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Addition of *C*-Nucleophiles to Carbohydrate-Derived 2,3-Dihydro-4*H*-pyran-4-ones: A New Entry to Thromboxane Analogues

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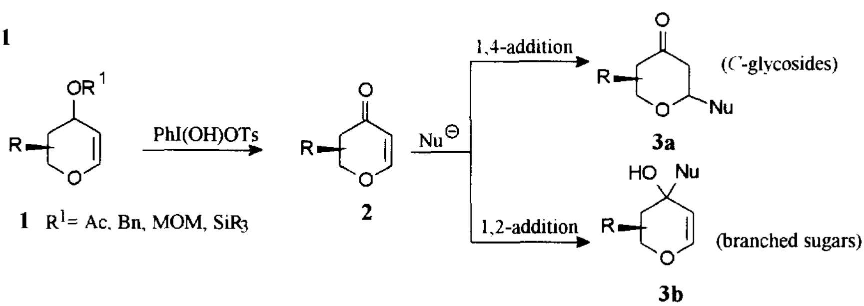
Abstract: Nucleophilic additions of silyl- and sulfur-stabilized carbanions **5a-c** to carbohydrate-derived 2,3-dihydro-4H-pyran-4-ones **4a,b** are described. Depending on the combination of substituents attached to the C_1-anion, either 1,2- or 1,4-adducts are preferentially formed. Coupling of vinyl cuprate derived from **16** with enone **4a** stereoselectively afforded pyranone **17** which is a potential precursor for thromboxane analogues. © 1997 Elsevier Science Ltd.

Carbohydrate-derived 2,3-dihydro-4*H*-pyran-4-ones (hex-1-en-3-uloses) **2** comprise a relatively unexplored class of highly functionalized chiral building blocks.[1] So far, a broad synthetic application of **2** has been hampered by their limited availability from carbohydrate sources.[2] In context with formation of *C*-glycosides **3a**[3] or branched chain sugars **3b**,[4] however, 1,2- and 1,4-additions of *C*-nucleophiles have been studied in some detail. Furthermore, silyl and stannyl glycosides have been prepared by 1,4-addition of silyl- and stannyl anions to **2**.[5] Recently, we established an efficient and straightforward access to **2** by organoiodine(III)-mediated regioselective oxidative deblocking of fully protected glycals **1** (Scheme 1).[6] In particular, per-*O*-benzylated 2,3-dihydro-4*H*-pyran-4-ones are easily accessible now, which are ideally protected to serve as carbohydrate-derived electrophiles in reactions with complex carbanions.

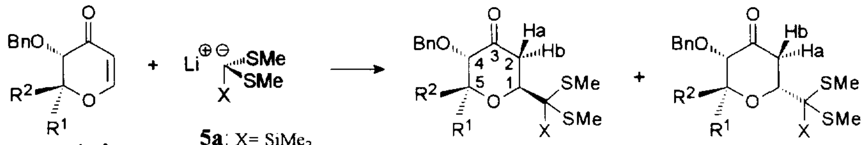
Scheme 1



We now wish to report on the reaction of 2,3-dihydro-4*H*-pyran-4-ones **4a,b** with carbanions **5a-c** that contain a masked formyl functionality. As is demonstrated, the combination of thio- and silyl substituents in **5** can advantageously be utilized for controlling the 1,2- *vs.* 1,4-selectivity (Table 1).

Thus, the lithio derivative of bis(phenylthio)trimethylsilyl methane **5a** smoothly reacted with enones **4a** and **4b** in a 1,4-fashion to give the *C*-glycosides **6a**, **8** and **9**. For *threo*-configurated enone **4a** stereocontrol was excellent. The isomer **6b** resulting from β-attack on **5a** was not observed. In contrast, the *erythro*-configurated 2,3-dihydro-4*H*-pyran-4-ones **4b**, which lacks a pseudoaxial substituent, led to a 1:1 mixture.

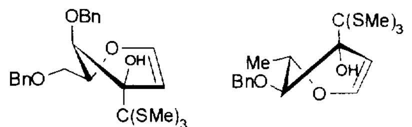
Table 1: Nucleophilic Addition of Carbanions **5a** and **5b** to 2,3-Dihydro-4*H*-pyran-4-ones **4a** and **4b**



4a,b + **5a**: X= $SiMe_3$ **5b**: X= SMe → **6a - 9a**[a] + **6b - 9b**

enone	R^1	R^2	X	conditions	ratio[b]	yield %[c](%)[d]
4a	CH_2OBn	H	$SiMe_3$	THF, -78°C to -60°C	**6a,b** >10 : 1[e]	45 (92)
4a	CH_2OBn	H	SMe	THF, -78°C to -55°C	**7a,b** >10 : 1[f]	8 (88)
4b	H	CH_3	$SiMe_3$	THF, -78°C to -60°C	**8a,b** 1 : 1	67 (98)
4b	H	CH_3	SMe	THF, -78°C to -55°C	**9a,b** 1 : 1[g]	62 (97)

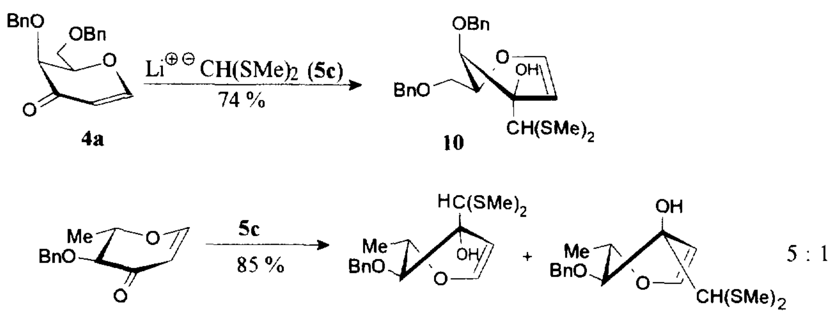
[a] carbohydrate numbering given. - [b] ratios determined from the crude ^{1}H NMR spectra. - [c] 1,4-adducts after separation of diastereoisomers by column chromatography. - [d] yields of crude product. [e] labile. - [f] besides **7c** (65%). - [g] besides **9c** (18%).



