Pergamon

Tetrahedron Letters 41 (2000) 4949–4953

TETRAHEDRON LETTERS

Preparation of (2-naphthyl)methylene acetals of glycosides and their hydrogenolytic transformation into 2-naphthylmethyl (NAP) ethers†

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Received 6 April 2000; accepted 4 May 2000

Abstract

Dioxane- and dioxolane-type (2-naphthyl)methylene acetals of glycosides were prepared by acid-catalyzed transacetalization reactions. The acetals were cleaved using either AlH_3 ($LiAlH_4$:$AlCl_3$ = 3:1), $NaCNBH_3$–HCl or $BH_3{\cdot}Me_3N$–$AlCl_3$ reagents. Reaction of the 4,6-*O*-acetals with AlH_3 yielded 4-*O*NAP ethers whereas the other two reagents gave 6-*O*NAP derivatives with excellent regioselectivity. In dioxolane-type acetals the direction of the cleavage with all three reagents is determined by the stereochemistry of the acetal center; *equatorial O*NAP/*axial*-hydroxy derivatives are obtained from the *exo*-naphthyl isomers; *endo*-naphthyl acetals, on the other hand, give rise to the formation of *axial O*NAP/*equatorial*-hydroxy compounds. The NAP ether and the (2-naphthyl)methylene acetal protecting groups can both be readily removed by treatment with DDQ.

The protecting group strategy is an essential component in the design and syntheses of complex oligosaccharides.[1] Acetals[2] and easily removable ether[3] groups are among those most frequently used. The well-controlled transformation of benzylidene acetals into benzyl ethers[4–8] by hydrogenolysis has become an important route to prepare differentially substituted compounds. The blocking group strategy based on benzyl ethers is well supplemented by the *p*-methoxy counterpart.[9]

Although 2-naphthylmethyl (NAP) ethers have been previously described,[10–12] their preparative usefulness was rediscovered[13,14] only very recently. It was shown that NAP ethers can be hydrogenolyzed in the presence of benzyl ethers or esters,[11] and they are less sensitive to acids

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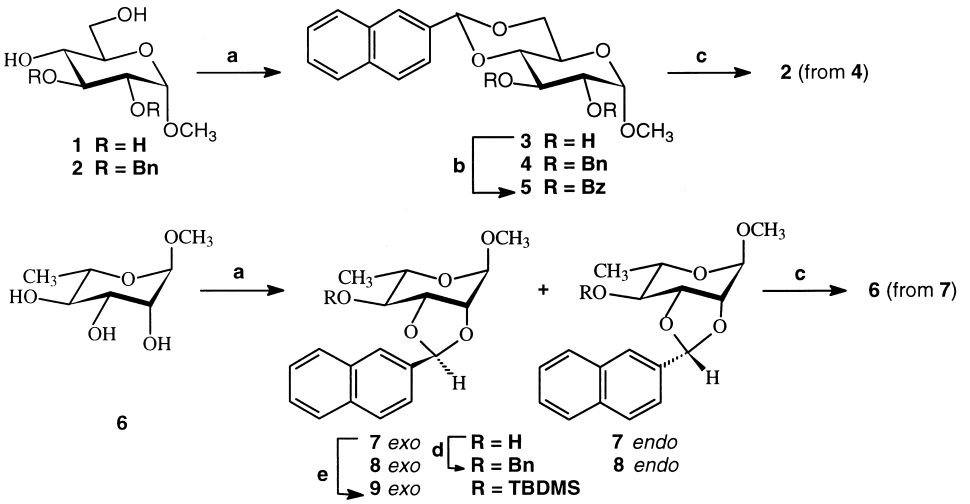
† Dedicated to Prof. Ralf Miethchen on the occasion of his 60th birhday.

0040-4039/00/$ - see front matter
PII: S0040-4039(00)00735-8

than *p*-methoxybenzyl ethers. The most important observation, however, is that NAP ethers can easily be removed by DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone) under conditions when other usual protecting groups like acetyl, pivaloyl, phthalimido, benzyl and benzylidene survive.[13,14] Although the NAP group can be removed from the anomeric position, it is, on the other hand, stable under very different glycosylation reaction conditions. Syntheses of very complex oligosaccharides, e.g. a branched hexasaccharide containing the NeuAcα2,3(SO_3Na-6)Galβ1,3Gal-*N*Acα sequence, have also been accomplished.[14]

