

available in optically pure form, we were ready to address their coupling. We opted for a sulfone anion coupling sequence, based on available precedents¹⁴ and on previous experience within our own laboratory.¹⁵ Direct thioetherification¹⁶ of the alcohol **8**, followed by oxidation gave the sulfone **9**, $[\alpha]_D$ 54.2°. Condensation of the anion of **9** with ketone **10**, followed by reductive cleavage of the intermediate β -hydroxy sulfone cleanly gave the trans olefin **11**, $[\alpha]_D$ 46.7°. Deprotection led to the target triol **12**, $[\alpha]_D$ 52.5°, which was shown by high-field ¹H NMR spectroscopy to be stereochemically pure.

Concurrent with our synthetic studies, we have developed an efficient degradation of the natural product to obtain the "southern" C₁–C₁₀ aldehyde subunit **14** in high overall yield.^{17,18} As before, we adopted a sulfone anion strategy in which **13**, $[\alpha]_D$ 24.8°, readily prepared from the triol **12**, was coupled with the aldehyde **14**. The desired **15**, $[\alpha]_D$ 141°, was obtained as the only detectable dienic product after reductive cleavage of the β -hydroxy sulfone. Removal of the silyl groups, hydrolysis of the seco acid, and macrolactonization with DCC–DMAP¹⁹ gave the α,β -unsaturated macrocyclic lactone **16**, $[\alpha]_D$ 213°. As anticipated, the tertiary hydroxyl group at C₇ remained unaffected during these operations.

At this juncture, we chose to attach the disaccharide moiety at C₁₃ since it also serves as a "protective group". This was effected by a silver triflate mediated stereocontrolled glycosylation of the monosilyl derivative **17**, $[\alpha]_D$ 220°, with the 2-pyridyl thioglycoside derivative of the disaccharide subunit,²⁰ based on methodology previously developed in our laboratory,^{21,22} to give the desired glycoside **18**, $[\alpha]_D$ 144°.

The last major hurdle to overcome depended upon a critical deconjugation²³ of the C₂–C₃ double bond in **18**. Thus, treatment of **19** with LDA and Me₃SiCl₂²⁴ followed by rapid quenching with acetic acid and deprotection of the silyl ethers gave avermectin B_{1a}, $[\alpha]_D$ 52°, which was shown by high-field ¹H NMR spectroscopy to be identical with the natural product except for the absence of signals corresponding to the minor B_{1b} isomer (~15%) which is normally found in the commercially available avermectin complex, $[\alpha]_D$ 55.1° (CHCl₃).³

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Laboratories. We thank Dr. Phan Viet Tan for assisting in obtaining 2D ¹H NMR spectra for several of the intermediates and Michael Evans for mass spectra.

Supplementary Material Available: ¹H NMR, IR, and 2D ¹H NMR spectra (33 pages). Ordering information is given on any current masthead page.

Effect of Charge on Bond Formation and Cleavage in Main-Group–Transition-Metal Clusters: The Reactions of Bi₂Fe₃(CO)₉ with [Fe(CO)₄]²⁻ and [Co(CO)₄]⁻

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Transition-metal clusters containing p-block elements have been known for some time, but the chemical and structural importance of the main-group element has often been overshadowed by the interest in the transition-metal part of the molecule. The recent discovery of molecules such as M₂[W(CO)₅]₃ (M = As, Sb, Bi)¹ and [Et₄N]₂[Bi₄Fe₄(CO)₁₃]² has prompted a renewed interest in these clusters with an emphasis on the main-group portion. Rauchfuss' recent discovery of hypervalency in (RC₃H₄)MoFe-(Te₂X)(CO)₅³ (X = monovalent functionality) is another interesting example. Key aspects of these systems include the formation of direct bonds between main-group elements, the effect of the main-group element on the transition-metal bonding, and the nature of the bonding between the main-group and transition elements.

In efforts to synthesize new Zintl-metal carbonylates, we have examined the reaction of Bi₂Fe₃(CO)₉ with the metal carbonyl anions [Fe(CO)₄]²⁻ and [Co(CO)₄]⁻. These two reactions proceed quite differently, in one case leading to Bi–Bi bond formation and in the other to Fe–Fe bond cleavage. The available information suggests that these differences may be attributed to charge effects.

