SCIENTIFIC LETTER 16

Edito

Notre nouvelle lettre scientifique nous fait partager toute la chimie du groupement protecteur benzyle à travers des exemples de la littérature qui illustre bien les difficultés que nous rencontrons au quotidien…. et les solutions que nous avons apportées. Aussi, notre prochain Webinaire intitulé « Groupements protecteurs de type benzyle: problèmes et solutions » qui aura lieu le 2 décembre prochain abordera également cette thématique au-delà des éthers benzyliques. Depuis 17 ans, nous capitalisons sur nos expériences passées et les compétences de chacun pour accompagner nos clients dans leurs projets. La réussite de ceux-ci est le fruit d'une collaboration étroite entre vous et l'équipe AtlanChim Pharma.

La chimie étant en constante évolution et de nombreux chimistes de part le monde cherchent à simplifier les conditions opératoires nécessaires à l'obtention de leurs produits. L'une des avancées les plus importantes du début du siècle concernant la synthèse organique vient justement d'être récompensée.

En effet, le 6 octobre dernier, le Prix Nobel de la Chimie a été attribué à l'Allemand Benjamin List et au Britannique David MacMillan pour avoir développé un nouvel outil de construction des molécules, « l'organocatalyse asymétrique ». Ben List et David MacMillan ont alors démontré de façon simultanée au début des années 2000 que des composés organiques tels que des bases ou des acides (de BrØnsted ou de Lewis) ainsi que des composés issus du pool chiral pouvaient permettre de synthétiser des produits de façon énantiopure avec des résultats comparables aux précédents types de catalyse.

Vous pouvez continuer à nous suivre sur notre page LinkedIn sur laquelle nous prenons toujours autant de plaisir à vous partager #TheMinuteOfChemistry et des informations relatives à nos services. Nos chimistes sont continuellement à votre écoute pour répondre à vos besoins en synthèse à façon, en marquage à froid ou bien encore sur de la synthèse d'impuretés pour faire de votre projet un succès.

Prenez soin de vous et de vos proches,
Bonne lecture,

L'équipe AtlanChim Pharma

Editorial

Our new scientific letter will give you an overview of the benzyl protecting group chemistry through examples from the literature which clearly illustrate the difficulties we encounter daily in our lab ... and solutions we provide ! Our next webinar entitled : « Benzyl-type protective groups : problems and solutions » will be held on the 2nd of December and will address this topic beyond benzyl ethers. For 17 years, we have been capitalizing on our team experience and skills to support our customers in their projects. Their success is due to a close collaboration between you and AtlanChim Pharma's team.

Chemistry is constantly evolving and many chemists around the world are looking to simplify synthetic conditions in order to obtain their products. One of the most important breakthrough in organic synthesis for this century has just been recognized.

On October the 6th, The Nobel Prize in Chemistry was awarded jointly to Benjamin List and David Mac Millan for the development of asymmetric organocatalysis. They have simultaneously demonstrated in the early 2000's that organic compounds such as bases and acids (BrØnsted or Lewis) as well as compounds from the chiral pool could help to synthesize enantiopure compounds with same results as regular metal or enzymatic catalysis.

In addition, you can follow us on LinkedIn where we enjoy sharing with you #TheMinuteOfChemistry and informations about our services/expertise. Our team of chemists is at your disposal for discussing custom synthesis, stable isotope labeling or synthesis of impurities to make your project a success !
During this particular period where responsiveness is essential, we would like to warmly thank our customers for their trust and loyalty placed in AtlanChim Pharma.

Look after yourself and your loved ones.

Enjoy your reading,

AtlanChim Pharma's team

About O-Benzyl protecting groups*

Jacques Lebreton
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** This microreview is dedicated to my colleague, Dr. Clémence Queffelec, on the occasion of her 40th birthday.*

O-Benzyl protecting group has been very useful in organic synthesis and is certainly one of the most widely used protecting groups for alcohols, especially in sugar chemistry, due to its stability towards acidic and basic conditions. The objective of this new scientific letter is to present, through recent examples from the literature, the various challenges we have had to face with the manipulation of *O*-benzyl ether protecting groups during our projects, in the past years.

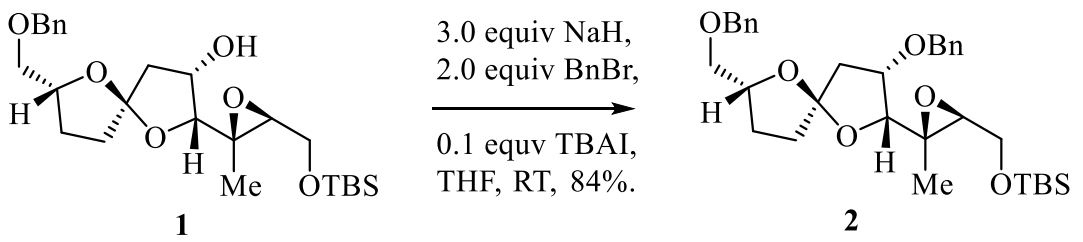
Formation

The *O*-benzyl protecting groups were easily introduced from their corresponding alcohols, as presented in this paragraph.

Williamson ether synthesis

O-Benzyl ethers could be readily prepared by reaction of an alcohol with benzyl halide in the presence of strong base. Nevertheless, this popular Williamson synthesis requires strongly basic conditions to generate an alkoxide nucleophile and is sometimes incompatible with starting alcohol derivatives containing base sensitive functional groups.

As shown in Scheme 1, benzylation of the alcohol **1** with NaH and benzylbromide, in the presence of catalytic amount of tetrabutylammonium iodide (TBAI) proceeded in 84% yield to afford the corresponding *O*-benzyl ether **2**.[1]

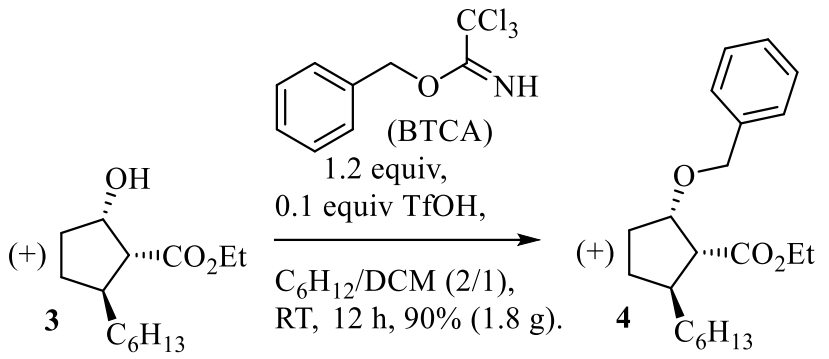


SCHEME 1

[1] Y. Hara, T. Honda, K. Arakawa, K. Ota, K. Kamaike, H. Miyaoka, *J. Org. Chem.* **2018**, *83*, 1976-1987.

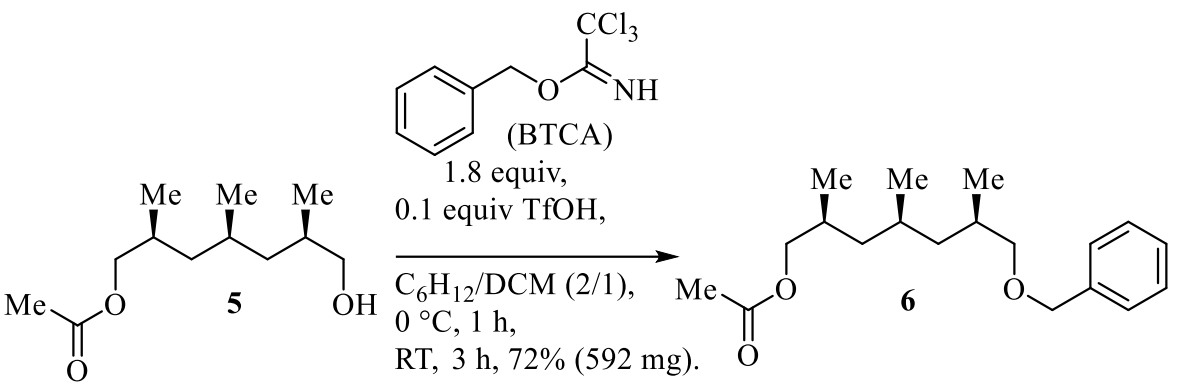
Formation of *O*-benzyl ethers in acidic conditions

To prepare *O*-benzyl ethers in acidic rather than basic conditions, benzyl trichloroacetimidate (BTCA, price 228 €/100g), in the presence of triflic acid (TfOH) as a promoter, has been extensively used as outlined in the following Schemes 2-7. For example, β-hydroxy ester **3** has been proved to be particularly sensitive to β-elimination and α-epimerisation under basic conditions.[2] Therefore, treatment of the β-hydroxy ester **3** with BTCA in the presence of catalytic amount of TfOH, to generate in situ the benzyl cation species, furnished efficiently the corresponding *O*-benzyl ether **4** in high yield, as described in Scheme 2.



