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Tryptophan-replacement and indole-modified apicidins: synthesis of potent and selective antiprotozoal agents

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Abstract

A ruthenium tetraoxide catalyzed degradation of apicidin's tryptophan indole provided access to two useful carboxylic acid homolog intermediates. The synthesis of a series of potent and/or selective ketone homologs and 2-arylindoles derived from apicidin is described. © 2000 Elsevier Science Ltd. All rights reserved.

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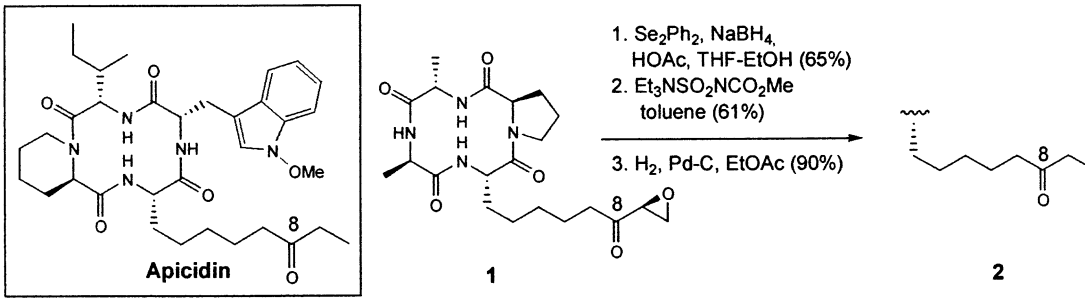
Histone deacetylase (HDAC), a nuclear enzyme that regulates gene transcription and the assembly of newly synthesized chromatin, has received much attention in recent literature.[1] The explosion of activity in this field has yielded the cloning of a mammalian gene which encodes a HDAC catalytic subunit,[2] the discovery in yeast of HDAC isoforms[3] and the identification of complementary histone acetyl transferases.[4] Several cyclic tetrapeptide inhibitors of HDAC have been reported[5] to affect the hyperacetylation of mammalian and plant histones.[6] Apicidin, a natural product HDAC inhibitor recently isolated at Merck Research Laboratories,[7] induces both mammalian and parasite histone hyperacetylation.[8] Consequently, apicidin may have therapeutic applications as a broad spectrum antiprotozoal agent to multi-drug resistant malaria, AIDS-related cryptosporidiosis/toxoplasmosis and coccidiosis. However, apicidin's lack of parasite selectivity must be resolved,[9] and the chemical modification of apicidin to introduce selectivity while retaining potency is therefore described in this letter.



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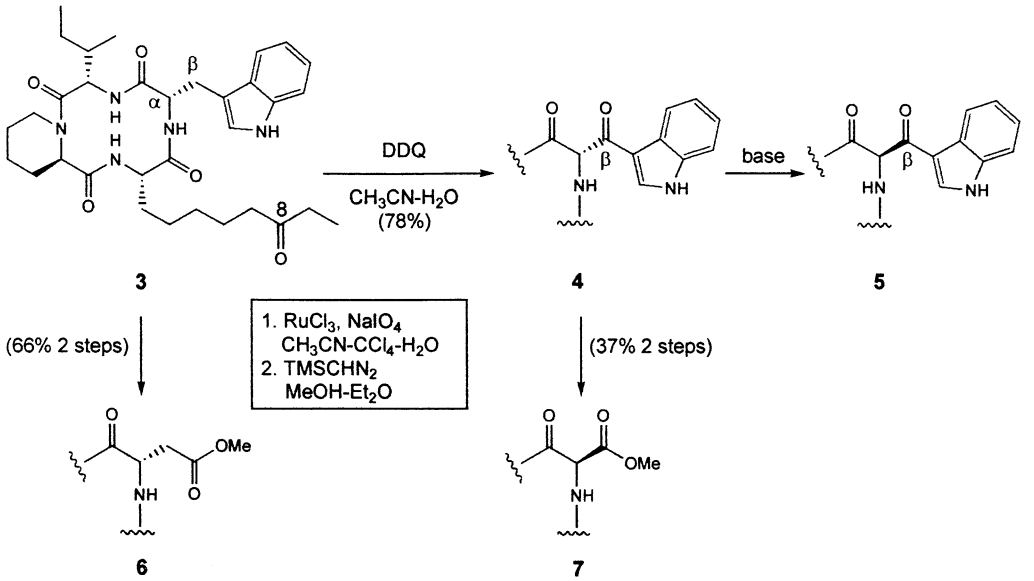
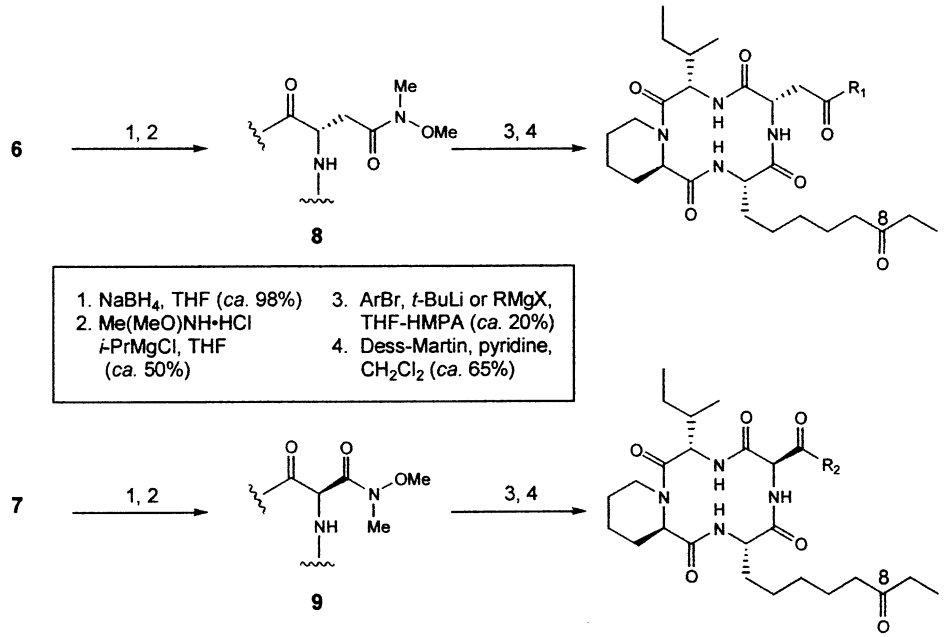
Unique to apicidin is its ethyl ketone side chain, a structural feature not present in related cyclic tetrapeptide HDAC inhibitors such as the equipotent α-ketoepoxide-bearing HC Toxin (**1**).[5a,8] Interestingly, the reduction of **1** to ethyl ketone **2** yielded a biologically inactive compound, implicating the indole's contribution to apicidin binding, HDAC activity and in vitro potency. Reported here is the synthesis of apicidin derivatives in which the tryptophan moiety has been either replaced or modified, yielding both potent and parasite-selective analogs.

