Carbohydrate Research, 185 (1989) 77–89
Elsevier Science Publishers B.V., Amsterdam – Printed in The Netherlands

SYNTHESIS OF 4-SELENO-D-FRUCTOSE DERIVATIVES AND AN INVESTIGATION OF THEIR UTILITY AS PRECURSORS OF UNSATURATED HEXULOFURANOSIDES

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(Received December 21st, 1987; accepted for publication, April 28th, 1988)

ABSTRACT

4-Seleno-D-fructose derivatives were prepared by opening of the epoxide ring of methyl 2,3-anhydro-α- and -β-D-tagatofuranosides with phenyl selenide ion. The resulting β-hydroxyselenide system or the corresponding methanesulfonate could not be induced to undergo elimination, thus providing the first examples of stable β-methylsulfonyloxyselenides. Oxidation of methyl 1,6-di-*O*-(*tert*-butyldimethylsilyl)-3-*O*-methylsulfonyl-4-*Se*-phenyl-4-seleno-α-D-fructofuranoside to the corresponding selenoxide, followed by thermally induced *syn*-elimination of benzeneselenenic acid, provides a convenient route to the novel unsaturated hexulofuranoside, methyl 1,6-di-*O*-(*tert*-butyldimethylsilyl)-4-deoxy-β-L-*glycero*-hex-4-enulofuranoside, which was readily converted into methyl 4-deoxy-α-D-*threo*-hexulofuranoside.

INTRODUCTION

Anhydro sugars **1** and **2**, readily available from methyl α- and β-D-fructofuranosides[1,2], were considered as potential precursors of 3,4-dideoxy-D-*glycero*-hexulose ("3,4-dideoxyfructose"), an important compound in the context of our studies[3,4] on the sweetness of D-fructose and analogs. Our initial efforts to convert **1** or **2** into the desired 3,4-unsaturated sugar were unsuccessful; however, these investigations revealed some interesting aspects of seleno sugar chemistry, which are described in this article. In particular, β-methylsulfonyloxyselenides **8** and **11** were found to be remarkably stable, a feature presumably illustrating the extremely low reactivity of hexulofuranosides towards nucleophilic displacement at C-3. Moreover, the β-hydroxyselenide **7** proved to be a useful intermediate for the preparation of **15**.

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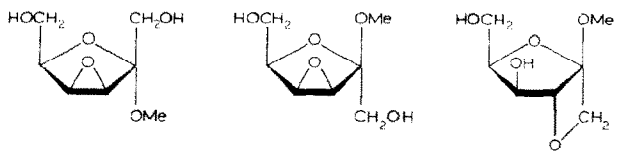
0008-6215/89/$ 03.50

RESULTS AND DISCUSSION

Several methods are available for the deoxygenation of oxiranes into the corresponding alkenes, and many of them have been applied to **1** (or **2**) and derivatives in attempts to prepare the corresponding 3,4-unsaturated hexulofuranoside **A** (or **B**). Thus, treatment of the β anomer **2** with zinc–copper couple and sodium iodide in a mixture of *N*,*N*-dimethylformamide and 1,2-dimethoxyethane, a system[5] which has been used to deoxygenate 2,3-anhydro-α-D-mannopyranosides[6], led unexpectedly to compound **3**, an unusual anhydro derivative of methyl β-D-sorbofuranoside. The presence, in the ^{1}H-n.m.r. spectrum of **3**, of a signal for HO-4 ($J_{4,OH}$ 3.5 Hz), as well as a very small coupling between H-3 and H-4 ($J_{3,4}$ ~0 Hz), is in agreement with the 1,3-anhydro structure and rules out the possible, isomeric 1,4-anhydro structure (see ref. 7 for the description of a 1′,4′-anhydro derivative of sucrose obtained by a similar reaction). Moreover, the presence of an oxetane ring in compound **3** is supported by the magnitude of the geminal coupling between the protons of the methylene group at C-1 ($J_{1A,1B}$ 7.1; $J_{1A,1B} = J_{6A,6B} = 7.3$ in 1,3:2,5:4,6-trianhydro-L-iditol[8]; $6.2 \leq |J_{2A,2B}| \leq 7.3$ Hz in simple oxetanes[9]), and by the large downfield shift of the signal of C-1, in the ^{13}C-n.m.r. spectrum of **3**, at δ 81.4 with respect to that of C-6 (δ 61.6). Starting from the α anomer **1**, in which the formation of such an anhydro derivative is not possible, the analogous reaction gave a very polar product that was not further investigated.

Attempted deoxygenation of the 1,6-di-*O*-trimethylsilyl derivative of **2** with iodotrimethylsilane[10,11] led to a complex mixture of several unidentified products, whereas treatment with the less reactive bromotrimethylsilane (prepared *in situ* from lithium bromide and chlorotrimethylsilane in acetonitrile[12]) gave a major component whose ^{1}H-n.m.r. spectrum was similar to that of 5-hydroxymethyl-2-furaldehyde. Also, treatment of methyl 3,4-anhydro-1,6-di-*O*-trimethylsilyl-β-D-tagatofuranoside with triphenylphosphine, imidazole, and iodine in refluxing toluene (Garegg's deoxygenation procedure[13]), even in the presence of tetrabutylammonium iodide, did not lead to any appreciable transformation of the starting material. Furthermore, no satisfactory results were obtained from the reactions of methyl β-D-fructofuranoside or its 1,6-di-*O*-trityl ether[14] with triphenylphosphine, iodoform, and imidazole in refluxing toluene (Bessodes *et al.*'s modification[15] of Garegg's procedure[13] for the conversion of vicinal diols into olefins).

