285.1728, found 285.1719. Anal. Calcd: C, 75.75; H, 8.12; N, 4.91. Found: C, 75.55; H, 8.07; N, 4.85.

Biohydroxylation of *N*-Benzoyl-1,8,8-trimethyl-3-azabrendane (3). Starting from 960 mg of 1*RS*-3[10] (300 mg/L of culture), one obtains, after HPLC purification (10% EtOH–hexane eluant), 186 mg of starting material, 45 mg of **6** (5%), 310 mg of **4** (30%), and 310 mg of **5** (30%).

***N*-Benzoyl-11-hydroxy-1,8,8-trimethyl-3-azabrendane (4):** mp 124–125 °C; IR (cm^{-1}) 3400, 1600; ^1H NMR 0.84–1.06 (m, 6 H, CH_3) (main peaks at 0.84 and 0.90),[11] 1.10–1.40 (m, 2 H), 2.00–2.50 (m, 5 H), 3.20–4.40 (m, 5 H), 7.40 (m, 5 H); ^{13}C NMR 57.3 (55.4) (C_1),[12] 67.1 (64.7) (C_2), 52.4 (54.7) (C_4), 41.2 (43.1) (C_5), 37.1 (36.7) (C_6), 39.8 (40.1) (C_7), 53.7 (C_8), 40.0 (38.6) (C_9), 12.1 (12.4) (C_{10}), 66.1 (66.4) (C_{11}), 15.8 (C_{12}), 169.9 (C_{13}), 127.1 (126.9), 128.3, 129.7, 137.4 (ar). Exact mass calcd for $C_{18}H_{23}NO_2$ 285.1728, found 285.1719. Anal. Calcd: C, 75.75; H, 8.12; N, 4.91. Found: C, 75.65; H, 8.18; N, 4.86.

***N*-Benzoyl-12-hydroxy-1,8,8-trimethyl-3-azabrendane (5):** mp 126–127 °C; IR (cm^{-1}) 3400, 1600; ^1H NMR 0.85–1.08 (m, 6 H, CH_3) (main peaks at 0.85 and 1.05),[11] 1.14–2.50 (m, 7 H), 3.18–4.22 (m, 5 H), 7.40 (m, 5 H); ^{13}C NMR 57.3 (55.3) (C_1),[12] 66.2 (63.8) (C_2), 51.3 (53.7) (C_4), 41.9 (43.8) (C_5), 37.7 (37.2) (C_6), 40.0 (40.1) (C_7), 53.9 (C_8), 39.3 (38.0) (C_9), 12.0 (12.2) (C_{10}), 15.3 (15.2) (C_{11}), 66.6 (C_{12}), 169.9 (C_{13}), 127.1 (126.9), 128.3, 129.7, 137.4 (ar). Exact mass calcd for $C_{18}H_{23}NO_2$ 285.1728, found 285.1730. Anal. Calcd: C, 75.75; H, 8.12; N, 4.91. Found: C, 75.50; H, 8.03; N, 4.87.

***N*-Benzoyl-6-*exo*-hydroxy-1,8,8-trimethyl-3-azabrendane (6):** IR (cm^{-1}) 3400, 1600; ^1H NMR 0.76–1.25 (m, 11 H) (main peaks at 0.76, 0.87, and 1.15),[11] 1.74 (m, 1 H), 2.01–2.38 (m, 2 H), 2.8 (m, 1 H, OH), 3.25–4.20 (m, 3 H), 7.40 (m, 5 H, ar); ^{13}C NMR 58.2 (56.2) (C_1),[12] 65.3 (62.8) (C_2), 50.5 (52.8) (C_4), 51.1 (51.5) (C_5), 84.1 (83.9) (C_6), 53.2 (54.8) (C_7), 48.4 (C_8), 36.6 (35.0) (C_9), 11.2 (11.4) (C_{10}), 21.8 (C_{11}*),[13] 21.4 (21.3) (C_{12}*), 169.9 (C_{13}), 127.2 (126.9), 128.3, 129.8, 137.3 (ar). Exact mass calcd for $C_{18}H_{23}NO_2$ 285.1728, found 285.1719.

