Biological Inhibitors

Deutsche Ausgabe: DOI: 10.1002/ange.201511672
Internationale Ausgabe: DOI: 10.1002/anie.201511672

Bioisosteric Exchange of C_{sp^3}-Chloro and Methyl Substituents: Synthesis and Initial Biological Studies of Atpenin A5 Analogues

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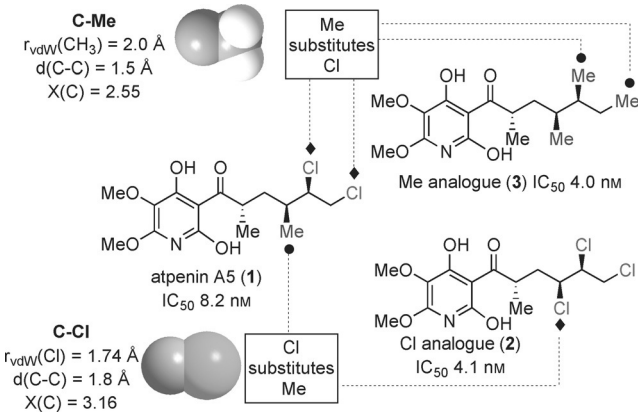
Abstract: *Asymmetric synthesis and initial biological studies of two analogues of a naturally occurring chlorinated antifungal agent, atpenin A5, are described. These analogues were selected on the basis of Cl→CH_3 or H_3C→Cl exchanges in the side-chain of atpenin A5. The interchange of chloro and methyl substituents led to complex II inhibitors with equal IC_{50} values. This suggests that Cl↔Me bioisosteric exchange can be realized in aliphatic settings.*

Bioisosteric replacement is an important and widely used strategy for optimizing biological activity and physicochemical properties of lead candidates in the development of pharmaceuticals and agrochemicals.[1] Typical examples include the exchange of hydrogen with deuterium[2] or fluorine,[3] and new types of bioisosteres for common functional groups (such as CO_2H) continue to be developed.[4] While chloro and methyl substituents at sp^2-hybridized carbon atoms are routinely interchanged in the process of optimizing the properties of a lead structure,[5] the analogous Cl↔Me interchange at stereogenic sp^3-hybridized carbons is less explored in biologically active small molecules.[6] Seeking to fill this gap, herein we report the synthesis and biological evaluation of two analogues of a naturally occurring inhibitor of complex II in the mitochondrial respiratory chain, atpenin A5 (**1**; Scheme 1). The analogues were targeted for study on the basis of H_3C→Cl (atpenin A5→analogue **2**) or Cl→CH_3 (atpenin A5→analogue **3**) bioisosteric exchanges. The collection of compounds **1**–**3**, which display variation in Me/Cl substitution patterns, were found to be equally potent complex II inhibitors.

Since chloro and methyl groups are univalent and have van der Waals radii that differ by about 15% (1.74 Å for Cl,[7] 2.0 Å for Me[8]), it is not anticipated that Cl↔Me interchange leads to significant changes in steric demand. However, the markedly different electronic properties of the two substituents allow tuning of physicochemical parameters such as polarity, solubility, lipophilicity, reactivity, resistance to metabolic degradation, and pK_a.[5] Unlike methyl groups, chlorides can engage in halogen bonding[9] and C-Cl···C=O(NR_2) interactions.[10] Substituent effects are the subject of increased attention in medicinal chemistry as design elements for optimization of ligand–receptor binding.[9a,11]



Scheme 1. Structures and biological activities of atpenin A5 (**1**) and the targeted chloro and methyl analogues **2** and **3**.

Classic examples of the use of chloro as a hydroxy isostere in aliphatic systems are found in the development of the antibiotic clindamycin[12] and the artificial sweetener sucralose.[13] In these cases, alcohols in the naturally occurring parent structures are replaced with chlorides in the commercial products. In contrast, Me/Cl replacement has generally been reported for arenes only, and typically involves exchanging an aromatic methyl group with a chloro substituent, which results in increased stability because of blocking of oxidative metabolism.[5g–i] In light of the classic examples above, we became interested in exploring Cl↔Me bioisosteric replacement in an aliphatic setting. Our investigative plan necessitated identification of a biologically active molecule as a model. The model system needed to incorporate both C_{sp^3}-Cl and C_{sp^3}-Me substituents to allow for a comparative study.

