A Concise Synthesis of the Fredericamycin A DEF Ring System: [4 + 2] Cycloaddition Reactions of 1-Aza-1,3-butadienes

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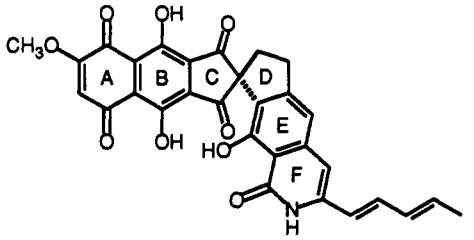
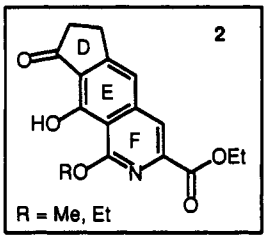
A concise four-step synthesis of the fredericamycin A DEF ring system is detailed based on the $LUMO_{diene}$-controlled Diels–Alder reaction of *N*-sulfonyl-1-azadiene **3** for introduction of the pyridone F ring.

Fredericamycin A (**1**), a structurally unique and potent antitumor antibiotic isolated from *Streptomyces griseus*,[1] has been the subject of extensive synthetic[2-4] and biological[5] studies since its unambiguous structure determination by single-crystal X-ray analysis[6] after extensive spectroscopic studies[7] failed to resolve tautomeric structures. Recent studies on the biological origin of the antitumor effects of **1**[5] and the complementary examination of the structural features of **1** responsible for its properties[3,5] coupled with the current lack of naturally-derived material have provided the incentive for the development of a practical total synthesis of fredericamycin A applicable to the preparation of key partial structures. In contrast to extensive efforts on the preparation of the fredericamycin A ABCD ring system including the key spiro[4.4]nonene segment,[3] only a limited number of studies have addressed the preparation of the lower DEF subunit.[2,4] Herein, we detail a concise, four-step synthesis of **2** constituting an appropriately functionalized skeletal precursor to the fredericamycin A DEF ring system based on a key $LUMO_{diene}$-controlled Diels–Alder reaction[8] of the *N*-sulfonyl-1-aza-1,3-butadiene **3**.[9]

The [4 + 2] cycloaddition reactions of **3**[9] with **4a–b** provided the sensitive adducts **5a–b** under pressure-promoted Diels–Alder reaction conditions, Scheme I. The strong electron-withdrawing C-2 ethoxycarbonyl group of **3** serves to lower the *N*-sulfonylazadiene LUMO to the extent that the modestly reactive dienophiles **4a–b** participate in productive Diels–Alder reactions with **3**. The sensitivity of **3** to tautomerization to the *N*-sulfonylenamine at 100 °C required for practical observation of a thermal cycloaddition was avoided by conducting the reaction under room-temperature, pressure-promoted (13 kbar) reaction conditions. Under such conditions, the sensitive [4 + 2] cycloadduct **5** could be isolated in excellent yield (82–85% based on **4**)[10] as a 1:1 mixture of C-3 diastereomers and was converted directly to pyridine **6** by subsequent base treatment (DBU, 70 °C, THF, 91%). In the examination of this sequence, the conversion of the starting oxime to **6** proved most convenient if crude **3**[10] was taken directly into the pressure-promoted [4 + 2] cycloaddition reaction with **4** and subsequently treated with DBU without the intermediate purification of **3** or **5**.



1 Fredericamycin A



Deprotonation of **6** with LDA carried out in a 0.01 M solution in THF (4.0 equiv of LDA, THF, −78 °C, 30–90 s) followed by immediate treatment of the metalated pyridine with cyclopentenone (5.0 equiv, −78 °C, 60 s, HOAc quench) provided **7** in excellent yield under carefully defined reaction conditions. A surprisingly rapid and predominate formation of dimeric and trimeric self-Claisen condensation products of **6b** was observed[11] in preliminary

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(10) Generally, we have found that only the anti oxime participates productively in the *O*- to *N*-sulfinyl rearrangement and only the *N*-sulfonyl *E*-diene (vs *Z*-diene) effectively reacts in the Diels–Alder reaction. The crude diene **3** prepared from a mixture of *Z,E*-olefins and mixture of syn,anti oximes was found to consist of a major (anti *N*-sulfonylimine, *E*-olefin) and two significant minor diene isomers. The conversion of **3** to **6b** based on crude **3** as the limiting reagent (1.0 equiv of **4b**) was 46% overall for the three steps.

(11) For the dimer Claisen condensation product of **6b**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.60 (1 H, s, C5-H), 7.51 (1 H, s, C5′-H), 4.55 (2 H, s, C4-CH_2CO), 4.50–4.27 (10 H, five q, J = 7.0 Hz, five CH_2CH_3), 2.31 (3 H, s, C4′-CH_3), 1.37–1.23 (15 H, five t, J = 7.0 Hz, five CH_2CH_3).