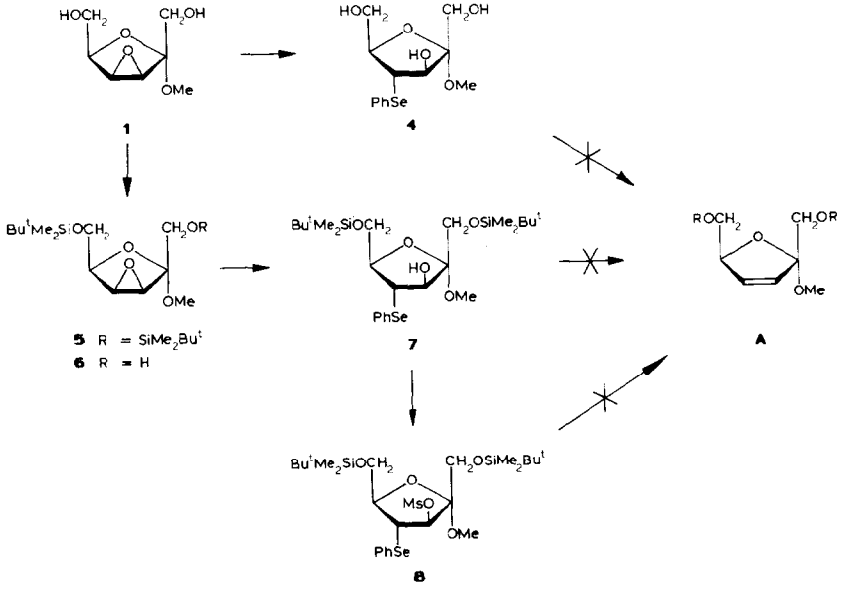
Epoxide-ring opening with a selenide ion followed by reductive elimination of the resulting β-hydroxyselenide under very mild conditions constitutes undoub-



1 **2** **3**

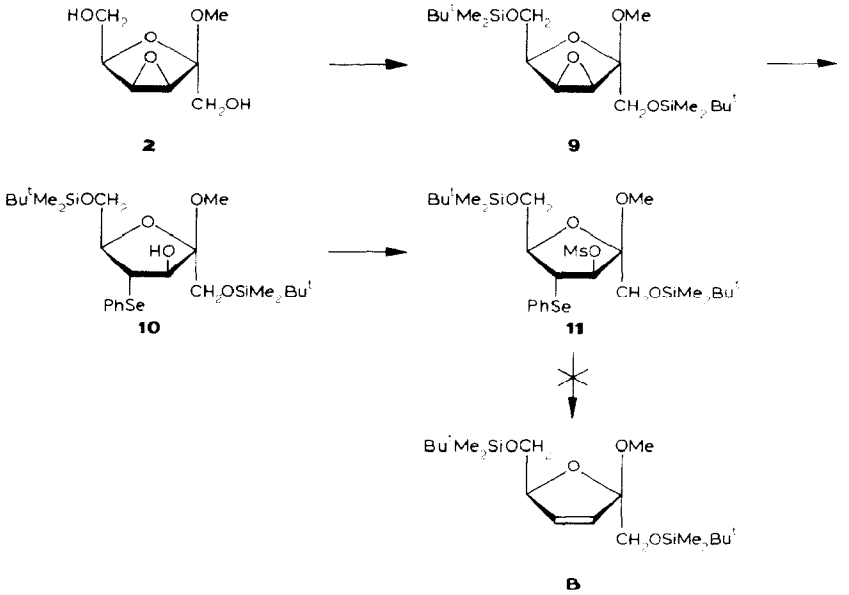
tedly one of the best methods for the conversion of epoxides into alkenes[16]. Accordingly, treatment of epoxide **1** with sodium phenyl selenide (prepared from diphenyl diselenide and sodium borohydride in ethanol) under the conditions described by Sharpless and Lauer[17] afforded the corresponding 4-seleno-D-fructose derivative **4** in good yield (75%). The coupling constants between the ring protons of **4** ($J_{3,4}$ 4.7, $J_{4,5}$ 7.2 Hz) are in agreement with a furanoid ring having the α-D-*fructo* configuration and adopting an average conformation of the type $^4T_5$–E_5 (this conformation is the preferred one in most α-D-fructofuranosides, see ref. 18). Reductive elimination of β-hydroxyselenides can be achieved in several ways[16]; the procedure[19] involving the treatment of the substrate with trifluoroacetic anhydride in dichloromethane in the presence of triethylamine at 20° was considered to be particularly well suited to the case of **4**. However, no reaction occurred under these conditions; with 1,2-dichloroethane as the solvent, a complex mixture of products was obtained after several hours at reflux temperature.

β-Hydroxyselenides have been converted into alkenes in one step by treatment with an excess of methanesulfonyl chloride in the presence of triethylamine[20], most probably by way of an unstable β-methylsulfonyloxyselenide which eliminates spontaneously the components of phenylselenenyl methanesulfonate (see ref. 16). In order to prepare a derivative of **4** suitable for such reaction, epoxide **1** was silylated with *tert*-butylchlorodimethylsilane in the presence of 4-*N*,*N*-dimethylaminopyridine and triethylamine[21] to afford compound **5** in high yield (83%) (direct silylation of **4** under the same conditions did not lead to the formation of compound **7**). Interestingly, partial silylation of **1** gave only one of the two possible monosilyl derivatives of **1**, presumably the 6-*O*-*tert*-butyldimethylsilyl



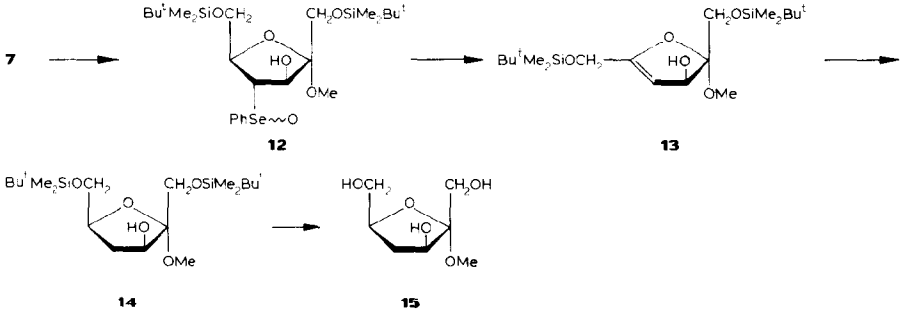
derivative of **6**, as a result of the lower reactivity of OH-1 in 2-hexulofuranoid derivatives[22]. The epoxide ring of compound **5** was then opened with phenyl selenide ion, and the resulting β-hydroxyselenide **7** treated with methanesulfonyl chloride and triethylamine in dichloromethane. Very little transformation occurred under these conditions; a 60–70% conversion of the starting material was attained, only, after a large excess of reagent and 1,2-dichloroethane had been added, and the mixture heated at reflux temperature overnight. Isolation of compound **8** as the main product of the reaction (~30%) indicated that mesylation of OH-3 occurred without concomitant reductive elimination, even under the drastic conditions used for the reaction. Compound **8** is stable at room temperature, but decomposed very slowly in 1,2-dichloroethane or *N*,*N*-dimethylformamide at reflux temperature.

