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Concise Syntheses of the Abyssinones and Discovery of New Inhibitors of Prostate Cancer and MMP-2 Expression

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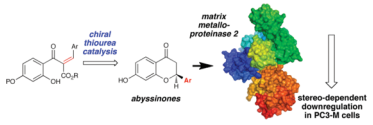
ABSTRACT The first asymmetric syntheses of four members of the abyssinone class of natural products (I, II, III, and IV 4′-OMe) via quinine- or quinidine-derived thiourea-catalyzed intramolecular conjugate additions of β-keto ester alkylidenes are reported. This concise strategy delivers all four natural products and their corresponding antipodes. A preliminary evaluation of all of these small molecules against a metastatic human prostate cancer cell line has identified that these compounds selectively and differentially inhibit cell growth and downregulate the expression of matrix metalloproteinase-2 (MMP-2) at nontoxic concentrations.

KEYWORDS Abyssinones, prostate cancer, MMP-2 expression, hydrogen-bonding catalysis



The abyssinones are a family of chiral, enantiomerically enriched flavanones that exhibit a diverse range of promising biological activities (see Figure 1).[1−3] Although extracts containing these small molecules have been used as traditional remedies, any investigation of their specific anticancer properties necessitates a general synthetic approach that can access them in enantiomerically enriched form. Our program geared toward the synthesis of pyran-containing natural products prompted our interest in these compounds.[4,5] Despite their therapeutic promise, the abyssinones have not been (a) synthesized with control over the absolute stereochemistry and (b) evaluated for their ability to inhibit cancer progression.[6−8] The unadorned structure of flavanones belies the challenge in executing a strategy that installs and maintains the configuration at the C2 position.[9] This stereocenter in the abyssinones is quite sensitive—mildly basic conditions promote reversible ring-opening to achiral 2′-hydroxychalcones.[10] In addition, flavanones containing electron-donating substituents in the C4′ position are particularly susceptible to racemization.[9,11] A limited number of approaches for the stereoselective synthesis of flavanones have been developed, but these approaches are not general and would not provide the abyssinone core in a concise manner.[12−16]

Our synthetic plan is outlined in Figure 1. The key step in the strategy is the application of our asymmetric thiourea-catalyzed cyclization, which can provide controlled access to either stereoisomer of these natural products.[9,11] A Knoevenagel condensation between an appropriately protected β-keto ester and different aldehydes corresponding to each abyssinone would provide the requisite alkylidenes for our thiourea-catalyzed cyclization. Our greatest concern was maintaining the integrity of the newly formed C2 stereocenter, which would depend heavily on the identification of mild decarboxylation/deprotection conditions. We anticipated that we could maximize efficiency if the decarboxylation and unmasking of the C7 phenol were performed in a single flask as the last step of the synthesis.

The first challenge encountered in the total synthesis of the abyssinones involved accessing the alkylidene substrates for the thiourea cyclization (see Figure 2 for a representative example with abyssinone I). Using the requisite aldehyde **5**, prepared from 4-hydroxybenzaldehyde,[17] we attempted the condensation with the protected β-keto ester **7** under standard Knoevenagel conditions (piperidinium acetate, Dean−Stark apparatus). These reactions produced the desired *E* alkylidene **8** in >95:5 *E*:*Z* for all aldehydes employed in the Knoevenagel condensation. (We were not able to generate and isolate in quantity the *Z* alkylidene species with which to conduct cyclization studies.) Unfortunately, the reaction conditions also led to the formation of significant amounts of racemic cyclization adducts (±**9**). After we surveyed various conditions, we discovered that bis-morpholine aminal **6**, used directly without purification, underwent smooth Knoevenagel condensation with β-ketoester **7** (2 equiv of glacial acetic acid at 22 °C in toluene) to deliver alkylidene **8** with minimal levels of racemic cyclized compounds. As predicted, the resulting alkylidene **8** underwent the desired intramolecular conjugate addition when exposed to 10 mol % quinine-derived C6′ thiourea catalyst **I**.[18] Multiple iterations of the cyclization of alkylidene