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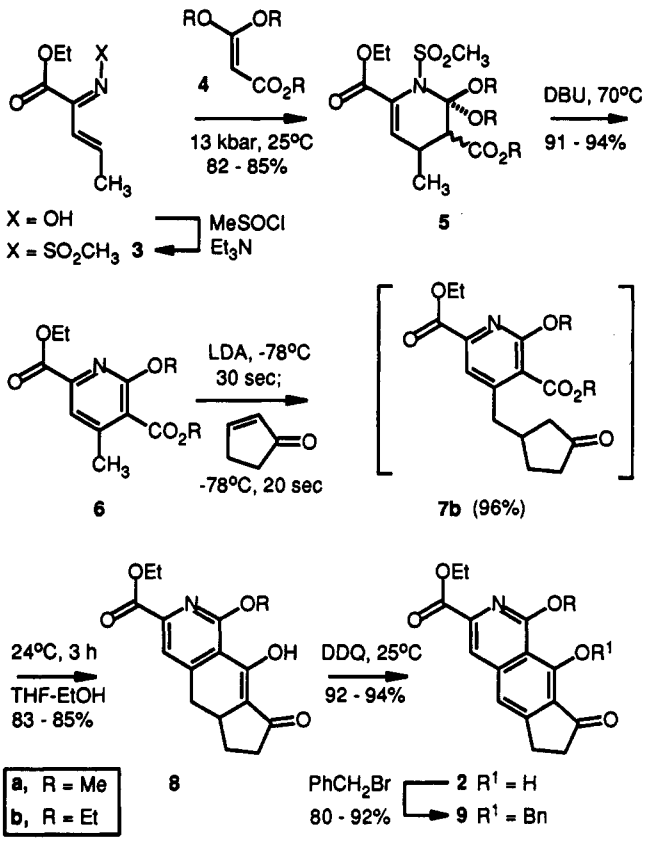
Scheme I



studies using slightly longer metalation periods (0.15 M **6b**, THF, 1.1 equiv of LDA, −78 °C, 5 min; 1.6 equiv of cyclopentenone, −78 °C, 1 h). Further, it was determined that the use of less base led to incomplete consumption of **6b** and the use of longer metalation periods with or without excess LDA at higher reaction concentrations led to significant or predominate self-Claisen condensation of the substrate. The initial Michael addition product **7b** was isolated (96%, HOAc quench), characterized, and subsequently carried into a Dieckmann condensation to provide **8b** (2.5 equiv NaH, THF, 0.2 equiv of EtOH, 25 °C). However, it proved more convenient to simply extend the reaction time employed to promote the Michael addition of **6** with cyclopentenone (−78 °C, 20–60 s to 24 °C, 3 h) to provide **8** (83–85%) directly, and the addition of EtOH (20 equiv) to the reaction mixture shortly after the addition of cyclopentenone (20–60 s) served to improve the overall conversion of **6** to **8**. DDQ oxidation of **8** to the naphthol **2** (92–94%) followed by protection of the free phenol provided **9** (92–94%). In practice, the preparation of **2** may be conducted with only the intermediate isolation and purification of **6** and without the deliberate purification or characterization of **5** and **7**–**8**. The extension of these efforts to the synthesis of fredericamycin A[2] and structurally related analogs is in progress and will be reported in due course.

Experimental Section

2,2-Dimethoxy-6-(ethoxycarbonyl)-3-(methoxycarbonyl)-4-methyl-1-(methylsulfonyl)-1,2,3,4-tetrahydropyridine (5a). A solution of ethyl (*E*)-2-(hydroximino)-3-pentenoate[9] (0.94 g, 6.0 mmol) in CCl_4 (60 mL) under Ar at 0 °C was treated sequentially with Et_3N (1.0 mL, 7.2 mmol, 1.2 equiv) and CH_3SOCl[12] (0.50 mL, 7.5 mmol, 1.2 equiv). The mixture was stirred at 0 °C (15 min) before the ice bath was removed, and stirring was continued at 25 °C (15 min). A white precipitate was formed upon the addition of CH_3SOCl, and the color of the reaction mixture changed from colorless to light yellow and finally light orange. The reaction mixture was decanted, and the precipitate was rinsed with CH_2Cl_2 (20 mL). The combined organic phase was extracted once with H_2O (70 mL), the organic layer was dried (Na_2SO_4) and filtered, and solvent was removed in vacuo.

