COMMUNICATION

New preparative routes to isosorbide 5-mononitrate

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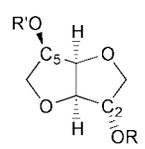
Three new methods for the preparation of the vasodilator isosorbide 5-mononitrate are described. In the first method enzymatic regioselective acetylation of isosorbide gave isosorbide 2-butyrate. Nitration and deprotection of this material afforded isomerically pure isosorbide 5-mononitrate in high overall yield. Secondly, regioselective hydrogenation of isosorbide dinitrate over platinum oxide (PtO_2) furnished the 5-mononitrate in 45% yield. Similarly, regioselective reduction of the dinitrate was achieved using sodium borohydride ($NaBH_4$) activated with cobalt or iron phthalocyanine. All three methods show advantages over existing procedures.

1,4 : 3,6-Dianhydro-D-glucitol 2,5-mononitrate (isosorbide dinitrate **1**) and its 5- and 2-mononitrates (**2** and **3** respectively) are all well-documented pharmaceuticals for the treatment of cardiovascular disease. However, because of advantageous pharmacokinetics, 1,4 : 3,6-dianhydro-D-glucitol 5-mononitrate (isosorbide 5-mononitrate) (**2**) is preferred in the clinic over isosorbide 2-mononitrate or isosorbide dinitrate.[1] As a result the synthesis of isomerically pure 5-mononitrate (**2**) has been a continuing feature of world-wide interest.



1 R = R' = NO_2
2 R = H, R' = NO_2
3 R = NO_2, R' = H
4 R = R' = H
5 R = COC_3H_7, R' = H

Over the years a number of pathways have been devised for the synthesis of isosorbide 5-mononitrate (**2**). Isosorbide (**4**), a diol possessing two sterically distinct hydroxy groups which is obtained by dehydration of D-glucitol,[2] is one obvious starting point. The 5-*endo* hydroxy group normally exhibits enhanced reactivity over that of the 2-*exo* hydroxy group. This increase in reactivity is due to the ability of the C-5-OH group to form a hydrogen bond to the adjacent ring oxygen atom.[3] As a consequence direct protection/nitration of isosorbide (**4**) at the 2-hydroxy position is generally unfavourable. The greater reactivity of the 5-*endo* functionality was utilised in one synthesis of isosorbide 5-mononitrate which involved enzymatic hydrolysis or alcoholysis of isosorbide diacetate. After nitration of the resultant 2-acetate followed by deprotection isosorbide 5-mononitrate (**2**) was obtained.[4]

Chemical procedures have been employed to regioselectively protect the 2-hydroxy function of isosorbide (**4**).[5] However, to our knowledge, no enzymatic transesterification protocol has been reported for the selective protection of the 2-hydroxy group of this molecule, although this would provide more directly a key intermediate for the conversion to isosorbide 5-mononitrate (**2**).

An alternative synthetic route, the reduction of isosorbide 2,5-dinitrate (**1**) to mononitrate (**2**) has also received attention. The best method for accomplishing this reduction, reported by Modena,[6,7] utilises zinc in acetic acid, whereupon isosorbide 5-mononitrate (**2**) is obtained as the major product in 44% yield. Reductions involving hydrazine hydrate,[8] Pd/C in the presence of nickel chloride,[7] titanium(III) tetrahydroborates[9] and tetrathiomolybdate[10] reagents have all been described but met with limited success. Bioconversions of isosorbide dinitrate (**1**) to the mononitrate (**2**) have also been explored and have shown good selectivity and promising yields, albeit on a small scale.[11]

Within this communication we report three new methods for the preparation of isosorbide 5-mononitrate (**2**), one utilising isosorbide (**4**) and two employing isosorbide dinitrate (**1**) as starting materials.

Results and discussion

Enzyme-catalysed regioselective acylation of isosorbide

The potential of enzymes for the selective functionalisation of diols is widely described in the literature.[12] On screening some commercially available enzymes[13] a number displayed the ability to perform regioselective esterification of isosorbide; the results are displayed in Table 1.