The atpenins are naturally occurring substances[14] that have attracted attention as potential fungicides/agricultural pest control agents,[15] and for their antiproliferative[16] and cardioprotective effects.[17] They inhibit complex II in the mitochondrial respiratory chain, and thus, the production of ATP.[18] The core structure of the atpenins is characterized by a pyridine ring with an appended acyl side-chain. Researchers at DuPont[15c] and Bayer[15d] have shown that structural modification of the side-chain of the atpenin scaffold can lead to analogues with unchanged or diminished biological

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Supporting information and the ORCID identification number(s) for the author(s) of this article can be found under http://dx.doi.org/10.1002/anie.201511672.

activity. Naturally occurring members of this family also display a dependence of activity on the structure of the side-chain. For example, the absence of a terminal chloride substituent in atpenin A4 (**4**) leads to a 13-fold reduction in activity when compared to atpenin A5 (**1**), and harzianopyridone (**5**) exhibits activity more than two orders of magnitude lower in an assay measuring NADH-fumarate reductase activity (Figure 1).[18,19] Accordingly, atpenin A5 (**1**), with its side-chain incorporating an array of chloro and methyl substituents, was identified as a suitable model for examining the effect of bioisosteric Cl↔Me replacement upon synthesis of analogues **2** and **3**.

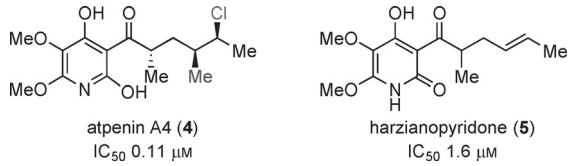


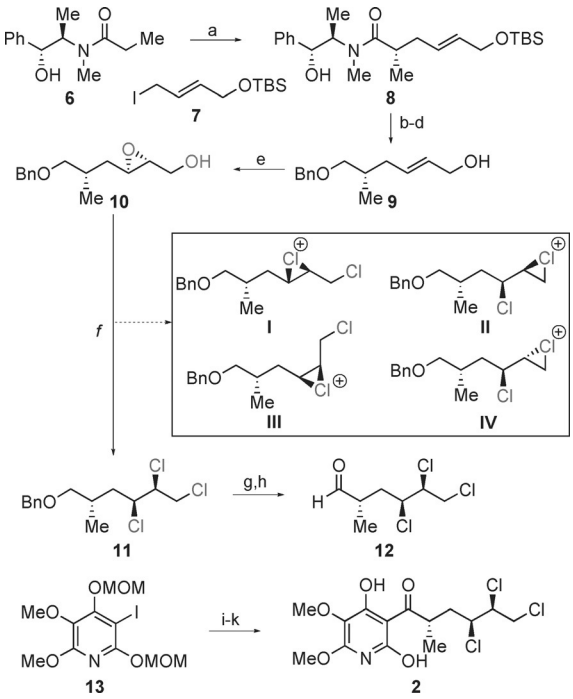
Figure 1. Structures and biological activities of atpenin A4 (**4**) and harzianopyridone (**5**). IC_{50} values refer to activities against complex I + II in *A. suum* adult muscle, measured by NADH-fumarate reductase activity.[18]

In line with previous studies,[20] synthetic strategies towards **2** and **3** relied on addition of a pyridine-derived organometallic nucleophile to advanced aldehyde intermediates. The central problem in the synthesis of Cl analogue **2** was stereocontrolled construction of the trichlorinated motif in the side-chain. Stereoselective synthesis of acyclic (poly)-chlorinated molecules often presents challenges,[21] and a number of diastereo-[22] and enantioselective[23] methods have only been developed quite recently. Among these, a report from Yoshimitsu documented an approach for the stereospecific synthesis of vicinal dichlorides from epoxides readily prepared by Sharpless asymmetric epoxidation of allylic alcohols.[22a]

Synthesis of the chloro analogue of atpenin A5 (**2**) (Scheme 2) commenced with allylic iodide **7**, which was obtained from 2-butyne-1,4-diol. Myers alkylation[24] of pseudoephedrine amide **6** with **7** afforded **8** in 94% yield, and reductive cleavage of the auxiliary using lithium amidotrihydroborate[25] furnished the corresponding primary alcohol. Subsequent protecting group manipulations and Sharpless epoxidation[26] of allylic alcohol **9** furnished epoxy alcohol **10**.

