3-(3-Pyrrolyl)thiopyrrolidones as Precursors of Benzo[1,2-*b*:4,3-*b*']dipyrroles. Synthesis of Intermediates and Analogues Related to the Phosphodiesterase Inhibitors PDE I and PDE II and Antitumor Antibiotic CC-1065

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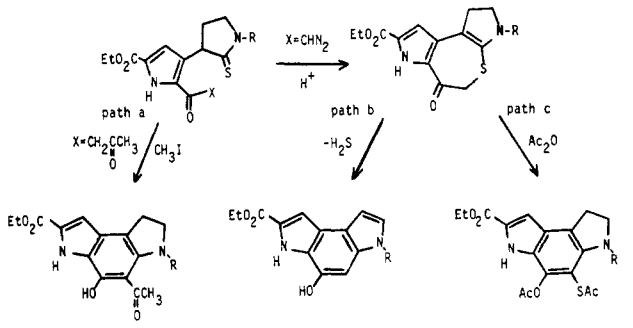
Received August 26, 1987

The 4-lithio derivative of ethyl 5-(3-methylisoxazol-5-yl)pyrrole-2-carboxylate adds to the 3-position of 1-allylpyrrolidine-2,3-dione to give ethyl 4-(1-allyl-3-hydroxy-2-oxopyrrolidin-3-yl)-5-(3-methylisoxazol-5-yl)-pyrrole-2-carboxylate in 53% yield. This adduct has been converted to ethyl 4-(1-allyl-2-thioxopyrrolidin-3-yl)-5-(1,3-dioxobutyl)pyrrole-2-carboxylate. This thiolactam is cyclized to ethyl 5-acetyl-6-allyl-4-hydroxy-3,6,7,8-tetrahydrobenzo[1,2-*b*:4,3-*b*']dipyrrole-2-carboxylate by reaction with methyl iodide at 80 °C. The cyclization product has been converted to methyl 5-acetyl-4-methoxy-3,6,7,8-tetrahydrobenzo[1,2-*b*:4,3-*b*']dipyrrole-2-carboxylate, an intermediate in a synthesis of PDE II methyl ester (Boger and Coleman, 1986). The thiolactam has also been converted to ethyl 7-allyl-4-oxo-3,4,5,6,7,8-hexahydrothiepino[2,3-*b*:5,4-*b*']dipyrrole-2-carboxylate. This thiepinone undergoes ring contraction to ethyl 6-allyl-4-hydroxy-3,6-dihydrobenzo[1,2-*b*:4,3-*b*']dipyrrole-2-carboxylate. This compound has been converted to ethyl 6-acetyl-4-methoxy-3,6,7,8-tetrahydrobenzo[1,2-*b*:4,3-*b*']dipyrrole-2-carboxylate, the 5-deoxy analogue of PDE II ethyl ester.

The benzo[1,2-*b*:4,3-*b*']dipyrrole ring occurs in the phosphodiesterase inhibitors PDE I and PDE II isolated by Umezawa and co-workers.[1] It is also found, with the same substitution pattern, in the potent antitumor antibiotic CC-1065.[2] There has been much activity directed toward the synthesis of this ring system recently.[3-8] In earlier work it was shown that 3-(3-pyrrolyl)thiopyrrolidones could serve as intermediates in the synthesis of benzo[1,2-*b*:4,3-*b*']dipyrroles.[9] The most efficient reaction was the intramolecular condensation (path a), but two additional pathways to benzodipyrroles represented by b and c were also observed as summarized in Scheme I. In the initial study, the nitrogen substituent R was benzyl. We were unable to develop effective methods for debenzylation of that series of benzodipyrrole derivatives.

Scheme I



A major problem was the facile dehydrogenation of the indoline ring by the usual debenzylation catalysts. In this paper we report the exploration of the analogous system in which the nitrogen substituent is allyl. Satisfactory methods for deallylation have been found and have led to the synthesis of methyl 5-acetyl-4-methoxy-3,6,7,8-tetrahydrobenzo[1,2-*b*:4,3-*b*']dipyrrole-2-carboxylate (**13d**), which is an intermediate in the synthesis of PDE I and PDE II methyl ester reported by Boger and Coleman,[7b,c] and ethyl 6-acetyl-4-methoxy-3,6,7,8-tetrahydrobenzo-[1,2-*b*:4,3-*b*']dipyrrole-2-carboxylate (**24**), the 5-deoxy analogue of PDE II ethyl ester.

The early steps of the synthesis of the *N*-allyl thiolactam **4b** parallel those used for the benzyl compound.[9] The addition of ethyl 4-lithio-1-sodio-5-(3-methylisoxazol-5-yl)pyrrole-2-carboxylate (**1c**) to 1-allylpyrrolidine-2,3-dione (**2**)[10] proceeds in 50–55% yield. The remainder of the reactant is consumed by enolization, and the debrominated pyrrole **1a** can be recovered and recycled. A modification of the method for reductive dehydroxylation of **3** was necessary because the hydrogenolysis used in the benzyl series is incompatible with the *N*-allyl substituent. It was found that the reduction could be effected with triethylsilane–trifluoroacetic acid.[11] Dehydration giving **5a** occurred in competition to the extent of up to 20%. This deoxygenation sequence is an improvement over the hydrogenolysis used in the benzyl case since the isoxazole ring is unaffected. In the benzyl case this ring was opened by

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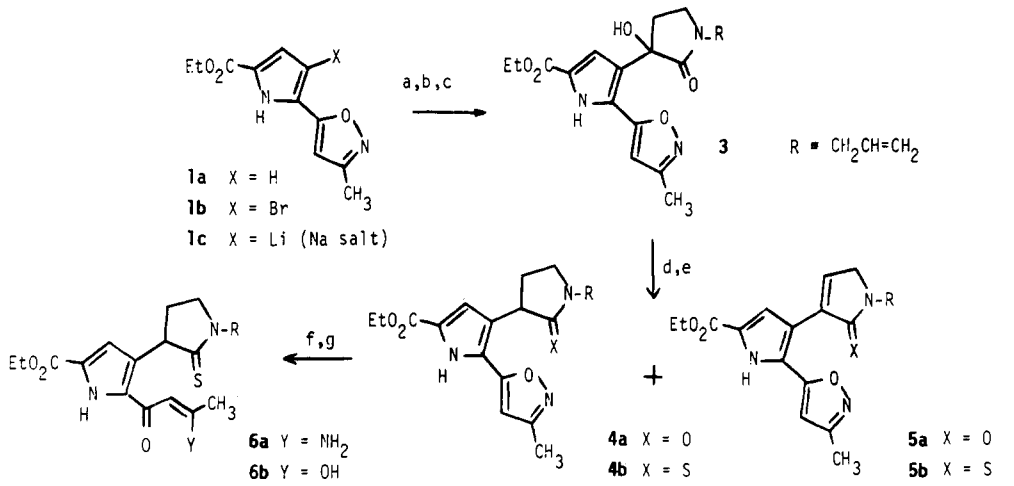
Scheme II[a]

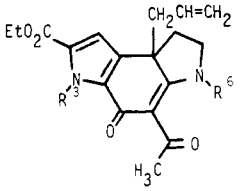


[a] (a) NaH; (b) *n*-BuLi; (c) 1-allylpyrrolidine-2,3-dione (**2**); (d) Et_3SiH, TFA; (e) P_2S_5; (f) $Mo(CO)_6$; (g) H_2O, H^+.

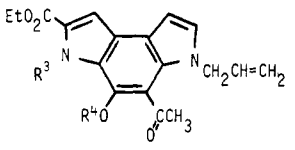
hydrogenolysis, requiring an additional step to reform the isoxazole ring.

The lactam **4a** was not easily separated from the by-product **5a**. However, after conversion of the mixture to the corresponding thiolactams **4b** and **5b**, separation was readily achieved by chromatography. Molybdenum hexacarbonyl effected the reduction of the isoxazole ring of **4b**, giving **6a**. This was hydrolyzed to the key intermediate **6b**. These transformations are summarized in Scheme II. The overall yield of the cyclization substrate **6b** from the adduct **3** is 50–60%.

