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1,3:4,6-Di-*O*-benzylidene-D-mannitol as a source for novel chiral intermediates through regioselective reductive cleavage

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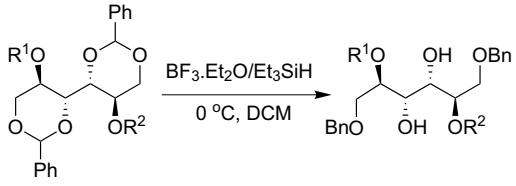
Abstract—Synthetically useful chiral intermediates have been synthesized starting from 1,3:4,6-di-*O*-benzylidene-D-mannitol by regioselective reductive cleavage using $BF_3{\cdot}Et_2O$ and Et_3SiH in high yields.

Development of C_2 symmetric chiral ligands has played a significant role in transition metal-catalyzed asymmetric synthesis[1] and has attracted much attention from synthetic chemists. D-Mannitol and its derivatives are widely used as C_2 symmetric chiral reagents as well as chiral auxiliaries.[2] In addition, mannitol, an inexpensive chiral pool hexitol with four asymmetric centres, is recognized as the most easily available starting material for many organic transformations leading to biologically active and pharmaceutically important products.[3] Successful synthesis of these chiral intermediates relies heavily on the selective protection and deprotection of hydroxyl functional groups.[4] The regioselective reductive cleavage of the bis-benzylidene acetal of D-mannitol would lead to the selective formation of synthetically useful di-protected tetrols. Recently we reported the regioselective reductive cleavage of various benzylidene acetals using $EtAlCl_2/Et_3SiH$ as a novel reagent system.[5] In this communication, we report our approach to the generation of chiral intermediates through regioselective reductive cleavage of 1,3:4,6-di-*O*-benzylidene-D-mannitol derivatives with $BF_3{\cdot}Et_2O/Et_3SiH$.

The reductive cleavage of benzylidene acetals to form monoprotected diols can be achieved using various reagent systems.[6] We anticipated that the regioselective reductive cleavage of bis-benzylidene acetals derived from D-mannitol would lead to highly functionalized chiral intermediates under mild reaction conditions.



Scheme 1. Reductive cleavage using $BF_3{\cdot}Et_2O/Et_3SiH$.

Thus, treatment of 1,3:4,6-di-*O*-benzylidene-D-mannitol with $BF_3{\cdot}Et_2O$ (3.2 equiv) in combination with Et_3SiH (2.2 equiv)[7] at 0 °C gave the corresponding dibenzyl ether as the only isolable product in good yield and with high regioselectivity (Scheme 1).

The generality of this methodology was further examined with 1,3:4,6-di-*O*-benzylidene-D-mannitol derivatives with different sensitive functional groups and the results are shown in Table 1. In all cases the benzylidene acetals underwent smooth reductive cleavage under very mild conditions to the corresponding primary dibenzyl ethers in good yields. The regioselectivity can be rationalized by chelation-controlled cleavage of the bis-benzylidene acetal.[61] Labile functional groups such as OTBDPS, OMs, OBn, OAc and OTs were found to be stable under these reaction conditions. The benzylidene acetal of dimesylate **1** was smoothly cleaved to the diol **2**, which was isolated as the corresponding acetonide using DMP and CSA in acetone. Similarly, the benzylidene acetals of diacetate **3** and the dibenzyl ether **5** also underwent reductive cleavage and yielded the diols **4** and **6**, respectively, in a highly regioselective manner. Diol 6 is a known non-nitrogen containing