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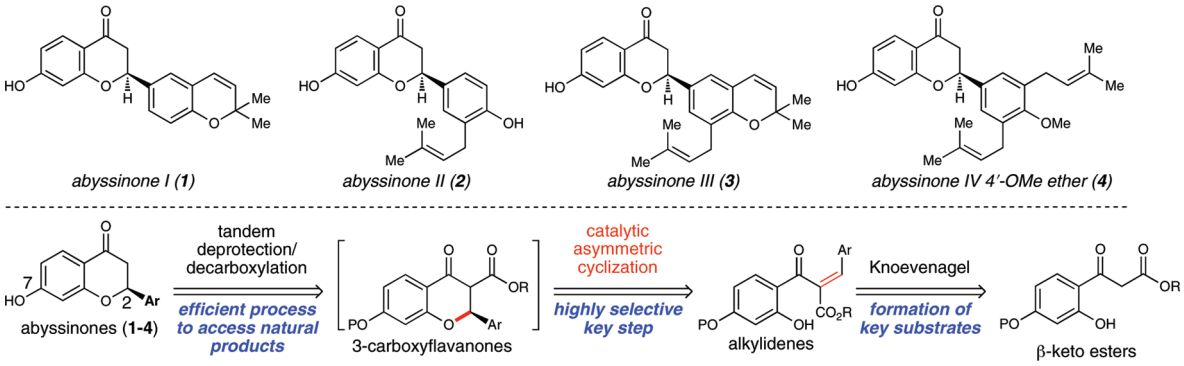

Figure 1. Retrosynthetic analysis of abyssinone natural products.

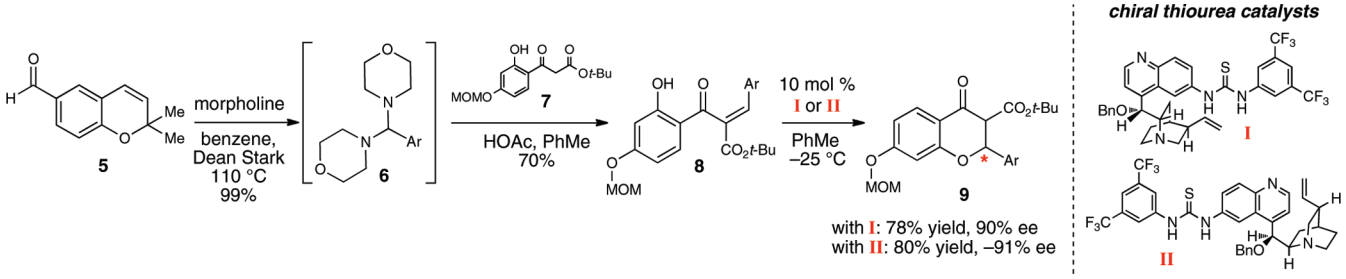

Figure 2. Initial route to abyssinone I (**1**).

8 consistently afforded carboxyflavanone **9** in good yield (78−80%) and with excellent enantioselectivity (90−91% ee). Importantly, the alkylidene precursors underwent smooth cyclization with excellent control over the newly formed C2 stereocenter using our chiral thiourea catalysis conditions.

