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Sequential removal of the benzyl-type protecting groups PMB and NAP by oxidative cleavage using CAN and DDQ

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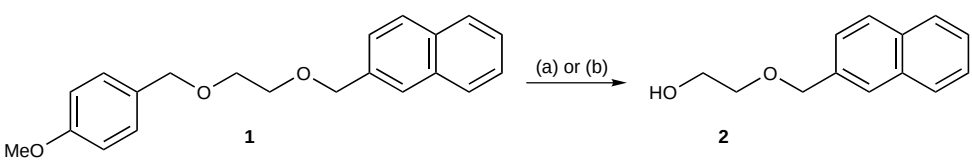
Abstract—The selective cleavage of the PMB (4-methoxybenzyl) group in the presence of the NAP (2-naphthylmethyl) group was achieved using CAN with a range of mono-saccharides. The NAP group can then be removed selectively in the presence of a benzyl group using DDQ. This provides a strategy for sequential deprotection of hydroxyl groups.

Previously, we discovered that the NAP (2-naphthylmethyl) group was more reactive towards catalytic hydrogenolysis than the benzyl group.[1] This observation has encouraged us to develop the NAP group as a new protecting group, and it has been demonstrated with a variety of substrates that NAP can be preferentially removed in the presence of other benzyl-type groups by hydrogenolysis.[1,2] Oxidative cleavage using DDQ (1,2-dichloro-4,5-dicyanobenzoquinone) or CAN [ammonium cerium(IV) nitrate] is an alternative method for the removal of benzyl-type groups. PMB can be selectively removed in the presence of a benzyl group[3] and recently the NAP group was cleaved in the presence of a benzyl group using DDQ.[4] In light of this, it would be interesting to probe the relative reactivities of PMB and NAP with DDQ and CAN. This could potentially lead to a new protection strategy, if PMB could be removed in the presence of NAP or vice versa. A model system with PMB and NAP linked to ethanediol was subjected to oxidative cleavage by CAN or DDQ (Scheme 1).

Removal of the PMB group predominated under both oxidation regimes, with the product **2** being isolated in each case. However, the isolated yields of the two reactions clearly pointed to CAN being a more selective reagent for the model system. To explore the synthetic utility of this observation, a series of glucose-based substrates were prepared by standard literature methods (Scheme 2).[5] These various glucose substrates were deprotected using CAN to give moderate isolated yields of the mono-deprotected sugars.[6]

A second series of galactose-based substrates were also prepared (Scheme 3). These were again subjected to the CAN oxidation conditions, in this case good yields of the expected mono-deprotected sugars were obtained.

In order to achieve a further level of selectivity, the four products from the galactose series (**16**, **18**, **22** and **25**) were further reacted with CAN. Unfortunately, poor selectivity was observed with all the substrates. A previous report found that NAP could be successfully removed in the presence of a benzyl group using DDQ.[4] Therefore, we investigated the removal of the NAP group from the four substrates using this oxidizing agent. With substrates **18** and **25** good yields were obtained. However, with substrates **16** and **22** a low yield was obtained. In the latter case **22** the low yield was a result of the free primary hydroxyl group competing with water to form the cyclic acetal side product.[7]



Scheme 1. *Reagents and conditions*: (a) CAN, acetone–H_2O 9:1, 81%; (b) DDQ, DCM–MeOH 9:1, 36%.

