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A Novel Biomimetic Route to the 3-Acyl-5-hydroxy-3-pyrrolin-2-one and 3-Acyl-3,4-epoxy-5-hydroxypyrrolidin-2-one Ring Systems

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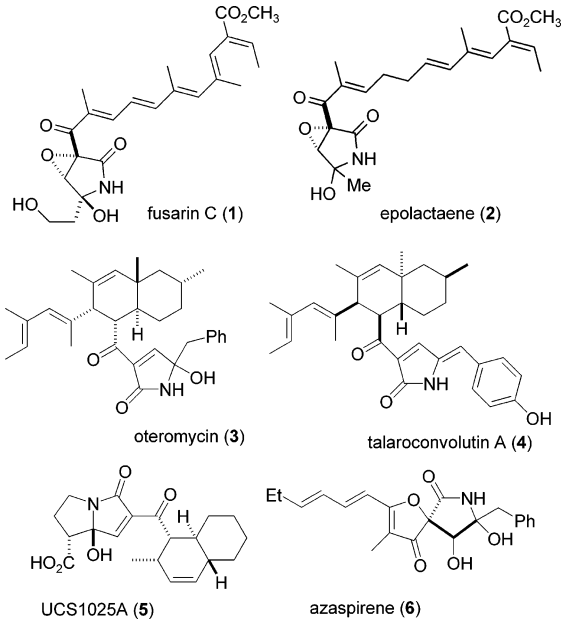
Received August 10, 2004

Abstract: Modified Moffat oxidation of alcohols **17**, **22**, and **25** afforded aldehydes that underwent intramolecular aldol reactions on treatment with a NaOH solution to yield 4-pyrrolin-2-ones **16**, **23**, and **26**. Oxidation with DMDO at −40 °C provided 3-acyl-5-hydroxy-3-pyrrolin-2-ones **18**, **24**, and **27** with the ring system of oteromycin (**3**), UCS1025A (**5**), and related natural products. Further oxidation of **18** yielded 3-acyl-3,4-epoxy-5-hydroxy-pyrrolidin-2-one **19** with the ring system of fusarin C (**1**) and epolactaene (**2**). Dehydration of **18** afforded **20** with the talaroconvolutin A (**4**) ring system.

Over the past twenty years, a wide variety of biologically active natural products have been isolated that contain either the 3-acyl-5-hydroxy-3-pyrrolin-2-one or the 3-acyl-3,4-epoxy-5-hydroxypyrrolidin-2-one moiety. These include fusarin C (**1**) and congeners,[1] epolactaene (**2**),[2] oteromycin (**3**),[3] talaroconvolutin A (**4**), ZG-1494α, and congeners,[4] UCS1025A (**5**),[5] azaspirene (**6**) and CJ-16,367,[6] NG-391,[7] lucilacataene,[8] L-755,807,[9] pramanicin,[10] pyrrocidine A,[11] and PI-090[12] and acosalipyrrolidinone A (see Chart 1).[13] Total syntheses of epolactaene (**2**),[14] NG-391,[15] azaspirene (**6**),[16] PI-091,[17] pramanicin,[18] and the pyrrolidinone moieties of fusarin C (**1**)[19] and L-755,807[20] have been reported. Kobayashi reported that both enantiomers of epolactaene (**2**) and an analogue with a simple dodecanoyl side chain, lacking the two methyl groups, ester, and four double bonds of **2**, had comparable activity to **2** in inhibiting mammalian DNA polymerase α and *β*, and human DNA topoisomerase II and in inducing apoptosis in BALL-1 cells. This suggests that the pyrrolidinone moiety is largely responsible for the biological activity of these compounds.[14g,21] The pyrrolidinone moiety is usually constructed by an intramolecular aldol reaction of a dicarbonyl compound with a protected α-hydroxyaldehyde followed by ring closure of a keto amide to form the 5-hydroxy-3-pyrrol-2-one or 3,4-