SCHEME 2

In the next example (see Scheme 3), the presence of an acetate group is incompatible with Williamson ether synthesis, so the previous protocol with BTCA has been successfully applied on the alcohol **5** to provide the desired *O*-benzyl ether **6** in 72% yield.[3]



SCHEME 3

To avoid retro-aldol side-reactions, *O*-benzylation of aldols with BTCA under mild acidic conditions cleanly resulted in the corresponding *O*-benzyl ethers in high yields, as illustrated in Scheme 4.[4]

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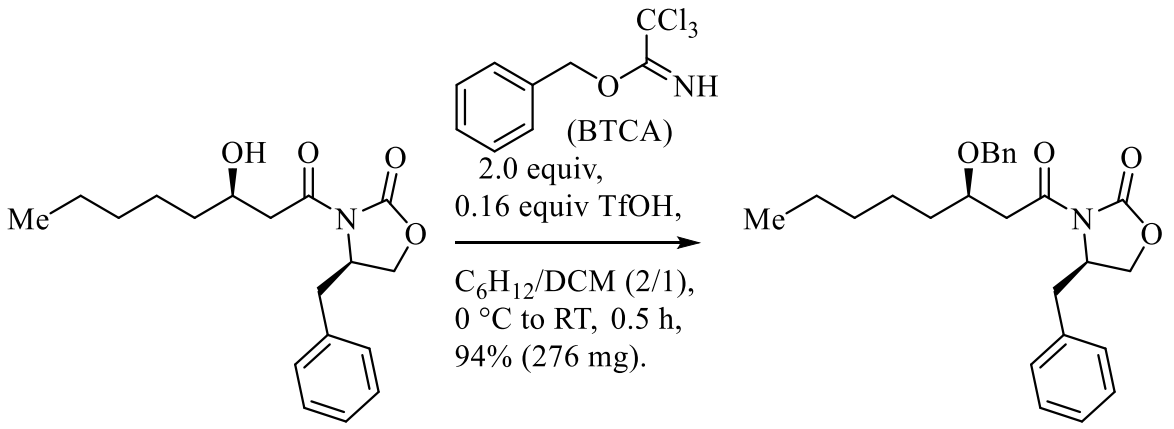
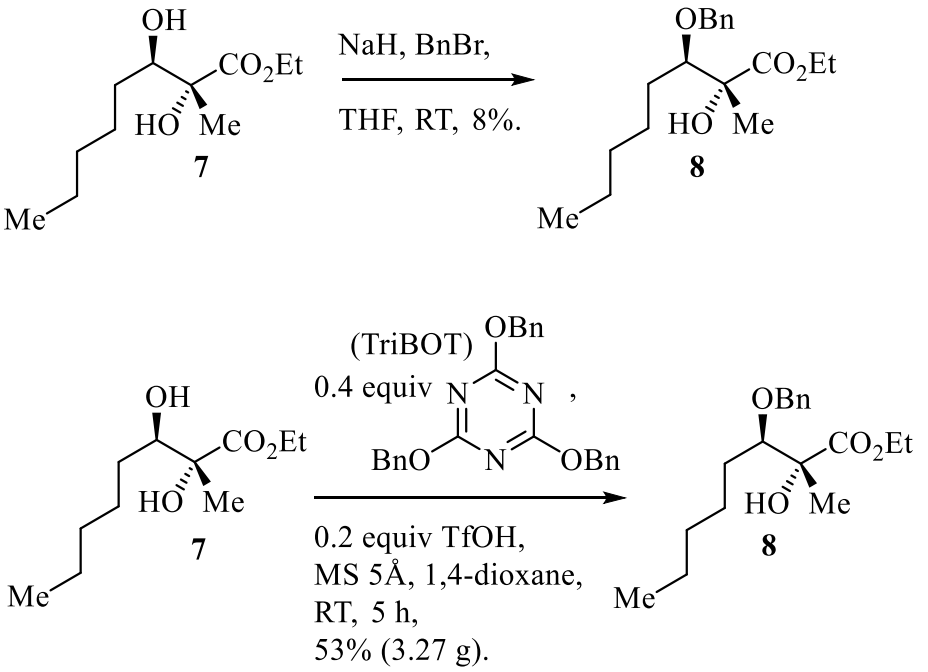
[2] Y.-T. Liu, J.-Q. Chen, L.-P. Li, X.-Y. Shao, J.-H. Xi, Q.-L. Zhou, *Org. Lett.* **2017**, *19*, 3231-3234.
[3] S. Sengupta, M. Bae, D.-C. Oh, U. Dash, H. J. Kim, W. Y. Song, I. Shin, T. Sim, *J. Org. Chem.* **2017**, *82*, 12947-12966.
[4] M. Ohtawa, E. Shimizu, A. Saito, S. Sakamoto, A. Waki, A. Kondo, A. Yagi, R. Uchida, H. Tomoda, T. Nagamitsu, *Org. Lett.* **2019**, *21*, 5596-5599.



SCHEME 4

In 2012 Kunishima *and Coll*. published the preparation and use of a new acid-catalyzed benzylating reagent, the 2,4,6-tris(benzyloxy)-1,3,5-triazine (TriBOT, price 700€/10g) which could be considered as a formal trimer of the smallest unit of alkyl imidate (see Scheme 5). TriBOT is easily prepared from benzyl alcohol and cyanuric chloride in the presence of NaOH in large-scale synthesis (several hundred grams).[5] Compared to BTCA, TriBOT is a stable and crystalline reagent easy to handle. During the course of a total synthesis of ent-Phaeosphaeride A, the chiral diol 7 treated under Williamson's conditions with BnBr and NaH afforded the desired monobenzyl ether on the secondary alcohol 8 in only 8% yield (see Scheme 5).[6] On the other hand, the previous diol **7** was subjected at room temperature to TriBOT and TfOH as a catalyst, in 1,4-dioxane containing powdered molecular sieves (5 Å) as a dehydrating agent to remove residual moisture. Under these conditions, the monobenzyl ether **8** was isolated as the major product in 53% yield.



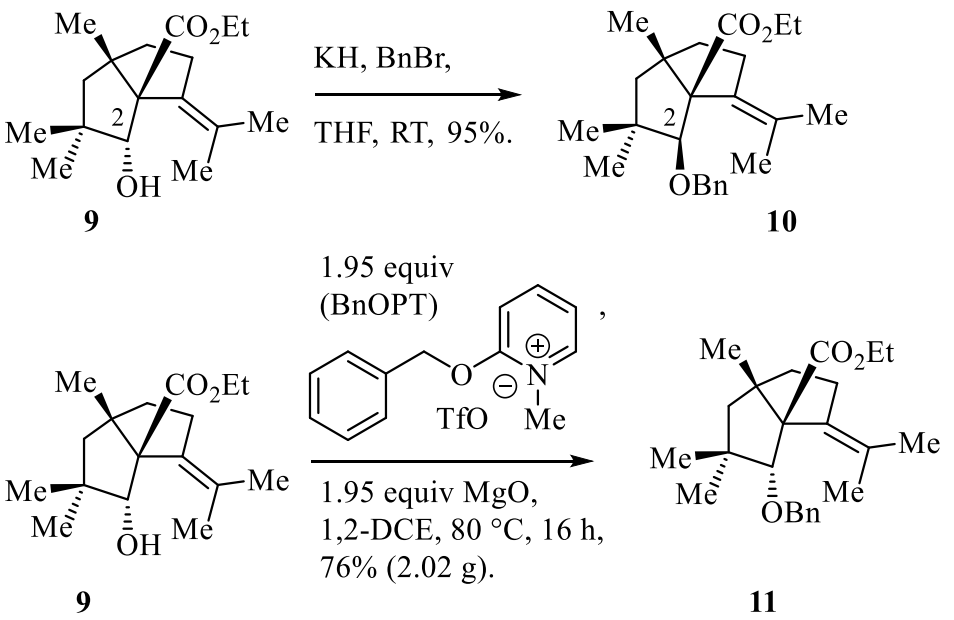
SCHEME 5

[5] K. Yamada, H. Fujita, M. Kunishima, *Org. Lett*. **2012**, *14*, 5026-5029.
[6] K. Kobayashi, Y. Kobayashi, M. Nakamura, O. Tamura, H. Kogen, *J. Org. Chem*. **2015**, *80*, 1243-1248.

