

Titanium (IV) Promoted Rearrangement of 6-Deoxy-hex-5-enopyranosides into Cyclohexanones

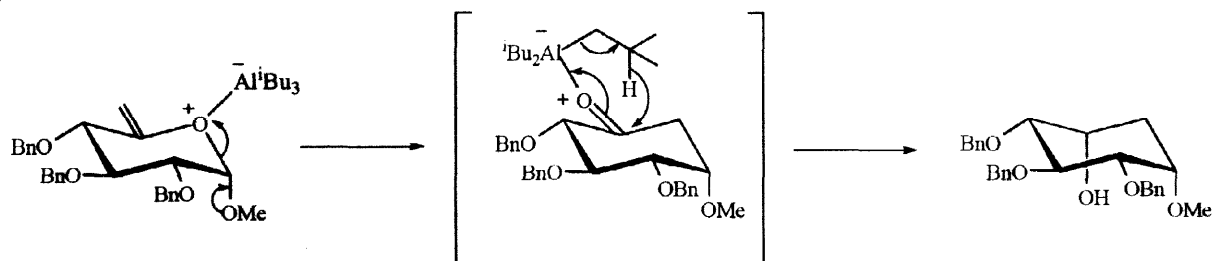
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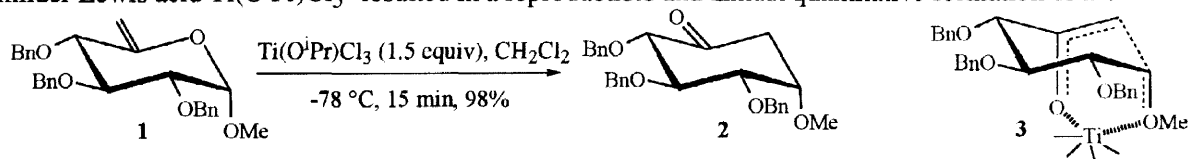
Abstract: The Lewis acid $Ti(O^iPr)Cl_3$ was found to mediate under very mild conditions ($-78\text{ }^\circ\text{C}$) the high-yielding (82-98%) rearrangement of benzylated 6-deoxy-hex-5-enopyranosides of the α -D-*gluco*, *galacto* and *manno* series into substituted cyclohexanones. © 1998 Published by Elsevier Science Ltd. All rights reserved.

We have recently reported¹ the triisobutylaluminum-assisted reductive rearrangement of 6-deoxy-hex-5-enopyranosides as an entry to substituted cyclohexane derivatives². As depicted in scheme 1, the first step of this reaction involves an *endo*-cleavage of glycosidic bond. A distinctive feature of this novel rearrangement in carbohydrate chemistry - in contrast with the classical Ferrier-II reaction³ - is thus the non-cleavage of the glycosidic bond.

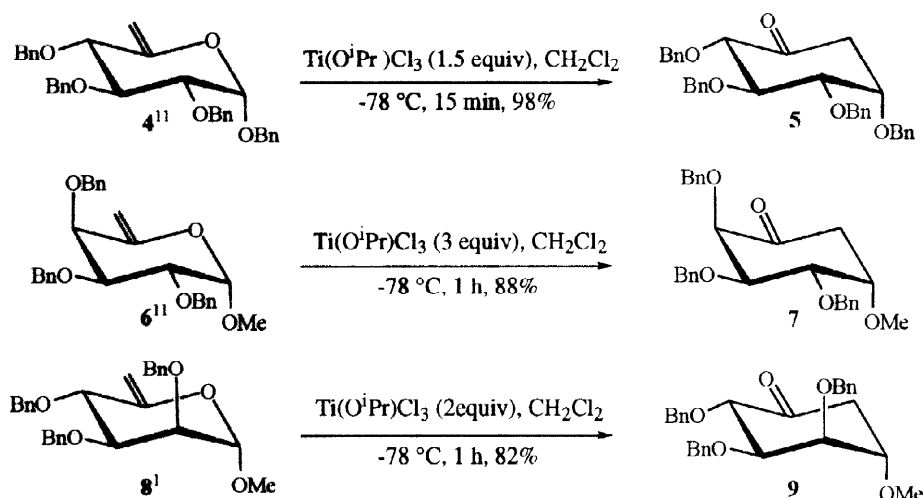


Scheme 1 : Reagent and conditions¹ : Al^iBu_3 (4 equiv), toluene, $40\text{ }^\circ\text{C}$, 6 h, 79%.

