

Studies on the hydrogenolysis of benzyl ethers

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Abstract—Selective hydrogenolysis of benzyl ethers can be achieved by the appropriate choice of the catalyst, solvent, and concentration, which facilitates the design of *O*-benzyl based protecting group strategies for the synthesis of natural products.

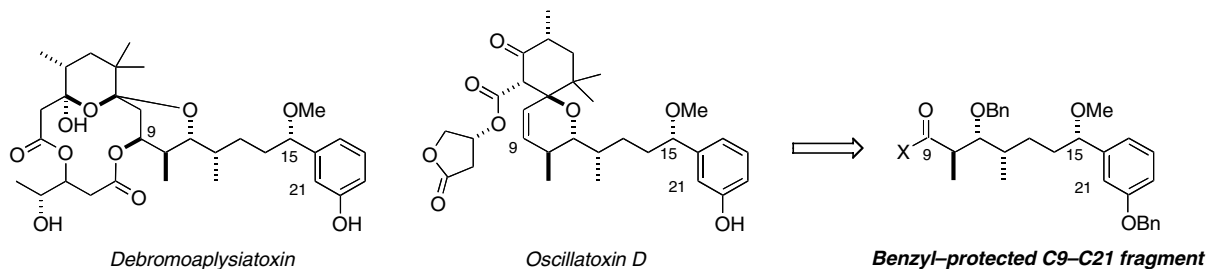
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Benzyl ether is one of the most widely used protecting groups of alcohols since it is easily installed, stable to a broad scope of reaction conditions and readily removed in the presence of many common functionalities through hydrogenation, dissolving metal reduction, oxidative treatments, or Lewis acid mediated cleavage.¹ Among these methodologies, catalytic hydrogenolysis offers the mildest option for removing benzyl protecting groups because of its technical simplicity and the quantitative yields usually achieved without the requirement of further purification of the reaction mixture. In spite of these advantages, studies on the selective hydrogenolysis of benzyl ethers are scarce and, more importantly, there is a lack of information about the experimental conditions that permit the removal of true benzyl protecting groups of alcohols when other oxygenated benzylic positions present in the same structure have to remain intact.^{2–4} These limitations have traditionally been addressed through the development of more elaborate benzyl-like protecting groups. However, the usefulness

of some of these is compromised by a loss of robustness that often introduces additional synthetic difficulties.^{5–7} Therefore, it would be worth gaining insight into the experimental conditions required for the selective cleavage of benzyl protecting group of alcohols in the presence of other ethers placed at a benzylic position.

We came across the abovementioned limitations during the preparation of the C9–C21 fragment of debromoaplysiatoxin and oscillatoxin D.⁸ As represented in Scheme 1, we envisaged that protection of C11 and C20 alcohols as benzyl ethers would fulfil the stability requirements expected along the synthesis in such a way that they could be cleanly and simultaneously removed by catalytic hydrogenolysis in a late step.⁹

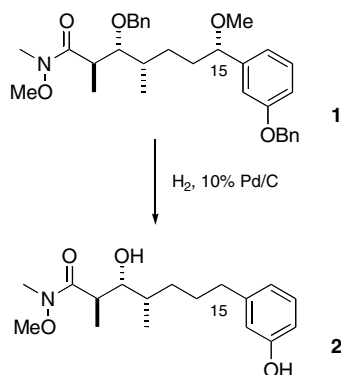
Surprisingly, this approach earlier proved troublesome. Indeed, preliminary trials of hydrogenolysis on the C9–C21 advanced intermediate **1** shown in Scheme 2 in the presence of 10% Pd/C in methanol (1 atm, rt,



Scheme 1.

Keywords: Protecting groups; Benzyl ether; Selective hydrogenolysis.

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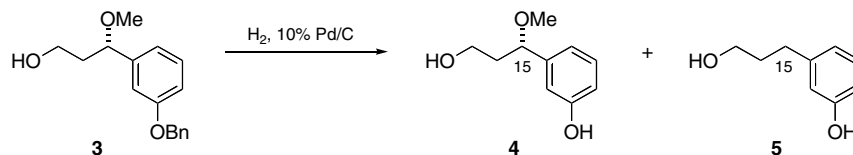


Scheme 2.