In order to examine the influence of the anomeric configuration on the reductive elimination process, the β anomer **10** of **7** was prepared from methyl 2,3-anhydro-β-D-tagatofuranoside (**2**) by way of its disilylated derivative **9**. Compound **10** was then treated with methanesulfonyl chloride and triethylamine in refluxing dichloromethane to afford compound **11** in 94% yield. This compound was found to be also extremely thermally stable and did not give any trace of unsaturated hexulofuranoside **B** by refluxing in 1,2-dichloroethane for 90 min. Although the structures of **8** and **11** would seem ideally suited for the internal displacement of a good leaving group by a powerful nucleophile (as the first step of the reductive elimination of $PhSeOSO_2Me$[16]), their remarkable stability is attributable to steric effects and the deactivating effect exerted by the anomeric center on the nucleofugal ability of the substituent at C-3 of hexulofuranosides. This interpretation is supported by the observation that 2,3-anhydro-β-D-ribofuranosides, and even 2,3-



anhydro-β-D-lyxofuranosides, react with nucleophiles at C-3 mostly or exclusively[23]. Thus, compounds **8** and **11** constitute the first examples of stable β-sulfonyloxyselenides. In a further attempt to promote a reductive elimination from **7**, this compound was treated with trifluoromethanesulfonic anhydride in dichloromethane in the presence of triethylamine, a reaction which led to the formation of an intractable mixture.

The *syn*-elimination of selenoxides is a well-known olefin-forming reaction that occurs at or below room temperature and represents the mildest, general olefin-forming reaction known[24,25]. Since the elimination reaction in selenoxides derived from β-hydroxyselenides involves the β-hydrogen atom that is not at the carbon atom bearing the hydroxyl group, the process involving opening of an oxirane ring with phenyl selenide ion, oxidation of the selenide to the corresponding selenoxide, and *syn*-elimination of benzeneselenenic acid constitutes a very convenient procedure for the conversion of oxiranes into allylic alcohols[17].



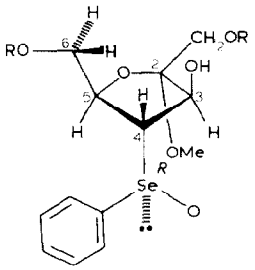
Oxidation of the selenium atom of **7** with hydrogen peroxide was exceedingly easy and afforded compound **12** (78%) as a 13:7 mixture of diastereomeric selenoxides. As shown by the coupling constants listed in Table I, the furanoid ring of compound **12** adopts a preferential conformation (E_4-type, see Scheme 1) completely different from that of the parent selenide **7**, an observation which indicates that the conformation of the flexible ring is highly sensitive to polar effects. The chemical shifts of H-3, -5 and -6 (see Table I) are strongly influenced by the configuration of the selenium atom; thus, the signals of H-5 and -6 of the minor isomer

TABLE I

^{1}H-N.M.R. DATA[a] OF SELENOXIDE **12**

Isomer	*Coupling constants (Hz)*		*Chemical shifts (δ)*				
	$J_{3,4}$	$J_{4,5}$	*H-3*	*H-4*	*H-5*	*H-6A*	*H-6B*
Se-S (65%)	~0	2.0	3.84	2.94	4.65	3.53	3.90
Se-R (35%)	~1	3.5	4.36	3.05	3.96	3.00	3.50

[a]For a solution in $(^2H)_2$dichloromethane.



Scheme 1

appeared at an unusually high field, whereas H-3 of the major isomer is highly shielded. Considering that the rotation around the crowded C-4–Se bond is restricted, these differences are attributable to the anisotropy effect of the phenyl substituent and enabled us to assign the *R* and *S* configuration to the selenium atom of the minor and major diastereoisomer, respectively.

Syn-elimination of phenylselenenic acid was achieved by heating selenoxide **12** in 1,2-dichloroethane, and afforded rapidly and cleanly the novel unsaturated hexulofuranoside derivative **13**. Owing to its slow decomposition at room temperature, in particular on contact with chromatographic adsorbents, compound **13** is difficult to isolate in a pure state. However, the constitution and structure of **13** were established unambiguously by its spectroscopic properties and by its conversion into methyl 4-deoxy-α-D-*threo*-hexulofuranoside (**15**). The conversion involved catalytic hydrogenation of **13**, to afford preponderantly the D-*threo*-hexulofuranoside **14**, followed by desilylation using tetrabutylammonium fluoride in oxolane. A pure sample of **15** was prepared by treatment of epoxide **1** with lithium aluminum hydride in oxolane at reflux temperature to afford almost exclusively the 4-deoxy regioisomer in good yield. The latter process provides a very convenient and short route to "4-deoxyfructose", since epoxide **1** can be prepared in a single step from methyl α-D-fructofuranoside as described by Guthrie *et al.*[1,2]. The utilization of **1** and the β anomer **2** as precursors of "4-deoxyfructose", the conformational behavior and the organoleptic properties of this compound, as well as of "3-deoxyfructose", will be described separately.

EXPERIMENTAL

General methods. — Melting points were determined with a Fisher–Johns apparatus and are uncorrected. Optical rotations were measured with a Perkin–Elmer model 141 automatic polarimeter in a 0.1-dm cell at 26 ±3°. I.r. spectra were recorded with a Perkin–Elmer 598 spectrophotometer. N.m.r. spectra were recorded with a Bruker CXP-200 spectrometer at 200 (^{1}H) and 50.306 (^{13}C) MHz, or a Bruker AM-400 spectrometer at 400 (^{1}H) and 100.6 (^{13}C) MHz, for solutions in (^{2}H)chloroform with tetramethylsilane (Me_4Si) as the internal standard, unless otherwise stated; in the cases of the spectra of compounds in ($^2H)_2$dichloro-

methane, the signal of $CDHCl_2$ (δ 5.285/Me_4Si) was used as the internal standard. Chemical shifts are given in parts per million downfield from Me_4Si. Chemical shifts and coupling constants were obtained from first-order analyses of the n.m.r. spectra; s, d, t, and q are used to denote the multiplicities of the signals in off-resonance decoupled ^{13}C-n.m.r. spectra.

Analytical t.l.c. was performed on precoated glass-plates with Merck Silica Gel 60F-254 as the adsorbent (layer thickness: 0.25 mm). The developed plates were air-dried and irradiated with u.v. light, or sprayed (or both) with a solution of $Ce(SO_4)_2$ (1%) and H_2MoO_4 (1.5%) in 10% aqueous H_2SO_4, and heated at 150°. Column chromatography was performed on Silica Gel 60 (70–230 mesh, Merck). The following solvent systems (v/v) were used: (*A*) ethyl acetate; (*B*) 10:1 hexanes–ethyl acetate; hexanes–acetone: (*C*) 20:1, (*D*) 10:1, and (*E*) 1:1; (*F*) 5:1 hexanes–methyl *tert*-butyl ether; dichloromethane–2-propanol: (*G*) 20:1, (*H*) 15:1, (*J*) 10:1, (*K*) 5:1, and (*L*) 4:1; (*M*) 5:1 dichloromethane–methanol; and (*N*) 4:1 dichloromethane–hexanes.

