Pergamon

Tetrahedron Letters, Vol. 36, No. 47, pp. 8595-8598, 1995
Elsevier Science Ltd
Printed in Great Britain
0040-4039/95 $9.50+0.00

0040-4039(95)01849-2

Stereoselective Syntheses of Branched-Chain Carbohydrates Bearing Furan and Pyrrole Moieties

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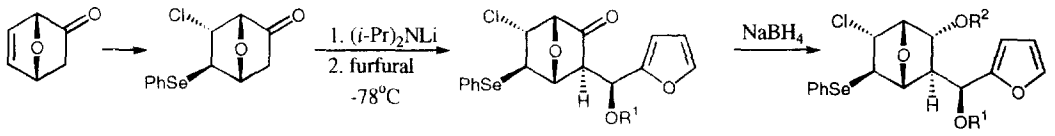
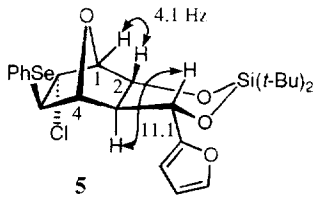
Abstract: The racemic 7-oxanorborn-5-en-2-one has been converted into 1,5-anhydro-3-deoxy-3-[1'--(α-furyl)-1'-hydroxymethyl]-α-galacto furanose and into 1,5-anhydro-3-deoxy-3-[1'-(α-pyrryl)-1'--hydroxymethyl]- α-galactofuranose derivatives.

Branched-chain sugars occur in plant polysaccharides and glycosides.[1] They are also part of antibiotics derived from micro-organisms, mainly of the various strains of *Streptomyces*,[1,2] and of nucleoside antibiotics such as amipurimycin[1,3] and the miharamycins.[4] The addition of carbon nucleophiles to ketones, oxiranes, allylic esters, activated alkenes or enones derived from hexoses has been frequently used to prepare branched--chain carbohydrates.[5] Radical additions to unsaturated sugars especially their intramolecular versions,[6] and *de novo* synthesis[7] have also been successful. Optically pure 7-oxabicyclo[2.2.1]hept-5-en-2-yl derivatives such as (+)-**1** ("naked sugars")[8] are powerful intermediates for the preparation of rare carbohydrates and analogues[9] and have allowed Wagner et al.[5] to prepare 5-C-methyl hexoses and the first examples of azasugars branched at C(5). We report here on the synthesis of a new kind of 3-deoxy-3-substituted galactose derivatives that incorporate α-furyl- and α-pyrryl-1-hydroxymethyl groups.



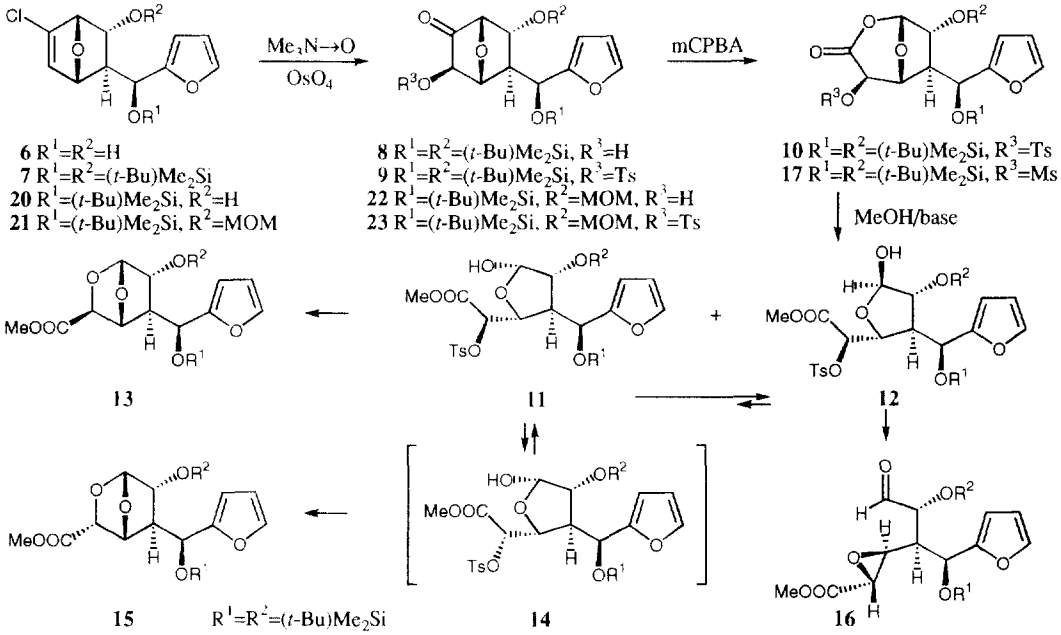
(+)-**1** **2** **3** R^1=H; **18** R^1=(*t*-Bu)Me_2Si **4** R^1=R^2=H; **19** R^1=(*t*-Bu)Me_2Si, R^2=H