Most enzymes, such as *Candida antarctica* B lipase (entry 1), promoted formation of the 5-ester as promulgated previously by Schneider *et al.*[4] and Guibé-Jampel *et al.*[14] Other enzymes such as the lipase from *R. oryzae* (entry 2) and the protease from *Bacillus* sp. (entry 3) showed selectivity towards 2-acylation but in reactions that gave only very low conversions after 5 days. However pig liver esterase (entry 4) and the protease *Subtilisin* Carlsberg[15] (entry 5) demonstrated the unexpected potential for relatively rapid derivatisation at the 2 position. *Subtilisin* Carlsberg was chosen for further study and with a moderate loading (5% w/w enzyme:substrate) catalysed an even more efficient transesterification of isosorbide using vinyl butyrate[16] in tetrahydrofuran, to yield isosorbide 2-butyrate (**5**) (62%) after just 26 hours. Subsequent nitration of the monoester (**5**) and removal of the butyrate moiety (sodium carbonate–methanol) gave isosorbide 5-mononitrate (**2**) in 58% overall yield from isosorbide.

Regioselective reduction of isosorbide 2,5-dinitrate (4)

In isosorbide 2,5-dinitrate the 5-*endo* group is sterically more crowded than the same group in the 2-*exo* position, hence reduction at the latter position is generally dominant. Hydrogenation, using palladium on carbon, had previously shown potential for this regioselective denitration.[8] However the excessively long reaction times militate against this methodology being employed on a large scale.

In an attempt to find a more rapid rate for this hydrogenation platinum (5% on C) and platinum oxide were evaluated. Platinum oxide provided an inexpensive and efficient means to obtain isosorbide 5-mononitrate in an acceptable yield (45%). The reaction proceeded smoothly with a catalytic loading of 1% w/w (PtO_2 : substrate) in methanol to yield the desired compound after only 3 h.

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Table 1 Esterification reactions of isosorbide[a]

Entry	Enzyme	2-Acyl[b] derivative (%)	5-Acyl[b] derivative (%)	Isosorbide[b] (%)
1	*Candida antarctica* B	4.7	31.1	64.2
2	*Rhizopus oryzae* lipase	8.0	—	92.0
3	*Bacillus protease*	7.8	—	92.2
4	Pig Liver esterase	33.0	—	67.1
5	ChiroClec™-BL (dry) *Subtilisin* Carlsberg	71.0	15.0	14.0

[a] All reactions were performed in chloroform using vinyl acetate (3 equivalents). No diacylated material was formed. [b] Values from gas chromatographic analysis after 5 days.

Table 2 Regioselective reduction of isosorbide 2,5-dinitrate with sodium borohydride and cobalt phthalocyanine

Product	Composition (%)
Isosorbide 5-mononitrate (**2**)	69.90
Isosorbide 2-mononitrate (**3**)	18.74
Isosorbide 2,5-dinitrate (**1**)	8.15
Isosorbide (**4**)	3.21

Further investigations into the regioselective denitration of isosorbide 2,5-dinitrate (**1**) highlighted the potential of sodium borohydride. Although sodium borohydride alone was unable to facilitate the regioselective reduction of **1**, it is known that when employed in conjunction with a metal phthalocyanine[17] altered reduction characteristics may be observed.

Gratifyingly addition of sodium borohydride to a solution of isosorbide 2,5-dinitrate and cobalt or iron phthalocyanine in methanol led to the rapid formation of the desired product (**2**) as shown in Table 2. After removal of the recyclable catalyst and simple purification crystalline isosorbide 5-mononitrate was obtained in greater than 50% yield.

The three methods highlighted within this paper are all efficient, cost effective and industrially applicable preparations of isosorbide 5-mononitrate from either isosorbide or isosorbide 2,5-dinitrate.

Experimental

Preparation of isosorbide 5-mononitrate

To the dinitrate (**1**) (500 mg, 2.12 mmol) in methanol (20 mL) was added cobalt phthalocyanine (200 mg, 0.35 mmol). To this stirred solution was added sodium borohydride (600 mg, 15.86 mmol). After 10 min the reaction was quenched with 2 M HCl (20 mL) and the catalyst removed by filtration. The solution was extracted with dichloromethane (300 mL) and the organic phase dried and evaporated. Purification by chromatography over silica yielded isosorbide 5-mononitrate (**2**) in 52% yield, mp 89.6–90.5 °C (lit.,[4] (89–91 °C) $[\alpha]_D^{23} = +192$ (lit.,[4] +181) (Found C, 37.7; H, 4.7; N, 7.3. $C_6H_9NO_6$ requires C, 37.7; H, 4.75; N, 7.3%).

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