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Total Asymmetric Synthesis of Long-chain, Branched Carbohydrates and of an Aza-C-Disaccharide

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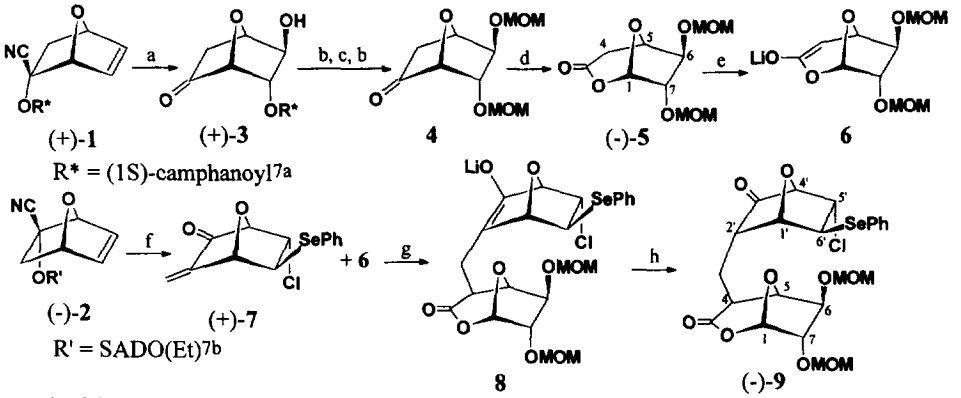
Abstract: Michael addition of (-)-(1S,5R,6R,7S)-6,7-bis(methoxymethoxy)-2,8-dioxabicyclo[3.2.1]-octan-3-one lithium enolate to (+)-(1R,4S,5S,6S)-5-benzeneselenyl-6-chloro-3-methylidene-7-oxabicyclo[2.2.1]heptan-2-one gives a single adduct with high stereoselectivity. It was converted into a derivative of β-D-(1→3)-C-linked 1,5-dideoxy-1,5-imino-lyxopyranoside of α-D-mannofuranurono-6,1-lactone and other long-chain, branched sugars.

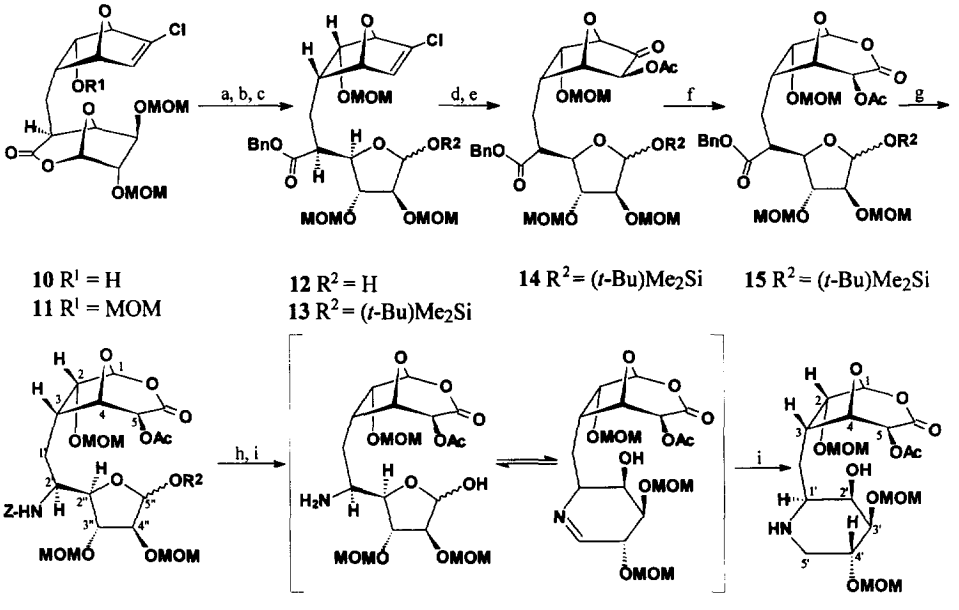
Glycosidases are key enzymes in the biosynthesis and processing of glycoproteins, which are macromolecules involved in recognition (cell-cell, host-pathogene interactions) and control of biological mechanisms and structures.[2] Inhibition of glycosidases[3] may be useful for the treatment of diseases such as diabetes, cancer, viral and bacterial infections, and inflammation.[4] Polyhydroxypiperidines and pyrrolidines (azasugars) are promising inhibitors; unfortunately, they often inhibit more than one enzyme *in vivo*. It is believed that selectivity would be increased if the azasugar would include not only the steric and charge information of the glycosyl moiety which is liberated during the glycosidase-catalysed hydrolysis, but also that of the aglycone which it is attached to. Such inhibitors could be dideoxy-iminoalditols linked to other sugars through non-hydrolysable links such as in the aza-C-disaccharides. A first example (1,5-dideoxy-1,5-imino-D-mannitol linked at C(6) of D-galactose through a CH_2 unit) has been prepared by Johnson and co-workers[5] applying the Suzuki reaction. Recently, Baudat and Vogel[6] have used the cross-aldolisation of a 7-oxabicyclo[2.2.1]heptan-2-one derivative with a protected form of 2,6,7-trideoxy-2,6-imino-D-*glycero*-L-*manno*-heptose to generate the first example of a (1→3)-C-linked azadisaccharide in which 1,5,6-trideoxy-1,5-imino-β-galactose is linked at C(3) of D-*altro*-hexouronic acid through a hydroxymethylene unit.



