ChemPubSoc Europe

DOI: 10.1002/open.201800214

Open Access ChemistryOPEN Communications

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

Arvind Kumar[+], Michael Saleeb[+], Dominik Werz, and Mikael Elofsson*[a]

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.[1] Among those heterocyclic compounds, the benzofuran scaffold exists widely in natural and synthetic compounds with an enormous range of pharmacological activities, such as antibacterial,[2] antifungal,[3] anti-inflammatory,[4] antioxidative,[5] antiviral[6] and antineoplastic.[7] Furthermore, benzofuran derivatives are used as fluorescent sensors in organic chemistry.[8] 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*.[9] 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 (±)-ε-viniferin.[10] Subsequently, we reported the total synthesis of other benzofuran based natural products *viz.* viniferifuran, anigopreissin A and resveratrol–piceatannol hybrid;[11] as well as natural product inspired libraries based on the benzofuran scaffold.[12] Anigopreissin A, a naturally occurring dimer of resveratrol, shows low antimicrobial activity against *S. aureus* and *S. pyogene*.[13] It is also a potent inhibitor of the HIV-1 reverse transcriptase ($IC_{50} = 8\,\mu M$) and two mutant enzymes which are resistant to the clinical drug nevirapine.[14] Resveratrol-piceatannol hybrid was isolated in 2015 from a grape extract (*vitis vinifera*), which was first fractionated using a hepatitis C virus replication inhibition assay.[15] These natural products have previously been synthesized using methyl protecting groups, which are removed under harsh acidic conditions such as BBr_3 or BCl_3/TBAI. These conditions are frequently not compatible with the target compound and result in formation of undesired products and low yields.[16] For example, BBr_3 failed to give anigopreissin A[11] or shoreaphenol[17] from their corresponding permethylated analogues, whereas anigopreissin A was only obtained in 23% yield when using BCl_3/TBAI.[11] 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.[18] 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.[10] 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,[12] we herein described the successful use of cPrMe as a protecting group in the total synthesis of anigopreissin A and resveratrol–piceatannol hybrid.

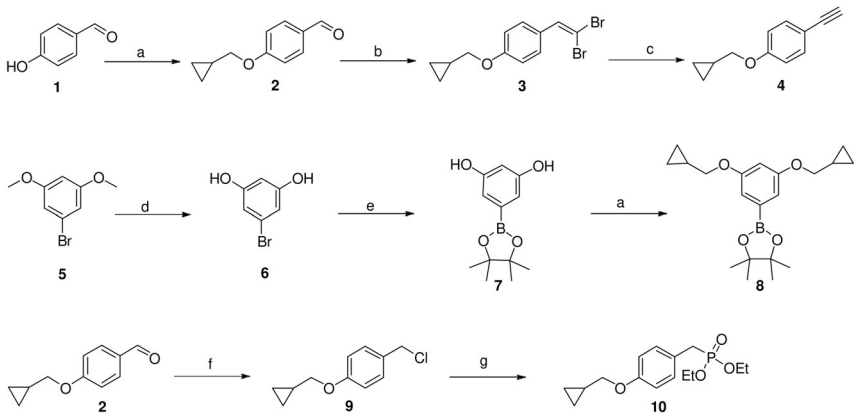
To date, three synthetic strategies for preparation of anigopreissin A have been published.[11,19] The earlier two synthesis were reported with the constraint that only permethylated anigopreissin A was obtained.[19] Despite several attempts to deprotect the methyl ether groups using for example, BBr_3, $BBr_3{\cdot}SMe_2$ and L-Selectride, the authors observed either decomposition or partial deprotection.[19a] 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 BCl_3/TBAI.[11] 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-

[a] *Dr. A. Kumar,[+] Dr. M. Saleeb,[+] D. Werz, Prof. M. Elofsson*
Department of Chemistry, Umeå University
90187, Umeå (Sweden)
E-mail: mikael.elofsson@umu.se

[+] *These authors contributed equally to this work*

Supporting Information and the ORCID identification number(s) for the author(s) of this article can be found under: https://doi.org/10.1002/open.201800214.



