Intramolecular Tishchenko Reactions of Protected Hexos-5-uloses: a Novel and Efficient Synthesis of L-Idose and L-Altrose

M. Adinolfi, G. Barone, F. De Lorenzo, A. Iadonisi*

Dipartimento di Chimica Organica e Biologica, Università degli Studi Federico II, Via Mezzocannone 16, I-80134 Napoli, Italy
Fax +39 0815521217; E-mail iadonisi@unina.it

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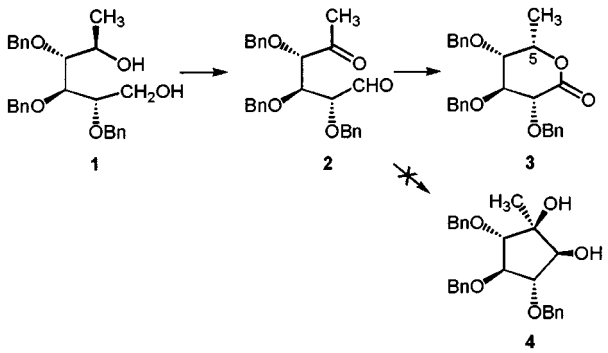
Abstract: Protected *t*-butyl esters of aldonic acids with the rare L-*ido* and L-*altro* configuration can be effectively obtained by a diastereoselective Tishchenko reaction of hexos-5-uloses induced by *t*-BuOSmI$_2$. These compounds can be easily converted into the corresponding protected lactones and free sugars.

Key words: Tishchenko reaction, trivalent samarium reagents, L-idose, L-altrose, aldonic acids *t*-butyl esters

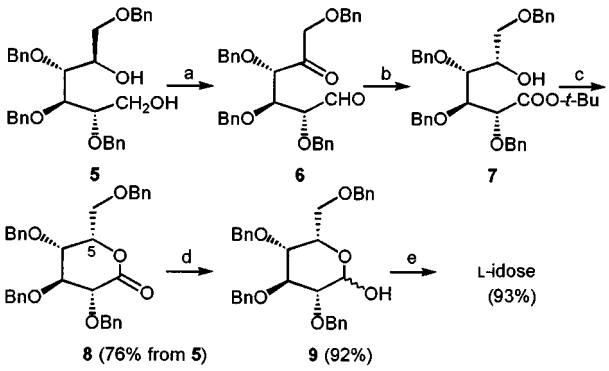
During our synthetic studies toward the monosaccharide caryose[1] the fully diastereoselective formation of 2,3,4-tri-*O*-benzyl-6-deoxy-L-iditono-1,5-lactone **3** rather than the expected pinacolic condensation[2] to the desired diol **4** was observed when 2,3,4-tri-*O*-benzyl-6-deoxy-D-*xylo*-hexos-5-ulose **2**, obtained by Swern oxidation of alditol **1**, was treated with an old commercial solution of SmI_2 in THF (Scheme 1).



Scheme 1

Actually, the use of trivalent samarium reagents, and in particular *t*-BuOSmI$_2$, for the conversion of 1,5-ketoaldehydes into δ-lactones through an intramolecular Tishchenko oxidoreduction had been already reported by Uenishi.[3] Interestingly however, lactone **3** presented the opposite configuration at its 5 position with respect to alditol **1** from which it was generated. Thus an intramolecular Tishchenko reaction could be potentially exploited as the key-step for a straightforward synthesis of rare L-sugars such as Lidose, L-gulose and L-altrose starting from suitably protected alditols easily obtained from D-glucose, D-mannose and D-galactose, respectively. These rare L-sugars are synthetic targets of current interest.[4] Taking advantage of our recently reported[5] general approach for the preparation of 2,3,4,6-tetra-*O*-benzyl-hexos-5-uloses, we explored the proposed path.

Aldulose **6** was first generated from 2,3,4,6-tetra-*O*-benzyl-D-glucitol **5** through a double Swern oxidation, and then treated with *t*BuOSmI$_2$ (5 eq.) following a one-pot procedure.[6] Under these conditions *t*-butyl ester **7**, possessing the desired L-*ido* configuration, was obtained in place of lactone **8**. Lactonization of **7** was easily accomplished in a further step by acid treatment (Scheme 2).