CHART 1



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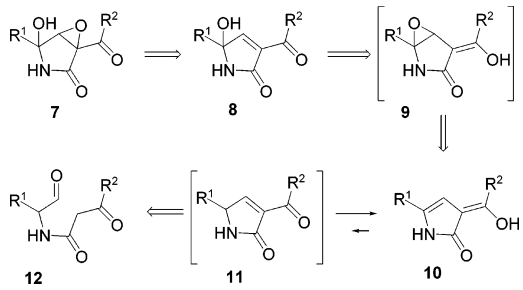
10.1021/jo048605r CCC: $27.50
Published on Web 11/06/2004

epoxy-5-hydroxypyrroldin-2-one.[14a−d,f,15,20] Oxidations of furans to give pyrrolidinones have also been used.[17,19] Kobayashi has developed a general procedure using the aldol reaction of a lactone-derived oxiranyl anion to construct the skeleton.[14e,g]

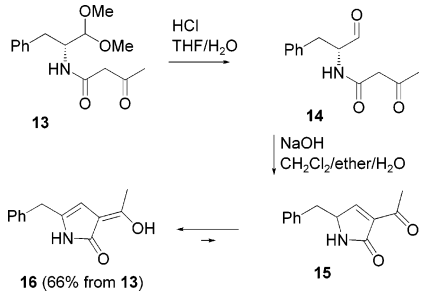
We envisaged that the functionalized pyrrolidinone ring system could be easily constructed by a biomimetic route that has not been previously reported.[22] 3,4-Epoxypyrrolidin-2-one (**7**) should be accessible by oxidation of 3-pyrrolin-2-one **8**, which should be formed spontaneously from epoxide **9**, which in turn should be accessible by oxidation of enamide **10**. An intramolecular aldol reaction of aldehyde **12** should give adduct **11**, which will tautomerize to the more stable enamide **10** (see Scheme 1).

SCHEME 1. Retrosynthesis of Epoxypyrrolidinones and Pyrrolinones



As part of their model studies for the synthesis of cytochalasins, Schmidlin and Tamm prepared **16** in 66% yield by hydrolysis of acetal **13** with HCl in aqueous THF, followed by treatment of freshly prepared aldehyde **14** in a CH_2Cl_2/ether mixture with 2 M aqueous NaOH to give **15**, which tautomerized to **16** (see Scheme 2).[23] We

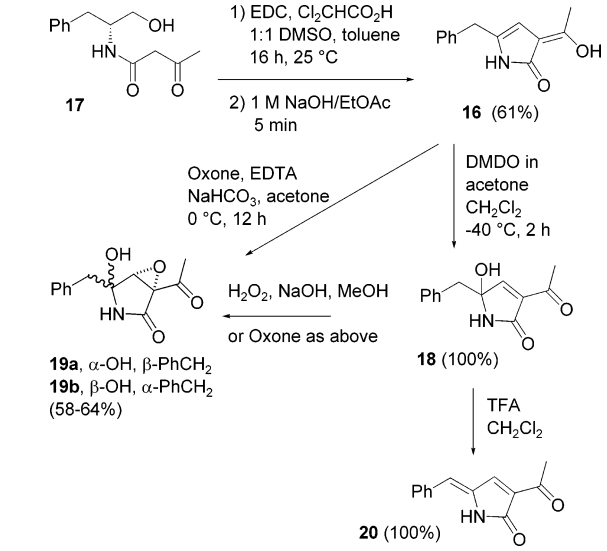
SCHEME 2. Schmidlin and Tamm's Synthesis of 16



chose to explore a variation of this route in which the aldehyde was constructed by oxidation of an alcohol rather than by hydrolysis of the somewhat inaccessible acetal.

