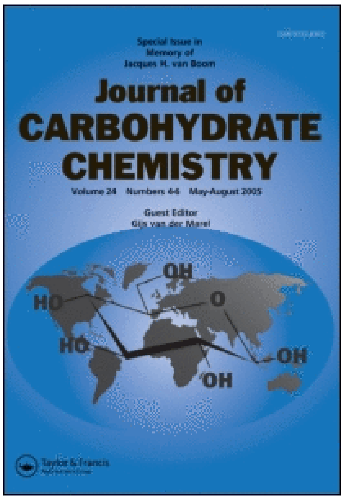

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BRANCHING OF KETOSUGARS BY ETHYL TRIMETHYLSILYLACETATE/TETRA-n-BUTYLAMMONIUM FLUORIDE

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ABSTRACT

Hexopyranose- and hexofuranose-uloses, on treatment with ethyl trimethylsilylacetate/tetra-n-butylammonium fluoride, form β-hydroxy esters or derivatives thereof instead of their TMS-enol ethers. ^{29}Si NMR studies confirm the proposed mechanism.

The tetra-n-butylammonium ester enolate, reasonably assumed to be formed in the reaction of ethyl trimethylsilylacetate (ETSA) with tetra-n-butylammonium fluoride (TBAF), is described to react differently with aldehydes than with ketones.[2] While the former generally yield β-trimethylsilyloxy esters, the latter, with the exception of those lacking α-hydrogen atoms, were found to give trimethylsilyl enol ethers exclusively,[3] any exception having been recently ruled out.[4] This result must be attributed to the voluminous quaternary ammonium counterion, rendering the ester enolate insufficiently nucleophilic for rapid addition to ketones, which are only subject to α-proton abstraction.[3] The reaction sequence was proposed to be completed by the silylation of the ketone enolate by flurotrimethylsilane, under the provision of anhydrous conditions.

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When we applied the ETSA-TBAF-reagent to carbohydrate derived ketones,[5,6] bearing neighboring deoxy groups, the results disagreed with those previously anticipated to be general for ketones.[2,4] Thus, instead of their respective TMS-enol ethers, methyl 4,6-O-benzylidene-2-(or 3-)deoxy-α-D-erythro-3-(or 2-)-hexulopyranoside,(1),(2) respectively, and 3,6-anhydro-1,2-O-isopropylidene-α-D-xylo-hexofuranos-5-ulose (3), invariably and independently of conditions formed β-hydroxy esters or derivatives thereof.[14]

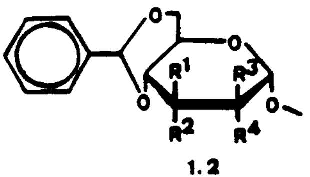
In view of these unprecedented results a closer investigation appeared to be called for. Reaction of 1, 2, or 3 in anhydrous tetrahydrofuran with ETSA[7] in the presence of equimolar or catalytic (1 mole %) amounts of anhydrous TBAF[11] yielded the O-trimethylsilylated branched sugar derivatives 1a-3a exclusively. Equimolar amounts of TBAF•$3H_2O$, however, afforded the unsilylated β-hydroxyesters 1b-3b together with 2-3% each of 1a-3a. Catalytic amounts of TBAF•$3H_2O$ again gave 1a-3a, formed in similar amount as above, 1b-3b in this case being the by-products.

^{29}Si NMR[8](Bruker WH-90, 17.88 MHz, in C_6D_6, inverse-gated-decoupled, δ in ppm to internal tetramethylsilane) clearly showed that hexamethyldisiloxane (δ=7.3) is invariably formed in all experiments employing TBAF•$3H_2O$. This product most likely originates from immediate hydrolysis of fluorotrimethylsilane rather than from products 1a-3a. In contrast, under anhydrous conditions, flurotrimethylsilane can be detected (δ=32.2;$^1J(^{29}Si-^{19}F)$=275.64 Hz)[9,10] but is rapidly disappearing due to subsequent trimethylsilylation of the intermediate enolate.