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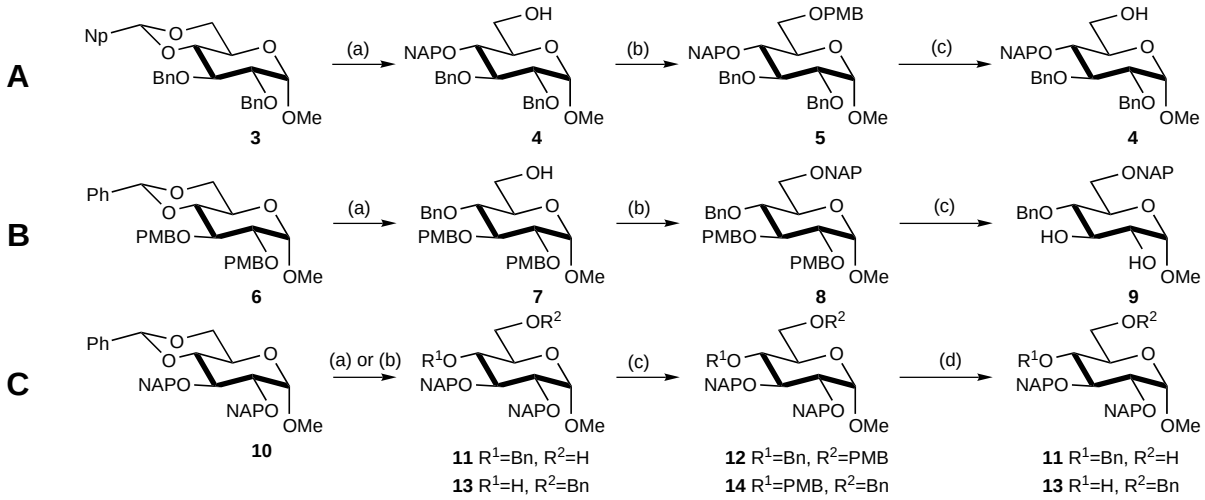
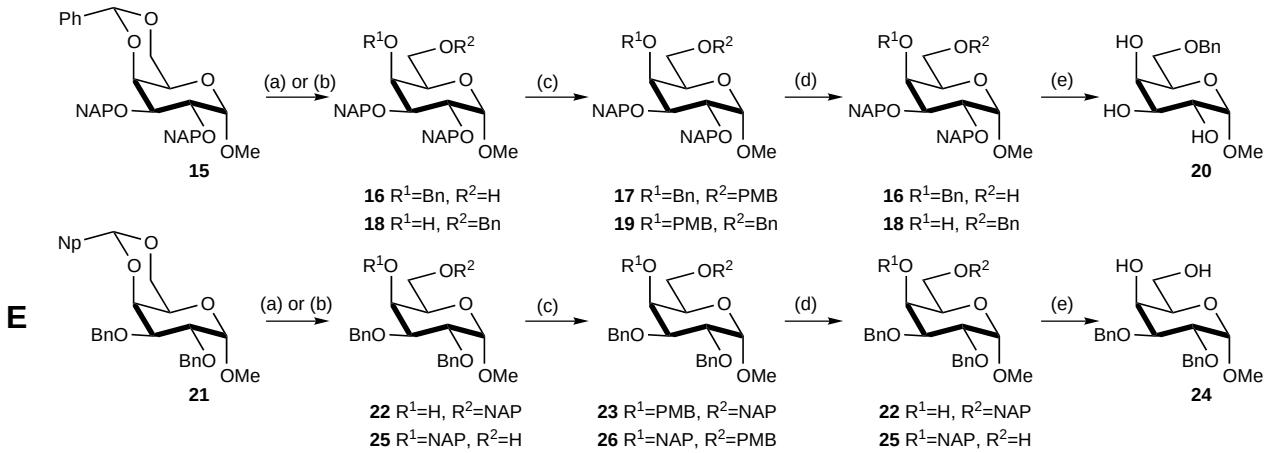


Scheme 2. *Reagents and conditions*: **A**: (a) DIBAL-H, toluene–DCM, 60%; (b) PMB-Cl, NaH, DMF, 84%; (c) CAN, acetone–H_2O 9:1, 68%. **B**: (a) DIBAL-H, toluene–DCM, 52%; (b) NAP-Br, NaH, DMF, 40%; (c) CAN, acetone–H_2O 9:1, 61%. **C**: (a) DIBAL-H, toluene–DCM, 76%; (b) Et_3SiH, TfOH, DCM, 4 Å MS, 50%; (c) PMB-Cl, NaH, DMF, 69% for **12**, 96% for **14**; (d) CAN, acetone–H_2O 9:1, 65% for **11**, 62% for **13**.



