Novel Route to L-Hexoses from L-Ascorbic Acid: Asymmetric Synthesis of L-Galactopyranose and L-Talopyranose

Preliminary Communication

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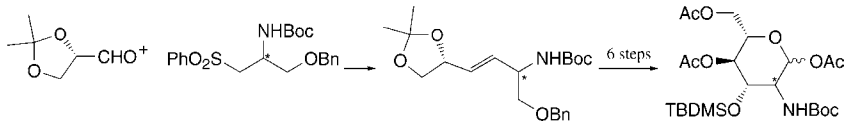
Dedicated to Professor *Duilio Arigoni* on the occasion of his 75th birthday

A novel route with L-ascorbic acid as a single common starting material to asymmetric synthesis of all eight diastereomers of L-hexoses is described. Assessment of this new approach is demonstrated by the expedient synthesis of L-galactopyranose and L-talopyranose derivatives. Key steps involve stereoselective preparation of chiral (*E*)- and (*Z*)-γ-hydroxy-α,β-unsaturated esters and their stereo-controlled dihydroxylation by OsO_4.

Introduction. – L-Sugars often play an essential role in physiological events of biologically active compounds, even though their occurrence in nature is rather rare compared with natural D-homologues [1][2]. However, limited natural sources and few efficient synthetic methods for this class of compounds have long hindered research on oligosaccharides and glycoconjugates of the L-sugars, in particular, L-hexoses (for recent asymmetric syntheses of L-hexoses, see [3]). Therefore, it is of great interest to develop a practical methodology that provides any one of the eight diastereoisomers. In this preliminary communication, we report a novel protocol for the synthesis of enantiomerically pure hexoses of L-configuration from L-ascorbic acid as a single starting material.

Results and Discussions. – *General Strategy.* Recently, we demonstrated that enantiomerically pure L-2-amino-2-deoxy hexoses can easily be prepared from (2*S*)-2,3-*O*-isopropylideneglyceraldehyde and L-serine-derived 2-amino-3-(phenylsulfonyl)-propan-1-ol derivatives (*Scheme 1*) [4].

Scheme 1. *Synthesis of* L-*2-Amino-2-deoxy Sugars*

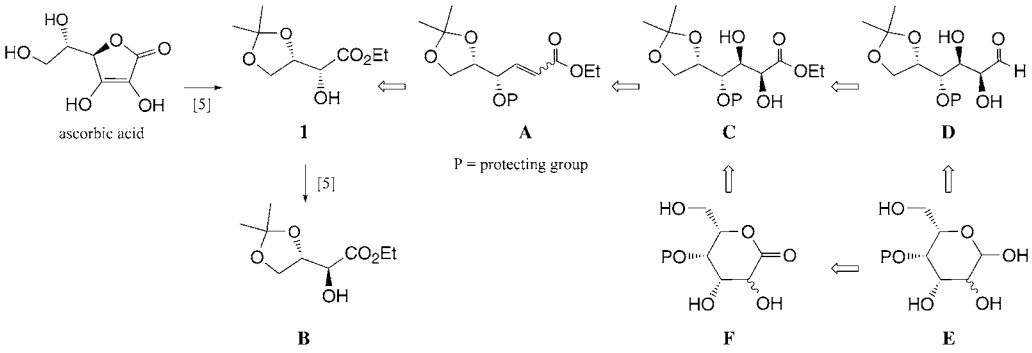


TBDMS = (*t*-Bu)Me_2Si

A similar approach is conceivable for the synthesis of L-hexoses when the ester **1** is transformed into γ-hydroxy-α,β-unsaturated ester **A**, a key chiral intermediate with specific (*E*)- or (*Z*)-configuration *via* a *Wittig* reaction or a *Horner–Emmons* reaction, respectively. It is reported that **1** is easily available from L-ascorbic acid in three steps, and that inversion at C(3) of **1** *via* the *Mitsunobu* reaction provides its (2*S*,3*S*)-diastereoisomer **B** [5]. In principle, stereoselective catalytic dihydroxylation of **A**

affords pentol **C**, which can be reduced into aldehyde **D**, followed by the regioselective removal of 5,6-*O*-protection to give hexose **E**. Alternatively, the pentol **C** can be cyclized to lactone **F** and in turn be reduced to hexose **E** (*Scheme 2*).