7c **9c**

When **5b** was coupled with 2,3-dihydro-4*H*-pyran-4-ones **4a,b**, both 1,2- **7c**, **9c** as well as 1,4-adducts **7a** and **9a,b** were formed. Deletion of one methylthio substituent, as in the lithiated bis(methylthio)methane **5c**, led to exclusive 1,2-addition in good yield, which can be rationalized by the absence of steric hindrance between the carbanion and the substituents adjacent to the carbonyl group in **4a** or **4b** (Scheme 2). When *threo*-**4a** was employed, in all cases the pseudoaxial substituent exerted total control on the stereochemical outcome of the reaction.

Scheme 2



4b (3*S*)- **11a** (3*R*)- **11b**

Adducts **6-7** were sufficiently pure for further synthetic transformations. For full characterization, the isomeric products were separated by column chromatography. While branched glycals **7c**, **9c**, **10** and **11** were isolated without loss of material, *C*-glycosides **9a,b** and particularly **6a**, **8a,b** could only be purified with reduced yields.

The configuration of the newly formed stereogenic center at C-3 (carbohydrate numbering) in glycals **7c**, **9c** and **11a,b** was determined by comparison of the chemical shifts of 1-H, 2-H, and the coupling constant values $J_{1,2}$ and $J_{4,5}$ in the ^1H NMR spectra with those of alkyl-branched glycals reported in the literature.[4,7] Selected ^1H NMR data for 1,4-adducts **6a**, **7a**, **8a,b** and **9a,b** are presented in Table 2.[8] From the *J*-values (particularly $J_{1,2a}$, $J_{1,2b}$ and $J_{4,5}$) in the ^1H NMR spectra, it can be reasoned that the bulky $C(SMe)_3$ and $C(SMe)_2SiMe_3$ group in the α-isomers **6a**, **7a**, **8b** and **9b** cause an interconversion into the alternate chair or twist-boat conformation leaving the substituents at C-1 in a pseudoequatorial position.[9]

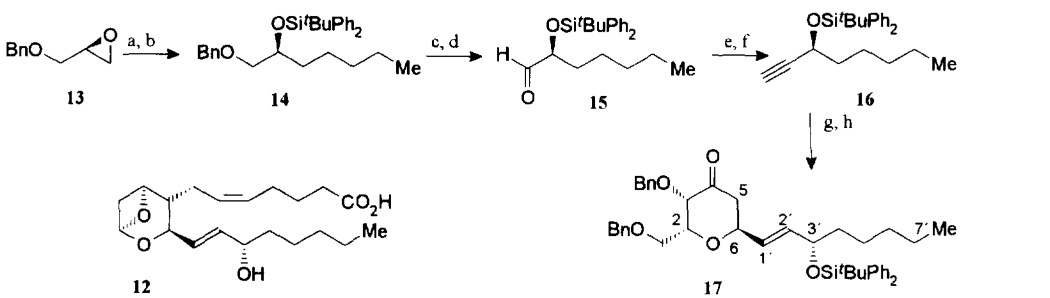
Table 2: Selected ^1H NMR Data of *C*-Glycosides **6a**, **7a**, **8a**, **8b**, **9a** and **9b**.

	1-H	2-Ha	2-Hb	4-H	5-H δ [ppm]	$J_{1,2a}$	$J_{1,2b}$	$J_{2a,2b}$	$J_{2a,4}$	$J_{4,5}$	$J_{5,6}$	$J_{5,6'}$	$J_{6,6'}$ [Hz]
6a	4.77	2.93	2.67	4.09	4.38	10.6	2.8	14.0	1.0	7.0	2.0	4.4	10.8
7a	~4.8	3.10	2.84	4.11	4.41	10.6	3.0	14.8	1.0	7.2	2.4	4.6	11.2
8a	3.89	2.93	2.77	3.64	3.52	11.2	2.4	13.2	1.2	9.2	6.0	--	--
8b	4.26	3.37	2.54	3.47	4.47	10.4	3.4	13.6	--[a]	3.2	7.0	--	--
9a	3.86	3.15	2.95	3.64	3.54	11.2	2.6	14.0	1.4	9.6	6.0	--	--
9b	4.17	3.55	2.70	3.54	4.51	10.0	3.6	14.2	--[a]	3.6	7.2	--	--

[a] $J_{2b,4}$= 0.8 Hz.

As part of a program directed towards the synthesis of potential receptor level agonists/antagonists of thromboxane A_2 (TXA_2) **12**, we have further examined use of 2,3-dihydro-4*H*-pyran-4-one **4a** as a chiral precursor for the TXA_2-nucleus. It was anticipated, that strategies which have been developed for introducing the prostaglandine side chains into a cyclopentenone framework might be applicable to enones like **4a**.[10]

Scheme 3



a) BuLi, CuI, Et_2O, -78 °C to -40 °C; b) ^{t}BuPh$_2$SiCl, imidazole, DMF, rt, 12h; c) Pd (10%)/C, H_2, ethyl acetate, rt; d) *Dess-Martin* oxidation; e) CBr_4, Zn, PPh_3, CH_2Cl_2, rt, 24h, then addition of **15**, rt, 2h; f) ^{n}BuLi (2.2 equiv.), -78 °C, 1h, and 1.5h, then NH_4Cl_{aqu}; g) $Cp_2Zr(H)Cl$, THF, rt, 15 min, then addition of MeLi (2 equiv.), -78 °C to -30 °C; h) CuCN, MeLi, -78 °C to -30 °C, then addition of **4a**, -78 °C to -50 °C.