The Yoshimitsu protocol cited above has only been reported for the conversion of protected epoxyalcohols into *vic*-dichlorides.[22a] When it was applied to the TBDPS-protected derivative of **10**, the corresponding dichloride was isolated in 86% yield, contaminated with approximately 20% of a mixture of vinyl chlorides as an inseparable mixture. The dichloride was converted to **11** following a two-step procedure involving deprotection and chlorination (see Supporting Information).

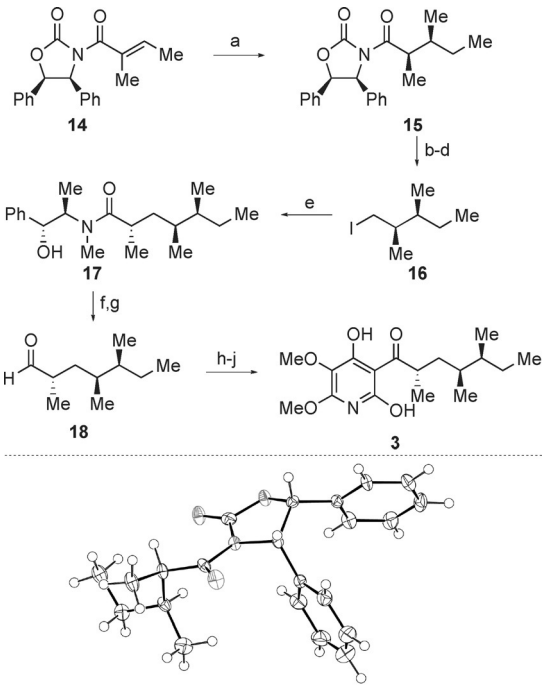
We were eager to examine whether epoxyalcohol **10** would afford the targeted trichloride product directly. Treatment of **10** with Ph_3P and *N*-chlorosuccinimide in toluene at



Scheme 2. Synthesis of chloro analogue **2**. Reagents and conditions: a) 1) LDA (3.5 equiv), LiCl (12.5 equiv), **6** (2.0 equiv), THF, −78 °C, 1 h; 2) **7** (1.0 equiv), 0 °C to RT, 15 h, 94%; b) LiH_2NBH_3 (5.0 equiv), THF, RT, 3 h, 86%; c) 1) NaH (1.5 equiv), THF, 0 °C, 1 h; 2) $^n Bu_4NI$ (0.1 equiv), BnBr (1.5 equiv), RT, 40 h, 76%; d) HCl (1 M), THF/H_2O 1/1, 0 °C, 2 h, 79%; e) (−)-DET (7.5 mol%), $Ti(O^iPr)_4$ (5 mol%), ^{t}BuOOH (2.0 equiv), 4 Å MS, CH_2Cl_2, −18 °C, 68%, 11:1 d.r.; f) NCS (4.5 equiv), PPh_3 (4.5 equiv), toluene, 90 °C, 2 h, 77%; g) H_2, 10% Pd/C (1.0 equiv), MeOH, 71%; h) Dess–Martin periodinane (1.5 equiv), $NaHCO_3$ (3.0 equiv), CH_2Cl_2, RT, 30 min, 79%; i) 1) ^{t}BuLi (2.0 equiv), THF, −78 °C; 2) **12** (1.0 equiv), THF, −78 °C, 30 min, 56%; j) Dess–Martin periodinane (1.5 equiv), CH_2Cl_2, 45 min, 38%; k) F_3CCO_2H, CH_2Cl_2, 0 °C, 30 min, 88%. LDA = lithium diisopropylamide; THF = tetrahydrofuran; Bn = benzyl; DET = diethyltartrate; NCS = *N*-chlorosuccinimide.