Formation of *O*-benzyl ethers in nearly neutral conditions

As complement of these methodologies of benzylation of alcohols in strongly basic or acidic conditions presented above, Dudley *and Coll*. developed the benzyloxy-1-methylpyridinium trifluoromethanesulfonate (BnOPT, Dudley Reagent, price 300€/5g, see Scheme 6), an efficient reagent for benzylation under mild and nearly neutral conditions.[7]

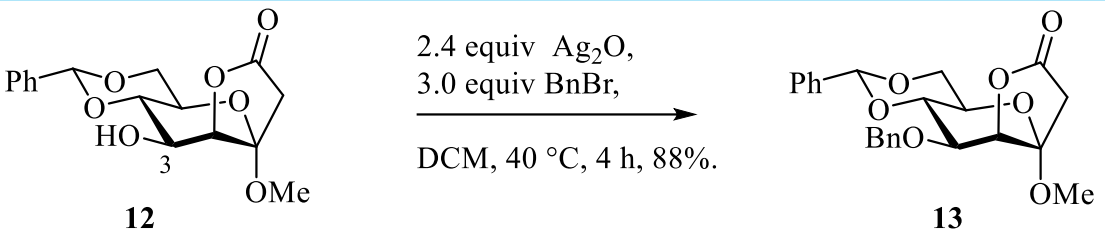
In the total synthesis of (-)-Cameroonan-7α-ol, benzylation of the β-hydroxy ester **9** using a Williamson ether synthesis protocol afforded the *O*-benzyl derivative **10**, in an excellent yield, but with complete inversion of the secondary carbinol center at C-2, presumably by a retro-aldol/aldol process (see Scheme 6). Fortunately, benzylation reaction carried out with BnOPT in refluxing dry 1,2-DCE with magnesium oxide (MgO), as acid scavenger to neutralize the slightly acidic hydroxypyridine formed *in situ*, provided the desired *O*-benzyl stereoisomer **11** in 76% yield on gram scale.[8]



SCHEME 6

Attempts to benzylate the hydroxyl at C-3 of the α-manno derivative **12** under Willianson etherification conditions resulted in the degradation of the lactone moiety (Scheme 7). Treatment of this α-manno derivative **12** with BTCA under various conditions in the presence of additives such as TfOH, trimethylsilyl trifluoromethanesulfonate (TMSOTf) and $BF_3.OEt_2$ gave the 3-*O*-benzyl lactone **13** in 12 to 57% yield, and with BnOPT under standard conditions the yield increased to 74%. This *O*-benzylation performed under neutral conditions with silver(I) oxide (Ag_2O) and BnBr in DCM at 40 °C in sealed tube afforded the 3-*O*-benzyl lactone **13** in 88% yield.[9]

[7] K. W. C. Poon, G. B. Dudley, *J. Org. Chem*. **2006**, *71*, 3923-3927.
[8] D. F. Taber, C. G. Nelson, *J. Org. Chem*. **2011**, *76*, 1874-1882.
[9] K. Mébarki, M. Gavel, F. Heis, A. Y. P. Joosten, T. Lecourt, *J. Org. Chem*. **2017**, *82*, 9030-9037.



SCHEME 7

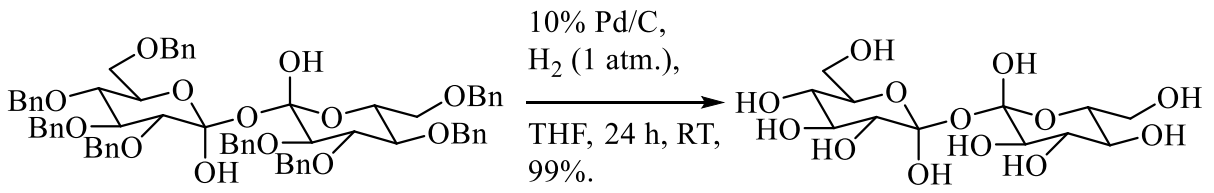
Cleavage

Removal of *O*-benzyl protecting groups has been reported using a variety of protocols including hydrogenolysis or oxidative cleavage, as well as Lewis acid-promoted cleavage conditions. They also could be easily cleaved reductively with one-electron reduction agents such as lithium naphthalenide.

Hydrogenolysis under standard conditions

Pd is the preferred metal catalyst, since the use of Pt or Rh results in ring hydrogenation. The most popular catalysts are 5% or 10% Pd/C and 20% $Pd(OH)_2/C$ (Pearlman's catalyst). The rate of *O*-benzyl protecting groups hydrogenolysis with Pd/C is strongly affected by the nature of the solvent, with this ascending order of efficiency: toluene < MeOH < EtOH << AcOH < THF.[10] Also, addition of strong acids such as hydrochloric acid or use of AcOH as a solvent, results in the protonation of the oxygen atom of the *O*-benzyl ether and thereby facilitates the debenzylation process. A series of typical examples of hydrogenolysis are depicted in the following Schemes 8-11.

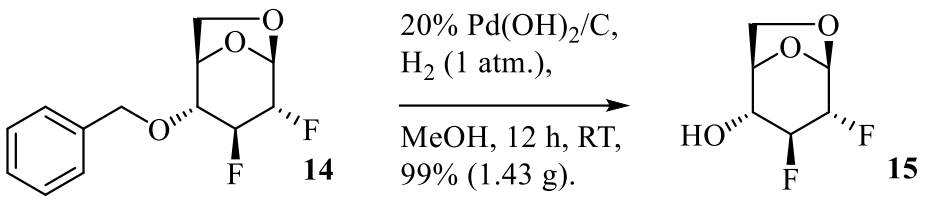
In polysaccharide synthesis, the last step is quite often the removal of all the *O*-benzyl protecting groups by hydrogenolysis as reported in Scheme 8.[11]



SCHEME 8

In the context of an experimental and theoretical study of intramolecular hydrogen bonding in levoglucosan derivatives, the difluoro derivative **14** was debenzylated with Pearlman's catalyst under standard conditions to afford the compound **15** in near-quantitative yield, as shown in Scheme 9.[12]

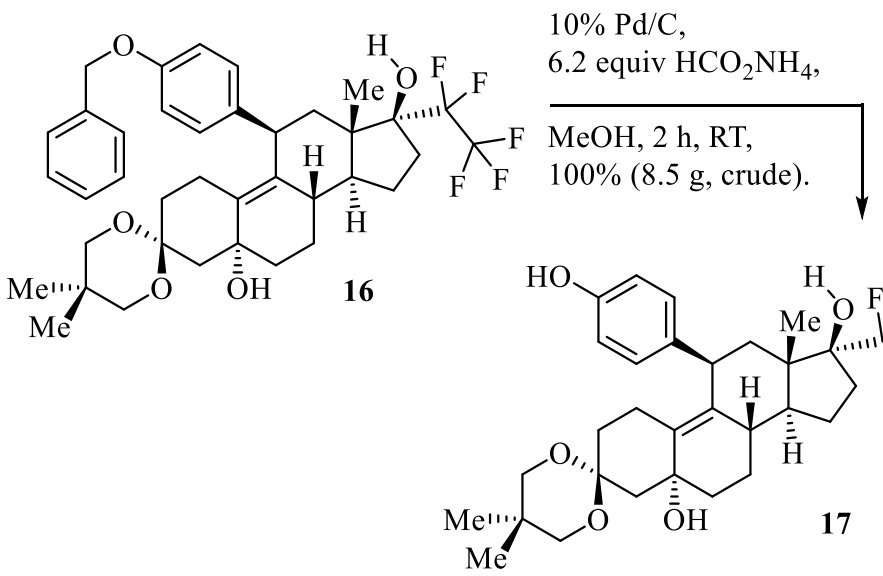
[10] S. Hawker, M. A. Bhatti, K. G. Griffin, *Chim. Oggi* **1992**, *10*, 49-51.
[11] M. Bayer, S. Stocker, C. Maichle-Mössmer, T. Ziegler, *Eur. J. Org. Chem.* **2020**, 4347-4360.
[12] L. Quiquempoix, E. Bogdan, N. J. Wells, J.-Y. Le Questel, J. Graton, B. Linclau, *Molecules* **2017**, *22*, 518; doi:10.3390/molecules22040518.