Solvents were evaporated under reduced pressure below 40°. Dry oxolane was distilled under Ar from $LiAlH_4$ immediately before use.

*Methyl 1,3-anhydro-β-*D*-sorbofuranoside* (**3**). — To a solution of epoxide **1** (275 mg, 1.56 mmol) in a mixture of *N,N*-dimethylformamide (8 mL) and 1,2-dimethoxyethane (2 mL) were added, under vigorous stirring, Zn–Cu couple[26] (510 mg, 7.8 mmol, 5 equiv.) and NaI (1.17 g, 7.8 mmol, 5 equiv.). After having been heated at reflux temperature for 13 h, the suspension was cooled, diluted with chloroform (15 mL), and filtered through Celite. The yellow filtrate was extracted with water (5 × 8 mL) and the aqueous extracts were combined and concentrated. The yellow solid was triturated with several portions of ethyl acetate, the combined extracts were concentrated, and the residue was purified by column chromatography (solvent *A*) to afford **3** (53.8 mg, 19.6%) as a clear, colorless syrup, R_F 0.26 (solvent *A*), $[\alpha]_D^{26}$ −33° (*c* 1.03, methanol); ν_{max}^{film} 3400 (OH), 1460, 1445, 1345, 1245, 1185, 1145, 1105, 1085, 1015, 980, 955, 920, 865, and 730 cm^{-1}; ^1H-n.m.r. (200 MHz): δ 3.42 (s, 3 H, OMe), 3.50 (t, 1 H, $J_{6,OH}$ 6 Hz, exchanged in D_2O, HO-6), 4.16 (m, 2 H, $J_{5,6A}$ 3.2, $J_{5,6B}$ 3.7 Hz, H-6A,6B; after D_2O-exchange: δ 4.11 and 4.21, AB, 2 H, $J_{6A,6B}$ 12 Hz, H-6A,6B), 4.21 (d, 1 H, $J_{4,OH}$ 3.5 Hz, exchanged in D_2O, HO-4), 4.31 (t, d after D_2O exchange, 1 H, $J_{3,4}$ <0.5, $J_{4,5}$ 3.5 Hz, H-4), 4.40 (q, 1 H, H-5), 4.54 (d, 1 H, $J_{1A,1B}$ 7.1 Hz, H-1A), 4.79 (d, 1 H, H-1B), and 4.93 (s, 1 H, H-3); ^{13}C-n.m.r.: δ 52.3 (q, OMe), 61.6 (t, C-6), 74.8 (d, C-4), 80.3 (d, C-5), 81.4 (t, C-1), 93.1 (d, C-3), and 107.7 (s, C-2).

Anal. Calc. for $C_7H_{12}O_5$: C, 47.73; H, 6.87. Found: C, 47.81; H, 6.96.

*Methyl 4-*Se*-phenyl-4-seleno-α-*D*-fructofuranoside* (**4**). — A solution of sodium phenyl selenide in absolute ethanol (10 mL) was prepared from diphenyl diselenide (237 mg, 0.76 mmol, 0.55 equiv.) and $NaBH_4$ (58 mg, 1.53 mmol), as described by Sharpless and Lauer[17]. To the solution of selenide was added slowly a solution of methyl 3,4-anhydro-α-D-tagatofuranoside[1] (**1**) (243 mg, 1.38 mmol) in absolute ethanol (5 mL), and the mixture was heated at reflux temperature for 80

min. After being cooled, the solution was concentrated and the resulting yellow syrup dissolved in ether (20 mL). The solution was washed with a saturated aqueous solution of $NaHCO_3$ (2 × 6 mL). The aqueous phase was extracted with chloroform (5 × 6 mL), and the combined organic phases (ether and chloroform) were dried (Na_2SO_4) and concentrated. Column chromatography (solvent *E*) afforded compound **4** (339.5 mg, 75%) as a colorless syrup, R_F 0.28 (solvent *E*), $[\alpha]_D^{26}$ +51.5° (*c* 2.4, chloroform); ν_{max}^{film} 3460 (OH), 1575, 1475, 1435, 1050, 1018, 738, and 690 cm^{-1}; ^{1}H-n.m.r. (200 MHz; after D_2O exchange): δ 3.21 (s, 3 H, OMe), 3.46 (dd, 1 H, $J_{3,4}$ 4.7, $J_{4,5}$ 7.2 Hz, H-4), 3.59 (dd, 1 H, $J_{5,6A}$ 2.6, $J_{6A,6B}$ 12.0 Hz, H-6A), 3.80 (AB, 2 H, $J_{1A,1B}$ 12.0 Hz, H-1A,1B), 3.86 (dd, 1 H, $J_{5,6B}$ 2.3 Hz, H-6B), 4.16 (dt, 1 H, H-5), 4.29 (d, 1 H, H-3), 7.28 (m, 3 H), and 7.58 (m, 2 H) (C_6H_5Se).

Anal. Calc. for $C_{13}H_{18}O_5Se$ (333.24): C, 46.86; H, 5.44. Found: C, 46.83; H, 5.58.

*Methyl 3,4-anhydro-1,6-di-*O*-(*tert*-butyldimethylsilyl)-α-*D*-tagatofuranoside* (**5**). — To a cold (0°) solution of *tert*-butyldimethylchlorosilane (1.577 g, 10.5 mmol), triethylamine (1.59 mL, 11.4 mmol), and 4-*N*,*N*-dimethylaminopyridine (581 mg, 4.8 mmol) in dry dichloromethane (50 mL) was added, under N_2, a solution of methyl 3,4-anhydro-α-D-tagatofuranoside[1] (**1**) (838 mg, 4.8 mmol) in dichloromethane (10 mL). After being stirred for 4 h at room temperature, the mixture was washed with water (2 × 10 mL), then with a saturated aqueous solution of NH_4Cl (10 mL), dried (Na_2SO_4) and concentrated. Column chromatography (solvent *C*, then *J*) afforded compound **5** (1.59 g, 82.6%) as a clear, colorless syrup, and a trace (~80 mg) of monosilyl derivative **6**. Compound **5**: R_F 0.32 (solvent *C*), $[\alpha]_D^{26}$ +9.4° (*c* 2.2, dichloromethane); ν_{max}^{film} 1470, 1460, 1255, 1105, 1060, 910, 832, and 775 cm^{-1}; ^{1}H-n.m.r. (200 MHz, $CHCl_3$, δ 7.25, as the internal standard): δ 0.06 (s, 6 H) and 0.08 (s, 6 H) (2 Me_3CSiMe_2), 0.88 (s, 9 H) and 0.90 (s, 9 H) (2 Me_3CSiMe_2), 3.31 (s, 3 H, OMe), 3.53 (d, 1 H, $J_{1A,1B}$ 11.0 Hz, H-1A), 3.64 (dd, 1 H, $J_{5,6A}$ 8.0, $J_{6A,6B}$ 9.5 Hz, H-6A), 3.70 (d, 1 H, $J_{3,4}$ 2.8 Hz, H-3), 3.72 (dd, 1 H, $J_{5,6B}$ 5.0 Hz, H-6B), 3.77 (d, 1 H, $J_{4,5}$ ~0.5 Hz, H-4), 3.78 (d, 1 H, H-1B), and 4.05 (dd, 1 H, H-5).