When Bi₂Fe₃(CO)₉ is treated with [Co(CO)₄]⁻, replacement of an iron vertex occurs with concurrent formation of a Bi–Bi bond as shown by X-ray analysis.⁴ The molecule [Et₄N][Bi₂Fe₂Co(CO)₁₀] (**1**) is shown in Figure 1, with selected bond angles and distances in Table I. The incorporation of cobalt and extrusion of iron is confirmed by elemental analysis. The molecule is best

(13) Prepared from (2S,3S)-2-hydroxy-3-methylsuccinic acid (Seebach, D.; Wasmuth, D. *Helv. Chim. Acta* **1980**, *63*, 197) via the following sequence: (a) aqueous KOH; then Dowex 50 (H⁺); (b) cyclohexanone, BF₃·Et₂O; (c) BH₃·Me₂S; then BF₃·Et₂O (50%, four steps); (d) Ag₂O, BnBr, CH₂Cl₂; (e) MeLi, THF, –78 °C; (f) *t*-BuPh₂SiCl, imidazole, CH₂Cl₂ (87%, three steps).

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(4) Excess Co₂(CO)₈ (0.16 mmol) was dissolved in 10 mL of tetrahydrofuran (THF) and reduced with 1 mL of 1% Na/Hg. The THF solution was removed via syringe and filtered through Celite onto Bi₂Fe₃(CO)₉ (0.24 mmol). The solution was stirred overnight, then the solvent was removed under vacuum, and the product dissolved in methanol. [Et₄N]Br (0.12 g) was added to the methanol solution followed by addition of water to precipitate the product in yields >45%. Anal. Calcd for [Et₄N][Bi₂Fe₂Co(CO)₁₀]: Bi, 41.84; Fe, 11.13; Co, 5.90. Found: Bi, 40.53; Fe, 10.65; Co, 5.12. IR (MeOH): 2030 sh, 2025 w, 2000 s, 1980 vs, 1960 s, 1944 m, 1918 mw. Crystal data: triclinic, space group P1, a = 10.205 (4) Å, b = 11.250 (8) Å, c = 13.125 (6) Å, α = 70.30 (5)°, β = 76.94 (3)°, γ = 76.89 (5)°; V = 1363.1 (14) Å³; Z = 2, R₁ = 0.083, R₂ = 0.074 for I > 3 σ and R₁ = 0.064, R₂ = 0.069 for I > 6 σ .

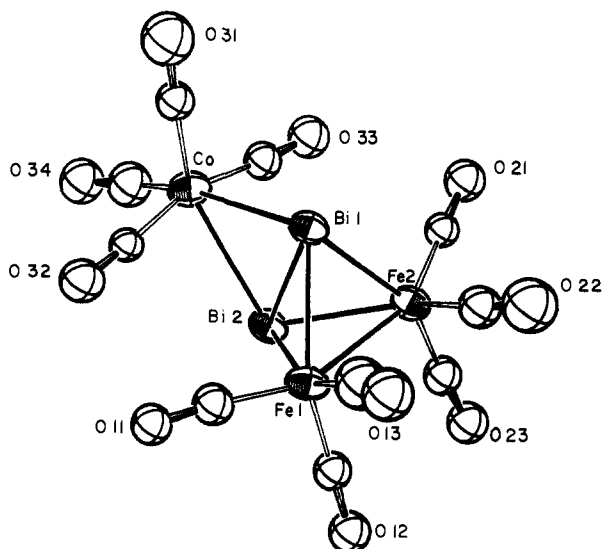


Figure 1. ORTEP diagram of the $[\text{Bi}_2\text{Fe}_2\text{Co}(\text{CO})_{10}]^-$ ion.