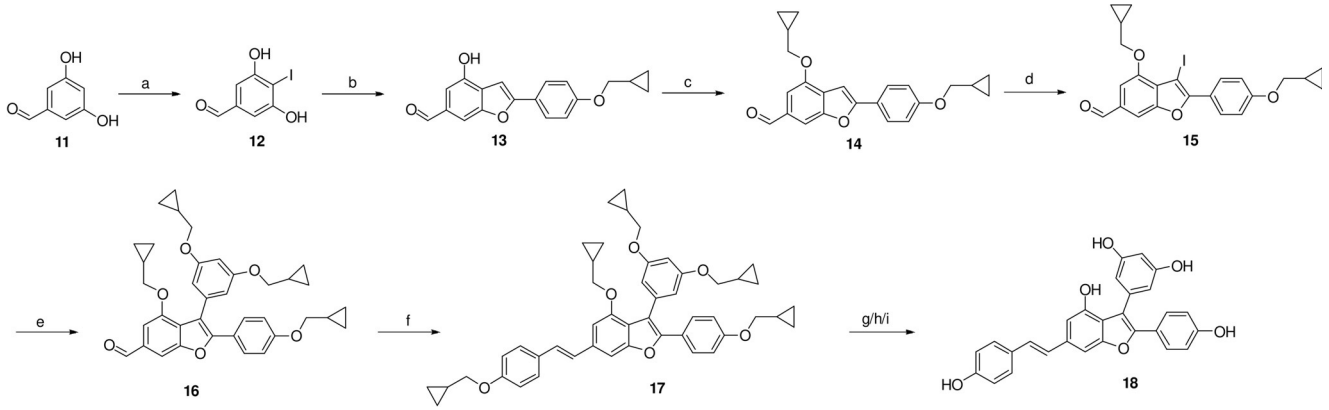
Scheme 1. Construction of key intermediates. Reagents and conditions: a) bromomethyl-cyclopropane, K_2CO_3, acetone, 80 °C, 12 h, 92% for **2** and 89% for **8**; b) CBr_4, PPh_3, DCM, 0 °C, 0.5 h, 81%; c) LDA, THF, −78 °C to rt, 16 h, 87%; d) BBr_3, CH_2Cl_2, 0 °C to rt, 4 h, 90%; e) bis(pinacolaton)diboron, potassium acetate, $Pd_2(dba)_3$·$CHCl_3$, X-Phos, dioxane, 110 °C, 18 h, 74%; f) $NaBH_4$, MeOH, 0 °C to rt, 1 h; then $SOCl_2$, Et_2O, rt, 2 h, 83% over two steps; g) triethylphosphite, 130 °C, 15 h, 81%.

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 BBr_3 to give intermediate **6**. Subsequently, pinacol boronate **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 reduction with $NaBH_4$ and 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 I_2 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.

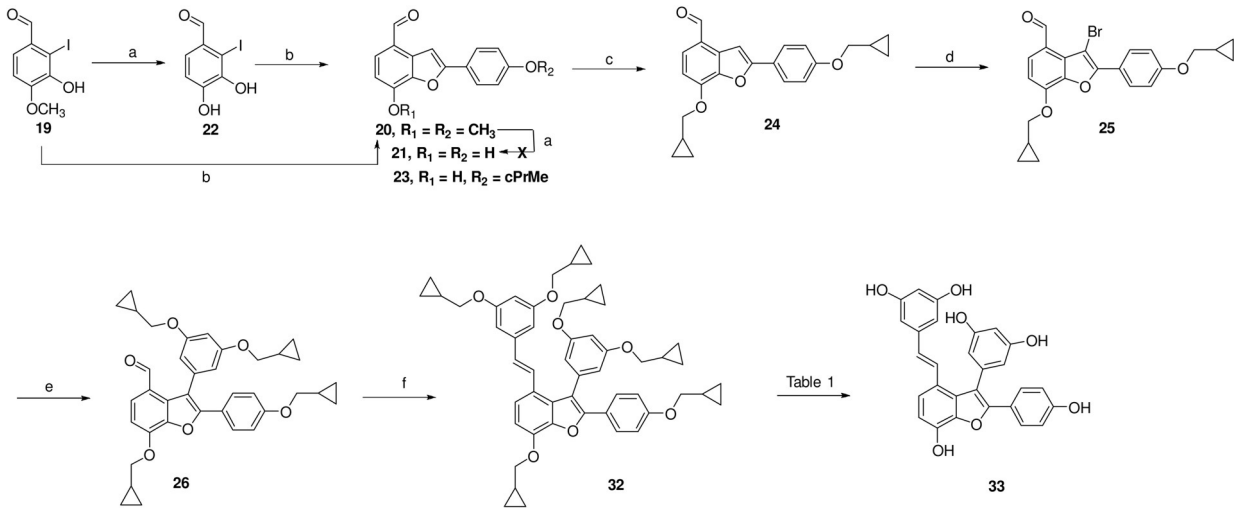
With this promising result, we went forward to confirm the feasibility of cleaving cPrMe ethers with other reagents that are typically used for the methyl ether cleavage such as BBr_3 and BCl_3. To our delight, both BBr_3 and BCl_3/TBAI were success-