The enone (±)-**1** added PhSeCl to give the adduct **2**.[10] The lithium enolate of **2** reacted with furfural at -78°C to yield a single aldol **3** isolated in 95% yield. As expected for steric reasons (Zimmerman-Traxler model,[11] *like* mode of addition, *exo* face selective) the *anti* aldol was obtained, the relative configuration of which was proven by the ^{1}H-NMR data of derivative **5** prepared in the following way. Reduction of ketone **3** with $NaBH_4$ (MeOH/THF, 0°C) afforded diol **4** (91%) that reacted with (*t*-Bu)$_2$Si(OTf)$_2$ and 2,6-lutidine in CH_2Cl_2 (0-20°C, 15 h) to give **5** in mediocre yield (15%). The *exo* relative configuration of the aldol was confirmed by the absence of coupling between the bridgehead proton H-C(4) and the vicinal H_{endo}-C(3) proton, the *endo* relative configuration of the alcoholic moiety at C(2) was given by ^3J(H-C(1),H_{exo}-C(2)) = 4.1 Hz and ^3J(H_{exo}-C(2),H_{endo}-C(3))=3.7 Hz,[12] and the *anti* aldol by the *trans* coupling ^3J(H_{endo}C(3), H-C(1'))=11.1 Hz (see **5**).



5

Oxidative elimination of the phenylseleno group of diol **4** with 55% meta-chloroperbenzoic acid (mCPBA, 1.3 equiv., CH_2Cl_2) afforded the corresponding chloroalkene **6** (82%), the treatment of which with (*t*-Bu)Me_2SiCl and imidazole (anh. DMF, 60°C, 15 h) gave **7**. Double hydroxylation of **7** with $Me_3NO/NaHCO_3$ and a catalytical amount of OsO_4 (4:1 THF/H_2O, 1% equiv. OsO_4) furnished the α-hydroxyketone **8** (86%, 53% based on the aldol **3**) which was esterified into the corresponding tosylate **9** (69%) with TsCl (1.2 equiv.) and Et_3N (1.5 equiv.) in CH_2Cl_2 (0°C, 4 h). Baeyer-Villiger oxidation of **9** with mCPBA/$NaHCO_3$ (CH_2Cl_2, 0°C, 6 h) provided the β-altrofuranurono-1,6-lactone **10** in 77% yield.



6 $R^1=R^2=H$
7 $R^1=R^2=$(*t*-Bu)Me_2Si
20 $R^1=$(*t*-Bu)Me_2Si, $R^2=H$
21 $R^1=$(*t*-Bu)Me_2Si, $R^2=$MOM

8 $R^1=R^2=$(*t*-Bu)Me_2Si, $R^3=H$
9 $R^1=R^2=$(*t*-Bu)Me_2Si, $R^3=$Ts
22 $R^1=$(*t*-Bu)Me_2Si, $R^2=$MOM, $R^3=H$
23 $R^1=$(*t*-Bu)Me_2Si, $R^2=$MOM, $R^3=$Ts

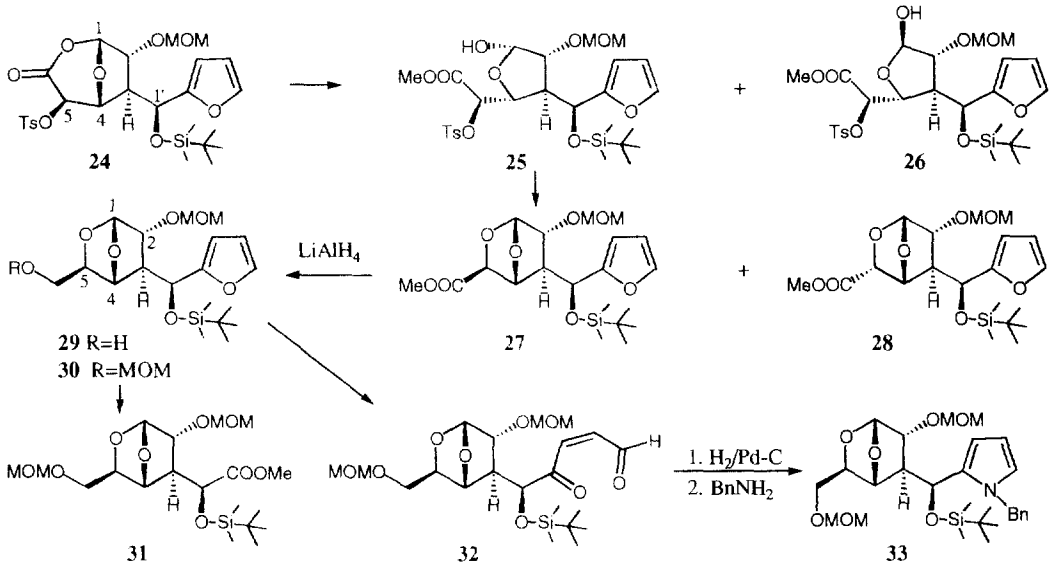
10 $R^1=R^2=$(*t*-Bu)Me_2Si, $R^3=$Ts
17 $R^1=R^2=$(*t*-Bu)Me_2Si, $R^3=$Ms

