This is the published version of a paper published in *ChemistryOpen*.

Citation for the original published paper (version of record):

https://doi.org/10.1002/open.201800214

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Cyclopropylmethyl Protection of Phenols: Total Synthesis of the Resveratrol Dimers Anigopreissin A and Resveratrol–Piceatannol Hybrid

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We demonstrate the versatile use of the cyclopropylmethyl group to protect phenols through the total synthesis of two benzofuran-based natural products, that is, anigopreissin A and the resveratrol–piceatannol hybrid. This protecting group is a good alternative to the conventional methyl group, owing to the feasibility of introduction, stability under a variety of conditions, and its relative ease of removal under different acidic conditions.

Heterocyclic compounds are of vital importance in medicinal chemistry and appear in a variety of approved drugs and biologically active compounds. Among those heterocyclic compounds, the benzofuran scaffold exists widely in natural and synthetic compounds with an enormous range of pharmacological activities such as antibacterial, antifungal, anti-inflammatory, antioxidative, antiviral and antineoplastic. Furthermore, benzofuran derivatives are used as fluorescent sensors in organic chemistry. Our interest in these scaffolds originates from our finding of the resveratrol tetramer, (−)-hopeaphenol—a complex plant stilbenoid isolated from the Papua Guinean tree species Anisoptera thurifera and Anisoptera polyandra—as an irreversible inhibitor of the type III secretion in gram-negative pathogens Yersinia pseudotuberculosis and Pseudomonas aeruginosa. Based on this finding, we initiated studies to expand our knowledge on the chemistry and biology of these scaffolds and recently published total syntheses of benzofuran based natural products (±)-ampelopsin B and (±)-e-viniferin. Subsequently, we reported the total synthesis of other benzofuran based natural products viz. viniferuran, anigopreissin A and resveratrol–piceatannol hybrid as well as natural product inspired libraries based on the benzofuran scaffold. Anigopreissin A, a naturally occurring dimer of resveratrol, shows low antimicrobial activity against S. aureus and S. pyogenes. It is also a potent inhibitor of the HIV-1 reverse transcriptase (IC50 = 8 μM) and two mutant enzymes which are resistant to the clinical drug nevirapine. Re- sveratrol–piceatannol hybrid was isolated in 2015 from a grape extract (vitis vinifera), which was first fractionated using a hepatitis C virus replication inhibition assay. These natural products have previously been synthesized using methyl protecting groups, which are removed under harsh acidic conditions such as BBr3 or BCl3/TBAI. These conditions are frequently not compatible with the target compound and result in formation of undesired products and low yields. For example, BBr3 failed to give anigopreissin A or shoreapenol from their corresponding permethylated analogues, whereas anigopreissin A was only obtained in 23% yield when using BCl3/TBAI. Thus, the unpredictability of the demethylation step for many of these polyphenolic natural products indicate a need for alternative protecting groups.

In this work, we explored the use of cyclopropylmethyl (cPrMe) ether inspired by a report from Nagata et al., in which the cPrMe ethers were selectively cleaved under acidic conditions and yet stable to a wide range of reaction conditions. Our group has applied the cPrMe protection during the total synthesis of the resveratrol oligomer (±)-ampelopsin B that allowed an ultimate three-step one-pot deprotection, epimerization and cyclization to form the target compound. Given the lability of the cPrMe ethers to acids and the feasibility to cleave it off under variety of conditions, and in continuation of our efforts on the polyphenol natural products, herein described the successful use of cPrMe as a protecting group in the total synthesis of anigopreissin A and resveratrol–piceatannol hybrid.

To date, three synthetic strategies for preparation of anigopreissin A have been published. The earlier two synthesis were reported with the constraint that only permethylated anigopreissin A was obtained. Despite several attempts to deprotect the methyl ether groups using for example, BBr3, BBr3·SMe2 and L-Selectride, the authors observed either decomposition or partial deprotection. The third and successful total synthesis of this natural product was published by our group in 2016 in which the permethylated anigopreissin A was deprotected in 23% yield using BCl3/TBAI. Based on these results we moved on and explored the cPrMe group as an alternative phenolic protecting group.

The synthesis of anigopreissin A using cPrMe protection commenced with preparation of the key intermediates 4, 8 and 10 (Scheme 1). The terminal alkyne 4 was synthesized in three steps from 4-hydroxybenzaldehyde 1, starting with the protection of the free phenolic group with the cyclopropyl-
methyl bromide to afford protected 4-hydroxybenzaldehyde 2. The desired terminal alkyne 4 was then synthesized from compound 2 via Corey–Fuchs reaction over two steps going through the dibromoalkene intermediate 3 as shown in Scheme 1.

