Notes

A Novel Deoxygenation from α,β-Epoxy Silanes to Vinylsilanes by the Copper-Catalyzed Grignard Reactions: A Dramatic Effect by Alkoxy Groups on Silicon[1]

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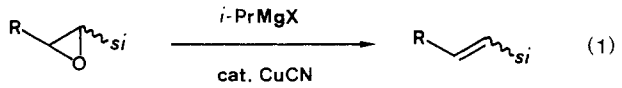
In the course of current research on the synthetic applications of silafunctional α,β-epoxy silanes,[1a,2] we have found a novel deoxygenation reaction of α,β-epoxy silanes by reaction with isopropyl Grignard reagent in the presence of a catalytic amount of CuCN, as shown by the general scheme in eq 1.



(1)

(*si* = alkoxysilyl group)

Described herein are examples of this novel reaction and the significant role of alkoxy groups on silicon therein. Table I summarizes ratios of the deoxygenation to the normal ring opening with variation of silyl groups, organometallic reagents, and stereochemistry of the epoxy silanes. There are several significant features. (1) The reaction courses are dramatically dependent on the nature of the silyl groups. Thus, trimethylsilyl derivative **1a** reacted with the isopropyl Grignard reagent in the presence of CuCN to give a normal ring-opening product (**2**), no deoxygenation being observed (entry 1).[3] In contrast, with either the methoxydimethylsilyl (**1c**) or isopropoxydimethylsilyl derivative (**1d**), the deoxygenation reaction occurred to give the corresponding vinylsilane **3** in higher than 90% selectivity (entries 3 and 5). Diisopropoxymethylsilyl derivative **1e** gave almost exclusively the deoxygenation product (entry 9). Comparison of data in entries 1, 2, 3, and 5 reveals that the steric bulk of the silyl groups is not a crucial factor for the deoxygenation, but the electronic effect exerted by the alkoxy groups on silicon is most important. (2) The deoxygenation was characteristic of secondary and tertiary alkyl Grignard reagents (entry 4 vs entries 5 and 8). The reaction with the tertiary alkyl Grignard reagent was rather slow and proceeded at room temperature. Solvent effects were not significant (entries 5 and 6). Even in the absence of the copper catalyst **1d** underwent, although rather slowly, the deoxygenation reaction with the isopropyl Grignard reagent (entry 7). (3) While the deoxygenation proceeded with almost retention of stereochemistry in the case of (*E*)-epoxy silanes bearing a monoalkoxysilyl group (entries 3, 5–8)

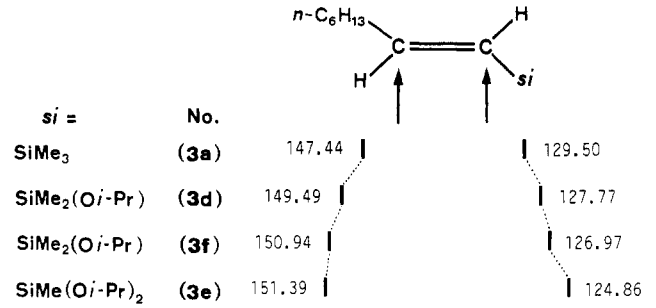
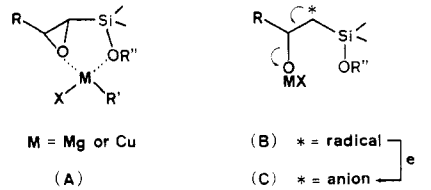


Figure 1. ^{13}C NMR chemical shifts of olefin carbons in (*E*)-vinylsilanes **3a**, **3d**, and **3e** and *Z* isomer (**3f**) in $CDCl_3$: δ (ppm) from TMS.

with a few exceptions, a considerable loss of stereochemistry was observed with the *Z* isomer (entry 10) and with dialkoxysilyl-substituted *E* epoxide (entry 9). A temperature dependence of the stereoselectivity was observed with the *Z* isomer (entries 10 and 11). (4) In some cases, α-silyl ketones were formed in substantial amounts possibly owing to the known rearrangement of epoxy silanes induced by magnesium halides.[4]