Initially, the decarboxylation and deprotection of **9** were accomplished in a single flask utilizing $MgBr_2 \cdot OEt_2$, but the low yields for this reaction sequence (less than 25%) led us to investigate higher yielding reactions conditions. Unfortunately, various *O*-aryl-protected *t*-butyl carboxyflavanones could not be converted into **1**−**4** without significant epimerization or functionalization of the abyssinones containing prenyl side chains. We anticipated that exchanging the *t*-butyl ester for an allyl ester and replacing the methoxymethyl group with an allyl group might allow for mild, single-flask decarboxylation/deprotection employing palladium catalysis.[19] The requisite allyl-protected alkylidenes **10**−**13** were synthesized directly from the corresponding aldehydes using our mild bis-aminal approach. The key asymmetric cyclizations of **10**−**13** were catalyzed by exposure to 10 mol % of either the quinine- or quinidine-derived thiourea **I** or **II**[20] at −25 °C in toluene (Table 1). The use of morpholine in the presence of 5 mol % $Pd(PPh_3)_4$ promoted the deprotection and decarboxylation at 22 °C to afford the natural product abyssinones I, II, III, and IV 4′-OMe ether cleanly and in high yields.[21] The levels of enantioenrichment for each compound from the asymmetric conjugate addition (i.e., **10**−**13** to **14**−**17**) were excellent. The quinidine-derived thiourea catalyst **II** provided each of the abyssinones (after deprotection/decarboxylation) with the naturally occurring configuration at C2, while employing the pseudoenantiomeric thiourea **I** generated the unnatural (*R*)-abyssinones with comparable levels of stereoselectivity. These results are especially satisfying since (1) flavanones containing alkoxy or hydroxy substituents in the C4′ position are susceptible to epimerization due to stabilized benzylic cation formation and (2) flavanones can undergo reversible ring opening to form 2′-hydroxychalcones upon exposure to mild bases. The overall yields for this process (conjugate addition, allyl deprotection, and decarboxylation) provided an efficient method for the construction of these flavanones and allowed for the evaluation of our synthetic method in terms of more complex synthetic efforts.

We next sought to determine if the enantiomerically enriched abyssinones and their corresponding enantiomers would elicit important and stereodependent biological activity. Members of the broad flavonoid family (over 5000 natural products) have exhibited a wide variety of anticancer effects, acting as antioxidants, angiogenesis inhibitors, and potent cytotoxic agents.[22] In addition, several flavonoids have been shown to inhibit the activity and downregulate the expression of pro-metastatic enzymes, such as the matrix metalloproteinases (MMPs), in a variety of tumor cell lines.[23−26] However, these studies have focused primarily on achiral isoflavones, and none of these investigations to date have been conducted on the abyssinone family of flavanone natural products.

Our studies focused on prostate cancer (PCa), which is the second most common cause of cancer-related death in U.S. men. Mortality from PCa is caused primarily by the development of metastatic disease, in which PCa cells move from the prostate gland to distant sites in the body and continue their unchecked growth.[27] Proteases such as MMPs increase cell invasion, and thus, their synthesis by cancer cells facilitates movement and metastatic behavior.[28] MMP-2 has been shown

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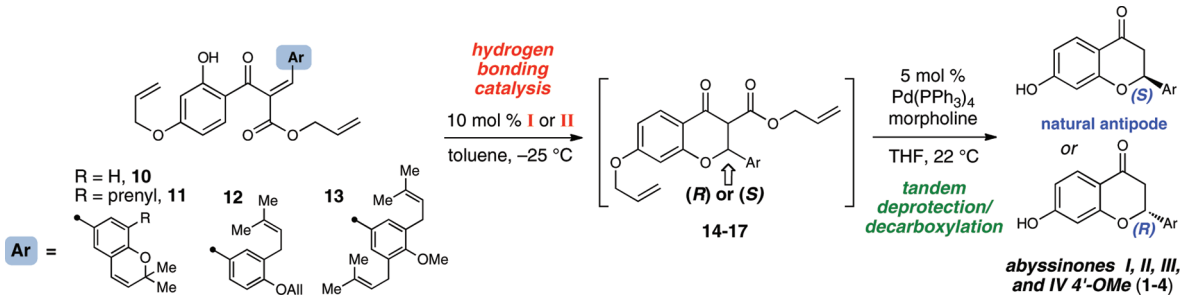
Table 1. Catalytic Asymmetric Synthesis of Abyssinones



entry	thiourea catalyst	alkylidene	ee (%)[a]	yield (%)[b]	product	
1	I	**10**	87	71	(*R*)-**1**	*ent*-abyssinone I
2	II	**10**	82	76	(*S*)-**1**	abyssinone I
3	I	**12**	88	61	(*R*)-**2**	*ent*-abyssinone II
4	II	**12**	89	72	(*S*)-**2**	abyssinone II
5	I	**11**	86	75	(*R*)-**3**	*ent*-abyssinone III
6	II	**11**	84	70	(*S*)-**3**	abyssinone III
7	I	**13**	95	65	(*R*)-**4**	*ent*-abyssinone IV 4'-OMe
8	II	**13**	94	65	(*S*)-**4**	abyssinone IV 4'-OMe