Table I. Selected Distances (Å) and Bond Angles (deg) for the $[\text{Bi}_2\text{Fe}_2\text{Co}(\text{CO})_{10}]^-$ Ion

Distances			
Bi(1)–Bi(2)	3.092 (2)	Bi(2)–Fe(2)	2.693 (5)
Bi(1)–Fe(1)	2.682 (5)	Bi(1)–Co	2.894 (5)
Bi(1)–Fe(2)	2.680 (6)	Bi(2)–Co	2.868 (5)
Bi(2)–Fe(1)	2.669 (5)	Fe(1)–Fe(2)	2.682 (7)
Angles			
Fe(1)–Bi(1)–Fe(2)	60.03 (15)	Bi(1)–Fe(1)–Bi(2)	70.60 (13)
Fe(1)–Bi(1)–Co	102.98 (15)	Bi(1)–Fe(1)–Fe(2)	59.95 (15)
Fe(2)–Bi(1)–Co	103.56 (15)	Bi(2)–Fe(1)–Fe(2)	60.43 (15)
Fe(1)–Bi(2)–Fe(2)	60.02 (15)	Bi(1)–Fe(2)–Bi(2)	70.27 (13)
Fe(1)–Bi(2)–Co	104.01 (15)	Bi(1)–Fe(2)–Fe(1)	60.02 (15)
Fe(2)–Bi(2)–Co	103.94 (15)	Bi(2)–Fe(2)–Fe(1)	59.55 (15)
Bi(1)–Co–Bi(2)	64.92 (11)	Co–Bi(1)–Bi(2)	57.13 (11)
Co–Bi(2)–Bi(1)	57.96 (11)		

viewed as an edge-bridged tetrahedron similar in some respects to molecules such as $\text{As}_2\text{Co}_2(\text{CO})_6$,⁵ $\text{Cp}_2\text{M}_2(\text{CO})_4\text{As}_2$ (M = Mo, W),⁶ and $\text{Te}_2\text{Fe}_2(\text{CO})_6$.⁷ The metal framework is similar to that found in $\text{Te}_2\text{Fe}_3(\text{CO})_9(\text{PPh}_3)$ ⁸ where no Te–Te bond was originally proposed; however, the more recent characterization of structurally similar $\text{Cp}_2\text{Mo}_2\text{FeTe}_2(\text{CO})_7$ is thought to have a main-group–main-group bonding interaction.⁹ Our results tend to support this hypothesis. The tetrahedral Fe_2Bi_2 framework possesses five skeletal electron pairs and requires six for conventional tetrahedral bonding. The additional two electrons are provided by the $[\text{Co}(\text{CO})_4]^-$. This analysis is opposite that observed for the Mo_2FeTe_2 cluster where the Te–Te bond is proposed to act as a donor to the FeL_4 unit. The Bi–Bi distance is in agreement with known single-bond values.¹⁰ The Bi–Fe distances are normal¹¹ while the Bi–Co values are quite long.¹² This structural feature may be the cause of the slow decomposition of the molecule in solution

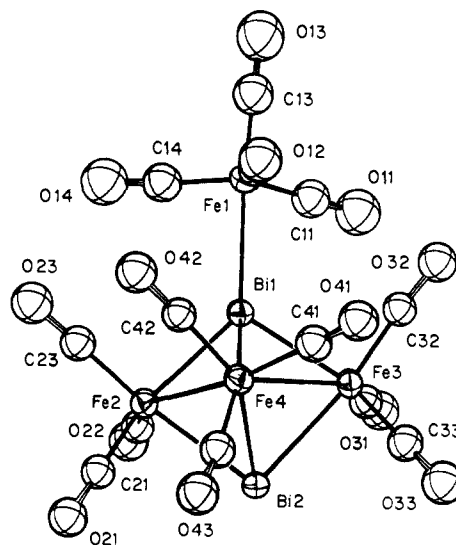


Figure 2. ORTEP diagram of the $[\text{Bi}_2\text{Fe}_4(\text{CO})_{13}]^{2-}$ ion.