Our initial choice of triisobutylaluminum as a Lewis acid stemmed from some related precedents in non carbohydrate organic chemistry⁴. We now turned our attention to titanium (IV) chloride, which is known⁵ to promote the rapid anomerization of protected methyl β -D-glucopyranosides into the corresponding α -D-glucopyranosides. Such a reaction was also assumed to involve^{5,6} in the first step an *endo*-cleavage of the glycosidic bond to give an acyclic oxocarbenium ion, which underwent intramolecular recyclization to form the α -glycoside. We thus tried the reaction of the known⁷ methyl 2,3,4-tri-*O*-benzyl-6-deoxy- α -D-xylo-hex-5-enopyranoside **1** with 1 equivalent of $TiCl_4$. This strong Lewis acid indeed promoted the transposition of the oxygen atom of the ring with the exocyclic carbon atom, but in rather moderate yield (around 50%). The use of the milder Lewis acid $Ti(O^iPr)Cl_3$ ⁸ resulted in a reproducible and almost quantitative formation of **2**⁹.



The chair like transition state **3**, where titanium (IV) is coordinated to two oxygens, may explain the stereoselectivity of the reaction¹⁰. Other examples are shown in scheme 2, demonstrating that this reaction can be extended to the benzylated α -D-*galacto* and *manno* series. The application of this reaction to the corresponding β -D-glycosides resulted in a mixture of products, making this reaction not practical in this case.



Scheme 2

In summary, we have delineated a novel stereoselective access to polyhydroxylated cyclohexanones, starting from benzylated 6-deoxy-hex-5-eno-pyranosides, and promoted by titanium (IV). In comparison with the recently described¹ triisobutylaluminum mediated rearrangement, this Ti (IV) version involves much milder reaction conditions and does not result in the reduction of the keto function.

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- Bradley, D. C.; Hancock, D. C.; Wardlaw, W. *J. Chem. Soc.* **1952**, 2773-2778. The 0.1 M solution of Ti(OⁱPr)Cl₃ was prepared by adding TiCl₄ (167 μL, 1.5 mmol) to a solution of Ti(OⁱPr)₄ (144 μL, 0.5 mmol) in dry dichloromethane (20 mL) under argon at 0 °C. The mixture was stirred at room temperature for 2 h before being used in the reaction described below.
- Typical procedure** : A 0.1 M solution of preformed⁸ Ti(OⁱPr)Cl₃ (3.3 mL) was added to a cooled (-78 °C) solution of **1** (100 mg, 0.22 mmol) in dry dichloromethane (1 mL) under argon. The reaction mixture was stirred at -78 °C for 15 min, and then poured into a stirred solution of ice-cold aqueous solution of NaHCO₃; the organic phase was dried (MgSO₄), concentrated and the residue was purified by column chromatography to afford (2S, 3R, 4S, 5S)-2,3,4-tribenzyloxy-5-methoxy-cyclohexanone **2** (98 mg, 98%), m.p. 90 °C (ethyl acetate : cyclohexane); [α]_D²⁰ -56 (c, 1.0, CHCl₃); ¹H-NMR (250MHz; CDCl₃) δ : 7.35-7.17 (m, 15H, H-arom.), 4.86-4.49 (m, 6H, 6 x Ph-CH₂-O-), 4.05 (dd, 1H, J_{3,4} = J_{3,2} 8.9 Hz, H-3), 3.94 (d, 1H, H-2), 3.71 (m, 2H, H-4 H-5), 3.31 (s, 3H, -OCH₃), 2.69 (dd, 1H, J_{6a,5} 4.0; J_{6a,6e} 14.4 Hz, H-6a), 2.29 (dd, 1H, J_{6e,5} 2.1 Hz; H-6e); ¹³C-NMR (63MHz; CDCl₃) δ : 203.5 (C-1), 138.4, 138.0, 137.7 (3 C-arom), 128.3-127.5 (15 C-arom), 85.4 (C-2), 82.0 (C-3), 81.3 (C-4), 75.7, 75.2, 73.0 (3 x Ph-CH₂-O-), 73.4 (C-5), 57.3 (-OCH₃), 40.5 (C-6); MS *m/z* (CI; NH₃): 464 (M+NH₄)⁺; Anal. Calc. for C₂₈H₃₀O₅ : C, 75.31; H, 6.77; Found : C, 75.24; H, 6.85.
- A similar transition state has been proposed in the case of the Pd(II) promoted Ferrier-II rearrangement : Iimori, T.; Takahashi, H.; Ikegami, S. *Tetrahedron Lett.* **1996**, *37*, 649-652.
- The new compounds **4** and **6** have been prepared as described in ref. 1 for the corresponding β-glycosides.