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Biomimetic Kinetic Resolution: Highly Enantio- and Diastereoselective Transfer Hydrogenation of Aglain Ketones To Access Flavagline Natural Products

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ABSTRACT: We have previously reported asymmetric syntheses and absolute configuration assignments of the aglains (+)-ponapensin and (+)-elliptifoline and proposed a biosynthetic kinetic resolution process to produce enantiomeric rocaglamides and aglains. Herein, we report a biomimetic approach for the synthesis of enantiomerically enriched aglains and rocaglamides via kinetic resolution of a bridged ketone utilizing enantioselective transfer hydrogenation. The methodology has been employed to synthesize and confirm the absolute stereochemistries of the pyrimidone rocaglamides (+)-aglaiastatin and (−)-aglaroxin C. Additionally, the enantiomers and racemate of each metabolite were assayed for inhibition of the heat-shock response, cytotoxicity, and translation inhibition.

INTRODUCTION

Plants of the genus Aglaia are known to produce a variety of unique secondary metabolites including the cyclopenta[b]-benzofurans methyl rocaglate (1),1 aglaiastatin (2),2 and aglaroxin C (3)2b,3 and the cyclopenta[b,c]benzopyran (aglain) ponapensin (4)4 (Figure 1). These metabolites and derived synthetic analogues thereof have been reported to have potent antitumor,2−5 anti-inflammatory,6 neuroprotective,7 cardioprotective,8 and serine hydrolase inhibitory activities.9 The natural product families are proposed10 to arise from a common aglain intermediate. From previous work in our laboratory assigning the absolute stereochemistry of (−)-ponapensin (4),11a it was determined that rocaglates/rocaglamides and the aglains (−)-ponapensin (4) and (−)-elliptifoline11 arise from intermediates with opposite absolute configuration.

In previous studies, we proposed11a that ketoreductase or reductoisomerase enzymes12 could differentiate between the enantiomers of ketone 5a, selecting for either direct reduction or rearrangement followed by reduction as part of a parallel kinetic resolution13 process (Figure 2). In the case of kinetic resolution of aglain ketone 5a, both enantiomers may be converted to bioactive natural products which led us to investigate the application of a reductive, chemical kinetic resolution approach to enantiopure ketone 5a.

Noyori and co-workers have previously used chiral ruthenium complexes in the kinetic resolution of racemic secondary alcohols.14 Metz and co-workers15 recently demonstrated the utility of this approach for the reductive, kinetic resolution of racemic flavanone substrates. Herein, we report the kinetic resolution of aglains such as 5a via reduction of a chiral, racemic bridged ketone and its application toward the total syntheses of the pyrimidones (+)-aglaiastatin (2) and (−)-aglaroxin C (3).

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RESULTS AND DISCUSSION

Biomimetic Kinetic Resolution. Our initial investigations utilized conditions recently reported by Metz and co-workers\textsuperscript{15} for asymmetric transfer hydrogenation of racemic flavanones via Rh (III) catalysis employing hydrate\textsuperscript{5b,11a} which to our delight afforded \((−)-\)6 in 95\% ee after 40\% conversion (Table 1, entry 1). The absolute stereochemistry was determined through comparison to \((+)-\)6, previously assigned through X-ray crystal structure analysis and synthesis of \((−)-\)methyl rocaglate from a common intermediate.\textsuperscript{11a} Even after a more than 5-fold increase in reaction time (entry 2), we could not push the reaction to 50\% conversion. After further optimization, CH\textsubscript{2}Cl\textsubscript{2} was found to be the solvent of choice, providing optimal conversion (entry 5). Low conversions observed (entries 1, 2, and 4) were likely due to the insolubility of hydrate \(5\text{b}\) in both ethyl acetate and THF. \textit{In situ} dehydration of \(5\text{b}\) with 4 Å molecular sieves (entry 3) led to no reaction, suggesting that the molecular sieves were interfering with the process. Furthermore, subjection of ketone \(5\text{a}\) to the reaction conditions did not produce significantly different results from use of hydrate \(5\text{b}\). Other metal hydride and ligand systems were tested (entries 6–8), each affording lower enantioselectivity or in one case no reactivity (entry 8).

