chloride by the known procedure,[5] and 2-bromooctane having $[\alpha]^{20}_D$ +38.71° (neat) was obtained in 92% yield. This represents 97% inversion.[12]

Acknowledgment. We thank the Korea Advanced Institute of Science and Technology for financial support.

Registry No. $C_6H_5(CH_2)_2OTBDMS$, 78926-09-7; $C_6H_5(CH_2)_2OTBDPS$, 105966-41-4; $CH_3(CH_2)_8OTBDMS$, 71733-81-8; (–)-$CH_3(CH_2)_5CH(OTBDMS)CH_3$, 114127-43-4; $CH_3(CH_2)_5CH(OTBDPS)CH_3$, 105966-42-5; (*E*)-$CH_3(CH_2)_2CH{=}CHCH_2OTBDMS$, 113997-32-3; (*E*)-$CH_3(CH_2)_2CH{=}CHCH_2OTBDPS$, 11997-33-4; $CH_2{=}CHCH(OTBDMS)(CH_2)_4CH_3$, 107220-03-1; $C_6H_5CH_2OTBDMS$, 53172-91-1; $C_6H_5CH(OTBDMS)CH_3$, 92976-56-2; $C_6H_5CH(OTBDPS)CH_3$, 105966-44-7; $C_6H_5(CH_2)_2Br$, 103-63-9; $CH_3(CH_2)_8Br$, 693-58-3; (*E*)-$CH_3(CH_2)_2CH{=}CHCH_2Br$, 73881-10-4; $C_6H_5CH_2Br$, 100-39-0; $C_6H_5CHBrCH_3$, 585-71-7; (–)-2-bromooctane, 5978-55-2; (+)-2-bromooctane, 1191-24-8; *cis*-1-*tert*-butyl-4-[(*tert*-butyldimethylsilyl)oxy]cyclohexane, 71009-12-6; *trans*-1-*tert*-butyl-4-[(*tert*-butyldimethylsilyl)oxy]cyclohexane, 71009-16-0; 1-methyl-1-[(*tert*-butyldimethylsilyl)oxy]cyclohexane, 76358-83-3; 1-bromo-*trans*-2-octene, 56318-83-3; *cis*-1-bromo-4-*tert*-butylcyclohexane, 5009-36-9; *trans*-1-bromo-4-*tert*-butylcyclohexane, 5009-37-0; 1-bromo-1-methylcyclohexane, 931-77-1.

Synthesis of Monocyclic β-Lactams by the Photolytic Reaction of Chromium Carbene Complexes with *s*-1,3,5-Triazines

Louis S. Hegedus* and Stan D'Andrea

Department of Chemistry, Colorado State University, Fort Collins, Colorado 80523

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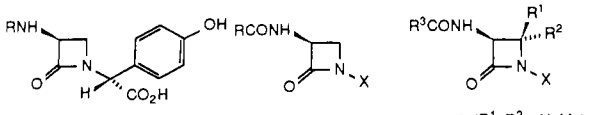
Introduction

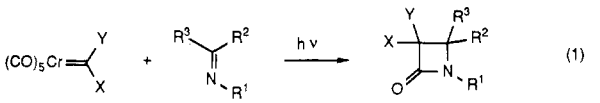
Following the discovery of naturally occurring monocyclic β-lactams such as the nocardicins **1** and the monobactams **2**, many synthetic analogues having more desirable biological properties have been developed.[1] These include monobactams alkylated at the 4–position (**3**).[2]



1 **2** (X = SO_3^-) **3** (R^1, R^2 = H, Me) (X = SO_3^-, OSO_3^-)

Nocardicins have been synthesized by the reaction of acid chlorides with a Schiff base,[3] by Ugi four-component condensation chemistry,[4] by β-halopropionamide ring closure, ring expansion, or azetidine carboxylate oxidative decarboxylation,[5] by Pd(0)-catalyzed carbonylation of α-bromoallylamine,[6] and by cyclization of the hydroxamic acid of *N*-boc-L-serine.[7] Monobactams have been synthesized from 6-APA,[8] and by cyclization of β-hydroxyacyl sulfamates[9] or of β-hydroxy hydroxamic acid derivatives.[10]

A new approach to β-lactams involving the photolytic reaction of chromium carbene complexes with imines has recently been developed in these laboratories (eq 1).[11] The application of this approach to the synthesis of monocyclic and bicyclic β-lactams is described below.