The reactions described with enolizable carbohydrate uloses 1, 2, and 3 are without precedence and allow facile stereospecific aldolizations, in some respects superior to Reformatzky reactions. Reactions of this kind are going to be extended to other potentially nucleophilic trimethylsilylated reagents for branching in carbohydrate chemistry.

EXPERIMENTAL

In a typical experiment 1, 2, or 3 (5 mmol each) in anhydrous tetrahydrofuran (20 mL) was treated at 5°C with equimolar amounts of ETSA in 10 mL of anhydrous tetrahydrofuran and TBAF (or TBAF-trihydrate; catalytic or equimolar amounts, respectively; reaction conditions cf. table); the solvent was evaporated in vacuo and the residue purified by chromatography.[13]

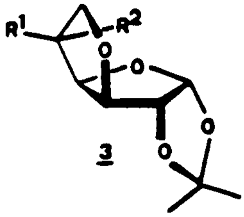


1,2

	R^1	R^2	R^3	R^4
1	=O		H	H
1a	R	OTMS	H	H
1b	R	OH	H	H
2	H	H	=O	
2a	H	H	OTMS	R
2b	H	H	OH	R

R= $-CH_2-COOC_2H_5$

OTMS= $-O-Si(CH_3)_3$



3

	R^1	R^2
3	=O	
3a	R	OTMS
3b	R	OH

No	yield (%)	$[\alpha]_D^{20}$ [d]	mp	conditions[c]	R_F [b]	analytical data
1a	55	78.0 (c 3.9)	oil	5h; catal. anhydrous	0.69	$C_{21}H_{32}SiO_7$ (424.6) Calcd: C,59.41; H,7.60; Si,6.62 Found: C,60.64; H,7.70; Si,6.74
1b	68	72.0 (c 0.2)	90-91° 90-91°[a]	2h; equim.	0.51	$C_{18}H_{24}O_7$ (352.4) Calcd: C,61.35; H,6.86 Found: C,62.04; H,6.96
2a	57	52.2 (c 3.0)	oil	2h; catal. anhydrous	0.77	$C_{21}H_{32}SiO_7$ (424.6) Calcd: C,59.41; H,7.60; Si,6.62 Found: C,60.81; H,7.77; Si,6.77
2b	62	58.0 (c 8.5)	87-90°	2h; equim.	0.25	$C_{18}H_{24}O_7$ (352.4) Calcd: C,61.35; H,6.86 Found: C,62.42; H,6.97
3a	64	34.2 (c 1.5)	oil	5h; catal. anhydrous	0.55	$C_{16}H_{28}SiO_7$ (360.5) Calcd: C,53.31; H,7.83; Si,7.70 Found: C,54.58; H,7.96; Si,7.96
3b	67	10.2 (c 1.0)	76-79[a]	3h; equim.	0.32	$C_{13}H_{20}O_7$ (288.3) Calcd: C,54.16; H,6.99 Found: C,54.71; H,7.07

a. cf. Lit 12.
b. TLC was performed with toluene/ ethyl acetate 4/1 on Merck-pre-coated sheets, silica gel 60, # 5554; for 2a toluene/ ethyl acetate 3/1 was used
c. The reaction conditions refer to: time of reactions; amounts of TBAF or TBAF-trihydrate
d. in chloroform

The ^1H NMR spectra were recorded in $CDCl_3$ containing 1% tetramethylsilane as the internal standard with a VARIAN XL-200 spectrometer. The ^{13}C NMR spectra were measured in $CDCl_3$ with a BRUKER WH-90-instrument at 22.63 MHz; δ in ppm from TMS, $^nJ_{XY}$ in Hz.