Anal. Calc. for $C_{19}H_{40}O_5Si_2$ (404.69): C, 56.39; H, 9.96. Found: C, 56.45; H, 10.09.

*Methyl 3,4-anhydro-6-*O*-tert-butyldimethylsilyl-α-*D*-tagatofuranoside* (**6**). — Partial silylation of methyl 3,4-anhydro-α-D-tagatofuranoside[1] (**1**) with less than 2 equiv. of *tert*-butylchlorodimethylsilane, under the same conditions as those described above, led to a mixture containing the disilylated derivative **5** and compound **6** as the sole monosilyl derivative. Compound **6** was separable from **5** by column chromatography (solvent *C*, then *L*); syrup, R_F 0.42 (solvent *H*), $[\alpha]_D^{26}$ +10.1° (*c* 5.2, chloroform); ν_{max}^{film} 3460 (OH), 1465, 1455, 1255, 1138, 1100, 1080, 1055, 910, 835, and 780 cm^{-1}; ^{1}H-n.m.r. (200 MHz, $CHCl_3$, δ 7.25, as the internal standard; after D_2O-exchange): δ 0.04 (s, 6 H, Me_3CSiMe_2), 0.87 (s, 9 H, Me_3CSiMe_2), 3.33 (s, 3 H, OMe), 3.59 (d, 1 H, $J_{1A,1B}$ 11.8 Hz, H-1A), 3.64 (dd, 1 H, $J_{5,6A}$ 8.0, $J_{6A,6B}$ 9.5 Hz, H-6A), 3.74 (d, 1 H, $J_{3,4}$ 2.8 Hz, H-3), ~3.74 (dd, 1 H, $J_{5,6B}$ 5.5 Hz, H-6B), 3.75 (d, 1 H, H-1B), 3.82 (d, 1 H, $J_{4,5} \leq 0.5$ Hz, H-4), and 4.10 (dd, 1 H, H-5).

Anal. Calc. for $C_{13}H_{26}O_5Si$ (290.43): C, 53.76; H, 9.02. Found: C, 53.79; H, 9.02.

*Methyl 1,6-di-*O*-(*tert*-butyldimethylsilyl)-4-*Se*-phenyl-4-seleno-α-*D*-fructofuranoside* (**7**). — To a solution of sodium phenyl selenide in ethanol (20 mL) [prepared from diphenyl diselenide (254 mg, 0.82 mmol) and $NaBH_4$ as described by Sharpless and Lauer[17]] was added a solution of compound **5** (188.5 mg, 0.47 mmol) in absolute ethanol (7 mL), and the mixture was heated at reflux temperature for 4 h. After being cooled, the mixture was concentrated, the residue dissolved in methanol (10 mL), and the solution concentrated. The treatment with methanol was repeated twice and the resulting yellow syrup dissolved in ether (15 mL). The solution was washed with water (2 × 5 mL), the combined aqueous phases were extracted with ether (3 × 5 mL), and the combined organic phases dried (Na_2SO_4) and concentrated. Column chromatography (solvent *K*) of the residue afforded compound **7** (81 mg, 31%) as a syrup, R_F 0.26 (solvent *C*), $[\alpha]_D^{26}$ +46° (*c* 0.93, dichloromethane); ν_{max}^{film} 3430 (OH), 1575, 1465, 1455, 1250, 1105, 1070, 832, and 772 cm^{-1}; ^{1}H-n.m.r. (200 MHz): δ 0.01 (s, 3 H), 0.02 (s, 3 H) and 0.07 (s, 6 H) (2 Me_3CSiMe_2), 0.86 (s, 9 H) and 0.89 (s, 9 H) (2 Me_3CSiMe_2), 3.26 (s, 3 H, OMe), 3.31 (dd, 1 H, $J_{3,4}$ 3.0, $J_{4,5}$ 6.0 Hz, H-4), 3.56 (dd, 1 H, $J_{5,6A}$ 3.5, $J_{6A,6B}$ 11.5 Hz, H-6A), 3.79 (dd, 1 H, $J_{5,6B}$ 2 Hz, H-6B), 3.82 (AB, 2 H, $J_{1A,1B}$ 11.5 Hz, H-1A,1B), 4.25 (m, 2 H, H-3,5), 7.25 (m, 3 H) and 7.58 (m, 2 H) (C_6H_5Se).

Anal. Calc. for $C_{25}H_{46}O_5SeSi_2$ (561.77): C, 53.45; H, 8.25. Found: C, 53.43; H, 8.11.