13 **11** **12**

15 $R^1=R^2=$(*t*-Bu)Me_2Si **14** **16**

With the goal to convert (inversion at C(5)) the altrose derivatives **10** into a galactose derivative we treated **10** with anh. MeOH under basic conditions. With MeONa/THF (-78°C), a 2:1 mixture of **11** and **12** was obtained. Prolonged exposure to the basic medium led to further anomerization, the β-furanose **12** being more stable than **11**. This reaction was faster than the desired intramolecular displacement of the tosylate of **11** into the anhydrogalactouronate **13**. Epimerization of the tosylate **11** into **14** appeared to compete also as the anhydroaltrouronate derivative **15** was formed concurrently with **13**. Furthermore, and depending on the nature of the base (Li_2CO_3, Et_3N, K_2CO_3) and solvent (CH_3CN, DMF, THF), the epoxide **16** was also formed together with **13** + **15**, the former resulting probably from the intramolecular displacement of the tosylate by the alcoholic moiety at C(4). The best yield for **13** + **15** + **16** never surpassed 50% (K_2CO_3, DMF, 70-75°C, 4 h). With the hope to improve the electrophilicity of the ester we replaced the tosylate in **10** by a mesylate as in **17**. Unfortunately, all our attempts to convert **17** into **13** were not met with success; only decomposition was observed. We reasoned that the chances for the desired intramolecular displacement reaction implying the α-furanose intermediate **11** would be increased if the β-furanose **12** would not be so much more stable than **11**. This goal could be reached by diminishing the gauche effect between the OH group of the α-furanose and the

adjacent protected alcoholic moiety. We therefore exchanged the voluminous silyl ether protective group of HO-C(2) by a MOM ether. Aldol **3** was protected as the silyl ether **18** ((*t*-Bu)Me_2SiCl/ imidazole, DMF, 20°C, 4 h) in 96% yield. Reduction of **18** with $NaBH_4$ in 1:1 THF/MeOH (0°C, 10 min) gave **19** (91%). Oxidation with mCPBA (CH_2Cl_2, -78°C, 3 h) afforded **20** (91%). Protection of the alcohol **20** with CH_3OCH_2Cl/(*i*-$Pr)_2NEt$/Bu_4NI (20°C, 4 h) provided the MOM ether **21** (84%). Double hydroxylation of the chloroalkene **21** with $Me_3N{\rightarrow}O$/$NaHCO_3$ (4:1 THF/H_2O, 1% equiv. of OsO_4, 20°C, 3 h) gave **22** which was tosylated into **23** (72%). Baeyer-Villiger oxidation of ketone **23** (mCPBA/$NaHCO_3$, CH_2Cl_2, 0°C) furnished uronolactone **24** (77%).[13] Treatment of tosylate **24** with $NaHCO_3$ in anhydrous methanol led to a 2:1 mixture of the α- and β-furanose **25** and **26**. With MeONa (1.5 equiv.) in THF (-78°C) the **25/26** ratio was 9:1. When treated with K_2CO_3 (3 equiv.) in 4:1 DMF/MeOH (20°C, 4 h) **24** was converted into a 85:15 mixture of anhydrogalacto and anhydroaltrouronate **27** and **28**, respectively, (69%) from which pure **27** was isolated in 55% yield. Ester **28** could not be equilibrated with **27** in the presence of K_2CO_3/DMF/MeOH, thus confirming that epimerization occurred at C(5) of tosylate **25**.