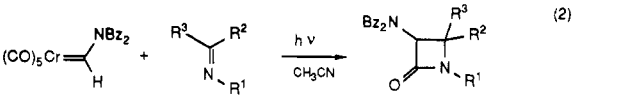
(1)

X = R; Y = OR', NR_2'

X = H; Y = NR_2'

Results and Discussion

The process described in eq 1 is very general, in that a wide variety of substituted imines are cleanly converted to β-lactams by this chemistry. A potential problem with its application to monobactam syntheses results from existence of the requisite aldehyde imines predominantly as cyclic trimers—hexahydro-1,3,5-triazines—rather than as imine monomers. One of the few formaldehyde imines that is monomeric is *N*-methylidene *tert*-butylamine, and this substrate converted cleanly to β-lactam **2a** upon irradiation in the presence of carbene complex **1** (eq 2). The monomeric *N*-benzyl imine of acetone also was converted to the corresponding β-lactam **2b**, in modest yield (eq 2).



(2)

1

2a R^1 = t-Bu; R^2, R^3 = H 72%

2b R^1 = Bz; R^2, R^3 = Me 56%

(Bz = $PhCH_2$)

Cyclic trimers of formaldehyde imines (eq 3) and carbocyclic imines (eq 4) also underwent efficient reaction with carbene complex **1**, producing azetidinone **3a,b**, carbapenam **4a**, and carbacepham **4b** derivatives in good yield.

Nocardicin precursors have recently been synthesized by the reactions of ketenes with the chiral imine produced in situ from the BF_3·etherate assisted cleavage of chiral, optically active trimer **5**. These reactions went in good yield and gave a 3:1 mixture of diastereoisomers, thus showing modest asymmetric induction.[12] In an attempt to use a similar process, chiral, optically active trimer **5** was photolyzed with carbene complex **1** (eq 5). Although

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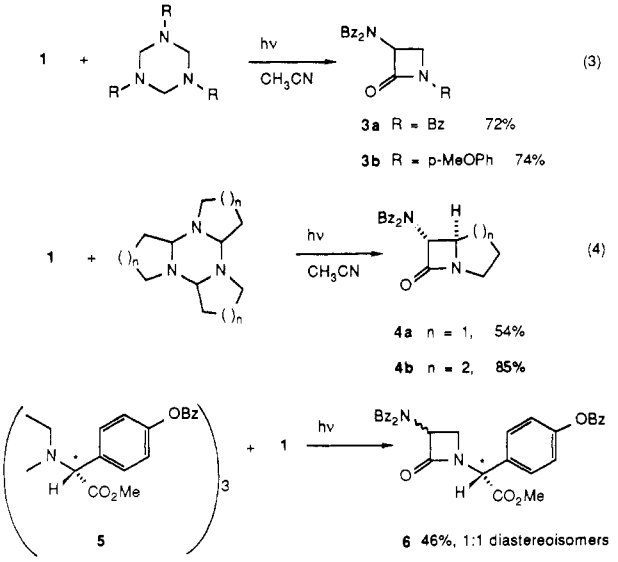
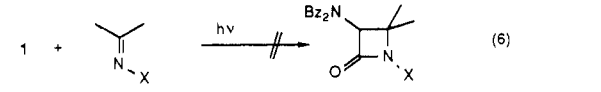
0022-3263/88/1953-3113$01.50/0

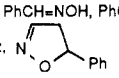


the unoptimized yield was reasonable (>85% crude yield, 46% purified yield), *no* asymmetric induction from the chiral center on the imine was observed, and a 1:1 mixture of diastereoisomers was obtained. Previous studies with sterically more demanding chiral, optically active imines had shown varying degrees of asymmetric induction, ranging from virtually 100% de with rigid cyclic imines to 15–58% de with various imines of benzaldehyde.[11b] The absence of asymmetric induction in eq 5 is attributed to the absence of a substituent at the imine sp^2 carbon. Asymmetric induction in a nocardicin synthesis using chiral optically active carbene complexes[13] is under current study.

In principle, biologically active O-sulfonated *N*-hydroxyazetidinones and oxoazetidine-1-sulfonic acids **2** should be available by the reaction of carbene complex **1** with appropriate oxime or sulfamic acid imine precursors, respectively (eq 6). In practice, both classes of C=N substrates failed to undergo productive conversion to the desired β-lactams, although very low yields could be detected in some instances. The substrates that failed are listed below eq 6.