[a] Enantiomeric excess of abyssinones (**1**−**4**) after palladium(0) deprotection determined by HPLC analysis (Chiralcel OD-H or AD-H). [b] Isolated yield from **10**−**13**.

to be a particularly important target for human PCa, since its increased expression in tissue portends metastasis.[29] Decreased MMP-2 expression also leads to decreased invasion of human PCa cells in vitro and to decreased metastasis of human PCa cells in a murine model of metastasis.[25,30] Consequently, the MMPs, and MMP-2 in particular, represent an important and extensively studied therapeutic target. However, while some first-generation MMP inhibitors have been effective in preclinical models, there has been little success in subsequent clinical trials, predominantly due to severe systemic toxicity.[31,32]

An alternative promising strategy for counteracting the pro-invasive effect of MMP-2 is controlling the amount of this enzyme produced by tumor cells (i.e., upregulation and downregulation).[30] We have demonstrated that PCa cells treated with the isoflavone genistein exhibit decreased levels of both MMP-2 gene transcript and protein, which leads to an overall reduction in invasive potential.[25] Furthermore, studies performed on additional cancer cell lines have demonstrated that siRNA knockdown of MMP-2 leads to a reduction of both invasion and tumor-induced angiogenesis.[33] Developing a method to downregulate MMP expression levels also has the advantage of being potentially less toxic than traditional MMP inhibitors. Thus, we sought to evaluate the ability of the abyssinones generated in our laboratory to inhibit PCa cell growth and downregulate the expression of MMP-2, since these types of interventions could both attenuate/prevent metastasis and increase survival rates for PCa. We were also eager to evaluate the effect of stereochemistry on the ability of the abyssinones to inhibit cell proliferation and downregulate MMP-2 expression.

Our studies began by evaluating the impact of enantioenriched and racemic abyssinones (I, II, III, and IV 4′-OMe) on metastatic PCa (PC3-M) cell growth. Given that enantioenriched abyssinones have never been synthesized, we were particularly

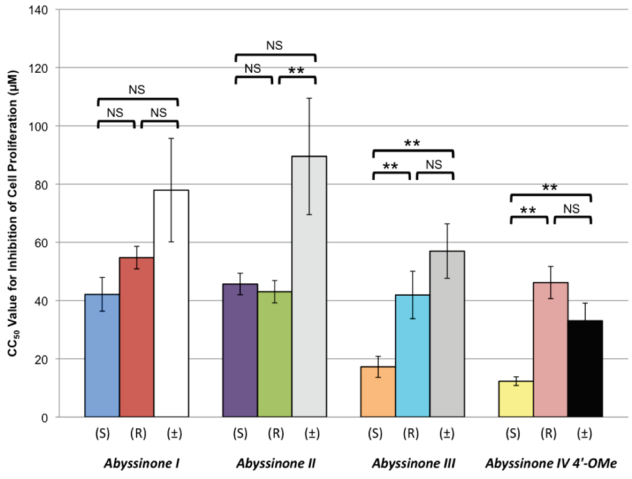


Figure 3. CC_{50} values for each enantiomer and the racemic mixtures of abyssinones **1**−**4** against proliferation of PC3-M cells. For experimental details, see the Supporting Information.