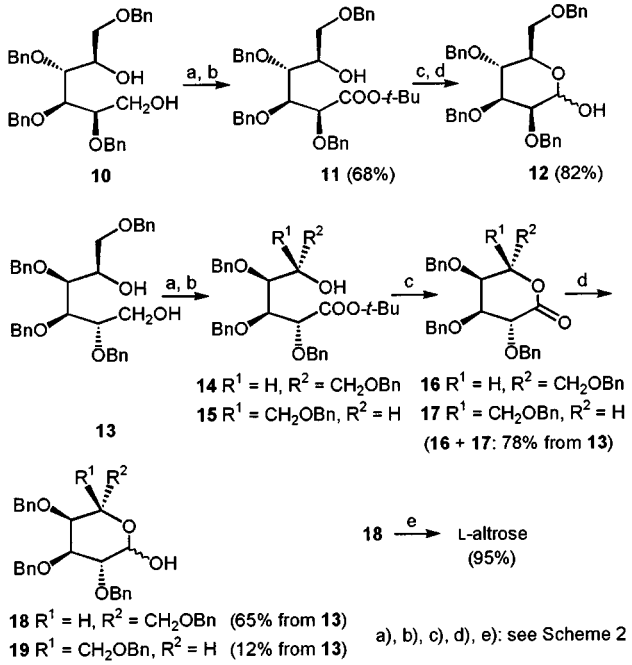


a) Swern oxidation $(COCl)_2$/DMSO/Et_3N in THF; b) *t*-BuOSmI$_2$, THF; c) 1:1 CF_3COOH/CH_2Cl_2, 0 °C, 30 min; d) DIBAL (1.1 eq), toluene, -70 °C, 1h; e) C-Pd, 1:9 HCOOH-CH_3OH, sonication, 2h.

Scheme 2

However, disappointing yields were achieved (35% of **7** from **5** after 36 h at r.t. or 25% after 2 h at reflux), probably due to interference of triethyl ammonium salts produced by the Swern oxidation in the reaction. As a matter of fact, when the salts were removed by centrifugation under argon prior to the Tishchenko step only 2.5 eq of *t*BuOSmI$_2$ in THF at room temperature (12 hours) were needed to afford almost pure *t*-butyl ester **7** (^{1}H NMR).[7,9] This compound was directly submitted to lactonization, reduction and debenzylation[10] to give L-idose with an overall 65% yield from **5**.[9, 11]

The optimized procedure was then applied to protected D-mannitol **10** and D-galactitol **13**. In the first case we observed that the Tishchenko reaction furnished almost exclusively *t*-butyl ester **11** having the *manno* configuration as demonstrated by its conversion into a product having spectroscopic properties identical with authentic 2,3,4,6-tetra-*O*-benzyl-D-mannopyranose **12** (Scheme 3).



10 **11** (68%) **12** (82%)

13

14 R^1 = H, R^2 = CH_2OBn **16** R^1 = H, R^2 = CH_2OBn

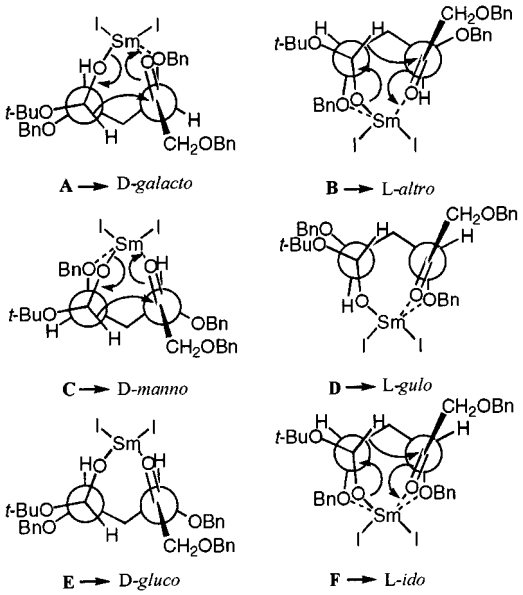
15 R^1 = CH_2OBn, R^2 = H **17** R^1 = CH_2OBn, R^2 = H

(**16** + **17**: 78% from **13**)