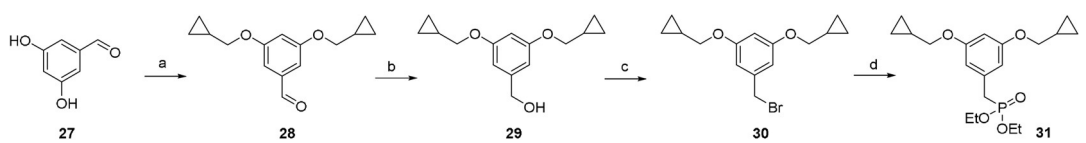
Scheme 2. Synthesis of anigopreissin A. Reagents and conditions: a) I_2, H_2O_2, H_2O, 50 °C, 12 h, 61%; b) $Pd(PPh_3)_2Cl_2$, CuI, **4**, DMF, TEA, 50 °C, 12 h, 61%; c) bromomethyl-cyclopropane, K_2CO_3, DMF, 80 °C, 12 h, 82%; d) NIS, TFA, DCM, 0 °C to rt, 4 h, 61%; e) $Pd(dppf)Cl_2$·CH_2Cl_2, K_2CO_3, **8**, THF:H_2O (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) BBr_3, DCM, −78 °C to rt, 16 h, 38%; i) BCl_3/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 BBr_3 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 BCl_3/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 BCl_3/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 BBr_3, 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 phosphonate 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 $NaBH_4$. This alcohol intermediate **29** was then transformed into bromide **30** under Appel reaction conditions. Subsequently, treatment of benzyl bromide with triethylphosphite provided the required phosphonate ester **31.** Eventually, Wittig–Horner olefination of aldehyde **26** and phosphonate ester **31** using NaH as a base under microwave irradiation gave the desired penta-protected resveratrol–piceatannol hybrid **32**. 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 BBr_3 and BCl_3/TBAI systems and we found that BBr_3 produced the desired polyphenol **33** in 69% yield (Table 1, entry 6), while BCl_3/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) BBr_3, DCM, −78 °C to rt, 12 h, 77% for **22** and 0% for **21**; b) $Pd(PPh_3)_2Cl_2$, CuI, 4-ethynylanisole for **20** and alkyne **4** for **23**, THF, TEA, MWI, 0.5 h, 40 °C (i); CH_3CN, MWI, 0.5 h, 100 °C, 82% for **20** and **23** (ii); c) K_2CO_3, bromomethyl-cyclopropane, acetone, 80 °C, 16 h, 75%; d) NBS, DCM, rt, 4 h, 75%; e) $Pd(dppf)Cl_2{\cdot}CH_2Cl_2$, **8**, K_2CO_3, THF:H_2O (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, K_2CO_3, bromomethyl-cyclopropane, 80 °C, 12 h, 90%; b) MeOH, $NaBH_4$, 0 °C to rt, 1 h, 93%; c) CBr_4, PPh_3, DCM, 0 °C, 0.5 h, 92%; d) triethylphosphite, 130 °C, 15 h, 71%.

Table 1. Summary of reagents and conditions tested to deprotect the penta-protected resveratrol–piceatannol hybrid.