Scheme 2. *Retrosynthetic Plan for* L-*Hexoses*



Synthesis of L-*Galactopyranose.* Treatment of the ester **1** with TBDPSCl provided the TBDPS-protected ester **2** in 98% yield (*Scheme 3*). Reduction of **2** to the 1,2-*O*-isopropylidene tetrol **3** with $LiBH_4$ in anhydrous Et_2O was easily accomplished in 95% yield. Subsequent *Swern* oxidation of **3**, followed by the *Wittig* reaction with [(ethoxycarbonyl)methylidene]triphenylphosphorane ($Ph_3P{=}CHCO_2Et$) furnished α,β-unsaturated ester **5** in 80% yield (for two steps) as a single (*E*)-isomer. Having prepared the desired olefin **5** in *ca.* 75% overall yield, attention was turned to the stereoselective dihydroxylation. From our earlier experience, we anticipated that osmium-catalyzed dihydroxylation without a chiral auxiliary might proceed with high stereoselectivity and reaction rate [4]. To our delight, treatment of **5** with a catalytic amount of OsO_4 in the presence of 4-methylmorpholine *N*-oxide as the re-oxidant in the mixture of THF/H_2O 9 : 1 afforded the pentol **6** in 98% yield. The *anti*/*syn* ratio was *ca.* 50 : 1 judging from ^{1}H-NMR. The major *anti*-diastereoisomer was easily separated from its *syn*-isomer by silica-gel chromatography. The pentol **6** was then treated with 2,2-dimethoxypropane in acetone in the presence of a catalytic amount of TsOH to afford the fully protected pentol **7** in 90% yield. Reduction of the ester function of the pentol **7** with DIBAL in toluene at $-78°$ gave the aldehyde **8** in 95% yield. Regioselective removal of the 2,3-isopropylidene group of **8** by TFA in CH_2Cl_2, followed by treatment with Ac_2O, provided the L-galactopyranose **9** as a single β-anomer in 60% yield (for two steps)[1]). The configuration of the lactone **10**, obtained by heating the pentol **6** in $AcOH/H_2O$ 4 : 1 at 50° for 24 h, was established by X-ray crystallography as depicted in the *Figure.*

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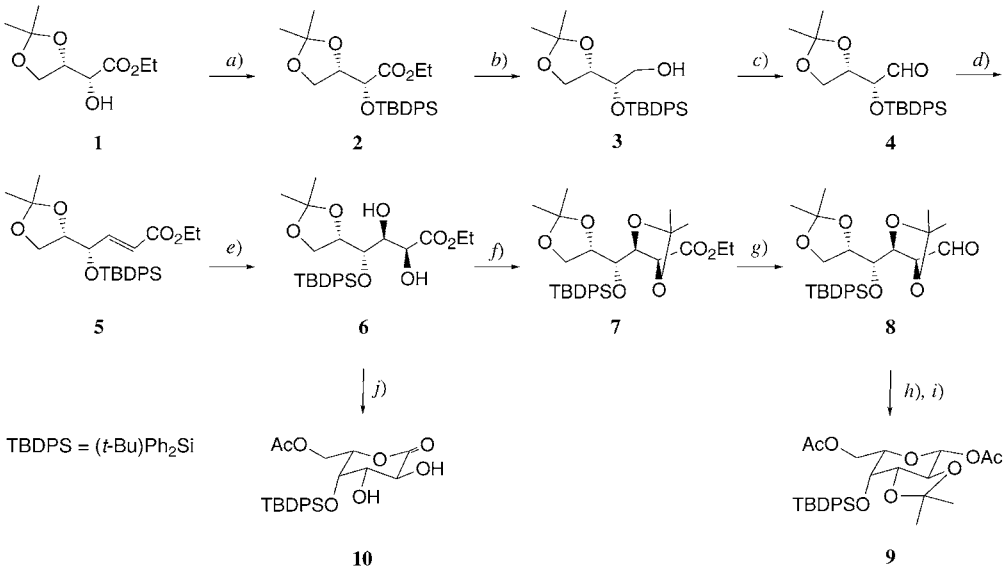
[1]) Data for L-galactopyranose **9**: $[\alpha]_D = +35.7$ ($c = 1.65$). IR (neat): 3480, 3073, 2934, 2859, 1753, 1590, 1472, 1428, 1371, 1227, 1155, 1114, 1088, 1059, 1013, 955, 935, 822, 757, 703, 608. ^{1}H-NMR 7.75 (*m*, 2 H); 7.65 (*m*, 2 H); 7.40 (*m*, 6 H); 5.90 (*d*, $J = 7.4$, H–C(1)); 4.70 (*dd*, $J = 7.4$, 9.6, H–C(2); 4.35 (*dd*, $J = 3.0$, 2.2, H–C(5)); 4.25 (*m*, H–C(3), H–C(4)); 4.05 (*d*, $J = 14.0$, H–C(6)); 3.68 (*dd*, $J = 2.2$, 14.0, H–C(6)); 2.18 (*s*, 3 H); 1.92 (*s*, 3 H); 1.46 (*s*, 3 H); 1.42 (*s*, 3 H); 1.14 (*s*, 9 H). ^{13}C-NMR 170.3; 169; 136.2; 135.9; 130.2; 130.0; 127.9; 111.2; 95.2 (C(1)); 76.2 (C(3)); 74.4 (C(2)); 71.9 (C(5)); 69.3 (C(4)); 60.1 (C(6)); 27.1; 27.0; 26.6; 21.4; 20.8; 19.4. ESI-MS: 579 ($[M + K]^+$), 565 ($[M + Na]^+$), 505.

