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Highly Selective Synthesis of Aldonolactones from Protected Alditols by Ruthenium Complex-Catalyzed Dehydrogenation. A Method of Converting Aldopentoses to Their Stereoisomers

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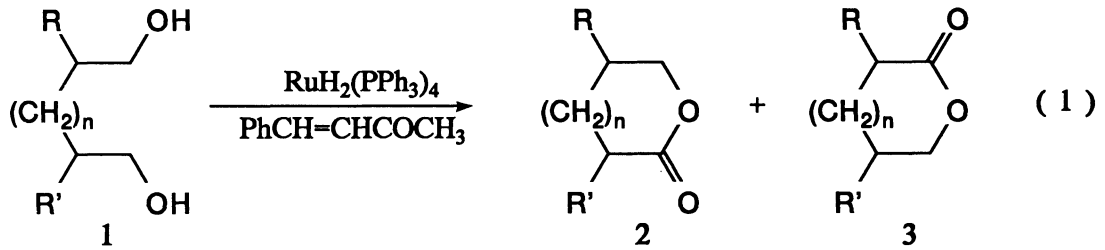
Highly selective hydrogen transfer reaction of substituted diols catalyzed by $RuH_2(PPh_3)_4$ was applied to the conversion of aldopentoses into their stereoisomers via protected pentitols. Thus, the selective transformations of L-arabinose and L-ribose into protected L-lyxonolactone and D-ribonolactone, respectively, were achieved.

Ruthenium complex catalyzed hydrogen transfer reactions are adaptable for preparing a lactone from a diol.[1-3] Among these reactions, the dehydrogenation catalyzed by $RuH_2(PPh_3)_4$ (PPh_3 = triphenylphosphine) provides a unique oxidation method of obtaining substituted lactones from 2-substituted 1,4- or 1,5-diols with high selectivity under very mild conditions.[3] The Eq.1 exemplifies the dehydrogenation of 2-substituted diol **1a** to produce the lactone isomers **2a** and **3a**, where the product ratio **2a:3a** is higher than 9:1 regardless of the substituent examined. The selectivity was attributed to the steric effect of the substituent R, which dramatically reduces the reactivity of the adjacent hydroxy group compared to that of the remote one.

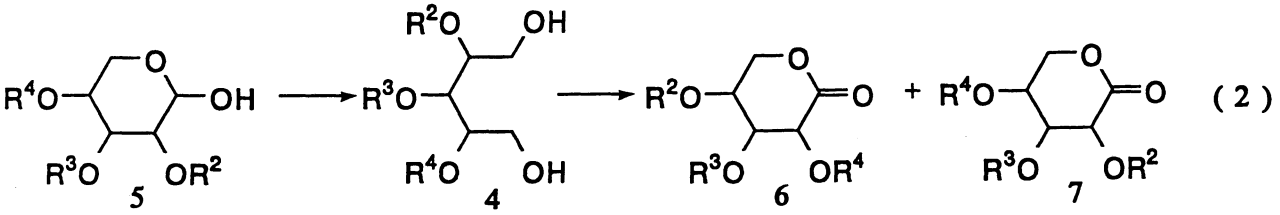


1 2 3 (1)

a: R= alkyl, phenyl, or alkoxy, R'= H

b: R, R'= alkyl or alkoxy n= 0 or 1

The selective dehydrogenation of disubstituted diols such as **1b** (R, R' = alkyl or alkoxy) is an interesting and significant extension of this lactonization. When the substituent R is bulkier than R', lactone **2b** is expected to be

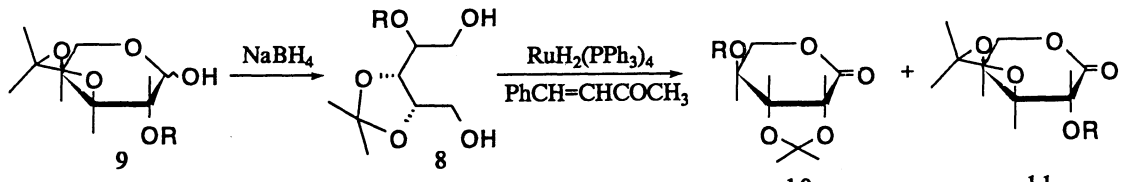


(2)

formed in preference to **3b**. In this respect, we examined the dehydrogenation of a protected alditol **4** having different protecting groups R^2, R^3, and R^4 at secondary hydroxy groups, as **4** is readily available by reducing a properly protected pentose **5** (Eq.2). Among the protecting groups, R^2 and R^4 should play a decisive role in the selective formation of **6** or **7**, but R^3, remote from the center of the reaction site, is considered less significant. If R^2 is considerably bulkier than R^4, the aldonolactone **6** will be produced over **7** applying the same reasoning as in the conversion of **1a** to **2a**. The lactone skeleton of **6** has the reverse sequence of asymmetric carbon centers to that in the starting pentose **5**, while **7** has the same. Hence the process shown in Eq.2 serves as a possible method of converting an aldopentose into its stereoisomer via the lactone **6**. The process should be particularly useful when the starting pentose **5** is naturally abundant and the product **6** is rare.

