Stereoselective Protecting Group Free Synthesis of D,L-Gulose Ethyl Glycoside *via* Multicomponent Enyne Cross Metathesis – Hetero Diels-Alder Reaction

Daniele Castagnolo,[a] Lorenzo Botta,[a] Maurizio Botta[a,b,]*

a) Dipartimento Farmaco Chimico Tecnologico, Università degli Studi di Siena, via A. de Gasperi 2, 53100 Siena, Italy. b) Sbarro Institute for Cancer Research and Molecular Medicine, Center for Biotechnology, College of Science and Technology, Temple University, BioLife Science Bldg., Suite 333, 1900 N 12th Street, Philadelphia, PA 19122, USA. Corresponding author: botta@unisi.it

Abstract

An efficient and stereoselective synthesis of D,L-gulose was described. The key step of the synthetic route is represented by a multicomponent enyne cross metathesis – hetero Diels-Alder reaction which allows the formation of the pyran ring from cheap and commercially available substrates in a single synthetic step. The synthesis of D,L-gulose was accomplished without the use of protecting groups making this approach highly desirable also in terms of atom economy.

1. Introduction.

L-Hexoses, which are known as rare sugars in the natural resources, sometimes play important roles in the microbial world. As notable examples, L-gulose **1**, the C-3 epimer of galactose **2**, is the key building block of the carbohydrate moiety of antitumor antibiotic bleomycin A2[1] and L-iduronic acid **3** is a typical component of mammalian dermatan sulfate, heparan sulfate, and heparin.[2] (Figure 1). Gulose is an unnatural monosaccharide that exists as a syrup with a sweet taste. Both the D- and L-forms are not fermentable by yeast. L-Gulose is commercially available but it is very expensive. Syntheses of L-gulose[3] have been reported so far as well as the synthesis of D-gulose which has been prepared in a multistep process from D-glucose.[4] However, most of these synthetic approaches showed low convenience because they require creating new stereocenters by various reactions and making a large use of protecting groups. Hence, it is clear that the development of new and efficient methodologies that makes rare sugars "common" are highly desirable. Herein we describe a novel and practical stereoselective synthesis of D,L-gulose ethyl glycoside through a multicomponent enyne metathesis – hetero Diels-Alder reaction carried out in a few minutes under microwave irradiation.[5] The synthesis was accomplished without the use of protecting groups making this approach also desirable for its "atom economy" benefits.

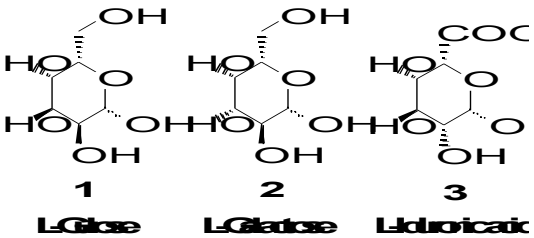
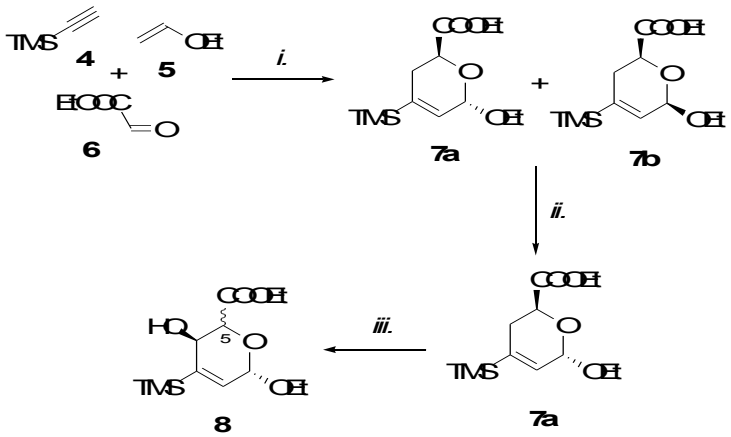