Crude diene **3** was dissolved in CH_2Cl_2 (6.0 mL), treated with **4a**[13] (0.44 g, 3.0 mmol, 0.5 equiv), transferred to a Teflon tube, and sealed with brass clamps at both ends. The reaction vessel was placed in a Leco pressure reactor[14] and pressurized to 13 kbar (25 °C) for 67 h. After depressurization, the reaction mixture was chromatographed (SiO_2, 2.5 × 20 cm, 40% EtOAc–hexane) to afford **5a** (0.94 g, 1.10 g theoretical, 85%) as a 1:1 mixture of endo–exo isomers: viscous pale yellow oil; ^1H NMR ($CDCl_3$, 400 MHz) δ 6.43 and 6.17 (1 H, two d, J = 3.2 and 3.2 Hz, C5-H), 4.28 (2 H, two q, J = 7.1 and 7.1 Hz, CH_2CH_3), 3.75 and 3.73 (3 H, two s, CO_2CH_3), 3.39, 3.37 and 3.57, 3.32 (6 H, four s, two C2-OCH_3), 3.31 (3 H, s, SO_2CH_3), 3.31 and 3.14 (1 H, two d, J = 6.4 and 8.0 Hz, C3-H), 2.94 and 2.83 (1 H, two ddq, J = 3.2, 6.4, 7.2 and 3.2, 8.0, 7.6 Hz, C4-H), 1.33 and 1.34 (3 H, two t, J = 7.1 and 7.1 Hz, CH_2CH_3), 1.11 and 1.19 (3 H, two d, J = 7.2 and 7.6 Hz, C4-CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.5 and 168.0 (e, CO_2R), 163.8 and 164.2 (e, CO_2R), 132.5 and 129.1 (o, C5), 127.3 and 129.1 (e, C6), 107.7 and 107.6 (e, C2), 61.04 and 60.98 (e, CH_2CH_3), 53.4, 49.7 and 48.1 (o, C2-OCH_3), 52.2 and 49.2 (o, C3), 51.8 and 50.1 (o, CO_2CH_3), 43.84 and 43.79 (o, SO_2CH_3), 33.7 and 31.4 (o, C4), 17.9 (o, C4-CH_3), 14.7 and 13.9 (o, CH_2CH_3); IR (neat) ν_{max} 2955, 1731, 1652, 1437, 1334, 1278, 1253, 1161, 1085, 1045, 970, 778, 748, 736 cm^{-1}; FABHRMS (NBA) m/e 366.1223 ($M + H^+$, $C_{14}H_{23}NO_8S$ requires 366.1223).

3,6-Bis(ethoxycarbonyl)-2,2-diethoxy-4-methyl-1-(methylsulfonyl)-1,2,3,4-tetrahydropyridine (5b). Crude diene **3** (6.1 mmol) generated as detailed above was dissolved in CH_2Cl_2 (7.0 mL), treated with **4b**[13] (0.35 mL, 1.86 mmol, 0.30 equiv), transferred to a Teflon tube, and sealed with brass clamps at both ends. The reaction vessel was placed in a Leco pressure reactor[14] and pressurized to 13 kbar (25 °C) for 48 h. After depressurization, the reaction mixture was chromatographed (SiO_2, 2.5 × 20 cm, 30% EtOAc–hexane) to afford **5b** (0.61 g, 0.75 g theoretical, 82%) as a 1:1 mixture of endo–exo isomers: viscous pale yellow oil; ^1H NMR ($CDCl_3$, 400 MHz) δ 6.39 and 6.14 (1 H, two d, J = 3.3 and 2.9 Hz, C5-H), 4.30–3.54 (8 H, eight q, J = 7.0 Hz, four CH_2CH_3), 3.26 and 3.30 (3 H, two s, SO_2CH_3), 3.09 and 3.24 (1 H, two d, J = 8.2 and 6.9 Hz, C3-H), 2.92 and 2.83 (1 H, two ddq, J = 3.3, 8.2, 7.3 and 2.9, 6.9, 7.5 Hz, C4-H), 1.33–1.16 (12 H, eight t, J = 7.0 Hz, four CH_2CH_3), 1.09 and 1.19 (3 H, two d, J = 7.3 and 7.5 Hz, C4-CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.0 and 167.7 (e, CO_2Et), 164.0 and 164.4 (e, CO_2Et), 132.4 and 128.9 (o, C5), 127.5 and 129.3 (e, C6), 107.0 and 107.2 (e, C2), 61.0 (e, CH_2CH_3), 60.9 (e, CH_2CH_3), 58.3 and 57.8 (e, CH_2CH_3), 56.6 and 53.9 (e, CH_2CH_3), 50.0 (o, C3), 44.0 and 43.9 (o, SO_2CH_3), 34.0 and 31.6 (o, C4), 14.8 and 14.7 (o, $CHCH_3$), 14.4 and 14.3 (o, two CH_2CH_3), 13.9 (o, CH_2CH_3), 13.8 and 13.7 (o, CH_2CH_3); IR (neat) ν_{max} 2980, 1732, 1446, 1370, 1348, 1248, 1166, 1067, 1045, 967, 776 cm^{-1}; FABHRMS (NBA) m/e 408.1696 ($M + H^+$, $C_{17}H_{29}NO_8S$ requires 408.1692).