Cyclization of **6b** to **7a** occurred on heating to 80 °C in the presence of 2–3 equiv of methyl iodide. The yield was >90%. It was found that **7a** was thermally unstable toward a Claisen rearrangement to give **8a**. The identifi-



8a R^3, R^6 = H
8b R^3 = CH_3, R^6 = H
8c R^3 = H, R^6 = CH_3

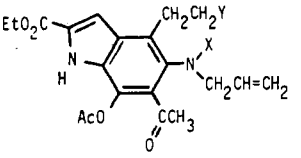


9a R^3, R^4 = H
9b R^3 = H, R^4 = CH_3
9c R^3 = H, R^4 = $COCH_3$

cation of **8a** was based on spectral data. The allyl methylene group appears as an AB quartet, J = 14 at 2.31 and 2.39. Each doublet is further coupled to the vinyl proton at 5.59. The indoline protons which appear as a pair of triplets in **7a** become a series of complex multiplets in **8a** due to the nonequivalence induced by the chiral center at C-8a. The four protons appear at 3.92 (a), 3.85 (b), 2.55 (c), and 2.20 (d). The coupling is as follows: J_{ab} = 9, J_{ac} = 6.5, J_{ad} = 9, J_{bc} = 0, J_{bd} = 9, and J_{cd} = 12.5 Hz. The UV maximum of **7a** at 308 nm is replaced by maxima at 284 and 336 nm. It is interesting that the nonbenzenoid structure is thermodynamically stable. It is stabilized by both the 2-acylpyrrole conjugation and the vinylogous amide structure (enaminone), which is presumably also stabilized by an intramolecular hydrogen bond.

Numerous attempts to methylate **7a** at the 4-hydroxy group were unsuccessful. These included diazomethane in methanol, in methylene chloride, or in ether in the presence of boron trifluoride etherate. Methylation was also attempted with 2,2,2,3-tetrahydro-2,2,2-trimethoxy-5-methyl-1,2-dioxaphosphole.[12] Base-catalyzed methylation using methyl sulfate or methyl iodide with the potassium salt of **7a** or under phase-transfer conditions was also tried. Various mixtures were obtained, which included the enone **8a**, its *N*(3)-methyl (**8b**) and *N*(6)-methyl (**8c**) derivatives, the aromatized indolic phenol **9a**, its *O*-methyl derivative **9b**, recovered starting material, and its *N*(3)-methyl derivative **7b**. None of these conditions were preparatively useful, and they served only to confirm the previously noted resistance of the *o*-hydroxyphenyl ketone moiety to methylation.[9,13] In contrast, **7a** was easily acetylated to **7c** (Scheme III).

Two general approaches for removal of the *N*-allyl group were examined. These were acylative dealkylation[14] and metal-catalyzed isomerization to a hydrolytically unstable *N*-propenyl isomer.[15] The *O*-acetyl derivative **7c** was allowed to react with cyanogen bromide, vinyl chloroformate,[14a] and 2,2,2-trichloroethyl chloroformate[14b] in attempts to effect deallylation. The major product in each case was the result of ring opening, **10a–c**, rather than deallylation. The cleanest reaction was with trichloroethyl chloroformate, which gave **10c** in 85% yield. The preference for reaction at the ring carbon rather than the allyl group must reflect steric encumbrance of the allyl group since normally the allylic bond would be preferentially cleaved.[14c]



10a X = CN, Y = Br
10b X = $CO_2CH{=}CH_2$, Y = Cl
10c X = $CO_2CH_2CCl_3$, Y = Cl

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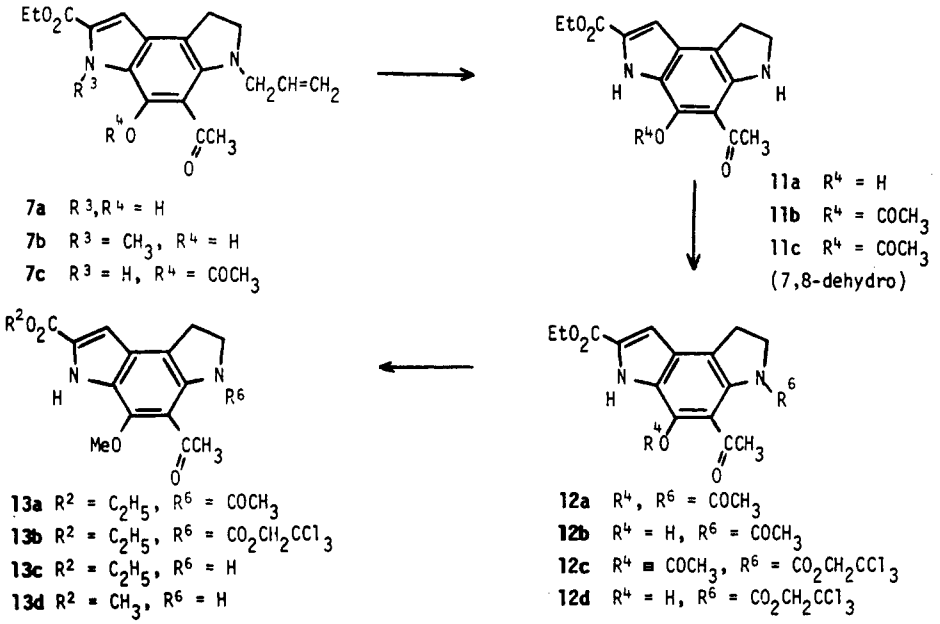
Scheme III

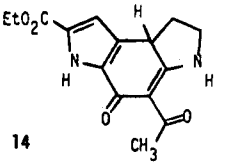


Metal-catalyzed deconjugation–hydrolysis was then examined. Preliminary experiments in which **7c** was heated with tetrakis(triphenylphosphine)rhodium hydride[16] at 100 °C in ethanol gave mixtures of the desired deallylation product **11b** with the thermal rearrangement product **8a**. The latter was presumably formed from **7a** after solvolysis of the *O*-acetyl group. Better results were achieved by use of 1.0 equiv of trifluoroacetic acid and 0.25 equiv of the rhodium complex in refluxing ethanol. The desired product **11b** was formed in 70% yield under these conditions. Acetylation gave the more stable compound **12a**.

The diacetyl derivative **12a** was readily deacetylated to **12b**, which reacted with diazomethane to give **13a**. The efficient O-methylation of **12b** is in striking contrast to the *N*-allyl compound **7a**, which was unreactive to diazomethane. We attribute the change in reactivity to steric disruption of the hydrogen bond of **12b**. In contrast to **7a**, where rotation of the allyl group is available to minimize steric interaction with the 5-acetyl substituent, the amide group in **12b** presumably prefers one of the two possible planar amide rotamers. (The NMR spectrum shows a single unbroadened methyl group indicating a preference for one rotamer.) This would force the 5-acetyl group to adopt a conformation perpendicular to the benzene ring and thus weaken the hydrogen bond.

Reaction of **11b** with 2,2,2-trichloroethyl chloroformate gave the expected carbamate **12c**. It too was easily O-deacetylated and methylated to give **13b**. The structure of **13b** was proven after conversion to **13c** by removal of the (trichloroethoxy)carbonyl group with zinc. Ester interchange then gave the methyl ester **13d**, which was identical by NMR, IR, MS, and TLC with the material prepared by Boger and Coleman.[7b,c,17] The preparation of **13d** constitutes a formal total synthesis of PDE I and PDE II ethyl esters. These transformations are summarized in Scheme III.

Although it did not prove to be preparatively reliable, an interesting result was achieved when a bis(triphenylphosphine)palladium(II) chloride–tin hydride system[15e,f] was used as a deallylation catalyst with **7a**. The yields were variable, but the major identifiable products were **8a** and **14**, a nonbenzenoid tautomer of the expected product **11a**.



14

This compound was identified by spectroscopic data. In particular, the NMR spectrum reveals a series of five upfield multiplets whose mutual coupling is consistent with that expected for the nonaromatic protons in structure **14**. The coupling pattern is analogous to that for **8a**, with additional coupling of 7 and 14 Hz between the proton at position 8a and the C-8 methylene group. The isolation of **14** is consistent with the apparent thermodynamic preference for the nonbenzenoid system revealed by the Claisen rearrangement of **7a**. When **14** was acetylated, it was converted to a mixture containing the aromatized indole **11c** and the indolines **12a** and **12b**.

