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# Efficient Cleavage of Terminal Acetonide Group: Chirospecific Synthesis of 2,5-Dideoxy-2,5-Imino-D-Mannitol

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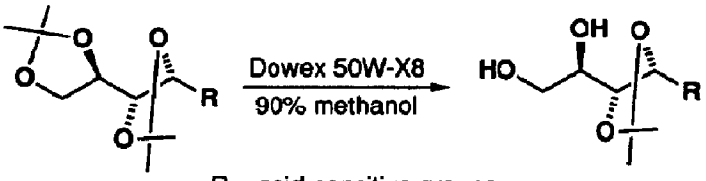
**Abstract:** Dowex 50W-X8 was efficient catalyst for selective cleavage of terminal actonide including acid-sensitive multifunctional groups. A facile and economically synthesis of DMDP (2,5-dideoxy-2,5-imino-D-mannitol) is described *via* selective hydrolysis and intramolecular nucleophilic amination.

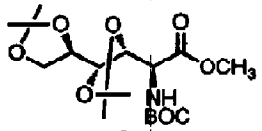
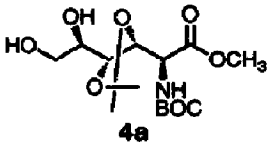
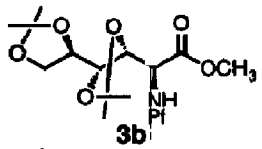
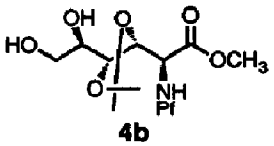
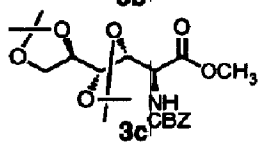
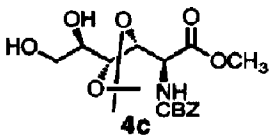
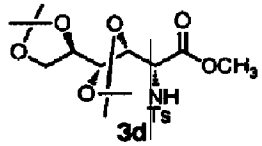
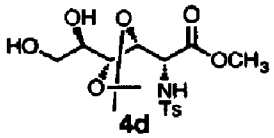
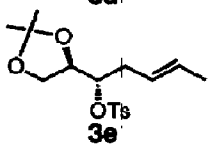
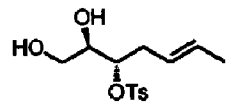
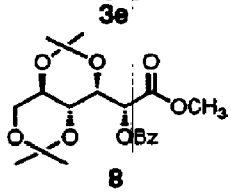
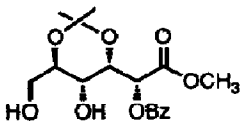
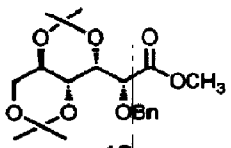
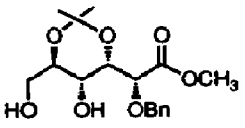
The selective derivatization in multifunctionalities of similar reactivity is an important step in synthetic methodology, especially, in carbohydrate and nucleoside chemistry. The acetonide has been used extensively in carbohydrate chemistry to mask selectively the hydroxyls of the many different sugar.[1] Although normal acidic catalysts such as HCl, HBr, TFA, AcOH have been acceptable reagents for selective hydrolysis primary-secondary hydroxy group of simple diactonide derivatives,[1] owing to their strong acidity and free protons, they are still undesirable for its derivatives having acid-sensitive groups. We report specific removal of primary-secondary acetonide having acid-sensitive groups.