The side chain **16** was constructed as described in Scheme 3.[11] (*R*)-Glycidol **13** was regioselectively opened with the reagent system *n*-BuLi / CuI followed by protection of the hydroxy group to afford benzyl ether **14** in 91% yield. Debenzylation and *Dess-Martin* periodinane-promoted oxidation[12] quantitatively yielded aldehyde **15** which was directly transformed into alkyne **16**.[13] Finally, hydrozirconization (1 equiv. $Cp_2Zr(H)Cl$, rt, 15 min) of **16**, activation (2 equiv. MeLi) followed by addition of CuCN (1 equiv.) and MeLi (1 equiv.) gave a solution of the corresponding (*E*)-vinyl cuprate which was directly coupled with **4a** in THF.[10] Pyran-4-one **17** was isolated as the only isomer indicating that the coupling had proceeded, as expected, in a highly stereoselective manner.

EXPERIMENTAL

General information. All temperatures quoted are uncorrected. Optical rotations were measured in a Perkin-Elmer 141 polarimeter. Infrared spectra (IR) were obtained using a Perkin-Elmer 399 spectrophotometer and wavelengths (ν) are reported in cm^{-1}. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker DPX 200 or ARX 400 spectrometer, respectively.[9] Secondary carbons are marked (-), primary as well as tetriary (+) and quaternary (o). Tetramethylsilane (TMS) was used as internal standard. Mass spectra (MS) were obtained using Finnigan MAT 95 spectrometer. Elemental analyses were carried out by the Institut für Pharmazeutische Chemie, Technische Universität Braunschweig. All solvents used were reagent grade and were further dried. Reactions were monitored by TLC on silica gel 60 PF^{254} (E. Merck, Darmstadt) and detected by UV absorption and either by charring with 5% H_2SO_4 in ethanol or with a mixture of H_2SO_4, AcOH and 4-methoxy benzaldehyde in methanol. Preparative column chromatography (cc) and flash chromatography (fc) were performed on silica gel 60 (E. Merck, Darmstadt). 2,3-Dihydro-4*H*-pyran-4-ones **4a** and **4b** were prepared according to the literature.[6] **13** was synthesized as previously described.[14]

General Procedure for the Nucleophilic Addition of Carbanions 5a and 5c to 2,3-Dihydro-4*H*-pyran-4-ones 4a,b

A solution of 1.1 equiv. of dithioacetals **5a** or **5c** in dry THF (1 mL/mmol) was cooled to -78 °C. Then *n*-BuLi (1.6 M solution in hexane; 1.1 equiv.) was added and the solution was allowed to warm to -10 °C within 1 h. This temperature was maintained for 1 h and the mixture was cooled again to -78 °C. To this solution one equiv. of 2,3-dihydro-4*H*-pyran-4-one **4a** or **4b** in dry THF (2 mL/mmol) was added dropwise. The yellow reaction mixture was allowed to warm to -40 °C and kept at this temperature until no starting material could be detected by TLC (PE/EE 3:1). For workup, it was hydrolyzed with a mixture of dichloromethane/saturated NH_4Cl solution (1:1). The aqueous phase was separated and extracted twice with dichloromethane. The combined organic layers were dried ($MgSO_4$), concentrated *in vacuo* and purified by cc.

Reaction of **4a** (0.2 g, 0.92 mmol) with **5a** gave **1,5-Anhydro-4,6-bis-*O*-benzyl-1-*C*-[1,1-bis(methylthio)-1-trimethylsilylmethyl]-2-deoxy-D-*lyxo*-hex-3-ulose (6a)** as a single isomer (426 mg, 92 %). Purification by fc using PE/EE (15:1) afforded a colorless oil (209 mg, 45 %). $[\alpha]^{20}_{D}$ -32.8° (c 1.02,

$CHCl_3$). ^1H NMR ($CDCl_3$): δ 7.36-7.25 (m, 10H, H aromatic), 4.97, 4.57, 4.54, 4.41 (4d, 4H, *J*= 12 Hz, 2x CH_2Ph), 4.77 (dd, 1H, 1-H), 4.38 (ddd, 1H, 5-H), 4.09 (dd, 1H, 4-H), 3.80 (dd, 1H, 6-H), 3.75 (dd, 1H, 6′-H), 2.93 (ddd, 1H, 2-Ha), 2.67 (dd, 1H, 2-Hb), 2.13, 2.11 (2s, 6H, 2x SMe), 0.20 (s, 9H, $Si(CH_3)_3$). Coupling constants *J* are listed in Table 2. ^{13}C NMR ($CDCl_3$): δ 204.7 (o, C-3), 137.8, 137.7 (o, aromat. C), 128.6 - 127.6 (+, aromat. C), 79.8, 78.9, 76.5 (+, C-1, C-4, C-5), 73.8, 72.9 (-, Ph-CH_2), 69.0 (-, C-6), 49.8 (o, $C(SMe)_2SiMe_3$), 44.4 (-, C-2), 13.3, 13.1 (+, $(SMe)_2$), 0.1 (+, $SiMe_3$). $C_{26}H_{36}O_4S_2Si$: (504.79): calcd. C 61.87, H 7.19, S 12.70; found: C 61.92, H 7.28, S 12.30.

Reaction of **4b** (0.48 g, 1.47 mmol) with **5a** gave **1,5-Anhydro-4-*O*-benzyl-1-*C*-[1,1-bis(methylthio)-1-trimethylsilylmethyl]-2,6-dideoxy-L-*arabino*-hex-3-ulose (8a)** and **1,5-Anhydro-4-*O*-benzyl-1-*C*-[1,1-bis(methylthio)-1-trimethylsilylmethyl]-2,6-dideoxy-L-*ribo*-hex-3-ulose (8b)** (1:1) (574 mg, 98 %). Purification by cc using PE/EE (30:1) gave two fractions (392 mg, 67 %).

