Radical Cyclization of *O*-Glycosides Using 1,1,2,2-Tetraphenyldisilane as a Radical Reagent: Preparation of Bicyclic Sugars

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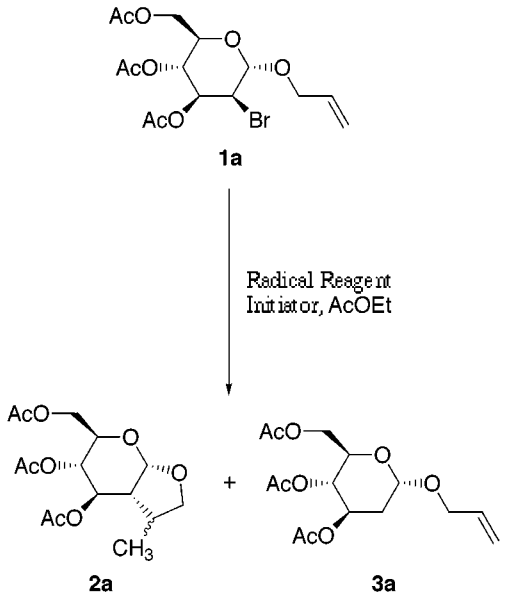
Today, the importance of radical reactions in organic synthesis has increased, since functional group conversion of organic compounds under mild conditions is critical for the preparation of natural products and fine chemicals.[1] Especially, radical cyclization reactions to carbon−carbon, carbon−oxygen, and carbon−nitrogen multi bonds through the 5-*exo*- and 6-*exo*-manners are the most powerful and versatile methods for the construction of cyclic systems.[2] These reactions have advantages such as high functional group tolerance, mild reaction conditions, and high levels of regio- and stereoselectivity. Generally, these radical reactions are promoted by 14-metal hydrides such as Bu_3SnH[3] and tris(trimethylsilyl)silane (TTMSS).[4] However, it is well-known that organotin compounds are highly toxic, and the complete removal of the tin species from the reaction products is difficult, while TTMSS, a less toxic alternative to Bu_3SnH, is an expensive and less stable oil which is easily oxidized by O_2 in air. Thus, these conventional radical reagents require complicated treatment for storage, workup, and disposal. Recently, we have reported the utilization of 1,1,2,2-tetraphenyldisilane($Ph_4Si_2H_2$) for radical reduction, reductive addition to olefins, and alkylation onto heteroaromatic bases with alkyl bromides, xanthates, and alkyl phenyl selenides.[5] $Ph_4Si_2H_2$ is an easily handlable reagent due to its stability. No decomposition of $Ph_4Si_2H_2$ was observed for 3 months under air at room temperature. Here, we describe a synthetic approach to bicyclic sugars via radical cyclization using $Ph_4Si_2H_2$ as a radical reagent, since the fused ring skeletons containing sugar moieties are frequently encountered in natural products. For example, a furo-[2,3-*b*]pyran skeleton is known in azadirachtin,[6] an insect antifeedant. Thus, bicyclic sugars are an interesting target compound because of their use as a building block for synthesis of natural products and their biological activities. Recently, bicyclic sugars have been prepared extensively through the radical cyclization of sugar halides and Bu_3SnH.[7]

Table 1. Radical Cyclization of 1a Using $Ph_4Si_2H_2$ and Bu_3SnH



reagent	initiator	yields/% 2a	3a
$Ph_4Si_2H_2$	Et_3B	84	0
	AIBN	78	0
Bu_3SnH	Et_3B	37	44
	AIBN	65	32

The precursors of the radical cyclization reaction **1a**−**f** were prepared from glycal with alcohols such as allyl alcohol, propargyl alcohol, and cinnamyl alcohol in the presence of NBS or PhSeBr in CH_3CN. The precursor **1g** was prepared from glucal with 2-bromoethanol in the

