chromatographed, yielding 0.30 g of **8** (57%), although attempts to obtain a sample of analytical purity failed because of decomposition: ^{1}H NMR δ 5.0–4.3 (CH_2F, CHI, 3 H, m), 4.2 (OCH_2, 2 H, q, J_{HH} = 6 Hz), 1.3 (CH_3, 3 H, t, J_{HH} = 6 Hz); ^{13}C NMR δ 170.4 (C=O, d, $^3J_{CF}$ = 3.5 Hz), 84.9 (CH_2F, d, J_{CF} = 177.1 Hz), 63.8 (OCH_2), 17.6 (CHI, d, $^2J_{CF}$ = 22.8 Hz), 15.5 (CH_3); MS *m/e* 246 (M^+), 226 [$(M - HF)^+$], 201 [$(M - EtO)^+$], 173 [$(M - CO_2Et)^+$], 154 [$(C_2H_3I)^+$], 119 [$(M - I)^+$], 91 [$(C_3H_4FO_2)^+$].

5α-Fluoro-6β-iodocholesteryl Acetate (10). **10** was prepared in a similar way as the above compounds, using a solution of cholesteryl acetate in anhydrous CH_2Cl_2 (15 mL) as starting olefin. **10** was crystallized from the crude of the reaction using ethyl alcohol (mp 131–133 °C, lit.[4a] mp 132 °C), giving 58% of pure **10** with the same spectral data as reported in the literature.[4a]

Reaction of 6 with DBU. 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU, 0.9 mL, 6 mmol) was added to a solution of 2-fluoro-1-iodo-3-phenylpropane (**6**) (0.79 g, 3 mmol) in benzene (10 mL). After reflux for 5 h, the mixture was quenched with water (20 mL) and extracted with benzene (2 × 10 mL), and the organic layer was washed with water (10 mL) and then dried over Na_2SO_4. Benzene was distilled through a fractionating column, and crude fluoroalkene **11** was purified by distillation at reduced pressure, 62–65 °C (20 mm): ^{1}H NMR δ 4.65 (=CH_2, H cis to F, 1 H, dd, J_{HF} = 15 Hz, J_{HH} = 3 Hz), 4.3 (=CH_2, H trans to F, 1 H, dd, J_{HF} = 50 Hz, J_{HH} = 3 Hz), 3.55 ($PhCH_2$, 2 H, d, J_{HF} = 16.3 Hz); ^{13}C NMR δ 165.8 (=CF, d, J_{CF} = 256.7 Hz), 135.9 (ipso-Ar, d, $^3J_{CF}$ = 5 Hz), 128.8 (Ar), 128.4 (Ar), 126.8 (Ar), 91.1 (=CH_2, d, $^2J_{CF}$ = 19.6 Hz), 38.3 ($PhCH_2$, d, $^2J_{CF}$ = 28.7 Hz); MS *m/e* 136 (M^+), 135 [$(M - H)^+$], 133 [$(M - H_3)^+$], 115 [$(M - H_2F)^+$], 91 [$(C_7H_7)^+$]. Anal. Calcd for C_9H_9F: C, 79.39; H, 6.66. Found: C, 79.62; H, 6.47.

Acknowledgment. This research was supported by the Comisión Asesora de Investigación Científica y Técnica (CAICYT). One of us (J.M.G.) thanks the Ministerio de Educación y Ciencia for a predoctoral scholarship. We also thank Bayer Hispania Comercial, SA, for a gift of DBU.

Registry No. **1**, 19869-79-5; **2**, 1786-51-2; **3**, 6906-08-7; **4**, 6906-08-7; **5**, 132047-45-1; **6**, 129976-36-9; **7**, 19997-66-1; **8**, 132047-46-2; **9**, 132047-47-3; **10**, 2560-88-5; **11**, 66622-72-8; $(H_3C)_2C{=}CH_2$, 115-11-7; $H(CH_2)_4CH{=}CH_2$, 592-41-6; $H_2C{=}CH(CH_2)_4CH{=}CH_2$, 3710-30-3; $PhCH_2CH{=}CH_2$, 300-57-2; $(Ph)_2C{=}CH_2$, 530-48-3; $H_2C{=}CHCO_2Et$, 140-88-5; IPy_2BF_4, 15656-28-7; HBF_4, 16872-11-0; 1-cyclohexene, 110-83-8; 1,4-cyclohexadiene, 628-41-1; cholesteryl acetate, 604-35-3.