3 h) produced quantitatively the corresponding diol **2** lacking methyl ether at C15.¹⁰

It was clear that the overreduction of the C15 benzylic position jeopardized the whole synthetic approach and more selective hydrogenolysis conditions were required. Thus, we first carefully examined the hydrogenolysis of alcohol **3**, a precursor of Weinreb amide **1**, catalyzed by 10% Pd/C in a wide range of solvents. Keeping in mind that the experimental conditions evolved from such a model should be applied to tiny amounts of a structurally more complex substrate, we restricted our analysis to hydrogenolysis (1 atm, rt) of highly diluted solutions (0.035 M) in the presence of moderately important amounts of catalyst (25 mol % of Pd). The results are summarized in Table 1.

Analysis of the former data clearly proved that the kinetics of the deprotection of **3** was highly solvent dependent (EtOAc \gg hexane $>$ methanol $>$ toluene).¹¹ Additionally, concentration played a crucial role (compare entries 3–4 and 6–7) and must be carefully considered in order to minimize the formation of diol **5**. Thus, undesired overreduction of C15 methyl ether could only be avoided when hydrogenolysis in the presence of 10% Pd/C was carried out in toluene at low concentrations.

Table 1. Hydrogenolysis of **3** in the presence of 10% Pd/C

Entry	Solvent	Time (h)	3 ^a (%)	4 ^a (%)	5 ^a (%)
1	EtOAc	1	—	—	100
2	Hexane	1	—	25	75
3	MeOH	1	50	50	—
4 ^b	MeOH	1	—	85	15
5	Toluene	1	80	20	—
6	Toluene	5	10	70	20
7 ^c	Toluene	5	60	40	—

^a Determined by analysis of the ¹H NMR of the reaction mixture.

^b Concentration 0.1 M.

^c Concentration 0.02 M.

However, it was difficult to anticipate the behavior of an aliphatic benzyl ether and it was advisable to look for more selective and reliable conditions. Therefore, other catalysts were next surveyed. The results are summarized in Table 2.¹²

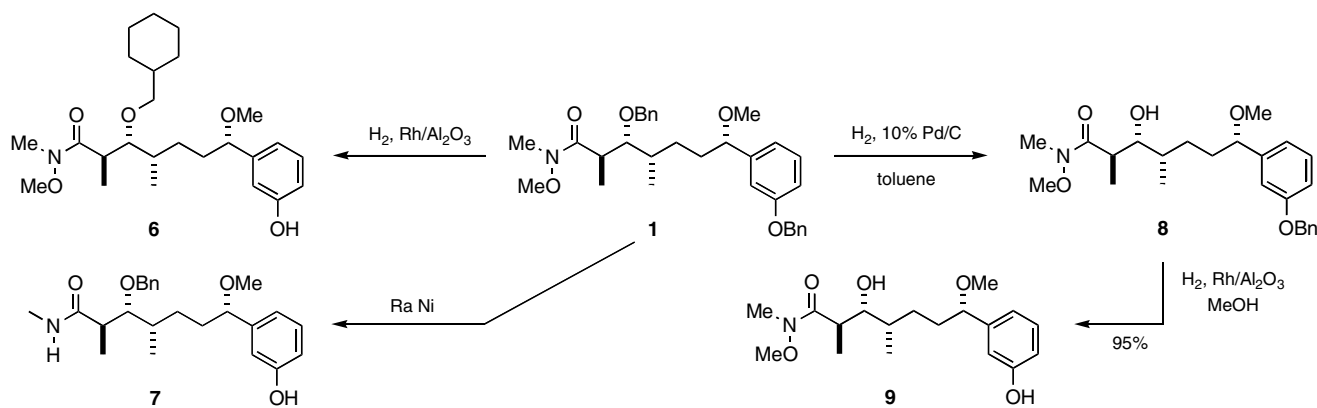
Pearlman's catalyst, Pd(OH)₂/C, turned out to be more active than 10% Pd/C and led to the overreduced diol **5** both in methanol and toluene more easily (compare entries 1 and 2 in Table 2 to entries 3 and 5 in Table 1, respectively). Interestingly, this side reaction was completely suppressed using rhodium or Raney nickel catalysts (see entries 3–5 and 6–8 in Table 2, respectively). Indeed, both catalysts were able to promote the deprotection of C20 phenol without affecting methyl ether at the C15 benzylic position in such a way that hydrogenolyses of **3** in their presence afforded the desired alcohol **4** in quantitative yields irrespective of the reaction times (see entries 3–4 and 6–8 in Table 2). It is worth mentioning that Raney nickel removed the aromatic benzyl protecting group of **3** without hydrogen atmosphere (see entries 6 and 7 in Table 2), which undoubtedly increased its appeal for such reactions.¹³ Having found the experimental conditions that allowed for deprotection of C20 benzyl ether without affecting the integrity of C15 methyl ether, we focused back our attention on the Weinreb amide **1**. Unexpectedly, application of the