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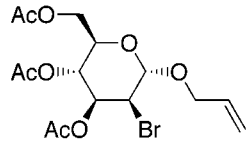
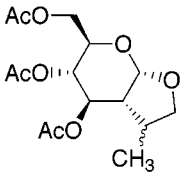
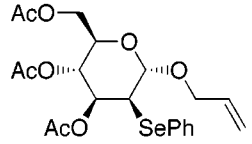
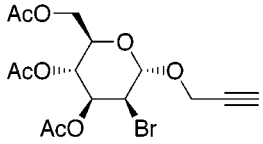
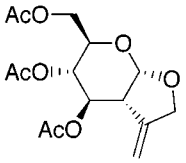
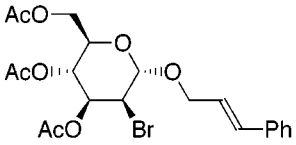
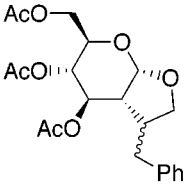
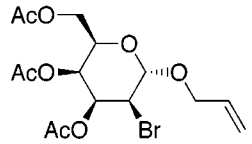
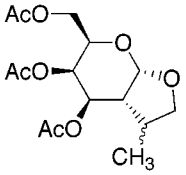
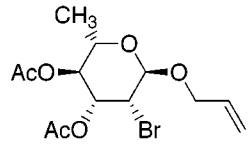
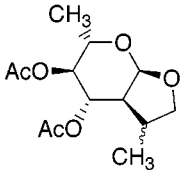
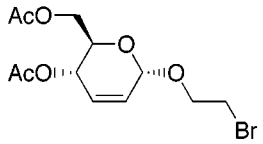
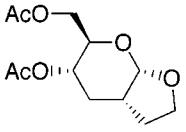
Table 2. Radical Cyclization Using $Ph_4Si_2H_2$

	Starting Material	Product	Initiator	Yield / % (isomeric ratio*)
1a		**2a** 	Et_3B	84 (52:48)
			AIBN	78 (51:49)
1b		**2a**	Et_3B	64 (50:50)
			AIBN	72 (55:45)
1c		**2c** 	Et_3B	57
			AIBN	44
1d		**2d** 	Et_3B	36 (80:20)
			AIBN	48 (73:27)
1e		**2e** 	Et_3B	60 (61:39)
			AIBN	63 (59:41)
1f		**2f** 	Et_3B	76 (56:44)
			AIBN	92 (52:48)
1g		**2g** 	Et_3B	68
			AIBN	72

*The ratio of isomers was determined from ^1H NMR.

presence of $BF_3{\cdot}OEt_2$.[7b] Using these precursors, radical cyclization reaction mediated by $Ph_4Si_2H_2$ was carried out with Et_3B under aerobic conditions and with AIBN at refluxing temperature of ethyl acetate. At first, radical cyclizations of compound **1a** mediated by $Ph_4Si_2H_2$ and Bu_3SnH were compared under the same conditions (Table 1).

As shown in Table 1, only cyclization product **2a** was obtained in 84% and 78% yields by the $Ph_4Si_2H_2-Et_3B$ method and the $Ph_4Si_2H_2$−AIBN method, respectively. However, Bu_3SnH mediated reaction gave the product **2a** in 37% and 65% yields together with reduction product **3a** in 44% and 32% yields by the $Bu_3SnH-Et_3B$ method and the Bu_3SnH−AIBN method, respectively. Probably, these results arise from the difference in bond strength between the 14-metal atom and the hydrogen atom. Therefore, the use of Bu_3SnH in this reaction requires quite low concentration of Bu_3SnH using such as a syringe-pump, to increase yield of the cyclization product. However, the same cyclization with $Ph_4Si_2H_2$ does not require such treatment. Here, the stereochemistry of the cyclized product (3*R*)-**2a** was established by X-ray analysis.[8]

Radical cyclization of compounds **1b**−**g** using $Ph_4Si_2H_2$ was carried out and the results are shown in Table 2. Bicyclic sugars were obtained in moderate to good yields. In each case, the produced bicyclic sugar consists of a *cis*-fused ring. *trans*-Fused product and 6-*endo* cyclization product were not formed. Stereoselectivity at the C(3) position was observed in the reaction of compound **1d**; however, remarkable stereoselectivity was not observed for other substrates.

(8) Crystal data for (3*R*)-**2a** (Mo Kα radiation, Rigaku RAXIS-II Imaging Plate diffractometer): $C_{15}H_{22}O_8$, FW = 330.33, a = 5.650(5) Å, b = 8.035(10) Å, c = 19.56(4) Å, β = 93.54(6)°, monoclinic, $P2_1$, Z = 2, V = 886(2) Å^3, D_c = 1.237 g cm^{-3}. R factor = 0.082 for 1171 independent observed reflections ($I > 3.20\sigma(I)$); weighted RW factor = 0.099.

