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Total Synthesis of Anhydrolycorinone Utilizing Sequential Intramolecular Diels−Alder Reactions of a 1,3,4-Oxadiazole

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A convergent total synthesis of anhydrolycorinone is detailed, enlisting sequential intramolecular Diels−Alder reactions of a suitably substituted 2-amino-1,3,4-oxadiazole defining a novel oxadiazole → furan → benzene Diels−Alder strategy.

Anhydrolycorinone (**1**, Figure 1) is a member of the pyrrolophenanthridine class of natural products isolated from *Amaryllidaceae* plants.[1] In addition to containing the ring system characteristic of the larger class of lycorine alkaloids, it has served as an advanced intermediate in syntheses of the biologically active natural products anhydrolycorinium chloride[2] (**2**, cytotoxic agent)[3] and hippadine[1] (**3**, reversibly inhibits fertility in male mice).[4]

We recently disclosed a synthetic approach toward this class of alkaloids that utilized sequential intramolecular inverse electron demand ($LUMO_{diene}$-controlled) Diels−Alder reactions of an unsymmetrically substituted 1,2,4,5-tetrazine.[5] This approach, based on a tetrazine → diazine → benzene Diels−Alder strategy,[6] distinguished itself from preceding efforts[2,7−9] by assembling both the pyrrolidine and pyridone rings along with the D-ring via tandem intramolecular cycloaddition reactions.[9] Herein, we describe an alternative sequential heterocyclic cycloaddition approach to anhydrolycorinone (**1**) using a suitably substituted 2-amino-1,3,4-oxadiazole.

Although a limited number of reports describe the cycloaddition reactivity of electron-deficient 1,3,4-oxadiazoles, they typically employ symmetrical oxadiazoles bearing strongly electron-withdrawing substituents (CF_3, SO_2Et, CO_2Me) in intermolecular reactions.[10] Reactions with olefinic dienophiles proceed through an initial [4 + 2] cycloadduct that undergoes a loss of N_2 to generate a carbonyl ylide, which reacts further with the olefins in a

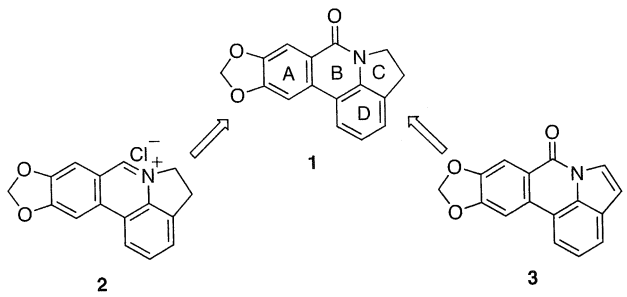

FIGURE 1.

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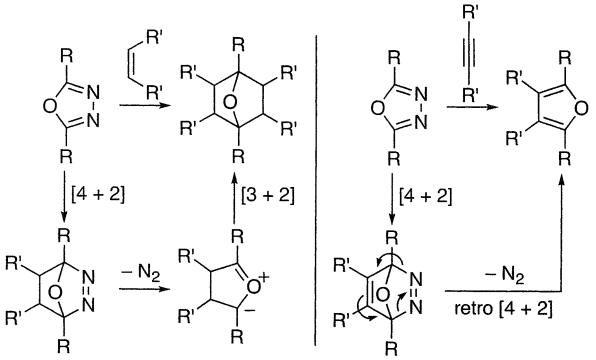
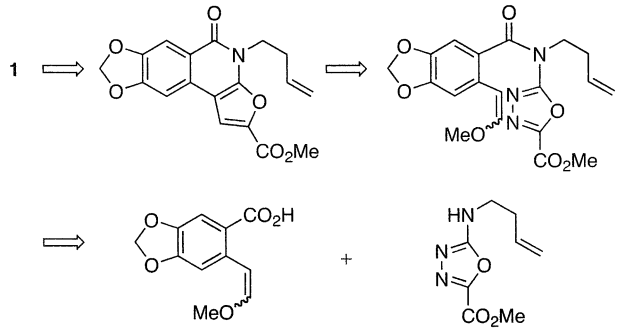


FIGURE 2.

1,3-dipolar cycloaddition (Figure 2, left). In recent efforts, we have extended the scope of this reaction beyond that which provides symmetrical 2:1 cycloadducts by implementing the reaction cascade in an intramolecular fashion.[11] In the cases examined, olefinic dienophiles tethered to a 2-amino-1,3,4-oxadiazole react to form fused oxabicyclo[2.2.1]heptane products with complete control of the regio- and diastereoselectivity.