The role of alkoxysilyl groups in the present novel deoxygenation reaction may be twofold. The electron-withdrawing ability of silyl groups increases steadily with the increased number of alkoxy groups on silicon, as judged from NMR chemical shifts of olefinic carbons[5] of vinylsilanes **3**, summarized in Figure 1. This electronic effect may be responsible in part to the deoxygenation. Furthermore, there would be a chelation by two oxygen atoms on the epoxide and on the alkoxy group in the early stage of the reaction, as illustrated in A, the formation of which



might be encumbered by the bulkiness of the organometallic reagents (R′). Taking these observations and considerations into account, we propose an electron-transfer mechanism for the deoxygenation. Thus, one-electron transfer from the electron-donating secondary or tertiary alkyl–copper species[6] to the epoxy silane[7] affords

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(6) For electron transfer from organocopper reagents, see: House, H. O. *Acc. Chem. Res.* **1976**, *9*, 59. There have been many examples of an electron-transfer mechanism in which the electron-donating ability of an alkyl group is more important than steric factors: Kochi, J. K. *Organometallic Mechanisms and Catalysis*; Academic Press: New York, 1978, Chapters 15–17, pp 445–529.

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an anion radical intermediate that undergoes ring opening at the α position to give an α radical (B). A partial loss of stereochemistry may compete with a fast second electron transfer to give an α anion (C). Elimination of the β-oxygen functionality from C results in the formation of vinylsilane. It should be noted here that these electron-transfer processes may be facilitated by the electron-withdrawing alkoxysilyl group which should stabilize both the α radical and anion.[8]

While many methods have been reported for the deoxygenation of epoxides,[9] little is known about Grignard or organocopper-induced deoxygenation.[10] Closely related reactions are diorganocuprate-induced reduction of α-heteroatom-substituted ketones and related systems.[11] Only a few examples have been described for the formation of α,β-enones from α,β-epoxy ketones.[11c] It is apparent that these reductions involve electron-transfer processes.[11]

The present clean deoxygenation observed with new systems, α,β-epoxy (alkoxy)silanes, may shed light on yet unclear reactivities of organocopper reagents as well as organosilicon compounds. In addition to the mechanistic interest, the present deoxygenation might find synthetic utilities. For example, α,β-epoxy silanes obtainable from aldehydes or ketones by the Magnus method[12] could be transformed into the corresponding vinylsilanes. For this purpose, we are now trying to develop this route by using $(i\text{-PrO})Me_2SiCH_2Cl$[13] instead of the originally used trimethylsilyl derivative Me_3SiCH_2Cl.

Experimental Section

^1H NMR spectra were recorded on a JEOL JNM-MH 100 spectrometer and a JNM-GX 400 (400 MHz) spectrometer in $CDCl_3$ or CCl_4 with Me_4Si as the internal standard. Chemical shifts are reported in δ. When peak multiplicities are reported, the following abbreviations are used: s, singlet; d, doublet; t, triplet; q, quartet; sep, septet; m, multiplet. ^{13}C NMR spectra were obtained on a Hitachi R-900 ^{13}C spectrometer and a JNM-GX 400 spectrometer. Infrared spectra were obtained on a Hitachi 270-30 spectrophotometer. Data are given in cm^{-1}. Abbreviations for peak intensities are as follows: s, strong; m, medium; w, weak; vw, very weak. Mass spectra were measured on a JEOL JMS-D300 mass spectrometer connected to a JEOL LGC-20K gas chromatograph, equipped with a 1-m glass column packed with OV-17 (3%) on Chromosorb, and a JMA-2000 data processing system. Ionization voltage was 24 eV for all compounds. GLC analysis was carried out on a Shimadzu GC-4B gas chromatograph coupled with a Shimadzu chromatopac-E1A integrator. A 3-m column of 30% Silicon DC-550 on Celite 545 was installed. (*E*)-1-(Trimethylsilyl)-1-octene (**3a**) was reported previously.[14]