Boger and Coleman have investigated the use of the Baeyer–Villiger oxidation of compounds such as **13d** to establish the naturally occurring oxygen substitution pattern. Such methods were not very satisfactory, and the oxidation procedure that was successfully employed to complete their synthesis involves formation and rearrangement of a hydroperoxide intermediate.[7b,c,18] We were interested in examining the conditions described by Nishinaga in which arylhydrazones of *o*-hydroxyacetophenones are catalytically oxidized to catechol derivatives.[19] Reaction of the *p*-bromophenylhydrazone of **12b** with O_2 in the presence of the Co(SALPR)$_2$ catalyst[20] gave a complex mixture. The Co catalyst and oxygen converted **12b** itself to a mixture of **15a** and **15b**. Treatment of the mixture with trimethyl phosphite converted it all to **15b**. These compounds were identified on the basis of the coupling pattern of the four indoline ring protons in **15b**, which is very similar to the pattern of **8a**. The four in-

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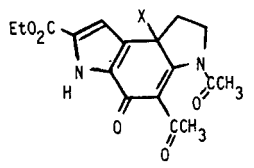


15a X = OOH
15b X = OH

doline protons occur at 4.19 (a), 3.98 (b), 2.66 (c), and 2.16 (d) with coupling constants similar to those in **8a**: J_{ab} = 9, J_{ac} = 6, J_{ad} = 9, J_{bc} = 0, J_{bd} = 9, and J_{bc} = 14 Hz. The C-3 proton and the ester peak are unchanged in intensity or multiplicity from **12b**. The *N*- and *C*-acetyl peaks are present at 2.23 and 2.63 ppm. Compound **12b** was inert to oxygen under similar conditions in the absence of Co(SALPR)$_2$.

The *N*-allyl series of compounds was also examined with respect to path b in Scheme I. The thiolactam **6b** was converted to diazoacetyl thiolactam **16a** by the method previously developed in the benzyl series involving diazo transfer and deacylation.[9] Treatment of **16a** with boron trifluoride followed by (dimethylamino)pyridine gave the thiepinone **17a** in quantitative yield (Scheme IV). Desulfurization and ring contraction to **18a** occurred on heating in ethanol with Raney nickel. This transformation parallels that developed earlier for the benzyl compound **16b**.[9] Small amounts of spiro thiolactams **20a** and **20b** were also isolated from these reactions. Both the *N*-benzyl and *N*-allyl phenolic compounds could be methylated with diazomethane, giving **18c** and **19c**, respectively.

Both the *N*-allyl and *N*-benzyl ethers **18c** and **19c** were selectively reduced at the more basic 7,8 double bond of the benzodipyrrole ring by using sodium cyanoborohydride in acetic acid,[22] a method successfully employed before for similar benzodipyrroles.[7,8] The relatively unstable (toward oxidation) dihydro derivatives **21a** and **21b** were immediately dealkylated with 2,2,2-trichloroethyl chloroformate, each giving the carbamate **22**. These dealkylations proceed smoothly and confirm that the steric effect of the adjacent acetyl substituent is the cause of the anomolous ring-opening reactions encountered with **7a**.

Reaction of **22** with zinc followed by acetylation gave **24**, the 5-deoxy analogue of PDE II ethyl ester. Compound **23**, which represents a component for preparation of analogues of CC-1065, is available from **16a** in six steps in 12% overall yield.

Experimental Section

General Experimental Methods. Where not otherwise detailed, workup consisted of extraction into an organic solvent, drying over sodium sulfate, and evaporation at reduced pressure. The 3,6,7,8-tetrahydrobenzo[1,2-*b*:4,3-*b*']dipyrroles were generally oxygen sensitive, and reactions were run under nitrogen or in sealed ampules. Diethyl ether, hexanes, tetrahydrofuran, toluene, and xylenes were distilled from the sodium ketyl of benzophenone for anhydrous use. Anhydrous methanol and ethanol were obtained by distilling from the magnesium alkoxide. Diisopropylamine, pyridine, pyrrolidine, and triethylamine were distilled from calcium hydride. Organolithium reagents were titrated with 2-butanol, with 1,10-phenanthroline as an indicator.

Ethyl 4-(1-Allyl-3-hydroxy-2-oxopyrrolidin-3-yl)-5-(3-methylisoxazol-5-yl)pyrrole-2-carboxylate (3). Sodium hydride (500 mg of a 60% oil dispersion, 12.5 mmol) was added to bromopyrrole **1b** (3.31 g, 11.1 mmol) in 150 mL of dry THF. The mixture was stirred for 10 min at room temperature and then cooled to −98 °C (liquid nitrogen–methanol bath). A solution of *tert*-butyllithium (1.7 M in hexane; 14 mL; 23.0 mmol) was added, giving rise to a deep red solution. There was quickly added a solution of 1-allylpyrrolidine-2,3-dione (2.01 g, 14.4 mmol) in 10 mL of THF precooled to −78 °C. The mixture was stirred for 1 h at −98 °C, allowed to come to room temperature, and stirred for an additional hour. Several mL of acetic acid was added, and the mixture was poured into 200 mL of water. Dilute HCl was added until the color lightened to a pale brownish orange (pH ~5). The product was extracted into ethyl acetate. Chromatography (1:1 hexanes–ethyl acetate) gave **3** (2.10 g, 53%) as a white crystalline compound, mp 174 °C. There was also recovered from the column 1.03 g of debrominated pyrrole **1a**. **3**: ^{1}H NMR (360 MHz) 1.40 (t, J = 7, 3 H), 2.25 (s, 3 H), 2.35–2.50 (m, 2 H), 3.40 (m, 1 H), 3.53 (m, 1 H), 4.00–4.20 (AB m, J_{AB} = 14, 2 H), 4.35 (q, J = 7, 2 H), 5.36 (m, 2 H), 5.90 (m, 1 H), 6.55 (s, 1 H), 6.74 (d, J = 2, 1 H); EI MS, m/z 359, 341, 263, 247, 201.

Anal. Calcd for $C_{18}H_{21}N_3O_5$: C, 60.16; H, 5.89; N, 11.69. Found: C, 60.33; H, 5.93; N, 11.60.

Ethyl 4-(1-Allyl-2-oxopyrrolidin-3-yl)-5-(3-methylisoxazol-5-yl)pyrrole-2-carboxylate (4a). Adduct **3** (129 mg, 0.36 mmol) was dissolved in 5 mL of trifluoroacetic acid. Triethylsilane (1.0 mL) was immediately added and the mixture was stirred vigorously at room temperature for 2 h. Several additional 0.5-mL aliquots of triethylsilane were added at 30-min intervals until the reactant was consumed. Evaporation left a tan gummy substance, which was purified by flash chromatography (1:1 hexanes–ethyl acetate). There was obtained 108 mg (0.31 mmol, 86%) of **4a** as a snowy white crystalline material, mp 122–124 °C. **4a**: ^{1}H NMR (360 MHz) 1.37 (t, J = 7, 3 H), 2.15 (m, 1 H), 2.32 (s, 3 H), 2.55 (m, 1 H), 3.50 (m, 2 H), 3.90–4.10 (m, 3 H), 4.35 (q, J = 7, 2 H), 5.25 (m, 2 H), 5.80 (m, 1 H), 6.45 (s, 1 H), 6.80 (d, J = 2, 1 H), 9.65 (br, 1 H); EI MS, m/z 343, 228, 145, 123. Variable amounts (<20%) of **5a** were also observed.

Ethyl 4-(1-Allyl-2-oxo-$\Delta^{3,4}$-pyrrolidin-3-yl)-5-(3-methylisoxazol-5-yl)pyrrole-2-carboxylate (5a). Adduct **3** (25 mg) was dissolved in 3 mL of concentrated hydrochloric acid and stirred at room temperature for 20 min. The mixture was poured into water and extracted. Flash chromatography (1:1 hexanes–ethyl acetate) gave **5a** (19 mg, 85%) as a crystalline solid, mp 154–155 °C. **5a**: ^{1}H NMR (360 MHz) 1.37 (t, J = 7, 3 H), 2.32 (s, 3 H), 4.05 (d, J = 2, 2 H), 4.17 (d, J = 6, 2 H), 4.35 (q, J = 7, 2 H), 5.25 (m, 2 H), 5.85 (m, 1 H), 6.29 (s, 1 H), 7.20 (t, J = 2, 1 H), 7.32 (d, J = 2, 1 H), 9.71 (br, 1 H).

Ethyl 4-(1-Allyl-2-thioxopyrrolidin-3-yl)-5-(3-methylisoxazol-5-yl)pyrrole-2-carboxylate (4b). Isoxazole **4a** (527 mg, 1.54 mmol) and P_4S_{10} (103 mg, 0.23 mmol) were refluxed in 30 mL of toluene for 30 min, at which point TLC indicated disappearance of starting material. The toluene was decanted, and the residue was triturated with several portions of hot toluene. The crude material obtained by evaporation of the combined toluene was purified by flash chromatography (1:1 hexane–ethyl acetate). Thiolactam **4b** was obtained as an off-white solid (377 mg, 68%). Recrystallization from ethyl acetate–hexanes provided fluffy, snow-white crystals, mp 149–150 °C. **4b**: ^{1}H NMR (360 MHz) 1.35 (t, J = 7, 3 H), 1.90–2.60 (m, 2 H), 2.30 (s, 3 H), 3.60 (m, 2 H), 4.10–4.60 (m, 5 H), 5.25 (m, 2 H), 5.90 (m, 1 H), 6.40 (s, 1 H), 6.70 (d, J = 2, 1 H), 9.70 (br, 1 H).