a) ref. 9, 2 steps, b) $CH_2(OCH_3)_2$, P_2O_5, c) DBU, MeOH, d) mCPBA, $CHCl_3$, e) LiHMDS, THF, f) ref. 11, 2 steps, g) THF, h) MeOH, AcOH

We report here a new approach to the total synthesis of long-chain, branched carbohydrates and of new kinds of (1→3)-C-linked azadisaccharides. These are obtained through the Michael addition of the lithium enolate of a protected 5-deoxy-*arabino*-hexofuranurono-6,1-lactone ((-)-**5**) to enone (+)-**7**. Both reactants are derived from the optically pure 7-oxabicyclo[2.2.1]hept-5-en-2-yl derivatives[7] (+)-**1** and (-)-**2**, respectively ("naked sugars of the first generation").[8]

Epoxidation of (+)-**1**, followed by acidic treatment provided (+)-**3**.[9] Acetalisation of the free hydroxyl in (+)-**3** using $(MeO)_2CH_2$ (CH_2Cl_2, P_2O_5, 20°C), methanolysis with MeOH (DBU, 20°C, 10 min, recovery of the chiral auxiliary: methyl camphanate) and treatment with $(MeO)_2CH_2$ (CH_2Cl_2, P_2O_5, 20°C, 20 min) gave ketone **4** (57% after flash chromatography on silica gel). Regioselective Baeyer-Villiger rearrangement of **4** with 1.1 eq. of *m*-chloroperbenzoic acid (mCPBA) in the presence of anhydrous $NaHCO_3$ (2.5 eq., CH_2Cl_2, 20°C, 16h) provided the uronolactone (-)-**5** (90%).[10] The lithium enolate **6** was generated by treatment of (-)-**5** with $(Me_3Si)_2NLi$ (THF, -78°C, 30 min.). A THF solution of enone (+)-**7** derived from the "naked sugar" (-)-**2** was added slowly (40 min) into a stirred THF solution of the lithium enolate of **6** (-70°C). The adduct **8** was quenched with 8:1 MeOH/AcOH at -78°C and furnished a single product (-)-**9** (90%).[12] Its ^{1}H-NMR spectrum (coupling constants, homonuclear shift correlation COSY 90 and C,H correlation) proved the relative configuration of the new stereogenic centers C(2') and C(4) (^3J(H-C(1')),H_{exo}-C(2')) = 6.0 Hz; ^3J(H_{endo}-C(4),H-C(5)) ~ 0 Hz)[13]. The high double-diastereoselectivity of the Michael addition of **6** to (+)-**7** can be explained by invoking steric factors: the *exo* face of **6** adds selectively to (+)-**7** giving enolate **8**, the *exo* face of which then reacts selectively with the proton source to afford (-)-**9**.