Preparation of (*E*)-1-Silyl-1-octenes 3b–e. A typical procedure is given for the preparation of (*E*)-1-(isopropoxydimethylsilyl)-1-octene (**3d**). A mixture of dimethylchlorosilane (18.3 mL; 165 mmol) and 1-octyne (22 mL; 150 mmol) was added dropwise to a catalyst solution, $[Pt[(CH_2{=}CH)Me_2Si]_2O]_2]$,[15] in xylene (0.25 M, 60 μL; 0.015 mmol) at room temperature over 2 h. An exothermic reaction started immediately and was controlled by intermittent cooling with a water bath. After being stirred at room temperature for an additional 2 h, the mixture was diluted with dry ether (500 mL) and triethylamine (25 mL; 180 mmol). To the white suspension was added dropwise isopropyl alcohol (15 mL; 258 mmol) with stirring at room temperature, and the mixture was stirred overnight. After filtration the filtrate was washed twice with ice-cold water and once with brine and dried over $MgSO_4$. GLC analysis showed the formation of **3d** and the regioisomer 2-(isopropoxydimethylsilyl)-1-octene in the ratio of 88:12. Fractional distillation through a short column packed with glass helicies gave 29.0 g (85% yield) of 95% isomerically pure **3d**: bp 111–112 °C/22 mmHg; ^1H NMR (100 MHz, CCl_4) 0.00 (s, 6 H), 0.82 (t, 3 H, J = 6.5 Hz), 1.01 (d, 6 H, J = 6.5 Hz), 0.94–1.58 (m, 8 H), 2.06 (dt, 2 H, J = 7.5 and 7 Hz), 3.88 (sep, 1 H, J = 6.5 Hz), 5.53 (d, 1 H, J = 19 Hz), 5.92 (dt, 1 H, J = 19 and 7.5 Hz); ^{13}C NMR ($CDCl_3$) −1.160 (q), 14.041 (q), 22.601 (t), 25.715 (q), 28.514 (t), 28.841 (t), 31.719 (t), 36.618 (t), 64.871 (d), 127.775 (d), 149.900 (d); IR 2968 (s), 2932 (s), 1619 (m), 1251 (m), 1127 (m), 1027 (s), 991 (w), 882 (m), 843 (m), 791 (m); MS, m/e (relative intensity) 228 (M^+, 5), 213 (95), 75 (100); high resolution mass spectrum, calcd for $C_{13}H_{28}OSi$ 228.1909, found 228.1922.

(*E*)-1-(Methoxydimethylsilyl)-1-octene (3c) was prepared by essentially the same procedure except for the use of methanol instead of isopropyl alcohol in 42% yield: bp 92–94 °C/16 mmHg; ^1H NMR ($CDCl_3$) 0.00 (s, 6 H), 0.84 (t, 3 H, J = 6.5 Hz), 0.93–1.56 (m, 8 H), 1.91–2.25 (m, 2 H), 3.29 (s, 3 H), 5.50 (d, 1 H, J = 18.5 Hz), 6.10 (dt, 1 H, J = 18.5 and 6 Hz); ^{13}C NMR ($CDCl_3$) −2.34 (q), 14.03 (q), 22.59 (t), 28.50 (t), 28.84 (t), 31.71 (t), 36.64 (t), 50.27 (q), 126.52 (d), 150.27 (d); IR 2926 (s), 2932 (s), 1619 (m), 1252 (s), 1093 (s), 993 (w), 843 (s), 793 (m); MS, m/e (relative intensity) 200 (M^+, 3), 185 (100), 89 (83), 75 (87). Anal. Calcd for $C_{11}H_{24}OSi$: C, 65.94; H, 12.07. Found: C, 66.09; H, 12.29.

(*E*)-1-(Dibutylmethylsilyl)-1-octene (3b) was prepared in 68% yield from 1-octyne via hydrosilation with dichloromethylsilane followed by treatment with *n*-BuLi in hexane: bp 96–99 °C/1 mmHg; ^1H NMR ($CDCl_3$) −0.11 (s, 3 H), 0.31–0.67 (m, 4 H), 0.67–1.01 (m, 9 H), 1.01–1.63 (m, 16 H), 1.87–2.30 (m, 2 H), 5.50 (d, 1 H, J = 18.5 Hz), 5.95 (dt, 1 H, J = 18.5 and 6 Hz); MS, m/e (relative intensity) 268 (M^+, 1), 211 (100), 155 (75).