Because the hydrogenolysis of benzylidene acetals results in benzyl ethers[4,5] and the direction of ring opening is well documented, we were keen to gain insight into the behaviour of 2-naphthylmethylene acetals under different hydrogenolytic conditions. To our knowledge, until now, only the synthesis of *n*-pentenyl-[2,3-di-*O*-benzoyl-4,6-*O*-(2-naphthyl)methylene-β-D-galactopyranosyl]-(1→4)-2,3,6-tri-*O*-benzoyl-β-D-glucopyranoside has been reported.[15] Methyl α-D-glucopyranoside (**1**) or its 2,3-di-*O*-benzyl derivative[16] (**2**) reacted with 2-naphthaldehyde or with its di-*O*-methyl acetal in DMF or MeCN/DMF in the presence of *p*-TSA to give crystalline dioxane-type acetals (**3** and **4**) (Scheme 1). Benzoylation of **3** gave **5**. In a similar way, two diastereoisomeric forms of the 2,3-*O*-(2-naphthyl)methylene acetals (**7***exo* and **7***endo*) were obtained from methyl α-L-rhamnopyranoside (**6**). The **7***exo*-isomer crystallized spontaneously. The mixture of **7***exo* and **7***endo* was benzylated and the products could be separated using column chromatography (**8***exo* and **8***endo*). The **7***exo*-isomer was converted into 4-*O*TBDMS (*tert*-butyldimethylsilyl) ether (**9***exo*).



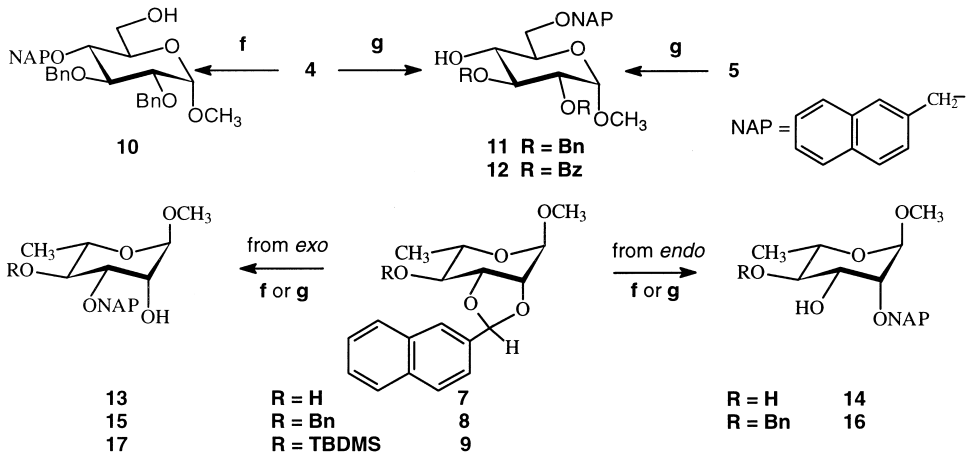
Scheme 1. Reaction conditions: (a) 2-(dimethoxymethyl)naphthalene (1.2 equiv.), *p*TSA, DMF, rt, overnight, or 2-naphthaldehyde (1.5 equiv.), CH_3CN–DMF, pTSA, 2 days (90–97%); (b) benzoyl chloride, pyridine; (c) DDQ (0.4 equiv.) in CH_3CN:H_2O (9:1), 2–3 h (95–97%); (d) benzyl bromide (1.1 equiv.), NaH (1.3 equiv.), DMF (98%); (e) TBDMsCl (1.2 equiv.), imidazole (2.4 equiv.), DMF, overnight (89%)

The structures of the synthesized acetals were ascertained on the basis of NMR spectra. Characteristic ^{1}H and ^{13}C NMR resonances were found to be between 5.6–5.8 and 101–102 ppm, respectively, for the acetal protons and carbons in the dioxane-type acetals (**3**, **4** and **5**). In the dioxolane-type acetals, on the other hand, the corresponding resonances were at ~6.3 and 103

ppm, respectively, for the *exo*-naphthyl isomers and below 6.1 and above 104 ppm for the *endo*-naphthyl isomers.

Three reagents are generally used for the ring-cleavage of dioxane-type acetals: (i) $LiAlH_4$–$AlCl_3$;[4,5] (ii) $NaCNBH_3$–HCl[7] (or other strong acids); and (iii) $BH_3{\cdot}Me_3N$–$AlCl_3$.[8] The first one gives rise to the formation of 4-*O*-alkyl/aryl/6-OH products predominantly. Reagents (ii) and (iii) induce reverse regioselectivity producing 4-OH/6-*O*-alkyl/aryl derivatives; the regioselectivity is, however, strongly dependent on the solvent used.