interested to determine if the enantiomers of each compound demonstrated differential cytotoxicity when compared to each other and also to the racemic mixture.[34] Furthermore, these cytotoxicity studies were instrumental for defining nontoxic levels of **1**−**4**, which guided the MMP-2 transcript expression evaluations (vide infra). Metastatic variant human PC3-M cells were treated for 3 days with 0−50 μM racemic, (*R*)- or (*S*)-**1**−**4** (12 compounds total) under conditions of exponential cell growth, and then, MTT assays were performed.[35] The CC_{50} values were determined for each compound and are shown in Figure 3. As indicated by Figure 3, (*S*)-abyssinones III (**3**) and IV 4′-OMe (**4**) both demonstrated statistically significant levels of inhibition of PC3-M cell proliferation when compared to the (*R*)-enantiomers and the racemic mixtures. In fact, both

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(*S*)-abyssinones III and IV 4′-OMe caused an approximate 2-fold decrease in the proliferation of PC3-M cells, as they possessed CC_{50} values of 17 and 12 μM, respectively, as compared to the CC_{50} values of the (*R*)-enantiomers and racemates at 42 [(*R*)-**3**], 57 [(±)-**3**], 46 [(*R*)-**4**], and 33 μM [(±)-**4**]. These results clearly indicate the key role of stereochemistry in the biological activity of these compounds and validate our enantioselective synthetic approach for these particular natural products. Further evidence for the importance of the enantioselective synthesis of the abyssinones is also provided by the growth inhibition data for the racemic compounds (Figure 3). Racemic abyssinone II was actually significantly less active than both of the enantioenriched compounds. This particularly interesting result indicates that there may be some functional antagonism between the enantiomers of abyssinone II that lead to a significant reduction of activity in the racemic mixture. Finally, we also performed some preliminary experiments to try to determine if the abyssinones were inhibiting cell growth via a cytotoxic (i.e., cell death) or cytostatic (i.e., cell cycle arrest) mechanism. Interestingly, when the absorbance values at 540 nm for the treated cells at 50 μM (t = 72 h) were compared with those for untreated cells at the start of the experiment (t = 0 h), (*S*)-abyssinones III and IV 4′-OMe both appeared to reduce the number of cells to a level at or below that of the start of the experiment. This result suggested that these compounds were acting through a cytotoxic mechanism, which was verified by cell imaging that indicated gross cell death at 72 h (see the Supporting Information). However, all of the other compounds, including (*R*)-abyssinones III and IV 4′-OMe, demonstrated absorbance values that were greater than that of the t = 0 measurement, indicating that they were most likely acting through a cytostatic or combination (cytostatic and cytotoxic) mechanism. Therefore, all of these combined findings highlight the importance of our hydrogen-bonding catalysis approach, since this information could not have been obtained without sufficient amounts of the enantioenriched compounds for analysis.

We next chose to evaluate the impact of (*R*)- and (*S*)-**1**−**4** (eight compounds total) on the levels of MMP-2 transcript, given that several members of the flavonoid family of natural products have been shown to downregulate the expression of this important pro-metastatic enzyme. Our aim was not only to determine the cytotoxicity of these compounds (i.e., their chemotherapeutic potential) but also to evaluate their ability to target MMP-2 synthesis and to act as chemopreventative agents capable of blocking progression to a more aggressive disease state. Cells were treated with each compound at 3 μM for 3 days, since this dose was not associated with cytotoxicity by the MTT assay. Importantly, we chose this nontoxic dose for our analysis to eliminate any confounding nonspecific effects due to cell toxicity. After abyssinone exposure, MMP-2 transcript levels were measured by isolating RNA and performing reverse transcription and quantitative real time polymerase chain reactions (qRT-PCR). MMP-2 transcript levels were measured instead of MMP-2 protein levels because MMP-2 expression is tightly regulated at the transcriptional level[36] and because flavonoids have been shown to inhibit MMP-2 transcript expression. Furthermore, decreased levels of MMP-2 mRNA expression have also been correlated with a lower pathological stage of PCa and, by extension, an improved clinical outcome.[29,37] The measurement of