What was perhaps more intriguing than the excellent enantioselectivity was the complete diastereoselectivity observed. Based on our previous reductions of ketone \(5\text{a}\) and hydrate \(5\text{b}\),\textsuperscript{11a} we hypothesized that non-coordinating reducing agents would preferably attack the \textit{in situ} generated ketone away from the phloroglucinol ring. Since the rhodium catalyst system is sterically encumbered, we believe that other modes of stabilization enhance attack from the phloroglucinol face. In the aforementioned example of kinetic resolution of flavanones through catalytic asymmetric transfer hydrogenation, Metz and co-workers\textsuperscript{15} proposed an assembly for kinetic resolution of flavanones featuring stabilizing CH–π interactions\textsuperscript{16} between the methyl groups on the Cp* ligand and the aromatic substituent of the ketone. Figure 3 depicts models generated using Spartan ‘\textsuperscript{10}’\textsuperscript{17} for both favored and disfavored diastereomeric assemblies.

To evaluate the scope of the kinetic resolution on different substrates, we synthesized a variety of aglain ketone analogs and subjected them to the optimized conditions (Table 2). Our aim was to manipulate the electronics of the aromatic system and

Table 1. Metal and Ligand Screen for Catalytic, Asymmetric Reduction

| entry | catalyst | solvent | time, h | conv (ee), % |
|-------|----------|---------|---------|-------------|
| 1     | A        | EtOAc   | 3       | 40 (95)     |
| 2     | A        | EtOAc   | 16      | 40 (96)     |
| 3     | A        | EtOAc\textsuperscript{a} | 6       | trace       |
| 4     | A        | THF     | 3.5     | 43 (95)     |
| 5     | A        | CH\textsubscript{2}Cl\textsubscript{2} | 5       | 50 (96)     |
| 6     | B        | CH\textsubscript{2}Cl\textsubscript{2} | 5       | 63 (69)     |
| 7     | C        | CH\textsubscript{2}Cl\textsubscript{2} | 5       | 60 (43)     |
| 8     | D        | CH\textsubscript{2}Cl\textsubscript{2} | 5       | nr          |

\textsuperscript{a}4 Å molecular sieves used.
observe its effect on the kinetic resolution. Desmethoxy substrate 7 produced both a lower conversion and decreased enantioselectivity (entry 2). When the aryl ring was not directly adjacent to the reactive ketone, the reaction did not occur as expected (entry 3). Results using the 4′-Br-substituted derivative 9 are identical to that of the trimethoxy system suggesting that the substitution of the aryl group coplanar to the ketone has little effect. Difluorinated substrate 10 led to an erosion of ee more so than the desmethoxy system. This is likely due to the less electron rich π system being unable to form a strong CH···π bond with the Cp* ligand thus slowing conversion. To evaluate the ee of the starting materials, the reisolated material was converted to methyl rogalte analogs 14 and 15. Enantioenriched (+)-7 was directly reduced to (+)-11 using NaBH(OAc)_2.11a

**Total Syntheses of (+)-Aglaiastatin and (−)-Aglaroxin C.** To demonstrate the utility of the kinetic resolution methodology, we targeted asymmetric syntheses of the pyrimidine rogalteamide natural products (+)-aglaiastatin (2) and (−)-aglaroxin C (3). The absolute configuration of (+)-aglaiastatin (2) has been proposed to be identical to other members of the rogalte family and circular dichroism spectra supports this notion.11b We intended to use our method to conclusively determine the absolute stereochemistry of 2 and to compare it to that of both (−)-ponapensin (4) and (−)-methyl rogalte (1). The synthesis of aglaiastatin (2, Scheme 1) involved base-mediated ketol rearrangement of aglain (+)-Sb to a keto-rogalte intermediate followed by ester amide exchange to afford butyramide dimethyl acetol similar to an intermediate employed by Watanabe and co-workers.22 Under acidic hydrolysis conditions, acetol 16 formed the hemiaminal derivative 17 (cf. Scheme 2) which was heated with ammonium acetate to form (+)-aglaiastatin (2) ([α]_D^27 = +86.1° synthetic (c 0.7, CHCl_3, [α]_D = +45.7° natural (c 0.19, CHCl_3)) in 55% yield (10:1 dr, 4 steps). (−)-Aglaroxin C (3) ([α]_D^27 = −49.2° synthetic (c 0.1, CHCl_3), [α]_D = −50.1° natural (c 0.41, CHCl_3)) was obtained in 66% yield via dehydrogenation of (−)-aglaiastatin (2) with DDQ. Interestingly, treatment of epi-aglaiastatin 18 (cf. Scheme 2) with DDQ also provided aglaroxin C (3).