Anal. Calcd for $C_{18}H_{21}N_3O_3S$: C, 60.15; H, 5.89; N, 11.69. Found: C, 60.06; H, 5.91; N, 11.62.

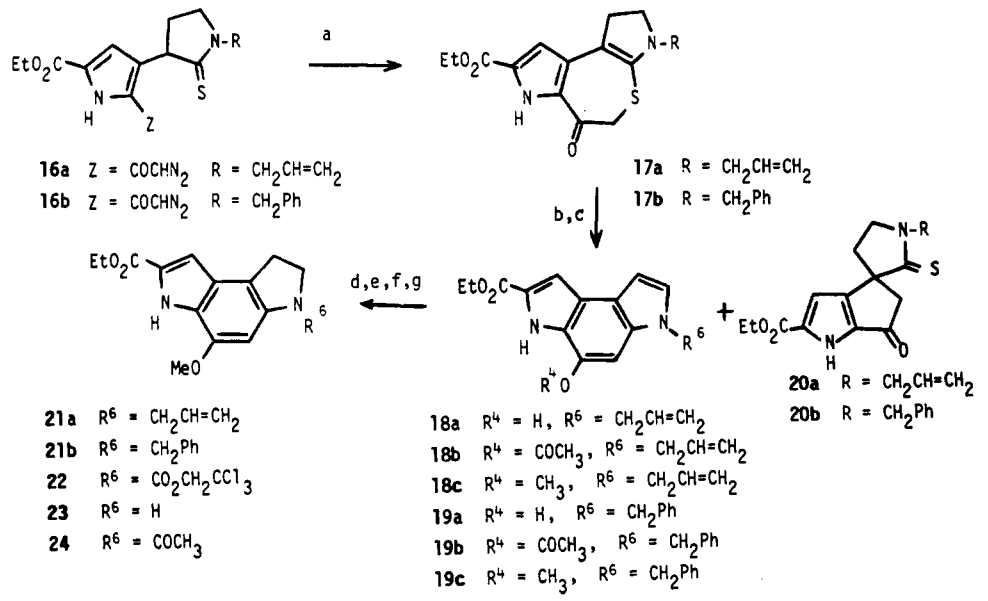
Ethyl 4-(1-Allyl-2-thioxopyrrolidin-3-yl)-5-(1,3-dioxobutyl)pyrrole-2-carboxylate (6b). Thiolactam **4b** (88 mg, 0.25 mmol) and molybdenum hexacarbonyl (36 mg, 0.14 mmol) were dissolved in 20 mL of moist acetonitrile (0.75 mL of water added) and refluxed for 90 min. During this time the mixture turned black. The black gum resulting from evaporation was purified by chromatography and gave enaminone **6a** (84 mg, 95%) as a brownish oil. **6a**: ^{1}H NMR (360 MHz) 1.35 (t, J = 7, 3 H), 2.05 (s, 3 H), 2.00–2.15 (m, 1 H), 2.60 (m, 1 H), 3.65–3.80 (m, 2 H), 4.30 (q, J = 7, 2 H), 4.40–4.55 (AB m, J_{AB} = 15, 2 H), 4.80 (t, J = 8, 1 H), 5.35 (m, 2 H), 5.57 (s, 1 H), 5.90 (m, 1 H), 6.70 (d, J = 2, 1 H), 9.55 (br, 1 H).

Enaminone **6a** (127 mg, 0.35 mmol) was dissolved in 15 mL of THF and treated with 15 mL of 5% HCl. After being stirred

(21) These data do not rigorously exclude the allylic isomers of structures **15a** and **15b** in which the oxygen is introduced at the 5-position with a 5a–8a double bond.

(22) Gribble, G. W.; Lord, P. D.; Skotnicki, J.; Dietz, S. E.; Eaton, J. T.; Johnson, J. L. *J. Am. Chem. Soc.* **1974**, *96*, 7812. Gribble, G. W.; Hoffman, J. H. *Synthesis* **1977**, 859.

Scheme IV[a]



[a] (a) BF_3, then DMAP; (b) Raney Ni; (c) CH_2N_2; (d) CH_3CO_2H, $NaBH_3CN$; (e) $ClCO_2CH_2CCl_3$; (f) Zn; (g) CH_3COCl.

at 50 °C for 20 min, the mixture was poured into water and extracted into ethyl acetate. The residue from workup was recrystallized from chloroform–hexanes to furnish diketone **6b** (115 mg, 91%) as an off-white solid, mp 144–145 °C. **6b**: ^{1}H NMR (360 MHz) 1.37 (t, J = 7, 3 H), 2.10 (m, 1 H), 2.18 (s, 3 H), 2.60 (m, 1 H), 3.70–3.85 (m, 2 H), 4.35 (q, J = 7, 2 H), 4.40–4.60 (AB m, J_{AB} = 15, 2 H), 4.70 (t, J = 8, 1 H), 5.35 (m, 2 H), 5.90 (m, 1 H), 6.05 (s, 1 H), 6.77 (d, J = 2, 1 H), 9.58 (br, 1 H).

Anal. Calcd for $C_{18}H_{22}N_2O_4S$: C, 59.65; H, 6.12; N, 7.73. Found: C, 59.68; H, 6.16; N, 7.70.

Ethyl 5-Acetyl-4-hydroxy-6-(2-propenyl)-3,6,7,8-tetrahydrobenzo[1,2-*b*:4,3-*b*']dipyrrole-2-carboxylate (7a). To a solution of **6b** (215 mg, 0.59 mmol) in 3 mL of THF was added 0.1 mL of methyl iodide (3 equiv). This mixture was placed in a glass tube, sealed, and heated to 80 °C for 15 h. A precipitate formed during this time. After cooling to −78 °C, the tube was opened and its contents were poured into 10 mL of water. The aqueous mixture was made slightly basic with sodium bicarbonate and extracted with dichloromethane. The product was a bright yellow-orange solid, which was recrystallized from chloroform–hexanes to provide **7a** as yellow needles, mp 132–134 °C (184 mg, 95%). **7a**: ^{1}H NMR (360 MHz) 1.40 (t, J = 7, 3 H), 2.80 (s, 3 H), 3.07 (t, J = 9, 2 H), 3.44 (d, J = 6, 2 H), 3.57 (t, J = 9, 2 H), 4.42 (q, J = 7, 2 H), 5.20 (d, J = 11, 1 H), 5.35 (d, J = 18), 5.90 (m, 1 H), 6.95 (d, J = 2, 1 H), 9.25 (br, 1 H).

Ethyl 5-Acetyl-8a-(2-propenyl)-3,4,5,6,7,8a-hexahydro-4-oxobenzo[1,2-*b*:4,3-*b*']dipyrrole-2-carboxylate (8a). Compound **7a** (24 mg, 0.07 mmol) in 2 mL of ethanol was frozen, degassed, and sealed in a glass tube. The tube was heated to 100 °C for 8 h, during which time the bright red-orange color faded to a light yellow. The tube was cooled and opened. After evaporation, the crude material was chromatographed (1:1 hexanes–ethyl acetate) to obtain the rearrangement product **8a** as the major component (14.5 mg, 60%), mp 208–210 °C. There was also recovered 0.8 mg of starting material. **8a**: ^{1}H NMR (360 MHz) 1.40 (t, J = 7, 3 H), 2.15–2.55 (multiplets, 4 H total), 2.65 (s, 3 H), 3.85 (m, 2 H), 4.35 (q, J = 7, 2 H), 4.95 (d, J = 18, 1 H), 5.13 (d, J = 11, 1 H), 5.6 (m, 1 H), 6.75 (d, J = 2, 1 H), 9.70 (br, 1 H); CI MS, m/z 329 (M + 1); EI MS, m/z 328, 286, 241; UV max 238, 274 (s), 284, 294 (s), 336 nm.

Anal. Calcd for $C_{18}H_{20}N_2O_4$: C, 65.84; H, 6.13; N, 8.53. Found: C, 65.70; H, 6.18; N, 8.47.

