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Selective hydrogenolysis of benzyl ethers in the presence of benzylidene acetals with Raney nickel

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Abstract—A simple method to remove selectively a benzyl group protecting a hydroxyl function in the presence of a benzylidene acetal by catalytic hydrogenolysis with Raney nickel is reported. This method was successfully applied to the synthesis of the C1–C14 fragment of dolabelides.

Benzylidene acetals are frequently used as 1,2- and 1,3-diol protecting groups. They can be conveniently removed under neutral conditions by hydrogenolysis, or by acid hydrolysis. However, discrimination among reactive sites of the same class of benzyl-type protecting group is required for the synthesis of complex natural products. Indeed, in the course of our studies toward the synthesis of dolabelides, we needed to deprotect selectively the benzyl group at C14 in the presence of a *para*-methoxybenzyl (PMB) ether at C3 and the benzylidene acetal protecting the diol at C9 and C11 (Fig. 1).

Catalytic hydrogenolysis offers the mildest method for deprotecting benzyl ethers. Moreover, the electronic properties of the aromatic ring introduce sufficient latitude in the rate of hydrogenolysis of benzyl ether protecting groups to allow selective deprotection. For example, selective hydrogenolysis of a secondary benzyl ether in the presence of a primary *para*-methoxybenzyl (PMB) ether is feasible using Raney nickel in ethanol.[1–3] However, when Tatsuta et al. used this method during their synthesis of herbimycin A, they observed the concomitant deprotection of a 4,5-disubstituted 1,3-benzylidene acetal.[4] Indeed, only a few cases of selective removal of benzyl groups in the presence of 1,3-benzylidene acetals have been reported, and only for carbohydrate derivatives. Three of these methods involve transfer hydrogenation catalyzed by palladium or palladium hydroxide on carbon with cyclohexene,[5] ammonium formate[6] or hydrazine hydrate.[7] The last one involves the oxidation of the benzyl ether with tetrabutylammonium peroxydisulfate, followed by debenzoylation with sodium methoxide.[8]

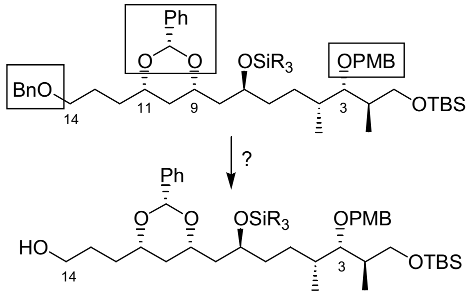

Figure 1. Selective deprotection of the Cl–Cl4 fragment of dolabelides.

In this letter, we describe the selective deprotection of benzyl ethers in some representative compounds in the presence of other benzyl-type protecting groups by hydrogenolysis with Raney nickel.[9]

We first examined the case of a simple monosubstituted 1,3-benzylidene acetal. Selective deprotection of even a primary benzyl group was not possible (Table 1, entry 1). Fortunately, primary and even secondary benzyl ethers can be selectively deprotected in the presence of 4,6-disubstituted 1,3-benzylidene acetals (entries 2 and 3). As expected, a PMB ether was stable under these conditions (entry 4). Application of this method to the C1–C14 fragment of dolabelides was successful, as we managed to deprotect the benzyl group at C14 without hydrogenolysis of the PMB group or the benzylidene