Reduction of the methyluronate **27** with $LiAlH_4$ in Et_2O (20°C, 30 min) gave the 1,4-anhydro-β-galacto-furanose derivative **29** (79%)[14] which was protected as di-MOM ether **30** (89%; CH_3OCH_2Cl/(*i*-$Pr)_2NEt$, Bu_4NI, CH_2Cl_2, 0-20°C). Oxidative cleavage of the furan ring in **30** with RuO_4/$NaIO_4$ in 3:2:2 CH_3CN/CCl_4/H_2O (20°C, 10 min), followed by esterification with CH_2N_2 in Et_2O provided the branched-chain carbohydrate **31** (80%).[15] Photooxidation (O_2, visible W-lamp, Bengal Rose B bound to polystyrene, CH_2Cl_2, -78°C, then Me_2S, -78°-20°C) led to **32** which was hydrogenated (H_2/Pd-C, 30 bar, EtOAc) and treated with benzylamine ($PyrH^+TsO^-$, molecular sieve 4 Å, PhH) to give the pyrrole **33** (45%).[16]

The chemistry disclosed here shows that the "naked sugars" can be converted readily with high stereoselectivity into all kinds of unusual branched-chain galactose and altrose derivatives. Since both enantiomeric forms of the starting enone ((+)-**1**, (-)-**1**) are available, both enantiomers of these branched-chain carbohydrates can be prepared with the same ease. We plan to use systems **30**, **31** and **33** to generate new kinds of disaccharide mimics.

Acknowledgments. This work was supported by the *Swiss National Science Foundation*, the *"Fonds Herbette"* (Lausanne) and *Hoffmann-La Roche & Cie*, AG (Basel).

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[13] Data for (±)-**24**: m.p. 74-76°C, ν_{CO}: 1770 cm^{-1}.

[14] Data for (±)-**29**: colorless oil; ^{1}H-NMR (400 MHz, $CDCl_3$) δ_H: 7.38 (dd, ^3J=1.8, ^4J=0.7), 6.33 (dd, ^3J=3.2, 1.8), 6.27 (dd, ^3J=3.2, ^4J=0.7), 5.60 (d, ^3J=2.4, HC(1)), 4.81, 4.64 (2d, ^2J=6.7), 4.52 (d, ^3J=9.7, HC(1')), 4.14 (br.s, HC(4)), 3.95 (dd, ^3J=2.5, 2.4, HC(2)), 3.85 (t, ^3J=5.1, HC(5)), 3.55-3.45 (m, H_2C(6)), 3.42 (s, 3 H), 2.16 (dd, ^3J=9.7, 2.5, HC(3)), 1.95 (t, ^3J=5.9, OH), 0.84 (s, 9H), 0.02, -0.18 (2s, 6H).

[15] Data for (±)-**31**: colorless oil; ^{1}H-NMR (400 MHz, $CDCl_3$) δ_H: 5.48 (d, ^3J=2.4), 4.73, 4.70 (2d, ^2J=8.0), 4.60 (s, 2H), 4.58 (s, 1H), 4.18 (d, ^3J=7.2), 3.94 (dd, ^3J=2.8, 2.4), 3.91 (dd, ^3J=8.0, 5.5), 3.72 (s, 3H), 3.43 (dd, ^2J=10.2, ^3J=5.5), 3.39 (dd, ^2J=10.2, ^3J =8.0), 3.38, 3.33 (2s, 2x3H), 1.97 (dd, ^3J=7.2, 2.8), 0.89 (s, 9H), 0.09, 0.089 (2s, 6H).

[16] Data for (±)-**33**: oil; ^{1}H-NMR (400 MHz, $CDCl_3$) δ_H: 7.36-7.22 (m, 3H), 6.93 (d, ^3J=7.4, 2H), 6.63 (dm, ^3J=2.2), 6.11 (dd, ^3J=3.3, 2.2), 6.10 (dm, ^3J=3.3), 5.52 (d, ^2J=16.9) 5.48 (d, ^3J=2.4, H-C(1)), 5.14 (d, ^2J=16.9), 4.74 (d, ^2J=6.6), 4.58 (d, ^2J=6.6), 4.55 (s, 2H), 4.52 (d, ^3J=11.2, HC(1')), 4.00 (s, HC(4)), 3.80 (dd, ^3J=2.4, 2, HC(2)), 3.34, 3.29 (2s, 6H), 3.40-3.16 (m, 3H, HC(6), HC(5)), 1.82 (dd, ^3J=11.2, 2, HC(3)), 0.87 (s, 9H), -0.02, -0.22 (2s, 6H).

(Received in France 18 August 1995, accepted 27 September 1995)