***N*-Benzyl-11-hydroxy-1,8,8-trimethyl-3-azabrendane (7).** A solution of **2** (100 mg, 0.35 mmol) in 6 mL of dry THF and $LiAlH_4$ (200 mg, 5.3 mmol) was heated under reflux for 18 h. After cooling, sequential addition of water (0.2 mL), 10% aqueous NaOH (0.6 mL), and water (0.2 mL), and filtration (THF wash), the filtrate was dried ($MgSO_4$) and concentrated in vacuo, affording 90 mg of crude **7** as a yellow oil. Purification by bulb-to-bulb distillation in a Kugelrohr apparatus at 220 °C (0.1 mm) gave 80 mg (84%) of **7**: IR (cm^{-1}) 3620 and 1030; ^1H NMR (CCl_4) 0.94 (s, 3 H, CH_3), 0.96 (s, 3 H, CH_3), 1.04–2.26 (m, 7 H), 2.40 (d, 1 H, H_4), 2.99 (d, 1 H, H_2), 3.16 (dd, 1 H, H_4), 3.30 (d, 1 H, H_{13}), 3.54 (d, 1 H, H_{13}), 3.70 (d, 1 H, H_{11}), 3.81 (d, 1 H, H_{11}), 7.21 (m, 5 H, ar); ^{13}C NMR 57.0 (C_1**),[13] 69.5 (C_2), 59.8 (C_4*), 43.5 (C_5#),[13] 32.6 (C_6), 39.6 (C_7#), 53.4 (C_8**), 38.9 (C_9), 13.2 (C_{10}), 67.0 (C_{11}), 16.0 (C_{12}), 58.4 (C_{13}*), 126.6, 128.2, 128.3, 141.0 (ar). Anal. Calcd for $C_{18}H_{25}NO$: C, 79.72; H, 9.29; N, 5.17. Found: C, 79.58; H, 9.37; N, 4.87. Reduction of **4** (70 mg, 0.24 mmol) with lithium aluminum hydride in THF by the procedure described above afforded 50 mg (75%) of **7** after Kugelrohr distillation. The spectral characteristics of the product are identical with those reported for the hydroxy amino compound from **2**.

***N*-Benzyl-12-hydroxy-1,8,8-trimethyl-3-azabrendane (8).** This product was obtained by LAH–THF reduction of 70 mg of **5** using the procedure described for **7**, which afforded 50 mg (75%) of an oily product **8**: IR (cm^{-1}) 3620 and 1000; ^1H NMR (CCl_4) 0.94 (s, 3 H, CH_3), 0.95 (s, 3 H, CH_3), 1.04–2.18 (m, 7 H), 2.41 (d, 1 H, H_4), 2.97 (d, 1 H, H_2), 3.09 (dd, 1 H, H_4), 3.27 (d, 1 H, H_{13}), 3.43 (d, 1 H, H_{13}), 3.72 (d, 1 H, H_{12}), 3.83 (d, 1 H, H_{12}), 7.21 (m, 5 H, ar); ^{13}C NMR 57.0 (C_1*), 68.6 (C_2), 58.5 (C_4), 44.3 (C_5#), 32.5 (C_6), 39.6 (C_7#), 54.0 (C_8*), 39.3 (C_9), 13.2 (C_{10}), 15.4 (C_{11}), 67.7 (C_{12}), 58.5 (C_{13}), 126.5, 128.1, 128.2, 141.0 (ar). Anal. Calcd for $C_{18}H_{25}NO$: C, 79.72; H, 9.29; N, 5.17. Found: C, 78.83; H, 9.26; N, 5.27.