10 R^1 = H
11 R^1 = MOM
12 R^2 = H
13 R^2 = (*t*-Bu)Me_2Si
14 R^2 = (*t*-Bu)Me_2Si
15 R^2 = (*t*-Bu)Me_2Si
16 R^2 = (*t*-Bu)Me_2Si
17 R^2 = H
18
19
(-)-20

a) MOMCl, (*i*-Pr)$_2$NEt, b) BnOH, BuLi, c) (*t*-Bu)$Me_2SiOSO_2CF_3$, 2,6-lutidine, d) OsO_4·$2H_2O$, Me_3NO, $NaHCO_3$, e) Ac_2O, NEt_3, DMAP cat.,f) mCPBA, $NaHCO_3$, g) H_2, Pd/C, DPPA, NEt_3, BnOH, h) Bu_4NF on silica, i) H_2, $Pd(OH)_2$/C.

Reduction of (-)-**9** with $NaBH_4$ (MeOH/THF, 0°C, 15 min), followed by oxidative elimination of the phenylseleno group with 1 eq. of mCPBA (THF/CH_2Cl_2, -78°C, 2h, then 20°C, 2h) furnished **10** (86%). Protection of the *endo* alcohol as a MOM ether (20 eq. $MeOCH_2Cl$, 30 eq. $(i\text{-}Pr)_2NEt$, CH_2Cl_2, 0-20°C, 48h; then more $MeOCH_2Cl$ (20 eq.), 20°C, 4h) led to **11** (75%). Alcoholysis of lactone **11** with BnOLi (THF, 0-15°C, 4h), followed by acidification with AcOH gave furanose **12** which was silylated with (*t*-Bu)-$Me_2SiOSO_2CF_3$ in 2,6-lutidine (-15°C, 1h) to yield **13** (61%, 4:1 mixture of α- and β-anomer). Double hydroxylation of the chloroalkene **13** with Me_3NO and OsO_4•2aq. and $NaHCO_3$ (5:1 THF/H_2O, 20°C, 1h), followed by acetylation with Ac_2O/Et_3N/DMAP (CH_2Cl_2, 20°C, 16 h) furnished **14** (65%), the Baeyer-Villiger oxidation (mCPBA, $NaHCO_3$,$CHCl_3$, 20°C, 16 h) of which provided the doubly-branched tredecuronolactone derivative **15** (61%). Debenzylation (H_2,Pd/C, AcOEt, 20°C, 16h), followed by reaction of the free carboxylic acid with $(PhO)_2P(O)N_3$ and Et_3N (anhydrous toluene, 20°C, 5h) led to the corresponding isocyanate. This product was treated without purification with BnOH (100°C, 16h) to give the benzylcarbamate **16** (61%).[14] Cleavage of the silyl group with Bu_4NF on silica gel (THF, 0°C), followed by hydrogenolysis of the benzylcarbamate moiety of **17** (H_2, $Pd(OH)_2$/C, AcOEt, 20°C, 24h) provided the partially protected aza-C-disaccharide (-)-**20** (70%)[15], the formation of which results from equilibration of free amine **18** with imine **19** which is then hydrogenated. All the structures of the new compounds described here were confirmed by their mode of formation, spectral data and elemental analysis.

This work demonstrates the unprecedented use of "naked sugar"- derived Michael donors and acceptors in the stereoselective construction of long-chain, branched sugars and analogues[16], as well as new disaccharide mimics including β-D-(1→3)-C-azapyranosides of hexoses.

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[10] Data for (-)-**5**: colorless oil, $[\alpha]^{25}_{D}$ = -81 (c = 0.8, $CHCl_3$). IR(film) ν 2936, 2834, 1747 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δH 5.85 (*dd*, ^3J = 4.2, 0.7), 4.71, 4.64 (2*AB*, ^2J = 6.9), 4.55 (*dd*, ^3J = 6.9, 1.1), 4.26 (*ddd*, ^3J = 4.2, 1.9, ^4J = 1.1), 4.00 (*d*, ^3J = 1.9), 3.39, 3.36 (2*s*), 3.07 (*dd*, ^2J = 18.3, ^3J = 6.9), 2.58 (*d*, ^2J = 18.3).

[11] Bimwala, R. M.; Vogel, P. *J. Org. Chem.* **1992**, *57*, 2076-2083.