14 **15**

SCHEME 9

During the development of Vilaprisan (BAY-1002670, Bayer Pharmaceuticals), a steroidal selective progesterone receptor modulator (SPRM) which is currently in phase III, various analogues were synthesized, such as the phenolic derivative **17** depicted in Scheme 10. Palladium-catalyzed transfer hydrogenolysis of *O*-benzylphenol intermediate **16** with ammonium formate as hydrogen donors, a safe alternative to the use of hydrogen gas, furnished compound **17** in quantitative crude yield. It should be pointed out that cyclohexene, 1,4-cyclohexadiene, hydrazine hydrate, formic acid can be used as hydrogen donors, nevertheless ammonium formate is more efficient due to the high hydrogen-donating ability of formate ion.[13]



16 **17**

SCHEME 10

In the preparation of tripeptides containing a *trans*-2-aminocyclopropane carboxylic acid, an important class of carbocyclic β-aminoacids, the protected dipeptide precursor **18** (see Scheme 11) was treated with 10% Pd/C under an atmosphere of hydrogen in THF containing 3.3 equivalents of AcOH, to promote hydogenolysis (*vide supra*). The expected alcohol **19** was obtained in excellent crude yield of 99%. It is worth noting that under these acidic hydrogenolysis conditions, the double *N*-Boc protected amine moiety as well as the *N*-Boc protected amide are stable.[14]

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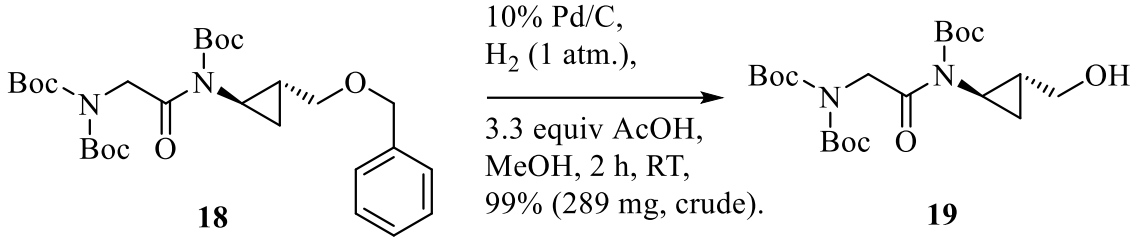
[13] C. Möller, W. Bone, A. Cleve, U. Klar, A. Rotgeri, A. Rottmann, M.-H. Schultze-Mosgau, A. Wagenfeld, W. Schwede, *ChemMedChem* **2018**, *13*, 2271-2280.
[14] T. Boddaert, J. E. Taylor, S. D. Bull, D. J. Aitken, *Org. Lett*. **2019**, *21*, 100-103.

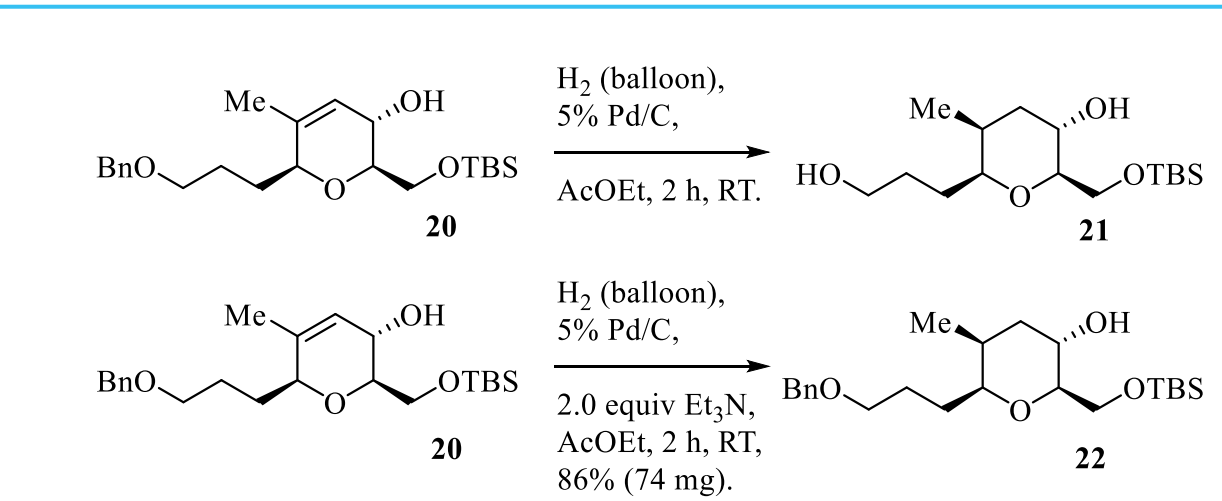


SCHEME 11

Hydrogenolysis in the presence of additives.

In multistep synthesis, suppression of the hydrogenolysis of benzyl ethers without affecting the hydrogenation of other reducible functionalities is a key problem and has increasingly attracted attention from synthetic chemists. In this context, amines and nitrogen-containing bases have been largely used as catalyst poisons of the palladium catalysts.[15]

In the context of a formal total synthesis of (-)-brevisamide, catalytic hydrogenation of intermediate **20** under standard reaction conditions with 5% Pd/C under hydrogen atmosphere (balloon) in AcOEt provided the hydrogenated compound **21** with concomitant debenzylation (see Scheme 12). Subsequent attempts of catalytic hydrogenation of **20** in various solvents, as well as with PtO_2 as the hydrogenation catalyst, also failed giving the desired product **22** in low yield with concomitant debenzylation. Fortunately, a simple addition of two equivalents of Et_3N into the previous reaction mixture cleanly afforded the desired alcohol **22** in 86% yield without debenzylation.[16]

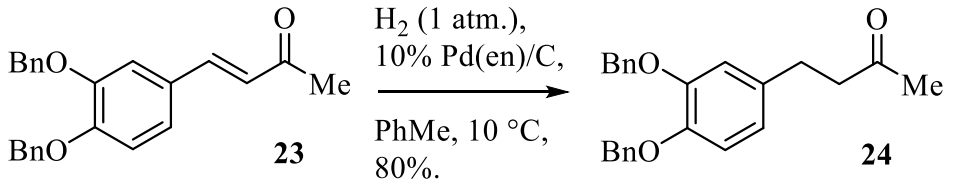


SCHEME 12

In 1998, Hirota *and Coll*. have published the preparation and use of a 5% Pd/C catalyst complex with ethylenediamine employed as the catalyst poison.[17] This new catalyst, denoted [Pd(en)/C], is a 1:1 complex of palladium and ethylenediamine. This heterogeneous catalyst [Pd(en)/C] allows selective catalytic hydrogenation of various functional groups under

[15] For a seminal reference, see: H. Sajiki, H. Kuno, K. Hirota, *Tetrahedron Letters* **1998**, *39*, 7127-7130.
[16] J. Lee, H.-S. Oh, H.-Y. Kang, *Tetrahedron Letters* **2015**, *56*, 1099-1102.
[17] H. Sajiki, K. Hattori, K. Hirota, *J. Org. Chem*. **1998**, *63*, 7990-7992.

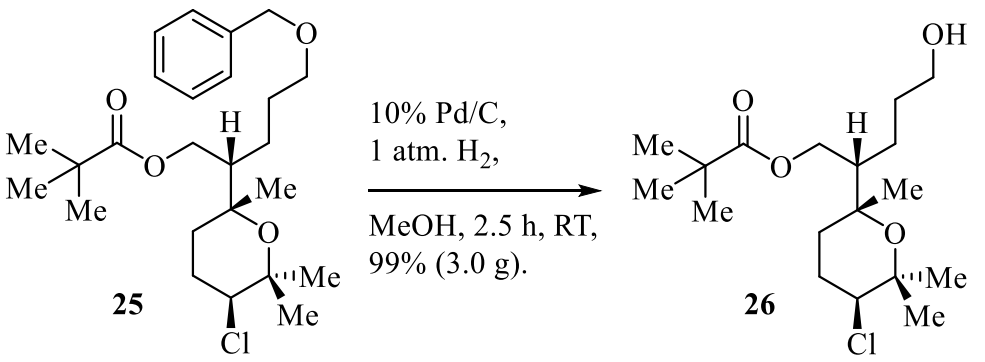
neutral conditions without deprotection of the *O*-benzyl and *N*-Cbz groups. For example, selective hydrogenation of the double bond of the enone **23** without affecting the benzyl protecting group has been successfully carried out using palladium ethylenediamine complex on activated carbon [Pd(en)/C] as catalyst, in toluene under hydrogen atmosphere to provide the methylketone **24** in 80% yield, as shown in Scheme 13.[18]



SCHEME 13

Chemoselective hydrogenolysis of *O*-benzyl ether protecting groups on halogen-containing substrates.