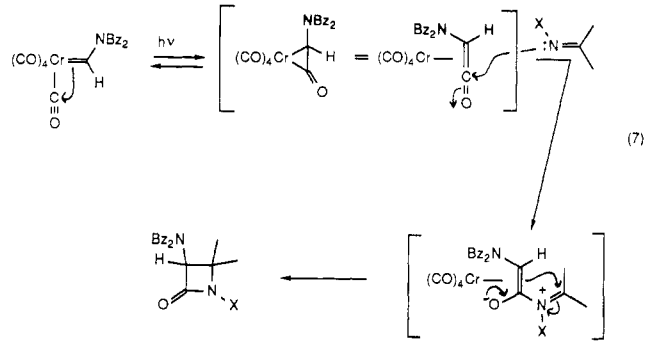


$(CH_2NOMe)_3$, PhCH=NOBz, H_2C=NOBz, H_2C=NOMe, PhCH=NOH, PhC(OMe)=NOH, PhC(OMe)=NOBz, Me_2C=$NOSO_2Ph$, EtO_2CCH=NOBz,



$(CH_2NSO_3^-NBu_4^+)_3$, $(CH_2NCO_2Bz)_3$, Me_2C=NCO_2Bz -- fail

Recent mechanistic studies[14] account for the lack of reactivity of these substrates. The β-lactam-forming reaction in eq 1 is now thought to involve the reaction of the imine substrate with a photogenerated, metal-bound ketene (eq 7). As such, it involves a two-step process that requires an imine nitrogen sufficiently *nucleophilic* to attack the metal–ketene complex, as well as an imine carbon sufficiently *electrophilic* to undergo the second step ring closure. Each of the unreactive substrates above lacks one of these essential features. While the oximes and oxime ethers are almost certainly sufficient nucleophiles to participate in the first step, they are not sufficient



electrophiles to undergo ring closure. In contrast, sulfamic and carbamic acid imines are probably insufficient nucleophiles to initiate the reaction, and hence fail to convert to β-lactams. Procedures to overcome this lack of reactivity of these interesting substrates are currently being studied.

Experimental Section

General Procedures. Melting points were taken on a Mel-Temp apparatus and are uncorrected. A Bruker/IBM-200 NMR spectrometer was used for the 200-MHZ ^1H NMR spectra. The 270-MHz ^1H NMR and the 67-MHz ^{13}C NMR spectra were obtained on a Bruker/IBM-270 NMR spectrometer. NMR spectra were recorded in $CDCl_3$ and chemical shifts are given in ppm relative to Me_4Si (=0 ppm; ^1H) or $CDCl_3$ (=77 ppm; ^{13}C). IR spectra were recorded on a Beckman 4240 spectrophotometer. Chemical ionization (CI) mass spectra were obtained on a V.G. Micromass Ltd., Model 16F spectrometer. Optical rotations were obtained on a Perkin-Elmer 24 polarimeter at a wavelength of 589 nm (sodium D line) using a 1.0 dm cell with a total volume of 1 mL. Specific rotations, $[\alpha]_D$, were reported in degrees per decimeter at room temperature (~23 °C) and the concentrations (*c*) given in grams per 100 mL in the specified solvent.

Irradiation of the reaction mixtures was carried out at a distance of 10 cm from a Conrad-Hanovia 7825 medium-pressure mercury lamp operating at 450-W, which was placed in a water-cooled immersion well. A Conrad-Hanovia 7830-C power supply was used.

For the purification of crude reaction mixtures, radial-layer (Chromatotron Model 7924) and column chromatographic techniques were applied in most cases. Merck silica gel 60 PF (for radial-layer chromatography) and Baker silica gel (60–200 mesh) (for column chromatography) were used as stationary phases.

Elemental analyses were performed by M-H-W Laboratories, Phoenix, AZ.

Materials. Hexane (technical grade) was distilled at atmospheric pressure. Ethyl acetate (technical grade) and methylene chloride (technical grade) were distilled from CaH_2. Acetonitrile (Fisher) was distilled from CaH_2 and stored over 4A molecular sieves. Diethyl ether (ASP, analytical reagent) was predried over CaH_2 and distilled from benzophenone ketyl under a nitrogen atmosphere just prior to use. Benzene (Mallinckrodt, analytical reagent) and 1,3,5-tribenzylhexahydro-*s*-triazine (Alfa) were obtained from commercial suppliers and used without further purification.