Reaction of phenylalaninol with diketene and Et_3N in CH_2Cl_2 for 16 h at 25 °C afforded 72% of acetoacetamide **17** (see Scheme 3). Attempts to improve the yield by using more diketene led to mixtures of **17** and the bis ester amide that could be hydrolyzed with K_2CO_3 in MeOH to give comparable yields of **17**. Modified Moffat oxidation[24] of **17** with EDC and Cl_2CHCO_2H in 1:1 DMSO/toluene provided aldehyde **14** that was taken up in EtOAc and shaken for 5 min with 1 M aqueous NaOH to give 61% of **16** after recrystallization. We were delighted to find that oxidation of **16** with dimethyldioxirane (DMDO)[25] in acetone/CH_2Cl_2 at −40 °C for 2 h gave the desired 3-pyrrolin-2-one **18** in quantitative yield. Further oxidation of **18** with H_2O_2 and NaOH in MeOH for 2 h at 25 °C afforded a 64% yield of a 1:3 mixture of fusarin C (**1**) and epolactaene (**2**) models **19a** and **19b**, whose stereochemistry was established by NOE experiments. Alternatively, oxidation of **18** with DMDO generated in situ with Oxone, Na_2EDTA, and $NaHCO_3$ in acetone at 0 °C[26] for 12 h provided a mixture of **19a** and **19b**. The conversion of **16** to **19** could be accomplished in a single step by oxidation with DMDO generated in situ as described above to give exclusively **19a**, which isomerized to give a 3:1 mixture of **19a** and **19b** in 58% yield during flash chromatography on silica gel. Attempted asymmetric oxidation of **16** with Shi's fructose-derived ketone[27] afforded a 3:1 mixture of **19a** and **19b** in 40% yield with $[\alpha]_D$ −2.6, suggesting that the epoxidation occurred with only modest enantioselectivity. Finally, treatment of **18** with TFA in CH_2Cl_2 for 12 h gave diene **20** with the talaroconvolutin A (**4**)[4a] ring system in quantitative yield.

SCHEME 3. Synthesis of 18, 19, and 20



3-Oxoamide **22** with a more complex side chain was prepared in 62% yield by heating **21**,[28] which was prepared from Meldrum's acid and cyclohexanecarbonyl

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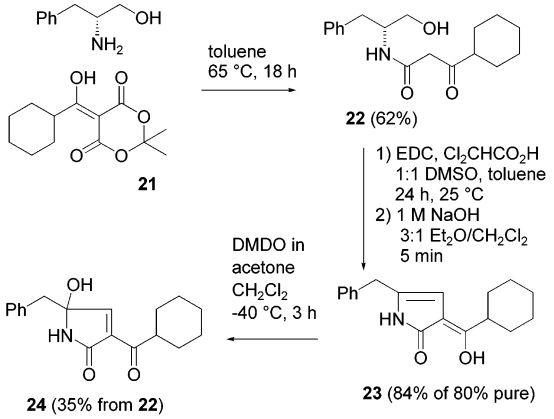
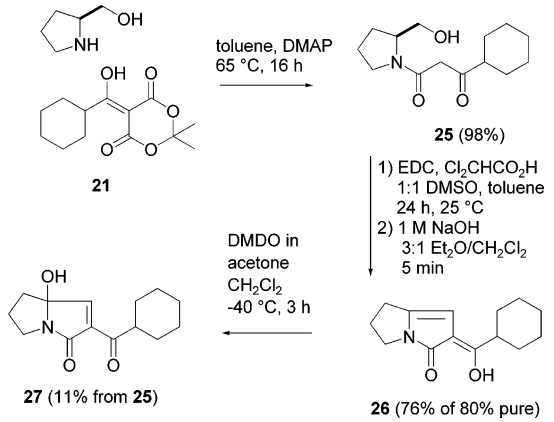
chloride, with phenylalaninol in toluene at 65 °C for 18 h (see Scheme 4).[29] The modified Moffat oxidation and aldol reaction afforded crude **23**, which was treated with DMDO[25] at −40 °C to provide oteromycin (**3**) model **24** in 35% overall yield from **22**. The lower yields in this sequence result in part from purification difficulties. Both **16** and **23** are not very stable to chromatography, but **16** can easily be purified by recrystallization while the oily **23** was carried on without purification.