Table II. Selected Distances (Å) and Bond Angles (deg) in the $[\text{Bi}_2\text{Fe}_4(\text{CO})_{13}]^{2-}$ Ion

Distances			
Bi···Bi	3.398 (1)	Bi(1)–Fe(4)	2.645 (2)
Bi(1)–Fe(1)	2.668 (2)	Bi(2)–Fe(2)	2.687 (2)
Bi(1)–Fe(2)	2.597 (2)	Bi(2)–Fe(3)	2.678 (2)
Bi(1)–Fe(3)	2.592 (2)	Bi(2)–Fe(4)	2.683 (2)
Fe(2)–Fe(4)	2.808 (2)	Fe(3)–Fe(4)	2.796 (2)
Angles			
Fe(1)–Bi(1)–Fe(2)	135.40 (6)	Fe(1)–Bi(1)–Fe(3)	122.48 (6)
Fe(1)–Bi(1)–Fe(4)	128.63 (5)	Fe(2)–Bi(1)–Fe(3)	101.91 (5)
Fe(2)–Bi(1)–Fe(4)	64.78 (5)	Fe(3)–Bi(1)–Fe(4)	64.52 (5)
Fe(2)–Bi(2)–Fe(3)	97.38 (5)	Fe(2)–Bi(2)–Fe(4)	63.06 (5)
Fe(3)–Bi(2)–Fe(4)	62.87 (5)	Fe(2)–Fe(4)–Fe(3)	91.96 (7)

and the solid state. The formation of the Bi–Bi interaction in this case may be related to the mechanism of formation of $[\text{Bi}_4\text{Fe}_4(\text{CO})_{13}]^{2-}$.

In contrast, when $\text{Bi}_2\text{Fe}_3(\text{CO})_9$ reacts with $[\text{Fe}(\text{CO})_4]^{2-}$ all the metals are retained and an anion of the formula $[\text{Bi}_2\text{Fe}_4(\text{CO})_{13}]^{2-}$ (2) is obtained cleanly in high isolated yields.¹³ The X-ray structural analysis shows the molecule to be based on a $\text{Bi}_2\text{Fe}_3^{2-}$ square-pyramidal framework with an $\text{Fe}(\text{CO})_4$ fragment attached to one bismuth (Figure 2, Table II). The electron count is conventional and the molecule is isoelectronic and isostructural with the known molecules $\text{M}_2\text{Fe}_3(\text{CO})_9$ (M = S, Se, Te, SO, NR, PR, AsR; R = alkyl, aryl).^{7a,b,14}

It appears that charge may be the controlling factor in determining the outcomes of these two different reactions. All the known examples of carbonyl clusters where bismuth is four-coordinate have a 2– charge or greater. The driving force for the loss of the iron vertex is probably the lack of basicity of the lone

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pair on bismuth in a cluster of only 1- charge. In support of this is the observation that when **2** is oxidized with Cu^+ , $\text{Bi}_2\text{Fe}_3(\text{CO})_9$ is produced along with $\text{Fe}(\text{CO})_5$ and $\text{Fe}_3(\text{CO})_{12}$.

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Supplementary Material Available: Tables of atomic coordinates, anisotropic thermal parameters, F_{obsd} and F_{calcd} , and bond angles and distances for $[\text{Et}_4\text{N}][\text{Bi}_2\text{Fe}_2\text{Co}(\text{CO})_{10}]$ and $\text{Me}_4\text{N}[\text{Bi}_2\text{Fe}_4(\text{CO})_{13}]\text{Cl}$ (56 pages). Ordering information is given on any current masthead page.

Calyculin A, a Novel Antitumor Metabolite from the Marine Sponge *Discodermia calyx*¹

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Marine sponges have proved to be a rich source of metabolites possessing novel structural features as well as interesting biological activities,^{2,3} as, e.g., okadaic acid⁴ and related compounds,^{5,6} tetrodotoxin⁷ and the latrunculins.⁸ In the course of our search for bioactive metabolites from Japanese marine invertebrates, we encountered a sponge *Discodermia calyx*⁹ whose lipophilic extract showed strong activity in the starfish egg assay¹⁰ and in the cytotoxicity test, which led us to isolate the active constituents. The major active constituent, calyculin A, is a novel spiro ketal of an unprecedented skeleton bearing phosphate, oxazole, nitrile, and amide functionalities.