Scheme 3. *Reagents and conditions*: **D:** (a) Et_3SiH, $PhBCl_2$, DCM, 4 Å MS, 71%; (b) Et_3SiH, TfOH, DCM, 4 Å MS, 86%; (c) PMB-Cl, NaH, DMF, 59% for **17**, 92% for **19**; (d) CAN, acetone–H_2O 9:1, 70% for **16**, 78% for **18**; (e) DDQ, DCM–MeOH, 75% from substrate **18**. **E**: (a) Et_3SiH, $PhBCl_2$, DCM, 4 Å MS, 77%; (b) Et_3SiH, TfOH, DCM, 4 Å MS, 84%; (c) PMB-Cl, NaH, DMF, 98% for **23**, 87% for **26**; (d) CAN, acetone–H_2O 9:1, 83% for **22**, 72% for **25**; (e) DDQ, DCM–MeOH, 82% yield from substrate **25**.

In summary, a sequential deprotection strategy for sugars has been demonstrated, based upon the PMB, NAP and benzyl groups. Interestingly, CAN is found to be superior to DDQ for the selective removal of the PMB versus NAP group, whereas DDQ is more efficient for the deprotection of NAP in the presence of a benzyl group.

Experimental

Sample experimental procedures for the deprotection experiments. CAN deprotection of compound **19**. Compound **19** (304 mg, 0.444 mmol) was dissolved in acetone (4.5 ml) and water (0.5 ml). CAN (463 mg, 0.845 mmol) was added as a solid, followed by the dropwise addition of a solution of CAN (463 mg, 0.845 mmol) in acetone (0.9 ml) and water (0.1 ml) over 70 minutes. After a further 15 minutes, the reaction was poured into aqueous sodium bicarbonate solution, and extracted with chloroform. The product was purified on silica, eluting with hexane–ethyl acetate 7:3. This gave 195 mg of the product (78%). DDQ deprotection of compound **18**. Compound **18** (101 mg, 0.179 mmol) was dissolved in dichloromethane (1.4 ml) and methanol (0.4 ml). DDQ (163 mg, 0.718 mmol) was added in three equal portions at half-hour intervals. Two hours after the initial DDQ addition, the solvent was removed by evaporation, the residue taken up in chloroform and standard aqueous work-up carried out. Chromatography on silica in dichloromethane–methanol 10:1 gave **24** as a clear oil (38 mg, 75%).

The selected physical data for compounds **5**, **8**, **12**, **18**, **19**, **20** and **23**. Compound **5**: ^1H NMR: δ (400 MHz,

