of an important goal in the field, i.e., the first total synthesis of the aglycon of 1 (i.e., calicheamicinone (2))[12] (Scheme I).

We drew from the general plan that was implemented in earlier work on simpler systems. However, it was necessary to provide the means to introduce the urethane function at the bridgehead double bond. The optimal timing for this installation emerged as a serious problem. The solution is described below.

Commercially available ester **3** (Scheme II) underwent regiospecific bromination (NBS, $CN_3C{\equiv}N$)[13] to afford **4**,[14] which upon formylation (Cl_2CHOMe; $TiCl_4$) gave **5**.[14] The aldehyde function was employed to direct regiospecific monodemethylation (via BCl_3), giving rise to the required phenol **6**[14] (65% from **3**). The sodium salt of **6** was subjected to reduction (DIBAH) to provide the unstable triol **7**, which, upon treatment with sodium periodate, afforded **8**.[15a] Upon oxidation of crude **8** with the Dess-Martin[15b] periodinane, there was obtained the spiroepoxy aldehyde **9**.[14] The yield for the three steps from **6** to **9** on large scale is ca. 40%.

The next phase of the effort involved insertion of the six-carbon enediyne bridge between the ketone and aldehyde functions. Dilithio enediyne **10**[16] was added to the ketone in the nominal presence of the aldehyde, using the logic of in situ protection as developed, in another context, in the pioneering research of Comins[17] (Scheme III). Reaction of **9** with **10** in the presence of lithium *N*-methylanilide afforded **11**. Silylation of the tertiary alcohol gave rise to **12**, which on cyclization (potassium 3-ethyl-3-pentoxide)[13,18] provided the core system **13**[14] (ca. 35-40% overall yield for the three steps from **9** on a 2-g scale). No stereoisomer of the secondary alcohol was observed. After considerable experimentation, it was found that the enol ether function was not suitable for the required subsequent manipulations. Accordingly, compound **13** was converted to ketal **14**[14] (CSA-ethylene glycol, 89% yield). Acetolysis of the epoxide (KOAc; AcOH; DMSO) led to crude **15**,[14] which upon deacylation (NH_3; MeOH) and oxidation (sodium periodate) gave rise to ketone-ketal **16**[14] (83% combined yield).

The bridgehead enone presented a target of opportunity for the introduction of an azido function. *For this to be possible, the ketone at the one-carbon bridge had to provide adequate enolate stabilization to support an addition-elimination mechanism, a possibility presaged by the research of Magnus.*[9c] In the event, reaction of **16** with sodium azide in methanol afforded an 82% yield of **17**.[14] As matters transpired, this stage was still too early to actually unveil the urethane. First the secondary alcohol was acylated ($(EtO)_2P(O)CH_2COCl$; Py)[19] and the resultant ester **18**[14] subjected to intramolecular Emmons condensation[11b,20] to produce **19**[14] (50% from **17**).

The conjugation afforded by the conjugated lactone provided a sufficiently stable setting for the steps required to transform the azide to the methyl carbamate function. Reduction of **19** (H_2S-piperidine-methanol; 95% yield) led to the remarkably robust vinylamine **20**.[14] The latter, upon treatment with phosgene in pyridine, gave rise to a bis acylation product, **21**, and thence, upon treatment with methanol and pyridine, to the carbamate-carbonate **22**[14] in 80% overall yield. Treatment of **22** first with DIBAH (which results in deprotection of the tertiary alcohol and reduction of the lactone to a lactol) followed by sodium borohydride produced the alcohol **23**[14] in 43% overall yield. The first sulfur atom was installed by a Mitsunobu reaction on **23** (thiolacetic acid, triphenylphosphine, diisopropyl azodicarboxylate) to produce **24** (45% yield).[14,21] Treatment of thioacetate **24** with DIBAH resulted in deacetylation. The crude product was subjected to the action of phthalimidomethyl disulfide,[22] thereby leading to trisulfide **25**[14] (65% from **24**). Finally, the ketal linkage was cleaved through the action of CSA in aqueous THF at room temperature. There was thus obtained *dl*-calicheamicinone (**2**) as a powder in 65% yield. While there exists, to our knowledge, no reference sample of this compound (**2**),[12] the structure proposed here is firmly supported by infrared, NMR, and mass spectral determinations. Furthermore, the assignments are supported by the close similarity of these compounds with those of the desureido series, which were in turn supported by crystallographic determinations.[10,11]

With the feasibility of the "end game" reactions having been demonstrated, various intermediates in this effort emerge as possibilities for other syntheses, which might be more concise and which might produce only the relevant antipode. Research toward these goals is continuing in our laboratory.

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Supplementary Material Available: NMR, IR, and mass spectral data for compounds **2**, **4-6**, **8**, **9**, **13-20**, and **22-25** (6 pages). Ordering information is given on any current masthead page.

(12) We suggest this name, which incorporates the standard suffix use to denote the aglycon substructure of the anthracycline antibiotics.
(13) These conditions were developed by Dr. Nobuharu Iwasawa.
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(22) The first synthesis of an allylic trisulfide in this general series was accomplished by Magnus and co-workers.[9c] The preparation of the desureido variants of **25** and **2** were first achieved in our laboratory by Dr. John Haseltine.