Removal of benzyl ether protecting groups on halogen-containing substrates using standard hydrogenolysis conditions is a challenging task. Competitive dehalogenation reaction provided the unwanted dehalogenated compound which reduced the yield of the hydrogenolysis process and greatly complicated the purification step. Nevertheless, this side-reaction is substrate-dependent as illustrated in the Scheme 14. Chemoselective Pd/C-catalyzed hydrogenolysis of the benzyl ether protecting group in intermediate **25** is efficiently carried out on 3 g scale under standard conditions to afford the desired chloroalcohol **26** in 99%, without affecting the C-Cl bond.[19]

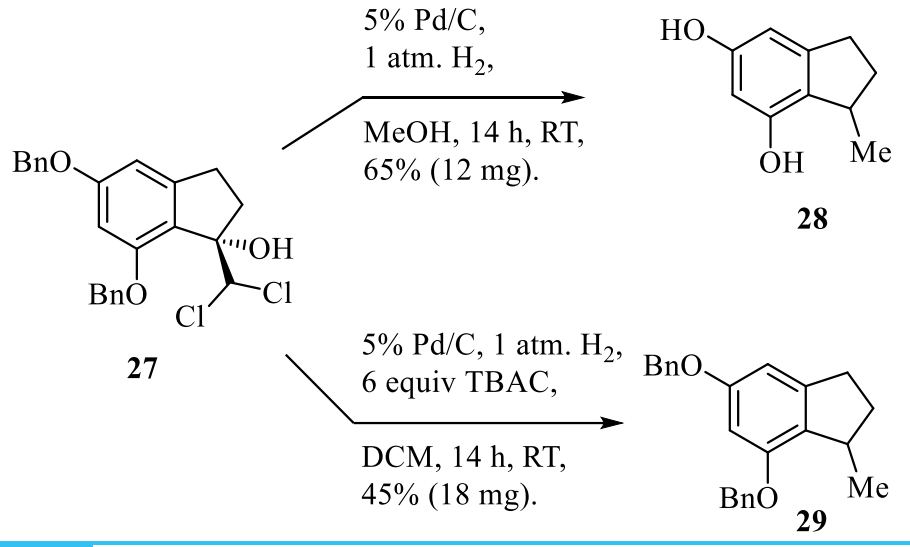


SCHEME 14

To avoid this dehalogenation side-reaction, it has been reported that addition of around one equivalent of tetrabutylammonium chloride (TBACl) resulted in chemoselective hydrogenolysis of *O*-benzyl ether protecting groups in the presence of aryl chloride.[20]

[18] T. Iwadate, Y. Kashiwakura, N. Masuoka, Y. Yamada, K.-i. Nihei, *Bioorg. Med. Chem. Lett*. **2014**, *24*, 122-125.
[19] H. Miyaoka, Y. Abe, N. Sekiya, H. Mitome, E. Kawashima, *Chem. Comm*. **2012**, *48*, 901-903.
[20] J. Li, S. Wang, G. A. Crispino, K. Tenhuisen, A. Singh, J. A. Grosso, *Tetrahedron Letters* **2003**, *44*, 4041-4043.

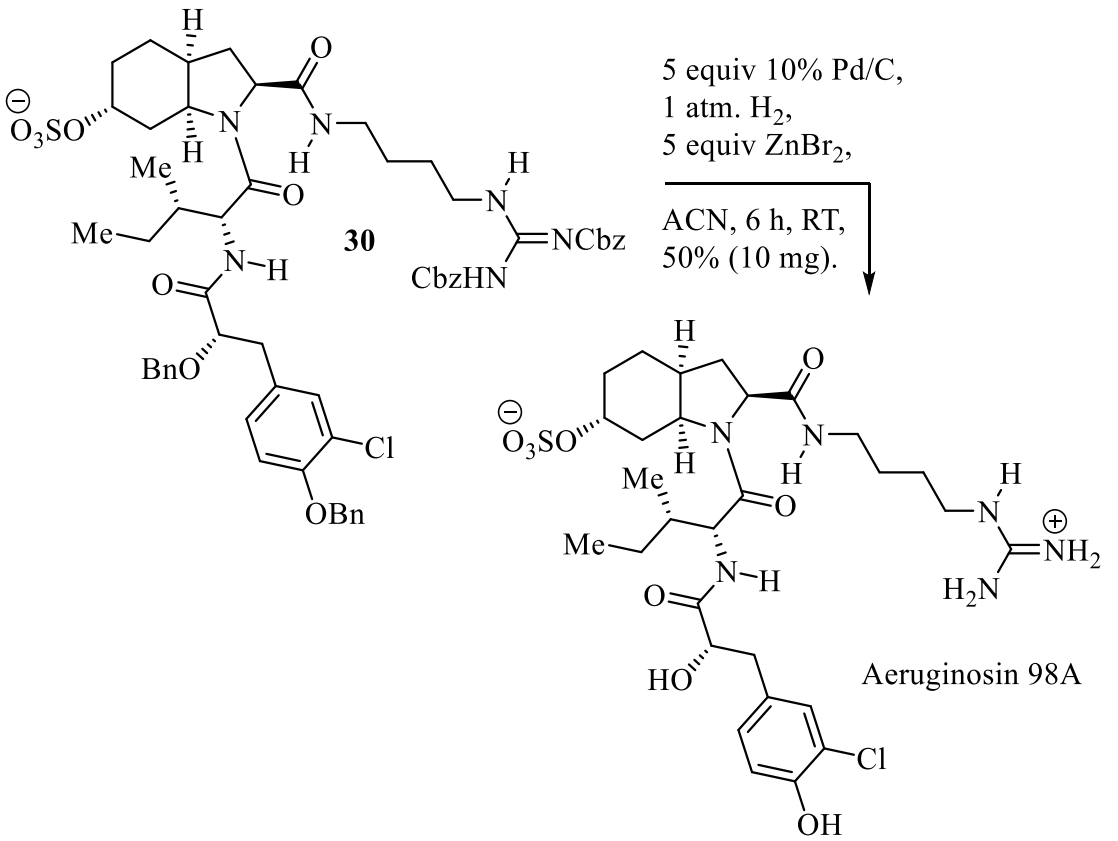
Some recent reports mentioned the inefficiency of this protocol as presented in Scheme 15. Treatment of the dihalogenated compound **27** under a hydrogen atmosphere in the presence of Pd/C in MeOH led to concomitant dehalogenation, and removal of *O*-benzyl ethers as well as hydrogenolysis of the tertiary benzylic alcohol leading to the indane derivative **28** in 65%. Surprisingly, addition of 6 equivalents of TBACl resulted in removal of the chlorine atoms and the tertiary hydroxyl group as previously observed but leaving benzyl groups intact to give compound **29.**[21]



SCHEME 15

On the other hand, Wu *and Coll*. from Schering-Plough reported that the addition of $ZnBr_2$ could effectively limit the dehalogenation.[22] Although the exact mechanism of inhibition is not clear, they speculated that the addition of this Lewis acid could slow the Pd insertion into the carbon-halogen bond and therefore inhibit the dehalogenation process. In the course of an elegant total synthesis of Aeruginosin 98A (see Scheme 16), a linear chlorohydroxyphenyllactic-containing peptide isolated from sponges and cyanobacterial water blooms, Baudoin *and Coll*. exposed at the final stage the *O*-benzyl ether derivative **30** to hydrogenolysis using a 1:1 ratio of $ZnBr_2$ and Pd/C, to cleave two *O*-benzyl ethers as well as two *N*-benzyloxycarbonyl (Cbz) protecting groups. In this optimized conditions, Aeruginosin 98A was isolated in 50% yield without observable dechlorination.[23]

[21] D. H. Dethe, R. Boda, *ACS Omega* **2018**, *3*, 9303-9309.
[22] G. Wu, M. Huang, M. Richards, M. Poirier, X. Wen, R. W. Draper, *Synthesis* **2003**, 1657-1660.
[23] D. Dailler, G. Danoun, B. Ourri, O. Baudoin, *Chem. Eur. J.* **2015**, 9370-9379.