1st Fraction: **8a**; colorless oil. $[\alpha]^{21}_D$ -124.4° (c 1.52, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 7.39-7.25 (m, 5H, H aromatic), 4.96, 4.50 (2d, 2H, *J*= 11.6 Hz, CH_2Ph), 3.89 (dd, 1H, 1-H), 3.64 (dd, 1H, 4-H), 3.52 (dq, 1H, 5-H), 2.93 (ddd, 1H, 2-Ha), 2.77 (dd, 1H, 2-Hb), 2.14, 2.13 (2s, 6H, 2x SMe), 1.38 (d, 3H, 6-H), 0.22 (s, 9H, $Si(CH_3)_3$). Coupling constants *J* are listed in Table 2. ^{13}C NMR ($CDCl_3$): δ 206.2 (o, C-3), 137.4 (o, aromat. C), 128.4, 128.3, 128.0 (+, aromat. C), 84.5 (+, C-4), 83.8 (+, C-1), 77.1 (+, C-5), 73.3 (-, Ph-CH_2), 49.2 (o, $C(SMe)_2SiMe_3$), 45.2 (-, C-2), 19.1 (+, C-6), 13.4, 12.8 (+, $(SMe)_2$), -0.2 (+, $SiMe_3$). $C_{19}H_{30}O_3S_2Si$: (398.66): calcd. C 57.24, H 7.58, S 16.09; found: C 57.24, H 7.67, S 15.40.

2nd Fraction: **8b** (contaminated with ~10 % of **8a**); colorless oil. ^1H NMR ($CDCl_3$): δ 7.39-7.25 (m, 5H, H aromatic), 4.47 (dq, 1H, 5-H), 4.65, 4.45 (2d, 2H, *J*= 11.6 Hz, CH_2Ph), 4.26 (dd, 1H, 1-H), 3.47 (dd, 1H, 4-H), 3.37 (dd, 1H, 2-Ha), 2.54 (ddd, 1H, 2-Hb), 2.17, 2.15 (2s, 6H, 2x SMe), 1.19 (d, 3H, 6-H), 0.25 (s, 9H, $Si(CH_3)_3$). Coupling constants *J* are listed in Table 2. ^{13}C NMR ($CDCl_3$): 208.2 (o, C-3), 137.1 (o, aromat. C), 128.4 - 128.0 (+, aromat. C), 83.5 (+, C-4), 77.9 (+, C-1), 74.3 (+, C-5), 71.9 (-, Ph-CH_2), 50.1 (o, $C(SMe)_2SiMe_3$), 42.8 (-, C-2), 15.4 (+, C-6), 13.2, 12.7 (+, $(SMe)_2$), 0.1 (+, $SiMe_3$). LRMS (DCI): *m/z* (relative intensity) $2M+NH_4^+$ 814.8 (13.6), $M+NH_4^+$ 416.4 (96), $M+H^+$399.4 (100), $M-SCH_3^+$ 351.3 (53). $C_{19}H_{30}O_3S_2Si$: (398.66): calcd. C 57.24, H 7.58, S 16.09; found: C 57.25, H 7.60, S 15.49.

Reaction of **4a** (250 mg, 0.77 mmol) with **5c** gave **1,5-Anhydro-4,6-bis-*O*-benzyl-3-*C*-[1,1-bis(methylthio)]-2-deoxy-D-*lyxo*-hex-1-enitol (10)** as a single isomer. Purification by fc using PE/EE (15:1) yielded a colorless oil (247 mg, 74 %). ^1H NMR ($CDCl_3$): δ 7.38-7.25 (m, 10H, H aromatic), 6.38 (d, 1H, $J_{1,2}$= 6.0 Hz, 1-H), 4.95 (dd, 1H, $J_{2,1}$= 6.0 Hz, $J_{2,4}$= 1.6 Hz, 2-H), 4.71, 4.67, 4.57, 4.46 (4d, 4H, *J*= 12 Hz, 2x CH_2Ph), 4.42 (dd, $J_{4,5}$= 2.6 Hz, $J_{4,2}$= 1.6 Hz, 1H, 4-H), 4.18 (ddd, 1H, $J_{5,6}$= 7.0 Hz, $J_{5,6'}$= 5.0 Hz, $J_{5,4}$= 2.6 Hz, 5-H), 3.77 (dd, $J_{6,6'}$= 10.0 Hz, $J_{6,5}$= 7.0 Hz, 1H, 6-H), 3.59 (dd, $J_{6',6}$= 10.0 Hz, $J_{6',5}$= 5.0 Hz, 1H, 6′-H), 3.59 (s, 1H, $CH(SMe)_2$), 2.79 (s, 1H, OH), 2.20, 2.19 (2s, 6H, 2x SMe). Coupling constants *J* are listed in Table 2. ^{13}C NMR ($CDCl_3$): δ 143.9 (+, C-1), 137.8, 137.3 (o, aromat. C), 128.7 - 127.7 (+, aromat. C), 105.2 (+, C-2), 74.8, 73.5 (-, Ph-CH_2), 74.8 (+, C-5), 74.4 (+, C-4), 73.2 (o, C-3), 68.5 (-, C-6), 64.7 (+, $CH(SMe)_2$), 15.3, 15.2 (+, $(SMe)_2$). $C_{23}H_{28}O_4S_2$: (432.60): calcd. C 63.86, H 6.52, S 14.82; found: C 63.81, H 6.89, S 14.36.

Reaction of **4b** (0.2 g, 0.92 mmol) with **5c** gave **1,5-Anhydro-4-*O*-benzyl-3-*C*-[1,1-bis(methylthio)]-2,6-dideoxy-L-*arabino*-hex-1-enitol (11a)** and **1,5-Anhydro-4-*O*-benzyl-3-*C*-[1,1-bis(methylthio)]-2,6-dideoxy-L-*ribo*-hex-1-enitol (11b)** (5:1) (306 mg crude). Purification by cc using PE/EE (15:1) gave two fractions (255 mg, 85 %).