Figure 1. L-Hexoses

2. Results and discussion.

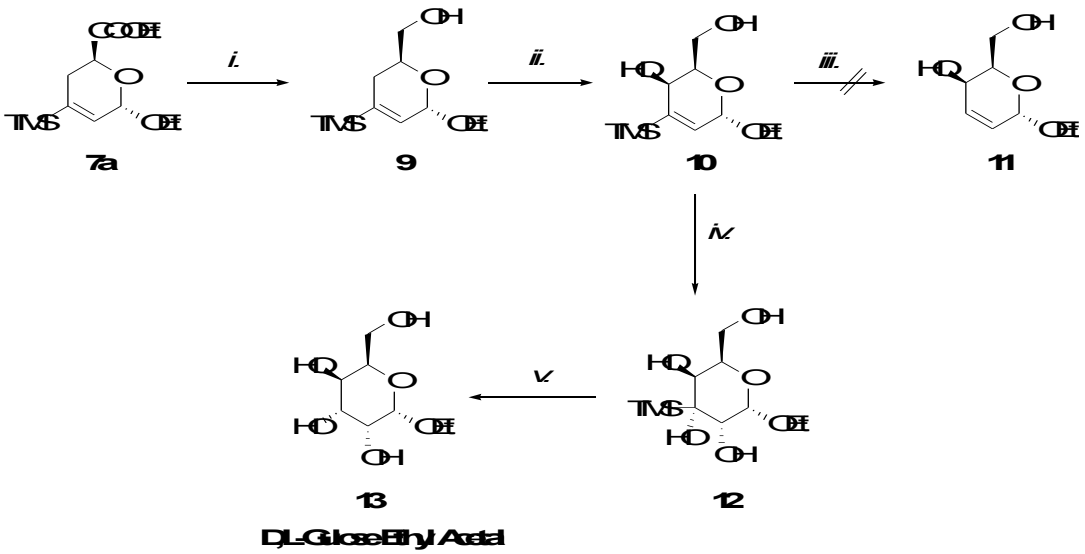
We first focused on the synthesis of the pyran ring through the reaction of trimethylsilylacetylene **4** with ethylvinyl ether **5** and ethyl glyoxalate **6** in the presence of Grubbs' catalyst 2nd gen. The multicomponent enyne cross metathesis – hetero Diels-Alder reaction was performed under microwave irradiation and was completed in only 20 min. (2 runs x 10 min.) leading to dihydropyrans **7a-b** as a mixture of *trans*/*cis* diastereoisomers in a 2:1 ratio. The diastereomeric mixture **7a-b** was equilibrated with $ZnCl_2$ affording **7a** as the single isomer.[6] Allylic oxidation of **7a** with SeO_2 in the presence of pyridine[7] led to diol **8** which was isolated as a mixture of diastereoisomers. Epimerization at C5 occurred due to the basic environmental reaction conditions. (Scheme 1).



Scheme 1. Reagents and conditions: *i.* Grubbs'cat. 2nd gen. 10mol%, toluene, 80 °C, µW, 20 min. *ii.* $ZnCl_2$, DCM, 24 h. *iii.* SeO_2, pyridine, dioxane, reflux, 2h.

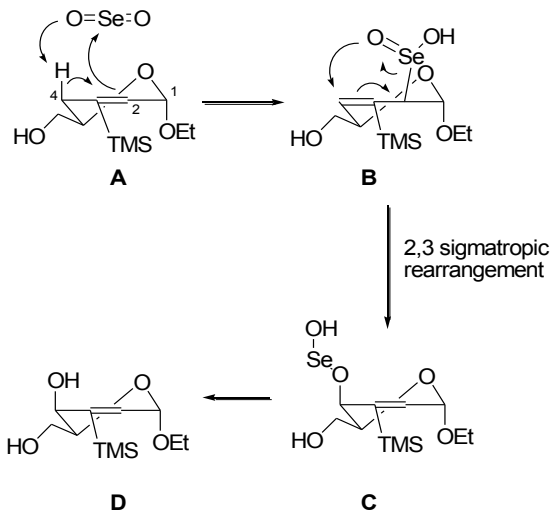
Hence, compound **7a** was reduced to alcohol **9** with $LiAlH_4$. The proton at C5 of **9** in fact is less acid than the corresponding hydrogen at C5 of **7a** and as a consequence it is less inclined to epimerize during the allylic oxidation step. Reaction of **9** with SeO_2 in pyridine led in fact to diol **10** as a single diastereoisomer. The relative stereochemistry was determined by 2D-NOESY