6-(Ethoxycarbonyl)-2-methoxy-3-(methoxycarbonyl)-4-methylpyridine (6a). A solution of **5a** (938 mg, 2.57 mmol) in THF (15 mL) at 25 °C was treated with DBU (0.9 mL, 5.90 mmol, 2.3 equiv). The mixture was stirred at 70 °C for 16 h under N_2 before it was concentrated in vacuo. Flash chromatography (SiO_2, 1.5 × 20 cm, 15% EtOAc–hexane) afforded **6a** (611 mg, 650 mg theoretical, 94%) as a white solid: mp 52–53 °C (Et_2O–hexane, white needles); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.58 (1 H, s, C5-H), 4.42 (2 H, q, J = 7.1 Hz, CH_2CH_3), 4.05 (3 H, s, OCH_3), 3.94 (3 H, s, OCH_3), 2.36 (3 H, s, C4-CH_3), 1.42 (3 H, t, J = 7.1 Hz, CH_2CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 166.7 (e), 164.5 (e), 160.5

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(13) Compound **4a** was prepared according to the procedure detailed for the preparation of **4b** (**4b** is available from Aldrich): Glickman, S. A.; Cope, A. C. *J. Am. Chem. Soc.* **1945**, *67*, 1017. For characterization of **4a**, see: Hoffmann, R. W.; Schäfer, W.; Bressel, U. *Chem. Ber.* **1972**, *105*, 2111.

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(e), 148.0 (e), 145.6 (e), 120.5 (e), 120.3 (o, C5), 61.6 (e, CH_2CH_3), 54.1 (o, OCH_3), 52.5 (o, OCH_3), 19.0 (o, C4-CH_3), 14.1 (o, CH_2CH_3); IR (KBr) ν_{max} 3038, 3015, 2994, 2976, 1747, 1715, 1588, 1490, 1465, 1450, 1372, 1348, 1291, 1240, 1193, 1144, 1114, 1089, 1032, 947, 932, 868, 829, 802, 778 cm^{-1}; FABHRMS (NBA) *m/e* 254.1038 (M + H^+, $C_{12}H_{15}NO_5$ requires 254.1028).

Anal. Calcd for $C_{12}H_{15}NO_5$: C, 56.91; H, 5.97; N, 5.53. Found: C, 56.86; H, 5.89; N, 5.89.

3,6-Bis(ethoxycarbonyl)-2-ethoxy-4-methylpyridine (6b). A solution of **5b** (527 mg, 1.29 mmol) in THF (12 mL) at 25 °C was treated with DBU (0.83 mL, 5.44 mmol, 4.2 equiv). The reaction mixture was stirred at 70 °C for 25 h under N_2 before it was concentrated in vacuo. Flash chromatography (SiO_2, 1.5 × 20 cm, 10% EtOAc–hexane) afforded **6b** (331 mg, 363 mg theoretical, 91%) as a pale yellow oil: ^1H NMR ($CDCl_3$, 400 MHz) δ 7.54 (1 H, s, C5-H), 4.48 (2 H, q, J = 7.1 Hz, CH_2CH_3), 4.41 (2 H, q, J = 7.1 Hz, CH_2CH_3), 4.40 (2 H, q, J = 7.2 Hz, CH_2CH_3), 2.34 (3 H, s, C4-CH_3), 1.40 (3 H, t, J = 7.1 Hz, CH_2CH_3), 1.38 (3 H, t, J = 7.2 Hz, CH_2CH_3), 1.37 (3 H, t, J = 7.1 Hz, CH_2CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 166.5 (e, CO_2Et), 164.8 (e, CO_2Et), 160.4 (e), 147.8 (e), 145.6 (e), 121.1 (e), 120.2 (o, C5), 62.7 (e, CH_2CH_3), 61.7 (e, CH_2CH_3), 61.6 (e, CH_2CH_3), 19.0 (o, C4-CH_3), 14.4 (o, CH_2CH_3), 14.3 (o, CH_2CH_3), 14.2 (o, CH_2CH_3); IR (neat) ν_{max} 2981, 1726, 1578, 1449, 1412, 1380, 1339, 1283, 1235, 1145, 1083, 1028, 850, 782 cm^{-1}; FABHRMS (NBA) *m/e* 282.1341 (M + H^+, $C_{14}H_{19}NO_5$ requires 282.1341).