Oxidation of the β-tryptophan position[10] in *N*-desmethoxy apicidin **3** (prepared from apicidin via hydrogenolysis: 1 atm H_2, Pearlman's catalyst, CH_2Cl_2–MeOH, 90%) provided β-oxo **4** (Scheme 1), which was quantitatively epimerized to the thermodynamic isomer **5** (Et_3N, CH_2Cl_2 or *t*-BuOK, *t*-BuOH–THF). Both β-oxo derivatives **4** and **5** were more potent in vitro than apicidin, prompting the synthesis of additional ketone analogs as tryptophan surrogates.



Scheme 1.

The oxidative degradation of the indole in **4** using reported ruthenium tetraoxide conditions[11] provided the crude *epi* acid, which was purified as its methyl ester **7** (Scheme 1). Similar oxidative protocols transformed **3** into its *nat* methyl aspartate derivative **6** in good yield.[12] The side chain C8 ketones of **6** and **7** were then protected by reduction to their respective C8 alcohols, and the methyl esters were transformed directly to the corresponding *N*-methoxy-*N*-methyl amides **8** and **9** (Scheme 2).[13,14] Alternative approaches to **8** and **9** via the activation of the homologous carboxylic acids failed (BOP, DCC, $(COCl)_2$ and MsCl). Weinreb amides **8** and **9** were treated at low temperature (−78°C→23°C, excess carbanion) with either Grignard reagents or aryllithiums (generated by lithium halide exchange of the precursor arylbromides) to provide the product ketones in modest yield. Representative derivatives prepared in these two series are shown in Fig. 1. Using 20% HMPA as a cosolvent with THF in these reactions was critical to their success. Subsequent oxidation of the sidechain C8 alcohols using Dess–Martin reagent (23°C, 2 h) yielded the requisite C8 ketones.[15]



Scheme 2.

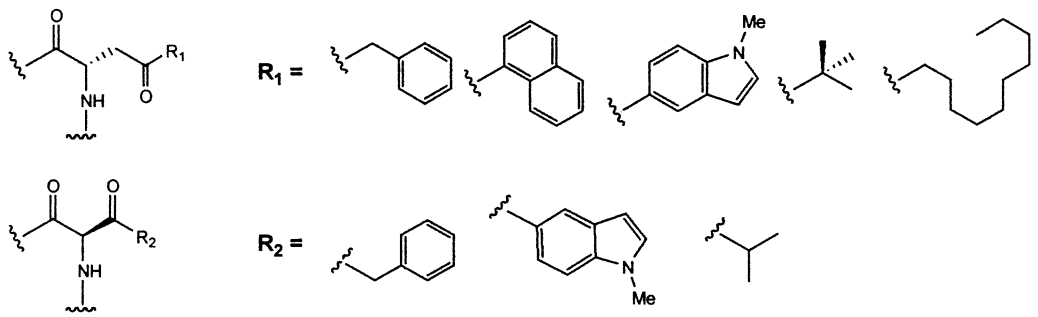


Figure 1. Ketone analogs of apicidin

The modification of apicidin's tryptophan moiety was also extended to the synthesis of a series of 2-arylindole derivatives using Suzuki methodology. Precursor 2-bromoindole **10** was prepared from **3** via bromination using either pyridinium bromide perbromide ($CHCl_3$, 0°C, 45 min, 45%) or NBS (CCl_4, 80°C, 15 min, 53%). Subsequent coupling of **10** with various aryl boronic acids[16] provided good yields of the desired 2-arylindoles as shown in Fig. 2. These Pd(0)-catalyzed coupling reactions were most successful in dioxane–ethanol (100°C, 2 h).