experiment. Compound **10** was reacted with TBAF and ^{t}BuOK with the aim to obtain derivative **11**. In both cases only starting material was recovered from the reaction mixtures and no traces of **11** were detected. On the contrary, dihydroxylation of **10** with OsO_4 and NMO led to compound **12**[8] which was then converted into D,L-gulose ethyl glycoside **13** through TBAF desilylation (Scheme 2).[9] In this case desilylation occurred due to the presence of the hydroxy moiety on C3 which favours the cleavage of carbon-silicon bond.[9a] The relative stereochemistry of was determined by 2D-NOESY experiment. No cross peak between H-2 and H-4 was observed.[8]



Scheme 2. Reagents and conditions: *i.* $LiAlH_4$, THF, r.t., 3h. *ii.* SeO_2, pyridine, dioxane, reflux, 2h. *iii.* TBAF, THF, r.t. *iv.* OsO_4, NMO, THF, r.t., 48 h. *v.* TBAF, THF, r.t., 3h.

The observed stereoselectivity of the SeO_2 oxidation step was explained as follows: dihydropyran **9** reacted with SeO_2 leading to intermediate **B**. The attack of selenium on the double bond occurred at C2 on the less hindered face,[10] namely opposite to the ethoxy moiety. Subsequent 2,3 sigmatropic rearrangement and hydrolysis of **C** led in a stereoselective way to the diol **10** having the hydroxy moiety at C4 and *anti* as regards to the ethoxy group (Scheme 3).



Scheme 3. Mechanism of the SeO_2 mediated hydroxylation step

In conclusion an efficient and stereoselective synthesis of D,L-gulose ethyl glycoside **13** was accomplished. Compound **13** was obtained stereoselectively in a few step and high yields starting from cheap substrates. Moreover the complete synthetic route was completed without the use of protecting groups making this approach highly desirable also in terms of atom economy.

3. Experimental

3.1 General methods.

Reagents were obtained from commercial suppliers and used without further purification. Anhydrous reactions were run under a positive pressure of dry argon. Silica gel 60 was used for flash chromatography (23-400 mesh). ^{1}H NMR and ^{13}C NMR spectra were measured on a 400 MHz spectrometer. Chemical Shifts for protons are reported in parts per million (δ scale) and internally referenced to the $CDCl_3$ signal at δ 7.24 ppm. Chemical Shifts for carbon are reported in parts per million n (δ scale) and referenced to the carbon resonances of the solvent ($CDCl_3$: δ 77.76 ppm, the middle peak). Mass spectra (MS) data were obtained using a LC/MSD VL system with a 0.4 mL/min flow rate using a binary solvent system of 95:5 methyl alcohol/ water. UV detection was monitored at 254 nm. Mass spectra were acquired in positive and negative mode scanning over the mass range. Elemental analyses (C, H, N) were performed in house.

3.1.1 HPLC and MS analysis. The purity of compounds was assessed by reverse-phase liquid chromatography and a mass spectrometer with a UV detector at λ = 254 nm and an electrospray ionization source (ESI). All the solvents were HPLC grade. Mass spectral (MS) data were obtained using a LC/MSD VL system with a 0.4 mL/min flow rate using a binary solvent system of 95:5 methyl alcohol/water. UV detection was monitored at 254 nm. Mass spectra were acquired in

positive mode scanning over the mass range of 50-1500. The following ion source parameters were used: drying gas flow, 9 mL/min; nebulize pressure, 40 psig; drying gas temperature, 350 °C.