In conclusion, stereoselective 5-*exo* radical cyclization of allylic 2-bromo (or phenylseleno)-2-deoxysugars with 1,1,2,2-tetraphenyldisilane as a radical reagent was carried out to give the corresponding *cis*-fused 5-*exo* cyclized bicyclic sugars, in moderate to good yields. The present $Ph_4Si_2H_2$ is less toxic and stable under air and, different from the Bu_3SnH, 5-*exo* radical cyclization reaction, using $Ph_4Si_2H_2$ gave no reduction (debromination) product without requiring control of the concentration. As mentioned above, $Ph_4Si_2H_2$ acts as an alternative to the conventional reagents, Bu_3SnH and tris(trimethylsilyl)silane, for its low toxicity and stability. Further application of the $Ph_4Si_2H_2$ method to other radical pathways and other radical precursors is underway in our laboratory.

Experimental Section

General Method. ^{1}H NMR were recorded on 400 and 500 MHz spectrometers. Chemical shifts are reported as ppm downfield from tetramethylsilane (TMS) in δ units. *J* Values are given in Hz. The matrix of mass spectra (FAB) used 3-nitrobenzyl alcohol. Melting points were determined on an electrochemical apparatus in open capillary tubes and are uncorrected. Kieselgel 60 F254 was used for TLC, Wakogel C-200 was used for column chromatography, and Wakogel B-5F was used for pTLC.

General Procedure for Radical Cyclization Initiated by Et_3B. Triethylborane in tetrahydrofuran (0.2 mL, 1 M) was added to a mixture of substrate (0.30 mmol) and radical reagent (0.36 mmol) in ethyl acetate (3.0 mL) under aerobic conditions at room temperature, and the reaction mixture was stirred for 1 h. After the reaction, K_2CO_3 (0.15 mmol) was added, and the reaction mixture was extracted with $CHCl_3$ and dried over Na_2SO_4. After removal of the solvent, the residue was purified by column chromatography and pTLC (eluent: hexane/ethyl acetate = 1/1−3/1).

General Procedure for the Radical Cyclization Initiated by AIBN. A solution of substrate (0.30 mmol), radical reagent (0.36 mmol), and AIBN (0.15 mmol) in ethyl acetate (3.0 mL) was refluxed under an argon atmosphere. The reaction mixture was monitored at every 2 h. When the substrate still remained, the same amount of AIBN was added again after every 4 h until the substrate was consumed. After the reaction, K_2CO_3 (0.15 mmol) was added, and the reaction mixture was extracted with $CHCl_3$, and dried over Na_2SO_4. After removal of the solvent, the residue was purified by column chromatography and pTLC (eluent: hexane/ethyl acetate = 1/1−3/1).

(3a*R*,4*R*,5*S*,6*R*,7a*S*)-6-Acetyloxymethyl-4,5-diacetyloxy-3-methylhexahydro-4*H*-furo[2,3-*b*]pyran[7a] **2a** (isomeric mixture): mp 92.0−94.0 °C; IR (KBr) 2950, 1750, 1460, 1360, 1240, 1025 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ = 0.95 (3H, d, *J* = 7.0 Hz), 1.09 (3H, d, *J* = 7.0 Hz), 2.02 (3H, s), 2.02 (3H, s), 2.04 (3H, s), 2.07 (3H, s), 2.08 (3H, s), 2.09 (3H, s), 2.29−2.36 (2H, m), 2.54−2.66 (1H, m), 3.54 (1H, dd, *J* = 8.9, 3.6 Hz), 3.68 (1H, dd, *J* = 10.9, 8.5 Hz), 4.01−4.12 (5H, m), 4.31−4.43 (3H, m), 4.95−5.06 (3H, m), 5.17 (1H, dd, *J* = 9.4, 9.4 Hz), 5.49 (1H, d, *J* = 4.3 Hz, 7a−H), 5.53 (1H, d, *J* = 4.8 Hz, 7a-−H); MS (FAB) found *m*/*z* = 331, calcd for $C_{15}H_{23}O_8$ (M + 1) = 331.