At first dehydrogenation of a protected L-arabinitol **8a**, prepared from a protected L-arabinose **9a**,[4] was explored under lactonization conditions[5] at room temperature for 48 h, and a mixture of lactones **10a** and **11a** was quantitatively obtained.[6] The product ratio **10a:11a** determined by 400 MHz ^{1}H NMR analysis was 63:37. This indicates that the benzyloxy group is sterically bulkier than the isopropylidene moiety for the ruthenium catalyst, although the difference in bulkiness is insufficient to effect highly selective formation of **10a** in preference to **11a**. Significant is the fact that **10a** has the rarely found L-lyxose arrangement.

Keeping the isopropylidene part unchanged, the introduction of a much bulkier protecting group R into **8** in place of the benzyl group seemed to improve the selective formation of **10**. Since the tetrahydropyranyl group was found to give no improvement in the product selectivity, we examined the use of a bulkier protecting group, that is, t-butyldimethylsilyl (TBS) group (Eq.3). The protected L-arabinitol **8b**, obtained by reducing the corresponding protected sugar **9b**,[7] was



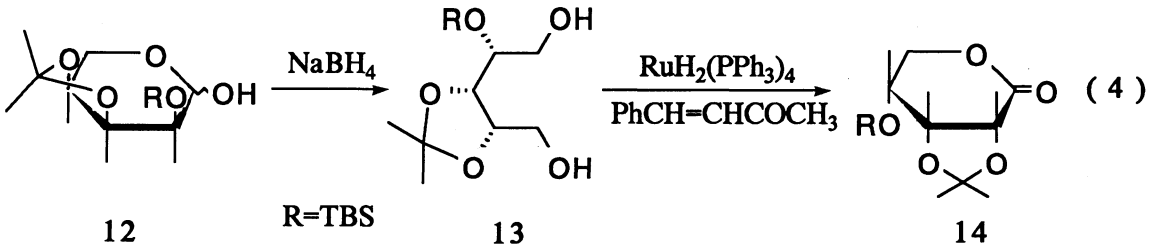
(3)

a: R=$CH_2C_6H_5$
b: R=$Si(CH_3)_2(C(CH_3)_3)$

dehydrogenated at 50 °C for 24 h to afford exclusively the lactone **10b**[6] (isolated yield; 84%). The presence of **11b** in the product could not be detected by ^{1}H NMR analysis. Since the treatment of **10b** with diisobutylaluminum hydride (DIBAH) should give rise to the corresponding pyranose, the conversion of L-arabinose into L-lyxose was achieved with excellent selectivity.

The above transformation (Eq.3) is a process of exchanging the terminal functional groups at C_1 and C_5; i.e., the formyl (C_1) and hydroxymethyl (C_5) groups of L-arabinose are converted respectively into the hydroxymethyl and formyl groups of L-lyxose. Such exchange of the terminal groups of aldoses is classified into two categories, depending on the stereochemical property of the intermediary alditols. When an alditol is chiral as is the case of arabinitol, the process results in the transformation of a parent aldose into a diastereomeric one. However, in the case of meso alditols such as xylitol and ribitol, the process corresponds to the conversion of an aldose to its enantiomer.

The conversion of a protected L-ribose to its antipodal lactone shown in Eq.4 belongs to the latter category mentioned above. The appropriately protected L-ribopyranose **12**[7] was reduced with $NaBH_4$, and the protected ribitol **13** thus obtained was dehydrogenated under the same condition as for **8b**.[5] As expected, the protected D-ribonolactone **14**[8] was obtained as the sole product in 75% isolated yield.



The conversion of aldopentoses into stereoisomers was successfully carried out as described above. This also demonstrates that the $RuH_2(PPh_3)_4$ catalyzed selective lactonization would be generally applicable to the conversion of 2,4-disubstituted 1,5-diols into 2,4-disubstituted δ-valerolactones. It is expected further that high selectivities will be achievable for the lactonizations of 2,3-disubstituted 1,4-diols (Eq.1, n = 0), when the difference in steric bulkiness between the substituents R and R' is sufficient. Further studies on the selective lactonization with ruthenium catalysts are in progress.