*Methyl 1,6-di-*O*-(*tert*-butyldimethylsilyl)-3-*O*-methylsulfonyl-4-*Se*-phenyl-4-seleno-α-*D*-fructofuranoside* (**8**). — To a solution of compound **7** (494.5 mg, 0.88 mmol) in dry dichloromethane (10 mL) under Ar was added triethylamine (0.74 mL, 5.28 mmol, 6 equiv.) and methanesulfonyl chloride (0.27 mL, 3.52 mmol, 4 equiv.). After being heated at reflux temperature for 3 h, the solution was cooled, diluted with additional dichloromethane (20 mL), and washed with a saturated aqueous solution of $NaHCO_3$ (10 mL). The aqueous phase was extracted with dichloromethane (2 × 5 mL), and the combined organic phases were dried (Na_2SO_4) and concentrated. Column chromatography [15:1, v/v, hexanes–ethyl acetate] afforded **8** as a syrup (467.5 mg, 83%), R_F 0.27 (solvent *D*), $[\alpha]_D^{26}$ +43.5° (*c* 1.03, chloroform); ν_{max}^{film} 1575, 1470, 1465, 1370, 1255, 1180, 1120, 1050, 1005, 955, 835, 780, 740, and 695 cm^{-1}; ^{1}H-n.m.r. (200 MHz, CD_2Cl_2, CH_2Cl_2, δ 5.35, as the internal standard): δ 0.02 (s, 6 H), 0.10 (s, 3 H), and 0.11 (s, 3 H) (2 Me_3CSiMe_2), 0.85 (s, 9 H) and 0.90 (s, 9 H) (2 Me_3CSiMe_2), 2.98 (s, 3 H, $MeSO_2$), 3.23 (s, 3 H, OMe), 3.59 (dd, 1 H, $J_{3,4}$ 3.5, $J_{4,5}$ 6.8 Hz, H-4), 3.70 (d, 1 H, $J_{1A,1B}$ 11.5 Hz, H-1A), 3.74 (AB, 2 H, H-6A,6B), 3.85 (d, 1 H, H-1B), 4.16 (dt, 1 H, $J_{5,6A} = J_{5,6B} = 4$ Hz, H-5), 5.07 (d, 1 H, H-3), 7.32 (m, 3 H) and 7.67 (m, 2 H) (C_6H_5Se).

Anal. Calc. for $C_{26}H_{48}O_7SSeSi_2$ (639.86): C, 48.81; H, 7.56. Found: C, 48.88; H, 7.43.

*Methyl 3,4-anhydro-1,6-di-*O*-(*tert*-butyldimethylsilyl)-β-*D*-tagatofuranoside* (**9**). — To a solution of methyl 3,4-anhydro-β-D-tagatofuranoside[1] (**2**) (1.61 g, 9.14

mmol) at 0° in dry dichloromethane (50 mL) were added triethylamine (3.1 mL, 22.0 mmol, 2.4 equiv.), 4-*N,N*-dimethylaminopyridine (1.12 g, 9.14 mmol), and *tert*-butylchlorodimethylsilane (3.03 g, 20.1 mmol, 2.2 equiv.). After being stirred at 0° and then at room temperature for 3 h, the mixture was washed sequentially with a saturated aqueous solution of $NaHCO_3$ (25 mL), water (25 mL), and a saturated aqueous solution of NaCl (25 mL), then dried (Na_2SO_4) and concentrated. The residual syrup was purified by column chromatography (solvent *C*) to afford compound **9** (3.02 g, 82%) as a clear, colorless syrup, R_F 0.38, $[\alpha]_D^{26}$ −35.5° (*c* 2.3, chloroform); ν_{max}^{film} 1470, 1460, 1260, 1110, 1070, 895, 835, and 775 cm^{-1}; ^{1}H-n.m.r. (400 MHz, $CHCl_3$, δ 7.25, as the internal standard): δ 0.08 (s, 6 H), 0.17 (s, 3 H), and 0.20 (s, 3 H) (2 Me_3CSiMe_2), 0.91 (s, 9 H) and 0.92 (s, 9 H) (2 Me_3CSiMe_2), 3.45 (s, 3 H, OMe), 3.61 (d, 1 H, $J_{1A,1B}$ 10.6 Hz, H-1A), 3.63 (d, 1 H, $J_{3,4}$ 3.4 Hz, H-3), 3.72 (d, 1 H, H-1B), 3.74 (d, 1 H, $J_{4,5} \leq 0.5$ Hz, H-4), 3.76 (m, 2 H, H_2-6), and 4.07 (dd, 1 H, $J_{5,6A}$ 6.2, $J_{5,6B}$ 6.0 Hz, H-5).

Anal. Calc. for $C_{19}H_{40}O_5Si_2$ (404.69): C, 56.39; H, 9.96. Found: C, 55.94; H, 9.92.

*Methyl 1,6-di-*O*-(*tert*-butyldimethylsilyl)-4-*Se*-phenyl-4-seleno-β-*D*-fructofuranoside* (**10**). — To a solution of sodium phenyl selenide [prepared from diphenyl diselenide (1.29 g, 4.13 mmol, 0.7 equiv.) and sufficient $NaBH_4$ to decolorize the alcohol solution] in absolute ethanol (40 mL), heated at reflux temperature under Ar, was added a solution of compound **9** (2.39 g, 5.91 mmol) in absolute ethanol (15 mL). The mixture was heated at reflux temperature for 3 h, and then cooled and evaporated; the residue was dissolved in methanol (50 mL) and the solution concentrated. The treatment with methanol was repeated twice, the resulting yellow syrup was dissolved in ether, and the solution was washed with a saturated aqueous solution of NaCl (50 mL). The aqueous phase was extracted with ether and the combined organic phases were dried (Na_2SO_4) and concentrated. Column chromatography (solvent *N*) afforded compound **10** (1.82 g, 54.8%) as a syrup, R_F 0.27, $[\alpha]_D^{26}$ −22° (*c* 1.2, chloroform); ν_{max}^{film} 3550 (OH), 1575, 1470, 1460, 1255, 1105, 835, and 775 cm^{-1}; ^{1}H-n.m.r. (400 MHz): δ 0.01 (s, 6 H) and 0.02 (s, 6 H) (2 Me_3CSiMe_2), 0.82 (s, 9 H) and 0.87 (s, 9 H) (2 Me_3CSiMe_2), 2.59 (d, 1 H, $J_{3,OH}$ 8.2 Hz, OH-3), 3.34 (s, 3 H, OMe), 3.44 (apparent t, 1 H, $J_{3,4} \approx J_{4,5}$ = 10.5 Hz, H-4), 3.61 (d, 1 H, $J_{1A,1B}$ 10.7 Hz, H-1A), 3.67 (d, 1 H,H-1B), 3.71 (dd, 1 H, $J_{5,6A}$ 4.4, $J_{6A,6B}$ 11.8 Hz, H-6A), 3.81 (dd, 1 H, $J_{5,6B}$ 2.2 Hz, H-6B), 3.85 (dd, 1 H, H-5), 4.12 (dd, 1 H, H-3), 7.28 (m, 3 H) and 7.66 (m, 2 H) (C_6H_5Se).

Anal. Calc. for $C_{25}H_{46}O_5SeSi_2$ (561.77): C, 53.45; H, 8.25. Found: C, 53.49; H, 8.22.