1st Fraction: **11b**; colorless oil. ^{1}H NMR ($CDCl_3$): δ 7.38-7.25 (m, 5H, H aromatic), 6.35 (d, 1H, $J_{1,2}$= 6.2 Hz, 1-H), 4.89, 4.73 (2d, 2H, J= 11.2 Hz, CH_2Ph), 4.69 (dq, 1H, $J_{5,4}$= 9.2 Hz, $J_{5,6}$= 6.4 Hz 5-H), 4.66 (d, 1H, $J_{2,1}$= 6.2 Hz 2-H), 4.15 (s, 1H, OH), 3.73 (d, 1H, $J_{4,5}$= 9.2 Hz, 4-H), 3.36 (s, 1H, $CH(SMe)_2$), 2.23, 2.20 (2s, 6H, 2x SMe), 1.33 (d, 3H, $J_{5,6}$= 6.0 Hz, 6-H). ^{13}C NMR ($CDCl_3$): δ 144.9 (+, C-1), 138.1 (o, aromat. C), 128.4, 128.0, 127.8 (+, aromat. C), 102.2 (+, C-2), 82.5 (+, C-4), 74.8 (-, Ph-CH_2), 74.3 (o, C-3), 73.0 (+, C-5), 63.1 (+, $CH(SMe)_2$), 18.4 (+, C-6), 15.8, 14.9 (+, $(SMe)_2$). LRMS (DCI) for $C_{16}H_{22}O_3S_2$ (326.48): *m/z* (relative intensity) M+NH_4^+ 344.3 (11), M+H^+ 327.3 (12), M-OH^+ 309.3 (100).

2nd Fraction: **11a**; colorless oil. ^{1}H NMR ($CDCl_3$): δ 7.40-7.30 (m, 5H, H aromatic), 6.44 (d, 1H, $J_{1,2}$= 6.0 Hz, 1-H), 4.86 (d, 1H, $J_{2,1}$= 6.0 Hz 2-H), 4.83, 4.73 (2d, 2H, J= 11.0 Hz, CH_2Ph), 4.15 (dq, 1H, $J_{5,4}$= 10.0 Hz, $J_{5,6}$= 6.0 Hz 5-H), 4.09 (d, 1H, $J_{4,5}$= 10.0 Hz, 4-H), 3.66 (s, 1H, OH), 3.20 (s, 1H, $CH(SMe)_2$), 2.23, 2.11 (2s, 6H, 2x SMe), 1.43 (d, 3H, $J_{6,5}$= 6.0 Hz, 6-H). ^{13}C NMR ($CDCl_3$): δ 147.3 (+, C-1), 137.6 (o, aromat. C), 128.5, 128.1, 128.0 (+, aromat. C), 101.7 (+, C-2), 79.9 (+, C-4), 75.2 (-, Ph-CH_2), 73.4 (o, C-3), 71.4 (+, C-5), 63.8 (+, $CH(SMe)_2$), 17.6 (+, $(SMe)_2$), 15.3 (+, C-6). LRMS (EI) for $C_{16}H_{22}O_3S_2$ (326.48): *m/z* (relative intensity) M-OH^+ 309.3 (34). $C_{16}H_{22}O_3S_2$: (326.48): calcd. C 58.86, H 6.79, S 19.64; found: C 59.18, H 6.35, S 19.53.

General Procedure for the Nucleophilic Addition of Carbanion 5b to 2,3-Dihydro-4*H*-pyran-4-ones 4a,b

A solution of 1.2 equiv. of tris(methylthio)methane (**5b**) in dry THF (1 mL/mmol) was cooled to -78 °C. Then *n*-BuLi (1.6 M solution in hexane; 1.1 equiv.) was added and the solution was allowed to warm to -60 °C within 30 min. This temperature was maintained for 30 min and the mixture was cooled again to -78 °C. To this solution one equiv. of 2,3-dihydro-4*H*-pyran-4-one **4a** or **4b** in dry THF (2 mL/ mmol) was added dropwise. The yellow reaction mixture was allowed to warm to -50 °C and kept at this temperature for 1h until no starting material could be detected by TLC (PE/EE 3:1). For workup, it was hydrolyzed with a mixture of dichloromethane/saturated NH_4Cl solution (1:1). The aqueous phase was separated and extracted twice with dichloromethane. The combined organic layers were dried ($MgSO_4$), concentrated *in vacuo* and purified by cc.

Reaction of **4a** (250 mg, 0.77 mmol) with **5b** gave **1,5-Anhydro-4,6-bis-*O*-benzyl-2-deoxy-1-*C*-[1,1,1-tris(methylthio)methyl]-D-*lyxo*-hex-3-ulose (7a)** and **1,5-Anhydro-4,6-bis-*O*-benzyl-2-deoxy-3-*C*-[1,1,1-tris(methylthio)methyl]-D-*lyxo*-hex-1-enitol (7c)** (8:1) (325 mg, 88 %). Purification by cc using PE/EE (15:1) gave two fractions (269 mg, 73 %).

1st Fraction: **7c**; colorless oil. $[\alpha]^{21}_D$ -17.3° (c 1.32, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 7.38-7.25 (m, 10H, H aromatic), 6.46 (d, 1H, $J_{1,2}$= 6.2 Hz, 1-H), 5.21 (dd, 1H, $J_{1,2}$= 6.2 Hz, $J_{2,4}$= 1.0 Hz, 2-H), 4.81 (ddd, 1H, $J_{5,6'}$= 7.4 Hz, $J_{5,6}$= 4.4 Hz, $J_{5,4}$= 2.6 Hz, 5-H), 4.81, 4.61, 4.53, 4.46 (4d, 4H, J= 11.2 and 12.0

Hz, 2x CH_2Ph), 4.45 (dd, $J_{4,5}$= 2.6 Hz, $J_{4,2}$= 1.0 Hz, 1H, 4-H), 3.75 (dd, 1H, $J_{6',6}$= 10.2 Hz, $J_{6',5}$= 7.4 Hz, 6´-H), 3.53 (dd, $J_{6,6'}$= 10.2 Hz, $J_{6,5}$= 4.4 Hz, 1H, 6-H), 3.15 (s, 1H, OH), 2.28 (s, 9H, 3x SMe). ^{13}C NMR ($CDCl_3$): δ 144.7 (+, C-1), 137.9, 137.1 (o, aromat. C), 128.7 - 127.5 (+, aromat. C), 105.5 (+, C-2), 77.3 (o, C-3), 76.9, 75.0 (+, C-4, C-5), 74.6, 73.4 (-, Ph-CH_2), 68.9 (-, C-6), 53.4 (o, *C*$(SMe)_3$), 15.4 (+, $(SMe)_3$). LRMS (DCI) for $C_{24}H_{30}O_4S_3$ (478.70): *m/z* (relative intensity) M+NH_4^+ 496.5 (46).
2nd fraction: **7a** (contaminated with ˜70 % of **7c**). ^{1}H NMR ($CDCl_3$): δ 7.36-7.25 (m, 10H, H aromatic), 5.0, 4.57, 4.54, 4.44 (4d, 4H, *J*= 12 Hz, 2x CH_2Ph), 4.41 (dd, 5-H), 4.11 (dd, 1H, 4-H), 3.78 (dd, 1H, 6´-H), 3.53 (dd, 1H, 6-H), 3.10 (ddd, 1H, 2-Ha), 2.84 (dd, 1H, 2-Hb), 2.14 (s, 9H, 3x SMe). Due to overlap with 5-H and *CH_2*Ph of **7c**, 1-H could not be detected. Selected ^{13}C NMR data: δ 204.4 (C-3), 79.4, 78.9, 77.2 (C-1, C-4, C-5), 73.7, 72.9 (2x CH_2Ph), 68.7 (C-6), 43.4 (C-2), 13.9 (Sme).