Hydrogenolysis of compound **4** with AlH_3 ($LiAlH_4$:$AlCl_3$, 3:1) reagent in ether:dichloromethane (1:1) at room temperature gave a 97:3 (HPLC) mixture of the methyl 2,3-di-*O*-benzyl-4-*O*-(2-naphthyl)methyl-α-D-glucopyranoside (**10**) and its regioisomer, methyl 2,3-di-*O*-benzyl-6-*O*-(2-naphthyl)methyl-α-D-glucopyranoside (**11**). The reaction required 2 h, and the main product **10** could be isolated in crystalline form (Scheme 2).



Scheme 2. Reaction conditions: (f) $LiAlH_4$ (3 equiv.), $AlCl_3$ (1 equiv.) CH_2Cl_2:Et_2O (1:1), rt, 20 min–3 h (90–98%); (g) $NaCNBH_3$ (12 equiv.), HCl in THF or $Me_3N{\cdot}BH_3$ (6 equiv.), $AlCl_3$ (6 equiv.), 4 Å MS in THF, 3–4 h (90–97%)

Hydrogenolysis of compound **4** by $NaCNBH_3$–HCl[7] in THF at room temperature required 2 h giving **10**:**11** in a ratio of 9:91; **11** was isolated by column chromatography as a syrupy compound. A very similar product distribution was observed in the case of the $BH_3{\cdot}Me_3N$–$AlCl_3$ reagent. The ratio of **10**–**11** was 7:93. Treatment of compound **5** with $BH_3{\cdot}Me_3N$–$AlCl_3$ the methyl 2,3-di-*O*-benzoyl-6-*O*-(2-naphthyl)methyl-α-D-glucopyranoside (**12**) was obtained with 74% yield.

The structures of **10**, **11** and **12** are evident from ^{13}C NMR data. In **10** the C-6 resonance at 61.8 ppm indicates the presence of a CH_2–OH group, whereas in **11** and **12** the downfield shifts for C-6s (69.4 and 69.3 ppm, respectively) clearly demonstrate the presence of the NAP group in position 6.

In the case of dioxolane-type acetals the direction of the ring-cleavage is determined by the configuration of the acetalic carbon. *Equatorial* ethers are obtained from the *exo* (alkyl, aryl)-acetals; the *endo*-isomers, on the other hand, react in an opposite way and *axial*-ethers are produced.[7,17,18] This general rule was observed for all of the three reagents mentioned above.

It was therefore interesting to investigate the ring-cleavage reaction of the new dioxolane-type (2-naphthyl)methylene acetals.

The crystalline **7***exo*-isomer reacted with AlH_3 to give 3-*O*-(2-naphthyl)methyl ether **13**, the amount of the 2-*O*-(2-naphthyl)methyl ether isomer (**14**) being less than 5%. Similarly, the **8***exo* furnished 4-*O*-benzyl-3-*O*-(2-naphthyl)methyl ether **15**, while 4-*O*-benzyl-2-*O*-(2-naphthyl)methyl isomer **16** was the product of hydrogenolysis of the **8***endo* compound. Only the traces of the other isomers could be detected. Using $BH_3 \cdot Me_3N–AlCl_3$ in the presence of powdered molecular sieves (4 Å) complete stereoselectivity could be observed; in the case of the *exo*-naphthyl isomers the reagent attacks at the *axial* oxygen of the dioxolane ring. With *endo*-naphthyl-isomers the place of the attack is, however, at the *equatorial* oxygen. The ring cleavage reaction of the dioxolane-type acetals proceeds under very mild conditions (rt, 15 min).

Compound **9***exo*, containing a silyl ether protecting group, also followed the rule observed above: reaction with AlH_3 resulted in the formation of 3-*O*NAP (**17**). Oxidation of compound **14** with $NaIO_4$ indicated the presence of a vicinal diol and proved that it is a 2-ether derivative; compound **13** was stable under these conditions. These analytical experiments proved not only the structure of the two isomeric ethers (**13** and **14**) but, at the same time, attested to the stability of the *O*NAP group in the presence of $NaIO_4$. The ^{13}C NMR spectra provided further proof for the structure of the 2-*O*NAP derivatives **14** and **16**: a ~–2 ppm β-shift could be observed for the anomeric carbon atom.

The ^{13}C NMR α-shifts of *O*NAP ethers are generally ~+7 ppm. Complete ^{1}H and ^{13}C NMR assignments were accomplished for all new compounds. The characteristic NMR and physical data are given in Ref. 19.