SCHEME 4. Synthesis of Oteromycin Model 24



Finally, we prepared UCS1025A (**5**) model **27** from **21** and prolinol. Heating in toluene with DMAP afforded **25** in 98% yield (see Scheme 5). Modified Moffat oxidation and aldol condensation gave crude **26**, which was treated with DMDO[25] at −40 °C to provide **27** in 11% yield from **25**. The spectral data for **27** correspond well with those for the open form of UCS1025A (**5**).[5]

SCHEME 5. Synthesis of UCS1025A Model 27



In conclusion, we have developed a short and efficient route to 3-acyl-5-hydroxy-3-pyrrolin-2-ones **18**, **24**, and **27** with the ring system of oteromycin (**3**), UCS1025A (**5**), and related natural products and 3-acyl-3,4-epoxy-5-hydroxypyrrolidin-2-one **19** with the ring system of fusarin C (**1**) and epolactaene (**2**). Modified Moffat oxidation of alcohols **17**, **22**, and **25** afforded aldehydes that underwent intramolecular aldol reactions on treatment with a NaOH solution to give 4-pyrrolin-2-ones **16**, **23**, and **26**. Oxidation with DMDO at −40 °C provided **18**, **24**, and **27** and further oxidation of **18** yielded 3-acyl-3,4-epoxy-5-hydroxypyrrolidin-2-one **19**. Dehydration of **18** afforded **20** with the talaroconvolutin A (**4**) ring system.

Experimental Section

General. NMR spectra were recorded at 400 MHz in $CDCl_3$. Chemical shifts are reported in δ and coupling constants in Hz. IR spectra are reported in cm^{-1}.

***N*-(1-Hydroxymethyl-2-phenylethyl)-3-oxobutyramide (17).** To a stirred solution of (*R*)-(+)-2-amino-3-phenyl-1-propanol (0.51 g, 3.4 mmol) and Et_3N (0.61 mL, 4.4 mmol) in CH_2Cl_2 (7.6 mL) at 0 °C was added a solution of diketene (0.24 mL, 3.1 mmol) in CH_2Cl_2 (3.1 mL). The reaction was stirred at 25 °C for 16 h and a solution of 5% aqueous HCl (10 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (5 × 15 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, and concentrated to give a red oil. Flash chromatography on silica gel (24:1 CH_2Cl_2/MeOH) gave 520 mg (72%) of **17** as a white solid: mp 74−76 °C; ^{1}H NMR 7.33−7.22 (m, 5), 7.12−7.10 (br, 1, NH), 4.24−4.20 (m, 1), 3.74−3.70 (m, 1), 3.60 (ddd, 1, J = 11.0, 5.5, 5.5), 3.41 (d, 1, J = 17.1), 3.36 (d, 1, J = 17.1), 2.92 (dd, 1, J = 14.0, 7.3), 2.85 (dd, 1, J = 14.0, 7.3), 2.55 (t, 1, J = 5.5, OH), 2.22 (s, 3); ^{13}C NMR 204.5, 166.1, 137.5, 129.2 (2 C), 128.5 (2 C), 126.6, 64.0, 53.1, 49.8, 37.0, 30.8; IR (KBr) 3500−3100, 1717, 1646; HRMS (DCI/NH_3) calcd for $C_{13}H_{18}NO_3$ (MH^+) 236.1287, found 236.1280.

Attempts to improve the yield by using more diketene led to mixtures ranging from 100:0 to 50:50 of **17** and the bis ester amide, which could be separated by flash chromatography on silica gel (99:1 to 24:1 CH_2Cl_2/MeOH). Selective hydrolysis of the bis ester amide was achieved with K_2CO_3 (6 equiv) in MeOH (0.1 M) for 12 h followed by treatment with 1 M HCl until the pH was neutral. The aqueous layer was extracted with EtOAc, washed with brine, dried over Na_2SO_4, and concentrated to give **17**. Flash chromatography on silica gel (24:1 CH_2Cl_2/MeOH) gave **17** as a white solid in 95−99% yield from the bis ester amide. The overall yield of **17** ranged from 65% to 72%.