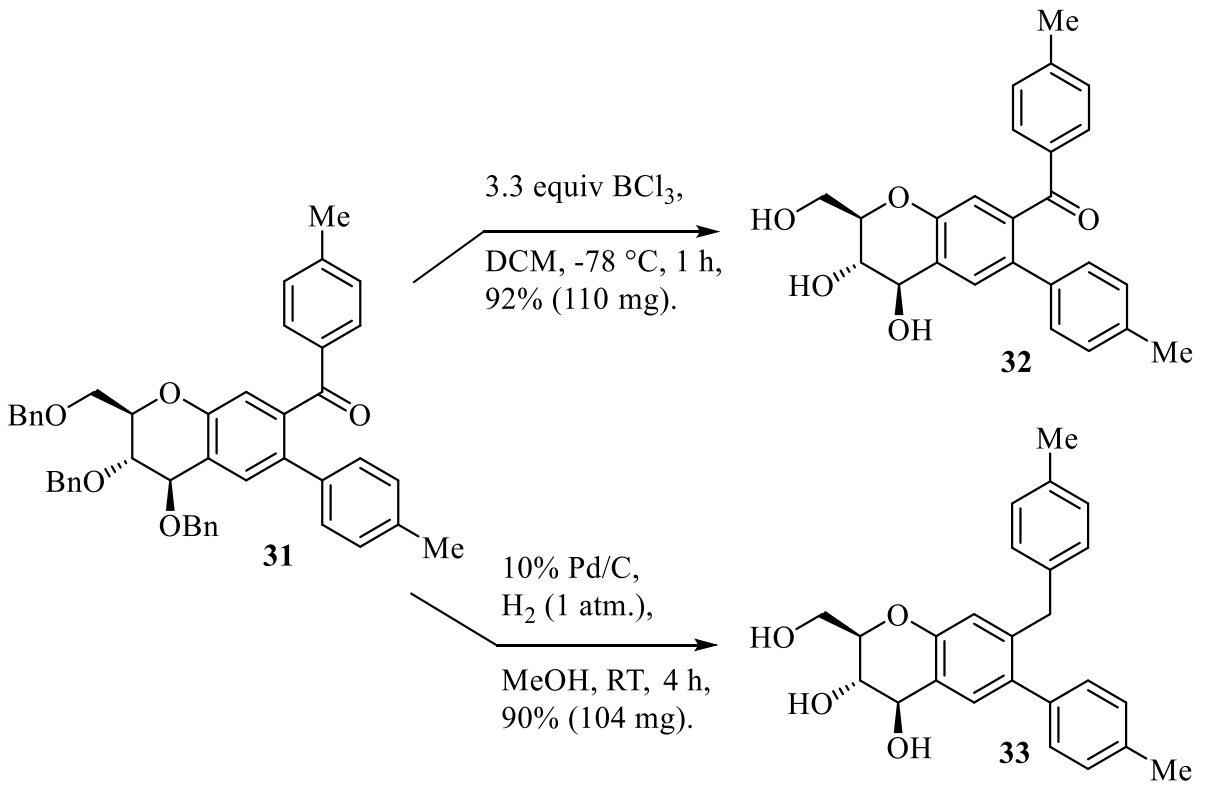
SCHEME 16

Cleavage of *O*-benzyl ethers with Lewis acids

In addition to the popular catalytic hydrogenolysis, different Lewis acids such as BBr_3, BCl_3, and $MeBCl_2$, as well as different combination systems of Lewis acids and Lewis bases have been used for the cleavage of *O*-benzyl ethers. These combinations exhibit a unique reactivity which is not exerted by the Lewis acid itself alone. Under these conditions, the cleavage of the *O*-benzyl ether protecting groups is considered to proceed *via* an initial coordination of the Lewis acid to oxygen atom of the ether followed by attack of the Lewis base on benzylic carbon.

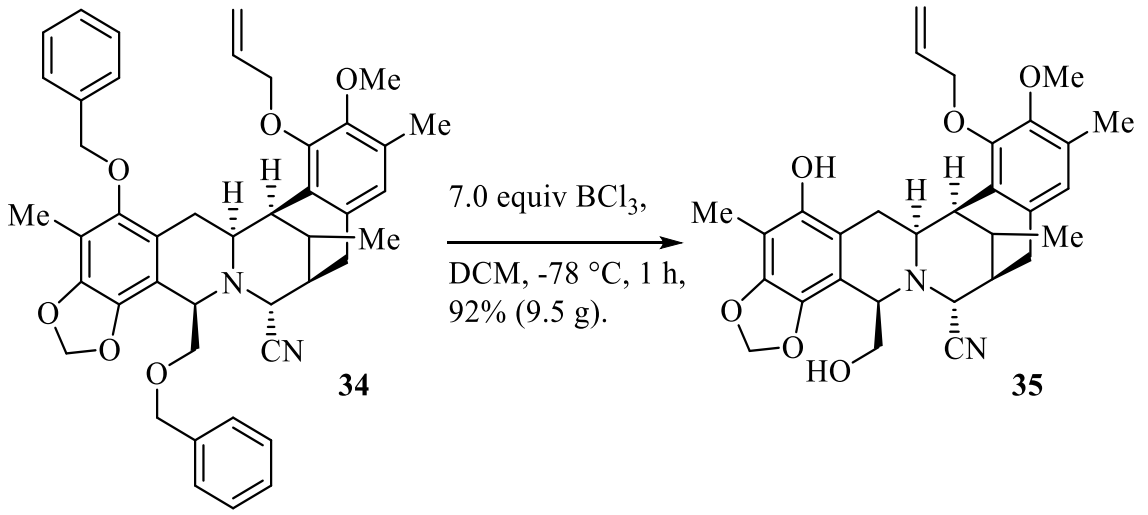
Very recently, Prasad *and Coll*. published the preparation of a set of chiral chromane derivatives such as **32** for drug discovery application (see Scheme 17).[24] In this context, complete debenzylation of chromane **31** was efficiently accomplished by using a 1 M solution of BCl_3 in DCM at -78 °C to give triol **32** in 92% yield. Initial attempts to carry out this step by hydrogenolysis led to the expected removal of *O*-benzyl ethers but also to the reduction of benzoyl to the benzyl group, *via* the benzylic alcohol intermediate, giving the unwanted chromane derivatives **33**, isolated in 90% yield.

[24] B. Shankar, V. Khatri, B. Kumar, V. K. Maikhuri, A. Kumar, R. Tomar, A. K. Prasad, *ACS Omega* **2021**, *6*, 11248-11259.



SCHEME 17

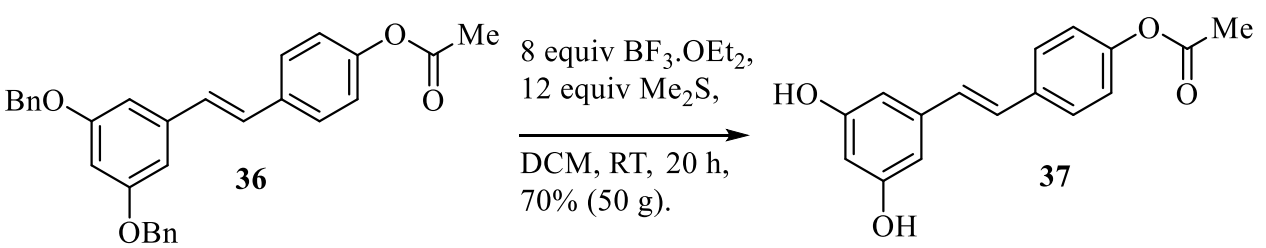
More generally, the use of BCl_3 can prove to be particularly chemoselective and efficient on a large-scale synthesis, as outlined in Scheme 18. In the context of a scalable total synthesis of the antitumor agents Et-743 and Lurbinectedin, treatment of the highly functionalized and complex polycyclic intermediate **34** with 7 equivalents of a 1 M solution of BCl_3 in DCM at -78 °C to remove the two *O*-benzyl protecting groups afforded in 95% yield on 10 gram scale the alcohol **35**, precursor of Et-743.[25]



SCHEME 18

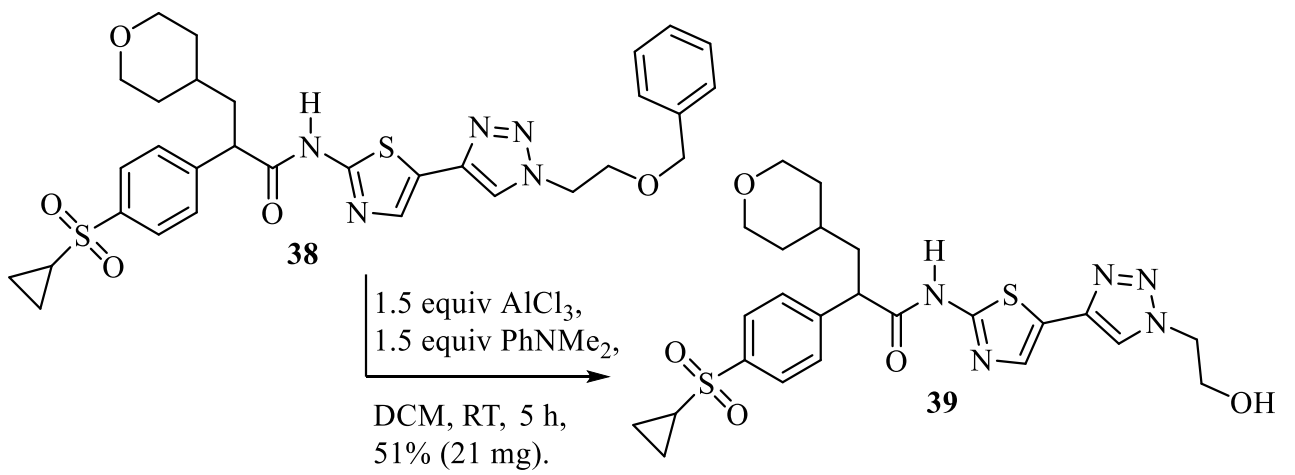
[25] W. He, Z. Zhang, D. Ma, *Angew. Chem. Int. Ed.* **2019**, *58*, 3972-3975.

