Highly Chemoselective Reduction of 2,5-Dinitro-1,4:3,6-dianhydro-D-glucitol with Titanium(III) Tetrahydroborates: Efficient Synthesis of Isomerically Pure 2- and 5-Nitro-1,4:3,6-dianhydro-D-glucitols

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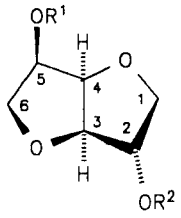
It has been found that the reduction of 2,5-dinitro-1,4:3,6-dianhydro-D-glucitol **(1)** with titanium(III) tetrahydroborate **(2)** (−78 → 0°C) affords exclusively 2-nitro-1,4:3,6-dianhydro-D-glucitol **(3)**. On the other hand, reduction of dinitrate **1** with diisopropoxytitanium(III) tetrahydroborate **(4)** (−78 → 0°C) yields 5-nitro-1,4:3,6-dianhydro-D-glucitol **(5)** as the only product.

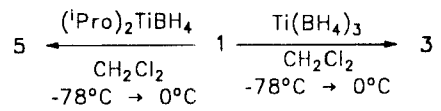
2,5-Dinitro-1,4:3,6-dianhydro-D-glucitol (isosorbide-2,5-dinitrate) **(1)** is a well established compound used in the treatment of coronary diseases. It is rapidly metabolized in the organism and 2-nitro-1,4:3,6-dianhydro-D-glucitol (isosorbide-2-nitrate) **(3)** and 5-nitro-1,4:3,6-dianhydro-D-glucitol (isosorbide-5-nitrate) **(5)** occur as metabolites.[2] The mononitrates **3** and **5** act as non-specific smooth muscle relaxants and as blood vessel dilators.[3] Compared with the dinitrate **1**, the mononitrates **3** and **5** are advantageously distinguished by various therapeutically important parameters such as resorption behaviour, half-life, toxicity and oral applicability.[4] Because of this fundamental difference in the pharmaceutical application of the two compounds, it is necessary to devise methods so as to obtain isomerically pure mononitrates **3** and **5**. A number of methods have been developed over the years for the synthesis of mononitrates **3** and **5** with varying degree of success.



	R^1	R^2
1	NO_2	NO_2
3	H	NO_2
5	NO_2	H
6	H	H

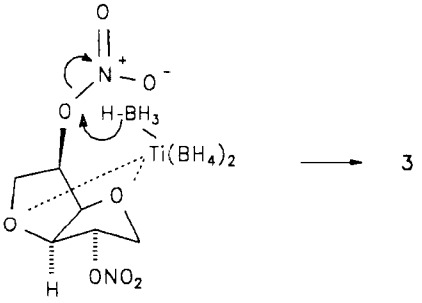
Direct nitration of isosorbide **6** gives a mixture of mononitrates **3** and **5** along with variable amounts of dinitrate **1**.[5] The synthesis of the more active isosorbide-5-nitrate **(5)** through the protection of the 2-*exo* hydroxy group in isosorbide **6** is circuitous and suffers from low overall yield.[6] Reagents such as hydrazine hydrate,[7] iron(II) sulfate,[8] copper(II) chloride,[9] powdered zinc,[9] and Pd/C in the presence of nickel chloride[9] have been used to cleave isosorbide-2,5-dinitrate **(1)** into one of the isomeric mononitrates **3** or **5**. Bioconversion of diesters of **6** into mononitrates **3** or **5** by various microorganisms have also been investigated.[10] Of all the methods available for the synthesis of mononitrates **3** or **5**, the one reported by Modena involving chemoselective reduction of isosorbide-2,5-dinitrate **(1)** with Zn/acetic acid or iron(II) sulfate is the most attractive.[8]

Recently we reported an unusual anti-Markovnikov hydration of alkenes with titanium(III) tetrahydroborate **(2)**.[11] We have also shown that diisopropoxytitanium(III) tetrahydroborate **(4)** effects a facile chemoselective reduction of α,β-unsaturated carbonyl compounds to produce exclusively the corresponding allylic alcohols in excellent yields.[12] In this communication we wish to report the use of these titanium(III) tetrahydroborates[15] **2** and **4** for the chemoselective reduction of isosorbide-2,5-dinitrate **(1)**.