(*E*)-1-(Diisopropoxymethylsilyl)-1-octene (3e) was prepared from 1-octyne via hydrosilation with dichloromethylsilane followed by treatment with isopropyl alcohol and triethylamine, as described for **3d**. Fractional distillation gave a 74% yield of the product: bp 95–97 °C/5 mmHg; ^1H NMR ($CDCl_3$) 0.03 (s, 3 H), 0.86 (t, 3 H, J = 6.5 Hz), 1.03–1.55 (m, 8 H), 1.11 (d, 12 H, J = 6.5 Hz), 1.88–2.28 (m, 2 H), 4.05 (sep, 2 H, J = 6.5 Hz), 5.43 (d, 1 H, J = 18.5 Hz), 5.99 (dt, 1 H, J = 18.5 and 6.5 Hz); ^{13}C NMR ($CDCl_3$) −3.21 (q), 14.03 (q), 22.60 (t), 25.64 (q), 25.66 (q), 28.38 (t), 28.85 (t), 31.71 (t), 36.56 (t), 64.77 (d), 124.86 (d), 151.31 (d); IR 2976 (s), 2932 (s), 1619 (m), 1382 (m), 1370 (m), 1257 (m), 1174 (m), 1132 (s), 1033 (s), 968 (vw), 887 (m), 822 (m), 805 (m); MS, m/e (relative intensity) 272 (M^+, 2), 257 (75), 161 (100). Anal.

(7) It has been well-established that a silyl group greatly facilitates the nucleophilic displacement at the α carbon atom: Eaborn, C.; Jeffrey, J. C. *J. Chem. Soc.* **1954**, 4266. See also: Colvin, E. *Silicon in Organic Synthesis*; Butterworths: London, 1981; pp 83–96. The high α-regioselective ring-opening of α,β-epoxy silanes in reactions with nucleophiles[1a] implies the presence of low-lying electron-accepting orbitals. These could be used also in the present electron-transfer processes.

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(9) Umbreit, M. A.; Sharpless, K. B. *Org. Synth.* **1981**, *60*, 29. Matsubara, S.; Nonaka, T.; Okuda, Y.; Kanemoto, S.; Oshima, K.; Nozaki, H. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 1480 and references cited therein.

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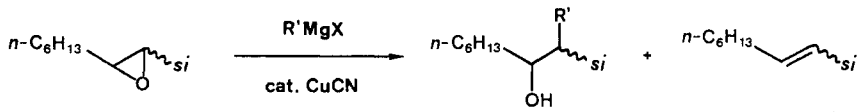
(14) Tamao, K.; Akita, M.; Maeda, K.; Kumada, M. *J. Org. Chem.* **1987**, *52*, 1100.

(15) Lewis, L. N.; Lewis, N. *J. Am. Chem. Soc.* **1986**, *108*, 7228 and references cited therein.

Table I. Reaction of α,β-Epoxy Silanes with Grignard Reagents in the Presence of CuCN as a Catalyst[a]



1 2 3

entry	epoxy silane[b] *E* or *Z*, *si* (no.)	R'MgX	conditions temp, time	2:3[c] (*E*/*Z*)[d]
1	*E*, $SiMe_3$ (**1a**)	*i*-PrMgCl	−30 to 0 °C, 6 h	100:0[e]
2	*E*, $SiMe(n\text{-}Bu)_2$ (**1b**)	*i*-PrMgCl	−30 to −20 °C, 3 h	70:30 (15/85)[e,f]
3	*E*, $SiMe_2(OMe)$ (**1c**)	*i*-PrMgCl	−30 to −20 °C, 1.5 h	8:92 (>95/<5)
4	*E*, $SiMe_2(O\text{-}i\text{-}Pr)$ (**1d**)	EtMgBr	−40 to −25 °C, 1.5 h	65:35 (60/40)
5	*E*, $SiMe_2(O\text{-}i\text{-}Pr)$ (**1d**)	*i*-PrMgCl	−40 to −25 °C, 1.5 h	10:90 (>95/<5)
6	*E*, $SiMe_2(O\text{-}i\text{-}Pr)$ (**1d**)	*i*-PrMgCl[g]	−30 to −10 °C, 1 h	28:72 (>95/<5)
7	*E*, $SiMe_2(O\text{-}i\text{-}Pr)$ (**1d**)	*i*-PrMgCl[g,h]	−30 to −10 °C, 9 h	10:90 (>95/<5)[e]
8	*E*, $SiMe_2(O\text{-}i\text{-}Pr)$ (**1d**)	*t*-BuMgCl	room temp, 1.5 h	16:84 (>95/<5)[e]
9	*E*, $SiMe(O\text{-}i\text{-}Pr)_2$ (**1e**)	*i*-PrMgCl	−30 to −20 °C, 2 h	2:98 (60/40)[i]
10	*Z*, $SiMe_2(O\text{-}i\text{-}Pr)$ (**1f**)	*i*-PrMgCl	−78 °C, 18 h	16:84 (30/70)
11	*Z*, $SiMe_2(O\text{-}i\text{-}Pr)$ (**1f**)	*i*-PrMgCl	−30 °C, 4 h	15:85 (50/50)