18 R^1 = H, R^2 = CH_2OBn (65% from **13**)

19 R^1 = CH_2OBn, R^2 = H (12% from **13**)

Scheme 3



Scheme 4

In the case of *galacto* precursor **13**, the sequence of Swern oxidation/Tishchenko reaction afforded a 5:1 mixture of *t*-butyl esters **14**[9] and **15** having the L-*altro* and D-*galacto* configuration, respectively. The subsequent lactonization afforded an unseparable mixture of compounds **16**[9] and **17** (78% overall yield from **13**) which was submitted to reduction with DIBAL. The resulting epimeric hemiacetals could be separated by silica gel chromatography to yield the L-*altro* and D-*galacto* derivatives **18**[9] and **19** (65 and 12% yield from **13,** respectively). Debenzylation of **18** afforded L-altrose[11] free from any detectable (NMR) amount of 1,6-anhydro-β-L-altropyranose though the deprotection implied an acid treatment.[4a]

A possible explanation of the observed diastereoselectivities of the Tishchenko step can be based on the model proposed by Uenishi.[3] However, the extensive presence of benzyloxy groups on the chain of the studied sugar derivatives must be considered. As shown in Scheme 4, the conversion of *galacto* derivative **13** to ester **14** can occur through the samarium complex **B** rather than **A**, both complexes being stabilized by further coordination of samarium to the oxygen atoms of the adjacent benzyloxy substituents, but the latter being disfavoured by some eclipsing of 1-O-*t*-Bu and 2-OBn groups. Similarly, intermediate **C** should be favoured over intermediate **D** in the reversion of *manno* derivative **10** to *manno* ester **11**, and intermediate **F** over intermediate **E** in the conversion of *gluco* derivative **5** to L-*ido* ester **7**.

In summary, Tishchenko reaction of hexos-5-uloses has been shown to proceed in a highly stereoselective fashion. The reaction has been exploited as the key-step of a convenient synthesis of L-idose and L-altrose and leads to useful synthons such as *t*-butyl esters of aldonic acids.

Acknowledgement

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References and Notes

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(4) a) So, Y. K.; Lee, A. W. M.; Masamune, S.; Reed III, L. A., Sharpless, K. B., Walker, F. J. *Tetrahedron* **1990**, *46*, 245. b) Dondoni, A.; Marra, A.; Massi, A. *J. Org. Chem.* **1997**, *62*, 6261 and references therein.
(5) Adinolfi, M.; Barone, G.; Iadonisi, A.; Mangoni, L. *Tetrahedron Lett.* **1998**, *39*, 2021.
(6) Isolation of aldulose **6** was avoided because of the easy hydration of hexos-5-uloses (ref. 5 and 7). However, the pure aldehyde form can be obtained (Boiron, A.; Zillig, P.; Faber, D.; Giese, B. *J. Org. Chem.* **1998**, *63*, 5877) by removing water over molecular sieves.
(7) In a typical procedure compound **5** (162 mg, 0.3 mmol) was submitted to Swern oxidation in THF at -60 °C as previously reported,[5] but in a centrifugation tube closed with a rubber septum. The clear solution obtained after centrifugation was transferred *via cannula* with an argon stream to a 0.1 M THF solution of *t*-BuOSmI_2[8] (7.5 mL, 0.75 mmol) and stirred at r.t. for 12 hours. The reaction mixture was added with few drops of acetic acid and filtered through a short column of 1:1 Celite/Florisil to remove the samarium salts and to give almost pure **7**. This compound was directly submitted to lactonization (1:1 CF_3COOH/CH_2Cl_2, 0°C, 30 min). Usual work-up and chromatography on Florisil ($CHCl_3$) gave pure **8** (122 mg, 76% from **5**).
(8) Namy, J. L.; Souppe, J.; Collin, J.; Kagan, H. B. *J. Org. Chem.* **1984**, *49*, 2045.