Treatment of dinitrate **1** with titanium(III) tetrahydroborate **(2)**, derived from benzyltriethylammonium borohydride–titanium tetrachloride in dichloromethane (−78 → 0°C, 2 h) effected a smooth and highly chemoselective reduction of the 5-*endo* nitrate group to afford the mononitrate **3** as the only product in 71% yield. Interestingly when the dinitrate **1** was allowed to react with diisopropoxytitanium(III) tetrahydroborate **(4)**, derived from diisopropoxytitanium dichloride[16] and benzyltriethylammonium borohydride in dichloromethane (−78 → 0°C, 2 h), chemoselective reduction of the 2-*exo* nitrate group took place to produce isomerically pure mononitrate **5** exclusively in 57% yield. Thus, these two reactions are complementary: the reduction with **2** produces mononitrate **3** whereas reduction with **4** produces mononitrate **5**. It is pertinent to point out, however, that when these reductions on **1** were carried out at −20°C, the chemoselectivity was lost, and mixtures of mononitrates **3** and **5** were formed.

It has been demonstrated that there is interaction between the 5-*endo* nitrate group and the oxygen of the adjacent ring in **1**.[13] The origin of chemoselectivity in the reduction of **1** with $Ti(BH_4)_3$ probably arises from intramolecular hydride transfer in complex **7** to the 5-*endo* nitrate group to produce exclusively the mononitrate **3**.



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On the other hand, the use of sterically more demanding diisopropoxytitanium(III) tetrahydroborate as a reducing agent does not favour the formation of a complex similar to **7** and the hydride transfer takes place in an intermolecular fashion to the more easily accessible 2-*exo* nitrate group, yielding only the mononitrate **5**.

The efficient synthesis of isomerically pure mononitrates **3** or **5** as desired from the readily available dinitrate **1** thus represents a useful synthetic methodology for the selective protection of a single hydroxy group in isosorbide **6**.[14]

Melting points were determined with a uni-melt capillary melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 781 spectrophotometer. ^{1}H NMR and ^{13}C NMR were recorded on a Bruker AC 300 spectrometer with tetramethylsilane as internal standard. Mass spectra were recorded on a JEOL Dx-303 spectrometer. All reactions were carried out under nitrogen and prior to use, the reaction vessels were baked out, and purged with nitrogen. CH_2Cl_2 was purified and dried by distilling from phosphorus pentoxide and stored over Type 4A molecular sieve. TLC were performed on 0.25 mm E. Merck precoated silica plates (60F-254). All the products were purified by flash column chromatography on silica gel. A stock solution of diisopropoxytitanium dichloride in dry CH_2Cl_2 (11.8% w/v) was used.[16] A stock solution of $TiCl_4$ in dry CH_2Cl_2 (19% w/v) was used.

Isosorbide-2,5-dinitrate (1):[1]
Fuming HNO_3 (spec. gr. 1.57, 40 mL, 1 mol) was slowly added to AcOH–Ac_2O (1:1, 120 mL) maintained at −5 to −10 °C. The mixture was added dropwise with stirring to isosorbide **6** (14.6 g, 0.1 mol) in AcOH–Ac_2O (2:1, 120 mL) maintained at −5 to −10 °C. After standing for 2 h at 5 to 10 °C, the mixture was poured into ice (600 g). The solid that separated was filtered, dried, and recrystallised from petroleum ether (bp 60–80 °C). Yield: 21.6 g (92%); mp 51–52 °C (lit.[1] 50.5–51.5 °C); $[\alpha]_D^{22}$ +139.7 (c = 2.1, EtOH) (lit.[1] +141°).

IR (thin film): ν = 2930, 1650, 1290, 1120, 860 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 3.90 (2H, dd, J = 11.3, 7.5 Hz), 4.05–4.20 (2H, m), 4.55 (1H, d, J = 6.0 Hz), 5.00 (1H, t, J = 6.0 Hz), 5.35 (2H, m).