90 °C furnished **11** in 77% yield, contaminated with 10% impurities (presumably vinyl chlorides). This experiment is the first example of direct transformation of an epoxy alcohol into the corresponding trichloride, considerably streamlining preparation of **11**. Synthesis of aldehyde **12** was completed by hydrogenolytic cleavage of the benzyl group followed by oxidation of the liberated alcohol. The organolithium derivative of **13**[20] was coupled with aldehyde **12,** and the resulting mixture of diastereomeric alcohols oxidized to furnish the corresponding ketone. Cleavage of the MOM-protecting groups then afforded the Cl analogue of atpenin A5 (**2**). *J*-based configuration analysis of **2** confirmed the *syn*-arrangement of the two vicinal chlorides.[27] It is interesting that conversion of **10** to **11** is stereochemically well-behaved. On the basis of our previous investigations, there are a priori numerous chloronium intermediates **I**–**IV**, among others, that could lead to products resulting from stereochemical scrambling of the chlorides.[21c,h]

Stereocontrolled construction of vicinally arranged dimethyl groups posed the main challenge in the synthesis of analogue **3** (Scheme 3). Conjugate addition of ethyl



Scheme 3. Synthesis of methyl analogue **3**. Reagents and conditions: a) EtMgBr (3.0 equiv), CuBr·SMe_2 (1.5 equiv), Me_2S, THF, −40 °C, 1 h, then **14** (1.0 equiv), −30 °C, 4 h, 58%, 4:1 d.r.; b) LiOH (1.6 equiv), H_2O_2 (4.0 equiv), 0 °C, 2 h, 90%; c) $LiAlH_4$ (1.2 equiv), THF, reflux, 66%; d) I_2 (1.2 equiv), PPh_3 (1.1 equiv), imidazole (1.4 equiv), 0 °C, 90 min, 70%; e) 1) LDA (3.4 equiv), LiCl (12.4 equiv), **6** (2.0 equiv), THF, −78 °C, 1 h; 2) **16** (1.0 equiv), 0 °C to RT, 18 h, 47%; f) LiH_2NBH_3 (5.0 equiv), THF, RT, 2.5 h, 75%; g) Dess–Martin periodinane (1.5 equiv), $NaHCO_3$ (3.0 equiv), CH_2Cl_2, RT, ca. 50%; h) 1) ^{t}BuLi (4.2 equiv), **13** (2.0 equiv), THF, −78 °C, 5 min; 2) **18** (1.0 equiv), THF, −78 °C, 45 min, 39%; i) Dess–Martin periodinane (1.5 equiv), CH_2Cl_2, 60 min, 62%; j) TFA, CH_2Cl_2, 0 °C, 30 min, 88%. TFA = trifluoroacetic acid.

cuprate to α,β-unsaturated acyl oxazolidinone **14** produced **15** in 58% yield, as a 4:1 mixture of inseparable diastereomers.[28] Cleavage of the chiral auxiliary,[29] reduction, and Appel reaction, furnished iodide **16**. Pseudoephedrine amide **6** was then alkylated with iodide **16**, setting the remaining stereogenic center and affording **17**. Synthesis of the side-chain was completed by reductive cleavage of the auxiliary followed by oxidation of the resulting alcohol to aldehyde **18**. Addition of the organolithium derivative of **13** to aldehyde **18** gave a mixture of benzylic alcohol epimers, which was inconsequential as they were oxidized to the corresponding ketone in the next step. Finally, MOM deprotection furnished **3** as a 4:1 mixture of diastereomers (from the initial cuprate addition), which were separated by HPLC on a chiral stationary phase.

The biological activities of the two analogues were evaluated against respiratory enzymes from the roundworm *Ascaris suum*, as well as from bovine heart (Table 1). The overall trends observed with **2** and **3** match those found for atpenin A5. In this respect, **2** and **3** exhibited virtually no activity against complexes I, III and IV, underscoring the remarkable selectivity with which the atpenin scaffold inhibits complex II activity. Crucially, **2** and **3** inhibited NADH-fumarate reductase activity with IC_{50} values of 4.1 and 4.0 nM, respectively. Additionally, the two analogues inhibited succinate-cytochrome c reductase activity with essentially identical IC_{50} values of 10 and 15 nM.