Solid-State ^{199}Hg Nuclear Magnetic Resonance as a Probe of Coordination Number and Geometry in Hg(II) Complexes

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Although Hg(II) chemistry is dominated by linear, two-coordinate compounds, studies of Hg(II)-biopolymer complexes including Hg-substituted blue copper proteins[1] and the Hg(II) biosensor, MerR,[2] have revealed important primary bonding interactions with additional ligands.[3,4] Unfortunately, even for simple model compounds, vibrational,[5] electronic absorption,[6] and solution NMR[7] spectroscopic data are unable to clearly differentiate between Hg(II) thiolate complexes with primary coor-

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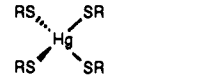
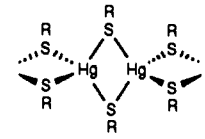
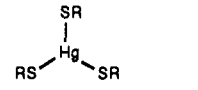
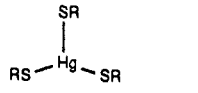
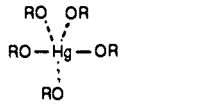
Table I. Solid-State ^{199}Hg Nuclear Magnetic Resonance Spectroscopic Data

compound[a]	structure[b]	tensor elements,[c]	solution shift: δ,[c] ppm	anisotropy: $\Delta\sigma$,[c,d] ppm	asymmetry,[e] η
$[(CH_3)_4N]_2[Hg(SC_6H_4Cl)_4]$ (I)		$\sigma_{11} = -424$ $\sigma_{22} = -428$ $\sigma_{33} = -602$ $\sigma_{iso} = -485$	−569[f]	−176	0.03
$Hg(SBu^t)_2$ (II)		$\sigma_{11} = -454$ $\sigma_{22} = -557$ $\sigma_{33} = -984$ $\sigma_{iso} = -665$	−793[g]	−478	0.32
$[(C_2H_5)_4N][Hg(SBu^t)_3]$ (III)		$\sigma_{11} = 316$ $\sigma_{22} = -83$ $\sigma_{33} = -704$ $\sigma_{iso} = -158$	−157[h]	−821	0.73
$[(C_4H_9)_4N][Hg(SPh)_3]$ (IV)		$\sigma_{11} = 180$ $\sigma_{22} = -216$ $\sigma_{33} = -996$ $\sigma_{iso} = -344$	−354[f]	−978	0.61
$Hg(OOCCH_3)_2$ (V)		$\sigma_{11} = -1770$ $\sigma_{22} = -2106$ $\sigma_{33} = -3594$ $\sigma_{iso} = -2490$	−2389[i]	−1656	0.30

[a] I–IV were prepared according to published procedures (see text for references); purity was established by solution NMR and by vibrational spectroscopy. Data for V was generated from the solid-state spectrum published in ref 14. [b] As determined from crystallographic studies (see text for references). [c] Referenced to $Hg(CH_3)_2$ ($\delta = 0$ ppm). [d] $\Delta\sigma = \sigma_{33} - (\sigma_{11} + \sigma_{22})/2$. [e] $\eta = (\sigma_{22} - \sigma_{11})/(\sigma_{33} - \sigma_{iso})$. [f] In DMSO solution, [Hg(II)] = 100 mM. [g] In $CHCl_3$ solution, [Hg(II)] = saturated (Dean, P. A. W.; Vittal, J. J.; Trattner, M. H. *Inorg. Chem.* **1987**, *26*, 4245–4251). [h] In DMSO solution, [Hg(II)] = 5 mM. [i] In 1 M CH_3CO_2H.

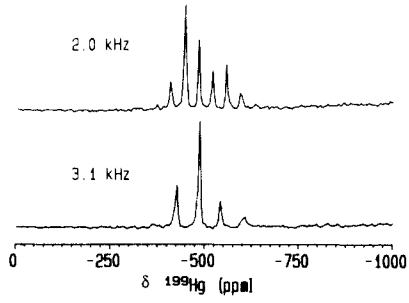


Figure 1. Solid-state CPMAS ^{199}Hg NMR spectra of $[(CH_3)_4N]_2[Hg(SC_6H_4Cl)_4]$ (I) at 53.7 MHz. Acquisition time = 0.15 s, pulse width = 4.8 μs (90°), contact time = 7 ms, recycle delay = 15 s, with applied line broadening of 200 Hz. Top: spinning speed = 2.0 kHz, 496 scans. Bottom: spinning speed = 3.1 kHz, 240 scans. The isotropic chemical shift is −485 ppm.

dination numbers[8] (CN) of 3 and 4, due to extensive secondary bonding interactions in the solid state[8,9] and rapid ligand exchange in solution.[7] CPMAS[10] solid-state ^{113}Cd NMR spectroscopy has been invaluable in understanding Cd–ligand interactions in numerous model compounds and metalloproteins,[11-13] but only a single solid-state ^{199}Hg NMR spectrum has been reported.[14] Herein we demonstrate this technique to be an effective probe of Hg(II) structure and bonding in two-, three-, and four-coordinate complexes, which allows assignment of primary coordination numbers for Hg(II) thiolates in the solid state and provides insights into the secondary bonding interactions unique to this member of the zinc triad.[9] Solid-state ^{199}Hg NMR of structurally characterized complexes provides a definitive structure/chemical shift correlation that can facilitate structural assignment on the basis of solution ^{199}Hg NMR data.