Keywords: Regioselective; Reductive cleavage; Chiral intermediates; Chemoselective; Benzylidene acetals.
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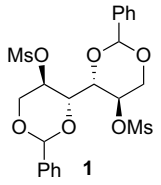
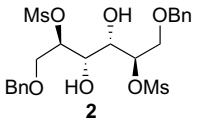
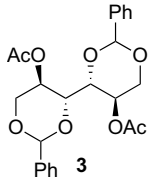
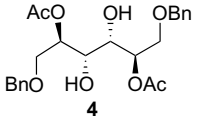
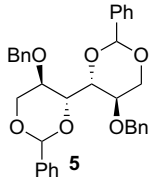
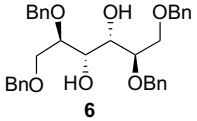
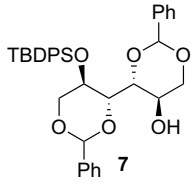
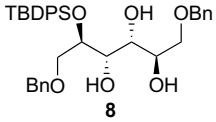
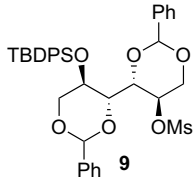
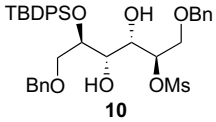
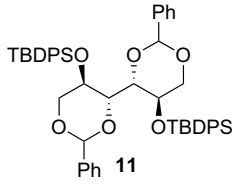
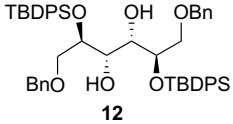
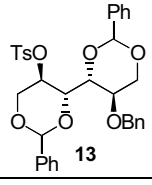
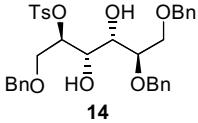
Table 1. Regioselective reductive cleavage using $BF_3{\cdot}Et_2O/Et_3SiH$[a]

Entry	Substrate	Product	Yield[b] (%)
1			70[c]
2			88
3			86
4			90
5			84
6			72
7			72[c]

[a] 3.2 equiv $BF_3{\cdot}Et_2O$ and 2.2 equiv Et_3SiH were used for the reaction.
[b] Isolated yield.
[c] The crude diol after reductive cleavage was isolated as the corresponding acetonide.

HIV-protease inhibitor.[8] Diols **2**, **4**, **6** and **12** are highly functionalized C_2 symmetric intermediates and have considerable scope for further functional group manipulations to produce novel chiral synthons. Moreover, these diols are key intermediates in the stereoselective synthesis of glycosidase inhibitors.[2f,3e] Apart from the C_2 symmetric benzylidene acetals (entries 1, 2, 3 and 6), reductive cleavage of unsymmetrical compounds (entries 4, 5 and 7) was also achieved in good yields and with high regioselectivity. Furthermore, the compounds **8**, **10** and **14** are also unsymmetrical and thus could have importance in enantiospecific syntheses.[9] Under the reaction conditions, the reductive cleavage of benzylidene acetal derivative of TBDPS ethers (entries 4, 5 and 6) gave the corresponding diols in good yields. The acid labile TBDPS ethers were stable under these conditions.

In a typical procedure, to a solution of 1,3:4,6-di-*O*-benzylidene-D-mannitol **3** (500 mg, 1.13 mmol) in dry CH_2Cl_2 (25 mL) at 0 °C was added Et_3SiH (397 μL, 2.48 mmol) followed by $BF_3{\cdot}Et_2O$ (454 μL, 3.61 mmol). After stirring the reaction mixture at 0 °C for 30 min, it was quenched with saturated $NaHCO_3$ solution (15 mL) and extracted with CH_2Cl_2 (2×25 mL). The organic layer was dried over anhydrous Na_2SO_4, concentrated under reduced pressure and the crude product was purified by column chromatography over silica gel using a 20–50% EtOAc–hexane solvent gradient to yield the pure compound **4** (443 mg, 88%) as a colourless liquid.

In conclusion, we have developed an efficient and novel method for the regioselective reductive cleavage of 1,3:4,6-di-benzylidene-D-mannitol derivatives using $BF_3{\cdot}Et_2O$ and Et_3SiH. We strongly believe that our chemoselective reductive cleavage methodology leading to highly functionalized chiral intermediates[10] will find wide application in enantiospecific syntheses.