Ethyl 4-Acetoxy-5-acetyl-6-(2-propenyl)-3,6,7,8-tetrahydrobenzo[1,2-*b*:4,3-*b*']dipyrrole-2-carboxylate (7c). Benzodipyrrole **7a** (180 mg, 0.54 mmol) in 5 mL of dry methylene chloride was treated with acetic anhydride (0.5 mL) and (dimethylamino)pyridine (DMAP) (10 mg). After 30 min, the reaction mixture was concentrated to a crude material, which was subjected to flash chromatography (1:1 hexanes–ethyl acetate). Acetate **7c** was obtained as an orange oil (190 mg, 94%). In some runs, a small amount of the aromatized indole **9c** was isolated. **7c**: ^{1}H NMR (360 MHz) 1.42 (t, J = 7, 3 H), 2.37 (s, 3 H), 2.58 (s, 3 H), 3.20 (t, J = 9, 2 H), 3.45–3.60 (m, 4 H), 4.40 (q, J = 7, 2 H), 5.22 (d, J = 12, 1 H), 5.28 (d, J = 18, 1 H), 7.00 (d, 1 H), 8.67 (br, 1 H); EI MS, m/z 370, 326, 310, 264, 168, 85. **9c**: ^{1}H NMR (360 MHz) 1.42 (t, 3 H), 2.40 (s, 3 H), 2.60 (s, 3 H), 4.42 (q, 2 H), 4.67 (m, 2 H), 4.80–5.20 (m, 2 H), 5.80–5.95 (m, 1 H), 6.80 (d, 1 H), 7.15 (d, 1 H), 7.45 (d, 1 H), 8.80 (br, 1 H).

Reaction of 7c with Cyanogen Bromide. Acetate **7c** (26 mg, 0.07 mmol) and cyanogen bromide (23 mg, 0.22 mmol) were dissolved in 2 mL of dry 1,2-dichloroethane. The solution was placed in a glass tube, frozen, degassed, and sealed under vacuum. After heating at 92 °C for 3 h, the tube was cooled and opened and its contents were partitioned between water and methylene chloride. The crude material was purified by flash chromatography to furnish two fractions. The first, 7.9 mg, was not identified. The second, 6.3 mg, was assigned structure **10a** on the basis of NMR and mass spectral data. **10a**: ^{1}H NMR (360 MHz) 1.42 (t, 3 H), 2.42 (s, 3 H), 2.67 (s, 3 H), 3.57 (m, 2 H?), 3.70–4.00 (m, 4 H?), 4.45 (q, 2 H), 5.40 (d of m, 2 H), 6.0 (m, 1 H), 7.30 (d, 1 H), 9.13 (br, 1 H); EI MS, m/z 475, 477 (Br isotope pattern), 433, 369, 354, 340, 327, 286, 240.

Reaction of 7c with Vinyl Chloroformate. Compound **7c** (41 mg, 0.11 mmol) and vinyl chloroformate (45 mg, 0.42 mmol) were dissolved in 2 mL of dichloroethane. After freezing and degassing, the tube was sealed under vacuum and heated to 100 °C for 15 h. The reaction mixture was partitioned between water and methylene chloride. Purification by flash chromatography (1:1 hexanes–ethyl acetate) afforded 37 mg of **10b**: ^{1}H NMR (360 MHz)[23] 1.45 (t, J = 7, 3 H), 2.40 (s, 3 H), 2.42 (s, 3 H), 3.20–3.40 (m, 2 H), 3.68 (t, J = 8, 2 H), 3.80 (m, 2 H), 4.40–4.50 (q + m, 4 H), 4.60 (m, 1 H), 5.15 (m, 2 H), 5.85–6.00 (m, 1 H), 7.30 (d, J = 2, 1 H), 9.13 (br, 1 H); EI MS, m/z 476, 461, 433, 391, 349, 301.

Reaction of 7c with 2,2,2-Trichloroethyl Chloroformate. Compound **7c** (20 mg, 0.05 mmol) was dissolved in 5 mL of acetonitrile and treated with 0.5 mL of 2,2,2-trichloroethyl chloroformate. After 30 min, the reaction mixture was concentrated in vacuo and eluted through a flash column, with 2:1 hexanes–ethyl acetate. A single compound was isolated (25 mg, 0.04 mmol, 85%) and identified as **10c** on the basis of spectral data. **10c**: ^{1}H NMR (360 MHz)[23] 1.43 (t, J = 7, 3 H), 2.40 (s,

(23) The values quoted are for the major rotamer in a rotameric mixture.

3 H), 2.48 (s, 3 H), 3.20–3.40 (m, 2 H), 3.55–3.85 (m, 2 H), 4.45 (q, J = 7, 2 H), 4.63, 5.11 (AB q, J_{AB} = 11, 2 H), 5.13 (m, 2 H), 6.0 (m, 1 H), 7.30 (d, J = 2, 1 H), 9.30 (br, 1 H); EI MS, m/z 542, 540, 538 (Cl_4 isotope pattern), 522, 498, 433, 298, 267.

Reaction of 7c with Tetrakis(triphenylphosphine)rhodium Hydride–Trifluoroacetic Acid. Ethyl 4-Acetoxy-5-acetyl-3,6,7,8-tetrahydrobenzo[1,2-*b*:4,3-*b'*]dipyrrole-2-carboxylate (11b). Acetate **7c** (78 mg, 0.21 mmol) was dissolved in 3 mL of absolute ethanol and treated with trifluoroacetic acid (31 mg, 0.27 mmol) in 1.5 mL of ethanol. Tetrakis(triphenylphosphine)rhodium hydride[16] (0.46 mg, 0.04 mmol) was added to the solution, and this mixture was stirred under reflux for 90 min. The reaction mixture was concentrated to a crude solid and chromatographed (1:1 hexanes–ethyl acetate → 1:2 hexanes–ethyl acetate) to provide compound **11b** as a bright red semisolid (48.5 mg, 70%). **11b**: ^{1}H NMR (360 MHz) 1.40 (t, J = 7, 3 H), 2.49 (s, 3 H), 2.58 (s, 3 H), 3.17 (t, J = 9, 2 H), 3.75 (t, J = 9, 2 H), 4.41 (q, J = 7, 2 H), 6.94 (d, J = 2, 1 H), 8.45 (br, 1 H); EI MS, m/z 330, 288, 242, 214, 84.

Ethyl 4-Acetoxy-5,6-diacetyl-3,6,7,8-tetrahydrobenzo[1,2-*b*:4,3-*b'*]dipyrrole-2-carboxylate (12a). Indoline **11b** (48 mg, 0.15 mmol) in dry methylene chloride (5 mL) was treated with acetyl chloride and pyridine (3 drops each). After the mixture was stirred for 15 min, TLC indicated complete conversion. The reaction mixture was worked up and chromatographed (1:2 hexanes–ethyl acetate → ethyl acetate) to obtain amide **12a** as an off-white solid, mp 162–164 °C (53 mg, 98%). **12a**: ^{1}H NMR (360 MHz) 1.35 (t, J = 7, 3 H), 2.18 (s, 3 H), 2.35 (s, 3 H), 2.45 (s, 3 H), 3.27 (t, J = 9, 2 H), 4.20 (t, J = 9, 2 H), 4.35 (q, J = 7, 2 H), 7.04 (d, J = 2, 1 H), 8.80 (br, 1 H).

Ethyl 5,6-Diacetyl-4-hydroxy-3,6,7,8-tetrahydrobenzo-[1,2-*b*:4,3-*b'*]dipyrrole-2-carboxylate (12b). Amide **12a** (32 mg, 0.09 mmol) was dissolved in 2 mL of ethanol and treated with 2 drops of ammonium hydroxide. After the mixture was stirred for 10 min, TLC showed complete conversion. Removal of the solvent and chromatography of the residue (1:1 hexanes–ethyl acetate) resulted in phenol **12b** (24 mg, 86%) as a bright yellow oil. **12b**: ^{1}H NMR (360 MHz) 1.42 (t, J = 7, 3 H), 2.32 (s, 3 H), 2.42 (s, 3 H), 3.22 (t, J = 9, 2 H), 4.30 (t, J = 9, 2 H), 4.43 (q, J = 7, 2 H), 7.07 (d, J = 2, 1 H), 9.35 (br, 1 H).

Ethyl 5,6-Diacetyl-4-methoxy-3,6,7,8-tetrahydrobenzo-[1,2-*b*:4,3-*b'*]dipyrrole-2-carboxylate (13a). Compound **12b** (17 mg, 0.05 mmol) was dissolved in 2 mL of absolute methanol, and 1.5 mL of 2,2,2-trifluoroethanol was added. This mixture was treated with an ethereal solution of diazomethane (ca. 18 mg of diazomethane) and stirred at room temperature for 1.5 h. An additional aliquot of diazomethane was added, and stirring was continued for another hour. The reaction mixture was quenched with several drops of acetic acid and worked up. The crude product was chromatographed (1:2 hexanes–ethyl acetate) to furnish methoxy amide **13a** (16 mg, 90%) as a white crystalline substance, mp 192–194 °C. **13a**: ^{1}H NMR (360 MHz) 1.45 (t, J = 7, 3 H), 2.25 (s, 3 H), 2.75 (s), 3.28 (t, J = 9, 2 H), 3.93 (s, 3 H), 4.25 (t, J = 9, 2 H), 4.45 (q, J = 7, 2 H), 7.10 (d, J = 2, 1 H), 9.05 (br, 1 H).