The boronate ester 8 was synthesized over three steps starting with the demethylation of the commercially available 1-bromo-3,5-dimethoxybenzene 5 using BBr₃ to give intermediate 6. Subsequently, pinacolboronate 8 was prepared via Pd-catalyzed coupling of arylbromide 6 and diboronyl reagent to give boronic ester 7, which was protected with cPrMe groups to afford the key intermediate 8. The phosphonate ester 10 was synthesized using our previously reported route[10] from cPrMe-protected 4-hydroxybenzaldehyde 2, which was transformed to the corresponding benzyl chloride 9 upon treatment with thionyl chloride. The resultant benzyl chloride 9 was reacted with triethylphosphite to yield the required phosphonate ester 10.

To construct the benzofuran ring, 3,5-dihydroxy-4-iodobenzaldehyde 12 was prepared via iodination of aldehyde 11 with I₂ and used for the tandem Pd-Cu mediated domino Sonogashira-hetero-annulation reaction with alkyne 4 to give intermediate 13 (Scheme 2). O-alkylation of the free hydroxyl group with the cyclopropylmethyl bromide gave the protected intermediate 14, which was converted to aryl iodide 15 upon iodination with NIS/TFA. Next, the C-3-aryl-group was introduced through microwave-assisted Suzuki-cross-coupling of intermediate 15 with boronate ester 8 to provide compound 16.

The microwave-assisted Wittig–Horner olefination of aldehyde 16 with the phosphonate ester 10 afforded only trans-isomer of penta-protected anigopreissin A 17, which was subjected to deprotection under various conditions. Firstly, we started to study the acid lability of this protecting group using HCl/THF under microwave irradiation. Under these conditions anigopreissin A was fully deprotected at 100 °C under microwave in 43 % yield.

With this promising result, we went forward to confirm the feasibility of cleaving cPrMe ethers with other reagents that are typically used for the methyl ether cleavage such as BBr₃ and BCl₃. To our delight, both BBr₃ and BCl₃/TBAI were successful.

Scheme 1. Construction of key intermediates. Reagents and conditions: a) bromomethyl-cyclopropane, K₂CO₃, acetone, 80 °C, 12 h, 92 % for 2 and 89 % for 8; b) CBr₄, PPh₃, DCM, 0 °C, 0.5 h, 81 %; c) LDA, THF, –78 °C to rt, 16 h, 87 %; d) BBr₃, CH₂Cl₂, 0 °C to rt, 4 h, 90 %; e) bis(pinacolatodiboron, potassium acetate, Pd₂(dba)₃·CHCl₃, X-Phos, dioxane, 110 °C, 18 h, 74 %; f) NaBH₄, MeOH, 0 °C to rt, 1 h; then SOCl₂, Et₂O, rt, 2 h, 83 % over two steps; g) triethylphosphite, 130 °C, 15 h, 81 %.

Scheme 2. Synthesis of anigopreissin A. Reagents and conditions: a) I₂, H₂O₂, H₂O, 50 °C, 12 h, 61 %; b) Pd(PPh₃)₄, CuI, 4, DMF, TEA, 50 °C, 12 h, 61 %; c) bromomethyl-cyclopropane, K₂CO₃, DMF, 80 °C, 12 h, 82 %; d) NIS, TFA, DCM, 0 °C to rt, 4 h, 61 %; e) Pd(dppf)Cl₂·CH₂Cl₂, K₂CO₃, 8, THF:HO (2:1), MWI, 70 °C, 1 h, 70 %; f) 10, NaH, THF, MWI, 140 °C, 110 min, 52 %; g) 12 m HCl, THF, MWI, 100 °C, 0.5 h, 43 %; h) BBr₃, DCM, –78 °C to rt, 16 h, 38 %; i) BCl₃/TBAI, THF, 0 °C to rt, 4 h, 34 %.
ful to yield anigopreissin A 18 in 38% and 34% respectively compared to the methyl ether protecting group in which BBr₃ failed to give the desired polyphenol.\[11\] In terms of yield, the cPrMe group is superior to the methyl ether, which resulted only in 23% yield using BCl₃/TBAI.\[11\]