R = acid-sensitive groups

As shown Table 1, when acetonide derivatives containing BOC, Pf (9-phenylfluorenyl),[2] Bz, CBZ, alkene, Ts and ester groups were exposed to 110 w/w% of Dowex 50W-X8 in 90% methanol, terminal acetonide group was selectively hydrolysized in excellent yields. The use of this condition for selective cleavage of 1,3- and 2,4-diacetonide has been quite successful too (Entry 10, 11). From $^{1}H$ and $^{13}C$-NMR (300MHz) and next steps, it is clear that indeed the terminal acetonide had been cleaved. Especially, it is notable that terminal acetonide of **3a** (Entry 2) was removed without touching BOC group, which has similar reactivity under acidic conditions.[3] This high selectivity is believed to be due to bounded protons and steric effect of heterogeneous catalyst (Dowex 50W-X8). The procedure for hydrolysis is remarkably simple and mild.[4]

**Table1**: Selective Cleavage of Terminal Acetonide Group

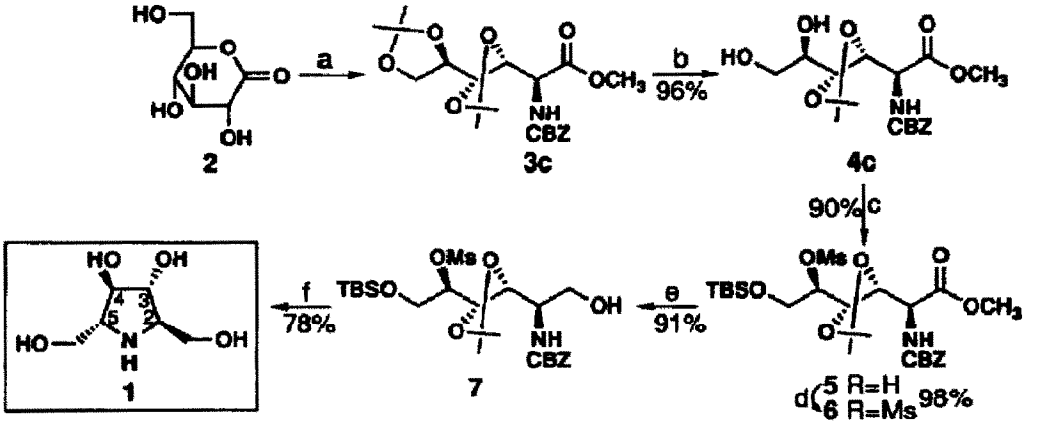
| Entry | Substrate | Catalyst/Temp[a]./ Time/Solvent | Product[b] | Yield[c] % |
|---|---|---|---|---|
| 1 |  **3a** | Dowex/8days/ abs.MeOH |  **4a** | 87 |
| 2 | **3a** | Dowex/25h/90%MeOH | **4a** | 93 |
| 3 | **3a** | HCl/0°C/6h/$Et_2O$ | **4a** | 17 |
| 4 | **3a** | AcOH/12h/MeOH, $H_2O$[d] | **4a** | 23 |
| 5 |  **3b** | Dowex/32h/ 90%MeOH |  **4b** | 95 |
| 6 |  **3c** | Dowex/27h/ 90%MeOH |  **4c** | 96 |
| 7 | **3c** | HCl/0°C/5h/$Et_2O$ | **4c** | 57 |
| 8 |  **3d** | Dowex/22h/ 90%MeOH |  **4d** | 92 |
| 9 |  **3e** | Dowex/7h/ 95%MeOH |  **4e** | 97 |
| 10 |  **8** | Dowex/25h/ 90%MeOH |  **9** | 87 |
| 11 |  **10** | Dowex/20h/ 90%MeOH |  **11** | 92 |

(a) rt except where noted; (b) All products gave satisfactory $^1H$ and $^{13}C$ NMR data; (c) isolated yield; (d) MeOH/$H_2O$, 1/1

Aza analogue of fructofuranose DMDP, isolated from *Derris elliptica*,[5] has been shown to be a potent inhibitor of viral glycoprotein processing glucosidase.[6] Since its initial isolation, several synthetic efforts have been developed to get this valuable compound economically from L-sorbose, D-glucose and D-manitol.[7] Here we also report facile and efficient route to prepare enantiomerically pure DMDP from D-glucono-δ-lactone *via* selective cleavage of terminal acetonide group.