In these studies, it was observed that tethered alkynyl dienophiles generate high yields of the furan products resulting from a single cycloaddition reaction (Figure 2, right).[11] Additionally, some tethered olefin dienophiles bearing a leaving group were shown to serve as alkyne equivalents providing the analogous furan cycloaddition reaction products presumably arising from the intermediate carbonyl ylide via elimination of the dienophile substituent. This furan-forming cycloaddition reactivity is complementary to the well-established oxazole to furan Diels–Alder transformation[12] and represents a novel alternative strategy for construction of substituted furans in which the retro-Diels–Alder reversion entails the more facile loss of N_2 (N≡N) versus a nitrile (RC≡N).[13] The furan products, themselves reactive toward intramolecular cycloadditions, offer the potential to further extend the scope of this oxadiazole reactivity to include the synthesis of fused carbocyclic aromatic products. The intramolecular [4 + 2] cycloaddition reactions of furans with tethered alkenes or alkynes to generate benzene

SCHEME 1



systems are well-documented,[9,14] and this reactivity defines a novel oxadiazole → furan → benzene strategy (Scheme 1). Herein, we describe the application of this strategy to the total synthesis of anhydrolycorinone.

The starting 2-amino-1,3,4-oxadiazole **6** was prepared from 4-amino-1-butene[15] in three steps as indicated in Scheme 2. Treatment of the hydrochloride salt of 4-amino-1-butene with carbonyl diimidazole and Et_3N afforded **4** in 91% yield, which was converted to the oxadiazole precursor **5** by treatment with methyl oxalylhydrazide[16] in THF–HOAc (64%). Cyclization of **5** to form the corresponding oxadiazole was mediated by TsCl and Et_3N and proceeded in superb yield (86%). Coupling of **6** with the known carboxylic acid **7**[5] was effected by EDCI (1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride), DMAP, and $NaHCO_3$ to provide the Diels–Alder reaction substrate **8**.

Sequential cycloaddition reactions were observed upon warming **8** first at 165 °C for 30 min and then at 230 °C for 18 h. The mild conditions required for the first Diels–Alder reaction indicate a favorable electronic pairing of the dienophile and oxadiazole diene in agreement with the expectation that the initial [4 + 2] cycloaddition is $LUMO_{diene}$-controlled (inverse electron demand). The observed product **9** is consistent with an initial cycload-

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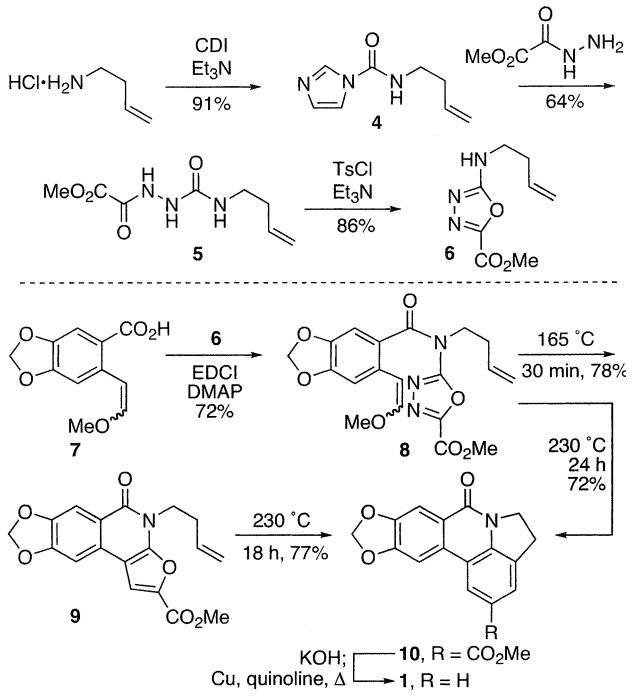
SCHEME 2