3.1.2 Microwave irradiation experiments. Microwave irradiations were conducted using a CEM Discover Synthesis Unit. The machine consists of a continuous focused microwave power delivery system with operator-selectable power output from 0 to 300 W. The temperature of the contents of the vessels was monitored using a calibrate infrared temperature control mounted under the reaction vessel. All the experiments were performed using a stirring option whereby the contents of the vessel are stirred by means of rotating magnetic plate located below the floor of the microwave cavity and a Teflon-coated magnetic stirbar in the vessel.

3.2 General procedures

Synthesis of 7a-b

Alkyne **4** (0.14 mL, 1.0 mmol), ethylvinyl ether **5** (0.86 mL, 9.0 mmol), ethyl glyoxalate **6** (0.39 mL of a 50% solution in toluene, 2.0 mmol) and Grubbs' catalyst 2nd generation (85 mg, 0.1 mmol) were suspended in degassed toluene (4.0 mL) in a 10 mL glass vial equipped with a small magnetic stirring bar. The mixture was irradiated under microwaves for 2 x 10 minutes at 80 °C, using an irradiation power of 300 W. Microwave irradiations were conducted using a CEM Discover Synthesis Unit (CEM Corp., Matthews, NC). The mixture was then poured into a solution of $NaHCO_3$ (20 mL) and stirred for 10 minutes. The mixture was then extracted with Et_2O (2 x 10 mL). The combined organic phases were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (SiO_2) using 1:2 Et_2O/hexanes, as the eluent to yield the 2,3-dihydropyrans **7a-b** (as a 1/2 mixture of *cis*/*trans* isomers, 206 mg) as tan oil. Signals of both isomers were reported.
Yield: 71%. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 5.88 (s, 1H, C=C*H*CHOEt, *trans*), 5.80 (s, 0.5H, C=C*H*CHOEt, *cis*), 5.01 (s, 0.5H, CHC*H*OEt, *cis*), 4.98 (s, 1H, CHC*H*OEt, *trans*), 4.39-4.36 (m, 1H, C*H*COOEt, *trans*), 4.25 (m, 0.5H, C*H*COOEt, *cis*), 4.18-4.11 (m, 3H, COOCH_2CH$_3$, *trans* and *cis*), 3.93-3.89 (m, 0.5H, CHOCH_2CH$_3$, *cis*), 3.82-3.78 (m, 1H, CHOCH_2CH$_3$, *trans*), 3.53-3.48 (m, 1.5H, CHOCH_2CH$_3$, *trans* and *cis*), 2.39-2.35 (dd, J = 7.2 Hz, 17.2 Hz, 0.5H, CCH_2CHCOOEt, *cis*), 2.23 (m, 2.5H, CCH_2CHCOOEt, *trans* and *cis*), 1.35-1.15 (m, 9H, COOCH$_2$CH_3 and CHOCH$_2$CH_3, *trans* and *cis*), 0.02 (s, 13.5H, TMS, *trans* and *cis*) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 171.6, 133.2, 131.9, 94.7, 94.5, 66.2, 65.3, 64.6, 64.1, 61.1, 60.9, 28.9, 27.8, 15.0, 14.1, -2.6 ppm. MS (ESI): *m/z*= 295.2 [M+Na$^+$].

Equilibration of 7a-b in the presence of $ZnCl_2$. Synthesis of (2S,6S)-ethyl 6-ethoxy-4-(trimethylsilyl)-3,6-dihydro-2H-pyran-2-carboxylate 7a

Into an oven-dried round bottom flask equipped with magnetic stirbar and rubber septum was added **7a-b** (2:1 *trans/cis*, 147 mg, 0.5 mmol) dissolved in 2 mL CH_2Cl_2. The flask was then cooled to 0 °C (ice bath), and 22.5 mg $ZnCl_2$ was added. The flask was swirled to ensure all of the $ZnCl_2$ was in solution, and the reaction was stirred at r.t. for 24 h under an argon atmosphere. The solution was quenched with saturated $NaHCO_3$ and then extracted twice with ether. The combined ether layers were washed with brine, dried ($NaSO_4$), filtered and concentrated *in vacuo* (rotary evaporator). The obtained oil was purified via flash chromatography on silica gel (eluted with 10 % ethyl acetate-hexanes) to give 140 mg of *trans*-**7a**.