3-(Ethoxycarbonyl)-9-hydroxy-1-methoxy-5,5a,7,8-tetrahydro-6*H*-cyclopent[*g*]isoquinolin-8-one (8a). Freshly distilled THF (390 mL) was introduced into a oven-dried 1-L flask under Ar. *i*Pr_2NH (2.83 mL, 20 mmol, 5.0 equiv) and *n*BuLi (6.4 mL of 2.5 M in hexane, 16.0 mmol, 4.0 equiv) were added at −20 °C with stirring. The solution was cooled to −78 °C and stirred for 10 min before 10 mL of 0.40 M solution of **6a** in THF (4.0 mmol, 1 equiv) was introduced by syringe over 10 s. The reaction mixture was stirred at −78 °C for an additional 80 s before 2-cyclopentenone (1.54 mL, 18.0 mmol, 4.5 equiv) was introduced. After 60 s, EtOH (5.0 mL) was added, the cold bath was removed, and the mixture was stirred at 25 °C (3.0 h) under Ar. The mixture was acidified with the addition of HOAc (5.0 mL), and the solution was concentrated in vacuo. The residue was diluted with H_2O (150 mL), extracted with CH_2Cl_2 (100 mL, 50 mL × 2), dried (Na_2SO_4), filtered, and concentrated. Flash chromatography (SiO_2, 3.0 × 20 cm, 25–40% EtOAc–hexane gradient elution) afforded **8a** (1.01 g, 1.21 g theoretical, 83%) as a yellow solid: mp 136–137 °C (EtOAc–hexane, yellow flakes); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.55 (1 H, s, C4-H), 4.42 (2 H, q, J = 7.1 Hz, CH_2CH_3), 4.12 (3 H, s, OCH_3), 3.12 (1 H, m, C6-*H*H), 3.04 (1 H, dd, J = 6.0, 15.0 Hz, C7-*H*H), 2.66 (1 H, app t, J = 15.0 Hz, C7-H*H*), 2.49 (2 H, m, C5-H_2), 2.36 (1 H, ddt, J = 3.2, 12.8, 7.2 Hz, C6-H*H*), 1.63 (1 H, tt, J = 11.7, 9.2 Hz, C5a-H), 1.42 (3 H, t, J = 7.1 Hz, CH_2CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 203.9 (e, C8), 164.5 (e, CO_2Et), 162.8 (e), 161.7 (e), 153.7 (e), 147.0 (e), 118.9 (o, C4), 116.5 (e), 112.8 (e), 61.9 (e, CH_2CH_3), 54.4 (o, OCH_3), 37.4 (e, CH_2), 37.1 (e, CH_2), 33.6 (o, C5a), 28.8 (e, CH_2), 14.2 (o, CH_2CH_3); IR (KBr) ν_{max} 3069, 2944, 2864, 1716, 1662, 1609, 1553, 1466, 1386, 1257 cm^{-1}; FABHRMS (NBA) *m/e* 304.1188 (M + H^+, $C_{16}H_{17}NO_5$ requires 304.1185).

Anal. Calcd for $C_{16}H_{17}NO_5$: C, 63.36; H, 5.65; N, 4.62. Found: C, 63.21; H, 5.71; N, 5.00.

1-Ethoxy-3-(ethoxycarbonyl)-5,5a,7,8-tetrahydro-9-hydroxy-6*H*-cyclopent[*g*]isoquinolin-8-one (8b). Freshly distilled THF (90 mL) was introduced into a flame-dried 250-mL flask under Ar through a syringe. *i*Pr_2NH (0.67 mL, 4.8 mmol, 4.8 equiv) and *n*BuLi (1.60 mL of 2.5 M in hexane, 4.0 mmol, 4.0 equiv) were added at −20 °C with stirring. The solution was cooled to −78 °C and stirred for 10 min before 10 mL of a 0.10 M solution of **6** in THF (1.0 mmol, 1 equiv) was introduced by syringe over 5 s. The reaction mixture was stirred at −78 °C for an additional 25 s before 2-cyclopentenone (0.40 mL, 5.0 mmol, 5.0 equiv) was introduced. Immediately following the addition, the reaction mixture turned from blood-red to bright yellow. After 20 s, EtOH (1.0 mL) was added, the cold bath was removed, and the mixture was stirred at 25 °C (3.0 h) under Ar. The mixture was acidified with the addition of HOAc (1.0 mL), diluted with saturated aqueous NH_4Cl (150 mL), extracted with CH_2Cl_2 (100 mL, 50 mL × 2), dried (Na_2SO_4), filtered, and concentrated. Flash chromatography (SiO_2, 1.5 × 20 cm, 25–40% EtOAc–hexane gradient elution) afforded **8b** (271 mg, 317 mg theoretical, 85%) as a bright yellow solid: mp 125–126 °C (EtOAc–hexane, yellow flakes); ^1H NMR ($CDCl_3$ 400 MHz) δ 9.48 (1 H, br s, OH), 7.53 (1 H, s, C4-H), 4.59 (2 H, q, J = 7.1 Hz, CH_2CH_3), 4.42 (2 H, q, J = 7.1 Hz, CH_2CH_3), 3.11 (1 H, m, C6-*H*H), 3.03 (1 H, dd, J = 6.0, 15.2 Hz, C7-*H*H), 2.62 (1 H, app t, J = 15.2 Hz, C7-H*H*), 2.49 (2 H, m, C5-H_2), 2.36 (1 H, ddt, J = 3.2, 12.8, 7.2 Hz, C6-H*H*), 1.63 (1 H, tt, J = 11.2, 6.8 Hz, C5a-H), 1.46 (3 H, t, J = 7.2 Hz, CH_2CH_3), 1.42 (3 H, t, J = 7.1 Hz, CH_2CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 204.1 (e, C8), 164.5 (e, CO_2Et), 162.3 (e), 161.4 (e), 153.5 (e), 147.0 (e), 118.5 (o, C4), 116.4 (e), 112.7 (e), 63.0 (e, CH_2CH_3), 61.8 (e, CH_2CH_3), 37.5 (e, CH_2), 37.0 (e, CH_2), 33.6 (o, C5a), 28.7 (e, CH_2), 14.4 (o, CH_2CH_3), 14.2 (o, CH_2CH_3); IR (KBr) ν_{max} 3355, 2980, 1734, 1654, 1624, 1420, 1384, 1331, 1248, 1234, 1057 cm^{-1}; FABHRMS (NBA/NaI) *m/e* 340.1161 (M + Na^+, $C_{17}H_{19}NO_5$ requires 340.1161).