$CDCl_3$): δ 7.78 (t, 2H, $J=5.0$ Hz, ArH), 7.71 (d, 2H, $J=7.6$ Hz, ArH), 7.51 (br s, 1H, ArH), 7.44 (m, 2H, ArH), 7.35–7.24 (m, 10H, ArH), 7.20 (d, 2H, $J=8.4$ Hz, ArH), 6.77 (d, 2H, $J=8.4$ Hz, ArH), 4.98 (d, 1H, $J=11.2$ Hz), 4.93 (d, 1H, $J=11.2$ Hz), 4.81 (d, 1H, $J=11.2$ Hz), 4.78 (d, 1H, $J=12.0$ Hz), 4.65 (d, 1H, $J=12.0$ Hz), 4.62 (d, 1H, $J=3.6$ Hz), 4.55 (d, 1H, $J=12.0$ Hz), 4.55 (d, 1H, $J=11.2$ Hz), 4.35 (d, 1H, $J=12.0$ Hz), 3.98 (dd, 1H, $J=9.2$ Hz, 9.2 Hz), 3.67 (s, 3H, MeO), 3.76–3.67 (m, 3H), 3.60 (dd, 1H, $J=10.0$ Hz, 9.4 Hz), 3.56 (dd, 1H, $J=9.6$ Hz, 3.6 Hz), 3.37 (s, 3H, MeO); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.6, 139.3, 138.6, 136.2, 133.6, 133.3, 130.3, 130.0, 128.8, 128.8, 128.5, 128.4, 128.3, 128.0, 127.9, 126.8, 126.4, 126.2, 114.1, 98.7, 82.6, 80.2, 78.0, 76.1, 75.4, 73.8, 73.5, 70.5, 68.3, 55.6, 55.5; HRMS (EI+) calcd for $C_{40}H_{42}O_7Na$ (M^++Na) 657.282 82, found 657.285 00. Compound **8**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.83–7.75 (m, 4H, ArH), 7.47–7.43 (m, 3H, ArH), 7.29 (d, 2H, $J=8.4$ Hz, ArH), 7.25 (d, 2H, $J=8.4$ Hz, ArH), 7.19–7.13 (m, 3H, ArH), 7.01 (m, 2H, ArH), 6.87 (d, 2H, $J=8.4$ Hz, ArH), 6.84 (d, 2H, $J=8.4$ Hz, ArH), 4.89 (d, 1H, $J=10.8$ Hz), 4.81 (d, 1H, $J=11.2$ Hz), 4.76 (d, 1H, $J=12.0$ Hz), 4.74 (d, 1H, $J=12.0$ Hz), 4.73 (d, 1H, $J=10.8$ Hz), 4.62 (d, 1H, $J=12.0$ Hz), 4.60 (d, 1H, $J=12.4$ Hz), 4.58 (d, 1H, $J=3.2$ Hz), 4.42 (d, 1H, $J=11.2$ Hz), 3.95 (dd, 1H, $J=10.0$ Hz, 9.2 Hz), 3.80 (s, 3H, MeO), 3.79 (s, 3H, MeO), 3.73–3.58 (m, 5H), 3.53 (dd, 1H, $J=10.0$ Hz, 3.6 Hz), 3.37 (s, 3H, MeO); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.8, 159.6, 138.6, 135.8, 133.6, 133.4, 131.5, 130.8, 130.1, 130.0, 129.4, 128.6, 128.6, 128.3, 128.1, 127.9, 127.1, 126.5, 126.4, 126.3, 114.3, 114.2, 98.7, 82.3, 80.0, 78.1, 75.8, 75.4, 74.0, 73.4, 70.5, 68.9, 55.7, 55.7, 55.6; HRMS (EI+) calcd for $C_{41}H_{44}O_8Na$ (M^++Na) 687.293 39, found 687.292 90. Compound **12**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.83–7.71 (m, 8H, ArH), 7.51–7.44 (m, 6H, ArH), 7.25–7.22 (m, 5H, ArH), 7.11–7.09 (m, 2H, ArH), 6.82 (d, 2H, $J=8.4$ Hz, ArH), 5.16 (d, 1H, $J=11.2$ Hz), 4.99 (d, 1H, $J=11.2$ Hz), 4.95 (d, 1H, $J=12.4$ Hz), 4.86 (d, 1H, $J=12.4$ Hz), 4.83 (d, 1H, $J=11.2$ Hz), 4.67 (d, 1H, $J=3.6$ Hz), 4.55 (d, 1H, $J=11.6$ Hz), 4.45 (d, 1H, $J=11.6$ Hz), 4.39 (d, 1H, $J=11.6$ Hz), 4.06 (dd, 1H, $J=9.4$ Hz, 9.4 Hz), 3.81–3.76 (m, 1H), 3.74 (s, 3H, MeO), 3.70 (dd, 1H, $J=10.0$ Hz, 3.6 Hz), 3.65 (d, 1H, $J=9.4$ Hz), 3.65 (dd, 1H, $J=9.4$ Hz, 3.6 Hz), 3.60 (dd, 1H, $J=10.4$ Hz, 2.0 Hz), 3.40 (s, 3H, MeO); ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.4, 136.5, 134.6, 133.8, 131.5, 131.4, 131.3, 131.1, 128.1, 127.8, 127.6, 126.5, 126.2, 126.1, 125.9, 125.8, 125.8, 125.2, 124.6, 124.3, 124.2, 124.1, 124.1, 123.9, 111.9, 96.4, 80.3, 78.0, 75.9, 73.9, 73.2, 71.6, 71.3, 68.3, 66.1, 53.4, 53.4; HRMS (EI+) calcd for $C_{44}H_{44}O_7Na$ (M^++Na) 707.298 47, found 707.301 40. Compound **18**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.95–7.75 (m, 8H, ArH), 7.64–7.48 (m, 6H, ArH), 7.40–7.28 (m, 5H, ArH), 5.04–4.88 (m, 4H), 4.76 (d, 1H, $J=2.8$ Hz), 4.59 (dd, 2H, *Jgem* = 11.6, ABq), 4.12 (br s, 1H), 4.03 (dd, 1H, $J=10.0$ Hz, 3.6 Hz), 3.98 (dd, 1H, $J=10.0$ Hz, 2.8 Hz), 3.94 (t, 1H, $J=5.2$ Hz), 3.77 (dd, 1H, $J=10.0$ Hz, 5.2 Hz), 3.71 (dd, 1H, $J=10.0$ Hz, 5.8 Hz), 3.43 (s, 3H, MeO), 2.79 (br s, 1H, OH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.5, 136.3, 136.1, 133.7, 133.5, 128.9, 128.8, 128.7, 128.4, 128.2, 128.1, 127.3, 127.1, 126.6, 126.5, 126.4, 126.4, 126.3, 99.0, 78.1, 76.4, 74.2, 73.4, 70.2, 68.9, 68.8, 55.8; HRMS (EI+) calcd for $C_{36}H_{36}O_6$ (M^+) 564.251 18, found 564.251 25. Compound **19**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88–7.68 (m, 8H, ArH), 7.54 –7.40 (m, 6H, ArH), 7.38–7.23 (m, 5H, ArH), 7.16 (d, 2H, $J=8.4$ Hz, ArH), 6.72 (d, 2H, $J=8.4$ Hz, ArH), 5.01 (d, 1H, $J=12.4$ Hz), 4.97 (d, 1H, $J=12.8$ Hz), 4.90–4.86 (m, 3H), 4.71 (d, 1H, $J=4.0$ Hz), 4.54 (d, 1H, $J=11.6$ Hz), 4.48 (d, 1H, $J=12.0$ Hz), 4.38 (d, 1H, $J=12.0$ Hz), 4.11 (dd, 1H, $J=10.0$ Hz, 4.0 Hz), 4.00 (dd, 1H, $J=10.0$ Hz, 2.4 Hz), 3.95 (br, 1H), 3.89 (t, 1H, $J=6.4$ Hz), 3.73 (s, 3H), 3.49 (d, 2H, $J=6.4$ Hz), 3.37 (s, 3H, MeO); ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.5, 136.8, 136.4, 133.8, 133.7, 133.5, 133.4, 131.2, 130.3, 129.0, 128.8, 128.5, 128.4, 128.3, 128.2, 128.1, 128.1, 127.4, 127.3, 126.6, 126.5, 126.5, 126.4, 126.2, 126.1, 114.4, 114.0, 99.2, 79.5, 76.4, 75.3, 74.8, 74.0, 74.0, 73.9, 69.8, 69.7, 56.1, 55.8, 55.6; HRMS (EI+) calcd for $C_{44}H_{44}O_7Na$ (M^++Na) 707.298 47, found 707.297 40. Compound **20**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40–7.24 (m, 5H), 4.83 (d, 1H, $J=4.0$ Hz), 4.59 (s, 2H), 4.07 (br s, 1H), 3.90 (t, 1H, $J=4.8$ Hz), 3.83 (td, 1H, $J=9.2$ Hz, 3.6 Hz), 3.80–3.73 (m, 2H), 3.74–3.70 (m, 1H), 3.42 (s, 3H), 2.91 (d, 1H, $J=2.0$ Hz, OH), 2.56 (d, 1H, $J=5.6$ Hz), 2.02 (d, 1H, $J=9.6$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.0, 128.9, 128.3, 128.1, 99.9, 74.3, 71.8, 70.5, 70.4, 70.2, 69.2, 56.0; HRMS (EI+) calcd for $C_{14}H_{20}O_6Na$ (M^++Na) 307.115 76, found 307.117 30. Compound **23**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85–7.60, 7.50–7.20 (m, 17H, ArH), 7.10 (d, 2H, $J=8.4$ Hz, ArH), 6.78 (d, 2H, $J=8.4$ Hz, ArH), 5.06 (d, 1H, $J=11.2$ Hz), 4.84 (dd, 2H, $J=12.0$, 6.8 Hz), 4.74–4.67 (m, 4H), 4.40–4.37 (dd, 2H, *Jgem* = 11.6 Hz, ABq), 4.06 (dd, 1H, $J=10.0$, 3.6 Hz), 3.98–3.86 (m, 3H), 3.94 (s, 3H, MeO), 3.54–3.47 (m, 2H), 3.36 (s, 3H, MeO); ^{13}C NMR (100 MHz, $CDCl_3$): δ 139.0, 136.5, 133.4, 130.4, 129.8, 128.8, 128.7, 128.5, 128.3, 128.0, 127.9, 127.9, 127.3, 126.8, 126.4, 126.3, 114.2, 99.3, 79.6, 77.0, 75.5, 75.1, 74.1, 73.8, 73.6, 69.6, 69.1, 55.8, 55.7; HRMS (EI+) calcd for $C_{40}H_{42}O_7$ (M^+) 634.293 05, found 634.295 95.