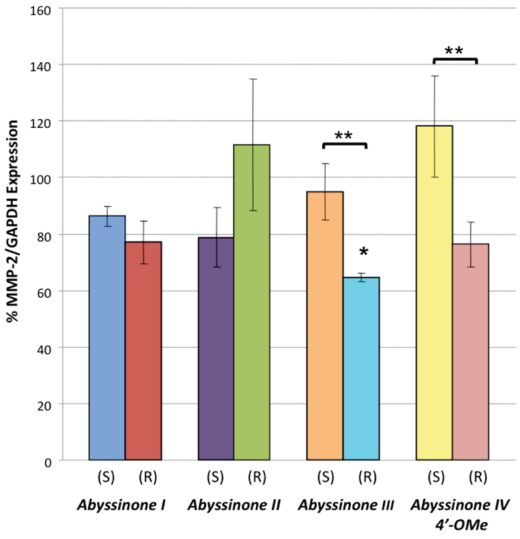

Figure 4. MMP-2 expression levels of abyssinone-treated PC3-M cells at 3 μM. For experimental details, see the Supporting Information.

transcript levels provides a direct measure of the ability of the abyssinones to target cell-based processes responsible for regulating this clinically relevant pro-metastatic enzyme. Once the MMP-2 transcript levels were measured by qRT-PCR, they were normalized to that of the internal control gene GAPDH (glyceraldehyde-3-phosphate dehydrogenase), which was measured in both the treated and the untreated cells.[38] GAPDH is expressed at constant levels across a wide array of biological systems and is widely used for control purposes. We found that the GAPDH expression levels were the same for both the treated and the untreated cells, which indicated that the effects on MMP-2 expression were not a result of nonspecific downregulation of transcription.

With both the MMP-2 studies and the cell growth studies, the abyssinone enantiomers exhibited statistically significant differential biological activity (Figure 4). In particular, for both abyssinones III and IV 4′-OMe, the (*R*)-enantiomers suppressed MMP-2 expression to 65−78% of untreated control cells, respectively, at a nontoxic concentration (3 μM). Interestingly, the activity against MMP-2 expression for the unnatural (*R*)-enantiomers was significantly greater than that for the corresponding natural (*S*)-enantiomers. While there are limited examples of natural products whose unnatural enantiomers demonstrate comparable biological potency (e.g., fredericamycin A[39]), we are not aware of compounds other than *ent*-roseophillin[40] and (*R*)-abyssinones III and IV 4′-OMe that are more active than their natural enantiomers. These examples clearly demonstrate that the construction of unnatural antipodes by stereoselective synthesis provides new avenues for potential therapeutic development. The in vitro assays described above interrogate distinctly different biological functions and highlight the importance of successfully installing the stereochemical elements during the syntheses of the abyssinones. The cytotoxicity and MMP-2 studies conducted using each enantiomer show different response profiles across the abyssinones (**1**−**4**), with promising abilities to differentially target cell growth and metastatic potential.

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In summary, the first asymmetric syntheses of abyssinones I−III and IV 4′-OMe have been accomplished using a chiral thiourea-catalyzed intramolecular conjugate addition. A tandem allyl deprotection/allyl ester decarboxylation generates the final products in a single flask while maintaining the stereochemical integrity at the C2 center. Our synthetic route delivers the natural products and the corresponding antipodes with excellent levels of enantioselectivity, thereby facilitating the evaluation of individual stereoisomers and fueling the discovery of their differential bioactivity. The key observations that the abyssinones specifically and differentially curtail cell growth and suppress MMP-2 expression in whole cells at nontoxic concentrations underscore the utility of our successful catalytic asymmetric synthesis of these natural products. These combined experiments fully integrate asymmetric catalysis, target synthesis application, and chemical biology discovery with medicinal relevance. Continued investigations of the abyssinones and related compounds to understand their biological activity against various cancer models are ongoing in our laboratories.

SUPPORTING INFORMATION AVAILABLE

General information, general procedures, comparative analysis, selected NMR spectra, HPLC traces, and general biological assay procedures and additional data. This material is available free of charge via the Internet at http://pubs.acs.org.

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