dition reaction followed by loss of N_2 to generate a carbonyl ylide that eliminates methanol to furnish the furan. Consistent with expectations based on earlier work, especially that of Padwa with the more reactive 2-aminofurans,[8,9,14] **9** serves as a competent substrate for a further cycloaddition reaction at elevated temperatures. The excellent conversion of **9** to **10** (77%) under the conditions employed compares favorably with other intramolecular Diels−Alder reactions of the reactive 2-aminofurans that form indolines.[9] The only observed product was **10** resulting from the initial [4 + 2] cycloaddition reaction followed by ring-opening of the resulting oxabicyclo[2.2.1]heptane cycloadduct and elimination of H_2O. The two sequential Diels−Alder reactions could be conducted in a single step by warming **8** at 230 °C (TIPB, 24 h) to provide **10** in better conversions (72%). As anticipated, the conversion of **8** to **9** was complete within 1 h and **9** more slowly converts to **10** under these conditions. Ester saponification of **10** and decarboxylation[8] provided anhydrolycorinone (**1**) identical in all respects (^{1}H and ^{13}C NMR, IR, mp) with properties reported for authentic material[1] and a sample of our own earlier synthetic material.[5]

A convergent total synthesis of anhydrolycorinone (**1**), which provides access to hippadine (**3**) and anhydrolycorinium chloride (**2**), was developed by enlisting a novel oxadiazole → furan → benzene strategy featuring two sequential intramolecular [4 + 2] cycloaddition reactions of a substituted 2-amino-1,3,4-oxadiazole. Further studies of the scope of such reactions and their applications are in progress and will be reported in due course.

Experimental Section

***N*-Carbonylimidazole But-3-en-1-ylamide (4).** A suspension of carbonyldiimidazole (950 mg, 5.84 mmol) in 23 mL of anhydrous THF was cooled to 0 °C under N_2 and treated with a solution of 4-amino-1-butene hydrochloride[15] (250 mg, 2.92 mmol) and Et_3N (0.325 mL, 2.92 mmol) in 7.5 mL of CH_2Cl_2 dropwise over 30 min. After being stirred for an additional 3 h, the reaction mixture was concentrated under reduced pressure and subjected to flash chromatography (SiO_2, 2.5 × 12 cm, 5% $CH_3OH/CHCl_3$) to provide **4** (436 mg, 91%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.17 (s, 1H), 7.90 (br s, 1H), 7.47 (s, 1H), 6.96 (s, 1H), 5.79−5.69 (m, 1H), 5.09−5.03 (m, 1H), 3.42 (dt, J = 5.8, 7.0 Hz, 2H), 2.33 (dt, J = 6.7, 7.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 149.1, 135.9, 134.7, 129.5, 117.5, 116.6, 40.1, 33.6; IR (film) ν_{max} 3448, 1729, 1528, 1477 cm^{-1}; MALDIFTMS (DHB) m/z 166.0975 ($C_8H_{11}N_3O$ + H^+ requires 166.0975).

1-Methoxalyl-4-(but-3-en-1-ylamide)semicarbazide (5). A solution of **4** (138 mg, 0.84 mmol) in 2 mL of anhydrous THF was treated with methyl oxalyl hydrazide[16] (98 mg, 0.84 mmol) and acetic acid (0.21 mL, 3.4 mmol) and allowed to stir at 30 °C under N_2 for 18 h. The reaction mixture was cooled to room temperature, concentrated under reduced pressure, and subjected to flash chromatography (SiO_2, 2 × 10 cm, 2.5% CH_3OH/25% acetone/CH_2Cl_2) to provide **5** (116 mg, 64%) as a white solid: mp 107−109 °C; ^{1}H NMR (DMSO-d_6, 500 MHz) δ 10.45 (s, 1H), 7.99 (s, 1H), 6.50 (br s, 1H), 5.81−5.73 (m, 1H), 5.07−4.99 (m, 2H), 3.79 (s, 3H), 3.05 (dt, J = 6.3, 7.0 Hz, 2H), 2.13 (dt, J = 7.0, 7.0 Hz, 2H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 161.1, 158.1, 157.6, 137.0, 117.1, 53.7, 39.6, 35.0; IR (film) ν_{max} 3374, 1728, 1708, 1528 cm^{-1}; FABHRMS (NBA/NaI) m/z 216.0986 ($C_8H_{13}N_3O_4$ + H^+ requires 216.0984).

