gory, giving 95.5% overall correct classification, which compared very well with the results obtained using the nearest neighbor method (93.5% correct[4]) using the leave-one-out procedure.[2,4] (Comparison of these performances is justified because leaving out any one of the 223 compounds would not have changed the conclusions drawn from the analysis or the resulting flowchart.)

The above analysis indicates that the previous classification scheme using pattern recognition methods[4] was able to produce satisfactory results using the 20 features[6] because of a favorable distribution of "inactive structural features" between the active and inactive classes, e.g., presence of sulfur (see point (i) above) and presence of phenyl. (Only ten compounds contained phenyl in structures other than structure **1**—all ten were inactive. There were 33 compounds that contained structure **1** and phenyl—31 of these were active.) This accounts for the misleading conclusions[4] that the presence of C–S bonds, S–H bonds, and phenyl or halogen substitution increase the tendency for a compound to be positive (i.e., active). Indeed, if the data set had contained more sulfur, phenyl, or bromine compounds with structures other than structure **1** (i.e., inactive sulfur, phenyl, and halogen compounds), the pattern recognition methods would not have made these correlations. This illustrates the advantage, with "difficult" data, of having an interactive system which enables the chemist to optimize the relevance of questions to be asked.

On the assumption that the incorporation of various biologically active features into one compound may enhance activity, the above analysis suggests different combinations of structures that may show enhanced activity. One such combination is structure **1** with the addition of either fluorine, iodine, or trimethylammonium ion. Several compounds combining structure **1** and fluorine have been tested[7]—none showed enhanced activity. Two recent reviews of biologically active nucleoside derivatives[9] make no mention of compounds incorporating iodine or trimethylammonium ion in structure **1.**

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(6) Data from Table I of ref 4.
(7) Data from Table 2 of ref 5.
(8) In this work we extracted the 259 compounds in ref 7 that had been tested for activity with the CA755 test and deleted the compounds that were toxic to test animals or had tumor weight inhibition (TWI) between 50 and 70%, as outlined.[4] This still left 101 compounds with TWI greater than 70% (i.e., active) and 122 compounds with TWI less than 50% (i.e., inactive), a total of 223, which we used. The previous investigators deleted a further 23 compounds and used only 200.[4]
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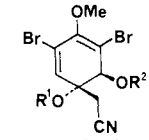
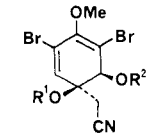
Synthesis of Aeroplysinin-1 and Related Compounds

Sir:

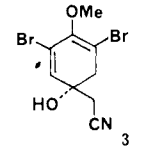
Marine sponges of the genus *Verongia* have yielded a number of interesting brominated metabolites,[1-3] some of which exhibit potentially useful biological activity. Aeroplysinin-1 (**1**), isolated as the (+)-enantiomer from *V. aerophoba*[2a] and as the (−)-enantiomer from *Ianthella ardis*,[4] displayed antibiotic activity against *S. Aureus* and antileukemia activity in the L-1210 screen. Aeroplysinin-1, the only naturally occurring 1-alkyl-1,2-dihydroxy-2*H*-arene, is of considerable biosynthetic interest since it is believed to be derived from an arene oxide *via* enzymatic hydration.[5] We wish to report the synthesis of aeroplysinin-1 (**1**) and the closely related compounds, isoaeroplysinin-1 (**2**) and 2-desoxyaeroplysinin-1 (**3**).



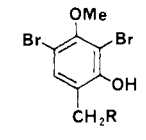
1 $R^1=R^2=H$
11 $R^1=R^2=Ac$



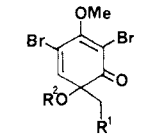
2 $R^1=R^2=H$
9 $R^1=Ac$, $R^2=H$
10 $R^1=R^2=Ac$



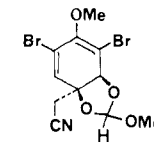
3



5 R=CN
7 R=H



6 $R^1=CN$, $R^2=Ac$
8 $R^1=H$, $R^2=Ac$
14 $R^1=CN$, $R^2=H$



12

3,5-Dibromo-2-hydroxy-4-methoxyphenylacetonitrile (**5**), mp 158°, obtained in 90% yield by the treatment of 2-hydroxy-4-methoxyphenylacetonitrile (**4**)[6] with 2 equiv of pyridinium hydrobromide perbromide in pyridine,[7] was oxidized with excess lead tetraacetate in acetic acid at 25° for 18 hr[8] to obtain the dienone **6**[9] in 35% yield. The presence of a nitrile function considerably lowered the yield of this reaction; using identical reaction conditions, the phenol **7** was oxidized to the corresponding dienone **8** in 75% yield. However, in a single step we had generated the correctly substituted diene system and introduced an oxygen atom at the required location.

