as well as a bidentate Asp112 carboxylate and possibly an axial carbonyl oxygen of Gly45 or a water molecule.[10]

It is well established that the unusual distorted trigonal pyramidal (pseudotetrahedral) coordination geometry of blue copper is forced on the metal ion by the rigidity of the polypeptide scaffold in the binding-site region (rack-induced bonding).[1c,d,18,19] Owing to the geometrical constraints imposed by the aspartate side chain, however, formation of a planar copper carboxylate group would require substantial rearrangement of the protein structure.[20] Since a large distortion of the protein structure is energetically unfavorable, it is likely that the copper is displaced significantly from the plane of the Asp112 carboxylate group in forming the Cu-$N_2O_2(O)$ structure.

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(20) Computer modeling of Cu^{II}-Cys112Asp azurin coordination was based on the 2.7 Å resolution structure of *P. aeruginosa* azurin (ref 1a). The Cys112 side chain of wild-type azurin was replaced by an aspartate side chain using Biograf (Version 2.20) from BIODESIGN, Inc. The backbone atoms were fixed while the C_β and C_γ atoms of the aspartate side chain were positioned as closely as possible to the C_β and S_γ atoms of cysteine, and the C_β–C_γ bond was rotated to make a pseudo square planar base containing the imidazole nitrogens of His46 and His117 and the carboxylate oxygens of Asp112. In this configuration, C_γ of Asp112 is forced well out of the plane defined by the copper center and the carboxylate oxygens. For a discussion of metal binding to isolated carboxylate groups in proteins, see: Glusker J. P. *Adv. Protein Chem.* **1991**, *42*, 1–76.

Formyltriisopropylsilane: The Synthesis and Chemistry of a Stable Formylsilane

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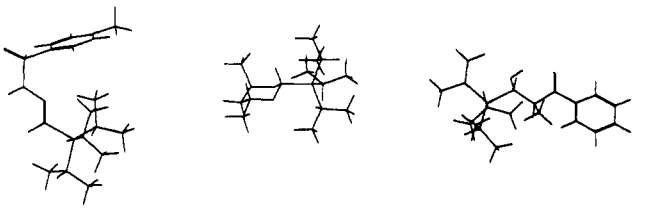
The only formylsilane isolated as a stable compound, $(Me_3Si)_3SiCHO$, reported by Tilley et al.[2] in 1988, represented an impressive synthetic achievement, being prepared from a mixed cyclopentadienyl acylzirconium precursor. Unlike Me_3SiCHO,[3,4] $(Me_3Si)_3SiCHO$ was found to be thermally stable although it decomposes exothermically in air.[2] We wish to report the convenient preparation of formyltriisopropylsilane (**2**) from a modified dithiane-based approach and its fascinating chemistry.

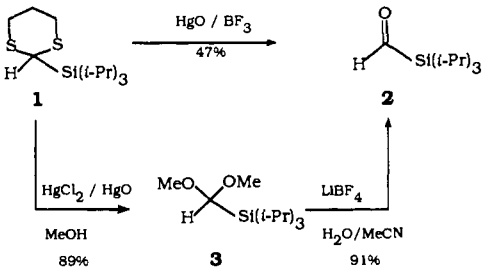
Previously, we have found that the triisopropylsilyl (TIPS) group not only significantly retards nucleophilic substitution at silicon but also greatly impedes reactions at adjacent centers.[5] This suggested that **2** should be stable, and **3** appeared to us to be its ideal precursor. By modifying the Corey–Seebach approach[6] to acylsilanes[7] to include an intermediate dithiane → acetal step,[6b] exposure of this sensitive system[8,9] to the dithiane hydrolysis conditions could be essentially avoided.



4b **(+)-8** **12**

Figure 1. MMX minimum energy structures for **4b**, **(+)-8**, and **12**.