Enzymatic Approach to the Synthesis of the Pyrrolo[1,4]benzodiazepine Antibiotics[1]

Ahmed Kamal

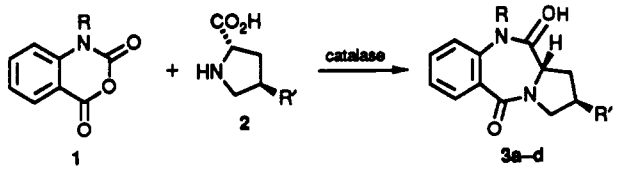
Division of Organic Chemistry, Indian Institute of Chemical Technology, Hyderabad-500 007, India

Received June 29, 1990

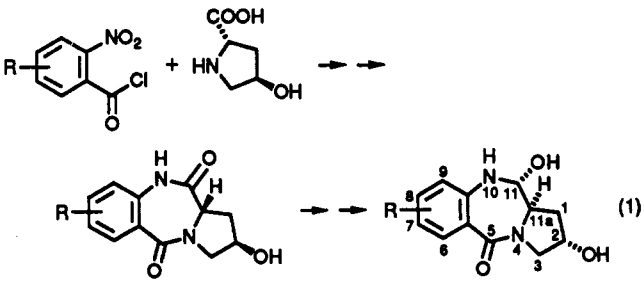
The pyrrolo[1,4]benzodiazepine (PBD) family of antitumor antibiotics[2] such as anthramycin, sibiromycin, tomaymycin, neothramycins A and B, prothacarcin, and chicamycins A and B are produced by various actinomycetes. These biosynthetically derived compounds are well known for inhibiting DNA replication on account of DNA–antibiotic adduct[3] through their C-11 carbinolamine functionality.

Leimgruber et al.[4] were the first to demonstrate the synthesis of anthramycin. This classical approach developed to the synthesis of PBD skeleton has proven sound enough that most of the syntheses devised for this antibiotic are based on it. Therefore, the dilactam obtained by the reaction of the pyrrolo ring with an aromatic electrophile[5] can be subsequently transformed to the carbinolamine or its equivalent imine in few steps (eq 1) by the combination of some methodologies.[6]

Scheme I[a]



[a] R = H, CH_3; R′ = H, OH.



(1)

We have been interested in the structural modifications for the synthetic analogues of PBD antibiotics[7] and also for the exploration of enzymes as biocatalysts[8] in organic synthesis. In this connection, enzymatic routes to the pyrrolo[1,4]benzodiazepine ring system are reported herein that utilize catalase-mediated condensation and liver microsomes mediated reductive cyclization. Furthermore, stereoselective reduction of pyrrolo[2,1-*c*][1,4]benzodiazepine-2,5,11-triones by bakers' yeast has been investigated.

Results and Discussion

Catalase-Mediated Condensations. The condensation of isatoic anhydride with proline is a well-established method for the preparation of aromatic ring unsubstituted PBD heterocyclic systems. This reaction is usually performed[7a] in solvents like DMSO/DMF at high temperatures (115–150 °C).

In an attempt to carry out this type of condensation under mild conditions many enzymatic methods were explored, as this can be of interest in the handling of sensitive groupings as well as their stereochemistry in the proline

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Table I. Catalase-Mediated Preparation of Pyrrolo[2,1-*c*][1,4]benzodiazepines, Esterification of *N*-(2-Nitrobenzoyl)prolines, and Their Reductive Cyclization by Liver Microsomes (3, 6, and 8)

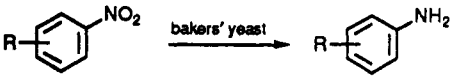
product	R	R^1	yield, %	mp, °C
3a	H	OH	76	221–222
3b	H	H	68	215–217
3c	CH_3	OH	72	149–151
3d	CH_3	H	65	198–200
6a	$C_6H_5CH_2$	OH	88	168–169
6b	$C_6H_5CH_2$	H	79	132–135
6c	C_66H_5CO	OH	83	149–150
6d	C_6H_5CO	H	85	126–128

