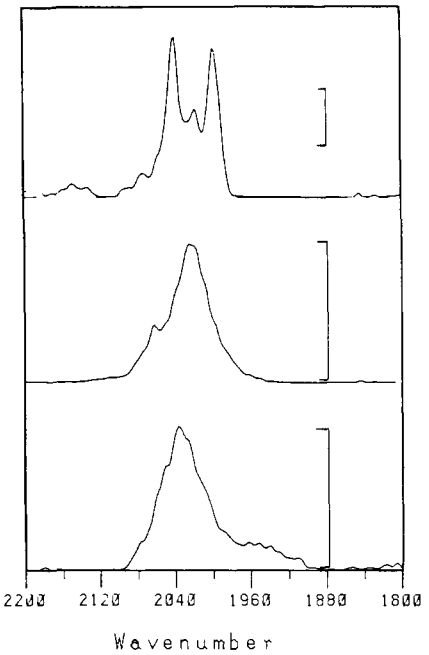

Figure 2. DRIFTs spectra of adsorbed CO on reduced carbon-supported metal crystallites under flowing He at 300 K: (A, top) 15% Fe/C with frequencies at 2042 (physisorbed CO on carbon), 2018, and 2000 cm^{-1}; (B, middle) 10% Ru/C with frequencies at 2063 and 2024 cm^{-1}; (C, bottom) 10% Os/C with frequency at 2035 cm^{-1}. (Scale = 0.00001 Kubelka-Munk units.)

known to occur at 2020 and 2000 cm^{-1}.[22,24] Although the formation of $HFe_3(CO)_{11}$ from $Fe_3(CO)_{12}$ on SiO_2 is well-known,[25] the partial decomposition of $Fe_3(CO)_{12}$ to $Fe(CO)_5$ on dehydroxylated SiO_2 has also been reported.[26] The latter reaction is clearly favored on carbon, as verified by Mössbauer spectroscopy.[27]

The IR spectra obtained after exposure of the decomposed, reduced clusters to CO (11 Torr of CO in He) and subsequent flushing in He are shown in Figure 2. The principal band at 2024 cm^{-1} for Ru corresponds well with that reported for CO on Ru on a Ru(001) single crystal[28] (2022 cm^{-1}) and on supported zerovalent Ru,[29-32] while the weak shoulder at 2063 cm^{-1} corresponds to the band for CO on partially oxidized Ru.[9,11,33] The observed frequency of 2035 cm^{-1} for adsorbed CO on Os corresponds well with reported values of 2025–2030 cm^{-1} for zerovalent Os.[34,35] Exposure of Fe/C to CO, however, leads to the formation of $Fe(CO)_5$, in agreement with chemisorption measurements[36-39] and Mössbauer spectroscopy.[27]

In conclusion, DRIFTS was successfully used to obtain the infrared spectra of the carbon-supported carbonyls of Fe, Ru, and Os and the adsorbed CO on these reduced metal crystallites. The results obtained are in good agreement with reported literature frequencies and demonstrate that the application of DRIFTS to carbon-supported catalysts is possible; however, substantial modifications must be made to commercial equipment to successfully acquire the data.

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Total Synthesis of Debromoaplysiatoxin and Aplysiatoxin