Anal. Calcd for $C_{17}H_{19}NO_5$: C, 64.34; H, 6.03; N, 4.41. Found: C, 64.45; H, 6.02; N, 4.61.

Compound **7b** was isolated by quenching the reaction mixture with HOAc (1.0 mL) 20 s after the addition of 2-cyclopentenone followed by workup as detailed for **8b** to afford **7b** (96%) as a pale yellow oil: ^1H NMR ($CDCl_3$, 400 MHz) δ 7.54 (1 H, s, C5′-H), 4.48 (2 H, q, J = 7.1 Hz, CH_2CH_3), 4.41 (2 H, q, J = 7.1 Hz, CH_2CH_3), 4.40 (2 H, q, J = 7.2 Hz, CH_2CH_3), 2.77 (1 H, dd, J = 13.6, 7.7 Hz, C3-C*H*H), 2.73 (1 H, dd, J = 13.6, 7.7 Hz, C3-CH*H*), 2.53 (1 H, m, C5-*H*H), 2.32 (2 H, m, C4-H_2), 2.16 (1 H, dd, J = 18.6, 9.0 Hz, C2-*H*H), 2.07 (1 H, m, C2-H*H*), 1.91 (1 H, ddd, J = 18.2, 10.1, 1.1 Hz, C5-H*H*), 1.61 (1 H, m, C3-H), 1.41 (3 H, t, J = 7.1 Hz, CH_2CH_3), 1.38 (3 H, t, J = 7.2 Hz, CH_2CH_3), 1.37 (3 H, J = 7.1 Hz, CH_2CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 217.9 (e, C1), 166.4 (e, CO_2Et), 164.6 (e, CO_2Et), 160.5 (e), 149.5 (e), 145.9 (e), 121.0 (e), 118.9 (o, C5′), 62.8 (e, CH_2CH_3), 61.8 (e, CH_2CH_3), 61.7 (e, CH_2CH_3), 44.6 (e, C3-CH_2), 38.2 (e, CH_2CO), 38.1 (e, $COCH_2$), 37.6 (o, C3), 29.1 (e, C4), 14.3 (o, CH_2CH_3), 14.2 (o, CH_2CH_3), 14.17 (o, CH_2CH_3); IR (neat) ν_{max} 2982, 1733, 1575, 1418, 1381, 1342, 1282, 1245, 1148, 1082, 850 cm^{-1}; FABHRMS (NBA/CsI) *m/e* 496.0716 (M + Cs^+, $C_{19}H_{25}NO_6$ requires 496.0736).

3-(Ethoxycarbonyl)-9-hydroxy-1-methoxy-7,8-dihydro-6*H*-cyclopent[*g*]isoquinolin-8-one (2a). A solution of **8a** (305 mg, 1.0 mmol) in CH_2Cl_2 (10 mL) at 25 °C was treated with DDQ (252 mg, 1.11 mmol, 1.1 equiv) portionwise. The reaction mixture was allowed to stir at 25 °C for 10 min before it was filtered (CH_2Cl_2 wash of the precipitate) and concentrated in vacuo. Flash chromatography (SiO_2, 3 × 25 cm, 0–20% EtOAc–CH_2Cl_2 gradient elution) afforded **2a** (279 mg, 303 mg theoretical, 92%) as an off-white solid: mp 186–187 °C (CH_2Cl_2–EtOAc, fluffy solid); ^1H NMR ($CDCl_3$, 400 MHz) δ 10.66 (1 H, s, OH), 7.92 (1 H, s, C4-H), 7.25 (1 H, s, C5-H), 4.43 (2 H, q, J = 7.2 Hz, CH_2CH_3), 4.24 (3 H, s, OCH_3), 3.20 (2 H, m, CH_2CH_2), 2.78 (2 H, m, CH_2CH_2), 1.43 (3 H, t, J = 7.2 Hz, CH_2CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 207.4 (e, C8), 165.0 (e), 162.4 (e), 156.9 (e), 154.7 (e), 144.7 (e), 141.5 (e), 120.7 (e), 118.4 (o, C4), 115.4 (o, C5), 109.6 (e), 61.7 (e, CH_2CH_3), 54.5 (o, OCH_3), 36.3 (e, CH_2), 25.4 (e, CH_2), 14.2 (o, CH_2CH_3); IR (KBr) ν_{max} 3368, 3080, 2924, 1741, 1706, 1636, 1597, 1365, 1242, 1104 cm^{-1}; FABHRMS (NBA) *m/e* 302.1019 (M + H^+, $C_{16}H_{15}NO_5$ requires 302.1028).

Anal. Calcd for $C_{16}H_{15}NO_5$: C, 63.78; H, 5.02; N, 4.65. Found: C, 63.69; H, 4.82; N, 4.74.