Acknowledgements

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10. Compound **2** (acetonide derivative) $[\alpha]_D^{25}$ +28.6 (*c* 1.0, $CHCl_3$); IR (neat): 1356, 1177 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.33 (s, 6H), 2.98 (s, 6H), 3.65 (dd, J = 7.3, 11.2 Hz, 2H), 3.79 (dd, J = 3.4, 11.7 Hz, 2H), 4.27 (d, J = 4.8 Hz, 2H), 4.47 (AB quartet, J = 11.7 Hz, 4H), 4.78–4.82 (m, 2H), 7.18–7.28 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.0, 38.5, 68.6, 73.2, 76.4, 80.2, 111.0, 127.6, 127.7, 128.3, 137.1; MS (EI) *m/z* (relative intensity %) 558 (32) (M+), 557 (10), 467 (23), 379 (15), 181 (100), 111 (20), 91 (60); HRMS (ESI) calcd for $C_{25}H_{34}O_{10}S_2Na$ $(M+Na)^+$: 581.1491, found: 581.1489.Compound **4**. $[\alpha]_D^{30}$ −20.4 (*c* 1.0, $CHCl_3$); IR (neat): 3472, 1724 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.03 (s, 6H), 3.10 (d, J = 6.6 Hz, 2H), 3.74–3.81 (m, 6H), 4.54 (AB quartet, J = 12.0 Hz, 4H), 5.01 (m, 2H), 7.25–7.35 (m, 10H); ^{13}C (100 MHz, $CDCl_3$) δ 21.1, 68.2, 68.7, 72.0, 73.4, 127.7, 127.8, 128.4, 137.6, 171.0; HRMS (ESI) calcd for $C_{24}H_{30}O_8Na$ $(M+Na)^+$: 469.1838, found: 469.1845.
Compound **6** $[\alpha]_D^{30}$ −15.1 (*c* 1.0, $CHCl_3$); IR (neat): 3472, 2912, 2864, 1452 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.13 (br s, 2H), 3.71 (dd, J = 10.1, 5.3 Hz, 2H), 3.79 (m, 4H), 4.03 (d, J = 5.9 Hz, 2H), 4.59 (s, 4H), 4.65 (AB quartet, J = 11.4 Hz, 4H), 7.31–7.37 (m, 20H); ^{13}C (100 MHz, $CDCl_3$) δ 69.9, 70.2, 73.0, 73.5, 79.1, 127.6, 127.6, 127.7, 127.9, 128.05, 128.4, 138.0, 138.1; HRMS (ESI) calcd for $C_{34}H_{38}O_6Na$ $(M+Na)^+$: 565.2566, found: 565.2549.
Compound **8**. $[\alpha]_D^{30}$ −23.9 (*c* 1.0, $CHCl_3$); IR (neat): 3440, 2944, 1107 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.05 (s, 9H), 3.42 (dd, J = 10.0, 4.0 Hz, 1H), 3.51 (dd, J = 10.0, 6.0 Hz, 1H), 3.61–3.68 (m, 2H), 3.82–3.90 (m, 2H), 3.99–4.03 (m, 2H), 4.21 (AB quartet, J = 11.6 Hz, 2H), 4.53 (s, 2H), 7.09–7.11 (m, 2H), 7.24–7.42 (m, 14H), 7.66–7.69 (m, 4H); ^{13}C (100 MHz, $CDCl_3$)δ 19.4, 27.0, 70.3, 71.1, 71.4, 71.6, 72.0, 73.1, 73.3, 73.4, 127.6, 127.7, 127.8, 127.9, 128.3, 128.4, 129.7, 130.0, 132.7, 133.8, 135.8 136.0, 137.4, 137.9; HRMS (ESI) calcd for $C_{36}H_{44}O_6SiNa$ $(M+Na)^+$: 623.2805, found: 623.2805.