The following chemicals were prepared according to the literature procedures: [(*N*,*N*-dibenzylamino)methylene]chromium(0) pentacarbonyl,[13] methyl D-*p*-(benzyloxy)phenylglycine hydrochloride,[15] hexahydro-1,3,5-tris(4-methoxyphenyl)-*s*-triazine,[17] formaldoxime *O*-benzyl ether,[18] *N*-benzylacetone imine,[19] *tert*-butylazomethine,[20] Δ^1-piperideine,[21] 1-pyrroline trimer.[22]

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General Procedure for the Synthesis of β-Lactams by the Photolytic Reaction of Hexahydro-*s*-triazines with [(*N*,*N*-Dibenzylamino)methylene]chromium(0) Pentacarbonyl. The chromium carbene complex 1 (0.80 g, 2.0 mmol) and the *s*-triazine (0.66 mmol) were dissolved in acetonitrile (120 mL) and divided into two Kontes Airless-ware storage tubes (22 × 330 mm, 75 mL). The reaction vessels were sealed with rubber septa, evacuated, and purged with argon (five cycles) to replace air with argon. The reaction vessels were irradiated with a 450-W UV lamp. The progress of the reaction was monitored by analytical TLC (silica gel). The reaction mixture turned from yellow to green or brown as the reaction proceeded. After complete consumption of the carbene complex (TLC), the solvent was evaporated from the combined reaction mixtures, and the residue was taken up in ethyl acetate. The mixture was then placed in a light box equipped with six 20-W Vitalite fluorescent lamps or on the roof top under sunlight to air-oxidize the chromium-containing by-product(s). After 1–2 days in the light box or 8 h on a sunny day on the roof, the solution was clear and contained a brown precipitate. The precipitate was removed by filtration through Celite. In some cases it proved helpful to filter the reaction mixture 1–2 times during the oxidation. The clear filtrate was evaporated under reduced pressure and the residue purified by chromatography as described in each synthesis.

Synthesis of 2a. According to the general procedure, the carbene complex 1 (0.80 g, 2.0 mmol) and *tert*-butylazomethine (0.19 g, 2.2 mmol) were irradiated for 18 h. Standard isolation gave 0.60 g of crude product which was purified by chromatography over Florisil (Aldrich, 60–100 mesh) eluting with 1:5 ether/hexane to give 0.46 g (72%) of **2a** as a colorless oil, which solidified upon standing: mp 54–56 °C; ^{1}H NMR (270 MHz) δ 1.29 (s, 9, $(CH_3)_3C$), 3.06 (dd, J = 6,[23] 2 Hz, 1, NCH_2CH), 3.10 (dd, J = 6, 6 Hz, 1, NCH_2CH), 3.68 (d, J = 14 Hz, 2, $PhCH_2$), 3.78 (d, J = 14 Hz, 2 $PhCH_2$), 4.07 (dd, J = 5, 2 Hz, 1, CH), 7.20–7.40 (m, 10, Ar H); ^{13}C NMR δ 167.2 (CO), 138.3, 128.7, 127.9, 126.8 (ArC), 66.4 (Bz_2NCH), 54.7 and 52.5 ($PhCH_2N$ and Me_3CN), 40.9 (NCH_2), 27.3 (CH_3); IR (film) ν 1740 (C=O) cm^{-1}. Anal. Calcd for $C_{21}H_{26}N_2O$: C, 78.22; H, 8.13; N, 8.69. Found: C, 78.42; H, 7.80; N, 8.79.

Synthesis of 2b. Following the general procedure, carbene complex 1 (0.80 g, 2.0 mmol) and *N*-benzylacetone imine (0.30 g, 2.1 mmol) were irradiated for 48 h. Standard isolation gave 0.71 g of crude product. Purification by Chromatotron chromatography (silica gel, 1:2 ether/hexane) gave 0.41 g (56%) of **2b** as a colorless oil: ^{1}H NMR (270 MHz) δ 0.92 (s, 3, CH_3), 1.21 (s, 3, CH_3), 3.77 (s, 1, CH), 3.88 (s, 2, $PhCH_2NCO$), 4.16 (d, J = 15 Hz, 2, $PhCH_2N$), 4.42 (d, J = 15 Hz, 2, $PhCH_2N$), 7.20–7.40 (m, 15, Ar H); ^{13}C NMR δ 167.0 (CO), 138.9, 137.3, 129.0, 128.5, 128.2, 128.2, 127.4, 127.0 (Ar C), 77.9 and 63.1 (Me_2C and Bz_2NCH), 56.5 ($PhCH_2N$), 42.7 ($PhCH_2NCO$), 24.7 and 21.6 (CH_3); IR (film) ν 1740 (C=O) cm^{-1}. Anal. Calcd for $C_{26}H_{28}N_2O$: C, 81.21; H, 7.34; N, 7.29. Found: C, 81.23; H, 7.23; N, 7.29.