substrate	R	R^1	product	R	R^1	yield, %
6a	$C_6H_5CH_2$	OH	**8a**	$C_6H_5CH_2$	OH	79
6b	$C_6H_5CH_2$	H	**8b**	$C_6H_5CH_2$	H	68
6c	C_6H_5CO	OH	**8c**	OH	OH	72
6d	C_6H_5CO	H	**8d**	OH	H	69
5a	$C_6H_5CH_2$	OH	**8a**	$C_6H_5CH_2$	OH	51
5b	$C_6H_5CH_2$	H	**8b**	$C_6H_5CH_2$	H	46
5c	C_6H_5CO	OH	**8c**	OH	OH	39
5d	C_6H_5CO	H	**8d**	OH	H	42

moiety. In this search, catalase has been found to be a useful biocatalyst in these condensations. Catalase[9] like peroxidases is well known to catalyze the hydroperoxy-dependent N-dealkylation of many aromatic secondary as well as tertiary amines. Recently, we have demonstrated the use of catalase in cyclization reactions.[10]

Condensation of isatoic anhydride 1 with proline 2 in presence of catalase at 22–25 °C gave the PBD's 3 in good yields (Table I, Scheme I). The reactions were monitored by TLC.

Reductive Cyclization Mediated by Liver Microsomes. Bakers' yeast catalyzed reduction of aromatic nitro compounds to the corresponding aromatic amines was recently reported[11] (eq 2). However, not much is known about the enzymatic reductive cyclizations. As such, the reductive cyclization of nitroamides 4 was investigated by the application of enzymes for the preparation of the PBD dilactam 6 and observed that liver microsomes gave good results.



(2)

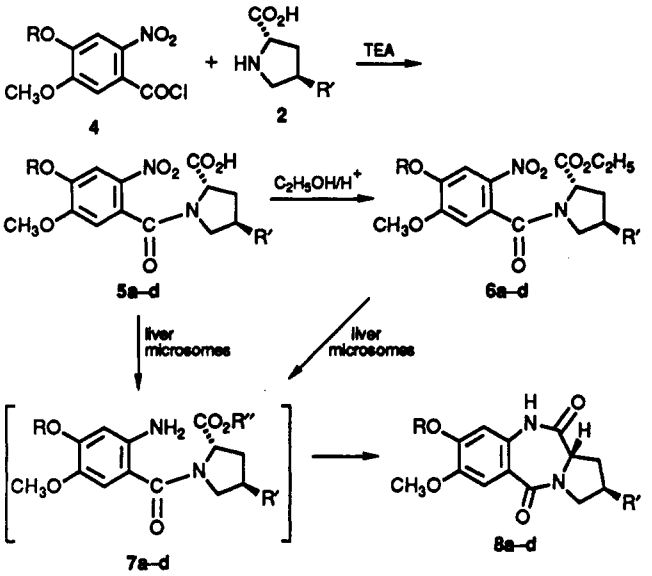
The appropriate precursor, *N*-(2-nitrobenzoyl)proline ethyl ester 6, was prepared by the reaction of substituted 2-nitrobenzoyl chlorides 4 with the respective proline 2 via its adduct 5 followed by its esterification. Thus, 6 on cyclization with rat liver microsomal fractions at 37 °C gave 8-substituted 1,2,3,10,11,11a-hexahydro-7-methoxy-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine-5,11-diones 8 in yields ranging from 68 to 81% (Table I, Scheme II).

However, enzymatic cyclization of 5 produced 8 but in low yields (Table I). In case of **5c–d** and **6c–d** the cyclization by liver microsomes was also accompanied by the enzymatic hydrolysis of the benzoyl functionality to afford 8-hydroxy dilactams **8c–d**.

It is conceived that the cyclization of 6 to 8 presumably takes place via the reduction of the nitro to amino but this intermediate 7 could not be isolated. A control incubation using a boiled microsomal preparation afforded 96% recovery of the starting compound 6.

The products were characterized by mass spectrometry and analtyical and spectroscopic data. These reactions

Scheme II[a]



[a] R = $C_6H_5CH_2$, C_6H_5CO; R' = H, OH; R'' = H, C_2H_5.

