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Communications

Tris(trimethylsilyl)silane. A New Reducing Agent[1]

Summary: Tris(trimethylsilyl)silane is an effective reducing agent for organic halides that functions by a free radical mechanism. It rivals tributyltin hydride in its efficiency and is a superior reagent from ecological and practical perspectives.

Sir: In basic synthesis, the best known and most useful free radical reaction is probably the reduction of alkyl halides by tributyltin hydride.[3] The reaction is an efficient two-step chain process (eq 1 and 2). However, the formation of tributyltin halides often makes workup and product isolation difficult. Moreover, the tin compounds themselves are toxic and create a disposal problem.

$$R^{\bullet} + Bu_3SnH \rightarrow RH + Bu_3Sn^{\bullet} \qquad (1)$$

$$Bu_3Sn^{\bullet} + RX \rightarrow Bu_3SnX + R^{\bullet} \qquad (2)$$

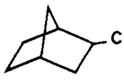
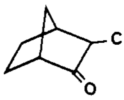
In his recent review,[4] Giese stressed the desirability of replacing toxic hydrogen-transfer agents by more ecologically acceptable compounds. Trialkylsilanes are possible alternatives since silyl radicals are better halogen-abstracting agents than their tin counterparts.[5] However, trialkylsilanes are poor H atom donors toward alkyl radicals and do not support chain reactions, except at elevated temperatures.[6]

We recently demonstrated that silicon–hydrogen bonds can be dramatically weakened by successive substitution of silyl groups at the Si–H function. In fact, the bond dissociation energy of the silicon–hydrogen bond in $(Me_3Si)_3SiH$ is 79 kcal mol^{-1} and is 11 kcal mol^{-1} less than that in Et_3SiH.[7] This result suggested that tris(trimethylsilyl)silane might be a good hydrogen donor[8] and that the compound would be capable of sustaining a radical chain reduction of alkyl halides analogous to reactions 1 and 2. The expectation turned out to be correct, and we now report our preliminary results on the use of this material as a new free radical reducing agent.

Representative Experimental Procedure. Tris(trimethylsilyl)silane was prepared by the literature method.[9] All other materials were commercially available and were used as received.

The reductions were carried out in two ways. In the first, the silane was mixed with an equivalent of an alkyl halide without solvent, while in the second, equimolar amounts of the halide and silane (ca. 0.2 M each; total volume of solution 1 mL) were mixed in monoglyme or a hydrocarbon solvent. The reactions were initiated by UV photolysis (λ = 254 nm) at 40 °C in a Rayonet reactor (35 W) or by the thermal decomposition of benzoyl peroxide (ca. 3 mol %) at 50 °C. Inhibition studies were carried out by using matched pairs of samples that were subjected to thermal initiation; addition of 2,6-di-*tert*-butyl-4-methylphenol (3 mol %) to one of the samples effectively inhibited the reaction in that tube. The reaction conditions and yields are reported in detail in Table I.

Table I. Reduction of Organic Halides by Tris(trimethylsilyl)silane

RX	method[a]	reactn time, h	yield RH,[b] %
$C_{18}H_{37}Cl$	A	5	93
	A	2.5	95
	A	0.25	100
$PhCH_2Br$	B	1.0	100
$C_{16}H_{33}Br$	A	0.5	100
$C_{16}H_{33}Br$	B	1.0	100
$C_{18}H_{37}I$	A	0.1	100

[a] Method A: photolysis of samples in quartz tubes containing equimolar amounts (ca. 0.2 m) of RX and $(Me_3Si)_3SiH$ in hydrocarbon or monoglyme solvent. Method B: reaction initiated with benzoyl peroxide at 50 °C, no solvent. [b] Yields by GC analysis based on formation of RH.

Sample analyses were carried out by using GC and GC/mass spectroscopy using authentic samples as calibrants wherever possible, and yields were quantified by GC using decane as an internal standard. In principle, low molecular weight reduction products are most readily separated by distillation.