Reduction of the dienone **6** with sodium borohydride in absolute ethanol at 0° gave three products: isoaeroplysinin-1 (**2**) (40%),[10] the corresponding monoacetate **9** (18%), and 2-desoxyaeroplysinin-1 (**3**) (22%).[11] On treatment with acetic anhydride in pyridine, the monoacetate **9** gave the diacetate **10,** which was not identical to the diacetate **11** obtained from authentic aeroplysinin-1 (**1**).[12] In order to show that the two hydroxyl functions in isoaeroplysinin-1 (**2**) were cis to one another, we converted **2** into a cyclic orthoformate **12,** using methyl orthoformate in refluxing benzene containing a catalytic amount of chloroacetic acid. Treatment of isoaeroplysinin-1 (**2**) with *p*-toluenesulfonic acid in refluxing benzene caused rapid dehydration to yield the phenol **5.** The structure of 2-desoxyaeroplysinin (**3**) was assigned on the basis of spectral data and confirmed by its dehydration under similar conditions to 3,5-dibromo-4-methoxyphenylacetonitrile (**13**).

The failure to obtain a trans diol was attributed to the influence of the acetoxy function. The dienone **6** was therefore converted into the corresponding keto alcohol **14** (45% conversion) by transesterification in methanol containing

p-toluenesulfonic acid. Reduction of the keto alcohol **14** with sodium borohydride in absolute ethanol at 0° for 10 min gave aeroplysinin-1 (**1**) in 60% yield. The synthetic racemate was identical in all respects with an authentic sample of (±)-aeroplysinin-1, prepared by mixing equal quantities of both natural enantiomers. This synthesis of aeroplysinin-1 (**1**) and isoaeroplysinin-1 (**2**) constitutes a novel approach to the synthesis of arene glycols and has the added advantage that both cis and trans glycols can be prepared stereospecifically.[13]

Acknowledgment. We wish to thank Dr. M. Stempien and Dr. J. S. Webb (Lederle Laboratories) for generous samples of aeroplysinin-1. This research was supported by a grant from the National Institutes of Health (AI-11969), and by a fellowship (to R.J.A.) from the National Research Council of Canada.

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(9) Mp 118°; ir (Nujol) 2250, 1745, 1680, and 1545 cm^{-1}; NMR ($CDCl_3$) δ 2.12 (s, 3 H), 2.66 (d, 1 H, J = 16 Hz), 2.90 (d, 1 H, J = 16 Hz), 4.14 (s, 3 H), and 6.75 ppm (s, 1 H).
(10) Mp 103–108°; ir (Nujol) 3420, 2260, 1635, and 1585 cm^{-1}; NMR ($CDCl_3$–C_3D_6O) δ 2.78 and 2.82 (ABq, 2 H, J = 16 Hz), 3.71 (s, 3 H), 4.22 (d, 1 H, J = 6 Hz), 4.59 (s, 1 H), 4.94 (d, 1 H), and 6.35 (s, 1 H).
(11) Ir (Nujol) 3350, 2260, 1610, and 1580 cm^{-1}; NMR ($CDCl_3$) δ 2.75 (s, 2 H), 3.12 (bs, 2 H), 3.79 (s, 3 H), and 6.44 (s, 1 H).
(12) Authentic aeroplysinin-1 diacetate was prepared by standard procedures from a sample of authentic aeroplysinin-1, kindly supplied to us by Dr. M. F. Stempien. We were unable to form isoaeroplysinin-1 diacetate directly from isoaeroplysinin-1.
(13) Previous trans dihydroxydihydrobenzene syntheses all created the trans glycol *via* epoxide opening.[14] The only other reported cis benzene glycol was synthesized from 3,4,5,6-tetrachlorocyclohexene.[15]
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1-Iodo-3,3-dibromo-2-heptanone, 1,1,3,3-Tetrabromo-2-heptanone, and Related Compounds from the Red Alga *Bonnemaisonia hamifera*[1]