In a program concerning the preparation of new 4'-resveratrol ester derivatives and the evaluation of their potential antidepressant activity, the debenzylation of the key intermediate **36** turned out to be tricky (Scheme 19). Initial attempts to selectively remove *O*-benzyl ether protecting groups in the presence of the alkene and the acetate moiety under various conditions (BBr_3, $AlCl_3$ with *N,N*-dimethyl aniline, various palladium catalyzed selective debenzylation conditions (with 1,4-cyclohexadiene or formate as hydrogen sources)), were performed without success. Ultimately, deprotection of the benzyl ethers was efficiently accomplished by using $BF_3.OEt_2$ with dimethylsulfide (Me_2S) in DCM at room temperature providing 4'-acetyl-resveratrol **37** in 70% yield after recrystallization on 50 gram scale.[26]



SCHEME 19

In the following example concerning the synthesis of novel arylacetamides designed to further explore the Glucokinase (GK) binding property at the aminothiazole C-5 position (see Scheme 20), the *O*-benzyl scaffold **38** was debenzylated by using $AlCl_3$ and *N,N*-dimethyl aniline to give the corresponding alcohol **39** in a modest yield of 51%.[27]



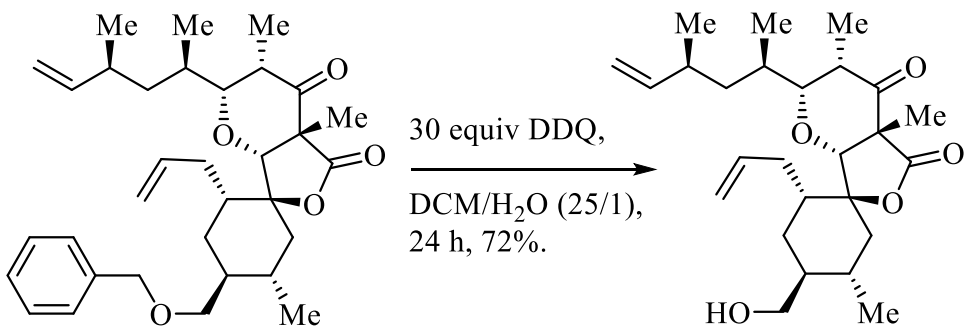
SCHEME 20

[26] M. J. Acerson, K. M. Fabick, Y. Wong, C. Blake, E. D. Lephart, M. B. Andrus, *Bioorg. Med. Chem. Lett*. **2013**, *23*, 2941-2944.
[27] Z. Liu, Q. Zhu, F. Li, L. Zhang, Y. Leng, A. Zhang, *Med. Chem. Commun*. **2011**, *2*, 531-535.

Cleavage of *O*-benzyl ethers with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ)

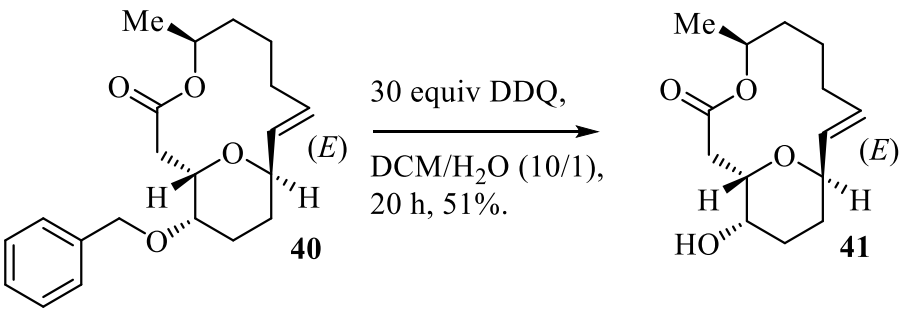
The *p*-methoxybenzyl (PMB) and 2-naphthylmethyl (Nap) ethers are very important protecting groups, especially in oligosaccharide synthesis, which are efficiently removed by oxidative cleavage with either 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) or ceric ammonium nitrate (CAN). Nevertheless, it should be pointed out that simple benzyl ethers are not totally inert under such oxidative cleavage conditions but generally react significantly more slowly.[28] In this context, oxidative debenzylation with DDQ is an alternative procedure offering the possibility to perform this transformation chemoselectively with substrates containing reducible functional groups, as illustrated in the following examples.

Oxidative debenzylation with a large excess of DDQ and long reaction time was successfully used to remove the benzyl protecting group in the RCM precursor with two terminal olefinic bonds, as outlined in Scheme 21.[29]



SCHEME 21

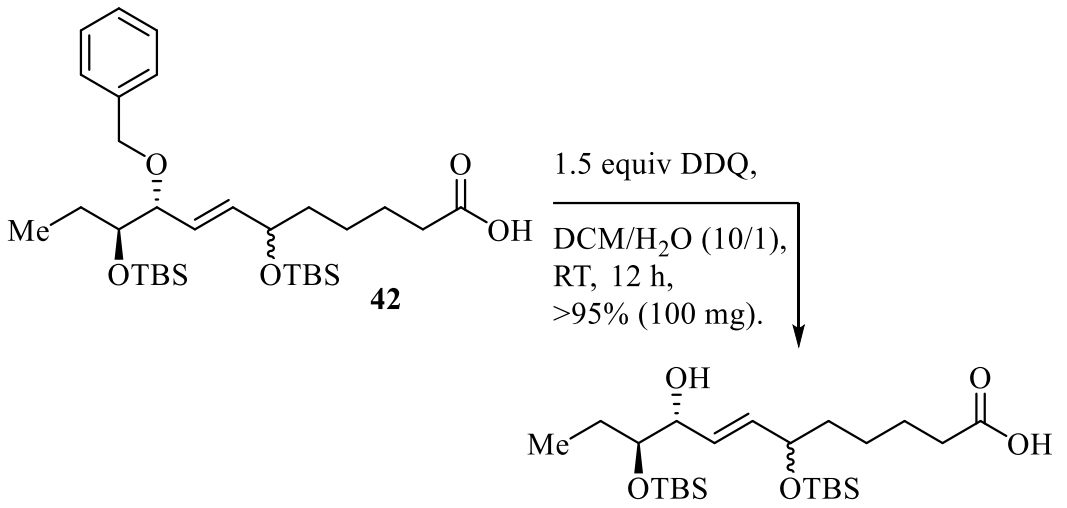
In the context of the total synthesis of aspergillide B, similar oxidative debenzylation conditions were applied to benzyl ether **40** providing the desired alcohol **41** in modest yield as depicted in Scheme 22.[30]



SCHEME 22

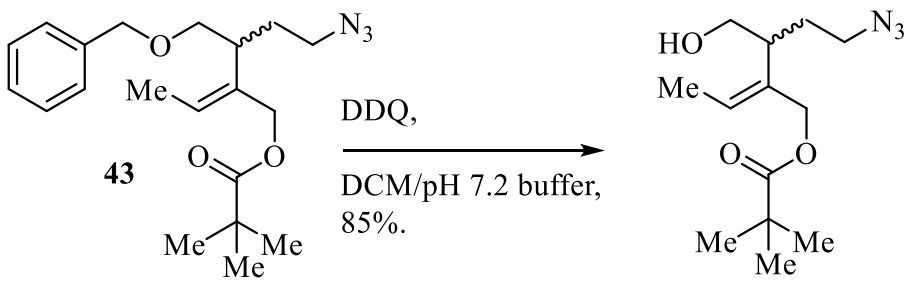
In sharp contrast, in the following example (Scheme 23), only a slight excess of DDQ in a mixture of DCM and water was used for chemoselective deprotection of the benzyl group of the oxylipin derivative **42**.[31]

[28] D. Crich, O. Vinogradova, *J. Org. Chem.* **2007**, *72*, 3581-3584.
[29] A. B. Smith, T. Bosanac, K. Basu, *J. Am. Chem. Soc.* **2009**, *131*, 2348-2358.
[30] S. Diaz-Oltra, C. A. Angulo-Pachon, J. Murga, E. Falomir, M. Carda, J. A. Marco, *Chem. Eur. J.* **2011**, *17*, 675-688.
[31] B. Saikia, T. J. Devi, N. C. Barua, *Tetrahedron* **2013**, *69*, 2157-2166.