Yield: 95%. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 5.88 (s, 1H, C=C*H*CHOEt), 4.98 (s, 1H, CHC*H*OEt), 4.39-4.36 (m, 1H, C*H*COOEt), 4.18-4.11 (m, 2H, COOCH_2CH$_3$), 3.82-3.78 (m, 1H, CHOCH_2CH$_3$), 3.53-3.48 (m, 1H, CHOCH_2CH$_3$), 2.23 (m, 2H, CCH_2CHCOOEt), 1.35-1.15 (m, 6H, COOCH$_2$CH_3 and CHOCH$_2$CH_3), 0.02 (s, 9H, TMS) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 171.6, 131.9, 94.6, 94.5, 66.1, 63.7, 61.1, 28.9, 27.8, 15.0, 14.1, -2.6 ppm. MS (ESI): *m/z*= 295.2 [M+Na$^+$]. Anal. Calcd for $C_{13}H_{24}O_4Si$: C 57.32, H 8.88. Found: C 57.48, H 8.90.

Synthesis of ((2S,6S)-6-ethoxy-4-(trimethylsilyl)-3,6-dihydro-2H-pyran-2-yl)methanol 9

A solution of **7a** (121.0 mg, 0.45 mmol) in dry THF (35 mL) under argon at 0 °C (ice bath) was added with $LiAlH_4$ (35.0 mg, 0.90 mmol). The reaction mixture was warmed at r.t. and then stirred for 3h at the same temperature. Rochelle salt (40 mL) was then added carefully. The reaction mixture was stirred for additional 30 min. and finally extracted twice with AcOEt (20 mL). The combined organic phases were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (SiO_2) using 1:1 Et_2O/hexanes, as the eluent to yield the alcohol **9** (93 mg) as tan oil.

Yield: 82%. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 5.88 (s, 1H, C=C*H*CHOEt), 4.88 (s, 1H, CHC*H*OEt), 3.86 (m, 1H, C*H*CH$_2$OH), 3.79-3.75 (m, 1H, CHOCH_2CH$_3$), 3.67-3.65 (m, 1H, CHOCH_2CH$_3$), 3.55-3.45 (m, 2H, CHCH_2OH), 2.05-1.96 (m, 2H, CCH_2CH), 1.18-1.15 (m, 3H, CHOCH$_2$CH_3), 0.01 (s, 9H, TMS) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 141.2, 132.0, 94.4, 67.1, 65.2, 63.3, 27.4, 15.3, -2.6 ppm. MS (ESI): *m/z*= 253.3 [M+Na$^+$]. Anal. Calcd for $C_{11}H_{22}O_3Si$: C 57.35, H 9.63. Found: C 57.62, H 10.12.

Synthesis of (2R,3S,6S)-6-ethoxy-2-(hydroxymethyl)-4-(trimethylsilyl)-3,6-dihydro-2H-pyran-3-ol 10

A solution of **9** (105 mg, 0.46 mmol) in dry dioxane (7 mL) and pyridine (75 μL, 0.93 mmol) was treated with SeO_2 (102 mg, 0.92 mmol). The whole mixture was then refluxed for 2 h under argon atmosphere. The mixture was quenched with saturated $NaHCO_3$ and then extracted twice with AcOEt. The combined organic phases were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (SiO_2) using 1:1 Et_2O/hexanes, as the eluent to yield the diol **10** (57 mg) as tan oil.
Yield: 46%. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.02 (s, 1H, C=C*H*CHOEt), 4.95 (s, 1H, CHC*H*OEt), 3.92-3.87 (m, 3H, CC*H*OHCH and C*H*CH_2OH and CHCH_2OH), 3.83-3.76 (m, 2H, CHCH_2OH and CHOCH_2CH_3), 3.52-3.48 (m, 1H, CHOCH_2CH_3), 2.20 (br s, 1H, OH), 1.77 (br s, 1H, OH), 1.18 (m, 3H, CHOCH_2CH_3), 0.08 (s, 9H, TMS) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 142.5, 135.4, 94.2, 70.3, 64.2, 63.8, 63.2, 15.3, -1.7 ppm. MS (ESI): *m/z*= 269.2 [M+Na^+]. Anal. Calcd for $C_{11}H_{22}O_4Si$: C 53.62, H 9.00. Found: C 53.88, H 9.34.