1-Ethoxy-3-(ethoxycarbonyl)-7,8-dihydro-9-hydroxy-6*H*-cyclopent[*g*]isoquinolin-8-one (2b). A solution of **8b** (304 mg, 0.96 mmol) in CH_2Cl_2 (10 mL) at 25 °C was treated with DDQ (240 mg, 1.0 mmol, 1.1 equiv) portionwise. The reaction mixture was allowed to stir at 25 °C for 10 min before it was filtered (CH_2Cl_2 wash of the precipitate) and concentrated in vacuo. Flash chromatography (SiO_2, 3.0 × 20 cm, 25% EtOAc–hexane) afforded **2b** (283 mg, 302 mg theoretical, 94%) as an off-white solid: mp 188–189 °C (CH_2Cl_2–EtOAc, fluffy solid); ^1H NMR ($CDCl_3$, 400 MHz) δ 10.66 (1 H, s, OH), 7.98 (1 H, s, C4-H), 7.30 (1 H, s, C5-H), 4.77 (2 H, q, J = 7.2 Hz, CH_2CH_3), 4.46 (2 H, q, J = 7.2 Hz, CH_2CH_3), 3.24 (2 H, m, CH_2CH_2), 2.80 (2 H, m, CH_2CH_2), 1.56 (3 H, t, J = 7.2 Hz, CH_2CH_3), 1.45 (3 H, t, J = 7.2 Hz, CH_2CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 206.0 (e, C8), 165.1 (e, CO_2Et), 162.1 (e), 156.5 (e), 155.5 (e), 144.4 (e), 141.4 (e), 121.1 (e), 118.5 (o, C4), 115.4 (o, C5), 109.6 (e), 63.8 (e, CH_2CH_3), 61.7 (e, CH_2CH_3), 36.6 (e, CH_2CH_2), 25.5 (e, CH_2CH_2), 14.33 (o, CH_2CH_3), 14.29 (o,

CH_2CH_3); IR (KBr) ν_{max} 3364, 3082, 2985, 1735, 1707, 1635, 1347, 1242, 1100 cm^{-1}; FABHRMS (NBA/NaI) m/e 338.1011 ($M + Na^+$, $C_{17}H_{17}NO_5$ requires 338.1004).

Anal. Calcd for $C_{17}H_{17}NO_5$: C, 64.75; H, 5.43; N, 4.44. Found: C, 64.53; H, 5.59; N, 4.47.

9-(Benzyloxy)-3-(ethoxycarbonyl)-1-methoxy-7,8-dihydro-6*H*-cyclopent[*g*]isoquinolin-8-one (9a). A solution of **2a** (72 mg, 0.24 mmol) in DMF (2.0 mL) was treated sequentially with K_2CO_3 (100 mg, 0.7 mmol, 3.0 equiv), Bu_4NI (10 mg, 0.25 mmol, 0.1 equiv), and $PhCH_2Br$ (100 μL, 0.75 mmol, 3.0 equiv). The reaction mixture was stirred at 70 °C (6 h) before it was cooled to 25 °C, diluted with H_2O (30 mL), extracted with CH_2Cl_2 (20 mL × 3), dried (Na_2SO_4), filtered, and concentrated in vacuo. Flash chromatography (SiO_2, 1.5 × 20 cm, 20% EtOAc–hexane) afforded **9a** (88 mg, 94 mg theoretical, 94%) as an off-white solid: mp 157–158 °C (CH_2Cl_2–EtOAc, off white solid); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.97 (1 H, s, C4-H), 7.66 (2 H, d, J = 7.2 Hz, Ph), 7.57 (1 H, s, C5-H), 7.41 (2 H, t, J = 7.2 Hz, Ph), 7.34 (1 H, t, J = 7.2 Hz, Ph), 5.19 (2 H, s, $PhCH_2$), 4.44 (2 H, q, J = 7.2 Hz, CH_2CH_3), 4.12 (3 H, s, OCH_3), 3.24 (2 H, m, CH_2CH_2), 2.77 (2 H, m, CH_2CH_2), 1.44 (3 H, t, J = 7.2 Hz, CH_2CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 203.2 (e, C8), 165.3 (e), 162.4 (e), 156.6 (e), 155.3 (e), 144.1 (e), 140.9 (e), 136.9 (e), 130.2 (e), 128.7 (o, two aromatic CH), 128.4 (o, two aromatic CH), 128.1 (o), 120.5 (o), 117.7 (o), 115.5 (e), 77.7 (e, $PhCH_2$), 61.6 (e, CH_2CH_3), 54.1 (o, OCH_3), 37.2 (e, CH_2CH_2), 25.1 (e, CH_2CH_2), 14.2 (o, CH_2CH_3); IR (KBr) ν_{max} 2946, 1735, 1712, 1616, 1567, 1348, 1257, 1115 cm^{-1}; FABHRMS (NBA) m/e 392.1498 ($M + H^+$, $C_{23}H_{21}NO_5$ requires 392.1498).

Anal. Calcd for $C_{23}H_{21}NO_5$: C, 70.58; H, 5.41; N, 3.58. Found: C, 70.19; H, 5.12; N, 3.58.