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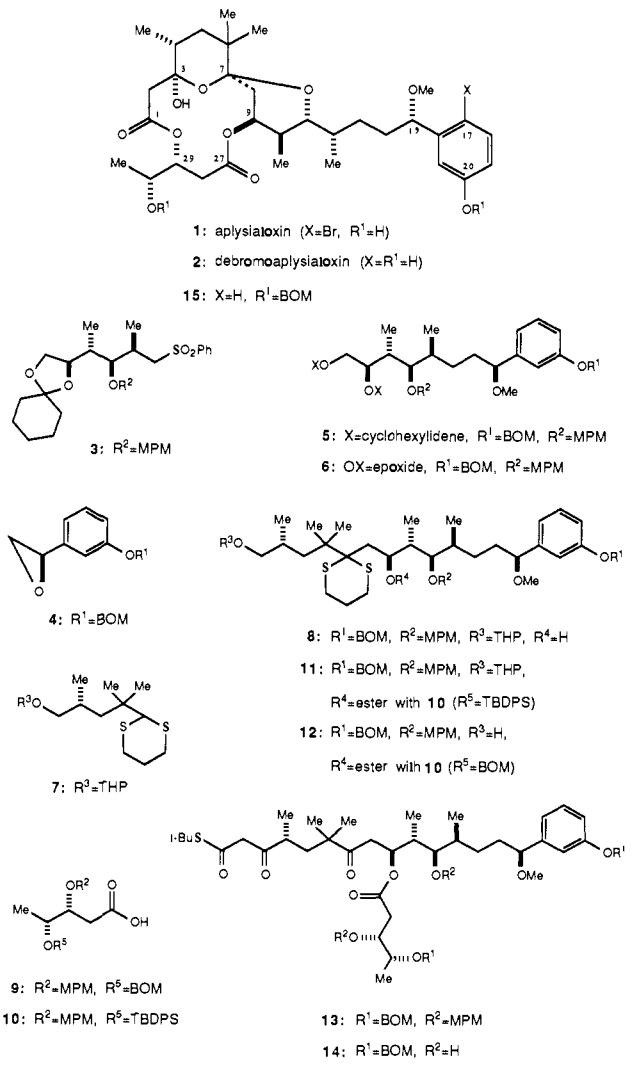
Aplysiatoxin (**1**) and debromoaplysiatoxin (**2**) were first isolated from the digestive gland of the sea hare *Stylocheilus longicauda* by Kato and Scheuer. On the basis of the elegant spectroscopic and chemical degradation studies, they elucidated the gross

Chart I



structures in 1974.[1] Moore and co-workers isolated aplysiatoxins and structurally closely related oscillatoxins from the marine blue-green alga *Lyngbya majuscula* and succeeded in establishing the complete structures including the absolute stereochemistry.[2,3] Among a variety of the biological activities observed, it is worthwhile to mention that aplysiatoxins and oscillatoxin A are remarkably active tumor promoters.[4] In this communication, we would like to report the first total synthesis of debromoaplysiatoxin and aplysiatoxin.

Our synthesis started with the coupling reaction of the sulfone **3**[5] with the epoxide **4**,[5] which was best achieved through the dianion formation of **3** [*n*-BuLi (2 equiv)/hexanes–THF (3:1)/room temperature/5 min], followed by the treatment with **4** at ambient temperature for 40 min.[6] The resultant diasteromeric mixture of sulfones was subjected to reductive desulfurization [6% Na–Hg (excess)/Na_2HPO_4/MeOH/room temperature] and the methylation [MeI (2 equiv)/KOH (4 equiv)/DMSO/room temperature] to furnish the cyclohexylidene **5**[7] in 54% overall yield from **3**. Applying the routine synthetic operations, i.e., (1) AcOH–H_2O (4:1)/40 °C and (2) KH (4 equiv)/TsCl (1.2 equiv)/THF/room temperature, **5** was transformed into the terminal epoxide **6** in 77% overall yield. Treatment of **6** with the anion generated from the dithiane **7**[5,8] [*n*-BuLi (1.0 equiv)/TMEDA (3.0 equiv)/THF/−20 °C/2.5 days] at −20 °C for 24 h gave the alcohol **8** in almost quantitative yield.

The next phase of synthesis was introduction of the acid side chain on the C.9 hydroxyl group. This seemingly simple synthetic transformation presented, however, an extremely difficult problem. With consideration given to the chemical instability of aplysiatoxins[1,2] as well as to our synthetic plan, we felt the best choice of the protecting group for the C.30 and C.29 hydroxyl groups should be benzyloxymethyl (BOM) and *p*-methoxybenzyl (MPM) groups, respectively. However, all the attempts to esterify the carboxylic acid **9**[9] with **8** were fruitless. When we applied a powerful activation method for **9**, such as the acid chloride, a facile γ-lactone formation was observed. On the other hand, a mild activation did not provide the desired ester. Under these circumstances, we opted to adjust the C.30 protecting group after the acid side chain was attached to the carbon backbone. Namely, the *tert*-butyldiphenylsilyl (TBDPS) group was stable enough under the conditions of acid chloride formation [(1) **10**[9] (2.45 equiv)/(*t*-Bu)$(Me)_2$SiCl (3.7 equiv)/imidazole (7.4 equiv)/DMF/45 °C/18 h and (2) $(COCl)_2$ (3.7 equiv)/DMF (2.45 equiv)/CH_2Cl_2/0 °C → room temperature][10] and coupling with **8** [DMAP (1 equiv)/py/room temperature/18 h]. The desired ester **11** was isolated in 95% yield based on **8**. After the adjustment of the C.30 protecting group in two steps, (1) $(n\text{-Bu})_4$NF (2.5 equiv)/THF/room temperature/3 days and (2) $PhCH_2OCH_2Cl$ (30 equiv)/*i*-$Pr)_2$(Et)N (60 equiv)/CH_2Cl_2/room temperature/1.5 days, acid treatment of **11** [AcOH–THF–H_2O (4:2:1)/55 °C/5.5 h] furnished the primary alcohol **12** in 45% overall yield. It is worthy to note that deprotection of the silyl group of **11** was performed under carefully controlled conditions, since a substantial amount of α,β-unsaturated ester formation at the acid side chain was otherwise observed.