Effective synthetic strategies permitting the access to both tryptophan-replacement and indole-modified apicidins via common intermediates **8**, **9** and **10** are described. The structurally diverse analogs that were prepared displayed significant parasite selectivity (5–20 fold) and increased potency (2–5 fold) relative to apicidin.[17]

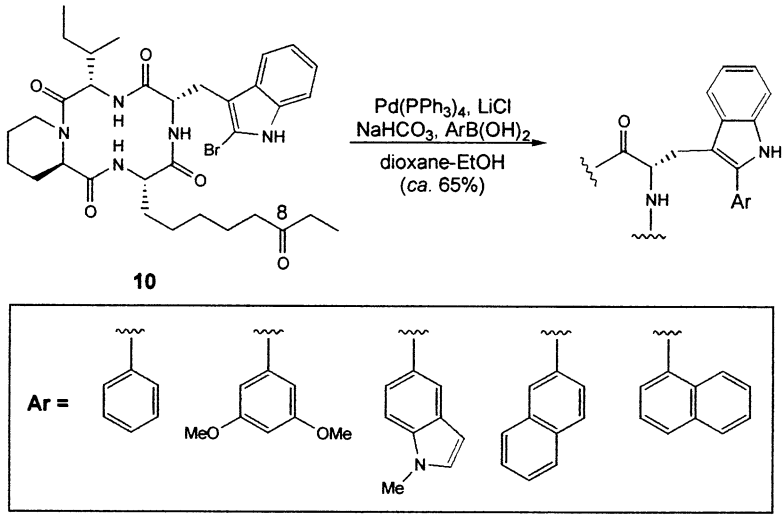


Figure 2. 2-Arylindole analogs of apicidin

Acknowledgements

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14. Synthesis of **8**: Desmethoxy apicidin (**3**) (1 g, 1.68 mmol) was dissolved in CH_3CN (18 mL) and CCl_4 (18 mL) and then treated with $RuCl_3\cdot xH_2O$ (7 mg, 0.03 mmol). A solution of $NaIO_4$ (6.5 g, 30.2 mmol) in water (18 mL) was sonicated to turbidity and then added to the reaction mixture at 23°C. The heterogeneous mixture was stirred vigorously at 23°C for 20 h over which time several color changes occurred (purple/red/brown/green), TLC control: (SiO_2, 10% HOAc–EtOAc, product acid $R_f = 0.20$). The mixture was partitioned between (1:1) NH_4Cl:brine and 30% isopropanol–$CHCl_3$, and the organics dried over Na_2SO_4 and conc. in vacuo. The acid (positive to bromocresol green TLC stain) was dissolved in (2:1) MeOH:Et_2O (40 mL) and treated with $TMSCHN_2$ (8 mL, 2 M hexanes) at 23°C to form a homogeneous yellow reaction mixture which was maintained 30 min, TLC control: (SiO_2, 5% HOAc–EtOAc, product ester $R_f = 0.62$). The mixture was quenched with the dropwise addition of glacial HOAc (TLC titrated to a positive bromocresol green stain), partitioned between (1:1) NH_4Cl:brine and CH_2Cl_2, dried over Na_2SO_4 and conc. in vacuo. The product was purified through a SiO_2 plug (1:3:96, NH_4OH:MeOH:$CHCl_3$) to provide 600 mg (66% two steps) of methyl ester **6** as a white powder. After standard reduction (1 equiv. $NaBH_4$, 0.03 M THF, 0°C, 3 h) of the C8 side chain ketone in **6**, the methyl (C8-hydroxy)aspartate intermediate (117 mg, 0.217 mmol) was combined with *N*,*O*-dimethylhydroxylamine–HCl (162 mg, 1.66 mmol), diluted into THF (7 mL) and cooled to −10°C. The reaction mixture was then treated dropwise with isopropylmagnesium chloride (1.7 mL, 2 M THF) and the reaction mixture was aged for 12 h at 0°C, TLC control: [SiO_2, 1:9:90, NH_4OH:MeOH:$CHCl_3$, $R_f = 0.45$ (**8**); $R_f = 0.55$ (ester)]. The mixture was partitioned between NH_4Cl and CH_2Cl_2, dried over Na_2SO_4, conc. in vacuo and purified by flash column chromatography (SiO_2, 1:3:96, NH_4OH:MeOH:$CHCl_3$) to provide **8** (73 mg, 60%). All compounds were characterized by MS and ^1H NMR. This supporting data, including HPLC, is available (81 pages).
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