Entry	Reagent	Condition[a]	Time[h]	Yield [%]
1.	HCl/THF	MWI 100 °C	1	0[b]
2	HCl/THF	MWI 130 °C	0.5	0[b]
3	HCl/THF	rt	24	0[b]
4	HBr/EtOH	MWI 100 °C	0.5	0[b]
5	TFA/DCM	rt	12	0[b]
6	BBr_3/DCM	−78 °C to rt	16	69[c]
7.	BCl_3/TBAI/DCM	0 °C to rt	6	34[c]

[a] MWI = microwave irradiation, rt = room temperature. Yields are based on [b] TLC and LCMS, [c] isolated yield

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 resulting 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

[1] a) T. Y. Zhang in *Advances in Heterocyclic Chemistry, Academic Press, Vol. 121*, **2017**, pp. 1–12; b) A. Radadiya, A. Shah, *Eur. J. Med. Chem.* **2015**, *97*, 356–376; c) R. Naik, D. S. Harmalkar, X. Xu, K. Jang, K. Lee, *Eur. J. Med. Chem.* **2015**, *90*, 379–393; d) H. Khanam, Shamsuzzaman, *Eur. J. Med. Chem.* **2015**, *97*, 483–504; e) R. J. Nevagi, S. N. Dighe, S. N. Dighe, *Eur. J. Med. Chem.* **2015**, *97*, 561–581; f) Y. J. Wu in *Progress in Heterocyclic Chemistry, Elsevier, Vol. 24*, **2012**, Pages 1–53; g) J. B. Sperry, D. L. Wright, *Curr. Opin. Drug Discov. Devel.* **2005**, *8*, 723–740.

[2] a) G. Khodarahmi, P. Asadi, F. Hassanzadeh, E. Khodarahmi, *J. Res. Med. Sci.* **2015**, *20*, 1094–1104; b) J. Renuka, K. I. Reddy, K. Srihari, V. U. Jeankumar, M. Shravan, J. P. Sridevi, P. Yogeeswari, K. S. Babu, D. Sriram, *Bioorg. Med. Chem.* **2014**, *22*, 4924–4934; c) Y. He, J. Xu, Z. H. Yu, A. M. Gunawan, L. Wu, L. Wang, Z. Y. Zhang, *J. Med. Chem.* **2013**, *56*, 832–842; d) K. M. Dawood, *Expert Opin. Ther. Pat.* **2013**, *23*, 1133–1156; e) H. A. Abdel-Aziz, A. A. Mekawey, K. M. Dawood, *Eur. J. Med. Chem.* **2009**, *44*, 3637–3644.

[3] a) M. Masubuchi, H. Ebiike, K. Kawasaki, S. Sogabe, K. Morikami, Y. Shiratori, S. Tsujii, T. Fujii, K. Sakata, M. Hayase, H. Shindoh, Y. Aoki, T. Ohtsuka, N. Shimma, *Bioorg. Med. Chem.* **2003**, *11*, 4463–4478; b) M. Masubuchi, K. Kawasaki, H. Ebiike, Y. Ikeda, S. Tsujii, S. Sogabe, T. Fujii, K. Sakata, Y. Shiratori, Y. Aoki, T. Ohtsuka, N. Shimma, *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1833–1837.

[4] a) Y. Ma, X. Zheng, H. Gao, C. Wan, G. Rao, *Molecules* **2016**, *21*, 1684–1693; b) M. Sun, C. Zhao, G. A. Gfesser, C. Thiffault, T. R. Miller, K. Marsh, J. Wetter, M. Curtis, R. Faghih, T. A. Esbenshade, A. A. Hancock, M. Cowart, *J. Med. Chem.* **2005**, *48*, 6482–6490.

[5] K. Chand, Rajeshwari, A. Hiremathad, M. Singh, M. A. Santos, R. S. Keri, *Pharmacol. Rep.* **2017**, *69*, 281–295 and references cited therein.

[6] a) W. J. Wang, L. Wang, Z. Liu, R. W. Jiang, Z. W. Liu, M. M. Li, Q. W. Zhang, Y. Dai, Y. L. Li, X. Q. Zhang, W. C. Ye, *Phytochemistry* **2016**, *122*, 238–245; b) S. A. Galal, A. S. Abd El-All, M. M. Abdallah, H. El-Diwani, *Bioorg. Med. Chem. Lett.* **2009**, *9*, 2420–2428.