Synthesis of 3a. The carbene 1 (0.80 g, 2.0 mmol) and hexahydro-1,3,5-tribenzyltriazine (0.24 g, 0.66 mmol) were irradiated (18 h) as described in the general procedure. Standard isolation, substituting hexane for ethyl acetate during air oxidation, gave 0.71 g of crude product. Purification by Chromatotron chromatography (silica gel, 3:2 ether/hexane) gave 0.51 g (72%) of **3a** as a colorless oil. Crystals were obtained from pentane for analytical purposes: mp 71 °C; ^{1}H NMR (270 MHz) δ 3.05 (m, 2, CH_2NCO), 3.65 (d, J = 14 Hz, 2, $PhCH_2$), 3.80 (d, J = 14 Hz, 2, $PhCH_2$), 4.29 (m, 1, CH), 4.32 (d, J = 15 Hz, 1, NCHPh), 4.40 (d, J = 15 Hz, 1, CONCHPh), 7.19–7.37 (m, 15, Ar H); ^{13}C NMR δ 168.5 (CO), 138.3, 135.6, 128.8, 128.6, 128.1, 128.0, 127.5, 127.0 (Ar C), 69.1 (Bz_2NCH), 55.1 ($PhCH_2N$), 45.6 and 43.8 ($PhCH_2NCO$ and $BzNCH_2$); IR (film) ν 1750 (C=O) cm^{-1}; mass spectrum (CI-NH_3), m/z 357 (M + 1). Anal. Calcd for $C_{24}H_{24}N_2O$: C, 80.87; H, 6.79; N, 7.86. Found: C, 80.67; H, 6.75; N, 7.82.

Synthesis of 3b. Following the general procedure, chromium carbene complex 1 (0.80 g, 2.0 mmol) and hexahydro-1,3,5-tris-(4-methoxyphenyl)triazine (0.41 g, 1.0 mmol) were irradiated for 18 h. Standard isolation gave 0.75 g of a yellow oil. Purification by Chromatotron chromatography (silica gel, 1:1 ether/hexane) gave 0.55 g (74%) of **3b** as white crystals: mp 104 °C; ^{1}H NMR (270 MHz) δ 3.44 (dd, J = 6, 3 Hz, 1, NCH_2CH), 3.50 (dd, J = 6, 6 Hz, 1, NCH_2CH), 3.76 (d, J = 14 Hz, 2, $PhCH_2$), 3.77 (s, 3, OMe), 3.85 (d, J = 14 Hz, 2, $PhCH_2$), 4.40 (dd, J = 5, 3 Hz, 1, CH), 6.84 (d, J = 7 Hz, 2, Ar H), 7.20–7.40 (m, 12, Ar H); ^{13}C NMR δ 165.3 (CO), 156.3, 138.2, 131.9, 128.9, 128.2, 127.2, 117.7, 114.4 (Ar C), 68.2 (Bz_2NCH), 55.4 and 55.2 (OMe and $PhCH_2N$), 43.6 (CH_2NCO); IR (film) ν 1740 (C=O) cm^{-1}. Anal. Calcd for $C_{24}H_{24}N_2O_2$: C, 77.39; H, 6.49; N, 7.52. Found: C, 77.22; H, 6.51; N, 7.52.