Anal. Calcd for $C_{18}H_{20}N_2O_5$: C, 62.78; H, 5.85; N, 8.13. Found: C, 62.66; H, 5.92; N, 8.10.

Ethyl 4-Acetoxy-5-acetyl-6-[(2,2,2-trichloroethoxy)-carbonyl]-3,6,7,8-tetrahydrobenzo[1,2-*b*:4,3-*b'*]dipyrrole-2-carboxylate (12c). Indoline **11b** (32 mg, 0.1 mmol) in dry methylene chloride (3 mL) was treated with 2,2,2-trichloroethyl chloroformate (0.2 mL). After the mixture was stirred for 10 min, TLC showed complete conversion. Workup and chromatography (1:1 hexanes–ethyl acetate) gave the carbamate **12c** (47 mg, 95%) as a greenish-gray oil. **12c**: ^{1}H NMR (360 MHz) 1.43 (t, J = 7, 3 H), 2.42 (s, 3 H), 2.49 (s, 3 H), 3.33 (t, J = 9, 2 H), 4.43 (t + q, 4 H), 4.85 (s, 2 H), 7.11 (d, J = 2, 1 H), 8.92 (br, 1 H); EI MS, m/z 506, 504, 466, 464, 462 (Cl_3 isotope pattern), 422, 374, 241.

Ethyl 5-Acetyl-4-hydroxy-6-[(2,2,2-trichloroethoxy)-carbonyl]-3,6,7,8-tetrahydrobenzo[1,2-*b*:4,3-*b'*]dipyrrole-2-carboxylate (12d). Carbamate **12c** (53 mg, 0.11 mmol) was dissolved in 3 mL of absolute ethanol and treated with 2 drops of ammonium hydroxide. After 20 min, the reaction mixture was concentrated and chromatographed to obtain phenol **12d** as a bright yellowish-green oil (36 mg, 73%).

Ethyl 5-Acetyl-4-methoxy-6-[(2,2,2-trichloroethoxy)-carbonyl]-3,6,7,8-tetrahydrobenzo[1,2-*b*:4,3-*b'*]dipyrrole-2-carboxylate (13b). Phenol **12d** (36 mg, 0.08 mmol) in 5 mL of methanol was treated with ethereal diazomethane (ca. 15 mg). After 1.5 h, TLC indicated conversion to a slightly more polar compound. The reaction mixture was quenched with acetic acid and worked up. Chromatography afforded methoxy carbamate **13b** (38 mg, 99%) as a light yellow crystalline compound: mp 168–170 °C; ^{1}H NMR (360 MHz) 1.45 (t, J = 7, 3 H), 2.70 (s, 3 H), 3.28 (t, J = 9, 2 H), 3.95 (s, 3 H), 4.35 (t, J = 9, 2 H), 4.42 (q, J = 7, 2 H), 4.83 (s, 2 H), 7.10 (d, J = 2, 1 H), 9.05 (br, 1 H); EI MS, m/z 480, 478, 476, 434, 432, 430 (Cl_3 isotope patterns), 329, 286, 255.

Anal. Calcd for $C_{19}H_{19}N_2O_6Cl_3$: C, 47.73; H, 4.01; N, 5.86. Found: C, 47.65; H, 4.07; N, 5.81.

Ethyl 5-Acetyl-4-methoxy-3,6,7,8-tetrahydrobenzo[1,2-*b*:4,5-*b'*]dipyrrole-2-carboxylate (13c). Carbamate **13b** (12 mg, 0.03 mmol) was stirred in 2 mL of acetic acid at room temperature, and zinc dust was added in portions over 2 h (50 mg total). TLC showed complete conversion to a more polar, orange-red compound. The reaction mixture was diluted with water, filtered, and worked up. Purification by flash chromatography furnished indoline **13c** as a bright red solid (7.5 mg, 96%), mp 140–142 °C. **13c**: ^{1}H NMR (360 MHz) 1.42 (t, J = 7, 3 H), 2.70 (s, 3 H), 3.14 (t, J = 9, 2 H), 3.73 (t, J = 9, 2 H), 3.93 (s, 3 H), 4.42 (q, J = 7, 2 H), 6.95 (d, J = 2, 1 H), 8.68 (br, 1 H).

Methyl 5-Acetyl-4-methoxy-3,6,7,8-tetrahydrobenzo[1,2-*b*:4,3-*b'*]dipyrrole-2-carboxylate (13d). Compound **13c** was dissolved in a solution of sodium methoxide in methanol and stirred for 5 h. Workup delivered the methyl ester **13d**, identical in all aspects with a sample of **13d** provided by Prof. Dale Boger. **13d**: ^{1}H NMR (360 MHz) 2.70 (s, 3 H), 3.13 (t, J = 9, 2 H), 3.72 (t, J = 9, 2 H), 3.96 (s, 6 H), 6.92 (d, J = 2, 1 H), 8.70 (br, 1 H); IR (neat) 3413, 3339, 3276, 2949, 1721, 1631, 1578, 1435, 1311, 1284, 1243, 1210, 1138, 1101, 755 cm^{-1}; EI MS, m/z 288.

Reaction of 7a with Bis(triphenylphosphine)palladium-(II) Chloride–Tri-*n*-butyltin Hydride. Benzodipyrrole **7a** (22 mg, 0.07 mmol) and bis(triphenylphosphine)palladium(II) chloride (4.8 mg, 0.007 mmol) in 3 mL of dry methylene chloride were stirred at room temperature under a nitrogen atmosphere. Freshly distilled tri-*n*-butyltin hydride (25 mg, 0.09 mmol) in 1.0 mL of methylene chloride was added dropwise via syringe, over 5 min. After the mixture was stirred for 30 min, TLC showed that several new spots were present. Aqueous 10% HCl (3 mL) was added, causing the formation of a precipitate. After being stirred for several minutes, the mixture was diluted with 20 mL of water and neutralized with sodium bicarbonate. The layers were separated, and the aqueous layer was extracted with methylene chloride. The crude product was separated into three components by flash chromatography eluting with 1:1 hexanes–ethyl acetate. A small amount (2 mg) of the dealkylated but aromatized product (**9a**) was identified, and another fraction (4 mg) proved to be the rearranged compound **8a**. The major fraction was assigned structure **14** (11 mg, 58%) on the basis of spectral data and especially comparison of the NMR data with that of compound **8a**. **14**: ^{1}H NMR (360 MHz) 1.38 (t, J = 7, 3 H), 2.04 (q of d, 1 H), 2.68 (s, 3 H), 2.74 (m, 1 H), 3.78 (t of d, 1 H), 3.90 (m, 1 H), 4.02 (d of d, J = 14, 7, 1 h), 4.35 (q, 2 H), 6.83 (d, 1 H), 9.75 (br, 1 H); EI MS, m/z 288, 260, 242, 227, 214, 143, 77.

Compound **14** (3.0 mg, 0.01 mmol) in methylene chloride (1 mL) was treated with 0.05 mL of acetic anhydride and a trace of (dimethylamino)pyridine. After 0.5 h, acetyl chloride (0.05 mL) was added. After and additional 0.5 h, the product mixture was worked up by extraction and chromatographed to yield **11c**, **12a**, and **12b** in approximately equal amounts. **11c**: ^{1}H NMR (360 MHz) 1.45 (t, J = 7, 3 H), 2.55 (s, 3 H), 2.75 (s, 3 H), 4.45 (q, J = 7, 2 H), 6.80 (t, J = 2, 1 H), 7.35 (t, J = 2, 1 H), 7.45 (d, J = 2, 1 H), 8.90 (br s, 1 H). Compounds **12a** and **12b** were identified by comparison with previously described samples.

Reaction of Phenol 13b with Dioxygen–Co(SALPR)$_2$. Oxygen was bubbled through a solution of **12b** (11 mg, 0.03 mmol) and Co(SALPR)$_2$[20] (97 mg) in 3 mL of ethanol. After 45 min, the mixture was concentrated to a crude solid and chromatographed (1:1 hexanes–ethyl acetate → ethyl acetate). Two fractions were isolated. The less polar (4.7 mg) consisted of a complex mixture containing at least three components and was not resolved further.