The reaction of 2-lithio-1,3-dithiane[6] with TIPSCl (3 h, −78 → 25 °C) gives **1** cleanly (96%, >99% GC purity, bp 120 °C, 0.1 Torr, 87% from $MeOH/H_2O$, mp 45.5–47.5 °C). The solvolysis of **1** was carried out ($HgCl_2$, HgO, MeOH),[6b] which afforded **3** as a colorless liquid (bp 72 °C, 0.6 Torr) in 89% yield. The hydrolysis of **3** on a 50-mmol reaction scale was optimized employing $LiBF_4$ (0.37 M, 1.04 equiv)[10] in refluxing aqueous MeCN (9:91, 15 s), providing pure **2** as a greenish-yellow liquid in 91% yield (bp 85 °C, 3 Torr, 99% GC purity). By contrast, even the mild Vedejs–Fuchs hydrolysis conditions[11] gave **2** in significantly lower yield and purity (47%, 97% GC purity containing 3% TIPSOH), and the standard aqueous MeOH conditions[6] result in a mixture of **2** and **3**.



(1)

As anticipated,[2] the spectral properties of **2** are considerably Si-shifted (e.g., ^1H NMR δ 12.10 (CHO) ppm; ^{13}C NMR δ 249.0 (CHO) ppm; IR (neat) 2588 (ν_{CH}), 1651 (ν_{CO}) cm^{-1}; UV (THF) 375 (sh, 28), 390 (sh, 55), 406 (86), 426 (87) nm)). The electron-impact MS of **2** provides a weak $M^{\cdot+}$ (0.2%), with $TIPS^+$ (157, 63%) and its degradation products (m/z 73 (67) and 59 (100)) being the major ion fragments.

Upon exposure to atmospheric oxygen, **2** spontaneously ignites! Limiting the amount of oxygen produces TIPSOH as the major Si-containing product, and in $CDCl_3$ solution, minor amounts of TIPSH(D) and TIPSCl are also observed (GCMS), implicating the intermediacy of TIPS radicals in the process. However, air-stable crystalline derivatives of **2** were easily prepared (**4a**, 2,4-DNP (75%, mp 109–110 °C); **4b**, tosylhydrazone (87%, mp 63.5–64.5 °C)) as single geometric isomers (anti)[12] (Figure 1).

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(12) ΔMMXE (anti vs syn) = 3 kcal/mol (see Figure 1). Since the submission of this manuscript, a single-crystal X-ray structure of **4b** has been obtained (with Dr. C. L. Barnes, University of Missouri) which confirms its anti configuration and the general structural features which are depicted in Figure 1.

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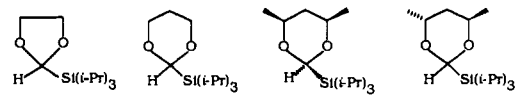
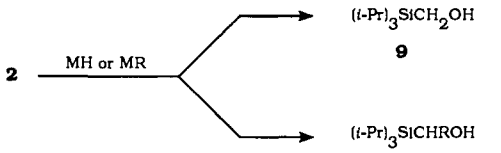
Also, GC analysis revealed that **2** was efficiently converted back to its precursors, **1** (81%, $CH_2(CH_2SH)_2$, BF_3·EE (0.16 equiv), $CHCl_3$ or 77%, $(CH_2)_3S_2SiMe_2$, BF_3·EE (0.4 equiv), CH_2Cl_2)[6a,13] and **3** (93%, $CH(OMe)_3$, TsOH or 100%, $CH(OMe)_3$, MeOH, Clay K 10).[14] Standard methodology (diol, TsOH, C_6H_6, reflux) produced the cyclic acetals (**5** (76%), **6** (72%)). For **6**, MMX calculations predict a strong preference for the $TIPS_{eq}$ chair conformation (>6 kcal/mol) which is revealed in its ^1H NMR through distinctly separated signals for each of the ring hydrogens and by vicinal coupling constants which are matched (±0.2 Hz) by calculation for this conformation. Thus, the reaction of **2** with a 60:40 meso/dl mixture of 2,4-pentanediols produces only the all-cis product, **7**, from the *meso*-diol. This is easily separated from the *dl*-diol derived racemic dioxane, **8**, by chromatography (SiO_2, C_6H_{14}) to obtain both isomers in pure form in yields of 29% and 57%, respectively. Similarly, (2*R*,4*R*)-(−)-2,4-pentanediol gave the interesting optically active acetal (+)-**8** (78%, $[\alpha]^{26}_D$ = +29.6° (neat)) (Figure 1).