Table 1: Inhibition of respiratory enzymes in nematode and mammalian mitochondria.

Species	Enzymes	IC_{50} [nM] **1**	**2**	**3**
Ascaris suum adult muscle	Complex I + II[a]	8.2	4.1	4.0
bovine heart	Complex II + III[b]	19	10	15
	Complex I + III + IV[c]	$>10^3$	$>10^3$	$>10^3$

[a] Measured by NADH-fumarate reductase activity ($n=3$). [b] Measured by succinate-cytochrome c reductase activity ($n=4$). [c] Measured by NADH oxidase activity ($n=4$).

In summary, we have accomplished the synthesis of two atpenin analogues **2** and **3**, involving Cl↔Me exchange, and evaluated their activities as complex II inhibitors. An important synthetic outcome of the study is the direct conversion of an epoxy-alcohol to the targeted trichloride array in a stereochemically defined manner. The finding that the synthetic atpenins with side-chains containing chloro or methyl substituents are equally biologically active suggest that these two types of substituents can be used interchangeably as bioisosteres in an aliphatic setting. We anticipate that the consequences of these findings will have broader applications in the discovery and optimization of bioactive lead structures, especially when coupled to recent advances in asymmetric chlorination.[22,23]

Acknowledgements

The European Research Council is acknowledged for partial support of this work (320666 CHLIP). We are grateful to Dr. Nils Trapp and Michael Solar for X-ray crystallographic analysis.

Keywords: antifungal agents · atpenins · bioisosterism · chlorinated natural products · inhibition of respiratory chain

How to cite: *Angew. Chem. Int. Ed.* **2016**, *55*, 4049–4053
Angew. Chem. **2016**, *128*, 4117–4121

[1] a) N. A. Meanwell, *J. Med. Chem.* **2011**, *54*, 2529; b) G. A. Patani, E. J. LaVoie, *Chem. Rev.* **1996**, *96*, 3147; c) *Bioisosteres in Medicinal Chemistry* (Ed.: N. Brown), Wiley-VCH, Weinheim, **2012**.

[2] For selected examples, see: a) A. E. Mutlib et al., *Toxicol. Appl. Pharmacol.* **2000**, *169*, 102; b) F. Maltais et al., *J. Med. Chem.* **2009**, *52*, 7993.

[3] For selected reviews, see: a) K. Müller, C. Faeh, F. Diederich, *Science* **2007**, *317*, 1881; b) H.-J. Böhm, D. Banner, S. Bendels, M. Kansy, B. Kuhn, K. Müller, U. Obst-Sander, M. Stahl, *ChemBioChem* **2004**, *5*, 637.

[4] N. Pemberton, H. Graden, E. Evertsson, E. Bratt, M. Lepistö, P. Johannesson, P. H. Svensson, *ACS Med. Chem. Lett.* **2012**, *3*, 574.

[5] For a general review of the influence of chlorides on biological activity, see: a) K. Naumann, *J. Prakt. Chem.* **1999**, *341*, 417; for

selected examples of Cl/Me interchange at C_{sp^2}, see: b) A. L. Ruchelman et al., *Bioorg. Med. Chem. Lett.* **2013**, *23*, 360; c) J. Bartroli, E. Turmo, M. Algueró, E. Boncompte, M. L. Vericat, L. Conte, J. Ramis, M. Merlos, J. García-Rafanell, J. Forn, *J. Med. Chem.* **1998**, *41*, 1869; d) E. R. Sørensen, N. R. El-Brollosy, P. T. Jørgensen, E. B. Pedersen, C. Nielsen, *Arch. Pharm.* **2005**, *338*, 299; e) N. Kudo, M. Taniguchi, S. Furuta, K. Sato, T. Endo, T. Honma, *J. Agric. Food Chem.* **1998**, *46*, 5305; f) P. L. McKibbin, A. Kobori, Y. Taniguchi, E. T. Kool, S. S. David, *J. Am. Chem. Soc.* **2012**, *134*, 1653; g) C. S. Burgey et al., *J. Med. Chem.* **2003**, *46*, 461; h) J. R. Tagat, et al., *J. Med. Chem.* **2001**, *44*, 3343; i) F. Z. Dörwald, *Lead Optimization for Medicinal Chemists: Pharmacokinetic Properties of Functional Groups and Organic Compounds*, Wiley-VCH, Weinheim, **2012**, p. 52; for a general reference, see: j) *Drug Metabolism Handbook: Concepts and Applications* (Eds.: A. F. Nassar, P. F. Hollenberg, J. Scatina), Wiley, Hoboken, **2009**; for a report on Cl/Me interchange in the context of olfactory response studies, see: k) R. L. Metcalf, W. C. Mitchell, T. R. Fukuto, E. R. Metcalf, *Proc. Natl. Acad. Sci. USA* **1975**, *72*, 2501.