Allyl 2-deoxy-3,4,6-tri-*O*-acetyl-α-D-arabinohexopyranoside 3a: syrup; IR (neat) 2950, 1745, 1430, 1370, 1240, 1050 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ = 1.82 (1H, ddd, *J* = 13.1, 11.7, 3.7 Hz), 1.99 (3H, s), 2.02 (3H, s), 2.24 (1H, ddd, *J* = 13.1, 5.3, 1.1 Hz), 3.92−3.99 (2H, m), 4.03 (1H, dd, *J* = 12.1, 2.3 Hz), 4.12 (1H, ddd, *J* = 12.9, 5.2, 1.4 Hz), 4.29 (1H, dd, *J* = 12.1, 2.3 Hz), 4.96−5.01 (2H, m), 5.19 (1H, ddd, *J* = 10.5, 2.8, 1.4 Hz), 5.25−5.36 (2H, m), 5.88 (1H, dddd, *J* = 17.2, 10.5, 6.1, 5.2 Hz); MS (FAB) found *m*/*z* = 331, calcd for $C_{15}H_{23}O_8$ (M + 1) = 331.

(3a*R*,4*R*,5*S*,6*R*,7a*S*)-6-Acetyloxymethyl-4,5-diacetyloxy-3-methylidenehexahydro-4*H*-furo[2,3-*b*]pyran[7d] **2c:** mp 87.5−92.0 °C; IR (KBr) 2945, 1740, 1680, 1370, 1230, 1165, 1035 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ = 2.02 (3H, s), 2.06 (3H, s), 2.09 (3H, s), 2.78 (1H, dd, *J* = 8.7, 4.1 Hz), 4.11 (1H, dd, *J* = 12.2, 2.2 Hz), 4.19 (1H, ddd, *J* = 9.6, 4.3, 2.2 Hz), 4.34−4.40 (2H, m), 4.69 (1H, ddd, *J* = 13.5, 3.6, 2.5 Hz), 4.97−4.98 (1H, m), 5.00 (1H, dd, *J* = 9.6, 9.1 Hz), 5.09 (1H, td, *J* = 2.5, 1.2 Hz), 5.15 (1H, dd, *J* = 9.1, 8.7 Hz), 5.43 (1H, d, *J* = 4.1 Hz); MS (FAB) found *m*/*z* = 329, calcd for $C_{15}H_{21}O_8$ (M + 1) = 329.

(3a*R*,4*R*,5*S*,6*R*,7a*S*)-6-Acetyloxymethyl-4,5-diacetyloxy-3-(phenylmethyl)hexahydro-4*H*-furo[2,3-*b*]pyran[7d] **2d** (isomeric mixture): syrup; IR (KBr) 2945, 2890, 1740, 1490, 1370, 1245, 1230, 1155, 1030 cm^{-1}; ^{1}H NMR ($CDCl_3$) major isomer δ = 1.86 (3H, s), 1.98 (3H, s), 2.05 (3H, s), 2.10−2.14 (1H, m), 2.48−2.84 (3H, m), 3.68 (1H, dd, *J* = 9.1, 3.3 Hz), 4.01−4.08 (2H, m), 4.27−4.41 (2H, m), 4.91 (1H, t, *J* = 9.1 Hz), 4.98 (1H, t, *J* = 8.5 Hz), 5.51 (1H, d, *J* = 4.8 Hz), 7.10−7.65 (5H, m); minor isomer δ = 1.87 (3H, s), 2.01 (3H, s), 2.06 (3H, s), 2.48−2.84 (4H, m), 3.81−3.85 (2H, m), 4.10−4.14 (1H, m), 4.27−4.41 (2H, m), 5.02 (1H, t, *J* = 9.9 Hz), 5.29 (1H, t, *J* = 9.4 Hz), 5.49 (1H, d, *J* = 4.3 Hz), 7.10−7.65 (5H, m); MS (FAB) found *m*/*z* = 407, calcd for $C_{21}H_{27}O_8$ (M + 1) = 407.