Reaction of **4b** (0.2 g, 0.92 mmol) with **5b** gave **1,5-Anhydro-4-*O*-benzyl-2,6-dideoxy-1-*C*-[1,1,1-tris(methylthio)methyl]-L-*arabino*-hex-3-ulose (9a)**, **1,5-Anhydro-4-*O*-benzyl-2,6-dideoxy-1-*C*-[1,1,1-tris(methylthio)methyl]-L-*ribo*-hex-3-ulose (9b)** and **1,5-Anhydro-4-*O*-benzyl-2,6-dideoxy-3-*C*-[1,1,1-tris(methylthio)methyl]-L-*arabino*-hex-1-enitol (9c)** (˜2:2:1) (332 mg, 97 %). Purification by cc using PE/EE (15:1) gave three fractions (274 mg, 80 %).
1st Fraction: **9c**; colorless oil. $[\alpha]^{19}_D$ -90.5° (c 0.63, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 7.40-7.25 (m, 5H, H aromatic), 6.53 (d, 1H, $J_{1,2}$= 6.0 Hz, 1-H), 5.68 (d, 1H, $J_{2,1}$= 6.0 Hz, 2-H), 5.26, 4.67 (2d, 2H, *J*= 10.6 Hz, CH_2Ph), 4.37 (d, 1H, $J_{4,5}$= 10.0 Hz, 4-H), 3.97 (dq, 1H, $J_{5,4}$= 10.0 Hz, $J_{5,6}$= 6.2 Hz, 5-H), 3.56 (s, 1H, OH), 2.28 (s, 9H, 3x SMe), 1.50 (d, 3H, $J_{6,5}$= 6.2 Hz,6-H). ^{13}C NMR ($CDCl_3$): δ 147.1 (+, C-1), 137.9 (o, aromat. C), 127.5 - 128.4 (+, aromat. C), 104.7 (+, C-2), 79.6 (+, C-4), 79.2 (o, C-3), 76.7 (o, *C*$(SMe)_3$), 73.3 (-, Ph-CH_2), 72.4 (+, C-5), 17.8 (+, C-6), 15.9 (+, $(SMe)_3$). LRMS (DCI) for $C_{17}H_{24}O_3S_3$ (372.57): *m/z* (relative intensity) 2M+NH_4^+ 762.7 (2.4), M+NH_4^+ 390.4 (36), M+H^+ 390.4 (36), M-OH^+ 355.3 (100), M-SCH_3^+ 325.3 (56).
2nd Fraction: **9a**; colorless oil; $[\alpha]^{20}_D$ -109.4° (c 0.76, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 7.40-7.28 (m, 5H, H aromatic), 4.97, 4.51 (2d, 2H, *J*= 11.4 Hz, CH_2Ph), 3.86 (dd, 1H, 1-H), 3.64 (dd, 1H, 4-H), 3.54 (dq, 1H, 5-H), 3.15 (ddd, 1H, 2-Ha), 2.95 (dd, 1H, 2-Hb), 2.18 (s, 9H, 3x SMe), 1.38 (d, 3H, 6-H). Coupling constants *J* are listed in Table 2. ^{13}C NMR ($CDCl_3$): δ 206.2 (o, C-3), 137.4 (o, aromat. C), 128.4, 128.2, 128.0 (+, aromat. C), 84.6 (+, C-4), 83.4 (+, C-1), 77.3 (+, C-5), 73.3 (-, Ph-CH_2), 72.9 (o, *C*$(SMe)_3$), 44.9 (-, C-2), 19.3 (+, C-6), 14.1 (+, $(SMe)_3$). LRMS (DCI): *m/z* (relative intensity) 2M+NH_4^+ 762.7 (5.6), M+NH_4^+ 390.3 (100), M+H^+ 373 (96). $C_{17}H_{24}O_3S_3$ (372.57): calcd. C 54.81, H 6.49, S 25.82; found: C 55.87, H 6.41, S 22.73.
3rd Fraction: **9b**; colorless oil. $[\alpha]^{20}_D$ -25.8° (c 1.14, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 7.38-7.26 (m, 5H, H aromatic), 4.66, 4.47 (2d, 2H, *J*= 11.6 Hz, CH_2Ph), 4.51 (dq, 1H, 5-H), 4.17 (dd, 1H, 1-H), 3.55 (dd, 1H, 2-Ha), 3.54 (dd, 1H, 4-H), 2.70 (ddd, 1H, 2-Hb), 2.21 (s, 9H, 3x SMe), 1.19 (d, 3H, 6-H). Coupling constants *J* are listed in Table 2. ^{13}C NMR ($CDCl_3$): δ 207.6 (o, C-3), 137.1 (o, aromat. C), 128.4, 127.9, 127.6 (+, aromat. C), 83.2 (+, C-4), 77.2 (+, C-1), 74.2 (+, C-5), 73.7 (o, C$(SMe)_3$), 71.9 (-, Ph-CH_2), 41.6 (-, C-2), 15.2 (+, C-6), 13.9 (+, $(SMe)_3$). LRMS (DCI) for $C_{17}H_{24}O_3S_3$ (372.57): *m/z* (relative intensity) 2M+NH_4^+ 762.7 (8), M+NH_4^+ 390.3 (100).