Synthesis of Carbapenam 4a. Chromium carbene complex 1 (0.40 g, 1.0 mmol) and 1-pyrroline trimer (0.07 g, 0.33 mmol) were dissolved in 60 mL of acetonitrile and placed in a large Pyrex test tube. After sealing the reaction vessel with a rubber septum, the system was evacuated and purged with argon (three cycles). The reaction mixture was irradiated at 0 °C for 43 h. Standard isolation gave 0.29 g of crude product as a yellow oil. Purification by Chromatotron chromatography gave 0.14 g (48%) of 1-carbapenam **4a** as a colorless oil, which solidified upon standing: mp 71 °C; ^{1}H NMR (270 MHz, benzene-d_6) δ 0.65 (m, 1, C1H); 1.27 (m, 3, two C2H, C1H), 2.32 (m, 1, C3H), 3.18 (m, 1, C5H), 3.29 (m, 1, C3H), 3.68 (d, J = 14 Hz, 2, $PhCH_2$), 3.67 (d, J = 2 Hz, 1, C6H), 3.81 (d, J = 14 Hz, 2, $PhCH_2$) (assignments were determined by a 2-D COSY experiment using a Bruker-500 NMR spectrometer), 7.1–7.4 (m, 10, Ar H); ^{13}C NMR δ 176.5 (CO), 138.6, 129.0, 128.3, 127.2 (Ar C), 75.7 (C5), 57.7 and 55.9 ($PhCH_2N$ and C6), 45.3 (C3), 29.6 and 28.7 (C1 and C2); IR (film) ν 1750 (C=O) cm^{-1}; mass spectrum (CI-NH_3), m/z 307 (M + 1). Anal. Calcd for $C_{20}H_{22}N_2O$: C, 78.40; H, 7.24; N, 9.14. Found: C, 78.19; H, 7.24; N, 8.99.

Synthesis of 1-Carbacepham 4b. Following the general procedure above, using chromium carbene complex 1 (0.80 g, 2.0 mmol) and Δ^1-piperideine (0.17 g, 0.66 mmol), the reaction was complete after 24 h. Standard isolation gave 0.55 g (85%) of 1-carbacepham **4b** as a colorless oil, which solidified upon standing: mp 100–101 °C; ^{1}H NMR (270 MHz) δ 1.10 (m, 1, CH_2), 1.31 (m, 2, CH_2), 1.68 (m, 1, CH_2), 1.82 (m, 2, CH_2), 2.72 (m, 1, CH_2), 3.33 (m, 1, CONCH), 3.67 (d, J = 14 Hz, 2, $PhCH_2$), 3.82 (d, J = 14 Hz, 2, $PhCH_2$), 3.82 (d, J = 1 Hz, 1, Bz_2NCH), 3.82 (m, 1, $CONCH_2$) (assignments confirmed by ^{1}H decoupling experiments), 7.23–7.39 (m, 10, Ar H); ^{13}C NMR δ 165.9 (CO), 138.4, 128.8, 128.0, 126.9 (Ar C), 77.8 (NCH_2), 55.5 and 52.9 ($PhCH_2N$ and Bz_2NCH), 38.5, 29.2, 24.2, 22.1 (CH_2); IR (film) ν 1745 (C=O) cm^{-1}. Anal. Calcd for $C_{21}H_{24}N_2O$: C, 78.72; H, 7.55; N, 8.74. Found: C, 78.81; H, 7.50; N, 8.75.

Synthesis of *s*-Triazine 5. Trimer **5** was prepared according to a modification of the method described by T. Kamiya et al.[12,16] Methyl D-*p*-(benzyloxy)phenylglycinate hydrochloride[15] (1.0 g, 3.3 mmol) was dissolved in 70 mL of ethyl acetate/water (1:1), 37% aqueous formaldehyde (0.26 g, 3.3 mmol) was added, and the mixture was cooled to 0 °C. With rapid stirring sodium bicarbonate (0.27 g, 3.3 mmol) was added all at once. The reaction mixture was stirred at 0 °C for 1 h and at room temperature for 2 h. At this time the reaction mixture was partitioned between diethyl ether (100 mL) and H_2O (100 mL). The layers were separated, and the aqueous layer was extracted with ether (2 × 50 mL). The combined ether layers were dried ($MgSO_4$), and the solvent was removed at reduced pressure to give 0.89 g (97%) of the desired product as a white foam which turns to glass: mp 67–69 °C; ^{1}H NMR (270 MHz, benzene-d_6) δ 3.23 (s, 3, OMe), 3.80 (br s, 2, NCH_2N), 4.61 (s, 2, $PhCH_2O$), 4.65 (s, 1, CH), 6.71 (d, J = 9 Hz, 2, Ar H), 7.1 (m, 5 Ar H), 7.43 (d, J = 9 Hz, 2, Ar H); ^{13}C NMR δ 171.5 (ester CO), 158.6, 136.7, 129.5, 128.1, 127.9, 127.5, 127.0, 114.7 (Ar C), 69.8, 69.0, and 66.9 (OCH_2Ph, NCH_2N, and $NCH(CO_2Me)(Ar)$), 51.1 (OMe); IR (film) ν 1740 (C=O), 1610, 1510, 1240, 1200, 1170, 1020 cm^{-1}. Anal. Calcd for $C_{51}H_{51}N_3O_9$: C, 72.07; H, 6.05; N, 4.94. Found: C, 72.02; H, 6.13; N, 5.00.