The more polar fraction (7.5 mg) was nearly pure. The NMR spectrum was similar to those of the rearrangement compound **8a** and enone tautomer **14**, though not identical with either. Mass spectrometry indicated incorporation of an additional oxygen relative to starting material. On the basis of the spectral data, structure **15b** was assigned. **15b**: ^{1}H NMR (360 MHz) 1.40 (t, J = 7, 3 H), 2.15 (m, 1 H), 2.25 (s, 3 H), 2.60 (s, 3 H), 2.65 (d of d, J = 6, 9, 1 H), 3.98 (t, J = 9, 1 H), 4.20 (m, 1 H), 4.40 (q, J = 7, 2 H), 7.00 (d, J = 2, 1 H), 9.80 (br, 1 H); EI MS, m/z 346, 304, 287, 276, 243, 230; UV max 254, 282, 352 nm.

In a second run, a mixture was isolated that consisted of **15b** and a second, closely related material. This compound had an NMR spectrum very similar to that of **15b** but with slight variations in chemical shifts for the pyrrolidine ring protons. The mass spectrum indicated inclusion of a second oxygen atom. Hydroperoxide structure **15a** was assigned to this compound. **15a**: ^{1}H NMR (360 MHz) 1.45 (t, J = 7, 3 H), 2.25 (s, 3 H), 2.30 (m, 1 H), 2.65 (s, 3 H), 2.80 (d of d, 1 H), 4.00 (t, 1 H), 4.12 (m, 1 H), 4.40 (q, J = 7, 1 H), 6.97 (d, J = 2, 1 H), 9.88 (br, 1 H); EI MS, m/z 362, 346, 304, 287, 276, 243, 230.

This mixture was dissolved in 2 mL of trimethyl phosphite and stirred overnight to effect reduction of the hydroperoxide to the alcohol. Removal of the phosphite and chromatography of the crude product delivered pure **15b**.

Ethyl 4-(1-Allyl-2-thioxopyrrolidin-3-yl)-5-(diazoacetyl)-pyrrole-2-carboxylate (16a). Thiolactam **6b** (187 mg, 0.52 mmol), *p*-nitrobenzenesulfonyl azide (134 mg, 0.58 mmol), and triethylamine (60 mg, 0.59 mmol) were stirred in 15 mL of THF for 4 h. The mixture was poured into water (50 mL), extracted into ethyl acetate, dried, and concentrated. Stirring the residue with 25 mL of chloroform precipitated most of the sulfonamide byproduct. The soluble material was chromatographed (1:1 hexanes–ethyl acetate) to afford the diazo transfer product as a yellow foam (170 mg, 84%): ^{1}H NMR (360 MHz) 1.40 (t, J = 7, 3 H), 2.05 (m, 1 H), 2.51 (s, 3 H), 2.58 (m, 1 H), 3.70 (m, 2 H), 4.37 (q, J = 7, 2 H), 4.41, 4.55 (AB m, 2 H), 4.95 (t, J = 8, 1 H), 5.32 (m, 2 H), 5.87 (m, 1 H), 6.85 (d, J = 2, 1 H). The diazo dione (170 mg, 0.44 mmol) in 30 mL of ethanol was stirred with 1 mL of pyrrolidine for 45 min. The reaction mixture was concentrated, and the crude solid was passed through a flash column (1:1 hexanes–ethyl acetate) to obtain diazo ketone **16b** (138 mg, 91%) as an oil. **16a**: ^{1}H NMR (360 MHz) 1.35 (t, J = 7), 2.20 (m, 1 H), 2.60 (m, 1 H), 3.75 (m, 1 H), 3.87 (m, 1 H), 4.32 (q, J = 7, 2 H), 4.45 (AB m, 2 H), 4.60 (t, J = 8, 1 H), 5.35 (m, 2 H), 5.85 (m, 1 H), 6.73 (d, J = 2, 1 H), 6.80 (s, 1 H), 9.75 (br, 1 H).

Ethyl 7-Allyl-4-oxo-3,4,5,6,7,8-hexahydrothiepino[2,3-*b*:5,4-*b*']dipyrrole-2-carboxylate (17a). Diazo ketone **16a** (35 mg, 0.1 mmol) in 2.0 mL of dry methylene chloride was treated with boron trifluoride etherate (20 mg, 0.14 mmol) in 1.0 mL of methylene chloride. There was immediate evolution of gas, and the solution darkened in color. After 20 min, the reaction mixture was poured into aqueous sodium carbonate and extracted into methylene chloride, giving a bright red extract. Evaporation afforded thiepinone **17a** (32 mg, 100%) as a bright orange-red solid. Recrystallization from chloroform–hexanes gave an analytical sample, mp 133–134 °C. **17a**: ^{1}H NMR (360 MHz) 1.40 (t, J = 7, 3 H), 2.90 (t, J = 10, 2 H), 3.40 (t, J = 10, plus overlapping s, 4 H total), 3.75 (d, J = 6.5, 2 H), 4.38 (q, J = 7, 2 H), 5.25 (m, 2 H), 5.82 (m, 1 H), 6.70 (d, J = 2, 1 H), 9.68 (br, 1 H); EI MS, m/z 318.

Anal. Calcd for $C_{16}H_{18}N_2O_3S$: C, 60.36; H, 5.70; N, 8.80. Found: C, 60.34; H, 5.75; N, 8.78.

Reaction of 17b with Raney Nickel. Ethyl 4-Acetoxy-6-benzyl-3,6-dihydrobenzo[1,2-*b*:4,3-*b*']dipyrrole-2-carboxylate (19b). Thiepinone **17b**[9] (15 mg, 0.4 mmol) was placed in a glass tube with 109 mg of Raney nickel and 3 mL of ethanol. The tube was sealed under vacuum, after freezing and degassing, and heated to 80 °C for 5 h. (Comparable results could be obtained in refluxing ethanol, and this was more convenient in large-scale runs where progress was monitored by TLC.) The tube was opened, and the contents were filtered through Celite. The residue in methylene chloride (5 mL) was treated with 0.3 mL of acetic anhydride and a little DMAP. After 30 min, the mixture was concentrated and chromatographed to obtain the *O*-acetyl derivative **19b** as the major product (6 mg, 36%). There was also isolated 1.5 mg of spiro thiolactam **20b**. **19b**: ^{1}H NMR (360 MHz) 1.45 (t, J = 7, 3 H), 2.42 (s, 3 H), 4.42 (q, J = 7, 2 H), 5.36 (s, 2 H), 6.77 (d, J = 2, 1 H), 7.10 (d, J = 7, 2 H), 7.17 (m, 2 H), 7.30–7.40 (m, 3 H), 7.47 (d, J = 2, 1 H), 8.89 (br, 1 H); EI MS, m/z 376, 334, 288, 260, 197, 91. **20b**: ^{1}H NMR (360 MHz) 1.39 (t, J = 7, 3 H), 2.35 and 2.45 (m, 2 H), 2.82 and 3.70 (AB q, J_{AB} = 18, 2 H), 3.60 and 3.75 (m, 2 H), 4.35 (d of q, 2 H), 4.95 and 5.20 (AB q, J_{AB} = 14, 2 H), 6.57 (d, 1 H), 7.35–7.40 (m, 5 H), 9.40 (br, 1 H); EI MS, m/z 368, 339, 293, 91.

Ethyl 6-Benzyl-4-methoxy-3,6-dihydrobenzo[1,2-*b*:4,3-*b*']dipyrrole-2-carboxylate (19c). Thiepinone **17b** (200 mg, 0.54 mmol) was converted to **19a** (151 mg) as described above. This material was immediately dissolved in 10 mL of methanol, an equal volume of 2,2,2-trifluoroethanol was added, and this solution was treated with several aliquots of ethereal diazomethane. After 2 h, TLC indicated complete conversion to a less polar material. The reaction mixture was worked up to give, after chromatography, methoxy compound **19c** as a light brown semisolid (102 mg, 54% overall from thiepinone **17b**). **19c**: ^{1}H NMR (360 MHz) 1.43 (t, J = 7, 3 H), 3.90 (s, 3 H), 4.40 (q, J = 7, 2 H), 5.35 (s, 2 H), 6.63 (s, 1 H), 6.73 (d, J = 2, 1 H), 7.05 (d, J = 2, 1 H), 7.20–7.40 (m, 5 H), 7.43 (d, J = 2, 1 H), 9.10 (br, 1 H).