With (+)-aglaiastatin (2) obtained in a 10:1 ratio to its C5α epimer 18 (epi-aglaiastatin), we conducted a number of experiments to explain the high diastereoselectivity of the putative N-acyliminium cyclization. When hemiaminal 17 was heated at 60 °C for 2 h in the presence of ammonium acetate, we observed a 10:1:1 ratio of (±)-aglaiastatin (2):oxazinone (+)-19: C5α epimer (±)-18 (Scheme 2) in 55% yield. Furthermore, we found that (±)-19 could be synthesized directly by heating (±)-17 overnight in the presence of magnesium sulfate (42%).19 The structure of 19 and its configuration at C5α was determined via X-ray crystal structure analysis (Figure 4).19 When hemiaminal (±)-17 was treated with formic acid and ammonium formate at room temperature,22 we observed a 1:2:1:2:1 ratio of (±)-2: (±)-19: (±)-18 in 69% yield (Scheme 2). The product ratio seems to be controlled by the nature of the N-acyliminium counterion, as thermolysis of (±)-17 in the presence of ammonium formate led to the same distribution of products (Scheme 2). Epimer (±)-18 could not be converted to (±)-aglaiastatin (2) when subjected to ammonium acetate/heat or ammonium formate/formic acid. Likewise, (±)-aglaiastatin (2) could not be converted to (±)-epi-aglaiastatin 18 through treatment with ammonium formate/formic acid or ammonium formate/heat. Interestingly, oxazinone (±)-19 was partially converted to (±)-aglaiastatin (2) and (±)-epi-aglaiastatin 18 in a 2:1 ratio

**Table 2. Substrate Scope for Reduction**

| entry | substrate | conv, % | ee of reduced product (yield), % | ee of starting material (yield), % |
|-------|-----------|---------|----------------------------------|----------------------------------|
| 1     | (±)-Sb   | 50      | >99 (42)                         | >99 (42)                         |
| 2     | (±)-7    | 20      | 78 (16)                          | 19 (22)                          |
| 3     | (±)-8    | n.r.    | N/A                              | N/A                              |
| 4     | (±)-9    | 47      | >99                              | 88                               |
| 5     | (±)-10   | 37      | 74 (13)                          | 41 (31)                          |

“For entries 1, 4, and 5, enantioenriched starting material was converted to the corresponding (−)-rogalte derivatives via ketol shift/reduction (vide supra) to measure ee. For entry 2, enantioenriched (+)-7 was converted to reduced product (+)-11.”
favoring (±)-2 when heated in the presence of ammonium acetate (60 °C, 12 h). Since the formation of aglaiastatin (2) and epi-aglaiastatin 18 is irreversible, the diastereoselectivity of these products may be controlled through the Curtin–Hammett principle wherein cyclization occurs faster when the N-acyliminium reaction center is above the convex face of the rocaglate scaffold. Figure 5 shows ground state conformers of N-acyliminium intermediates leading to aglaiastatin (2) and epi-aglaiastatin 18 calculated in the gas phase using the B3LYP/6-31G* level of theory. These N-acyliminiums feature acetate counterions that are hydrogen-bonded to both the hydroxyl and enamine on the convex face of the rocaglate scaffold. Intermediate 20a (leading to aglaiastatin) is 2.0 kcal/mol lower in energy than its corresponding rotamer 20b. This energetic difference appears to be due to steric repulsion between the 3‴-methylene of the pyrrolidine and the acetate counterion, and the N-acyliminium reaction center residing within the concave face of the cyclopenta[b]benzofuran scaffold. Through invoking the Hammond postulate, these intermediates provide a rationale for the observed 10:1 diastereoselectivity using acetate as counterion. When rotamers 20a and 20b were subjected to a similar computation with formate as the counterion, the corresponding formate structures were found to have an energy difference of 1.0 kcal/mol, presumably because of the smaller counterion size. Furthermore, acetate is more basic than formate for deprotonation of the enamine as the nitrogen attacks the N-acyliminium. This explains the greater production of aglaiastatin (2) vs oxazinone 19 when acetate is the counterion as compared with formate (cf. Scheme 2). We also considered that the N-acyliminium cyclization may also occur through 6σ-electrocyclization (Figure 6) in which formation of aglaiastatin (2) is torquoselective through the aforementioned steric effects. However, this mechanism would require