X-ray Analysis of *N*-Benzyl-11-hydroxy-1,8,8-trimethyl-3-azabrendan-4-one (2). Crystal data: $C_{18}H_{23}NO_2$, M_r 285.37; orthorhombic; a = 18.738 (8) Å, b = 11.561 (5) Å, and c = 7.090 (4) Å; space group $P2_12_12_1$; Z = 4, ρ_{calcd} = 1.234 g cm^{-3}; λ = 1.5418 Å.

A crystal of dimensions 0.5 × 0.16 × 0.16 mm was mounted on a four-circle diffractometer, Philips PW1100, using graphite-monochromated Cu Kα radiation. From a total of 1670 measured independent reflections, 1317 with $I > 3\sigma(I)$ were considered observed. Lorentz and polarization corrections were applied. The structure was solved by direct methods using a local program[14] and refined by a large blocks least-squares method.[15] The refinement converged at R and R_w values of 0.049 and 0.047 respectively:

$$R = \sum||F_o| - |F_c||/\sum|F_o|$$

$$R_w = \{\sum w(|F_o| - |F_c|)^2/\sum wF_o^2\}^{1/2}$$

$$w = 1/\sigma^2(F_o) + 0.010\,657F_o^2$$

All hydrogen atoms were found on difference Fourier syntheses, and their atomic coordinates and isotropic thermal parameters were refined. Maximum residuals were 0.10 e $Å^{-3}$.

Atomic coordinates of non-hydrogen atoms and hydrogen atoms (Tables 1 and 2), anisotropic thermal parameters (Table 3), bond lengths (Table 4), and angles (Table 5) are available as supplementary material. Structure factors are available from the crystallographer authors.

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Registry No. **1**, 113132-67-5; **2**, 113132-68-6; **3**, 105512-51-4; **4**, 105512-52-5; **5**, 105562-05-8; **6**, 105512-53-6; **7**, 113132-69-7; **8**, 113215-78-4.

Supplementary Material Available: Tables of atomic coordinates, anisotropic thermal parameters, bond lengths, and angles (3 pages). Ordering information is given on any current masthead page.

(11) Because of the existence of two rotamers of the amide moiety, the signals of several ^1H groups are doubled. We indicate here the chemical shifts related to the more abundant rotamer.

(12) Owing to the existence of two rotamers of the amide moiety, several carbon atoms do lead to two NMR signals. We indicate here the chemical shift of the major rotamers; the one corresponding to the same carbon atom in the minor isomer is indicated in parentheses.

(13) The assignments of the carbon atoms marked by the same signs are interchangeable.

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Monobromination of Deactivated Active Rings Using Bromine, Mercuric Oxide, and Strong Acid

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Electrophilic substitution of aromatic hydrocarbons by bromine is a well-known organic reaction.[1] Recently, the reagents such as NBS in DMF,[2] bromine and thallium(III) acetate,[3] and $CuBr_2$,[4] have been successfully used for the

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Table I

product	yield, %	reactn time, h
bromobenzene	89	1.0
m-bromonitrobenzene	50	3.0
m-bromobenzoic acid	79	2.5
ethyl *m*-bromobenzoate	80	2.5
methyl *m*-bromobenzoate	78	2.5
m-bromobenzaldehyde	25	1.0
m-bromobenzonitrile	68	2.5
1,4-dibromobenzene	76	2.5
1-bromo-4-chlorobenzene	70	2.5

selective monobromination of reactive aromatic rings. However, no reliable, mild, and selective method exists for the monobromination of deactivated aromatic rings, except some examples[5] where monobromination can be effected, but each example has its own specific set of conditions. The present paper describes a simple method of general applicability for the monobromination of deactivated aromatic rings.

A mixture of mercuric oxide and bromine has been used as brominating reagent for saturated hydrocarbons,[6] but its utility for the aromatic rings has been reported to offer no advantage over the conventional methods. On the contrary, we have found that a mixture of mercuric oxide and bromine in the presence of concentrated sulfuric acid as a catalyst in carbon tetrachloride can be effectively used for the selective monobromination of deactivated aromatic substrates. The products (Table I) were identified by their melting points/boiling points and checked for purity by ^{1}H NMR spectra.