As our chiral educt we choose mannonate **3c** which has four stereocenters in the same absolute stereochemistry as required for C-2, C-3, C-4 and C-5 in **1**. The mannonate **3c** was synthesized in easy steps from D-glucono-δ-lactone **3c** as described.[8] The terminal acetonide group was selectively cleaved by treatment of mannonate **3c** with Dowex 50W-X8 resin ($H^+$ form) in 90% methanol to give easily crystallized diol **4c** as the required key intermediate for the synthesis of the hydroxylated alkaloid (Scheme 1).

**Scheme 1**




Reagents: (a) ref. 8 (b) Dowex 50W-X8 (H+), 90% methanol, rt (c) TBDMSCl, imidazol, DMF, 0°C (d) MsCl, THF, rt (e) $LiAlH_4$, THF, 0°C (f) i) Dowex 50W-X8, 95% methanol, reflux ii) sodium acetate, Pd/C, methanol.

The primary hydroxy group of **4c** was selectively protected with t-butyldimethylsilyl chloride followed by mesylation of corresponding silylate **5** with mesylchloride gave ester **6** in 88% yield from **4c**. Reduction of the ester **6** with $LiAlH_4$ gave alcohol **7** in 91% yield. The remaining acetonide and TBS groups were easily removed treatment of alcohol **7** with Dowex 50W in methanol. Subsequent hydrogenolsis of corresponding benzyl carbamate in presence of palladium on charcoal and sodium acetate removed the CBZ group and led to direct neucleophilic amination to DMDP **1** in 78% yield. Its physical and spectral properties correlated well with previousiy reported data.[5]

In summary we have reported improved selective hydrolysis of terminal acetonide group. We have also achieved efficient and chirospecific synthesis of DMDP **1** in 60% over all yield from mannonate **3c**.