We also investigated the stability and the compatibility of the new acetals and of the NAP groups with other generally used protecting groups. In the presence of the (2-naphthyl)methylene acetals alkylation, acylation or silylation can be achieved with very high yield. The removal of isopropylidene, benzylidene as well as dithioacetal protecting groups of sugars by DDQ has been reported.[20,21] The new acetal blocking group reported here can also be removed using DDQ at room temperature within a relatively short reaction time (2–3 h), and the yields are nearly quantitative. These reactions required 0.4 equivalents of freshly crystallized DDQ.

The NAP ethers can also be cleaved in the presence of a variety of blocking groups (acetyl, pivaloyl, *N*Phth, Bn and benzylidene).[13,14] We have found that DDQ smoothly removed the NAP group while other protecting groups (benzoyl and TBDMS) survived. On the other hand, various reactions, like acid hydrolysis of acetal groups (isopropylidene, benzylidene), acylation, alkylation, glycosylation (under various conditions), 1-*O*-imidate formation or silylation of free OH groups, can be performed in the presence of NAP.

In summary, we have demonstrated the usefulness of the preparation of (2-naphthyl)methylene acetals and their transformation into NAP ethers by hydrogenolysis using three different reagents. These compounds can be regarded as challenging new protecting groups especially suitable for the preparation of very valuable sugar derivatives.

Acknowledgements

This work was supported by grants from the Hungarian Academy of Sciences (A.L.), the Hungarian Scientific Research Fund (OTKA T 25244) and the Ministry of Education (FKFP 500/97).

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19. The NMR spectra were recorded with Bruker AM-360 and Bruker DRX-500 spectrometers in $CDCl_3$. Optical rotations were measured in $CHCl_3$. All compounds gave satisfactory spectroscopic data. Selected spectroscopic and physical data are the following: compound **3**: mp 194°C (EtOAc) $[\alpha]_D$ +99.30 (*c* 0.50), ^{1}H NMR δ 5.61 (1H, s, acetalic); ^{13}C NMR δ 101.89 ($C_{acetalic}$); compound **4**: mp 118°C (EtOH), $[\alpha]_D$ –54.80 (*c* 0.33), ^{1}H NMR δ 5.68 (1H, s, acetalic); ^{13}C NMR δ 101.3 ($C_{acetalic}$); compound **5**: mp 216°C (EtOAc–*n*hexane), $[\alpha]_D$ +35.61 (*c* 0.40), ^{1}H NMR δ 5.74 (1H, s, acetalic); ^{13}C NMR δ 101.8 ($C_{acetalic}$); compound **7***exo*: mp 108°C (EtOAc–*n*hexane), $[\alpha]_D$ –2.42 (*c* 0.28), ^{1}H NMR δ 6.31 (1H, s, acetalic); ^{13}C NMR δ 103.1 ($C_{acetalic}$); compound **8***exo*: mp 70°C (EtOH), $[\alpha]_D$ –69.78 (*c* 0.44) ^{1}H NMR δ 6.14 (1H, s, acetalic); ^{13}C NMR δ 103.0 ($C_{acetalic}$); compound **8***endo*: $[\alpha]_D$ –21.30 (*c* 0.34), ^{1}H NMR δ 6.08 (1H, s, acetalic); ^{13}C NMR δ 104.08 ($C_{acetalic}$); compound **9**: $[\alpha]_D$ –14.83 (*c* 0.37), ^{1}H NMR δ 6.25 (1H, s, acetalic); ^{13}C NMR δ 102.7 ($C_{acetalic}$); compound **10**: mp 68–73°C (*c*hexane), $[\alpha]_D$ +1.07 (*c* 0.37), ^{13}C NMR δ 61.8 (C-6); compound **11**: $[\alpha]_D$ +8.24 (*c* 0.53), ^{13}C NMR δ 69.4 (C-6); compound **12**: $[\alpha]_D$ +109.95 (*c* 0.67), ^{13}C NMR δ 69.3 (C-6); compound **13**: mp 110°C (EtOAc–*n*hexane), $[\alpha]_D$ –12.16 (*c* 0.11), ^{13}C NMR δ 100.4 (C-1), 79.8 (C-3), 67.8 (C-2); compound **14**: $[\alpha]_D$ +15.84 (*c* 0.53), ^{13}C NMR δ 99.1 (C-1), 78.1 (C-2), 71.5 (C-3); compound **15**: $[\alpha]_D$ –30.29 (*c* 0.33); ^{13}C NMR δ 100.04 (C-1), 79.94 (C-3), 68.47 (C-2); compound **16**: $[\alpha]_D$ –11.31 (*c* 0.30); compound **17**: $[\alpha]_D$ –53.85 (*c* 0.40), ^{13}C NMR δ 100.1 (C-1), 80.4, 72.7, 68.4 (C-2, C-3, C-4).
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