Synthesis of (2R,3S,4R,6S)-6-ethoxy-2-(hydroxymethyl)-4-(trimethylsilyl)-tetrahydro-2H-pyran-3,4-diol 12

To a stirred solution of **10** (64 mg, 0.26 mmol) in THF with 10% of water, 4-methylmorpholine N-oxide (NMO) (30.4 mg, 0.26 mmol) was added. The solution was cooled to 0 °C, then OsO_4 (catalytic amount) was added and the reaction stirred at room temperature for 48 h. The mixture was concentrated under reduced pressure, diluted with ethyl acetate and extracted with AcOEt (2 x 12 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated. The crude product was purified by flash chromatography, using ethyl acetate/hexanes (1:1) as eluent to afford pure **12** (53 mg) as tan oil.
Yield: 68%. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 4.93 (s, 1H, CHC*H*OEt), 3.94-3.88 (m, 3H, H-2, H-5, CHCH_2OH,), 3.81-3.74 (m, 4H, CHOCH_2CH_3, H-4, CHCH_2OH, OH), 3.63 (m, 1H, CHOCH_2CH_3), 3.48-3.43 (m, 2H, OH), 3.31 (br s, 1H, OH), 1.21-1.15 (m, 3H, CHOCH_2CH_3), 0.07 (s, 9H, TMS) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 100.5, 71.8, 71.4, 69.2, 65.6, 64.4, 63.9, 14.9, -2.3 ppm. MS (ESI): *m/z*= 302.9 [M+Na^+]. Anal. Calcd for $C_{11}H_{24}O_6Si$: C 47.12, H 8.63. Found: C 47.45, H 8.87.

Synthesis of D,L-gulose ethyl glycoside 13

A solution of **12** (38.0 mg, 0.13 mmol) in anhydrous THF (10 mL) at 0 °C was added with TBAF (0.75 mL of an 1M solution in THF, 0.75 mmol). The mixture was stirred at room temperature for 3 hours. The mixture was quenched with saturated water and then extracted twice with AcOEt. The combined organic phases were washed with brine, dried over Na_2SO_4, filtered and concentrated

under reduced pressure. The crude product was purified by flash column chromatography (SiO_2) using 2:1 Et_2O/hexanes, as the eluent to yield the D,L-gulose ethyl glycoside **13** (30 mg) as tan oil. Yield: 74%. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 4.87 (m, 1H, CHC*H*OEt), 3.93 (m, 3H, H-2 and H-5 and C*H*$_2$OH), 3.82-3.75 (m, 3H, H-3 and H-4 and C*H*$_2$OH), 3.44-3.43 (m, 2H, CHOC*H*$_2$CH$_3$), 3.23 (m, 4H, OH), 1.19 (m, 3H, CHOCH$_2$C*H*$_3$) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$) δ 101.1, 74.4, 72.0, 67.2, 64.4, 63.6, 58.9, 19.7 ppm. MS (ESI): *m/z*= 321.1 [M+Na$^+$]. Anal. Calcd for $C_8H_{16}O_6$: C 46.15, H 7.75. Found: C 46.34, H 7.93.

4. Acknoledgements

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5. References

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8. A small amount of D,L-talose ethyl glycoside was formed during the dihydroxylation step as revealed by ^{1}H-NMR and 2D-NOESY analysis. The H-1 peak of talose was observed at 4.87 ppm.

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