Table II. Bakers' Yeast Mediated Stereoselective Reduction of Pyrrolo[2,1-*c*][1,4]benzodiazepine-2,5,11-triones

compd	R	R^1	yield,[a] %	ee,[b] %
10a	H	H	75	>99
10b	$OCH_2C_6H_5$	OCH_3	71	97
10c	$OCOC_6H_5$	OCH_3	66	98

[a] Isolated yield. [b] Determined by HPLC employing LKB Enantiopac, αhAGP 10-μm column (4.0 × 100 mm), mobile phase, 8 mM NaH_2PO_4/Na_2HPO_4 buffer with 0.1 M NaCl and 30% 2-propanol, pH 7.0 at 0.3 mL/min flow rate and 230-nm wavelength.

were monitored by HPLC.[12] The enzymatic route described here suggests a strategy to prepare such classes of compounds by cyclization via reduction, under mild conditions, without the use of heat or acid.

Stereoselective Reduction by Bakers' Yeast. It is well established that the stereochemistry at C-2 is important for DNA binding, particularly in Chicamycin[13] and its synthetic analogues[5] (eq 3). In view of the ability of

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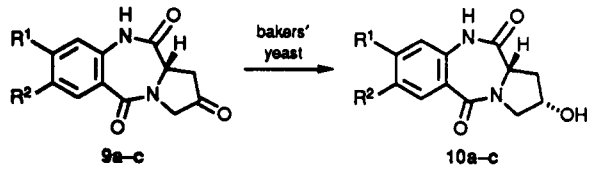
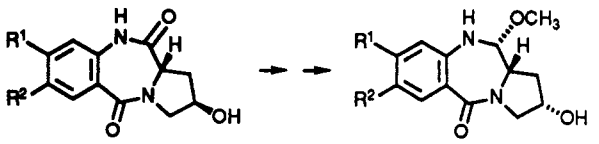
(12) Employing an UltroPac TSK ODS-120A, 5-m column (4.6 × 250 nm), water–methanol (70:30) with 0.5% AcOH (v/v) at 0.5 mL/min flow rate and 254-nm wavelength.
(13) Kaneko, T.; Wong, H.; Doyle, T. W. *J. Antibiot.* **1984**, *37*, 300.

Scheme III[a]



[a] R = H, $OCH_2C_6H_5$, $OCOC_6H_5$; R′ = H, OCH_3.

the microorganisms for the asymmetric reduction[14] of ketones, bakers' yeast was explored for the reduction of 2-oxo PBD's.



(3)

abbeymycin: $R^1 = R^2 = H$
chicamycin: $R^1 = OH$, $R^2 = OCH_3$

It was observed that the incubation of pyrrolo[2,1-*c*][1,4]benzodiazepine-2,5,11-trione with bakers' yeast gave stereoselective reduction of the C-2 carbonyl group in good yields with high ee's (Table II, Scheme III). The stereochemistry has been determined by NMR studies and is consistent with the literature findings[13] as the compound **10a** obtained is comparable to the sample prepared unambiguously.

In conclusion, the enzymatic approaches outlined here provide efficient synthesis of pyrrolobenzodiazepines. This study also demonstrates the condensation of an anhydride with an amino acid such as proline in presence of catalase and the liver microsomes mediated reductive cyclization of *N*-(2-nitrobenzoyl)proline for the first time.

Experimental Section

Melting points are uncorrected. ^1H and ^{13}C NMR (200 MHz) were taken in $CDCl_3$ + DMSO-d_6 with Me_4Si as internal standard.

(11a*S*)-2(*R*)-Hydroxy-1,2,3,10,11,11a-hexahydro-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine-5,11-dione (3a). General Procedure. To a solution of recrystallized isatoic anhydride (163 mg, 1.0 mmol) and *trans*-4-hydroxy-L-proline (170 mg, 1.3 mmol) in ethanol (10 mL) and 0.01 M phosphate buffer pH 7.2 (2 mL) was added catalase[15] (0.2 mL). The reaction mixture was incubated at 37 °C for 5 h with shaking (200 rpm). The incubation mixture was then extracted thrice with ethyl acetate (40 mL). The organic phase was separated, and the combined organic phases were dried over Na_2SO_4. The solvent was evaporated under reduced pressure to give the crude product **3a**, which was purified by column chromatography (silica gel, chloroform/methanol, 95:5) to afford 178 mg (77%) of the product as powder. This was recrystallized from ethyl acetate/hexane as colorless prisms: mp 221–222 °C; $[\alpha]^{25}_D$ +687° (*c* = 0.2, CH_3OH); IR (KBR) (cm^{-1}) 3420, 3240, 1670, 1605, 1435; ^1H NMR δ 2.12 (1 H, ddd, *J* = 12.6, 9.5, 4.2 Hz), 2.85 (1 H, dd, *J* = 14 Hz), 3.63 (1 H, dd, *J* = 13 Hz), 3.88 (1 H, dd, *J* = 13, 4 Hz), 4.23 (1 H, dd, *J* = 8, 6 Hz), 4.53 (1 H, m), 4.74 (1 H, d, *J* = 4 Hz), 7.09–7.47 (3 H, m), 7.93 (1 H, d, *J* = 8 Hz), 10.02 (1 H, br s); ^{13}C NMR 34.60, 54.30, 55.54, 68.07, 121.31, 124.28, 126.22, 130.70, 132.17, 136.04, 166.01, 170.58. Anal. Calcd for $C_{12}H_{12}N_2O_3$: C, 62.06; H, 5.12. Found: C, 62.29; H, 5.01.