[a] Carried out on a 2-mmol scale in the ratio of epoxy silane/R'MgX/CuCN = 1/3/0.3 in THF, unless otherwise stated. [b] Prepared by the MCPBA oxidation of the corresponding vinylsilanes in dichloromethane. [c] Determined by GLC analysis of the distillate of the reaction product; in all cases simple bulb-to-bulb distillation under reduced pressure gave a mixture of product in higher than 80% recovery by weight. In entries 3–11 ring-opening product **2** appeared as the Peterson elimination products, RCH=CHR', on GLC analysis. [d] The *E*/*Z* ratios of **3** were determined by 100-MHz NMR. [e] The corresponding α-silyl ketones, $RCOCH_2si$, were formed as a byproduct in 25–30% yields. In entries 7 and 8, the silyl ketone could not be isolated in a pure state, but its presence in the product mixture was suggested by the characteristic singlet at δ 2.22 ($-COCH_2si$) in ^1H NMR spectra. [f] Vinylic protons of *Z* isomer: ^1H NMR (CCl_4) 5.34 (d, 1 H, *J* = 14.5 Hz), 6.23 (dt, 1 H, *J* = 6.0 and 14.5 Hz). [g] In ether. [h] In the absence of CuCN. [i] Vinylic protons of *Z* isomer: ^1H NMR (CCl_4) 5.26 (d, 1 H, *J* = 15 Hz), 6.17 (dt, 1 H, *J* = 6.5 and 15 Hz).

Calcd for $C_{15}H_{32}O_2Si$: C, 66.11; H, 11.84. Found: C, 66.38; H, 12.11.

Preparation of (*Z*)-(Isopropoxydimethylsilyl)-1-octene (3f). This compound was prepared from 1-octyne in three steps as follows.

1-(Dimethylsilyl)-1-octyne. A solution of *n*-BuLi (206 mmol) in hexane was slowly added to a solution of 1-octyne (22.8 g; 206 mmol) in dry THF (100 mL) at 0 °C over 1 h, and the mixture was stirred at room temperature for 1 h. To the resulting orange solution was added dropwise at 0 °C a solution of dimethylchlorosilane HMe_2SiCl (25.2 mL; 227 mmol) in THF (50 mL) over 1 h. After being stirred at room temperature for 6 h, the mixture was quenched with an ice-cold 10% NH_4Cl solution, extracted with ether, and dried over Na_2SO_4. Distillation gave 31.4 g (91% yield) of 1-(dimethylsilyl)-1-octyne: bp 95–97 °C/43 mmHg; ^1H NMR (CCl_4) 0.16 (d, 6 H, *J* = 4 Hz), 0.8–1.0 (m, 3 H), 1.15–1.65 (m, 8 H), 2.16 (t, 2 H, *J* = 6.5 Hz), 4.80 (sep, 1 H, *J* = 4 Hz).

(*Z*)-1-(Dimethylsilyl)-1-octene. To a solution of 1-(dimethylsilyl)-1-octyne (5.08 g; 30 mmol) in hexane (60 mL) and ether (30 mL) was added dropwise diisobutylaluminum hydride (DIBAL) (7.54 mL; 42 mmol) at room temperature.[16] After being stirred overnight, a cold 10% NH_4Cl solution (ca. 25 mL) was added to the reaction mixture and the resulting white solid was filtered off. The organic layer of the filtrate was separated and dried over $MgSO_4$. Distillation gave 4.45 g (88% yield) of the title compound: bp 110–120 °C/65 mmHg; ^1H NMR (CCl_4) 0.10 (d, 6 H, *J* = 4 Hz), 0.8–0.95 (m, 3 H), 1.07–1.6 (m, 8 H), 2.05–2.21 (m, 2 H), 4.18–4.32 (m, 1 H), 5.42 (dd, 1 H, *J* = 13 and 5 Hz), 6.28 (dt, 1 H, *J* = 13 and 7 Hz); IR 2966 (s), 2930 (s), 2858 (s), 2120 (s), 1607 (m), 1250 (m), 893 (s), 838 (m), 772 (m). Anal. Calcd for $C_{10}H_{22}Si$: C, 70.50; H, 13.02. Found: C, 70.34; H, 13.30.