There were two obvious options available at this point, i.e., C.29 ester formation followed by the C.2–C.3 bond formation or vice versa. We hoped that the former option might be fulfilled by an intramolecular Blaise reaction,[11] but all the attempts made along this line did not yield any promising results. Thus, we prepared the β-keto thio ester **13** from **12** in four steps: (1) DCC (15 equiv)/TFA (7.5 equiv)/py (15 equiv)/DMSO/toluene/room temperature,[12] (2) NCS (2 equiv)/acetone–H_2O (9:1)/room temperature,[13] (3) $NaClO_2$ (6 equiv)/NaH_2PO_4 (6 equiv)/$(Me)_2C{=}CHMe$/*t*-BuOH/H_2O/0 °C → room temperature/30 min,[14] (4) carbonyldiimidazole (15 equiv)/THF/room temperature, followed by $Mg(O_2CCH_2COSBu\text{-}t)_2$ (15 equiv)/THF/40 °C/1 day,[15] in 55% overall yield. The DDQ treatment of **13** [DDQ (4 equiv) CH_2Cl_2–H_2O (9:1)/room temperature/45 min[16]] yielded the unstable diol **14** in 70% yield.

The stage was set to build the ring system of aplysiatoxin from an acyclic precursor such as **14**. In principle, the desired cyclization could take place in two different modes, i.e., hemiketal formation at the C.11 hydroxy and C.7 ketone groups followed by lactone formation or vice versa. Experimentally, it was accomplished by using the macrolactonization method developed by Masamune and co-workers [AgOTFA (10 equiv)/Na_2HPO_4 (40 equiv)/C_6H_6/room temperature/30 min].[17] Under these conditions, the desired product **15** was isolated in 60% yield. Although there is no experimental evidence available to detail the mode of the cyclization, it is interesting to note that **14** exists as the open form on the basis of the NMR study. Deprotection of both C.20 and C.30 benzyloxymethyl groups of **15** was accomplished by hydrogenation [H_2/10% Pd on C/$(Et)_3$N/EtOH/room temperature] in 61% yield. As noted in the literature,[1,2] aplysiatoxins are unstable especially under acidic conditions and decompose into anhydroaplysiatoxins. In order to avoid this complication, **15** and **2** needed to be handled under weakly basic conditions. Synthetic debromoaplysiatoxin was identical in every respect (^{1}H NMR, IR, α_D, MS, TLC) with natural debromoaplysiatoxin.[18] Since debromoaplysiatoxin has already been transformed into aplysiatoxin,[2b] this synthesis constitutes a formal total synthesis of aplysiatoxin as well.

The data accumulated over the past five years suggest that the acid side chain portion of aplysiatoxins may play an important role for the tumor-promoting activity.[19] In this connection, it

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(3) The C.30 configuration determined by X-ray analysis of 19,20-dibromoaplysiatoxin was opposite to the one concluded from the degradation studies coupled with spectroscopic analyses[2b] as first noticed by Professor Wender at Stanford University. We prepared the optically active lactone **18** reported in ref 2b and confirmed it to be identical with the lactone obtained from the natural sources.

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(18) We are indebted to Professor Moore for a sample of natural debromoaplysiatoxin.

is worthwhile to mention that the synthetic route reported herein is flexible enough to prepare aplysiatoxins with modified acid side chains in order to investigate the structure–activity relationships; indeed, all the possible stereoisomers with respect to the C.29 and C.30 positions of debromoaplysiatoxin have successfully been obtained by using the same sequence of reactions.

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Supplementary Material Available: Experimental details for the synthesis of **3**, **4**, and **7** and ^{1}H NMR spectra of key intermediates (26 pages). Ordering information is given on any current masthead page.