All reactions proceeded smoothly under reflux and gave good to excellent yields of the products. The same monobromo derivatives can also be obtained in slightly diminished yields by the prolonged (24–36 h) stirring of the reaction mixture at ambient temperature. Since no hydrogen bromide is evolved in these reactions, they may be carried out successfully in the open laboratory. The expense of using mercuric oxide as a reagent is compensated by its ease of recovery from mercuric oxide–mercuric bromide residue.[7]

The result with benzoic acid is noteworthy, since carboxylic acids are known to undergo decarboxylation to form bromides (modified Hunsdiecker reaction[8]) with bromine and mercuric oxide, but under our conditions no decarboxylation was observed. In case of esters a minor quantity of *m*-bromobenzoic acid was also isolated along with the desired products. In the reaction of benzaldehyde the main product was *m*-bromobenzoic acid (50%), presumably formed due to oxidation, along with a small quantity (25%) of the *m*-bromobenzaldehyde. These results indicate that the new reagent could be reliably used for the selective bromination of deactivated aromatic substrates.

General Method Used for Bromination. A mixture of the appropriate substrate (0.01 mol), bromine (0.01 mol), mercuric oxide (0.02 mol), concentrated sulfuric acid (1 mL), and carbon tetrachloride (60 mL) was refluxed with vigorous stirring till the reddish brown color of bromine disappeared from the reaction mixture. The reaction mixture was filtered in the hot state and residue extracted with more carbon tetrachloride. Evaporation of the filtrate and extracts gave the crude monobromo derivatives.

Registry No. Benzene, 71-43-2; bromobenzene, 108-86-1; nitrobenzene, 98-95-3; 3-bromonitrobenzene, 585-79-5; benzoic acid, 65-85-0; 3-bromobenzoic acid, 585-76-2; ethyl benzoate, 93-89-0; ethyl 3-bromobenzoate, 6091-64-1; methyl benzoate, 93-58-3; methyl 3-bromobenzoate, 618-89-3; benzaldehyde, 100-52-7; 3-bromobenzaldehyde, 3132-99-8; benzonitrile, 100-47-0; 3-bromobenzonitrile, 6952-59-6; 1,4-dibromobenzene, 106-37-6; chlorobenzene, 108-90-7; 1-bromo-4-chlorobenzene, 106-39-8.

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Cystodytins A, B, and C, Novel Tetracyclic Aromatic Alkaloids with Potent Antineoplastic Activity from the Okinawan Tunicate *Cystodytes dellechiajei*

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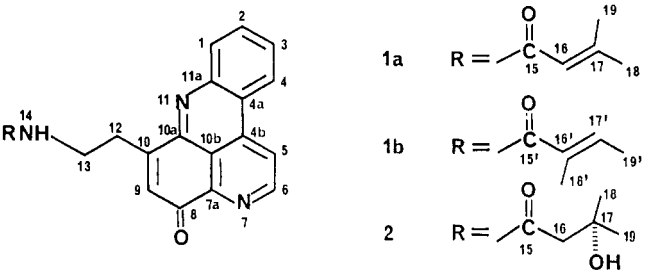
Many alkaloids, most of which exhibit a variety of biological activities, have been isolated from marine plants and animals.[2] During our studies on bioactive substances from tunicates,[3] cystodytins A (**1a**), B (**1b**), and C (**2**), novel



tetracyclic aromatic alkaloids with potent antineoplastic activity and powerful Ca-releasing activity in sarcoplasmic reticulum[3b] have been isolated from the Okinawan tunicate *Cystodytes dellechiajei*.[4] We report here the isolation and structure elucidation of **1a**, **1b**, and **2**. The carbon–carbon connectivities of **1a** and **1b** were unambiguously assigned on the basis of the results of ^{1}H-detected heteronuclear multiple-bond ^{1}H–^{13}C correlation (HMBC) recently reported by Bax.[5] The technique allows us to trace indirectly the complete carbon skeleton of a molecule by $^2J_{CH}$

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