(11a*S*)-1,2,3,10,11,11a-Hexahydro-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine-5,11-dione (3b). This dilactam was prepared from recrystallized isatoic anhydride and L-proline according to the general procedure: mp 215–217 °c; $[\alpha]^{25}_D$ +510° (*c* = 0.5, CH_3OH); IR (KBr) (cm^{-1}) 3230, 1665, 1610, 1430; ^1H NMR δ1.81–2.42 (4 H, m), 3.34–3.90 (3 H, m), 7.35–7.67 (4 H, m), 9.8 (1 H, s). Anal. Calcd for $C_{12}H_{12}N_2O_2$: C, 66.65; H, 5.60. Found: C, 66.52; H, 5.71.

(11a*S*)-2(*R*)-Hydroxy-10-methyl-1,2,3,10,11,11a-hexahydro-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine-5,11-dione (3c). This dilactam was prepared from *N*-methylisatoic anhydride (recrystallized from chloroform and hexane) and *trans*-4-hydroxy-L-proline according to the general procedure: mp 149–151 °C; $[\alpha]^{25}_D$ +435° (*c* = 0.008, $CHCl_3$); IR (KBr) (cm^{-1}) 3410, 2870, 1675, 1625, 1600, 1425; ^1H NMR δ 2.03 (1 H, m), 2.85 (1 H, m), 3.22 (1 H, br s), 3.38 (3 H, s), 3.63 (1 H, dd, *J* = 5, 13 Hz), 4.02 (1 H, br d, *J* = 13 Hz), 4.31 (1 H, dd, *J* = 5, 8 Hz), 4.72 (1 H, m), 7.22–7.49 (3 H, m), 7.83 (1 H, dd, *J* = 2, 8 Hz); ^{13}C NMR 35.21, 36.02, 54.21, 55.92, 68.78, 121.75, 125.82, 130.10, 130.51, 132.18, 140.67, 166.23, 170.02. Anal. Calcd for $C_{13}H_{14}N_2O_3$: C, 63.40; H, 5.73. Found: C, 63.56; H, 5.61.

(11a*S*)-10-Methyl-1,2,3,10,11,11a-hexahydro-5*H*-pyrrolo-[2,1-*c*][1,4]benzodiazepine-5,11-dione (3d). This dilactam was also prepared from recrystallized *N*-methylisatoic anhydride and L-proline according to the general procedure: mp 198–200 °C; $[\alpha]^{25}_D$ +485° (*c* = 0.2, CH_3OH); IR (KBr) (cm^{-1}) 3180, 1680, 1630, 1595, 1430; ^1H NMR δ 1.76–2.38 (4 H, m), 3.31–3.87 (6 H, m), 7.28–7.83 (4 H, m). Anal. Calcd for $C_{13}H_{14}N_2O_2$: C, 67.81; H, 6.13. Found: C, 67.78; H, 5.97.

