, $J = 7.6$, 2.0, 0.9 Hz, Ar), 7.63 (2H, m, Ar), 6.24 (1H, dd, $J = 15.2$, 10.3 Hz, H3), 6.01 (1H, dd, $J = 15.0$, 10.6 Hz, H4), 5.68 (1H, dt, $J = 15.2$, 6.4 Hz, H5), 5.53 (1H, dt, $J = 15.2$, 7.6 Hz, H2), 5.28–5.48 (2H, m, H8 and H9), 4.24 (2H, d, $J = 7.6$ Hz, H1), 1.92–2.14 (6H, m, H6, H7, and H10), 0.95 (3H, t, $J = 7.5$ Hz, H11). ^{13}C NMR (75 MHz, $CDCl_3$): 165.7, 152.9, 141.3, 138.4, 137.1, 133.0, 129.0, 128.2, 128.1, 127.8, 125.7, 122.5, 113.7, 59.0, 32.9, 32.1, 25.8, 18.7, 14.1. IR (film): 3026, 2996, 2921, 2846, 1654, 1554, 1471 1332, 1146 cm^{-1}.

2-((1*E*,3*E*,5*E*,9*E*)-Dodeca-1,3,5,9-tetraenyl)piperidine-1-carboxylic Acid *tert*-Butyl Ester (11)

Potassium bis(trimethylsilyl)amide or potassium hexamethyldisilazide (KHMDS) (0.5 M in THF, 1.41 mL, 0.705 mmol) was added dropwise to a solution of the sulfone **10** (238.5 mg, 0.677 mmol) and 18-crown-6 (193 mg, 0.732 mmol) in THF (5 mL) at −80°C. The solution was stirred for 1 h. N-Boc-piperidine-2-carbaldehyde **5** (115 mg, 0.542 mmol) in THF (10 mL) was added dropwise, and the reaction was stirred for 2.5 h at −80°C. The reaction was allowed to warm to room temperature overnight and then poured into saturated ammonium chloride (20 mL). The layers were separated, and the aqueous phase was extracted with EtOAc (3 × 10 mL). The combined organic phases were washed with brine, dried over Na_2SO_4, and filtered, and the solvent was removed in vacuo. The crude product was purified via column chromatography on silica gel using EtOAc/Et_3N/hexanes (10/1/89) to afford the tetraene **11** (183.6 mg, 98%) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): 6.00–6.18 (4H, m, H2′, H3′, H4′, H5′), 5.71 (1H, dt, $J = 14.6$, 6.2 Hz, H6′), 5.62 (1H, dd, $J = 14.6$, 5.0 Hz, H1′), 5.48 (1H, dt, $J = 15.3$, 5.7 Hz, H9′ or H10′), 5.39 (1H, dt, $J = 15.2$, 5.7 Hz, H9′ or H10′), 4.84 (1H, br s, H2), 3.93 (1H, apparent br d, H6a), 2.82 (1H, apparent br d, H6b), 1.95–2.21 (6H, m, H7′, H8′, H11′), 1.45–1.75 (6H, m, H3, H4, H5), 1.46 (9H, s, ^{t}Bu), 0.97 (3H, t, $J = 7.3$ Hz, H12′). ^{13}C NMR (75 MHz, $CDCl_3$): 155.5, 135.0, 132.8, 132.7, 132.0, 131.5, 130.7, 130.4, 128.5, 79.6, 52.2, 40.0, 33.2, 32.5, 29.6, 28.73, 28.68, 25.8, 19.8, 14.2. IR (film): 3014, 2855, 1693, 1453, 1409, 1163 cm^{-1}.

2-((1*E*,3*E*,5*E*,9*E*)-Dodeca-1,3,5,9-tetraenyl)piperidine (12)

2,6-Lutidine (178 μL, 1.53 mmol) was added to a solution of the protected piperidine **11** (134.7 mg, 0.390 mmol) in CH_2Cl_2 (5 mL) at 0°C. The solution was stirred for several minutes, and then trimethylsilyl trifluoromethanesulfonate or trimethylsilyl triflate (TMSOTf) (92 μL, 0.508 mmol) was added dropwise to the solution, which was then stirred for 3 h at room temperature. The reaction mixture was poured into saturated aq. $NaHCO_3$ and extracted twice with CH_2Cl_2. The combined organic extracts were washed with brine, dried over $MgSO_4$, and filtered, and the solvent was removed in vacuo. The crude product was purified via column chromatography on silica gel using methanol/CH_2Cl_2 (15/85) to afford the deprotected tetraene **12** (38 mg, 40%) as a yellow solid. Mp 48–51°C. ^{1}H NMR (300 MHz, $CDCl_3$): 6.01–6.22 (4H, m, H2′, H3′, H4′, H5′), 5.62–5.74 (2H, m, H1′, H6′), 5.48 (1H, dt, $J = 14.9$, 5.7 Hz, H9′ or H10′), 5.39 (1H, dt, $J = 15.4$, 5.7 Hz, H9′ or

H10′), 3.06–3.16 (2H, m, H2 and H6a), 2.67 (1H, td, $J = 11.7$, 3.0 Hz, H6b), 1.95–2.20 (6H, m, H7′, H8′, H11′), 1.81 (1H, m, ring H), 1.20–1.72 (6H, m, ring H's + NH), 0.96 (3H, t, $J = 7.3$ Hz, H12′). ^{13}C NMR (75 MHz, $CDCl_3$): 132.0, 130.0, 128.1, 128.0, 126.0, 125.9, 125.1, 123.8, 54.4, 42.3, 28.42, 28.37, 27.8, 21.4, 21.1, 20.1, 9.4. IR (KBr) 3013, 2924, 2848, 1448, 1002, 964, 892 cm^{-1}. MS (ESI) m/z: 246 $[M + H]^+$. High-resolution MS (EI, m/z): 245.2141, calcd. for $C_{17}H_{27}N$ 245.2143.

CONCLUSION

A tetraenyl piperidine compound (**12**), whose structure is analogous to corydendramine A, was successfully synthesized in eight steps. The results from the completion of the model study are currently being used in a synthesis of the complete natural product **1**.

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