(*Z*)-1-(Isopropoxydimethylsilyl)-1-octene (3f). To a solution of (*Z*)-(dimethylsilyl)-1-octene (4.25 g; 25 mmol) in 3 mL of isopropyl alcohol was added 30 μL of a solution of $H_2PtCl_6 \cdot 6H_2O$ in isopropyl alcohol (0.12 M) at 0 °C. Hydrogen evolution was immediately observed. The mixture was stirred at room temperature for 3 h to ensure the reaction as monitored by GLC and distilled to give 5.34 g (94% yield) of pure product: bp 113–115 °C/20 mmHg; ^1H NMR (CCl_4) 0.14 (s, 6 H), 0.91 (t, 3 H, *J* = 6.5 Hz), 1.1–1.62 (m, including d at 1.12, *J* = 6 Hz, total 14 H), 3.98 (sep, 1 H, *J* = 6.5 Hz), 5.40 (d, 1 H, *J* = 14.5 Hz), 6.29 (dt, 1 H, *J* = 14.5 and 7.5 Hz); ^{13}C NMR ($CDCl_3$) 0.722 (q), 14.035 (q), 22.607 (q), 25.727 (t), 29.060 (t), 29.631 (t), 31.798 (t), 33.753 (t), 65.017 (d), 126.976 (d), 150.935 (d); IR 2968 (s), 2930 (s), 2858 (m), 1607 (m), 1381 (m), 1369 (m), 1252 (m), 1126 (m), 1029 (s), 882 (m), 837 (s), 786 (m); MS, *m*/*e* (relative intensity) 228 (M^+, 4), 213 (100), 127 (82), 75 (51). Anal. Calcd for $C_{13}H_{28}OSi$: C, 68.35; H, 12.35. Found: C, 68.31; H, 12.52.

A Typical Procedure for a Sequence of Epoxidation of Vinylsilanes and Deoxygenation Reaction of α,β-Epoxy Silanes (Table I, Entry 5). To a solution of (*E*)-1-(isopropoxydimethylsilyl)-1-octene (**3d**) (1.00 g; 4.38 mmol) in dichloromethane (17 mL) was added *m*-chloroperbenzoic acid (MCPBA) (1.07 g, 70% purity; 4.40 mmol) at 0 °C. After being stirred at room temperature overnight, the mixture was cooled to 0 °C, diluted with hexane, and filtered to remove the white solid (ca. 1 g). Evaporation of the solvent gave almost pure epoxide (*E*)-1-(isopropoxydimethylsilyl)-1,2-epoxyoctane (**1d**) (1.12 g; 100% yield), as confirmed by ^1H NMR analysis in CCl_4: 0.03 (s, 3 H), 0.05 (s, 3 H), 0.8–1.05 (m, 3 H), 1.05–1.65 (m, including d at 1.13, *J* = 6.0 Hz, total 16 H), 1.84 (d, *J* = 4.0 Hz), 2.6–2.8 (m, 1 H), 4.05 (sep, 1 H, *J* = 6.0 Hz). This epoxy silane was used in the subsequent reaction without further purification. To a suspension of CuCN (52 mg; 0.58 mmol) in 2 mL of THF was added isopropylmagnesium chloride (5.6 mmol) in THF at −50 °C. After 1 h of stirring a solution of epoxy silane **1d** (451 mg; 1.85 mmol) in 2 mL of THF was added. The mixture was stirred at −40 to −25 °C for 1.5 h, quenched with 5 mL of isopropyl alcohol, and diluted with hexane, and insoluble materials were filtered. The filtrate was concentrated and the residue filtered through a short silica gel column to remove inorganic materials (eluted by ethyl acetate). The filtrate was concentrated and distilled bulb-to-bulb to give 341 mg (85% yield by weight) of a colorless distillate boiling over the range of 110–125 °C/5 mmHg (bath temperature). GLC analysis of the distillate showed two peaks, the ratio being 10/90. Each of them was isolated by preparative GLC. The minor product was 2-methyl-3-decene arising from the Peterson elimination[17] of the ring-opening product **2**: ^1H NMR (CCl_4) 0.65–1.0 (m, including d at 0.84, *J* = 7 Hz, total 9 H), 1.06–1.4 (m, 8 H), 2.75–3.0 (m, 2 H), 3.0–3.3 (m, 1 H), 5.25–5.4 (m, 2 H). The major product was 1-(isopropoxydimethylsilyl)-1-octene. The *E*/*Z* ratio was determined to be >95/<5 by ^1H NMR (olefinic protons).