[6] For a report of incorporation of chlorinated aliphatic amino acids into a protein, see: D. J. Stigers, Z. I. Watts, J. E. Hennessy, H.-K. Kim, R. Martini, M. C. Taylor, K. Ozawa, J. W. Keillor, N. E. Dixon, C. J. Easton, *Chem. Commun.* **2011**, *47*, 1839.

[7] *CRC Handbook of Chemistry and Physics*, 90th ed. (Eds.: D. R. Lide, W. M. Haynes), CRC Press, Boca Raton, FL, **2009**, pp. 9.

[8] L. Pauling, *The Nature of the Chemical Bond and the Structure of Molecules and Crystals: An Introduction to Modern Structural Chemistry*, 3rd ed., Cornell University Press, Ithaca, NY, **1960**, p. 260.

[9] a) R. Wilcken, M. O. Zimmermann, A. Lange, A. C. Joerger, F. M. Boeckler, *J. Med. Chem.* **2013**, *56*, 1363; b) P. Politzer, J. S. Murray, T. Clark, *Phys. Chem. Chem. Phys.* **2013**, *15*, 11178.

[10] a) K. J. Kamer, A. Choudhary, R. T. Raines, *J. Org. Chem.* **2013**, *78*, 2099; b) J. R. Horton, K. Sawada, M. Nishibori, X. Zhang, X. Cheng, *Structure* **2001**, *9*, 837.

[11] a) C. Bissantz, B. Kuhn, M. Stahl, *J. Med. Chem.* **2010**, *53*, 5061; b) E. Persch, O. Dumele, F. Diederich, *Angew. Chem. Int. Ed.* **2015**, *54*, 3290; *Angew. Chem.* **2015**, *127*, 3341.

[12] R. D. Birkenmeyer, F. Kagan, *J. Med. Chem.* **1970**, *13*, 616.

[13] a) M. Mathlouthi, A.-M. Seuvre, G. G. Birch, *Carbohydr. Res.* **1986**, *152*, 47; b) S. S. Schiffman, K. I. Rother, *J. Toxicol. Environ. Health Part B* **2013**, *16*, 399.

[14] a) S. Ōmura, H. Tomoda, K. Kimura, D.-Z. Zhen, H. Kumagai, K. Igarashi, N. Imamura, Y. Takahashi, Y. Tanaka, Y. Iwai, *J. Antibiot.* **1988**, *41*, 1769; b) H. Kumagai, H. Nishida, N. Imamura, H. Tomoda, S. Ōmura, *J. Antibiot.* **1990**, *43*, 1553; c) K. Oshino, H. Kumagai, H. Tomoda, S. Ōmura, *J. Antibiot.* **1990**, *43*, 1064; d) J. M. Dickinson, J. R. Hanson, P. B. Hitchcock, N. Claydon, *J. Chem. Soc. Perkin Trans. 1* **1989**, 1885; for a report on the activity of atpenins as angiogenesis inhibitors, see: e) T. Otsuka, S. Takase, H. Terano, M. Okuhara, *J. Antibiot.* **1992**, *45*, 1970.

[15] a) P. B. Rodgers, *Pestic. Sci.* **1989**, *27*, 155; b) H. G. Cutler, J. M. Jacyno, *Agric. Biol. Chem.* **1991**, *55*, 2629; c) T. P. Selby, K. A. Hughes, J. J. Rauh, W. S. Hanna, *Bioorg. Med. Chem. Lett.* **2010**, *20*, 1665; d) I. Adelt, R. Velten, W. B. Wiese, U. Wachendorff-Neumann, K.-H. Kuck, P. Dahmen, A. Voerste, R. Ebbert, F. von Nussbaum, Bayer CropScience AG, Patent WO 2010/069495 A1; for a patent covering the application of related compounds as insecticides and miticides, see: WO 2006/137389 A1.

