Bioisosteric Exchange of C_{sp^3}-Chloro and Methyl Substituents: Synthesis and Biological Evaluation of Atpenin A5 Analogs

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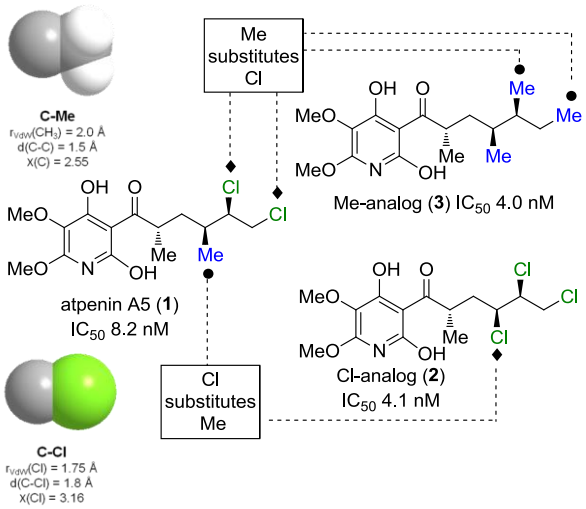
Abstract: Asymmetric synthesis and biological evaluation of two analogs of a naturally occurring chlorinated antimycotic, atpenin A5, are described. These analogs were selected on the basis of Cl → CH_3 or H_3C → Cl exchanges in the side chain of atpenin A5. The interchange of chloro and methyl substituents led to compex 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 unexplored in biologically active small molecules.[6] Seeking to fill this gap, herein we report the synthesis and biological evaluation of two analogs of a naturally occurring inhibitor of complex II in the mitochondrial respiratory chain, atpenin A5 (**1**) (Scheme 1). The analogs were targeted for study on the basis of Cl → CH_3 (atpenin A5 → analog **2**) or H_3C → Cl (atpenin A5 → analog **3**) bioisosteric exchanges. The collection of compounds **1**–**3** that display variation in Me/Cl substitution patterns were found to be equally potent complex II inhibitors.

Since chloro and methyls are univalent and have van der Waals radii that differ by 13-15% (1.74 Å for Cl,[7] 2.0 Å for Me[8]), Cl↔Me-interchange would not be expected to lead to dramatic conformational or structural changes. 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 methyls, chlorides can engage in halogen bonding[9] and C–Cl···C=O(NR_2) interactions.[10] These aspects 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 analogs **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, alcohols in the naturally occurring, parent structures are replaced with chlorides in the commercial products. In contrast, Me/Cl replacement has generally been reported only for arenes and typically involves exchanging an aromatic methyl group with a chloro substituent, which results in increased stability due to blocking of oxidative metabolism.[5g-5i] Consequently, in light of the classic examples above, we became interested in exploring this Cl↔Me bioisosteric replacement in an aliphatic setting. Our investigative plan necessitated the identification of a biologically active molecule as a model incorporating both C_{sp^3}–Cl and C_{sp^3}–Me substituents for a comparative study.

The atpenins are a family of naturally occurring antimycotics[14] that have attracted attention as potential agricultural pest control agents.[15] They inhibit complex II in the mitochondrial respiratory chain and, thus, the production of ATP.[16] The core structure of the atpenins is characterized by a pyridine with an appended acyl side chain, whose structure and substitution pattern have been shown to significantly influence inhibitory activity (Figure 1).[14,15,17] For example, the absence of a chloride in atpenin A4 (**4**) leads to 13-fold reduced activity when compared to atpenin A5 (**1**) in an assay measuring NADH-fumarate reductase activity. Accordingly, atpenin A5 (**1**), with its side chain incorporating an array of chloro and methyl substituents, was identified as a suitable platform to examine the effect of bioisosteric Cl↔Me replacement through the synthesis of analogs **2** and **3**.