1-*O*-Benzyloxy-2-*O*-*tert*-butyldiphenylsilyloxy-heptane (14)

A suspension of CuI (2.77 g, 14.5 mmol) in dry diethyl ether (25 mL) was cooled to -50 °C. Then 2.5 equiv. of *n*-BuLi (1.6 M solution in hexane; 19.0 mL, 30.3 mmol) were added and the solution was allowed to warm to -10 °C. The reaction mixture was cooled to -78 °C, treated with glycidol **13** (2 g, 12.1 mmol) in dry diethyl ether (12 mL) and slowly warmed to -40 °C. For workup, it was hydrolyzed with a mixture of dichloromethane/saturated NH_4Cl solution (1:1). For removal of copper salts, a few drops ammonia were added and the two layers were rapidly stirred under air. The aqueous phase was separated and extracted twice with dichloromethane. The combined organic layers were dried ($MgSO_4$), concentrated *in vacuo* and the crude semisolid product was partially purified by fc using PE/EE (30:1) as eluent. The crude material (2.7 g) and imidazole (1.3 g, 18.2 mmol) were dissolved in dry DMF (25 mL) at 0 °C and *tert*-butyldiphenylsilyl chloride (3.66 g, 13.3 mmol) was added. The reaction mixture was stirred at room temperature for 12 h. For workup, it was hydrolyzed with a mixture of PE/saturated NH_4Cl solution (1:1). The aqueous phase was separated and exhaustively extracted with PE. The combined organic layers were dried ($MgSO_4$), concentrated *in vacuo* and the crude product was purified by fc using PE/EE (50:1) as eluent to afford **14** (5.07 g, 91 %) as a colorless oil. ^1H NMR ($CDCl_3$): δ 7.65-7.55 and 7.37-7.06 (2m, 15H, H aromatic), 4.27, 4.23 (2d, 2H, $J_{A,B}$= 11.0 Hz, CH_2Ph), 3.80 (dddd, 1H, *J*= 11.0, 5.5, 5.0, 0.4 Hz, CHOSi), 3.32 (dd, 1H, *J*= 9.6, 5.0 Hz, *H*CHOBn), 3.28 (dd, 1H, *J*= 9.6, 5.5 Hz, HC*H*OBn), 1.49-1.34 and 1.25-1.0 (2m, 8H, 4x CH_2), 0.97 (s, 9H, ^{t}Bu), 0.75 (t, 3H, *J*= 7.2 Hz, CH_2CH_3). ^{13}C NMR ($CDCl_3$): δ 138.5, 134.6, 134.2 (o, aromat. C), 136.0, 129.5, 129.3, 128.2, 127.6,127.4, 127.3 (+, aromat. C), 74.0, 73.0 (-, $PhCH_2OCH_2$), 72.3 (+, CHOSi), 34.3 (-, $CH_2(CH_2)_3CH_3$), 31.9 (-, $CH_2CH_2(CH_2)_2CH_3$), 27.0 (-, ^{t}Bu), 24.4 (+, $(CH_2)_2CH_2CH_2CH_3$), 22.5 (-, $(CH_2)_3CH_2CH_3$), 19.4 (o, ^{t}Bu), 14.0 (+, CH_3).

3-*tert*-Butyldiphenylsiloxy-oct-1-yne (16)

A suspension of palladium on charcoal (10% Pd, 250 mg) in ethyl acetate (15 mL) was activated under an H_2-atmosphere. **14** (2.5 g, 5.43 mmol) was added and the reaction mixture was stirred for 12 h at room temperature For workup, it was filtered through a pad of Celite, concentrated *in vacuo* and purified by fc using PE/EE (10:1) as eluent to afford a colorless oil (1.85 g, 5.0 mmol, 92 %). To a solution of the alcohol thus obtained (0.5 g, 1.35 mmol) in dry dichloromethane (5 mL) was added the *Dess-Martin* reagent[13] (0.74 g, 1.75 mmol) in dry dichloromethane (5 mL) and the mixture was stirred at room temperature for 10 min. For workup, it was hydrolyzed with a mixture of dichloromethane/saturated $NaHCO_3$-solution (1:1). The aqueous phase was separated and extracted with dichloromethane (2x). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo* to afford **15**. This aldehyde was dissolved in dichloromethane (2 mL) and directly added to a suspension, which had been prepared as follows: A cold (0 °C) suspension of CBr_4 (0.96 g, 2.9 mmol) and Zn (0.19 g, 2.9 mmol) in dichloromethane (3 mL) and was treated with triphenylphosphine (0.76 g, 2.9 mmol) in dichloromethane (3 mL) and stirred for 24 h in the dark. The crude aldehyde **15** was added and the mixture was stirred for 2 h at 0 °C, poured into PE (20 mL), filtered, and the filtrate was concentrated under reduced pressure. The residue was diluted with PE (10 mL); triphenylphospine oxide was removed by filtration and washed with PE. This procedure was repeated until no more 1,1 dibromo olefin was detected by TLC (PE/ EE 50:1). The filtrates and washings were concentrated *in* *vacuo* to give a yellow oil (0.18 g, 0.34 mmol, 25 %). To a cold solution (-78 °C) of 1,1 dibromo olefin (0.18 g, 0.34 mmol) in THF (3 mL), n-BuLi ((1.6 M solution in hexane; 0.47 mL, 0.75 mmol, 2.2 equiv.) was added and the mixture was allowed to warm -30 °C and kept at this temperature for 1h until no starting material could be detected by TLC (PE/EE 50:1). For workup, it was hydrolyzed with a mixture of dichloromethane/saturated NH_4Cl-solution (1:1). The aqueous phase was separated and extracted twice with dichloromethane. The combined organic layers were dried ($MgSO_4$), concentrated *in vacuo* and purified by cc to afford **16** (85 mg, 0.24 mmol, 71 % from 1,1 dibromo olefin) as a colorless oil. $[\alpha]^{20}_D$ -0.08° (c 1.47, $CHCl_3$). IR ν 3309. ^{1}H NMR ($CDCl_3$): δ 7.80-7.64 and 7.48-7.32 (2m, 10H, H aromatic), 4.33 (ddd, 1H, *J*= 6.8, 5.8, 2.0 Hz, CHOSi), 2.30 (d, 1H, *J*= 2.0 Hz, H alkyne), 1.73-1.12 (4m, 8H, 4x CH_2), 1.08 (s, 9H, ^{t}Bu), 0.84 (t, 3H, *J*= 7.0 Hz, CH_2CH_3). ^{13}C NMR ($CDCl_3$): δ 136.0, 135.8, 129.7, 129.6, 127.6, 127.4 (+, aromat. C), 133.6, 133.5 (o, aromat. C), 85.2 (+, HCC), 72.5 (o, HC), 63.7 (+, CHOSi), 38.2 (–, $CH_2(CH_2)_3CH_3$), 31.3 (–, $CH_2CH_2(CH_2)_2CH_3$), 26.9 (+, ^{t}Bu), 24.3 (–, $(CH_2)_2CH_2CH_2CH_3$), 22.5 (–, $(CH_2)_3CH_2CH_3$), 19.3 (o, ^{t}Bu), 14.0 (+, CH_3).