Methyl 5-(But-3-en-1-yl)amino-1,3,4-oxadiazole-2-carboxylate (6). A solution of **5** (100 mg, 0.4 mmol) in 5 mL of anhydrous CH_2Cl_2 was treated with TsCl (76 mg, 0.4 mmol) and Et_3N (0.14 mL, 2.5 mmol) and stirred at 25 °C under N_2. After 18 h, the reaction mixture was diluted with 10 mL of H_2O and extracted with CH_2Cl_2 (3 × 10 mL). The combined extracts were dried (Na_2SO_4), concentrated under reduced pressure, and subjected to flash chromatography (SiO_2, 3 × 10 cm, 5% CH_3OH/CH_2Cl_2) to provide **6** (80 mg, 86%) as a white solid: mp 92−93 °C (EtOAc−hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.75 (m, 2H), 5.12 (m, 2H), 3.98 (s, 3H), 3.51 (dt, J = 6.2, 6.5 Hz, 2H), 2.40 (dt, J = 6.7, 6.7 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 164.3, 154.8, 150.8, 134.0, 118.4, 53.3, 42.4, 33.5; IR (film) ν_{max} 3422, 1743, 1620, 1155 cm^{-1}; FABHRMS (NBA/NaI) m/z 198.0881 ($C_8H_{11}N_3O_3$ + H^+ requires 198.0879).

Methyl 5-[(But-3-en-1-yl)(6-(2-methoxyvinyl)benzo[1,3]dioxole-5-carbonyl)amino)]-1,3,4-oxadiazole-2-carboxylate (8). A solution of **6** (6.0 mg, 0.030 mmol) and 6-(2-methoxyvinyl)benzo[1,3]dioxole-5-carboxylic acid[5] (**7**, 14 mg, 0.060 mmol) in 0.3 mL of DMF was treated with $NaHCO_3$ (7.5 mg, 0.090 mmol), EDCI (12 mg, 0.060 mmol), and DMAP (11 mg, 0.090 mmol) and stirred under Ar at 25 °C for 18 h. The reaction mixture was diluted with EtOAc (5 mL) and washed with H_2O (3 × 5 mL). The organic extract was dried (Na_2SO_4) and concentrated under reduced pressure before being subjected to flash chromatography (SiO_2, 1 × 5 cm, 25% EtOAc/hexanes) to provide **8** (8.5 mg, 72%) as a colorless oil: ^{1}H NMR (acetone-d_6, 500 MHz) δ 6.90 (d, J = 12.9 Hz, 1H), 6.88 (s, 1H), 6.82 (s, 1H), 6.02 (s, 2H), 5.88−5.80 (m, 1H), 5.83 (d, J = 12.9 Hz, 1H), 5.13−5.10 (m, 1H), 5.06−5.03 (m, 1H), 4.13 (dd, J = 7.0, 7.4 Hz, 2H), 3.92 (s, 3H), 3.62 (s, 3H), 2.55 (dt, J = 7.0, 7.4 Hz, 2H); ^{13}C NMR (acetone-d_6, 125 MHz) δ 168.8, 162.2, 154.6, 154.5, 150.9, 150.3, 146.3, 135.0, 130.3, 126.2, 117.3, 108.0, 105.3, 102.2, 101.8, 56.5, 53.2, 47.5, 32.8; IR (film) ν_{max} 2963, 1748, 1564, 1258 cm^{-1}; MALDIFTMS (DHB) m/z 402.1299 ($C_{19}H_{19}N_3O_7$ + H^+ requires 402.1301).

Methyl 4-(But-3-en-1-yl)-5-oxo-4,5-dihydro-3,7,9-trioxa-4-azadicyclopenta[*a*,*g*]naphthalene-2-carboxylate (9). A solution of **8** (7.1 mg, 0.018 mmol) in 1.5 mL of anhydrous, degassed 1,2-dichlorobenzene was warmed under Ar at 165−170 °C for 30 min. The reaction mixture was cooled and loaded directly onto SiO_2 (1 × 6 cm) equilibrated in hexanes. 1,2-Dichlorobenzene was eluted with hexanes, and the column was then eluted with 25% EtOAc/hexanes to provide **9** (4.8 mg,

78%) as a white solid: mp 182−184 °C (EtOAc−hexanes); ^{1}H NMR (acetone-d_6, 500 MHz) δ 7.96 (s, 1H), 7.65 (s, 1H), 7.48 (s, 1H), 6.20 (s, 2H), 5.93−5.85 (m, 1H), 5.04−5.00 (m, 1H), 4.98−4.95 (m, 1H), 4.35 (dd, J = 7.0, 7.3 Hz, 2H), 3.89 (s, 3H), 2.60 (dt, J = 7.0, 7.0 Hz, 2H); ^{13}C NMR (acetone-d_6, 125 MHz) δ 160.1, 158.8, 153.2, 150.8, 147.8, 147.6, 139.4, 135.1, 128.8, 118.9, 117.1, 115.3, 106.9, 102.8, 101.6, 51.6, 41.8, 32.7; IR (film) ν_{max} 2913, 1712, 1649, 1563, 1469 cm^{-1}; MALDIFTMS (DHB) m/z 342.0966 ($C_{18}H_{15}NO_6$ + H^+ requires 342.0978).