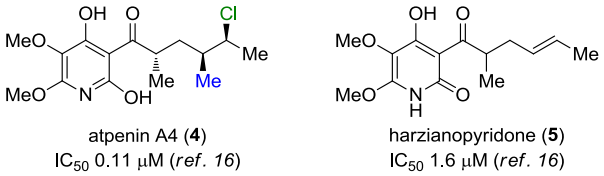


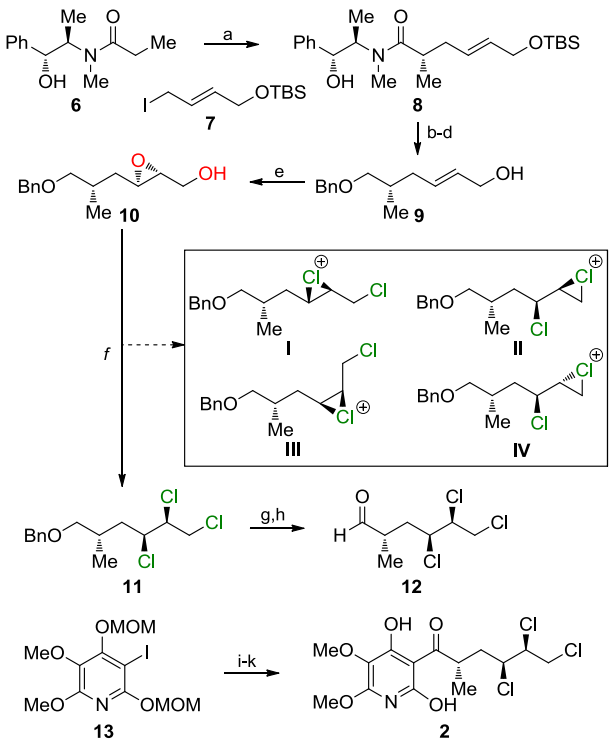
Figure 1. Structures and biological activities of atpenin A4 (**4**) and harzianopyridone (**5**). IC_{50} values refer to activities against complex I+II in A. *suum* adult muscle, measured by NADH-fumarate reductase activity.[16]

In line with previous studies,[18] the synthetic strategies towards **2** and **3** relied on adding a pyridine-derived organometallic nucleophile to advanced aldehyde intermediates. The central problem in the synthesis of Cl-analog **2** was the stereocontrolled construction of the trichlorinated motif in the side chain. Stereoselective synthesis of acyclic (poly)chlorinated molecules often presents challenges,[19] and a number of diastereo-[20] and enantioselective[21] methods have been developed only 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.[20a]

The synthesis of the chloro analog of atpenin A5 (**2**) (Scheme 2) commenced with allylic iodide **7**, which was obtained from 2-butyne-1,4-diol. Myers alkylation[22] of pseudoephedrine amide **6** with **7** afforded **8** in 94% yield, and reductive cleavage of the auxiliary using lithium amidotrihydroborate[23] furnished the corresponding primary alcohol. Subsequent protecting group manipulations and Sharpless epoxidation[24] of allylic alcohol **9** furnished epoxy alcohol **10**.

The Yoshimitsu protocol cited above has only been reported for the conversion of TBDPS-protected epoxyalcohols to *vic*-dichlorides.[20a] When it was applied to TBDPS-protected **10** the corresponding dichloride was isolated in 86% yield contaminated with ~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 SI for details).

We were keen on examining whether epoxyalcohol **10** would afford the targeted trichloride product directly. In the experiment, treatment of **10** with Ph_3P and *N*-chlorosuccinimide in toluene at 90 °C furnished **11** in 77% yield, contaminated with 10% impurities, presumably vinyl chlorides. This represents the first example of direct transformation of an epoxy alcohol to the corresponding trichloride, considerably streamlining the preparation of **11**. The 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**[18] was coupled with aldehyde **12,** and the resulting mixture of diastereomeric alcohols was oxidized to furnish the corresponding ketone. Cleavage of the MOM-protecting groups then afforded the Cl-analog of atpenin A5 (**2**). *J*-based configuration analysis of **2** confirmed the *syn*-arrangement of the two vicinal chlorides.[25] It is interesting that the 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.[19c,h]