Synthesis of Nocardicin Precursors 6. Following the general procedure, chromium carbene complex 1 (0.80 g, 2.0 mmol) and *s*-triazine **5** (0.57 g, 0.66 mmol) were dissolved in 60 mL of acetonitrile and irradiated for 18 h. Standard isolation gave 0.72 g of crude product as a yellow oil. Purification by Chromatotron chromatography (silica gel, 1:1 ether/hexane) gave 0.48 g (46%) of **6** as a 1:1 mixture of diastereoisomers. Separation of dia-

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stereoisomers by preparative TLC (silica gel, 9:1 benzene/ethyl acetate) gave 0.18 g (17%) of **6a** as a white solid and 0.20 g (19%) of **6b** as a colorless oil.

6a (low R_f): mp 123–125 °C; ^{1}H NMR (270 MHz) δ 3.02 (dd, J = 6, 2 Hz, 1, NCH_2), 3.50 (m, 1, CONCH_2), 3.53 (d, J = 14 Hz, 2, NCH_2Ph), 3.70 (s, 3, OMe), 3.72 (d, J = 14 Hz, 2, NCH_2Ph), 4.35 (dd, J = 5, 2 Hz, 1, NCH), 5.05 (s, 2, OCH_2Ph), 5.59 (s, 1, CHCO$_2$Me), 6.96 (d, J = 9 Hz, 2, Ar H), 7.17 (d, J = 9 Hz, 2, Ar H), 7.20–7.40 (m, 15, Ar H), ^{13}C NMR δ 169.9 (ester CO), 168.7 (β-lactam CO), 159.1, 138.3, 136.7, 129.3, 128.9, 128.5, 128.2, 128.0, 127.3, 127.1 126.1, 115.5 (Ar C), 70.2 (OCH_2Ph), 68.4 (Bz$_2$NCH), 56.8 (PhCH_2N), 54.9 and 52.2 (OMe and NCH(CO$_2$Me)(Ar)), 43.3 (CONCH_2); IR (film) ν 1745 (ester C=O and β-lactam C=O) cm^{-1}; $[\alpha]^{25}_D$ -98.4 (c 5.5, CH_2Cl_2). Anal. Calcd for $C_{33}H_{32}N_2O_4$: C, 76.13; H, 6.20; N, 5.38. Found: C, 76.12; H, 6.21; N, 5.43.

6b (high R_f): ^{1}H NMR (270 MHz) δ 3.00 (dd, J = 5, 5 Hz, 1, CONCH_2), 3.64 (dd, J = 6, 2 Hz, 1, CONCH_2), 3.72 (d, J = 14 Hz, 2, PhCH_2N), 3.72 (s, 3, OMe), 3.85 (d, J = 14 Hz, 2, PhCH_2N), 4.19 (dd, J = 5, 2 Hz, 1, Bz$_2$NCH), 5.04 (s, 2, OCH_2Ph), 5.57 (s, 1, CHCO$_2$Me), 6.94 (d, J = 9 Hz, 2, Ar H), 7.14 (d, J = 9 Hz, 2, Ar H), 7.20–7.40 (m, 15, Ar H); ^{13}C NMR δ 169.9 (ester CO), 168.5 (β-lactam CO), 159.1, 138.5, 136.7, 129.3, 128.8, 128.5, 128.2, 127.9, 127.2, 127.0, 125.8, 115.4 (Ar C), 70.1 (OCH_2Ph), 68.4 (Bz$_2$NCH), 56.6 (PhCH_2N), 54.8 and 52.2 (OMe and NCH(CO$_2$Me)(Ph)), 42.9 (CONCH_2); IR (film) ν 1750 (ester CO and β-lactam CO) cm^{-1}; $[\alpha]^{25}_D$ -102.2 (c 7.7, CH_2Cl_2).