Methyl 4,5-Dihydro[1,3]dioxolo[4,5-*j*]pyrrolo[3,2,1-*de*]-phenanthridin-7-one-2-carboxylate (10). From **9**: A solution of **9** (4.8 mg, 0.014 mmol) in 2 mL of anhydrous, degassed 1,3,5-triisopropylbenzene was warmed under Ar at 230 °C for 18 h. The reaction mixture was cooled and loaded directly onto SiO_2 (1 × 6 cm) equilibrated in hexanes. 1,3,5-Triisopropylbenzene was eluted with hexanes, and the column was then eluted with 50% EtOAc/hexanes to provide **10** (3.5 mg, 77%) as a white solid: mp 277−278 °C (lit.[8] mp 280−281 °C); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.52 (s, 1H), 7.95 (d, J = 1.2 Hz, 1H), 7.89 (s, 1H), 7.62 (s, 1H), 6.14 (s, 2H), 4.51 (dd, J = 8.2, 8.5 Hz, 2H), 3.96 (s, 3H), 3.45 (dd, J = 8.2, 8.2 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 167.1, 159.8, 152.4, 149.0, 142.9, 131.2, 130.4, 125.5, 124.9, 122.9, 122.8, 116.2, 107.0, 102.4, 101.3, 52.4, 47.1, 27.2; IR (film) ν_{max} 2916, 1704, 1645, 1606, 1241 cm^{-1}; MALDIFTMS (DHB) m/z 324.0871 ($C_{18}H_{13}NO_5$ + H^+ requires 324.0866).

From **8**: A solution of **8** (8.5 mg, 0.021 mmol) in 1 mL of anhydrous, degassed 1,3,5-triisopropylbenzene was warmed under Ar at 230 °C for 24 h. The reaction mixture was cooled and loaded directly onto SiO_2 (1 × 5 cm) equilibrated in hexanes. 1,3,5-Triisopropylbenzene was eluted with hexanes, and the column was then eluted with 50% EtOAc/hexanes to provide **10** (4.9 mg, 72%) as a white solid.

Anhydrolycorin-7-one (1). According to the method of Padwa et al.,[8] a solution of **10** (3.0 mg, 0.009 mmol) in 0.5 mL of a 10% methanolic KOH solution was heated at 80 °C for 15 min. The solvent was removed under reduced pressure and the residue suspended in 0.5 mL of cold 10% aqueous HCl. After being stirred at 0 °C for 15 min, the suspension was filtered, and the filtrate was concentrated under reduced pressure and dried under vacuum. The residue was then dissolved in 1 mL of freshly distilled quinoline, treated with 8 mg of Cu bronze, and warmed at 225 °C under N_2 for 2.5 h. The reaction mixture was cooled, filtered through Celite (CH_2Cl_2 wash), washed with 10% aqueous HCl (3 × 5 mL), dried (Na_2SO_4), and concentrated under reduced pressure before being subjected to flash chromatography (SiO_2, 0.4 × 4 cm, 10% ethyl ether/CH_2Cl_2) to provide **1** (1.5 mg, 61%) as a white solid: mp 231−232 °C (lit.[1] mp 228−230 °C); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.93 (s, 1H), 7.75 (d, J = 8.1 Hz, 1H), 7.56 (s, 1H), 7.29 (d, J = 7.3 Hz, 1H), 7.19 (t, J = 7.7 Hz, 1H), 6.12 (s, 2H), 4.48 (t, J = 8.1 Hz, 2H), 3.43 (t, J = 8.5 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 160.0, 152.3, 148.9, 139.9, 131.3, 131.1, 124.3, 123.7, 123.6, 119.9, 117.2, 107.3, 102.5, 101.3, 47.0, 27.9; IR (film) ν_{max} 2923, 1608, 1557, 1254 cm^{-1}; MALDIFTMS (DHB) m/z 266.0821 ($C_{16}H_{11}NO_3$ + H^+ requires 266.0812).

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Supporting Information Available: Copies of ^{1}H NMR spectra of **4**−**6**, **8**−**10**, and **1** are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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