1a: ^1H: 7.25-7.50 (m, 5H, aromat), 5.51 (s, 1H, benzylidene), 4.66 (X-part of an ABX-system, 1H, H-1, $^3J_{12}$ = 4.74, $^3J_{12'}$ = 1.26), 4.11 (q, 2H, CH_2-ester, ^3J = 7.0), 4.0 - 4.28 (m, 2H, H-4 and H-5), 3.74 and 3.75 (AB-system, 2H, H-6 and H-6', $^2J_{66'}$ = 9.25), 3.40 (s, 3H, OMe), 2.72 and 2.67 (AB-system, 2H,

CH_2-COOR, ^2J = 13.75), 2.22 and 2.09 (AB-part of an ABX-system, 2H, H-2 and H-2', $^2J_{22'}$ = 14.5), 1.95 (t, 3H, Me-ester), 0.25 (s, 9H, $SiMe_3$);

^{13}C:2.69 ($SiMe_3$), 14.38 (Me-ester), 40.53 (CH_2-COOR), 43.20 (C-2), 55.10 (OMe), 58.94 (CH_2-ester), 60.63 (C-5), 69.73 (C-6), 72.46 (C-3), 81.69 (C-4), 98.56 (C-1), 102.24 (CH-benzylidene), 126.55, 128.38, 129.09 and 138.06 (aromat), 170.64 (COOR).

1b: ^1H:7.20-7.60 (m, 5H, aromat), 5.58 (s, 1H, benzylidene), 4.75 (X-part of an ABX-system, 1H, H-1, $^3J_{12}$=3.90, $^3J_{12'}$=1.50), 3.4-4.5 (m, 7H, CH_2- ester, H-4, H-5, H-6, H-6', OH), 3.36 (s, 3H, OMe), 3.12 and 2.75 (AB-system, 2H, H-2 and H-2', $^2J_{22'}$=14.4), 1.15 (t, 3H, Me-ester, ^3J = 6.9);

^{13}C: 14.34 (Me-ester), 39.69 (CH_2-COOR), 42.23 (C-2), 55.62 (OMe), 59.65 (C-5), 60.76 (CH_2-ester), 69.47 (C-6), 69.73 (C-3), 81.57 (C-4), 98.99 (C-1), 102.24 (CH-benzylidene), 126.56, 128.44, 129.29 and 136.74 (aromat), 171.03 (COOR)

2a: ^1H:7.32-7.60 (m, 5H, aromat), 5.54 (s, 1H, benzylidene), 4.67 (s, 1H, H-1), 4.29 (m, 1H, H-4), 4.17 (q, 2H, CH_2-ester, ^3J = 7), 3.72-3.89 (m, 2H, H-6 and H-6'), 3.5-3.71 (m, 1H, H-5), 3.42 (s, 3H, OMe), 2.67 and 2.72 (AB system, 2H, CH_2-COOR, ^2J = 13.5), 2.11-2.39 (m, 2H, H-3 and H-3'), 1.29 (t, 3H, Me-ester), 0.10 (s, 9H, $SiMe_3$);

^{13}C: 2.37 (Me_3Si), 14.40 (Me-ester), 37.09 ($C\underline{H}_2$-COOR), 44.70 (C-3), 54.97 (OMe), 60.56 (CH_2-ester), 64.27 (C-5), 69.66 (C-6), 75.38 and 75.71 (C-2, C-4), 101.52 (C-1), 101.78 (CH-benzylidene), 126.36, 128.51, 129.22 and 139.90 (aromat), 167.33 (COOR).

2b: ^1H:7.33-7.58 (m, 5H, aromat), 5.54 (s, 1H, benzylidene), 4.68 (s, 1H, H-1), 4.16-4.36 (m, 3H, CH_2-ester, q, ^3J = 7; and X-part of an ABX-system, H-4), 3.79 (m, 2H, H-6 and H-6'), 3.52-3.72 (m, 1H, H-5), 3.47 (s, 3H, OMe), 3.23 (s, 1H, OH), 2.74 (s, 2H, CH_2-COOR), 2.28 and 2.02 (AB-part of an ABX-system, 2H, H-3 and H-3', $^2J_{33'}$= 12.0, $^3J_{34}$ = 12.3, $^3J_{3'4}$=4.3), 1.31 (s, 3H, Me-ester);