(9) Selected physical data. **7**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.48 (9H, s, -C(CH_3)$_3$), 2.50 (1H, d, exchanges with D_2O, $J_{OH,H-5}$ = 7.1 Hz, 5-OH), 3.36 (1H, dd, $J_{6a,6b}$ = 9.7 Hz, $J_{5,6a}$ = 6.1 Hz, H-6a), 3.47 (1H, dd, $J_{5,6b}$ = 6.3 Hz, H-6b), 3.75 (1H, m, H-5), 3.89 (1H, dd, $J_{4,5}$ = 2.9 Hz, $J_{3,4}$ = 6.9 Hz, H-4), 4.15 (1H, d, $J_{2,3}$ = 3.5 Hz, H-2), 4.37-4.87 (4 x benzylic CH_2), 7.15-7.40 (aromatic protons). ^{13}C NMR δ 28.2 (-C(*C*H$_3$)$_3$), 69.4, 71.3, 72.9, 73.2, 74.9, 77.1 78.2, 78.4, 80.3, 82.1 (C-2, C-3, C-4, C-5, C-6 and 4 x benzylic CH_2 and -*C*(CH$_3$)$_3$), 127.5-128.6 (aromatic CH), 137.2-138.3 (quaternary aromatic carbons), 169.7 (C-1).
8: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.65 (1H, dd, $J_{6a,6b}$ = 10.0 Hz, $J_{5,6a}$ = 5.3 Hz, H-6a), 3.79 (1H, dd, $J_{5,6b}$ = 5.6 Hz, H-6b), 3.79 (1H, t, $J_{3,4}$ = $J_{4,5}$ = 1.7 Hz, H-4), 3.93 (1H, dd, $J_{2,3}$ = 6.6 Hz, H-3), 4.17 (1H, d, H-2), 4.32-5.07 (4 x benzylic CH_2 and H-5), 7.2-7.5 (aromatic protons). ^{13}C NMR δ 67.9, 71.3, 72.4, 73.3, 73.5, 75.2, 75.9, 78.5, 79.9 (C-2, C-3, C-4, C-5 and C-6 and 4 x benzylic CH_2), 128-129 (aromatic CH), 137.3-137.7 (quaternary aromatic carbons), 169.4 (C-1).
9 was obtained as an anomeric mixture. ^{1}H NMR (400 MHz, $CDCl_3$) anomeric protons at δ 4.94 (1H, d, J = 2.3 Hz) and 5.18 (1H, d, J = 2.8 Hz). ^{13}C NMR (DEPT) δ 66.6, 71.9, 72.5, 73.3, 73.8, 74.5, 74.5, 75.7 (C-2, C-3, C-4, C-5), 68.2, 68.4, 72.2, 72.2, 72.3, 72.3, 72.4, 72.8, 72.9 and 72.9 (C-6 and 4 x benzylic CH_2), 91.7 and 93.2 (C-1).
14: ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.46 (9H, s, -C(CH_3)$_3$), 3.60 (1H, dd, $J_{6a,6b}$ = 10.9 Hz, $J_{5,6a}$ = 3.5 Hz, H-6a), 3.67 (1H, dd, $J_{5,6b}$ = 7.0 Hz, H-6b), 3.79 (1H, t, $J_{3,4}$ = $J_{4,5}$ = 5.8 Hz, H-4), 4.11 (1H, dd, $J_{2,3}$ = 4.6 Hz, H-3), 4.14 (1H, m, 5-H), 4.26 (1H, d, H-2), 4.35-4.80 (4 x benzylic CH_2), 7.15-7.40 (aromatic protons).
16: ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.71 (2H, d, $J_{5,6}$ = 4.8 Hz, H-6), 4.05 (1H, dd, $J_{3,4}$ = 2.2 Hz, $J_{4,5}$ = 5.9 Hz, H-4), 4.18 (1H, dd, $J_{2,3}$ = 5.9 Hz, H-3), 4.28 (1H, d, H-2), 4.55-5.00 (4 x benzylic CH_2 and H-5), 7.15-7.40 (aromatic protons). ^{13}C NMR δ 68.7, 72.1, 72.5, 72.8, 73.5, 73.5, 74.5, 75.6, 78.1 (C-2, C-3, C-4, C-5, C-6 and 4 x benzylic CH_2), 128-129 (aromatic CH), 137.3-137.7 (quaternary aromatic carbons), 168.8 (C-1).
18 was obtained as an anomeric mixture. Selected data: ^{1}H NMR (250 MHz, $CDCl_3$, exchanged with D_2O) anomeric protons at 5.05 (1H, d, J = 1.4 Hz) and 5.10 (1H, bs). ^{13}C NMR (DEPT) δ 67.1, 72.2, 72.5, 72.7, 74.6, 74.6, 74.8, 76.8 (C-2, C-3, C-4, C-5), 69.3, 69.4, 71.9, 72.0, 72.2, 73.2, 73.2, 73.6, 73.6, 74.1 (C-6 and 4 x benzylic CH_2), 91.9 and 93.1 (C-1).
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(11) L-idose and L-altrose prepared by the above procedure displayed ^{1}H and ^{13}C NMR spectra as reported.[12, 13]
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