***(Z)*-1,3-Dihydro-3-(1-hydroxyethylidene)-5-phenylmethyl-2*H*-pyrrol-2-one (16).** EDC (0.49 g, 2.55 mmol) and dichloroacetic acid (84 μL, 1.0 mmol) were added to a solution of **17** (0.12 g, 0.51 mmol) in toluene (3 mL) and DMSO (3 mL). The reaction was stirred at 25 °C for 16 h and 2 M aqueous HCl (6 mL) was added. The acidic aqueous layer was extracted with EtOAc (3 × 10 mL) to give a solution of the aldehyde.

The EtOAc solution of the crude aldehyde was shaken with 1 M NaOH (40 mL) for 5 min. The basic aqueous layer was extracted with Et_2O (4 × 40 mL) and the combined organic layers were washed with brine (100 mL), dried over $MgSO_4$, and concentrated to give a yellow-green solid. Recrystallization from Et_2O, CH_2Cl_2, and pentane (1:1:0.2) yielded 67 mg (61%) of **16** as white needles: mp 139−141 °C (lit. mp 139−141 °C);[23] ^{1}H NMR 8.53 (br, 1, NH), 7.33−7.21 (m, 5), 5.49 (s, 1), 3.69 (s, 2), 2.14 (s, 3); ^{13}C NMR 171.9, 171.0, 137.0, 132.4, 128.8 (2 C), 128.7 (2 C), 126.9, 107.1, 98.4, 34.7, 19.2; IR (KBr) 3200−3100, 1672, 1629. The data are identical with those reported by Tamm and Schmidlin.[23]

1,5-Dihydro-5-hydroxy-3-(1-oxoethyl)-5-phenylmethyl-2*H*-pyrrol-2-one (18). DMDO (7.5 mL, 0.46 mmol, 0.07 M solution in acetone)[25] was added to a solution of **16** (100 mg, 0.46 mmol) in CH_2Cl_2 (5 mL) at −40 °C. The solution was stirred for 2 h and then concentrated to yield 0.107 g (100%) of **18** as a yellow oil: ^{1}H NMR 7.54 (d, 1, J = 2.4), 7.36−7.25 (m, 5), 6.21 (br, 1, NH), 3.20 (d, 1, J = 13.4), 3.04 (d, 1, J = 13.4), 2.49 (s, 3); ^{13}C NMR 194.2, 168.1, 155.3, 134.9, 134.0, 130.4 (2 C), 128.5 (2 C), 127.5, 86.5, 43.8, 29.2; IR (neat) 3400−3200, 1716, 1614; HRMS (CI/NH_3) calcd for $C_{13}H_{17}N_2O_3$ (MNH_4^+) 249.1239, found 249.1243.

4-Hydroxy-1-(1-oxoethyl)-4-phenylmethyl-6-oxa-3-azabicyclo[3.1.0]hexan-2-one (19a and 19b). A 30% solution of H_2O_2 (81 μL, 0.71 mmol) was added to a solution of **18** (54.8 mg, 0.24 mmol) in MeOH (2.4 mL) in a 15−20 °C water bath. NaOH (6 M, 20 μL, 0.12 mmol) was added over 1 h keeping the

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water bath between 20 and 25 °C. The reaction was stirred for 2 h and poured into H_2O (5 mL). The aqueous layer was extracted with Et_2O (4 × 5 mL), and the combined organic layers were washed with H_2O (15 mL), dried over $MgSO_4$, and concentrated to give 51 mg (87%) of a 1:3 mixture of crude **19a** and **19b** as a yellow oil. Flash chromatography on silica gel (19:1 CH_2Cl_2/MeOH) yielded 38 mg (64%) of a 1:3 mixture of **19a** and **19b** as a clear oil.