9-(Benzyloxy)-1-ethoxy-3-(ethoxycarbonyl)-7,8-dihydro-6*H*-cyclopent[*g*]isoquinolin-8-one (9b). A solution of **2b** (270 mg, 0.86 mmol) in DMF (15.0 mL) was treated sequentially with K_2CO_3 (1.0 g, 7.2 mmol, 8.4 equiv), Bu_4NI (50 mg, 0.14 mmol, 0.16 equiv), and $PhCH_2Br$ (300 μL, 2.5 mmol, 2.9 equiv). The reaction mixture was stirred at 25 °C (38 h) before it was diluted with H_2O (100 mL), extracted with CH_2Cl_2 (60 mL × 3), dried (Na_2SO_4), filtered, and concentrated in vacuo. Flash chromatography (SiO_2, 3 × 12 cm, 20% EtOAc–hexane) afforded **9b** (318 mg, 347 mg theoretical, 92%) as an off-white solid: mp 159–160 °C (CH_2Cl_2–EtOAc, pale yellow plates); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.98 (1 H, s, C4-H), 7.64 (2 H, d, J = 7.0 Hz, Ph), 7.59 (1 H, s, C5-H), 7.39 (2 H, t, J = 7.0 Hz, Ph), 7.33 (1 H, t, J = 7.0 Hz, Ph), 5.26 (2 H, s, $PhCH_2$), 4.63 (2 H, q, J = 7.0 Hz, CH_2CH_3), 4.45 (2 H, q, J = 7.0 Hz, CH_2CH_3), 3.26 (2 H, m, CH_2CH_2), 2.78 (2 H, m, CH_2CH_2), 1.45 (3 H, t, J = 7.0 Hz, CH_2CH_3), 1.31 (3 H, t, J = 7.0 Hz, CH_2CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 203.2 (e, C8), 165.4 (e, CO_2Et), 162.2 (e), 157.0 (e), 155.2 (e), 144.3 (e), 141.1 (e), 137.0 (e), 128.4 (o, two aromatic CH), 128.2 (o, two aromatic CH), 128.0 (o), 120.4 (o), 117.5 (o), 115.6 (e), 96.1 (e), 77.8 (e, CH_2Ph), 63.0 (e, CH_2CH_3), 61.6 (e, CH_2CH_3), 37.2 (e, CH_2CH_3), 25.2 (e, CH_2CH_2), 14.3 (o, CH_2CH_3), 14.26 (o, CH_2CH_3); IR (KBr) ν_{max} 2929, 1734, 1706, 1616, 1559, 1333, 1228, 1105, 1043 cm^{-1}; FABHRMS (NBA/CsI) m/e 538.0615 ($M + Cs^+$, $C_{24}H_{23}NO_5$ requires 538.0631).

Anal. Calcd for $C_{24}H_{23}NO_5$: C, 71.10; H, 5.72; N, 3.45. Found: C, 71.15; H, 5.71; N, 3.44.

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Supplementary Material Available: ^1H NMR of **5a–b**, **6b**, **7b**, and **9b** (5 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

Synthesis of (–)-Slaframine and Related Indolizidines

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An enantioselective synthesis of the indolizidine alkaloid (–)-slaframine **1** is reported. Reductive double cyclization of the azido epoxy tosylate **48** afforded the indolizidine **52**, which was converted to (–)-slaframine in two steps. The cyclization substrate **48** was prepared in optically pure form from L-glutamic acid. A similar sequence starting with the epoxide **49** allowed the synthesis of (–)-1,8a-diepislaframine **56**. Other routes to slaframine were investigated, often using an intramolecular cycloaddition of an azide with an alkene as a key step. Although these routes did not produce slaframine, they illustrated novel and efficient methods for the assembly of the indolizidine skeleton. Cyclization of the azidodiene **20** afforded the indolizidine **21** in one step as a single diastereomer, presumably a result of a chairlike transition state in the initial dipolar cycloaddition. Desulfurization and deprotection produced (–)-8a-epidesacetoxyslaframine **27**. Cyclopropylimine rearrangement of **30** gave the indolizidine **31**, which was also converted into (–)-8a-epidesacetoxyslaframine **27**. Dipolar cycloaddition of **38** gave the 1-pyrroline **39**, which was converted to the indolizidine **40** in one operation using Evans' double alkylation of the 1-metalloenamine derivative of **40**. Attempted oxidation of **40** to the ketone **41** was unsuccessful, precluding a reductive amination approach to slaframine.

Forages contaminated with the fungus *Rhizoctonia leguminicola* are responsible for a disease in ruminants known as "black patch".[1] The most obvious symptom associated with ingestion of contaminated feed is excessive salivation, which is thought to be caused by the alkaloid slaframine **1**.[1-5] It has been proposed that slaframine is oxidized in the liver to an active metabolite which is a muscarinic agonist.[1] Beyond its potential in the treatment of diseases involving cholinergic dysfunction, slaframine has been under active investigation for its potentially

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