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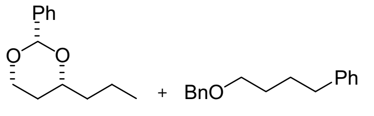
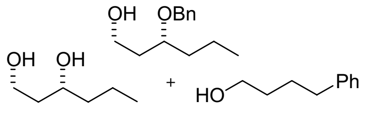
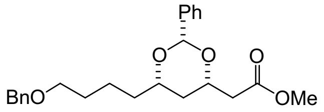
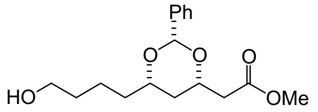
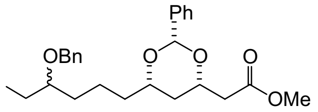
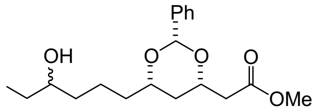
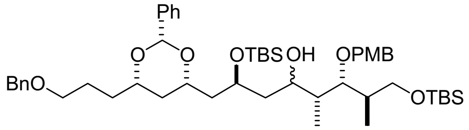
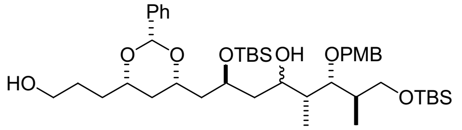
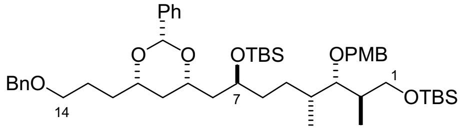
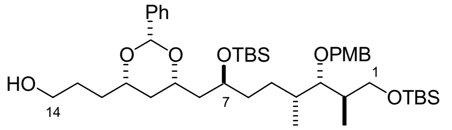
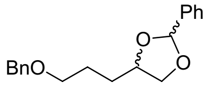
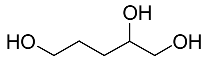
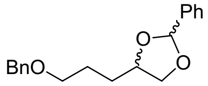
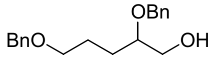
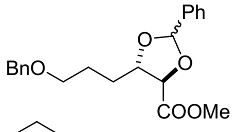
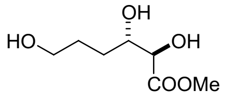
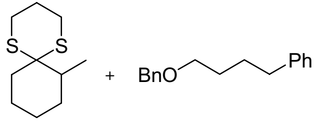
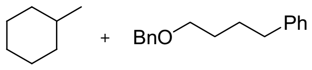
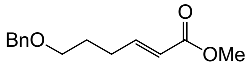
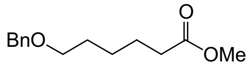
Table 1. Cleavage of benzyl ethers by catalytic hydrogenation using Raney nickel in ethanol

Entry	Starting materials	Products	Yield (%)
1			—
2			70–80
3			72–85
4			81
5			87
6			82
7			86[a,b]
8			79
9			—[c]
10			78

[a] Reaction carried out at 0 °C.

[b] Yield based on 25% recovered starting material.

[c] Quantitative recovery of the benzyl ether.

acetal (entry 5). However, the selectivity was not total for this substrate when a less bulky protecting group was present on the alcohol at C7: a 6:3:1 mixture of debenzylated product/starting material/triol was obtained with the TES derivative.

With 1,2-benzylidene acetals, selective deprotection of benzyl groups was not possible, even with a disubstituted acetal (entries 6 and 8). Interestingly, monoreduction of 1,2-benzylidene acetal occurred very cleanly without deprotection of the benzyl group when carrying out the experiment at 0 °C (entry 7).

On the other hand, we also showed that a 1,3-dithiane or a conjugated ester can be selectively hydrogenated with Raney nickel in the presence of a primary benzyl ether (entries 9 and 10).

In conclusion, we have investigated the hydrogenation of *O*-benzyl ether protecting groups in the presence of diverse functional groups by catalytic hydrogenolysis with Raney nickel in ethanol.

Acknowledgments

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References and notes

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9. General procedure for the hydrogenolysis of Bn groups over Raney Ni catalyst: a solution of a Bn ether in absolute EtOH (0.1 M) was stirred under a hydrogen atmosphere (1 bar) over excess Raney Ni (Fluka, used as received) at 20 °C. After the reaction was complete, the catalyst was removed by filtration and the filtrate concentrated in vacuo. The residue was purified by chromatography on silica gel to give the corresponding product.