*Methyl 1,6-di-*O*-(*tert*-butyldimethylsilyl)-3-*O*-methylsulfonyl-4-*Se*-phenyl-4-seleno-β-*D*-fructofuranoside* (**11**). — To a solution of compound **10** (103 mg, 0.18 mmol) in dry dichloromethane (3 mL), heated at reflux temperature under Ar, were added triethylamine (0.15 mL, 1.10 mmol, 6 equiv.) and methanesulfonyl chloride (0.057 mL, 0.73 mmol, 4 equiv.). After 10 min, the solution was cooled and treated with a saturated aqueous solution of $NaHCO_3$ (5 mL). The organic

phase was extracted with dichloromethane (3 × 5 mL). The organic phases were combined, dried (Na_2SO_4), and concentrated. Column chromatography (solvent *F*) afforded **11** (110.5 mg, 94.2%) as a syrup, R_F 0.19, $[\alpha]_D^{25}$ immeasurable (*c* 0.86, 1.6, or 6.6, chloroform); ν_{max}^{film} 1575, 1470, 1460, 1360, 1255, 1180, 1145, 1110, 1025, 960, 840, 780, 745, and 695 cm^{-1}; ^{1}H-n.m.r. (400 MHz): δ 0.03 (s, 3 H), 0.04 (s, 3 H), 0.06 (s, 3 H), and 0.07 (s, 3 H) (2 Me_3CSiMe_2), 0.89 (s, 18 H, 2 Me_3CSiMe_2), 3.13 (s, 3 H, $MeSO_2$), 3.44 (s, 3 H, OMe), 3.65 (d, 1 H, $J_{1A,1B}$ 10.4 Hz, H-1A), 3.73 (d, 1 H, H-1A), 3.84 (m, 3 H, $J_{6A,6B}$ 12.5, $J_{6A,5}$ 2.0 Hz, H-4,5,6B), 3.93 (dd, 1 H, $J_{5,6B}$ 2.0 Hz, H-6B), 5.34 (m, 1 H, H-3), 7.30 (m, 3 H) and 7.64 (m, 2 H) (C_6H_5Se).

Anal. Calc. for $C_{26}H_{48}O_7SSeSi_2$ (639.86): C, 48.41; H, 7.56. Found: C, 49.00; H, 8.09.

*Methyl 1,6-di-*O*-(*tert*-butyldimethylsilyl)-4-deoxy-4-phenylselenenyl-α-*D*-fructofuranoside* (**12**). — To a solution of compound **7** (72 mg, 0.13 mmol) in methanol (2.5 mL) was added a 30% aqueous solution of H_2O_2 (0.11 mL, ~9 equiv.). After 5 h at room temperature, the solution was poured onto ice–water (5 g) and the mixture extracted with ether (3 × 5 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated, and the residual syrup was purified by column chromatography (slurry-packed, solvent *J*) to afford syrupy compound **12** (58 mg, 78.3%) as a 13:7 (^{1}H-n.m.r.) mixture of isomeric selenoxides, R_F 0.42 and 0.45, $[\alpha]_D^{26}$ +24° (*c* 0.8, chloroform); ν_{max}^{film} 3350 (OH), 1470, 1460, 1440, 1360, 1255, 1115, 1070, 835, 815, 780, 740, and 690 cm^{-1}; ^{1}H-n.m.r. [200 MHz, CD_2Cl_2, CH_2Cl_2, δ 5.35, as the internal standard; 13:7 mixture of isomers (*S*),(*R*) at Se]: δ −0.12, −0.03, −0.01, 0.00, and 0.02 (5 s, 12 H, 2 Me_3CSiMe_2), 0.74 (s, 3.1 H) and 0.85 (s, 3.1 H) [2 Me_3CSiMe_2, isomer (*R*)], 0.79 (s, 5.9 H) and 0.83 (s, 5.9 H) [2 Me_3CSiMe_2, isomer (*S*)], 2.94 (d, 0.65 H, $J_{3,4}$ ~0, $J_{4,5}$ 2.0 Hz, H-4_S), 3.00 (dd, 0.35 H, $J_{5,6A}$ 3.5, $J_{6A,6B}$ 11.0 Hz, H-$6A_R$), 3.05 (br. d, 0.35 H, $J_{3,4}$ 1, $J_{4,5}$ 3.5 Hz, H-4_R), 3.26 and 3.27 (2 s, 3 H, OMe), 3.50 (dd, 0.35 H, $J_{5,6B}$ 3.5 Hz, H-$6B_R$), 3.53 (dd, 0.65 H, $J_{5,6A}$ 2.0, $J_{6A,6B}$ 11.0 Hz, H-$6A_S$), 3.75 [s, 1.3 H, H_2-1, isomer (*S*)], 3.79 [s, 0.7 H, H_2-1, isomer (*R*)], 3.84 (d, s after D_2O exchange, 0.65 H, $J_{3,OH}$ 11.0 Hz, H-3_S), ~3.85 (d, 0.35 H, $J_{3,OH}$ 9.5 Hz, exchanged in D_2O, HO-3_R), 3.90 (dd, 0.65 H, $J_{5,6B}$ 2.0 Hz, H-$6B_S$), 3.96 (q, 0.35 H, H-5_R), 4.12 (d, 0.65 H, exchanged in D_2O, HO-3_S), 4.36 (d, s after D_2O exchange, 0.35 H, H-3_R), 4.65 (q, 0.65 H, H-5_S), 7.50 (m, 3 H) and 7.71 (m, 2 H) (C_6H_5SeO).

*Methyl 1,6-di-*O*-(*tert*-butyldimethylsilyl)-4-deoxy-β-*L*-glycero-hex-4-enulofuranoside* (**13**). — A solution of compound **12** (38.5 mg, 0.07 mmol) in 1,2-dichloroethane (1 mL) was heated at reflux temperature for 0.5 h. The mixture was then cooled and concentrated. The residue was submitted to successive, rapid separations by column chromatography (solvent *G*) to afford a pure sample of syrupy **13** (compound **13** slowly decomposes at room temperature to a complex mixture of products), R_F 0.37, $[\alpha]_D^{26}$ +58.5° (*c* 0.58, dichloromethane); ν_{max}^{film} 3510 (OH), 1675 (C=C), 1470, 1460, 1255, 1105, 835, and 775 cm^{-1}; ^{1}H-n.m.r. (200 MHz, CD_2Cl_2, CH_2Cl_2, δ 5.35, as the internal standard): δ −0.01 (s, 6 H), 0.01 (s, 3 H), and 0.02 (s, 3 H) (2 Me_3CSiMe_2), 0.81 (s, 9 H) and 0.83 (s, 9 H) (2

Me_3CSiMe_2), 3.06 (d, 1 H, $J_{3,OH}$ 7.0 Hz, exchanged in D_2O, HO-3), 3.22 (s, 3 H, OMe), 3.75 (d, 1 H, $J_{1A,1B}$ 11.0 Hz, H-1A), 3.95 (d, 1 H, H-1B), 4.13 (narrow m, 2 H, H_2-6), 4.65 (dtd, td after D_2O exchange, 1 H, $J_{3,4}$ 2.4, $J_{3,6A} = J_{3,6B} = 1.2$ Hz, H-3), and 5.00 (m, 1 H, $J_{4,6A} = J_{4,6B} = 1$ Hz, H-4).