Data for **19b** were determined from the mixture: ^{1}H NMR 7.38−7.26 (m, 5), 7.36 (br, 1, NH), 4.66 (s, 1, OH), 4.05 (d, 1, J = 2.4), 3.13 (d, 1, J = 13.4), 3.07 (d, 1, J = 13.4), 2.11 (s, 3); ^{13}C NMR 199.6, 168.1, 134.4, 130.5 (2 C), 128.6 (2 C), 127.3, 85.1, 64.8, 61.2, 41.3, 26.2; IR (neat) 3200−3000, 1700, 1680; HRMS (DCI/NH_3) calcd for $C_{13}H_{14}NO_4$ (MH^+) 248.0923, found 248.0924.

NOESY 1D irradiation of the absorption at δ 4.05 showed small enhancements to δ 7.36, 4.66, and 2.11 and very small enhancements to δ 3.13 and 3.07.

4-Hydroxy-1-(1-oxoethyl)-4-phenylmethyl-6-oxa-3-azabicyclo[3.1.0]hexan-2-one (19a and 19b). A solution of **16** (42 mg, 0.20 mmol) in aqueous Na_2(EDTA) (4 × 10^{-4} M, 1.6 mL) was cooled to 0 °C and acetone (1.6 mL, 21.8 mmol) was added. A mixture of $NaHCO_3$ (130 mg, 1.56 mmol) and Oxone (0.60 g, 0.98 mmol) was added over a period of 1 h. The solution was stirred for an additional 6 h at 0 °C. The reaction mixture was filtered and concentrated under reduced pressure to remove the acetone. The resulting aqueous layer was extracted with CH_2Cl_2 (4 × 5 mL), which was dried over $MgSO_4$ and concentrated to yield 30 mg (63%) of crude **19a**. Flash chromatography on silica gel (19:1 CH_2Cl_2/MeOH) yielded 28 mg (58%) of a 3:1 mixture of **19a** and **19b**.

Data for **19a** were determined from the mixture: ^{1}H NMR 7.39−7.25 (m, 5), 7.26 (br, 1, NH), 6.28 (s, OH), 3.98 (d, 1, J = 2.4), 3.22 (d, 1, J = 13.4), 3.13 (d, 1, J = 13.4), 1.96 (s, 3); ^{13}C NMR 196.6, 167.0, 133.0, 130.6 (2 C), 128.8 (2 C), 127.7, 84.5, 63.5, 62.8, 43.5, 27.4; IR (neat) 3200−3000, 1700, 1680; HRMS (DCI/NH_3) calcd for $C_{13}H_{14}NO_4$ (MH^+) 248.0923, found 248.0924.

NOESY 1D irradiation of the absorption at δ 3.98 showed small enhancements of δ 7.26 and 1.96 and larger enhancements of δ 3.22 and 3.13.

***(Z)*-1,5-Dihydro-3-(1-oxoethyl)-5-(phenylmethylene)-2*H*-pyrrol-2-one (20).** To a solution of **18** (9 mg, 0.04 mmol) in CH_2Cl_2 (0.5 mL) was added TFA (3 μL, 0.04 mmol). The solution was stirred for 12 h and then poured into H_2O (3 mL). The aqueous layer was neutralized with 1 M NaOH and extracted with CH_2Cl_2 (3 × 3 mL). The combined organic layers were washed with H_2O (5 mL), dried over $MgSO_4$, and concentrated. Flash chromatography on silica gel (49:1 CH_2Cl_2/MeOH) yielded 8 mg (100%) of **20** as a yellow solid: ^{1}H NMR 8.51 (br, 1, NH), 7.73 (d, 1, J = 2.4), 7.51−7.38 (m, 5), 6.41 (s, 1), 2.62 (s, 3); ^{13}C NMR 193.6, 169.4, 144.1, 134.7, 134.1, 131.6, 129.6, 129.4 (2 C), 129.3 (2 C), 120.2, 29.3; IR (KBr) 3456, 1698, 1671, 1636; HRMS (DEI) calcd for $C_{13}H_{11}NO_2$ (M^+) 213.0790, found 213.0790.