^{13}C: 14.27 (Me-ester), 37.48 ($\underline{C}H_2$-COOR), 41.64 (C-3), 55.62 (OMe), 61.02 (CH_2-ester), 64.40 (C-5), 69.47 (C-6), 71.61 (C-2), 75.78 (C-4), 101.39 (C-1), 102.04 (CH-benzylidene), 126.36, 128.51, 129.29 and 137.54 (aromat), 170.32 (COOR).

3a: ^1H: 5.94 (d, 1H, H-1, $^3J_{12}$ = 4.0), 4.65 (d, 1H, H-4, $^3J_{34}$ = 3.5), 4.61 (d, 1H, H-2, $^3J_{23}$ = 0.5), 4.50 (d, 1H, H-3), 4.17 (q, 2H, CH_2-ester, ^3J = 7), 3.59 and 3.95 (AB-system, 2H, H-6, and H-6', $^2J_{66'}$ = 8.5), 2.53 (bs, 2H, CH_2-COOR), 1.50 (s, 3H, Me-isopropylidene endo), 1.11 (s, 3H, Me-isopropylidene, exo), 1.28 (t, 3H, Me-ester), 0.14 (s, 9H, $SiMe_3$); ^{13}C: 1.11 ($SiMe_3$), 14.40 (Me-ester), 26.90 and 27.50 (Me-isopropylidene), 40.66 ($C\underline{H}_2$-COOR), 61.15 (CH_2-ester), 73.95 (C-6), 81.63, 85.33, 85.53, and 85.85 (C-2, C-3, C-4 and C-5), 106.92 (C-1), 112.77 (isopropylidene), 170.05 (COOR).

3b: ^1H: 5.90 (d, 1H, H-1, $^3J_{12}$ = 3.5), 4.64 (d, 1H, H-4, $^3J_{34}$ = 3.6), 4.57 (d, 1H, H-2, $^3J_{23}$ = 0.5), 4.48 (d, 1H, H-3), 4.15 (q, 2H, CH_2-ester, ^3J = 7), 4.02 and 4.19 (AB-system, 2H, H-6, and H-6', $^2J_{66'}$ = 9.0), 2.56 (bs, 2H, CH_2-COOR), 2.65 (bs, 1H, OH), 1.51 (s, 3H, Me-isopropylidene, endo), 1.35 (s, 3H, Me-isopropylidene, exo), 1.19 (t, 3H, Me-ester); ^{13}C: 14.27 (Me-ester), 26.95 and 27.60 (Me-isopropylidene), 40.66 ($\underline{C}H_2$-COOR), 61.15 (CH_2-ester), 75.84, 76.04 (C-5 and C-6), 85.40, 85.59 and 85.92 (C-2, C-3, and C-4), 107.19 (C-1), 113.23 (isopropylidene), 170.57 (COOR)

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10. Traces of O-(trimethylsilyl)-O-ethyl ketene acetal (δ=15.4) and starting material (δ=2.7) but no hexamethyldisiloxane could be detected due to the rigorous anhydrous conditions.

11. Anhydrous TBAF was obtained by drying the commercially available TBAF·$3H_2O$ (Fluka Ag, Buchs, Switzerland) at 80 °C for three days in vacuo; cf. R. K. Sharma, and J. L. Fry, J. Org. Chem., 48, 2112 (1983).

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13. Unreacted starting material could be recovered; overall yield based on reacted starting material > 95%.

14. Due to the rigid conformation of the compounds the known difference between axial and equatorial ring substituents was used for the evaluation of the stereochemistry of the branching point (in addition cf. ref. 12); the carbon-13-shift of C-3 in 1a/1b as well as the shift of C-2 in 2a/2b is another proof for the stereochemistry (shielding effects of axial substituents).