Ethyl 4-Acetoxy-6-(2-propenyl)-3,6-dihydrobenzo[1,2-*b*:4,3-*b*']dipyrrole-2-carboxylate (18b). Thiepinone **17a** (20 mg, 0.06 mmol) and Raney nickel (100 mg) were refluxed under a nitrogen atmosphere for 2.5 h. After cooling, the reaction mixture was filtered through Celite and concentrated to give **18a**. The product was dissolved in methylene chloride and treated with 0.1 mL of acetic anhydride and a little DMAP. After 40 min, the reaction mixture was concentrated and chromatographed (1:1 hexanes–ethyl acetate) to deliver **18b** (11 mg, 53%). **18b**: ^{1}H NMR (360 MHz) 1.43 (t, J = 7, 3 H), 2.45 (s, 3 H), 4.42 (q, J = 7, 2 H), 4.75 (d, 2 *H*), 5.05–5.25 (m, 2 H), 6.00 (m, 1 H), 6.75 (d, J = 2, 1 H), 7.13 (d, J = 2, 1 H), 7.45 (d, 1 H), 8.95 (br, 1 H).

Ethyl 4-Methoxy-6-(2-propenyl)-3,6-dihydrobenzo[1,2-*b*:4,3-*b*']dipyrrole-2-carboxylate (18c). Phenol **18a** (14.2 mg) prepared as above was dissolved in 10 mL of absolute methanol and treated with ethereal diazomethane (ca. 30 mg). After 1.5 h, the reaction mixture was worked up. The crude material was purified by flash chromatography to afford **18c** as a light brown semisolid (10.6 mg, 80%). **18c**: ^{1}H NMR (360 MHz) 1.43 (t, J = 7, 3 H), 4.00 (s, 3 H), 4.42 (q, J = 7, 2 H), 4.75 (m, 2 H), 5.12 (d, J = 18, 1 H), 5.21 (d, J = 11, 1 H), 6.05 (m, 1 H), 6.70 (s + d, 2 H), 7.01 (d, J = 2, 1 H), 7.41 (d, J = 2, 1 H), 9.10 (br, 1 H).

Ethyl 4-Methoxy-6-[(2,2,2-trichloroethoxy)carbonyl]-3,6-dihydrobenzo[1,2-*b*:4,3-*b*']dipyrrole-2-carboxylate (22). Compound **19c** (18 mg, 0.05 mmol) was dissolved in 3 mL of glacial acetic acid and treated with sodium cyanoborohydride (2 mg total, 0.03 mmol, 6 equiv) in several portions over 2 h with stirring at room temperature.[22] The mixture was poured into aqueous sodium hydroxide and extracted into methylene chloride to provide, after workup, crude indoline **21b** as an orange-red solid. This material was dissolved in 3 mL of acetonitrile and treated with 0.25 mL of 2,2,2-trichloroethyl chloroformate. After the mixture was stirred for 1 h at room temperature, TLC indicated complete conversion. The reaction mixture was concentrated and chromatographed (1:1 hexanes–ethyl acetate) to deliver carbamate **22** (13 mg, 58%). Recrystallization from ethyl acetate–hexanes gave an analytical sample, mp 190–191 °C. **22**: ^{1}H NMR (360 MHz)[23] 1.42 (t, J = 7, 3 H), 3.30 (t, J = 9, 2 H), 4.00 (s, 3 H), 4.30 (t, J = 9, 2 H), 4.42 (q, J = 7, 2 H), 4.85 (s, 2 H), 7.05 (d, 1 H), 7.65 (s, 1 H), 9.03 (br, 1 H); EI MS, m/z 434, 436, 438 (Cl_3 isotope pattern) 390, 259, 186, 91.

Anal. Calcd for $C_{17}H_{17}N_2O_5Cl_3$: C, 46.87; H, 3.93; N, 6.43. Found: C, 46.91; H, 3.98; N, 6.39.

Use of the same methodology with *N*-allyl methoxy compound **18c** resulted in the same product in comparable yields.

Ethyl 6-Acetyl-4-methoxy-3,6,7,8-tetrahydrobenzo[1,2-*b*:4,3-*b*']dipyrrole-2-carboxylate (5-Deoxy PDE II Ethyl Ester) (24). Carbamate **22** (11.4 mg, 0.026 mmol) was dissolved in 2 mL of glacial acetic acid. Zinc dust was added, with stirring, in portions over 2 h (20 mg total). The reaction mixture was diluted with water, methylene chloride (10 mL) was added, and the mixture was filtered to remove unreacted zinc. After workup, the residue was dissolved in dry methylene chloride and treated with 2 drops each of acetyl chloride and pyridine. After several minutes, TLC indicated conversion to a very polar substance.

Workup and chromatography (1:2 hexanes–ethyl acetate → ethyl acetate) afforded compound **24** as a white crystalline solid (5.1 mg, 65%). Recrystallization from ethanol provided an analytical sample, mp 261–263 °C. **24**: ^{1}H NMR (360 MHz) 1.42 (t, J = 7, 3 H), 2.25 (s, 3 H), 3.30 (t, J = 9, 2 H), 4.00 (s, 3 H), 4.20 (t, J = 9, 2 H), 4.42 (q, J = 7, 2 H), 7.07 (d, J = 2, 1 H), 8.05 (s, 1 H), 9.01 (br, 1 H); EI MS, m/z 302, 256, 214, 186.

Anal. Calcd for $C_{16}H_{18}N_2O_4$: C, 63.56; H, 6.00; N, 9.26. Found: C, 63.65; H, 6.02; N, 9.20.

Acknowledgment. This research was supported by NIH Grant GM-34047.

Use of Bistrimethylsilylated Intermediates in the Preparation of Semisynthetic 7-Amino-3-substituted-cephems. Expedient Syntheses of a New 3-[(1-Methyl-1-pyrrolidinio)methyl]cephalosporin

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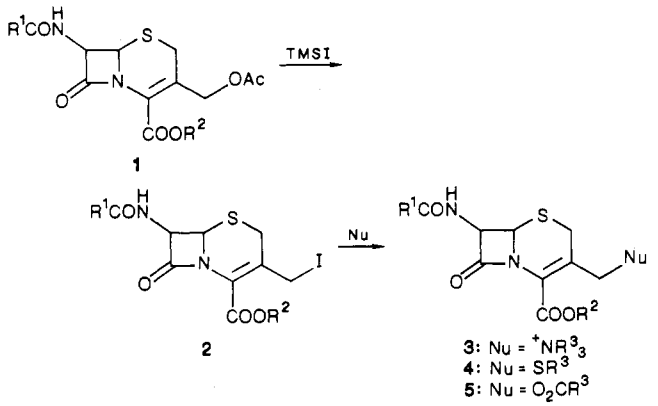
Received June 1, 1987

Several "one-pot" methods for conversion of 7-ACA (**6**) to a variety of 7-amino-3-(ammoniomethyl)- or 7-amino-3-[[(heteroaryl)thio]methyl]cephalosporin derivatives via bistrimethylsilylated intermediates are presented. For example, bistrimethylsilylation of 7-ACA (**6**) in 1,1,2-trichlorotrifluoroethane (Freon TF) using HMDS and 3 mol % TMSI, followed by treatment with 1.15 equiv of TMSI and subsequent reactions with tertiary alicyclic or heteroaromatic amines or heteroaromatic thiols, led to the desired products in good yields. Alternatively, novel reaction of the bistrimethylsilylated derivative **15** with amine/TMSI adducts in Freon TF at 35 °C provided an alternative approach to some 7-amino-3-(ammoniomethyl)cephalosporins. The solvent dependence of Δ^3/Δ^2 isomer ratios in quaternization reactions of **11** with *N*-methylpyrrolidine is presented. Hypotheses for the explanation of experimental results observed on reaction of **15** in Freon TF with amine/TMSI adducts are presented. Acylation of **17** (X = Cl, I) with **8** in aqueous THF provided **18** (BMY-28142) as its sulfate salt in overall yields of 18% and 43%, respectively, from 7-ACA (**6**).

During the past several years, the use of trimethylsilyl iodide (TMSI) in synthetic manipulations of various 3-(acetoxymethyl)cephalosporin nuclei, en route to compounds of medicinal interest (cf. **1** → **2** → **3–5**), has been



reported in the patent literature with increasing frequency. For example, quaternizations of **2** under anhydrous conditions with pyridines,[1-8] quinolines,[9] isoquinolines,[5,10] and various other heteroaromatic[4,11] and tertiary alicyclic[4,12-17] amines, and displacements using heteroaromatic thiols,[18,19] saccharin and related derivatives[20] and the trifluoroacetate anion[21] and other carboxylates[22] have been described. Furthermore, functionalization of 3-(acetoxymethyl)cephalosporins having a nonacylated 7-amino group [i.e., 7-ACA (**6**)] using TMSI-based chemistry has also been reported.[23-27] A prominent example in the literature was

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