(3a*R*,4*R*,5*R*,6*R*,7a*S*)-6-Acetyloxymethyl-4,5-diacetyloxy-3-methylhexahydro-4*H*-furo[2,3-*b*]pyran 2e (isomeric mixture): syrup; IR (neat) 2960, 1745, 1440, 1370, 1240, 1030 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ = 0.94 (3H, d, *J* = 7.0 Hz), 1.11 (3H, d, *J* = 7.2 Hz), 2.01 (3H, s), 2.05 (3H, s), 2.06 (3H, s), 2.06 (3H, s), 2.14 (3H, s), 2.14 (3H, s), 2.16−2.26 (1H, m), 2.26−2.34 (1H, m), 2.57−2.65 (1H, m), 3.53 (1H, dd, *J* = 8.9, 2.7 Hz), 3.60 (1H, dd, *J* = 10.6, 8.5 Hz), 4.02 (1H, t, *J* = 8.2 Hz), 4.07−4.15 (m), 4.23 (t, *J* = 7.0 Hz), 4.26 (dd, *J* = 3.8, 3.1 Hz), 4.84 (1H, dd, *J* = 10.1, 2.9 Hz), 4.99 (1H, dd, *J* = 10.4, 3.4 Hz), 5.29 (1H, dd, *J* = 2.9, 1.3 Hz), 5.32 (1H, d, *J* = 3.1 Hz), 5.52 (1H, d, *J* = 4.1 Hz), 5.54 (1H, d, *J* = 4.3 Hz); HRMS (FAB) found *m*/*z* 331.1373, calcd for $C_{15}H_{23}O_8$ (M + H) = 331.1393.

(3a*S*,4*S*,5*S*,6*S*,7a*R*)-4,5-Diacetyloxy-3,6-dimethylhexahydro-4*H*-furo[2,3-*b*]pyran 2f (isomeric mixture): syrup; IR (neat) 2970, 1750, 1725, 1380, 1240, 1060, 1030 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ = 0.94 (3H, d, *J* = 7.0 Hz), 1.08 (3H, d, *J* = 7.0 Hz), 1.19 (3H, d, *J* = 6.3 Hz), 1.21 (3H, d, *J* = 6.3 Hz), 2.01 (3H, s), 2.04 (3H, s), 2.05 (3H, s), 2.07 (3H, s), 2.27−2.34 (2H, m), 2.54−2.62 (1H, m), 3.52 (1H, dd, *J* = 8.7, 3.6 Hz), 3.66 (1H, dd, *J* = 10.9, 8.5 Hz), 3.89−4.03 (3H, m), 4.31 (1H, dd, *J* = 8.8, 6.6 Hz), 4.69−4.76 (2H, m), 4.99 (1H, t, *J* = 8.2 Hz), 5.12 (1H, t, *J* = 9.5 Hz), 5.43 (1H, d, *J* = 4.4 Hz), 5.46 (1H, d, *J* = 4.8 Hz); MS (FAB) found *m*/*z* = 273, calcd for $C_{13}H_{21}O_6$ (M + 1) = 273.

(3a*R*,5*S*,6*R*,7a*S*)-5-Acetyloxy-6-(acetyloxymethyl)hexahydro-4*H*-furo[2,3-*b*]pyran 2g: mp 64.0−68.0 °C; (lit.[7h] mp 69.0−71.5 °C); IR (KBr) 2960, 2920, 1740, 1445, 1380, 1240, 1135, 1070, 1030 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ = 1.50 (1H, ddd, *J* = 13.1, 10.1, 1.3 Hz), 1.74−1.80 (1H, m), 2.06 (3H, s), 2.09 (3H, s), 2.11−2.19 (2H, m), 2.32−2.37 (1H, m), 3.91 (1H, ddd, *J* = 8.6, 8.6, 3.1 Hz), 3.98 (1H, ddd, *J* = 9.6, 5.2, 2.3 Hz), 4.10−4.16 (2H, m), 4.30 (1H, dd, *J* = 12.1, 5.2 Hz), 4.80 (1H, ddd, *J* = 10.1, 9.6, 4.8 Hz), 5.33 (1H, d, *J* = 4.4 Hz); MS (FAB) found *m*/*z* = 259, calcd for $C_{12}H_{19}O_6$ (M + 1) = 259.

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Supporting Information Available: Copies of ^{1}H NMR spectra for compounds **1a**−**g**, **2a**,**c**−**g**, and **3a** and X-ray data of compound (3*R*)-**2a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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