(*E*)-(2*R*, 3*S*, 3′*S*)-3-Benzyloxy-2-(benzyloxymethyl)-6-[3-(*tert*-butyldiphenylsiloxy)-oct-1-enyl) tetrahydro-pyran-4-one (17)

A solution of **16** (80 mg, 0.22 mmol) and $Cp_2Zr(H)Cl$ (57 mg, 0.22 mmol) in dry THF (2 mL) was stirred for 15 min at room temperature The reaction mixture was cooled to -78 °C, treated with 2 equiv. methyl lithium (0.28 mL, 0.44 mmol, 1.6 M in diethyl ether) and allowed to warm to -30 °C. This temperature was maintained for 30 min. and the mixture was cooled again to -78 °C. CuCN (20 mg, 0.22 mmol) and methyl lithium (0.14 mL, 0.22 mmol, 1.6 M in diethyl ether) were added and the temperature was raised to -30 °C. This temperature was maintained for 30 min and the mixture was cooled again to -78 °C. **4a** (71 mg, 0.22 mmol) was added and the reaction mixture was slowly raised to -50 °C. For workup, it was hydrolyzed with a mixture of dichloromethane/saturated NH_4Cl-solution (1:1). The aqueous phase was separated and extracted twice with dichloromethane. The combined organic layers were dried ($MgSO_4$), concentrated *in vacuo* and purified by cc using PE/EE (50:1) as eluent to afford **17** (62 mg, 0.09 mmol, 41 %). $[\alpha]\Theta_{243.4nm}$= +1040°, $\Theta_{295.2nm}$= -2500°, $\Theta_{354.4nm}$= +323° (*c* 0.053 mM, MeOH, 25°C). ^{1}H NMR ($CDCl_3$): δ 7.89-7.72 and 7.33-7.07 (20H, Ph), 5.77 (ddd, 1H, 2′-H), 5.47 (ddd, 1H, 1′-H), 4.84, 2x 4.36, 4.26 (4d, 4H, $J_{A,B}$= 12.0 Hz, 2x CH_2Ph), 4.76 (dddd, 1H, 6-H), 4.29 (ddd, 1H, 2-H), 4.25 (dd, 1H, 3′-H), 3.82 (dd, 1H, 3-H), 3.77 (dd, $J_{A,B}$= 10.7 Hz, 1H, *H*CHOBn), 3.69 (dd, $J_{A,B}$= 10.7 Hz, 1H, HC*H*OBn), 2.56 (dd, 1H, 5-H_a), 2.04 (ddd, 1H, 5-H_b), 1.67-1.49 and 1.36-1.13 [2m, 8H, $(CH_2)_4$], 1.24 (s, 9H, ^{t}Bu), 0.86 (t, 1H, CH_3). - $J_{2,HCH}$= 5.3, $J_{2,HCH}$= 3.2, $J_{2,3}$= 5.7, $J_{3,5b}$= 1.1, $J_{5a,5b}$= 14.0, $J_{5a,6}$= 14.2, $J_{5b,6}$= 8.5, $J_{6,1'}$= 5.0, $J_{6,2'}$= 1.5, $J_{1',2'}$= 15.6, $J_{1',3'}$= 1.0, $J_{2',3'}$= 6.8 Hz, $J_{3',4'}$= 6.8 Hz, $J_{3',4''}$= 1.0 Hz, $J_{7',Me}$= 7.0 Hz. ^{13}C NMR ($CDCl_3$): δ 203.5 (o, C-3), 138.7, 138.4, 135.9 (o, aromat. C), 136.5 – 129.8 (+, aromat. C, C-1', C-2'), 79.8 (+, C-5), 76.4 (+, C-4), 74.3, 73.2 (+, C-1,C-3'), 73.7, 72.7 (–,$PhCH_2$), 69.5 (–, C-6), 45.8 (–, C-2), 38.2 (–, $CH_2(CH_2)_3CH_3$), 32.1 (–, $CH_2CH_2(CH_2)_2CH_3$), 27.3 (+, ^{t}Bu), 24.7 (–, $(CH_2)_2CH_2CH_2CH_3$), 22.9 (–, $(CH_2)_3CH_2CH_3$), 19.6 (o, ^{t}Bu), 14.3 (+, CH_3). LRMS (DCI): *m/z* M+NH_4^+ 708.6.

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7 We also prepared the methyl-branched derivatives by reaction of **4a** and **4b**, respectively, with MeLi and compared the NMR data with those reported in *ref.* 4b-d.

8 This phenomenon has also been reported for the bulky *tert.*-butyl, the silyl and stannyl as well as for the 1,3-dithiolane-2-carboxylate group. For configurational and conformational aspects of 1-alkylated 3-uloses refer to *refs.* 3b, f, g and 5.

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