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Dragmacidin, a New Cytotoxic Bis(indole) Alkaloid from a Deep Water Marine Sponge, *Dragmacidon* sp.[1]

Shigeo Kohmoto, Yoel Kashman,† Oliver J. McConnell,* Kenneth L. Rinehart, Jr., Amy Wright, and Frank Koehn

Harbor Branch Oceanographic Institution/SeaPharm Project, 5600 Old Dixie Highway, Fort Pierce, Florida 33450

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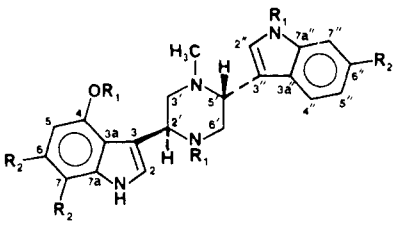
From our efforts to identify marine natural products with cytotoxic and antitumor activity, we found an extract from a deep water marine sponge, *Dragmacidon* sp. Hallman, 1917,[2] which inhibited the in vitro growth of P388 murine leukemia cells. The active constituent of the extract is a new bis(indole) alkaloid, dragmacidin (**1a**) (6,7-dibromo-3-[5-(6-bromoindol-3-yl)-4-methyl-2-piperazinyl]-indol-4-ol.[3] In in vitro assays, **1a** yielded IC_{50} values of 15 μg/mL against P388 cells and 1–10 μg/mL against A-549 (human lung), HCT-8 (human colon), and MDAMB (human mammary) cancer cell lines. Although numerous marine natural products contain an indole or a tryptamine unit,[4] few marine natural products contain two such groups, and none, to our knowledge, contains an unoxidized piperazine ring.

The molecular formula of **1a** was deduced as $C_{21}H_{19}Br_3N_4O$ from HRFABMS and DEPT and proton-decoupled ^{13}C NMR experiments (5 sp^3 (2 d, 2 t, and 1 q) and 16 sp^2 (10 s and 6 d) hybridized carbon signals observed) and requires eight double bonds and five rings.



1a: R_1 = H, R_2 = Br
1b: R_1 = Ac, R_2 = Br
1c: R_1 = R_2 = H

The presence of the partial structure 6-bromoindol-3-yl was suggested by the proton chemical shifts and respective coupling constants at δ 7.13 (H-5″, dd, J = 1.8 and 8.6 Hz), 7.59 (H-7″, d, J = 1.8 Hz), and 7.84 (H-4″, d, J = 8.6 Hz). The chemical shifts and coupling constants for H-4″, H-5″, and H-7″ are similar to those observed for eudistomin K,[5] clionamide,[6] and aplysinopsin-related indoles.[7] Several 2D NMR experiments, including COSY,[8] HETCOR,[9] COLOC,[10] and HETCOSY,[11] facilitated complete carbon and proton assignments for C-2″–C-7″ (Table I). This partial structure was supported by data from the IR and UV spectra.[12] The large extinction coefficients in the UV spectrum argue for the presence of two indole chromophores in **1a**.

The presence of a second indole moiety in **1a** was also apparent in the (LREI) mass spectral fragmentation pattern of the triacetyl derivative (**1b**). The base peaks observed at m/z 289/291/293, which contain two bromines, are consistent with the presence of dibromohydroxyindole ($C_8H_5NOBr_2$). Further evidence for dibromohydroxyindole in **1a** came from long-range HETCOR and HETCOSY experiments (Table I). The proton and carbon signals observed at δ 7.27 and 122.2, respectively, were assigned to C-2, and the carbon signals observed at δ 117.7, 118.2, and 138.1 were assigned to C-3a, C-3, and C-7a, respectively. In addition, the proton signal observed at δ 6.7 (s) showed direct scalar coupling to a carbon resonating at δ 110.5 (d) and long-range coupling to carbon signals observed at δ 153.1 (s), 118.5 (s), 95.6 (s),

† On leave from the Department of Chemistry, Tel-Aviv University, 69978 Tel-Aviv, Israel.

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(2) The sponge was identified by C. Diaz (HBOI/SeaPharm Project) and R. W. M. VanSoest (University of Amsterdam, Institute for Taxonomic Zoology) per the description of *Dragmacidon* sp. (family Axinellidae) in Hallman, E. F. *Proc. Linn. Soc. N.S.W.* **1917**, *41*, 634–675. A voucher specimen of the sponge (2-VI-84-3-15) is located at the HBOI/SeaPharm Project research laboratory in Ft. Pierce, FL. As far as the authors are aware, specimens of this genus have not been studied chemically previously.

(3) We thank Dr. K. L. Loening, Chemical Abstracts Service, for assistance in naming dragmacidin (**1a**). The absolute configurations were not assigned.

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