4-(4,5-Disubstituted-2-nitrobenzoyl)prolines (5a–d). These were prepared by the reaction of acid chlorides **4** of 4,5-disubstituted 2-nitrobenzoic acid with prolines in THF using triethylamine as described in the literature.[5,16]

***N*-[5-Methoxy-4-(benzyloxy)-2-nitrobenzoyl]hydroxyproline Ethyl Ester (6a). General Procedure.** A solution of **5a** (2 g, 4.8 mmol) in ethanol (150 mL) with 5 drops of concentrated H_2SO_4 was refluxed for 5 h. Half of the ethanol was removed under vacuum. The reaction mixture was then poured into cold water (100 mL). The precipitate separated was filtered and recrystallized from aqueous ethanol to give the product **6a** (1.56 g, 88%): mp 168–169 °C; IR (KBr) (cm^{-1}) 3450, 1730, 1615, 1510, 1420; ^1H NMR δ 1.32 (3 H, t, *J* = 8 Hz), 2.18 (1 H, m), 3.17 (1 H, d, *J* = 11 Hz), 3.55 (1 H, dd, *J* = 11, 4 Hz), 3.98 (5 H, m), 4.27 (2 H, q, *J* = 7 Hz), 4.47 (1 H, br s), 4.82 (1 H, t, *J* = 8 Hz), 5.22 (2 H, s), 6.88 (1 H, s), 7.42 (5 H, m), 7.75 (1 H, s). Anal. Calcd for $C_{22}H_{24}N_2O_8$: C, 59.60; H, 5.41. Found: C, 59.32; H, 5.63.

Compounds **6b–d** were prepared according to the above general procedure.

(2*R*,11a*S*)-2-Hydroxy-8-(benzyloxy)-1,2,3,10,11,11a-hexahydro-7-methoxy-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine-5,11-dione (8a). General Procedure. To **6a** (50 mg, 0.1 mmol) dissolved in ethanol (1 mL) and 0.02 M phosphate buffer pH 7.4 (15 mL) was added freshly prepared microsomal suspension (3 mL). Incubation was performed under aerobic conditions at 37 °C for 20 h with shaking (250 rpm). Proteins were precipitated by the addition of acetonitrile (5 mL) to the incubation mixture. The incubation mixture was extracted thrice with ethyl acetate (30 mL). The organic phase was separated, and the combined organic phases were dried over Na_2SO_4. The solvent was evaporated under reduced pressure to afford the crude product **8a**, which was purified by column chromatography (silica gel, chloroform/ethyl acetate/methanol, 5:4:1): mp 232–233 °C; $[\alpha]^{25}$ +478° (*c* = 0.1, CH_3OH) (33 mg, 79% yield); IR (KBr) (cm^{-1}) 3500, 1680, 1600, 1550, 1435; ^1H NMR δ 2.07 (1 H, ddd, *J* = 14, 7, 6 Hz), 2.78 (1 H, dd, *J* = 13, 4 Hz), 3.45–3.82 (5 H, m), 3.89 (3 H, s), 4.19 (1 H, t, *J* = 7 Hz), 4.47 (1 H, m), 6.65–7.2 (6 H, m), 7.35 (1 H, s), 8.78 (1 H, br s). Anal. Calcd for $C_{20}H_{20}N_2O_5$: C, 65.20; H, 5.47. Found: C, 65.41; H, 5.33.

(11a*S*)-8-(Benzyloxy)-1,2,3,10,11,11a-hexahydro-7-methoxy-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine-5,11-dione (8b). This compound was prepared by the reductive cyclization of **6b** with rat liver microsomes and worked up according to the general procedure: mp 236–238 °C; $[\alpha]^{25}_D$ +452° (*c* = 0.12, CH_3OH); IR (KBr) (cm^{-1}) 3120, 1685, 1610, 1580; ^1H NMR δ 1.73–2.43 (4 H, m), 3.35–4.02 (6 H, m), 5.03 (2 H, s), 6.91–7.53 (7 H, m), 9.12 (1 H, br s). Anal. Calcd for $C_{20}H_{20}N_2O_4$: C, 68.17; H, 5.72. Found: C, 68.32; H, 5.68.

(14) Servi, S. *Synthesis* **1990**, 1, and references therein.
(15) Catalase from beef liver as solution in glycerol, 30% (v/v), ethanol 10% (v/v) ca. 260000 units/mL; obtained from Boehringer Mannheim.
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(2*R*,11a*S*)-2-Hydroxy-8-(benzoyloxy)-1,2,3,10,11,11a-hexahydro-7-methoxy-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine-5,11-dione (8c). This compound was prepared by the reductive cyclization of **6c** with rat liver microsomes and worked up according to the general pressure: mp 214–216 °C; $[\alpha]^{25}_D$ +471° (*c* = 0.14, CH_3OH); IR (KBr) (cm^{-1}) 3490, 1725, 1685, 1610, 1590; ^1H NMR δ 2.09 (1 H, m), 2.73 (1 H, m), 3.51–3.87 (3 H, m), 3.93 (3 H, s), 4.24 (1 H, m), 4.51 (1 H, m), 6.58–7.42 (7 H, m), 8.81 (1 H, br s). Anal. Calcd for $C_{20}H_{18}N_2O_6$: C, 62.82; H, 4.74. Found: C, 62.78; H, 4.89.