***N*-(1-Hydroxymethyl-2-phenylethyl)-3-cyclohexyl-3-oxopropionamide (22).** (*R*)-(+)-2-Amino-3-phenyl-1-propanol (30 mg, 0.20 mmol) was added to a solution of **21** (50 mg, 0.20 mmol) in toluene (2 mL). The cloudy solution was heated at 70 °C for 18 h giving a clear solution that was concentrated to afford a yellow oil. Flash chromatography on silica gel (1:4 hexanes/EtOAc) yielded 37 mg (62%) of **22** as a white solid: mp 77−79 °C; ^{1}H NMR 7.30−7.20 (m, 5), 4.21−4.18 (m, 1), 3.68 (dd, 1, J = 11, 5), 3.57 (dd, 1, J = 11, 5), 3.41 (d, 1, J = 16), 3.37 (d, 1, J = 16), 2.90 (dd, 1, J = 13, 7), 2.83 (dd, 1, J = 13, 7), 2.41−2.35 (m, 1), 1.82−1.61 (m, 4), 1.34−1.15 (m, 6); ^{13}C NMR 209.9, 166.3, 137.6, 129.2 (2 C), 128.4 (2 C), 126.5, 63.9, 53.1, 51.5, 47.0, 36.9, 27.89, 27.88, 25.6, 25.32, 25.29; IR (KBr) 3303, 1708, 1645; HRMS (DCI/NH_3) calcd for $C_{18}H_{26}NO_3$ (MH^+) 304.1913, found 304.1909.

***(Z)*-3-(Cyclohexyl(hydroxy)methylene)-1,3-dihydro-5-phenylmethyl-2*H*-pyrrol-2-one (23).** To a solution of **22** (41 mg, 0.14 mmol) in toluene (1.0 mL) and DMSO (1.0 mL) was added EDC (0.13 g, 0.68 mmol) and dichloroacetic acid (22 μL, 0.27 mmol). The solution was stirred for 36 h and 2 M HCl (3 mL) was added. The aqueous layer was extracted with Et_2O/CH_2Cl_2 (3:1, 3 × 5 mL). The combined organic layers were stirred with 2 M NaOH (5 mL) for 5 min. Ice was added and the aqueous layer neutralized with 2 M HCl. The organic layer was removed and the neutral aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were washed with 2.5 M NaCl solution (5 × 5 mL), dried over $MgSO_4$, and concentrated to give 32 mg (84%) of 80−90% pure **23** as a bluish oil: ^{1}H NMR 7.52−7.21 (m, 5), 5.59 (s, 1), 3.48 (br, 2), 2.50−2.40 (m, 1), 1.85−1.55 (m, 8), 1.35−1.29 (m, 2).

3-Cyclohexanecarbonyl-1,5-dihydro-5-hydroxy-4-phenylmethyl-2*H*-pyrrol-2-one (24). A crude solution of **23** (32 mg, 0.11 mmol) in CH_2Cl_2 (0.35 mL) was cooled to −40 °C and a solution of DMDO (2.4 mL, 0.07 M in acetone) was quickly added. The bright yellow solution was stirred for 3 h. The solution was then concentrated to a yellow oil. Flash chromatography on silica gel deactivated with 5% H_2O (13:7 CH_2Cl_2/EtOAc) yielded 13 mg (35% from **24**) of **22** as a yellow oil: ^{1}H NMR 7.38 (s, 1), 7.31−7.21 (m, 5), 6.82 (s, 1, NH), 3.83 (s, 1, OH), 3.20 (d, 1, J = 13.4), 3.11 (d, 1, J = 13.4), 3.07−2.95 (m, 1), 1.71−1.54 (m, 4), 1.30−1.04 (m, 6); ^{13}C NMR 200.3, 167.9, 154.3, 135.5, 134.0, 130.4 (2 C), 128.5 (2 C), 127.4, 86.7, 48.4, 43.8, 28.0, 27.7, 25.8, 25.4, 25.3; IR (neat) 3500−3200; 1713, 1681; HRMS (DCI/NH_3) calcd for $C_{18}H_{22}NO_3$ (MH^+) 300.1600, found 300.1610.