Scheme 3. *Synthesis of 1,6-*O*-Diacetyl-2,3-*O*-isopropylidene-4-*O*-(tert-butyldiphenylsilyl)-*L*-galactopyranose* **9**



a) ^{t}BuPh$_2$SiCl (TBDPSCl), 1*H*-imidazole, DMF; 98%. *b*) LiBH$_4$, THF, 0°; 95%. *c*) (COCl)$_2$, DMSO, Et$_3$N, CH$_2$Cl$_2$, −78°. *d*) Ph$_3$P=CHCO$_2$Et, CH$_2$Cl$_2$; 80% (from **3**). *e*) OsO$_4$ (cat.), 4-methylmorpholine *N*-oxide (NMO), THF, 90 h; 98%. *f*) Me$_2$C(OMe)$_2$, TsOH (cat.), acetone; 90%. *g*) (Me$_2$CHCH$_2$)$_2$AlH (DIBAL), toluene, −78°; 95%. *h*) CF$_3$COOH (TFA)/CH$_2$Cl$_2$, 0°, 15 min. *i*) Ac$_2$O, Et$_3$N, 4-(dimethylamino)pyridine, CH$_2$Cl$_2$; 60% from **8**. *j*) AcOH/H$_2$O 4 : 1, 50°, 24 h; 50%.

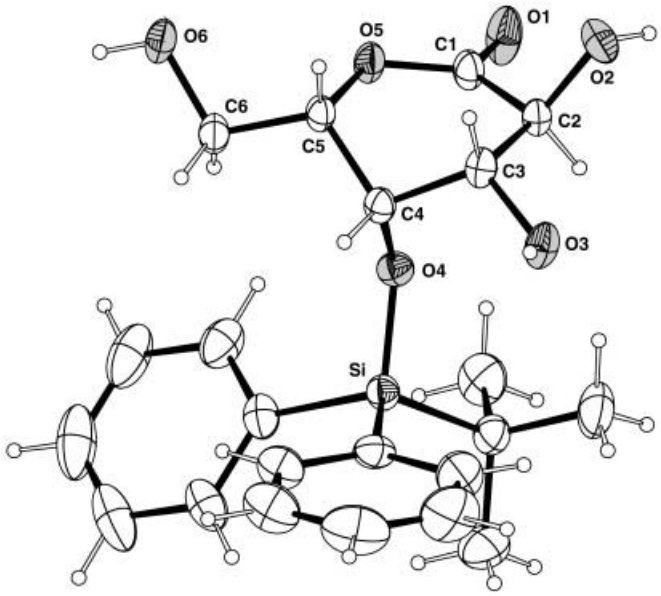
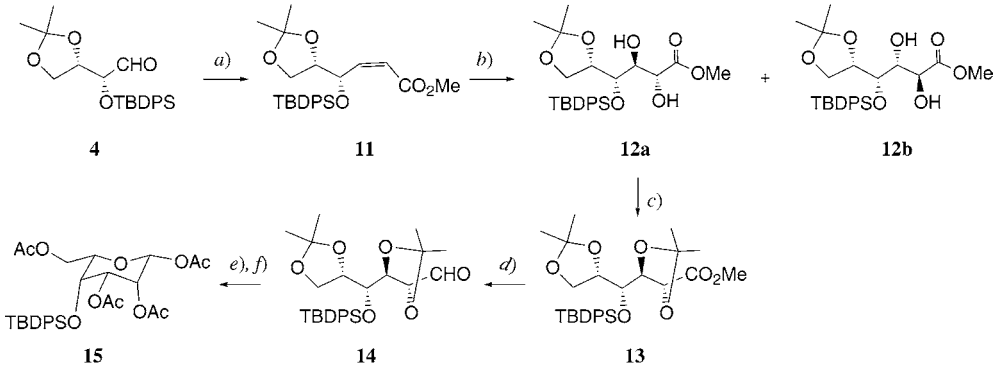