Sir:

During the course of our extensive investigations of marine organisms collected off Baja California while aboard the R/V Alpha Helix, a small sample of the red alga *Bonnemaisonia hamifera* (AHBE-21-III-74-1-103)[2] indicated extraordinarily high lipid total halogen content, high lipid bromine content, high antimicrobial activity against *Bacillus subtilis*, and a remarkably persistent, sweet odor associated with the wet alga.[3]

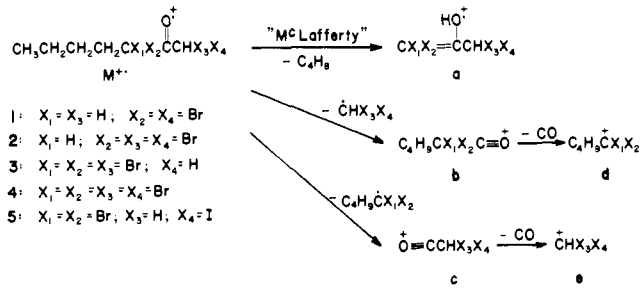

Figure 1. Mass spectral fragmentations of **4** and related halogenated heptanones. Values (*m/e*) for the individual molecular and fragment ions are found in Table I.

In an attempt to identify the compound or compounds responsible for the halogen content, antimicrobial activity, and characteristic odor of *B. hamifera*, a large sample of the alga was ground under ethanol, filtered, concentrated in a rotary evaporator, redissolved in petroleum ether, and chromatographed over silicic acid to give a sample of 1,1,3,3-tetrabromo-2-heptanone (**4**), isolated in ca. 0.01% yield (wet weight) from the alga. Compound **4** displays the characteristic odor of *B. hamifera* and shows activity at the 100 μg/ml level against the fungi *Monosporium apiospermum* and a *Geotrichum* species, at the 500 μg/ml level against *S. pyogenes* and *D. pneumoniae*, and at the 1 mg/ml level against *S. aureus, S. faecalis, K. pneumoniae*, and 15 additional fungal species.

The electron impact (EI) mass spectrum of **4** displayed no molecular ion except at reduced ionizing potential and maximum sensitivity, when the typical tetrabromo isotope pattern (symmetrical quintet) could be observed at *m/e* 426, 428, 430, 432, and 434. A far more intense ion in the EI spectrum, also containing four bromine atoms, was found at *m/e* 370, resulting from a McLafferty rearrangement (Figure 1, ion a), and the acylonium ions characteristic of α-cleavage of ketones were found at *m/e* 255 and 199 (Figure 1, ions b and c, both ions containing two bromine atoms). Alkyl ions stabilized by the two attached bromine atoms were also observed, at *m/e* 227 and 171 (Figure 1, ions d and e, two bromine atoms each). These fragments, which were confirmed by high resolution data (Table I) allow assignment of the structure $C_4H_9CBr_2COCHBr_2$. The infrared spectrum (CCl_4) of **4** shows carbonyl absorption characteristic of an α-halo ketone at 1738 cm^{-1}, and its nmr spectrum (60 MHz, CCl_4, ppm from TMS) shows absorption for a *n*-butyl group (CH_3, 1.00 t; $(CH_2)_2$, 1.2–1.8 m; deshielded $-CH_2-$, 2.4–2.7 m) and a deshielded singlet at 6.83 ppm ($-C(=O)CHBr_2$). Together, the ir, NMR, and mass spectral data assign structure **4.** The compound was synthesized by the (slightly modified) method of Rappe and Andersson.[4] Properties of the synthetic compound (ir, NMR, TLC, GC, and odor) were identical with those of the natural product. This compound (**4**) and the others in Table I are the first simple brominated aliphatic ketones observed in nature.[5]

The remaining compounds in Table I were identified in other column chromatographic fractions. As seen in Figure 1, these compounds are less brominated derivatives of 2-heptanone, obtained in less than 0.001% yield (wet weight) from the algae. Their mass spectral fragmentations to give ions a–e (Figure 1) established them as halogenated methyl pentyl ketones and assigned the degree of halogenation at the α- and α'-carbons. Although the mass spectra above would in principle allow four carbon skeletons for ketones **1–3** and **5,** the structures shown were confirmed by the observation that by-products in the synthesis of **4** from 2-heptanone had identical mass spectra and GC retention times