Catalytic hydrogenation of **13**. — Compound **13** (25 mg, 0.062 mmol) was dissolved in ethyl acetate (2 mL) and subjected to H_2 at a pressure of 276 kPa (gauge) in the presence of 10% Pd–C (spatula tip). The suspension was shaken overnight at room temperature. The catalyst was then removed by filtration and the filtrate concentrated to afford a clear, colorless syrup whose t.l.c. (solvent *D*) indicated the presence of a major component and traces of two slightly more polar products. The major component (**14**) could be isolated by column chromatography (solvent *B*); R_F 0.27, $[\alpha]_D^{26}$ +34.5° (*c* 1.1, chloroform); ν_{max}^{film} 3430 (OH), 1470, 1460, 1255, 1110, 1045, 840, and 780 cm^{-1}.

Desilylation of **14**. — To a solution of compound **13** (70 mg, 0.17 mmol), prepared as described above, in dry oxolane (5 mL) was added solid tetrabutylammonium fluoride (163 mg, 0.52 mmol, 3 equiv.). After 15 min, the mixture was concentrated and purified by column chromatography (solvent *M*) to afford a sample of **15** (29 mg, 94.5%) as a syrup whose R_F and i.r. data were in accord with those of an authentic sample of **15** prepared as described below.

*Preparation of methyl 4-deoxy-1,6-di-*O*-(*tert*-butyldimethylsilyl)-α-*D*-threo-hexulofuranoside* (**14**) *by way of $LiAlH_4$ cleavage of oxirane* **1**. — To a solution of compound **1** (2.01 g, 11.39 mmol) being heated at reflux temperature in dry oxolane (100 mL) under Ar was added slowly a M solution of $LiAlH_4$ in oxolane (12.5 mL, 1.1 equiv.). After 2 h, the solution was cooled to 0° and ethyl acetate (10 mL) was added to destroy the excess of hydride. Water (10 mL) was then added and the pH of the solution was adjusted to 7 with M HCl. The suspension was concentrated at 40° to afford a syrup that was treated with Celite until a free flowing powder resulted which was stirred in 5:1 (v/v) dichloromethane–methanol and separated by centrifugation. This extraction process was continued until t.l.c. indicated an absence of residual product. The combined supernatant liquids were concentrated, then submitted to column chromatography (solvent *M*) to afford methyl 4-deoxy-α-*D*-*threo*-hexulofuranoside (**15**) (1.50 g, 73.9%) as a clear, colorless syrup, R_F 0.45, $[\alpha]_D^{26}$ +94.5° (*c* 1.6, methanol); ν_{max}^{film} 3360 (OH), 1460, 1440, 1275, 1210, 1190, 1140, 1110, 1050, 870, and 690 cm^{-1}; ^{1}H-n.m.r. (400 MHz, CD_3OD): δ 1.77 (dd, 1 H, $J_{4A,4B}$ 13.5, $J_{4A,5}$ 3.8, $J_{3,4A}$ ~0 Hz, H-4A), 2.47 (ddd, 1 H, $J_{3,4B}$ 5.6, $J_{4B,5}$ 9.0 Hz, H-4B), 3.26 (s, 3 H, OMe), 3.53 (dd, 1 H, $J_{5,6A}$ 4.5 Hz, H-6A), 3.65 (dd, 1 H, $J_{5,6B}$ 3.0 Hz, H-6B), 3.75 (~s, 2 H, H_2-1), 4.04 (d, 1 H, H-3), and 4.19 (ddd, 1 H, H-5); ^{13}C-n.m.r.: δ 36.04 (C-4), 49.65 (OMe), 58.24 (C-1), 64.88 (C-6), 75.27 (C-3), 80.00 (C-5), and 111.11 (C-2).

To a solution of compound **15** (208 mg, 1.17 mmol) in dry dichloromethane (10 mL) at 0° were added triethylamine (0.39 mL, 2.8 mmol, 2.4 equiv.), 4-*N*,*N*-dimethylaminopyridine (143 mg, 1.17 mmol), and *tert*-butylchlorodimethylsilane (87 mg, 2.57 mmol, 2.2 equiv.). After 1 h, the mixture was warmed to room tempera-

ture and then washed with a saturated aqueous solution of NaCl (10 mL). The aqueous phase was extracted with dichloromethane (2 × 5 mL) and the combined organic phases were dried (Na_2SO_4) and concentrated. Column chromatography (solvent *D*) afforded syrupy **14** (304 mg, 64%); R_F and i.r. data were identical to those of the product obtained by catalytic hydrogenation of **13**; $[\alpha]_D^{26}$ +39.5° (*c* 1.0, chloroform); ^{1}H-n.m.r. (400 MHz): δ 0.12 (s, 6 H) and 0.14 (s, 6 H) (2 Me_3CSiMe_2), 0.94 (s, 9 H) and 0.96 (s, 9 H) (2 Me_3CSiMe_2), 1.76 (dd, 1 H, $J_{4A,4B}$ 13.3, $J_{4A,5}$ 3.0, $J_{3,4A}$ ~0 Hz, H-4A), 2.58 (ddd, 1 H, $J_{3,4B}$ 10.8, $J_{4B,5}$ 5.5 Hz, H-4B), 3.30 (s, 3 H, OMe), 3.59 (dd, 1 H, $J_{3,OH}$ 2.0 Hz, H-3), 3.84 (d, 1 H, $J_{6A,6B}$ 10.5 Hz, H-6A), 3.90 (d, 1 H, $J_{1A,1B}$ 6.0 Hz, H-1A), 3.92 (d, 1 H, H-1B), 4.01 (dd, $J_{5,6B}$ 5.2 Hz, H-6B), and 4.26 (m, 1 H, H-5).

Anal. Calc. for $C_{19}H_{42}O_5Si_2$ (406.71): C, 56.11; H, 10.41. Found: C, 55.92; H, 10.38.

ACKNOWLEDGMENT

The authors are grateful to the Natural Sciences and Engineering Research Council Canada for financial support of this research.

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