SCHEME 23

Azide are very sensitive to reductive conditions, and they are reduced into the corresponding amines under palladium-catalyzed hydrogenolysis of benzyl ethers. In the example presented in Scheme 24, DDQ was used to cleave the benzyl ether protecting group of **43** leaving the double bond and the azide group intact.[32]



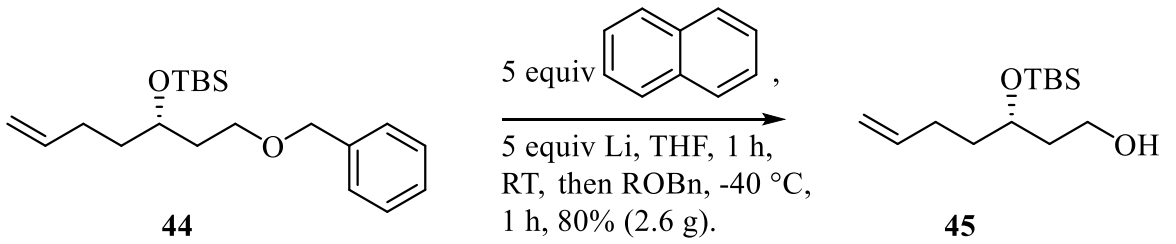
SCHEME 24

Cleavage of *O*-benzyl ethers using alkali metal dissolution conditions

The cleavage of *O*-benzyl ethers using alkali metal dissolution conditions, typically Li or Na/NH_3, involving transfer of electrons with formation of an anionic radical intermediate, has been widely used in the past. Nevertheless, new protocols have been described avoiding the use of liquid ammonia.

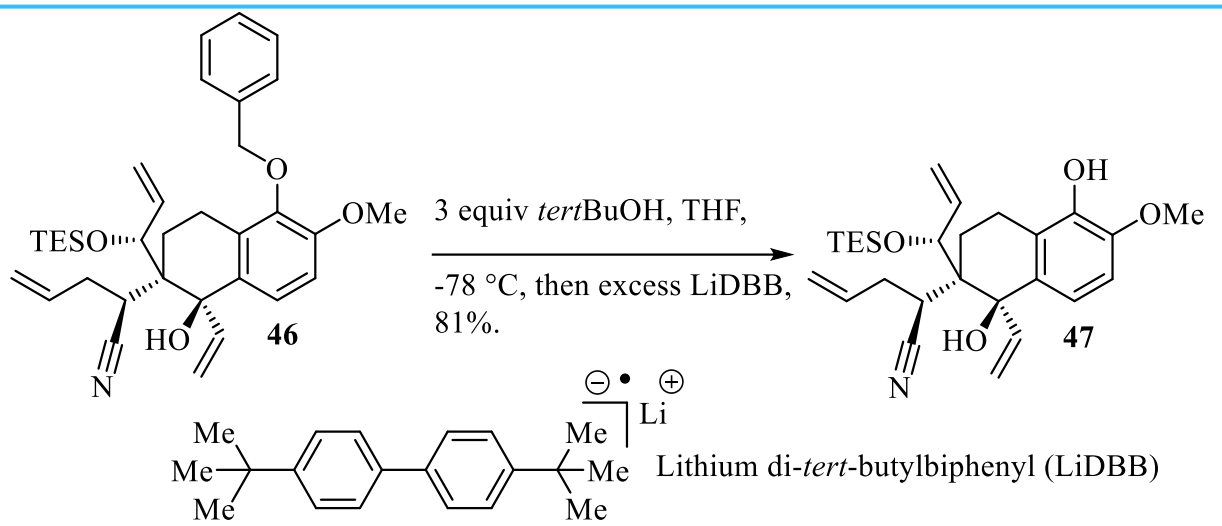
During the course of a total synthesis and stereochemical assignment of penicitide A, treatment of the *O*-benzyl ether **44** with excess of lithium naphthalenide (formed *in situ* from lithium and naphthalene) in THF at -40 °C provided the desired alcohol **45** in 80% yield, as reported in Scheme 25.[33]

[32] Y. Noguchi, T. Hirose, Y. Furuya, A. Ishiyama, K. Otoguro, S. Omura, T. Sunazuka, *Tetrahedron Letters* **2012**, *53*, 1802-1807.
[33] D. Saha, S. Guchhait, R. K. Goswami, *Org. Lett*. **2020**, *22*, 745-749.



SCHEME 25

Removal of *O*-benzyl ether in the highly functionalized tetralin derivative **46** with an excess of 4,4′-di-*tert*-butylbiphenylide (LiDBB, Freeman's reagent) in the presence of *tert*-butanol as a protic source led cleanly to the phenolic intermediate **47** in 81% yield on gram scale, as described in Scheme 26. From a practical point of view, the freshly prepared 1 M solution of LiDBB (prepared from lithium and 4,4′-di-*tert*-butylbiphenyl) was added at -78 °C to the reaction mixture until the color turned dark blue.[34]



SCHEME 26

Conclusion

Despite recent advances for selective and efficient introduction and removal of *O*-benzyl ether protecting groups, there is still room for improvement in increasing chemoselectivity, especially with highly functionalized complex molecules. For its introduction, Dudley's reagent is certainly an excellent candidate for the protection of alcohols which is carried out under relatively neutral reaction conditions. Concerning its removal, the chemoselectivity of hydrogenolysis of *O*-benzyl ethers with substrates containing multiple reducible functional groups is often a challenge and the transformation outcome is not always predictable and may be surprising. In addition, the differences between commercial sources of Pd/C, or even between different batches, are difficult to understand. Also, an improvement of the quality of Pd/C and a better physicochemical characterization of parameters such as small Pd/PdO particle size, homogeneous distribution of Pd/PdO on the carbon support, and palladium oxidation state which are good predictors of catalytic efficiency will be essential elements for the future of this cleavage method.[35]

[34] T. Suzuki, T. Koyama, K. Nakanishi, S. Kobayashi, K. Tanino, *J. Org. Chem*. **2020**, *85*, 10125-10135.
[35] C. J. Crawford, Y. Qiao, Y. Liu, D. Huang, W. Yan, P. H. Seeberger, S. Oscarson, S. Chen, *Org. Process Res. Dev*. **2021**, *25*, 1573-1578.

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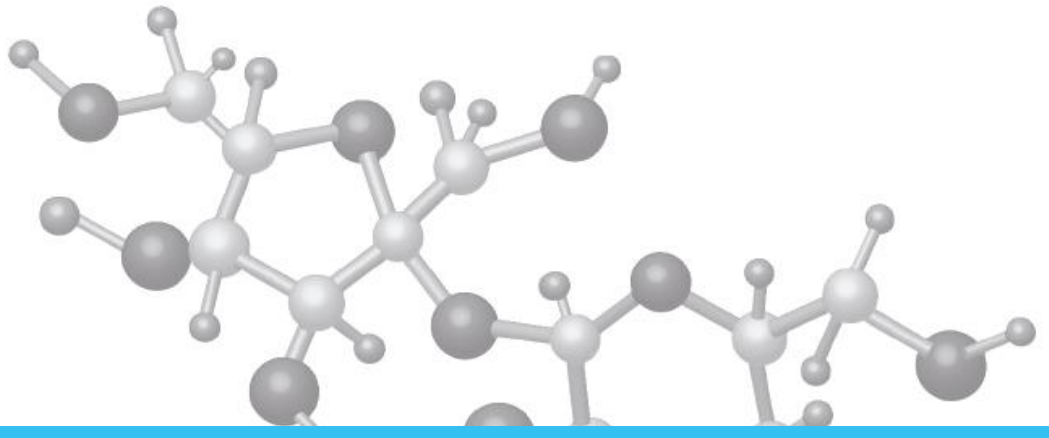

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