Results and Discussion

The reduction of alkyl halides by $(Me_3Si)_3SiH$ can be achieved under a variety of conditions. Salient results and conditions are presented in Table I. Evidence in favor of a free radical mechanism (eq 3 and 4) was provided by the following observations. The reaction was initiated by UV photolysis or by thermal decomposition of benzoyl peroxide. It was also inhibited by 2,6-di-*tert*-butyl-4-methylphenol, which acted as a scavenger of alkyl radicals.

$$R^{\bullet} + (Me_3Si)_3SiH \rightarrow RH + (Me_3Si)_3Si^{\bullet} \qquad (3)$$

$$(Me_3Si)_3Si^{\bullet} + RX \rightarrow (Me_3Si)_3SiX + R^{\bullet} \qquad (4)$$

The data in Table I show that the reductions were very efficient for alkyl bromides and iodides but were somewhat less efficient for chlorides. Preliminary laser flash photolysis results[10] support the reactivity order RI > RBr > RCl. The rate constant, k_4, for halogen abstraction from 1-bromopentane was found to be 2.0×10^7 M^{-1} s^{-1}. This is more than an order of magnitude slower than the corresponding reaction of $Et_3Si^{\bullet}$ (5.4×10^8 M^{-1} s^{-1}) but is approximately equal to that for $Bu_3Sn^{\bullet}$ (2.6×10^7 M^{-1} s^{-1}).[5]

The rate constant for hydrogen abstraction from $(Me_3Si)_3SiH$ by primary alkyl radicals was measured using the 5-hexenyl "radical clock"[11] and led to $k_3 = 6 \times 10^5$ M^{-1}

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s^{-1} (R = hexenyl), which is ca. 4 times slower than the corresponding reaction with tributyltinhydride.[12]

In conclusion, tris(trimethylsilyl)silane functions as a free radical reducing agent that rivals tributyltin hydride in its efficiency and is probably more acceptable from an ecological and toxicological perspective.[13] Further work on the kinetics and synthetic scope of these reactions is in progress.

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Registry No. $(Me_3Si)_3SiH$, 1873-77-4; $C_{18}H_{37}Cl$, 3386-33-2; $PhCH_2Br$, 100-39-0; $C_{16}H_{33}Br$, 112-82-3; $C_{18}H_{37}I$, 629-93-6; $C_{18}H_{38}$, 593-45-3; C_7H_8, 108-88-3; $C_{16}H_{34}$, 544-76-3; 2-norbornyl chloride, 29342-53-8; 3-chloro-2-norbornanone, 61914-03-2; norbornane, 279-23-2; 2-norbornanone, 497-38-1.

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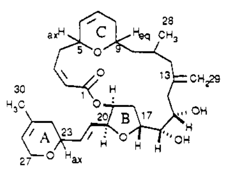
Fijianolides, Polyketide Heterocycles from a Marine Sponge

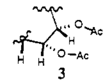
Summary: Two cytotoxic macrocyclic lactones, fijianolides A and B, were isolated from *Spongia mycofijiensis* collected from Vanuatu. These are the first 20-membered ring lactones to be observed from a marine sponge.

Sir: A chocolate sponge, *Spongia mycofijiensis*, became the object of an intense study because the liquid squeezed from freshly collected material rapidly killed (≈10 min) common tropical fish being held in an aquarium. Furthermore, its organic extracts showed anthelminthic activity. The first of the active principles, isolated from Fijiian material, included dendrolassin, a bioinactive furanosesquiterpene, and latrunculin A,[1] an ichthyotoxic ketide–amino acid previously reported by Kashman[2] which also exhibits in vitro anthelminthic activity.[1] Specimens from Vanuatu were chemically different, dendrolassin was absent and latrunculin A was accompanied by mycothiazole, an anthelminthic ketide–amino acid.[3] We now describe new cytotoxic polyketide constituents of the Vanuatu collection which are fijianolides A (1) and B (2).

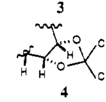
The previously described general workup of 1.7 kg (wet) of *S. mycofijiensis* from Vanuatu[3] involved successive extractions with methanol (twice) and CH_2Cl_2 which afforded three separate dark viscous oils (respectively 1.96 g, 2.06 g, 2.50 g). Fijianolide B (2) was isolated from the first oil and was accompanied by only traces of fijianolide A (1), but additional amounts of 1 were obtained from the other two oils. Structural work focused first on A whose molecular formula of $C_{30}H_{42}O_7$ was deduced by mass spectrometry [FAB (513 $M^+ - H$), LRCIMS (515 $M^+ + H$), LREIMS (514 M^+)] and a ^{13}C APT NMR spectrum (a difference of H_2 by APT versus the MF indicated a diol). The collective NMR data revealed five double bonds and an ester carbonyl which meant that four rings were also present.[4]



1 (fijianolide A)



3



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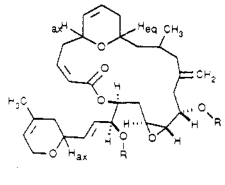