Compound **10**. $[\alpha]_D^{30}$ −16.0 (*c* 1.0, $CHCl_3$); IR (neat): 3472, 2928 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.05 (s, 9H), 2.99 (d, J = 6.3 Hz, 1H), 3.02 (s, 3H), 3.08 (d, J = 4.0 Hz, 1H), 3.42 (dd, J = 9.9, 4.0 Hz, 1H), 3.50 (dd, J = 9.9, 5.6 Hz, 1H), 3.78 (dd, J = 11.2, 6.4 Hz, 1H), 3.94 (dd, J = 11.2, 2.5 Hz, 1H), 3.96–3.99 (m, 2H), 4.07–4.17 (m, 1H), 4.23 (AB quartet, J = 11.7 Hz, 2H), 4.54 (AB quartet, J = 11.7 Hz, 2H), 4.76–4.80 (m, 1H), 7.09–7.13 (m, 2H), 7.27–7.36 (m, 14H), 7.65–7.68 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.3, 26.9, 38.4, 69.0, 69.6, 70.3, 71.3, 72.6, 73.1, 73.5, 80.5, 127.5, 127.6, 127.7, 127.7, 127.8, 128.3, 128.4, 129.7, 129.9, 132.4, 133.6, 135.7, 136.0, 137.4, 137.5; HRMS (ESI) calcd for $C_{37}H_{46}O_8SSiNa$ $(M+Na)^+$: 701.2580, found: 701.2588.
Compound **12**. $[\alpha]_D^{30}$ −18.7 (*c* 1.0, $CHCl_3$); IR (neat): 3472, 2928 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.04 (s, 18H), 2.94 (d, J = 5.4 Hz, 2H), 3.43–3.44 (m, 4H), 4.01 (dd, J = 10.6, 4.4 Hz, 2H), 4.15–4.20 (m, 6H), 7.07–7.09 (m, 4H), 7.22–7.25 (m, 8H), 7.29–7.34 (m, 8H), 7.38–7.41 (m, 2H), 7.69–7.71 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.4, 27.0, 70.7, 71.5, 72.9, 73.3, 127.3, 127.4, 127.4, 127.6, 128.1, 129.5, 129.7, 132.8, 134.3, 135.8, 136.1, 138.0; ESI-MS: $C_{52}H_{62}O_6Si_2Na$ $(M+Na)^+$: 861.3983; Anal. Calcd for $C_{52}H_{62}O_6Si_2$: C, 74.42; H, 7.45%. Found: C, 74.39; H, 7.49%.
Compound **14**. (acetonide derivative) $[\alpha]_D^{30}$ +10.9 (*c* 1.0, $CHCl_3$); IR (neat): 3472 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.35 (s, 6H), 2.31 (s, 3H), 3.56–3.60 (m, 2H), 3.67 (dd, J = 11.2, 3.6 Hz, 1H), 3.70 (dt, J = 5.6, 3.2 Hz, 1H), 3.77 (dd, J = 10.5, 3.2 Hz, 1H), 4.12 (t, J = 6.8 Hz, 1H), 4.23 (s, 2H), 4.38 (dd, J = 7.2, 4.0 Hz, 1H), 4.53 (s, 2H), 4.64 (d, J = 11.6 Hz, 1H), 4.77(d, J = 11.6 Hz, 1H), 4.90 (dt, J = 5.4, 3.2 Hz, 1H), 7.06 (d, J = 8.1 Hz, 2H), 7.08–7.11 (m, 4H), 7.24–7.35 (m, 11H), 7.63 (d, J = 8.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5, 27.0, 67.9, 70.1, 72.6, 72.9, 73.4, 76.7, 78.7, 79.1, 80.7, 110.2, 127.5, 127.5, 127.5, 127.6, 128.0, 128.0, 128.1, 128.2, 128.2, 128.3, 129.4, 134.0, 137.6, 138.2, 138.3, 144.3; HRMS (ESI) calcd for $C_{37}H_{42}O_8SNa$ $(M+Na)^+$: 669.2498, found: 669.2485.