(11a*S*)-8-(Benzoyloxy)-1,2,3,10,11,11a-hexahydro-7-methoxy-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine-5,11-dione (8d). This compound was prepared by the reductive cyclization of **6d** with rat liver microsomes and worked up according to the general procedure: mp 197–198 °C; $[\alpha]^{25}_D$ +432° (*c* = 0.21, CH_3OH); IR (KBr) (cm^{-1}) 3130, 1720, 1675, 1615, 1595; ^1H NMR δ 1.98 (1 H, m), 2.69 (1 H, m), 3.47–3.76 (3 H, m), 3.89 (3 H, s), 4.12 (1 H, m), 4.58 (1 H, m), 6.63–7.38 (7 H, m), 8.76 (1 H, br s). Anal. Calcd for $C_{20}H_{18}N_2O_5$: C, 65.93; H, 4.43. Found: C, 65.76; H, 4.32.

Preparation of Liver Microsomal Fraction from Rat. General Procedure. Phenobarbital-treated male Wistar rats (body weight 150–200 g), fasted for 1 day before being killed, were used. A 10-volume homogenate in 0.25 M sucrose solution containing KCl (1.15% w/v) was prepared from livers by a standard procedure[17] and as described in our earlier work.[8a]

Microsomes were obtained from the postmitochondrial supernatant fraction (centrifuged at 15000*g*) of the homogenate by centrifugation at 105000*g* for 2 h and resuspended in 0.1 M phosphate buffer (pH 7.4). Protein content of the suspension determined by the method of Lowry et al.[18] was 5.6 mg/mL.

(11a*S*)-Pyrrolo[2,1-*c*][1,4]benzodiazepine-2,5,11-triones (9a–c). These were prepared by the Jones oxidation of 2(*R*)-hydroxypyrrolo[2,1-*c*][1,4]benzodiazepine-5,11-diones as described in the literature.[7a]

(2*S*,11a*S*)-2-Hydroxy-1,2,3,10,11,11a-hexahydro-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine-5,11-dione (10a). General Procedure. To a solution of **9a** (500 mg, 2.16 mmol) in 0.1 M phosphate buffer (100 mL, pH 7.4) was added bakers' yeast (*Saccharomyces cerevisiae*, Sigma, Type I; 10 g). Incubation was carried out under aerobic conditions at 37 °C with gentle shaking. Glucose (500 mg × 9 portions) was added at every 6 h. After 3 days, the incubation mixture was extracted thrice with ethyl acetate (100 mL) and on workup the crude product was obtained. This was purified by column chromatography (silica gel, dichloromethane/ethyl acetate/methanol, 6:3:1): mp 238–240 °C; $[\alpha]^{25}_D$ +433° (*c* 0.2, CH_3OH) (378 mg, 75% yield); IR (KBr) (cm^{-1}) 3425, 3240, 1680, 1610, 1435; ^1H NMR δ 2.29 (1 H, ddd, *J* = 14, 9, 5 Hz), 2.79 (1 H, br d, *J* = 14 Hz), 3.75 (2 H, d, *J* = 3 Hz), 4.09 (1 H, d, *J* = 6 Hz), 4.17 (1 H, dd, *J* = 2 Hz), 4.50 (1 H, m), 7.14–7.51 (3 H, m), 7.93 (1 H, dd, *J* = 8, 2 Hz), 10.43 (1 H, br s); ^{13}C NMR 34.06, 55.94, 56.42, 68.99, 121.60, 124.58, 126.78, 130.73, 132.33, 136.17, 165.66, 171.56. Anal. Calcd for $C_{12}H_{12}N_2O_3$: C, 62.07; H, 5.17. Found: C, 62.26; H, 5.31.