**Acknowledgments:** We thank to professor Shin for the valuable discussion.

**Reference and Notes**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2. Lubell, W. D.; Rapoport, H. *J. Am. Chem. Soc.*, **1987**, *109*, 236.
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4. To a solution of acetonide derivative (**3a-3f**) in 90% methanol was added Dowex 50W-X8 (110 W/W%) . The reaction mixture was stirred for (20-30h) at room temperature, then was filtered, the filtrate was evaporateed. The crude residue was chromatographed on silicagel to give **4a-4f** in 90-96% yields.
5. Walter, A.; Dardenne, G.; Marlier, M.; Casimir. J. *Phytichem.*, **1976**, *25*, 747.
6. (a) Elbein, A. D.; Mitchell, M.; Sanford, B. A.; Fellows, L. E.; Evans, S. V. *J. Biol., Chem.*, **1984** *259*, 12409. (b) Fellows, L. E. *Pestic. Sci.* **1986**, *17*, 602.
7. (a) Card, P. J.; Hitz, W. D., *J. Org. Chem.*, **1985**, 50, 891. (b) Fleet, G. W. J.; Smith, P. W. *Tetrahedron*, **1987**, 43, 891. (c) Shing, T. K. M *J. Chem. Soc. Chem. Commun.*, **1987**, 262. (d) Dureault, A.; Portal, M.; Depezay, J. C. *Synlett.*, **1991**, 225.
8. Csuk, R.; Hugemer , M.; Vasella, A., *Hev. Chim Acta*, **1988**, 71, 609.
9. Physical and spectral data of the major products. **3c.** $[\alpha]_D^{20}$ +19.8° (c 1.8 in $CHCl_3$);$^1$H-NMR (300 MHz, $CDCl_3$): δ 1,28 (3H, s), 1.33 (3H, s), 1.35 (3H, s), 1.40 (3H, s), 3.35 (3H, s), 3.94-4.01 (3H, m), 4.13-4.19 (2H, m), 5.56 (1H, dd, J 6.9 and 5.7), 5.12 (2H, d, J 4.2), 5.80 (1H, br s), 7.32 (5H, m, ArH); $^{13}$C-NMR: δ 25.2, 26.6, 26.8, 27.2, 52.4, 56.5, 67.1, 67.8, 76.6, 78.8, 80.8, 110.1, 110.5, 128.1, 128.2, 128.5, 136.2, 155.8, 170.2. **4c.** mp 101-103°C; $[\alpha]_D^{20}$ +46.4° (c 1.65 in $CHCl_3$); $^1$H-NMR ( 300 MHz,$CDCl_3$): δ 1.33 (3H, s), 1.35 (3H, s), 3.58-3.87 (3H, m), 3.79 (3H, s), 4.09 (1H, dd, J 7.8, 7.6), 4.23 (1H, dd, J 7.8 and 3.0), 4.68 (1H, m), 5.12 (2H, s), 6.0 (1H, br s), 7.33 (5H, m); $^{13}$C-NMR: δ 26.7, 27.1, 52.2, 56.3, 64.0, 67.3, 73.4, 77.5, 81.2, 110.4, 128.1, 128.3, 128.5, 136.0, 156.3, 169.8. **5.** $[a]_D^{20}$ +23.5° (c 0.66 in $CHCl_3$); 1H-NMR (300 MHz, $CDCl_3$); δ 0.09 (6H, s, TBS), 0.91 (9H, s, TBS), 1.26 (3H, s, acetal), 1.35 (3H, s, acetal), 2.73 (1H, OH), 3.70 (2H, m), 3.77(3H, s, $OCH_3$), 3.83 (1H, dd, J 3, and 9.9), 4.02 (1H, dd, J 7.5 and 7.8), 4.25 (1H, dd, J 4.5 and 7.8), 4.64 (1H, m), 5.07 (2H, S, $OCH_2Ar$) 5.86 (1H, NH), 7.33 (5H, m, ArH). $^{13}$C-NMR δ -5.4, -5.4, 18.3, 25.9, 26.9, 27.2, 52.4, 55.6, 64.2, 67.1, 73.3, 80.8, 110.2, 128.1, 128.5, 136.3, 155.6, 170.2. **6.** $[\alpha]_D^{20}$ +29.8° (c 1.4 in $CHCl_3$); $^1$H-NMR (300 MHz, $CDCl_3$), d, 0.10 (6H, s), 0.91 (9H, s), 1.20 (3H, s), 1.28 (3H, s), 3.09 (3H, s, $CH_3$ in Ms), 3.67 (3H, s, $OCH_3$), 3.86 (1H, dd, J 5.1 and 11.1), 4.04 (1H, dd, J 3.3 and 11.1), 4.34 (1H, dd, J 4 and 7), 4.48 (1H, dd, J 7 and 6.6), 4.69 (1H, m), 5.12 (2H, d), 7.34 (5H, m); $^{13}$C NMR, d, -5.5, -5.4, 18.3, 25.8, 27.0, 27.1, 38.6, 52.5, 56.2, 62.4, 67.2, 75.7, 79.1, 81.4, 110.9, 128.1, 128.2, 128.5, 136.2, 156.5, 169.6. **7.** $[\alpha]_D^{20}$ +16.3° (c 0.45 in $CHCl_3$); $^1$H-NMR (300 MHz, $CDCl_3$): δ, 0.09 (6H, s), 0.90 (9H, s), 1.23 (3H, s), 1.27 (3H, s), 2.04 (1H, OH), 3.05 (3H, s), 3.78 (2H, m), 3.90 (2H, m), 4.18 (1H, m), 4.25 (1H, m), 4.67 (1H, m), 5.14 (2H, m), 5.56 (1H, NH), 7.35 (5H, m): $^{13}$C-NMR δ, -5.5, -5.4, 18.3, 25.9, 27.1, 27.2, 38.7, 54.5, 62.5, 67.0, 76.6, 78.7, 82.5, 110.7, 128.1, 128.5, 136.5, 156.


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