Encouraged by these results, we turned our attention towards the synthesis of resveratrol–piceatannol hybrid using cPrMe protection. Although resveratrol–piceatannol hybrid was successfully prepared using methyl ether protecting group, the final deprotection step resulted in low yield (13%) when using BCl₃/TBAI.\[11\] The synthetic strategy for resveratrol–piceatannol hybrid utilizing cPrMe protection is outlined in Scheme 3. Initially, we attempted to start from the commercially available 3-hydroxy-2-iodo-4-methoxybenzaldehyde 19 and 4-ethynylanisole to construct the benzofuran ring 20 via microwave-assisted Sonogashira-hetero-annulation reaction. However, all attempts to switch protecting groups from methyl ethers of 20 to reach the cPrMe-protected intermediate 24 were not successful and typically resulted in either mono-deprotection or decomposition. This result also further highlights the need for alternative protecting groups for this class of compounds. Instead, we prepared the dihydroxylated iodobenzaldehyde 22 by treating 19 with BBr₃, and used it directly for the construction of the benzofuran ring 23 followed by alkylation with cyclopropylmethyl bromide under basic condition to afford protected 2-aryl-benzofuran 24. The resulting product was brominated with N-bromosuccinimide to give aryl bromide 25, which was subjected to microwave-assisted Suzuki reaction with previously synthesized boronic ester 8 to furnish the cross-coupled product 26. The phosphate ester for the Wittig–Horner olefination (31) was synthesized in four steps from 3,5-dihydroxybenzaldehyde (Scheme 4). The free hydroxyl groups of 3,5-dihydroxybenzaldehyde 27 were protected as cPrMe-ethers 28 and aldehyde was reduced to the corresponding alcohol using NaBH₄. This alcohol intermediate 29 was then transformed into bromide 30 under Appel reaction conditions. Subsequently, treatment of benzyl bromide with triethylphosphite provided the required phosphate ester 31. Eventually, Wittig–Horner olefination of aldehyde 26 and phosphate ester 31 using NaH as a base under microwave irradiation gave the desired penta-protected resveratrol–piceatannol hybrid 33. To deprotect the resveratrol–piceatannol hybrid, we first applied HCl/THF that was successfully applied for anigopreissin A (Scheme 2). However, to our surprise this reagent failed to remove all cyclopropylmethyl groups even at elevated temperatures (Table 1, entry 1–3) and mixtures of inseparable products were formed. We also investigated the effect of other protic acids such as HBr or TFA, that also failed to produce the desired product (Table 1, entry 4–5). We then turned to BBr₃ and BCl₃/TBAI systems and we found that BBr₃ produced the desired polyphenol 33 in 69% yield (Table 1, entry 6), while BCl₃/TBAI gave the desired resveratrol–piceatannol hybrid 33 in 34% yield (Table 1, entry 7).

Scheme 3. Synthesis of the resveratrol–piceatannol hybrid. Reagents and conditions: a) BBr₃, DCM, –78 °C to rt, 12 h, 77% for 22 and 0% for 21; b) Pd(PPh₃)₄Cl₂, Cu, 4-ethynylanisole for 20 and alkyne 4 for 23, THF, TEA, MWI, 0.5 h, 40 °C (i); CH₂CN, MWI, 0.5 h, 100 °C, 82% for 20 and 23 (ii); c) K₂CO₃, bromomethyl-cyclopropane, acetone, 80 °C, 16 h, 75%; d) NBS, DCM, rt, 4 h, 75%; e) Pd(dppf)Cl₂·CH₂Cl₂, 8, K₂CO₃, THF:MeOH (2:1), MWI, 70 °C, 1 h, 81%; f) THF, NaH, 31, MWI, 140 °C, 110 min, 56%.

Scheme 4. Construction of phosphonate ester. Reagents and conditions: a) DMF, K₂CO₃, bromomethyl-cyclopropane, 80 °C, 12 h, 90%; b) MeOH, NaBH₄, 0 °C to rt, 1 h, 93%; c) CBr₃, PPh₃, DCM, 0 °C, 0.5 h, 92%; d) triethylphosphite, 130 °C, 15 h, 71%.
In summary, we have explored the use of the cPrMe protecting group in synthesis of resveratrol-based polyphenolic natural products. Generally, the cPrMe group offers more choices for removal compared to the conventional methyl ether, which typically requires harsh conditions and often results in unpredictable outcomes and low yields. We successfully applied the cPrMe protecting group in the total synthesis of anigopreissin A and resveratrol–piceatannol hybrid. The cPrMe group can readily incorporated in the synthetic sequences and is stable to a wide variety of chemistries. Finally, it can be removed using a variety of acidic conditions and proved to be more versatile than the methyl group that is typically used in syntheses of polyphenolic compounds. Given the chemostability and the relative ease of deprotection we believe that the cPrMe group can be applied as a general protecting group for polyphenols.

Acknowledgements

This work was supported by the Swedish Research Council (VR, 621–2014–4670) and Umeå Centre for Microbial Research (UCMR), Umeå, Sweden.

Conflict of interest

The authors declare no conflict of interest.

Keywords: anigopreissin A · cyclopropylmethyl protecting group · deprotection · resveratrol–piceatannol hybrid · total synthesis


Received: October 13, 2018