(2*S*,11a*S*)-2-Hydroxy-8-(benzyloxy)-1,2,3,10,11,11a-hexahydro-7-methoxy-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine-5,11-dione (10b). This material was obtained by the reduction of **9b** by bakers' yeast according to the general procedure: mp 241–243 °C; $[\alpha]^{25}_D$ +253° (*c* = 0.23, CH_3OH); IR (KBr) (cm^{-1}) 3490, 1685, 1610, 1595; ^1H NMR δ 2.36 (1 H, m), 2.81 (1 H, br d, *J* = 13 Hz), 3.58–3.78 (5 H, m), 3.93 (3 H, s), 4.37 (1 H, dd, *J* = 8, 3 Hz), 4.52 (1 H, m), 7.21–7.86 (6 H, m), 8.18 (1 H, dd, *J* = 8, 2 Hz), 8.91 (1 H, br s). Anal. Calcd for $C_{20}H_{20}N_2O_5$: C, 65.20; H, 5.47. Found: C, 65.07; H, 5.53.

(2*S*,11a*S*)-2-Hydroxy-8-(benzoyloxy)-1,2,3,10,11,11a-hexahydro-7-methoxy-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine-5,11-dione (10c). This material was obtained by the reduction of **9c** by bakers' yeast according to the general procedure: mp 251–252 °C; $[\alpha]^{25}_D$ +259° (*c* = 0.26, CH_3OH); IR (KBr) (cm^{-1}) 3505, 1720, 1680, 1610, 1590; ^1H NMR δ 2.39 (1 H, ddd, *J* = 13, 8, 5 Hz), 2.78 (1 H, d, *J* = 13 Hz), 3.56 (1 H, br d, *J* = 11 Hz), 3.79 (2 H, m), 3.97 (3 H, s), 4.38 (1 H, dd, *J* = 8, 3 Hz), 4.51 (1 H, m), 7.21–7.76 (6 H, m), 8.21 (1 H, dd, *J* = 8, 2 Hz), 8.85 (1 H, br s). Anal. Calcd for $C_{20}H_{18}N_2O_6$: C, 62.82; H, 4.74. Found: C, 62.63; H, 4.63.

Acknowledgment. Dr. A. V. Rama Rao, Director, for his interest and encouragement, and Mr. Zaheeruddin Ahmed for technical assistance are thanked.

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A Photochemically Based Synthesis of the Benzannelated Analogue of the CC-1065 A Unit

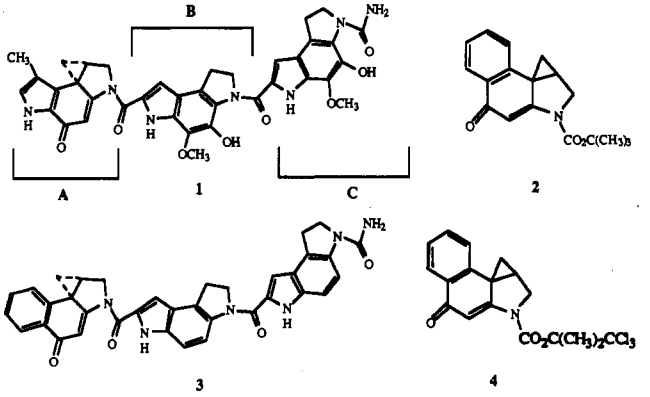
Kevin J. Drost and Michael P. Cava*

Department of Chemistry, The University of Alabama, Box 870336, Tuscaloosa, Alabama 35487-0336

Received August 20, 1990

The antibiotic CC-1065 (1) ranks among the most potent antineoplastic agents known, although its in vivo toxicity precludes its use as a practical anticancer agent.[1] For this reason, considerable effort has been directed toward the synthesis of potentially less toxic analogues containing modified B and C units[2] and, to a lesser extent, modified A units.[3]

Several recent communications have described the first reports of a simple derivative (2) of the benzannelated analogue (CBI) of the natural CC-1065 A unit (CPI),[3a] as well as a full A, B, C analogue (3) containing this unit.[3b] Since the cytotoxic potency of these compounds is equal to or better than their CPI analogues, alternate higher yielding routes to the CBI system are desirable objectives in order to facilitate the production of further CBI derivatives for biological studies. As part of our investigations in this area, we now report a photochemically based synthesis of (±)-TCBOC-CBI (4) which provides the target compound in 24% overall yield from *N*-benzylpyrrole-2-carboxaldehyde (5).



The synthesis of 4 began with heterostilbene 7, which was constructed via a Wittig–Horner reaction from al-

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0022-3263/91/1956-2240$02.50/0