^{13}C NMR ($CDCl_3$): δ = 69.34, 71.52, 80.66, 81.44, 84.74, 85.18.

MS: m/z = 237 (M + 1, 2), 190 (1), 144 (36), 127 (50), 85 (53), 69 (89), 57 (85), 46 (100), 43 (98).

Reduction of Dinitrate 1 with Titanium(III) Tetrahydroborate (2):
To a solution of benzyltriethylammonium borohydride (0.828 g, 4 mmol) in dry CH_2Cl_2 (4 mL), a stock solution of titanium tetrachloride (1 mL, 1 mmol) was slowly added under N_2 at −20 °C. The reaction mixture was stirred for 30 min, and the titanium tetrahydroborate solution was cooled to −78 °C. The dinitrate **1** (0.236 g, 1 mmol) in dry CH_2Cl_2 (2 mL) was added to the reagent solution. The reaction mixture was brought to 0 °C over 2 h. Sat. aq K_2CO_3 (5 mL) was added and stirring was continued for an additional 15 min (25 °C). The reaction mixture was extracted with EtOAc (3 × 25 mL) and dried (Na_2SO_4). Removal of solvent afforded a highly viscous liquid which on flash chromatography [EtOAc–petroleum ether (2:8)] afforded the mononitrate **3** as a solid (0.136 g, 71%). Mp 53–54 °C (lit.[16] 54 °C); $[\alpha]_D^{22}$ +70.4° (c = 1.35, EtOH) (lit.[7] +71°].

IR (thin film): ν = 3440, 2960, 1650, 1290, 1100, 870 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 2.60 (1H, OH), 3.55 (1H, dd, J = 11.3, 7.5 Hz), 3.85 (1H, dd, J = 11.3, 7.5 Hz), 4.1 (2H, m), 4.30 (1H, m), 4.55 (1H, d, J = 6.75 Hz), 4.65 (1H, t, J = 6.75 Hz), 5.35 (1H, m).

^{13}C NMR ($CDCl_3$): δ = 71.52, 71.92, 73.42, 81.89, 83.81, 86.08.

MS: m/z = 192 (M + 1, 33), 146 (17), 127 (47), 85 (96), 69 (100), 57 (39), 43 (93).

Reduction of Dinitrate 1 with Diisopropoxytitanium(III) Tetrahydroborate (4):
To a stock solution of diisopropoxytitanium dichloride (2 mL, 1 mmol) was slowly added benzyltriethylammonium borohydride (0.414 g, 2 mmol) in dry CH_2Cl_2 (4 mL) under N_2 at −20 °C, and the reaction mixture was stirred for 30 min. The solution of diisopropoxytitanium(III) tetrahydroborate thus obtained was cooled to −78 °C and the dinitrate **1** (0.236 g, 1 mmol) in dry CH_2Cl_2 (2 mL) was added. The reaction mixture was brought to 0 °C over 2 h. Sat. K_2CO_3 (5 mL) was added and stirring was continued for an additional 15 min (25 °C). The reaction mixture was extracted with EtOAc (3 × 25 mL) and dried (Na_2SO_4). Removal of solvent afforded a highly viscous liquid which on flash chromatography [EtOAc–petroleum ether (2:8)] afforded the mononitrate **5** as a solid (0.108 g, 57%); mp 87–89 °C (lit.[17] 88 °C); $[\alpha]_D$ 171.2° (c = 1.4, EtOH) (lit.[17] 173.5°).

IR (thin film): ν = 3400, 2920, 1640, 1290, 1100, 860 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 3.8–4.1 (5H, m), 4.35 (1H, d, J = 3.75 Hz), 4.38 (1H, d, J = 6.0 Hz), 4.98 (1H, t, J = 6.0 Hz), 5.35 (1H, td, J = 6.0, 3.8 Hz).

^{13}C NMR ($CDCl_3$): δ = 69.12, 75.50, 75.65, 81.07, 81.32, 88.69.

MS: m/z = 192 (M + 1, 0.5), 146 (2.5), 127 (47), 85 (45), 69 (54), 57 (46), 43 (100).

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