Spectral data of other products are listed below.

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2-Methyl-3-(trimethylsilyl)-4-decanol (**2a**; entry 1): ^{1}H NMR (CCl_4) −0.02 (s, 9 H), 0.66 (dd, 1 H, J = 3.0 and 3.3 Hz), 0.78 (br t, 3 H), 0.88 (d, 3 H, J = 7.0 Hz), 0.92 (d, 3 H, J = 7.0 Hz), 1.08–1.54 (m, 11 H), 1.7–2.14 (m, 1 H), 3.63–3.92 (m, 1 H); IR 3500 (m), 1248 (s), 836 (s); MS, m/e (relative intensity) 229 (M^+ − Me, 0.5), 226 (M^+ − H_2O, 0.5), 75 (100).

1-(Trimethylsilyl)-2-octanone (entry 1): ^{1}H NMR (CCl_4) 0.00 (s, 9 H), 0.84 (br t, 3 H), 1.03–1.63 (m, 8 H), 2.01 (s, 2 H), 2.19 (t, 2 H, J = 7.5 Hz); IR 1695 (s), 850 (s); MS, m/e (relative intensity) 200 (M^+, 11), 75 (62), 73 (100).

2-Methyl-3-(dibutylmethylsilyl)-4-decanol (**2b**; entry 2): ^{1}H NMR (CCl_4) −0.07 (s, 3 H), 0.36–0.68 (m, 5 H), 0.68–1.72 (m, 35 H), 3.63–3.89 (m, 1 H); IR 3504 (m), 1250 (m); MS, m/e (relative intensity) 310 (M^+ − H_2O, 0.3), 117 (100).

1-(Dibutylmethylsilyl)-2-octanone (entry 2): ^{1}H NMR (CCl_4) −0.07 (s, 3 H), 0.35–0.64 (m, 4 H), 0.70–1.03 (m, 9 H), 1.03–1.71 (m, 16 H), 1.97 (s, 2 H), 2.18 (t, 2 H, J = 7 Hz); IR 1698 (s); MS, m/e (relative intensity) 284 (M^+, 5), 227 (100).

(*Z*)-1-(Isopropoxydimethylsilyl)-1,2-epoxyoctane (a crude intermediate in entry 10): ^{1}H NMR (CCl_4) 0.11 (s, 6 H), 0.87 (br t, 3 H), 1.05–1.6 (m, including d at 1.11, J = 6 Hz, total 14 H), 2.22 (d, J = 5 Hz), 2.85–3.05 (m, 1 H), 4.07 (sep, 1 H, J = 6 Hz).

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Registry No. **1a**, 62427-09-2; **1b**, 111581-57-8; **1c**, 111581-58-9; **1d**, 111581-59-0; **1e**, 111581-60-3; **1f**, 111581-61-4; **2a**, 111581-62-5; **2b**, 111581-63-6; **2c**, 111581-66-9; **2d** (R′ = Et), 111581-68-1; **2d** (R′ = *i*-Pr), 111581-69-2; **2d** (R′ = *t*-Bu), 111581-70-5; **2e**, 111581-71-6; (*E*)-**3b**, 111581-64-7; (*Z*)-**3b**, 111581-65-8; (*E*)-**3c**, 111615-21-5; (*Z*)-**3c**, 111581-67-0; (*E*)-**3d**, 109786-60-9; (*Z*)-3d, 109786-61-0; (*E*)-**3e**, 111581-72-7; (*Z*)-**3e**, 111581-73-8; Pt-[[$(CH_2$=$CH)Me_2Si]_2O]_2$, 81032-58-8; *i*-PrMgCl, 1068-55-9; EtMgBr, 925-90-6; *t*-BuMgBr, 677-22-5; CuCN, 544-92-3; HMe_2SiCl, 1066-35-9; $HMeSiCl_2$, 75-54-7; 1-octyne, 629-05-0; 1-(dimethylsilyl)-1-octyne, 109786-62-1; (*Z*)-1-(dimethylsilyl)-1-octene, 111581-74-9; 2-methyl-3-decene, 78645-74-6.