***N*-(3-Cyclohexyl-1,3-dioxopropyl)-2-(hydroxymethyl)-pyrrolidine (25).** DMAP (30 mg, 0.25 mmol) and **21** (0.13 g, 0.49 mmol) were added to a solution of (*S*)-prolinol (50 mg, 0.49 mmol) in toluene (12 mL). The cloudy solution was heated to 70 °C for 16 h. The clear solution was cooled to 25 °C and poured into a solution of saturated NH_4Cl (12 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with 1 M HCl (2 × 20 mL). The combined acidic layers were extracted with CH_2Cl_2 (10 mL). The combined organic layers were washed with brine (30 mL), dried over $MgSO_4$, and concentrated to yield 0.123 g (98%) of oily **25** as a complex mixture of four keto, enol, and amide tautomers: ^{1}H NMR 4.97−4.95, 4.85−4.83, 4.58−4.54, 4.28−4.19, and 3.83−3.37 (5 m, 7 H for keto, 6 H for enol), 2.54−2.48 (m, 1), 2.12−1.62 and 1.41−1.18 (2 m, 14 H); IR (neat) 1710, 1626; HRMS (DCI/NH_3) calcd for $C_{14}H_{24}NO_3$ (MH^+) 254.1756, found 254.1753.

2-Cyclohexyl(hydroxy)methylene-2,5,6,7-tetrahydro-3*H*-pyrrolizin-3-one (26). To a solution of **25** (39 mg, 0.15 mmol) in toluene (1.0 mL) and DMSO (1.0 mL) was added EDC (0.15 g, 0.77 mmol) and dichloroacetic acid (25 μL, 0.31 mmol). The solution was stirred for 36 h and 2 M HCl (3 mL) was added. The aqueous layer was extracted with Et_2O/CH_2Cl_2 (3:1, 3 × 5 mL). The combined organic layers were stirred with 2 M NaOH (5 mL) for 5 min. Ice was added and the aqueous layer neutralized with 2 M HCl. The organic layer was removed and the neutral aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were washed with 2.5 M NaCl solution (5 × 5 mL), dried over $MgSO_4$, and concentrated to give 28 mg (76%) of 80−90% pure **26** as a bluish oil: ^{1}H NMR 5.51 (s, 1), 3.65 (t, 2, J = 7.3), 2.65 (t, 2, J = 7.3), 2.49−2.42 (m, 1), 2.35 (tt, 2, J = 7.3, 7.3), 1.85−1.55 (m, 8), 1.39−1.20 (m, 2).

2-Cyclohexanecarbonyl-7a-hydroxy-5,6,7,7a-tetrahydro-3*H*-pyrrolizin-3-one (27). A solution of crude **26** (28 mg, 12 mmol) in CH_2Cl_2 (0.35 mL) was cooled to −40 °C and a solution of DMDO (1.60 mL, 0.07 M in acetone) was quickly added. The bright yellow solution was stirred for 3 h. The solution was then concentrated to provide a yellow oil. Flash chromatography on silica gel deactivated with 5% H_2O (13:7 CH_2Cl_2/EtOAc) yielded 4 mg (11% from **25**) of >90% pure **27** as a yellow oil: ^{1}H NMR 7.63 (s, 1), 3.56 (ddd, 1, J = 8.5, 8.5, 8.5), 3.39−3.30 (m, 1), 3.28−3.20 (m, 1), 2.62−2.54 (m, 1), 2.40−2.25 (m, 1), 2.19−2.14 (m, 1), 1.80−1.60 (m, 5), 1.66−1.58 (m, 1), 1.41−1.23 (m, 5); ^{13}C NMR 200.0, 170.1, 153.1, 135.9, 95.4, 48.2, 42.3, 34.0, 28.5, 27.72, 27.71, 25.8, 25.6, 25.3; IR (neat) 3418, 1694.

Acknowledgment. We thank the NIH (GM50151) for generous financial support.

Supporting Information Available: ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

JO048605R