**Scheme 2. Experiments To Probe the Mechanism of N-Acyliminium Cyclizations**  

**Conditions:** (a) ammonium acetate (10 equiv), THF, 60 °C, 2 h; (b) formic acid (1 equiv), ammonium formate (15 equiv), THF, rt, 6 d (69% from (±)-5b; no conversion from (±)-2); (c) ammonium formate (10 equiv), THF, 60 °C, 12 h (58% from (±)-5b; no conversion from (±)-2); (d) ammonium acetate (10 equiv), THF, 60 °C, 12 h.

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Figure 4. X-ray structure of oxazinone 19.

Figure 5. Ground state conformers (B3LYP/6-31G*) of N-acyliminium rotamers 20a and 20b.

Figure 6. Alternative, torquoselective 6σ-electrocyclization.
The enantiomer of Rh(III) diphenylethylenediamine A in the kinetic resolution of substrate (+)-5b (Table 1 and Scheme 1), and tested (–)-aglaiastatin (2) and (+)-aglaroxin C (3) in the aforementioned assays. Figure 5 summarizes the data. The racemates of aglaiastatin (2), and tested both enantiomers of aglaiastatin (2) and aglaroxin C (3) for several of the most prominent bioactivities reported for this compound class and found that the natural enantiomers were most potent. Moreover, we observed a concordance in potency for all derivatives across the three bioassays, suggesting there may be a single, conserved molecular target responsible for their activity. Further work toward the synthesis and biological evaluation of aglaiastatin and rocalgate analogs is currently in progress and will be reported in due course.

### Table 3. Concentration-Dependent Biological Activities of Aglaiastatin and Related Compounds in Whole Cells

| entry | compound | heat-shock response IC$_{50}$, nM$^b$ | cytotoxicity IC$_{50}$, nM$^c$ | translation inhibition IC$_{50}$, nM$^d$ |
|-------|----------|--------------------------------------|-------------------------------|----------------------------------------|
| 1     | (+)-2    | 3.8                                  | 3.9                           | 15.6                                   |
| 2     | (±)-2    | 5.2                                  | 7.1                           | 26.0                                   |
| 3     | (–)-3    | 15.3                                 | 11.2                          | 77.7                                   |
| 4     | (±)-18   | 23.8                                 | 21.7                          | 117.6                                  |
| 5     | (±)-19   | 25.8                                 | 31.8                          | 241.1                                  |
| 6     | (±)-3    | 37.7                                 | 26.1                          | 210.7                                  |
| 7     | (–)-2    | 99.2                                 | 105.7                         | 761.8                                  |
| 8     | (±)-3    | >1000                                 | >1000                         | >1000                                   |
| 9     | (±)-RHT  | 14.8                                 | 18.5                          | 75.6                                   |

$^a$Four-parameter nonlinear fit of dose–response data in whole cell assays, all determinations in quadruplicate. $R^2 > 0.95$ for all curve fits. $^b$Concentration resulting in 50% reduction in heat-induced luciferase reporter activity. $^c$Concentration resulting in 50% reduction in relative viable cell number. $^d$Concentration resulting in half-maximal inhibition of constitutive luciferase activity.

The authors declare no competing financial interest.

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