[7] a) M. Choi, H. Jo, H. J. Park, A. S. Kumar, J. Lee, J. Yun, Y. Kim, S. Han, J. K. Jung, J. Cho, K. Lee, J. H. Kwak, H. Lee, *Bioorg. Med. Chem. Lett.* **2015**, *25*, 2545–2549; b) C. Salomé, N. Ribeiro, T. Chavagnan, F. Thuaud, M. Serova, A. de Gramont, S. Faivre, E. Raymond, L. Désaubry, *Eur. J. Med. Chem.* **2014**, *81*, 181–191; c) R. Romagnoli, P. G. Baraldi, M. D. Carrion, C. L. Cara, O. Cruz-Lopez, M. Tolomeo, S. Grimaudo, A. D. Cristina, M. R. Pipitone, J. Balzarini, N. Zonta, A. Brancale, E. Hamel, *Bioorg. Med. Chem.* **2009**, *17*, 6862–6871.

[8] O. Oter, K. Ertekin, C. Kirilmis, M. Koca, M. Ahmedzade, *Sens. Actuators B* **2007**, *122*, 450–456.

[9] C. E. Zetterstrçm, J. Hasselgren, O. Salin, R. A. Davis, R. J. Quinn, C. Sundin, M. Elofsson, *PLoS ONE* **2013**, *8*, e81969.

[10] A. E. G. Lindgren, C. T. Oberg, J. M. Hillgren, M. Elofsson, *Eur. J. Org. Chem.* **2016**, *3*, 426–429.

[11] D. D. Vo, M. Elofsson, *Adv. Synth. Catal.* **2016**, *358*, 4085–4092.

[12] a) M. Saleeb, S. Mojica, A. U. Eriksson, C. D. Andersson, Å. Gylfe, M. Elofsson, *Eur. J. Med. Chem.* **2018**, *143*, 1077–1089; b) L. Qin, D. D. Vo, A. Nakhai, C. D. Andersson, M. Elofsson, *ACS Comb. Sci.* **2017**, *19*, 370–376; c) D. D. Vo, M. Elofsson, *ChemistrySelect* **2017**, *2*, 6245–6248; d) A. Krzyzanowski, M. Saleeb, M. Elofsson, *Org. Lett.* **2018**, https://doi.org/10.1021/acs.orglett.8b02638.

[13] a) D. Holscher, B. Schneider, *Phytochemistry* **1996**, *43*, 471–473; b) B. Schneider, *Phytochemistry* **2003**, *64*, 459–462; c) R. Brkljača, J. M. White, S. Urban, *J. Nat. Prod.* **2015**, *78*, 1600–1608.

[14] a) C. Tancharoen, Master Thesis, Kasetsart University, **2012**; b) P. Convertini, F. Tramutola, V. Iacobazzi, P. Lupatteli, L. Chiummiento, V. Infantino, *Chem.-Biol. Interact.* **2015**, *237*, 1–8.

[15] C. H. Lee, K. D. Yoon, T. H. Heo, PCT Int. Appl. WO 2015126129 A2 20150827, **2015**.

[16] M. H. Keylor, B. S. Matsuura, C. R. J. Stephenson, *Chem. Rev.* **2015**, *115*, 8976–9027 and references cited therein.

[17] I. Kim, J. Choi, *Org. Biomol. Chem.* **2009**, *7*, 2788–2795.

[18] W. Nagata, K. Okada, H. Itazaki, S. Uyeo, *Chem. Pharm. Bull.* **1975**, *23*, 2878–2890.

[19] a) L. Chiummiento, M. Funicello, M. T. Lopardo, P. Lupattelli, S. Choppin, F. Colobert, *Eur. J. Org. Chem.* **2012**, 188–192; b) J. Liu, C. J. Simmons, H. Xie, F. Yang, X. Zhao, Y. Tang, W. Tang, *Adv. Synth. Catal.* **2017**, *359*, 693–697.

Received: October 13, 2018