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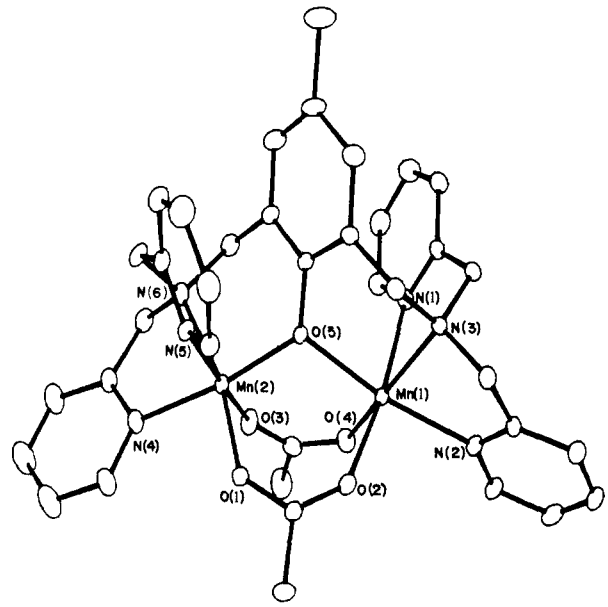

Figure 1. ORTEP plot of $[Mn_2(bpmp)(\mu\text{-}OAc)_2]^{2+}$ in complex **1**. Selected interatomic distances (Å) and angles (deg) are the following: Mn(1)–O(2), 2.166 (4); –O(4), 2.066 (5); –O(5) 2.193 (4); –N(1), 2.271 (6); –N(2), 2.210 (6); –N(3), 2.324 (5). Mn(2)–O(1), 1.927 (5); –O(3), 2.090 (4); –O(5), 1.903 (4); –N(6), 2.073 (5); –N(4), 2.052 (5); –N(5), 2.235 (6); Mn(1)···Mn(2), 3.447 (1). Mn(1)–O(5)–Mn(2), 114.4 (2).

Binuclear Mixed-Valence $Mn^{II}Mn^{III}$ Complexes: Insight About the Resolution of Hyperfine Structure in the EPR Spectrum

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A manganese protein containing two to four Mn ions,[4] and possibly other redox components,[4c] serves as the water oxidation center in photosynthesis. Substantial insight regarding the electronic structure of the Mn site has been obtained from an analysis of the hyperfine-structured EPR signal for the S_2 state in photosystem II.[5] Low molecular weight polynuclear Mn complexes that exhibit rich EPR spectra and/or catalytically oxidize water to O_2 are of interest. We report here the first structural characterization of binuclear $Mn^{II}Mn^{III}$ complexes $[Mn_2(bpmp)(\mu\text{-}OAc)_2](ClO_4)_2\cdot H_2O$[6] (**1**) and LMn_2Cl_2Br (**2**) and show how the development of EPR hyperfine structure at low

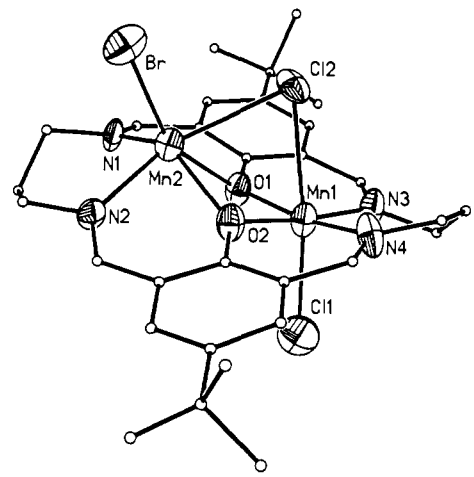

Figure 2. ORTEP plot of LMn_2Cl_2Br (**2**). The Cl(1) and Br atoms are disordered, see ref 11. Selected interatomic distances (Å) and angles (deg) are the following: Mn(1)–O(1), 1.941 (9); –O(2), 1.931 (10); –N(3), 1.973 (13); –N(4), 2.031 (12); –Cl(1), 2.491 (5); –Cl(2), 2.766 (6). Mn(2)–O(1), 2.386 (11); –O(2), 2.129 (10); –N(1), 2.182 (11); –N(2), 2.236 (12); –Cl(2), 2.763 (5); –Br, 2.514 (4); Mn(1)···Mn(2), 3.168 (3). Mn(1)–O(1)–Mn(2), 93.6 (4); Mn(1)–O(2)–Mn(2), 102.5 (4).

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