[16] a) M. Kawada, I. Momose, T. Someno, G. Tsujiuchi, D. Ikeda, *J. Antibiot.* **2009**, *62*, 243; b) M. Kawada, H. Inoue, S.-I. Ohba, T. Masuda, I. Momose, D. Ikeda, *Int. J. Cancer* **2010**, *126*, 810; for a review on mitochondrial complex II, as a chemotherapy target, see: c) K. Kluckova, A. Bezawork-Geleta, J. Rohlena, L. Dong, J. Neuzil, *Biochim. Biophys. Acta Bioenerg.* **2013**, *1827*, 552.

[17] a) A. P. Wojtovich, P. S. Brookes, *Basic Res. Cardiol.* **2009**, *104*, 121; b) S. Dröse, L. Bleier, U. Brandt, *Mol. Pharmacol.* **2011**, *79*, 814; c) C. L. Quinlan, A. L. Orr, I. V. Perevoshchikova, J. R. Treberg, B. A. Ackrell, M. D. Brand, *J. Biol. Chem.* **2012**, *287*, 27255.

[18] H. Miyadera et al., *Proc. Natl. Acad. Sci. USA* **2003**, *100*, 473.

[19] The effects of side-chain modification on binding interactions and physicochemical properties of the atpenins are not entirely clear at this point. Further studies are required to definitively establish the role of the side-chain in the atpenin scaffold. For a study on co-crystallization of succinate-ubiquinone reductase with atpenin A5 and structural analysis of the binding site, see: R. Horsefield, V. Yankovskaya, G. Sexton, W. Whittingham, K. Shiomi, S. Ōmura, B. Byrne, G. Cecchini, S. Iwata, *J. Biol. Chem.* **2006**, *281*, 7309.

[20] For previous syntheses of atpenins and related structures, see: a) F. Trécourt, M. Mallet, O. Mongin, G. Quéguiner, *J. Org. Chem.* **1994**, *59*, 6173; b) F. Trécourt, M. Mallet, O. Mongin, G. Quéguiner, *J. Heterocycl. Chem.* **1995**, *32*, 1117; c) M. Ohtawa, S. Ogihara, K. Sugiyama, K. Shiomi, Y. Harigaya, T. Nagamitsu, S. Ōmura, *J. Antibiot.* **2009**, *62*, 289; d) M. Ohtawa, K. Sugiyama, T. Hiura, S. Izawa, K. Shiomi, S. Ōmura, T. Nagamitsu, *Chem. Pharm. Bull.* **2012**, *60*, 898.

[21] a) J. Elovson, P. R. Vagelos, *Proc. Natl. Acad. Sci. USA* **1969**, *62*, 957; b) P. Ciminiello, E. Fattorusso, M. Forino, M. Di Rosa, A. Ianaro, R. Poletti, *J. Org. Chem.* **2001**, *66*, 578; for the first synthesis of a chlorosulfolipid, see: c) C. Nilewski, R. W. Geisser, E. M. Carreira, *Nature* **2009**, *457*, 573; for selected recent syntheses, see: d) C. Nilewski, N. R. Deprez, T. C. Fessard, D. B. Li, R. W. Geisser, E. M. Carreira, *Angew. Chem. Int. Ed.* **2011**, *50*, 7940; *Angew. Chem.* **2011**, *123*, 8087; e) D. K. Bedke, G. M. Shibuya, A. R. Pereira, W. H. Gerwick, C. D. Vanderwal, *J. Am. Chem. Soc.* **2010**, *132*, 2542; f) T. Yoshimitsu, R. Nakatani, A. Kobayashi, T. Tanaka, *Org. Lett.* **2011**, *13*, 908; g) T. Umezawa, M. Shibata, K. Kaneko, T. Okino, F. Matsuda, *Org. Lett.* **2011**, *13*, 904; h) A. Shemet, D. Sarlah, E. M. Carreira, *Org. Lett.* **2015**, *17*, 1878; for reviews on the chlorosulfolipids, see: i) W.-J. Chung, C. D. Vanderwal, *Acc. Chem. Res.* **2014**, *47*, 718; j) C. Nilewski, E. M. Carreira, *Eur. J. Org. Chem.* **2012**, 1685; k) D. K. Bedke, C. D. Vanderwal, *Nat. Prod. Rep.* **2011**, *28*, 15; l) T. Umezawa, F. Matsuda, *Tetrahedron Lett.* **2014**, *55*, 3003.