Table 2. Hydrogenolysis of **3** employing other catalysts than 10% Pd/C

Entry	Catalyst	Solvent	Time (h)	3 ^a (%)	4 ^a (%)	5 ^a (%)
1	Pd(OH) ₂ /C	MeOH	1	—	90	10
2	Pd(OH) ₂ /C	Toluene	1	40	55	5
3	Rh/Al ₂ O ₃	MeOH	4	—	100	—
4	Rh/Al ₂ O ₃	EtOH	18	—	100	—
5	Rh/Al ₂ O ₃	Toluene	5	>95	<5	—
6 ^b	Ra Ni	MeOH	1	10	90	—
7 ^b	Ra Ni	MeOH	2.5	—	100	—
8	Ra Ni	MeOH	24	—	100	—

^a Determined by analysis of the ¹H NMR of the reaction mixture.

^b Without H₂ atmosphere.



Scheme 3.

mildest conditions based on rhodium catalyst to **1** removed the C20 benzyl group but produced the reduction of the aromatic ring of the protecting benzyl group of C11 secondary alcohol, leading to ether **6**. Similarly, Raney nickel easily promoted the cleavage of C20 aromatic benzyl ether without affecting sensitive methyl ether at C15 but removal of benzyl protecting group of secondary alcohol proved to be too slow. In this case, long reaction times were required and competitive reduction of N–OMe bond took place instead, leading to *N*-methyl amide **7** as a major component of the reaction mixture (see Scheme 3). These unsatisfactory results suggest that both catalysts are unable to cleave benzyl protecting groups from sterically hindered positions as C11 secondary alcohol or C15 disubstituted methyl ether.^{14,15}

Having failed the mildest options, we turned our attention to the catalyst first evaluated, 10% Pd/C. After careful optimization, it was established that cleavage of benzyl ether from secondary aliphatic C11 alcohol took place faster than of the C20 aromatic one.¹⁶ Then, hydrogenolysis of **1** in toluene at low concentrations using 10% Pd/C (1 atm, rt, 3 h) selectively deprotected the C11 aliphatic alcohol to give hydroxy amide **8**, whose benzyl protecting group of C20 phenol was finally removed in the presence of Rh/Al₂O₃. This two-step hydrogenolysis sequence afforded the desired dihydroxy amide **9** in 95% yield (see Scheme 3).

In summary, the design of benzyl-based protecting group strategies should consider that other oxygenated benzylic positions can be affected. Keeping in mind this potential drawback, careful evaluation of the catalyst, solvent, and concentration allows for selective deprotective sequences. In our case, hydrogenolysis of aliphatic and aromatic *O*-benzyl protecting groups in the presence of benzylic methyl ether has been carried out through a suitable two-step hydrogenolysis sequence using 10% Pd/C and Rh/Al₂O₃ as catalysts consecutively.

Acknowledgments

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