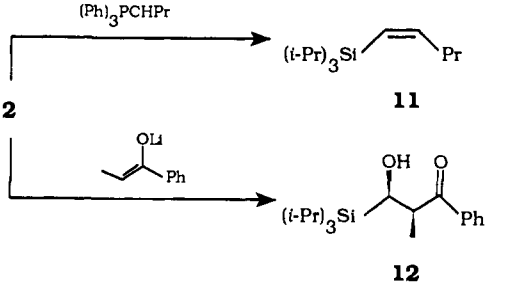
5 **6** **7** **8** (2)

The reduction of **2** is easily accomplished with borane/dimethyl sulfide complex (BMS) (1:1) in THF (1 h, room temperature) to afford pure $TIPSCH_2OH$ (**9**) in 75% yield. Virtually quantitative conversion to **9** (≥95%) was observed by GC with BMS, $LiAlH_4$, and $NaBH_4$ as well as with EtMgBr and *n*-BuMgBr. By contrast, Li(*n*-Bu) gives the expected addition product **10a** (R = *n*-Bu, 78% (100% GC yield)). LiMe produces **10b** (R = Me, 78% (84% GC yield) more efficiently than does MeMgBr (65% GC yield). Grignard reagents lacking a β-hydride source also give **10** (**c**, R = Ph, 80%; **d**, R = C≡CPr, 74%).



(3)

To illustrate that **2** also undergoes the very highly stereoselective reactions which are common for bulky aldehydes, the Wittig olefination of **2** was examined under salt-free conditions,[15] which gave the *cis*-vinylsilane (**11**) (78%, 98% *Z*).[16] Also, the aldol reaction of **2** with the *Z* lithium enolate of propiophenone[17] produced the expected *syn*-aldol adduct (**12**) (65%, >97% syn).[18]



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(16) Ph_3PCHPr in PhMe[15] was less efficient (61%) and selective (c/t = 96:4 by capillary GC) perhaps due to trace amounts of Li-containing impurities. ^{13}C NMR ($CDCl_3$) *cis*-**11** δ 150.50, 123.14, 36.92, 22.97, 18.89, 14.02, 12.20 ppm. *trans*-**11** δ 149.33, 123.55, 39.51, 22.16, 18.65, 13.59, 12.36 ppm.
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With these developments, formylsilanes emerge from their status as transient intermediates and laboratory curiosities to that of a rich new source of silicon-containing compounds.

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Supplementary Material Available: Listings of detailed procedures and complete spectral data for compounds **1–12** (14 pages). Ordering information is given on any current masthead page.

(18) For **12**, $^3J_{H(2)H(3)}$ = 1.3 Hz (δ 3.66, 4.19), which agrees well with the MMX-derived value for the syn (0.3 Hz) rather than the anti (12.8 Hz) isomer.[17b] Enolate to **2** addition at −78 °C gives a single aldol product (^{13}C NMR ($CDCl_3$) δ 206.6, 135.5, 133.2, 128.7, 128.3, 64.1, 42.0, 19.0, 18.98, 13.4, 11.1 ppm), whereas the reverse addition gives minor amounts of the anti isomer (δ 206.2, 43.7, 66.0, 13.5, 11.2 ppm) as well as recovered PhCOEt.

A de Novo Designed Protein Shows a Thermally Induced Transition from a Native to a Molten Globule-like State

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The de novo design of peptides and proteins[1] with predetermined structures provides an important test of our understanding of the principles that govern protein stability and folding. Several designed peptides and proteins have been described,[2,3] but the design of a compact, globular protein that shows all the hallmarks of a native protein has not yet been reported; instead, many of the designed proteins appear to adopt folded states with loosely packed hydrophobic cores such as those found in molten globules or compact intermediates (CI).[1,4] In this communication we describe

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