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4) 2-O-Benzyl-3,4-O-isopropylidene-L-arabinopyranose **9a** was prepared from 2-O-benzyl-L-arabinose by the method of Meslard et al. (J. C. Meslard, F. Subia, J. P. Vairon, A. Guy, and R. Garreau, Bull. Soc. Chim. Fr., 1985, 84). **9a** (major anomer): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.35 (s, 3H), 1.43 (s, 3H), 3.11 (broad d, 1H, J = 4.9 Hz), 3.60 (dd, 1H, J = 6.1, 3.5 Hz), 3.85 (dd, 1H, J = 13.1, 1.8 Hz), 4.13 (dd, 1H, J = 13.1, 2.9 Hz), 4.23-4.24 (m, 1H), 4.38 (fortuitous t, 1H, J = 6.1, 6.1 Hz), 4.68 (1H) and 4.80 (1H), (AB, J = 11.9 Hz), 5.14 (unresolved dd, 1H, J = 4.9, 3.5 Hz), 7.26-7.38 (m, 5H). **8a** was obtained by reducing **9a** with $NaBH_4$ in ethanol.

5) Reaction conditions for dehydrogenation: Protected alditol (5 mmol), 4-phenyl-3-buten-2-one (10.5 mmol), and $RuH_2(PPh_3)_4$ (0.2 mmol) were dissolved in toluene (5 cm^3), and the solution was stirred at room temperature or at 50° C until no alditol could be detected by TLC. The solvent was evaporated off, and the residue was distilled under reduced pressure on a Kugelrohr apparatus to remove any volatile materials. Then the product was purified by column chromatography.

6) **10a** (4-O-benzyl-2,3-O-isopropylidene-L-lyxono-δ-lactone); ^{1}H NMR ($CDCl_3$) δ 1.38 (s, 3H), 1.51 (s, 3H), 3.73 (ddd, 1H, J = 4.7, 3.3, 1.8 Hz), 4.33 (ddd, 1H, J = 11.9, 4.7, 1.6 Hz), 4.47 (dd, 1H, J = 11.9, 1.8 Hz), 4.54 (ddd, 1H, J = 7.0, 3.3, 1.6 Hz), 4.61 and 4.69 (AB, 2H, J = 11.9 Hz), 4.67 (d, 1H, J = 7.0 Hz), 7.25-7.39 (m, 5H); IR (KBr) 1745 cm^{-1} (C=O).
11a (2-O-benzyl-3,4-O-isopropylidene-L-arabinono-δ-lactone); ^{1}H NMR ($CDCl_3$) δ 1.34 (s, 3H), 1.44 (s, 3H), 4.15 (d, 1H, J = 3.0 Hz), 4.36 (dd, 1H, J = 12.2, 2.1 Hz), 4.49 (ddd, 1H, J = 7.5, 2.4, 2.1 Hz), 4.57 (dd, 1H, J = 7.5, 3.0 Hz), 4.56 and 4.72 (AB, 2H, J = 11.6 Hz), 4.72 (dd, 1H, J = 12.2, 2.4 Hz), 7.31-7.39 (m, 5H); IR (KBr) 1745 cm^{-1} (C=O).
10b (4-O-(t-butyldimethylsilyl)-2,3-O-isopropylidene-L-lyxono-δ-lactone); ^{1}H NMR ($CDCl_3$) δ 0.10 (fortuitous s, 6H), 0.91 (s, 9H), 1.39 (s, 3H), 1.47 (s, 3H), 3.94 (dd, 1H, J = 10.8, 6.6 Hz), 3.98 (dd, 1H, J = 10.8, 6.0 Hz), 4.52 (fortuitous dt, 1H, J = 6.6, 6.0, 2.4 Hz) 4.81 (unresolved, 2H); IR (KBr) 1772 cm^{-1} (C=O).

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8) **14** (4-O-(t-butyldimethylsilyl)-2,3-O-isopropylidene-D-ribono-δ-lactone); ^{1}H NMR ($CDCl_3$) δ 0.06 (s, 3H), 0.07 (s, 3H), 0.87 (s, 9H), 1.39 (s, 3H), 1.48 (s, 3H), 3.80 (dd, 1H, J = 11.4, 1.4 Hz), 3.89 (dd, 1H, 11.4, 2.0 Hz), 4.60 (m, 1H), 4.71 and 4.73 (AB, 2H, J = 5.5 Hz); IR (KBr) 1776 cm^{-1} (C=O).

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