2 R = H (fijianolide B)

5 R = Ac

The unsaturated substructures were established as follows. A but-2(*Z*)-enoyl array (as a lactone) was recognized by the IR 1720 cm^{-1}, and NMR ($CDCl_3$) resonances at ^{13}C $\delta = 165.6$, ^1H $\delta = 5.84$ (d = 11.7 Hz) and 6.20 (ddd = 11.4, 10.8, 6.9 Hz). A dihydropyran (the A ring) with a vinylic methyl and an equatorial (*E*)-ethenyl respectively γ and α to the ring oxygen was identified by NMR resonances ($CDCl_3$) at $\delta = 23.0/1.66$ (s) [C/H-30] and $\delta = 125.8/5.69$ ddd = 15.6, 6.0, 0.9 Hz [C/H-21], 134.0/5.90 dd = 15.6, 6.0 Hz [C/H-22], 73.4/3.97 ddd = 9.6, 5.1, 4.5 Hz [C/H-23] and the large *J* at H-23 was due to diaxial coupling with H-24. A second dihydropyran (the C ring) with a disubstituted double bond was deduced from $^3J_{6-7} = 10.5$ Hz. The 1,3-C-ring substituents were assigned as trans. The $^3J_{9-8} = {}^3J_{9-8'} = 3.6$ Hz indicated an equatorial H-9 as this would have equivalent dihedral angles to both adjacent H-8 protons, and the $^3J_{5-6} = 2.1$ suggested a pseudo-axial H-5 by analogy to our analysis of this same stereochemical situation in the xestins.[5] Analysis of ^1H–^1H COSY NMR data (regular and long range) and the regular and long range ^1H–^{13}C COSY NMR correlations that were observed allowed a 2-methyl-4-methylenepentanyl group

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(4) 1: $[\alpha]^{20}{}_D$ −8.0° (*c* 0.04, $CHCl_3$). NMR: in C_6D_6 with shifts in ppm from TMS and assignments based on results of ^1H–^1H and ^{13}C–^1H COSY [atom number], ^{13}C δ's at 75 MHz, ^1H δ's and *J*'s at 300 MHz (*J*'s from C_6D_6) or additional {*J*'s from $CDCl_3$} [1], 165.2; [2] 123.2, 5.80 (m) {d = 11.7}; [3] 142.2, 5.80 (m) {ddd = 11.4, 10.8, 6.9}; [4] 35.6, 3.09 (m) {ddd = 14.4, 11.4, 5.4}, 2.20 (m) {ddd = 14.4, 9.9, 7.2}; [5] 72.9, 4.34 (m) {ddd = 11.4, 4.5, 2.1}; [6] 128.5, 5.58 (bd = 10.8) {dd = 10.5, 2.7}; [7] 125.3, 5.69 (bd = 12.3); [8] 31.8, 1.80 (m) 1.65 (m); [9] 66.5, 3.50 (m) {dq = 8.7, 3.6}; [10] 42.9, 1.50 (m) {ddd = 14.4, 8.7, 2.7}, 0.95 (m) {ddd = 14.4, 9.9, 3.0}; [11] 27.0, 1.90 (m); [12] 45.4, 2.25 (m), 2.00 (m); [13] 145.6; [14] 35.6, 2.25 (m, 2 H); [15] 71.3, 4.18 (m) {ddd = 9.3, 3.6, 2.7}; [16] 75.7, 4.18 (m) {dd = 4.5, 2.7}; [17] 78.3, 4.46 (m) {ddd = 10.5, 5.1, 4.8}; [18] 34.9, 2.30 (m) {ddd = 15.0, 10.8, 4.2}, 2.20 (m); [19] 76.8, 5.57 (m) {ddd = 3.9, 3.6, <1}; [20] 81.5, 4.56 (dd = 4.2, 4.0); [21] 125.9, 5.85 (dd = 15.3, 5.4) {ddd = 15.6, 6.0, 0.9}; [22] 133.5, 6.04 (dd = 15.3, 5.1); [23] 73.4, 3.91 (m) {ddd = 9.6, 5.1, 4.5}; [24] 35.9, 1.90 (m) {dd = 13.8, 8.1}, 1.80 (m) {dd = 13.8, 3.5}; [25] 131.1; [26] 120.0, 5.19 (bs); [27] 65.4, 4.11 (bs), 4.04 (bs); [28] 19.7, 0.87 (d = 5.7, 3 H); [29] 113.4, 5.00 (s), 4.92 (s); [30] 22.7, 1.55 (s, 3 H). $CDCl_3$ NMR data in Table 1S, supplementary material. MS: FAB (thioglycerol/glycerol) scanned up to *m/z* 1300; 621 [M^+ + thioglycerol], 513 [$M^+ - H$]. IR: (neat) cm^{-1} 3600–3200, 2900, 1720, 1050. UV: (MeOH) 208 (10 500).

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