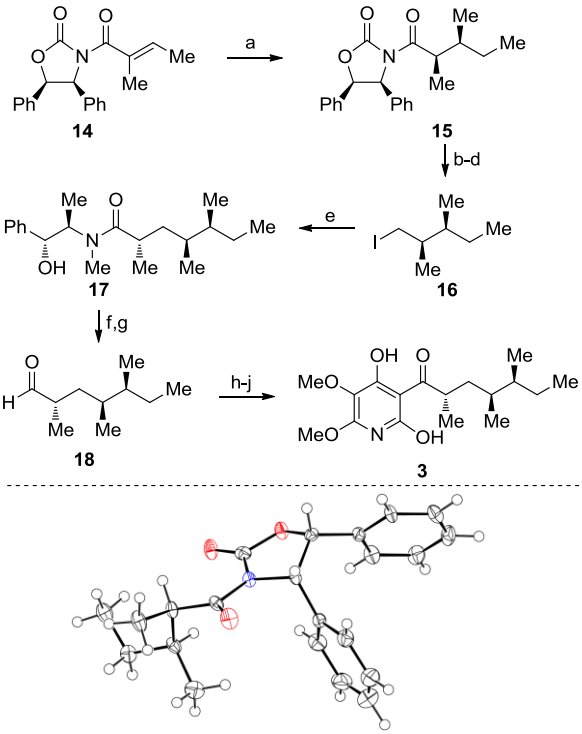


Scheme 2. Synthesis of chloro-analog **2**. Reagents and conditions: a) 1) LDA (3.5 equiv.), LiCl (12.5 equiv), **6** (2.0 equiv), THF, –78 °C, 1 h; 2) **7** (1.0 equiv), 0 °C to RT, 15 h, 94%; b) LiH_2NBH_3 (5.0 equiv), THF, RT, 3 h, 86%; c) 1) NaH (1.5 equiv), THF, 0 °C, 1 h; 2) *n*-Bu_4NI (0.1 equiv), BnBr (1.5 equiv), RT, 40 h, 76%; d) HCl (1M), THF/H_2O 1/1, 0 °C, 2 h, 79%; e) (–)-DET (7.5 mol%), Ti(O*i*-Pr)$_4$ (5 mol%), *t*-BuOOH (2.0 equiv), 4Å 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.

The stereocontrolled construction of the vicinal dimethyl arrangement posed the main challenge in the synthesis of analog **3** (Scheme 3). Conjugate addition of ethyl cuprate to α,β-unsaturated acyl oxazolidinone **14** produced **15** in 58% yield as a 4:1 mixture of inseparable diastereomers.[26] Cleavage of the chiral auxiliary,[27] reduction, and Appel reaction furnished

iodide **16**. Pseudoephedrine amide **6** was then alkylated with iodide **16**, setting the remaining stereogenic center and affording **17**. The 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 analogs 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. In addition, the two analogs inhibited succinate-cytochrome c reductase activity with essentially identical IC_{50} values of 10 and 15 nM.



X-ray crystal structure of **15** (ellipsoids at 50% probability)

Scheme 3. Synthesis of methyl-analog **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, ~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%.

In summary, we have accomplished the synthesis of the two atpenin analogs **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 the consequences of these findings to have broader applications in the discovery and optimization of bioactive lead structures, especially when coupled to recent advances in asymmetric chlorination.[20,21]

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

Species	Enzymes	IC_{50}[a] Atpenin A5 (**1**)	IC_{50}[a] Cl-analog (**2**)	IC_{50}[a] Me-analog (**3**)
A. *suum* adult muscle	Complex I+II[b]	0.0082	0.0041	0.0040
Bovine heart	Complex II+III[c]	0.019	0.010	0.015
	Complex I+III+IV[d]	> 1	> 1	> 1

[a] (μM). [b] Measured by NADH-fumarate reductase activity (n=3).

[c] Measured by succinate-cytochrome c reductase activity (n=4).

[d] Measured by NADH oxidase activity (n=4).

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Keywords: bioisosterism • chlorinated natural products • antimycotics • atpenins • inhibition of respiratory chain

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