[22] For selected reports on diastereoselective/-specific chlorination, see: a) T. Yoshimitsu, N. Fukumoto, T. Tanaka, *J. Org. Chem.* **2009**, *74*, 696; b) G. M. Shibuya, J. S. Kanaday, C. D. Vanderwal, *J. Am. Chem. Soc.* **2008**, *130*, 12514; c) T. Schlama, K. Gabriel, V. Gouverneur, C. Mioskowski, *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2342; *Angew. Chem.* **1997**, *109*, 2440; d) A. J. Cresswell, S. T.-C. Eey, S. E. Denmark, *Nat. Chem.* **2015**, *7*, 146.

[23] For selected reports on enantioselective chlorination, see: a) A. Sakakura, A. Ukai, K. Ishihara, *Nature* **2007**, *445*, 900; b) S. A. Snyder, Z. Y. Tang, R. Gupta, *J. Am. Chem. Soc.* **2009**, *131*, 5744; c) W. Adam, C. Mock-Knoblauch, C. R. Saha-Moller, M. Herderich, *J. Am. Chem. Soc.* **2000**, *122*, 9685; d) K. C. Nicolaou, N. L. Simmons, Y. Ying, P. M. Heretsch, J. S. Chen, *J. Am. Chem. Soc.* **2011**, *133*, 8134; e) D. X. Hu, F. J. Seidl, C. Bucher, N. Z. Burns, *J. Am. Chem. Soc.* **2015**, *137*, 3795; f) S. A. Snyder, D. S. Treitler, A. P. Brucks, *J. Am. Chem. Soc.* **2010**, *132*, 14303; for a review on catalytic enantioselective α-chlorination of carbonyls, see: g) K. Shibatomi, A. Narayama, *Asian J. Org. Chem.* **2013**, *2*, 812.

[24] a) A. G. Myers, B. H. Yang, H. Chen, J. L. Gleason, *J. Am. Chem. Soc.* **1994**, *116*, 9361; b) A. G. Myers, B. H. Yang, H. Chen, L. McKinstry, D. J. Kopecky, J. L. Gleason, *J. Am. Chem. Soc.* **1997**, *119*, 6496.

[25] A. G. Myers, B. H. Yang, D. J. Kopecky, *Tetrahedron Lett.* **1996**, *37*, 3623.

[26] a) T. Katsuki, K. B. Sharpless, *J. Am. Chem. Soc.* **1980**, *102*, 5974; b) Y. Gao, R. M. Hanson, J. M. Klunder, S. Y. Ko, H. Masamune, K. B. Sharpless, *J. Am. Chem. Soc.* **1987**, *109*, 5765.
[27] See the Supporting Information for details. a) N. Matsumori, D. Kaneno, M. Murata, H. Nakamura, K. Tachibana, *J. Org. Chem.* **1999**, *64*, 866; b) C. Nilewski, R. W. Geisser, M.-O. Ebert, E. M. Carreira, *J. Am. Chem. Soc.* **2009**, *131*, 15866.
[28] For an example of the use of this auxiliary in a similar process, see: J. Zhang et al., *Tetrahedron Lett.* **2009**, *50*, 1167.
[29] LiO_2H was used to cleave the auxiliary: a) D. A. Evans, T. C. Britton, J. A. Ellman, *Tetrahedron Lett.* **1987**, *28*, 6141; For a synthesis of the enantiomeric carboxylic acid, see: b) W. Oppolzer, A. J. Kingma, G. Poli, *Tetrahedron* **1989**, *45*, 479.

Received: December 16, 2015
Published online: February 17, 2016