The sponge (1 kg wet weight) was collected in the Gulf of Sagami by SCUBA (–5 to –15 m) and extracted with ethanol; this extract was partitioned between water and dichloromethane. The organic layer was subjected to low-pressure column chro-

matography on silica gel ($\text{CH}_2\text{Cl}_2/\text{MeOH}$), followed by reversed-phase HPLC (ODS, 80% MeOH) to give calyculin A (**1**) (150 mg, 0.15% wet weight), colorless needles, $[\alpha]_{\text{D}}^{15} +59.8^\circ$ (c 0.12, EtOH). Calyculin A was not only inhibitory against development of starfish (*Asterina pectinifera*) embryos at 0.01 $\mu\text{g}/\text{mL}$ but also strongly cytotoxic against L1210 cells (IC_{50} 1.75 $\times 10^{-3}$ $\mu\text{g}/\text{mL}$). The UV maxima at 342 (ϵ 12 000) and 230 (19 000) nm and IR bands at 3500, 3300, 3150, 2250, 1640, 1260, 1100, and 1060 cm^{-1} indicated the presence of two conjugated systems and hydroxyl, amide, nitrile, and phosphate functions. ¹³C NMR spectra¹¹ revealed 50 carbon signals, which are assignable to one amide, one nitrile, one ketal, one oxazole, nine oxymethines, two methoxys, two *N*-methyls, ten olefins, five methines, six methylenes, nine methyls, and one sp³ quaternary carbon. ³¹P NMR^{12,13} (–1.3 ppm, J_{POCH} 10.5 Hz) implied that **1** contained a phosphate ester linked to a methine carbon. These data and FABMS [m/z 1009 (MH^+)] together with combustion analysis [N 5.46% (calcd 5.55%)] led to the molecular formula of $\text{C}_{50}\text{H}_{81}\text{N}_4\text{O}_{15}\text{P}$. Detailed 500-MHz NMR analyses¹⁴ including COSY¹⁵ and C–H shift correlation experiments¹⁶ (¹*J* and long range) allowed us to construct a gross structure, in which two major portions were combined via two contiguous quaternary carbons. However, the position of two ether linkages remained ambiguous.

The structure including relative stereochemistry was deduced by single-crystal X-ray diffraction. Repeated crystallization from a mixture of *n*-hexane, diethyl ether, and acetone afforded colorless needles (mp 247–249 °C) belonging to the orthorhombic space group $P2_1P2_1P2_1$ with $a = 18.173$ (3) Å, $b = 20.138$ (4) Å, $c = 15.574$ (3) Å and $Z = 4$. Intensities were measured in the $\omega/2\theta$ scan mode on a Rigaku AFC-5R diffractometer, using graphite-monochromated Cu K α radiation ($\lambda = 1.54184$ Å). Correction was made for Lorentz and polarization factors but not for absorption. Of 5001 independent reflections with $2\theta < 120^\circ$, 3094 reflections with $F_o < 2\sigma$ were considered to be zero reflections.

The structure was determined by direct methods coupled with the MULTAN 78¹⁷ program and successive Fourier syntheses. Its parameters were refined by the blocked-diagonal least-squares method with isotropic temperature parameters to the current residual of 0.12 ($R_w = 0.083$) for 1626 reflections. The atomic identifications were carefully made on the basis of both their peak heights and isotropic thermal parameters. The structure thus

(11) 125-MHz ¹³C NMR (CDCl_3) δ 176.2 (C-33), 169.8 (C-29), 156.3 (C-3), 144.5 (C-8), 137.3 (C-27), 134.7 (C-7), 133.8 (C-5, 28), 132.6 (C-25), 132.4 (C-9), 128.2 (C-4), 123.7 (C-6), 117.3 (C-1), 116.1 (C-26), 108.7 (C-19), 94.6 (C-2), 84.8 (C-16), 81.9 (C-17), 80.7 (C-11), 77.3 (C-15), 74.9 (C-13), 73.4 (C-34), 71.4 (C-21), 68.9 (C-35), 67.1 (C-23), 65.6 (C-37), 63.7 (C-36), 60.9 (C-45), 58.9 (C-38), 50.1 (C-18), 44.3, 37.4 (C-39,40), 42.1 (C-12), 38.3 (C-14), 37.7 (C-22), 35.9 (C-24), 35.8 (C-10), 34.4 (C-32), 33.6 (C-31), 29.6 (C-20), 28.4 (C-30), 22.4, 17.5 (C-43, 44), 19.2 (C-50), 17.9 (C-47), 17.5 (C-41), 13.9 (C-49), 13.7 (C-48), 12.7 (C-46), 10.8 (C-42).

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