Figure 1 shows CPMAS solid-state ^{199}Hg NMR spectra for $[(CH_3)_4N]_2[Hg(4\text{-chlorothiophenolate})_4]$[15] (I in Table I), which consist of a series of sidebands separated by the spinning speeds

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2.0 kHz (top) and 3.1 kHz (bottom). Moment analysis[16] gives the chemical shift tensor elements σ_{11}, σ_{22}, and σ_{33} found in Table I, from which the chemical shift anisotropy, $\Delta\sigma$, and the axial asymmetry, η, are calculated. $\Delta\sigma$ is a measure of deviation from spherical symmetry and corresponds roughly to the width of the sideband envelope, while $\eta = 0$ for axially symmetric chemical shift tensors.[17] Linear alkyl Hg(II) complexes with no secondary bonding interactions are known to possess huge shift anisotropies (5000–7000 ppm);[18] accordingly, Harris and Sebald were unable to obtain meaningful solid-state spectra for linear organomercury species.[14] The $\Delta\sigma$ obtained for I, −176 ppm (Table I), indicates a high degree of charge symmetry around Hg(II), reflected further in the nearly axially symmetric value for η. Hg(II) in $Hg(SBu^t)_2$ (II) is surrounded by a very distorted tetrahedron of bridging thiolates in the solid state;[19] consequently, a larger shift anisotropy (−478 ppm) is found. Thus, our data reveal that CPMAS ^{199}Hg NMR is sensitive to changes in geometry *within* a given coordination number. The difference between the isotropic solid-state and solution chemical shifts (≈100 ppm) in both I and II highlights the problems implicit to interpretation of solution NMR in rapidly exchanging Hg–thiolate systems that are prone to ligand dissociation; titration of Hg(II) with 4-chlorothiophenolate shows that the chemical shift is dependent on ligand concentration, approaching the solid-state shift at high $RS^-/Hg(II)$ ratios.[20]

Solid-state spectra for two structurally characterized planar three-coordinate Hg(II) thiolates, $[(n\text{-}C_2H_5)_4N][Hg(SBu^t)_3]$[4,5b] (III) and $[(n\text{-}C_4H_9)_4N][Hg(SPh)_3]$[21] (IV), exhibit substantially higher shift anisotropy (−821 and −978 ppm, respectively) and asymmetry (0.6–0.7) than the tetrahedral thiolates (Table I); from differences in $\Delta\sigma$ and η, three- and four-coordinate complexes are easily distinguished. As seen in the four-coordinate compounds, $\Delta\sigma$ values are also sensitive to geometric variations among planar three-coordinate species. The greater distortion of IV toward a T-shape, relative to the more trigonal complex III, is reflected in a 159 ppm increase in $\Delta\sigma$. The close agreement between solid-state and solution isotropic shifts for both three-coordinate species implies that the predominant species in solution is three-coordinate, corroborating X-ray absorption studies on the $Hg(SBu^n)_3^-$ analogue.[22]

Analysis of the published solid-state spectrum[14] for $Hg(OOCCH_3)_2$ (V) yields a large anisotropy, −1656 ppm, that exceeds the $\Delta\sigma$ for trigonal compounds. Contrary to the four-coordinate label employed by Harris and Sebald, the compound is best described as two-coordinate linear, with three additional secondary bonding interactions [2 + 3] with neighboring acetate oxygen atoms ($Hg-O_1$ = 2.06 Å, $Hg-O_2$ = 2.09 Å, $Hg-O_3$ = 2.71 Å, $Hg-O_4$ = 2.76 Å, $Hg-O_5$ = 2.75 Å; $\angle O_1-Hg-O_2$ = 176°).[9,23] The anisotropy is considerably reduced in comparison to purely linear species, but an order of magnitude greater than that observed for complexes with a primary coordination number of 4. Thus, while the secondary oxygens in $Hg(OOCCH_3)_2$ are well outside the covalent-bonding distance for Hg(II)–O, they influence the observed anisotropy.

The ease with which CPMAS ^{199}Hg NMR can distinguish between three- and four-coordinate Hg(II) thiolates, yield information concerning structural distortion within a given coordination number, and clarify the role of secondary interactions makes it a powerful probe of Hg(II) coordination chemistry.

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All in all, this appears to be a useful program for collecting and organizing information obtained from on-line data services. The instruction booklet is clearly written and the program itself is quite easy to learn. However, since the nature of the data provided by the various on-line databases is necessarily restricted, the value of this program to a given user will be a function of how that individual collects, stores, and evaluates information gleaned from the current chemical literature.

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