Synthesis and Tubulin Binding of 4′-(1-Azi-2,2,2-trifluoroethyl)oncodazole, a Photolabile Analogue of Oncodazole

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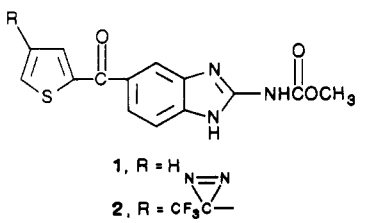
Oncodazole (**1**, methyl [5-(2-thienylcarbonyl)-1*H*-benzimidazol-2-yl]carbamate) is a tubulin binding agent[1] that has potent anthelmintic[2] and antifungal[3] activities and that has shown promise as an experimental antineoplastic agent.[4] The binding of tubulin by drugs that cause disruption or hyperstabilization of the mitotic apparatus is presently an area of great interest.[5] We became interested in characterizing the interaction of **1** with tubulin and for this required a photoaffinity analogue of **1**. Here we report a synthesis of the 4′-(1-azi-2,2,2-trifluoroethyl) analogue (**2**) of **1**.[6] The diazirine function was placed in the 4′-position on the basis of a systematic study of oncodazole derivatives that has shown this to be one of the positions on **1** that can be substituted with retention of biological activity. This compound, which is one of the few examples of a heterocyclic diazirine ring system and certainly one of the most highly functionalized, possesses both the requisite photolability ($t_{1/2}$ ~ 21 s upon irradiation at 350 nm in methanol) and the required tubulin binding affinity.



1, R = H

2, R = CF_3C(diazirine)

Results and Discussion

The synthesis of **2** was divided into three stages: (i) construction of the appropriate carbon skeleton, (ii) formation of the diazirine group, and (iii) formation of the benzimidazole carbamate group.

The synthesis began with 2,3,5-tribromothiophene as shown in Scheme I. Thiophene acid **3** was prepared from the tribromothiophene by sequential replacement of the 2-bromo with hydrogen, followed by replacement of the 5-bromo with carboxyl via a modification of a previously reported sequence.[7] Friedel–Crafts acylation of anisole with the acid chloride of **3** produced ketone **4**,[2] which was then protected as the ethylene ketal **5**. Metal–halogen exchange on **5** followed by reaction with *N*-(trifluoroacetyl)piperidine[6b] and removal of the protecting group gave the covalently hydrated diketone **6**. Reaction of **6** with nitric and sulfuric acids produced the appropriately substituted nitro derivative **7**. The electron-withdrawing power of the trifluoroacetyl group served to protect the reactive thiophene ring from nitration.

Next, the trifluoroacetyl group was converted into the 1-azi-2,2,2-trifluoroethyl group by the modification of known methods.[6b,8] Thus, diketone **7** was selectively oximated on the trifluoroacetyl carbonyl and the resultant mixture of syn and anti oximes **8** was converted to the oxime tosylates **9**. Selective oximation of the trifluoromethyl carbonyl in the presence of the diaryl ketone and the readily displaced aromatic methoxyl group required carefully controlled conditions employing 1.1 equiv of hydroxylamine. Reaction of **9** with ammonia in THF followed by oxidation of the intermediate diaziridine with *tert*-butyl hypochlorite gave diazirine **10**.

With the diazirine moiety completed the benzimidazole carbamate portion of the molecule was constructed next. The methoxyl group of **10** was displaced with ammonia in THF to produce **11**. The nitro group in **11** was selectively reduced with sodium hydrosulfite buffered with sodium

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