Figure. *X-Ray crystal structure of lactone* **10**

Synthesis of L-*Talopyranose.* Preparation of (*Z*)-α,β-unsaturated ester **11** was carried out by treatment of aldehyde **4** with bis(2,2,2-trifluoroethyl)(methoxycarbonylmethyl)phosphonate $(CF_3CH_2O)_2POCH_2CO_2Me$ (*Horner–Emmons* condition) in the presence of 18-crown-6 and $KN(TMS)_2$ in THF at $-78°$ to afford **11** in 85% yield (*Scheme 4*). Although (*Z*)-configured alkenes are reported to give higher levels of *anti*-selectivity than (*E*)-isomers [6], the same oxidation conditions used for the preparation of **6** provided a mixture of pentols **12a** and **12b** with a rather disappointing *anti*/*syn* ratio of 2.3:1 in 87% yield. The major *anti*-diastereoisomer was separated from its *syn*-diastereoisomer with ease by silica-gel chromatography, affording the pure *anti*-**12a** in 54% yield. The desired diastereoisomer **12a** was converted to the fully protected pentol ester **13** that was, in turn, reduced to the aldehyde **14** with DIBAL in toluene at $-78°$ (77% yield for two steps). Formation of the pyranose system was accomplished by treatment of **14** with catalytic amount of TFA in CH_2Cl_2 at 0° for 3 h, followed by acetylation. The last two-step sequence provided the L-talopyranose derivative **15** as a single β-anomer in 60% yield[2]).

Scheme 4. *Synthesis of 1,2,3,6-Tetra*-O-*acetyl-4*-O-*[(*tert-*butyl)diphenylsilyl]*-L-*talopyranose* **15**



a) $(CF_3CH_2O)_2POCH_2CO_2CH_3$, 18-crown-6, $KN(TMS)_2$, THF, $-78°$; 85%. *b*) OsO_4 (cat.), NMO, THF, 90 h; 54% (*anti*-**14**). *c*) $Me_2C(OMe)_2$, TsOH (cat.), acetone; 85%. *d*) $(Me_2CHCH_2)_2AlH$, toluene, $-78°$; 95%. *e*) TFA/CH_2Cl_2, 0°, 15 min. *f*) Ac_2O, Et_3N, 4-(dimethylamino)pyridine, CH_2Cl_2; 60% from **14**.

Conclusions. – We have developed an expedient route to asymmetric synthesis of L-hexoses starting from the ascorbic acid-derived ester **1**. The versatility of our method for the syntheses of the different L-hexopyranoses is demonstrated simply by changing the reagents used for the preparation of (*E*)- and (*Z*)-α,β-unsaturated esters, **5** and **11**, respectively. Furthermore, it is noteworthy that stereoselective dihydroxylation of the

[2]) Data for L-talopyranose **15**: $[\alpha]_D = +24.8$ ($c = 1.6$): IR (neat): 3481, 3073, 3019, 2934, 2860, 1755, 1473, 1428, 1370, 1228, 1138, 1113, 1073, 925, 822, 757, 704, 667, 611. ^{1}H-NMR 7.65 (*m*, 4 H); 7.40 (*m*, 6 H); 5.95 (*d*, $J = 7.3$, H–C(1)); 5.37 (*d*, $J = 3.2$, H–C(2)); 5.33 (*dd*, $J = 3.2$, 7.7, H–C(3)); 4.20 (*dd*, $J = 7.9$, 11.1, H–C(6)); 4.05 (*ddd*, $J = 1.3$, 4.3, 7.6, H–C(5)); 3.95 (*dd*, $J = 4.3$, 11.1, H–C(6)); 3.82 (*dd*, $J = 1.3$, 4.3, H–C(4)); 2.15 (*s*, 3 H); 1.97 (*s*, 3 H); 1.92 (*s*, 6 H), 1.13 (*s*, 9 H): ^{13}C-NMR: 170.5; 169.2; 136.1; 132.1; 130.2; 130.1; 127.9; 90.4 (C(1)); 73.4 (C(5)); 69.9 (C(2)); 68.7 (C(4)); 67.5 (C(3)); 63.1 (C(6)); 27.1; 27.0; 21.1; 21.4; 20.8; 20.7; 20.6; 19.5. ESI-MS: 609 ($[M + Na]^+$).

α,β-unsaturated esters such as **5** and **11** with the free OH group at C(4) in *syn*-selective manner can widen the scope of the present approach [7].

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