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References

1. Gaunt, M. J.; Yu, J.; Spencer, J. B. *J. Org. Chem.* **1998**, *63*, 4172–4173.
2. (a) Gaunt, M. J.; Boschetti, C. E.; Yu, J.; Spencer, J. B. *Tetrahedron Lett.* **1999**, *40*, 1803–1806; (b) Papageorgiou, E. A.; Gaunt, M. J.; Yu, J.; Spencer, J. B. *Org. Lett.* **2000**, *2*, 1049–1051.

3. Oikawa, Y.; Yoshioka, T.; Yonemitsu, O. *Tetrahedron Lett*. **1982**, *23*, 885–888.
4. Xia, J.; Abbas, S. A.; Locke, R. D.; Piskorz, C. F.; Alderfer, J. L.; Matta, K. L. *Tetrahedron Lett*. **2000**, *41*, 169–173.
5. (a) Formation of acetals: Ferro, V.; Mocerino, M.; Stick, R. V.; Tilbrook, D. G. M. *Aust. J. Chem*. **1988**, *41*, 813–815; (b) Selective ring–opening using DIBAH: Gaunt, M. J., PhD Thesis, University of Cambridge, 1999; (c) Selective ring-opening using Et_3SiH: Sakagami, M.; Hamana, H. *Tetrahedron Lett*. **2000**, *41*, 5547–5551; (d) Protection of alcohols: Amano, S.; Ogawa, N.; Ohtsuka, M.; Chida, N. *Tetrahedron* **1999**, *55*, 2205–2224.
6. Removal of the PMB group with CAN and DDQ was also compared using substrate **5**. CAN was shown, as was found with the linker experiment, to be superior to DDQ.
7. Oikawa, Y.; Yoshioka, T.; Yonemitsu, O. *Tetrahedron Lett*. **1982**, *23*, 889–892.