[12] Data for (-)-**9**: white foam; $[\alpha]^{25}_{D}$ = -32 (c = 2.4, $CHCl_3$). IR (KBr) ν 2949, 1767, 1737, 1438 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δH 7.67-7.65, 7.37-7.32 (2*m*, 5 H), 5.74 (*dd*, ^3J = 3.4, ^4J = 0.5, H-C(1)), 4.68 (*d*, ^3J = 6.0, H-C(1')), 4.72, 4.69 (2*AB*, ^2J = 6.1), 4.51 (*d*, ^3J = 5.9, H-C(4')), 4.29 (*dd*, ^3J = 5.9, 3.3, H-C(5')), 4.27 (br. *s*, H-C(5)), 4.18 (*dd*, ^3J = 3.4, 2.5, H-C(7)), 3.78 (*d*, ^3J = 2.5, H-C(6)), 3.61 (*d*, ^3J = 3.3, H-C(6')); 3.44, 3.38 (2*s*), 2.92 (*dt*, ^3J = 7.2, 6.0, H-C(2')), 2.44 (*t*, ^3J =7.3, H-C(4)); 2.14 (*ddd*, ^2J = 14.4, ^3J = 7.3, 7.2), 1.87 (*ddd*, ^2J = 14.4, ^3J = 7.3, 7.2).

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[14] Data for **16** (α-anomer, purified by flash chromatography on silica gel, EtOAc/light petroleum 3:7): colorless oil; IR (film) ν 3400, 2954, 2857, 2828, 2067, 1769, 1515, 1469 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$), δH 7.38-7.32(*m*), 5.90 (*d*, ^3J = 4.1, H-C(1)), 5.30 (*s*), 5.28 (*s*, H-C(5)), 5.16 (*d*, ^3J = 9.8, NH), 5.12, 5.08 (*AB*, ^2J = 12.3), 4.76-4.54 (*m*), 4.40 (*dd*, ^3J = 9.4, 4.1, H-C(2)), 4.34 (*d*, ^3J = 6.9, H-C(4)), 4.14-4.07 (*m*), 4.03 (*d*, ^3J = 1.5, H-C(4'')), 3.76 (*dd*, ^3J = 5.1, 1.5, H-C(3'')), 3.46, 3.36, 3.31 (3*s*), 2.58-2.54 (*m*), 2.11 (*s*, Ac), 1.82-1.78 (*m*, H_2C(1')), 0.90(*s*), 0.13, 0.12 (2*s*).

[15] Data for (-)-**20**: colorless oil; $[\alpha]^{25}_{D}$ = -83 (c = 0.28, $CHCl_3$). ^{1}H-NMR (400 MHz, $CDCl_3$) δH 5.92 (*dd*, ^3J = 4.2, ^4J = 0.6, H-C(1)), 5.38 (*s*), 4.81, 4.77 (*AB*, ^2J = 6.9), 4.73, 4.67 (*AB*, ^2J = 6.9), 4.64, 4.61 (*AB*, ^2J = 6.7), 4.49 (*d*, ^3J = 6.8, H-C(4)), 4.33 (*dd*, ^3J = 9.3, ^4J = 4.2, H-C(2)), 3.86 (*dd*, ^3J = 3.0, 1.1, H-C(4')), 3.71 (*ddd*, ^3J = 10.7, 9.3, 5.5, H-C(2')), 3.50 (*dd*, ^3J = 9.3, 3.0, H-C(3')), 3.46, 3.42, 3.37 (3*s*), 3.23 (*dd*, ^2J = 13.4, ^3J = 5.5), 2.73-2.66 (*m*, H-C(3)), 2.58 (*ddd*, ^3J = 9.0, 4.8, 1.1, H-C(5')), 2.39 (*dd*, ^2J = 13.4, 10.7), 2.18 (*s* Ac), 1.81-1.68 (*m*, CH_2-C(3)); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 170.2, 164.6 (2*s*), 101.4 (*d*), 97.0, 96.8, 96.2 (3*t*), 81.6, 80.8, 76.0, 74.6, 70.9, 67.7 (6*d*), 57.2, 55.7, 55.4 (3*q*), 56.8 (*d*), 49.3 (*t*), 39.7 (*d*), 26.4 (*t*), 20.7 (*q*).

[16] For other syntheses of long-chain carbohydrates starting from "naked-sugars", see e.g.: Emery, F.; Vogel, P. *J. Org. Chem.* **1995**, *60*, 5843-5854; Chen, Y.; Vogel, P. *Ibid*, **1994**, *59*, 2487-2496.

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