Published in final edited form as:

Org Lett. 2011 December 16; 13(24): 6592–6595. doi:10.1021/ol203041b.

De Novo Asymmetric Synthesis of Fridamycin E

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Abstract

A *de novo* asymmetric synthesis of (*R*)- and (*S*)-fridamycin E has been achieved. The entirely linear route required only nine steps from commercially available starting materials (16% overall yield). Key transformations included a Claisen rearrangement, a Sharpless dihydroxylation and a cobalt-catalyzed epoxide carbonylation to give a β -lactone intermediate. Antibacterial activities were determined for both enantiomers using two strains of *E. coli*, with the natural (*R*)-enantiomer showing significant inhibition against a Gram-(+)-like *imp* strain (MIC = 8 μ M).

The anthraquinone containing vineomycin members of the angucycline family of antibiotics have been of particular interest to both the synthetic and biological communities due to their unique structures and potent antitumor and antibacterial activities.¹ With the notable exception of fridamycin E (**1**), all other members of this class of natural products are mono- or bis-glycosylated with rare deoxysugars (Figure 1). When mono-glycosylated the mono-, di- and tri-saccharide fragments are attached via a β -C-aryl glycoside linkage to the anthraquinone ring system. When bis-glycosylated the additional sugar fragment is attached via an α -O-glycoside to the tertiary alcohol of the β -hydroxy carboxylic acid side chain.

Previously, we have described the synthesis and anticancer activity of the PMB-trisaccharide (α -L-aulose- α -L-rhodinose- β -D-olivose) portion of vineomycin C.² As part of a larger effort aimed at the development of a generalizable late stage glycosylation strategy for the synthesis and biological testing of this class of C-glycoside natural products, we required access to both enantiomers of fridamycin E (**1**).³ This simplest member of the angucycline family of antibiotics was isolated from a mutant of *Streptomyces parvulus* (strain Tu 1989)⁴ and shown to possess antibacterial activity.³ Biosynthetically fridamycin E can be regarded as the aglycon core and biosynthetic precursor of the more complex O- and C-glycosides of angucycline antibiotics (**2-9**).^{1,2,3,5,6,7,8} Its existence also suggests the existence of a biosynthetic C-glycosylation and the potential for a synthetic variant.⁴

The total syntheses of fridamycin E, as well as its unnatural (*S*)-enantiomer, have been achieved by several groups.^{3b,c,9} While these approaches vary in terms of overall efficiency, the routes all suffered in how asymmetry was introduced into the molecule. These methods

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Supporting Information Available: Experimental procedures and spectral data for all new compounds (**1** and **14-21**), as well as biological assay protocols and data are provided. This material is available free of charge via the Internet at <http://pubs.acs.org>.

varied from the use of chiral starting materials ((*S*)-lactic acid)^{3b} and auxiliaries (menthol based titanium enolate)^{9a,b} to the use of enzymatic (lipase and hydrolase)^{3c,9c} catalyzed kinetic resolutions. The most recent and arguably most successful of these routes was the one developed by Faber, who utilized a resolution of a *rac*-2,2-disubstituted epoxide to install the asymmetry of (*R*)-fridamycin E (84% *ee*).^{9c} Despite the success of these previous approaches, we felt a catalytic asymmetric approach had the potential for making the synthesis more efficient as well as providing access to either enantiomer for future synthetic and biological studies (*vide infra*). Herein, we describe our development of a new enantio-divergent route to natural (*R*)-fridamycin E and unnatural (*S*)-fridamycin E that uses the Sharpless dihydroxylation to install asymmetry and our initial evaluation of these enantiomers and antimicrobial agents. This route and structural complexity (*e.g.*, the easily reduced anthraquinone substrates) also provided us an excellent opportunity to test the functional group compatibility of the cobalt-catalyzed epoxide to β -lactone carbonylation reaction.¹⁰

Our approach to fridamycin E (**1**) is depicted in Scheme 1. We envisioned that **1** could be accessed from β -lactone **10**. The β -lactone in turn could be prepared from epoxide **11** via a cobalt-catalyzed carbonylation of epoxide **11**. An asymmetric epoxidation of a disubstituted alkene **12** could be used to install the desired asymmetry. Finally, alkenes like **12** could be prepared by a two-step ortho-*C*-methallylation sequence of commercially available anthrarufin **13**.¹¹

Our synthesis of fridamycin E began with the monomethallylation of anthrarufin (methallylCl, KI/K₂CO₃) to give **14** in 42% yield (Scheme 2). *In situ* dithionate reduction of **14** to an anthraquinol intermediate was followed by thermally promoted Claisen rearrangement to give *C*-methallylated anthrarufin **15**. Finally the two phenol hydroxyl groups were protected as benzyl ethers (BnBr/K₂CO₃, 89%).¹¹

With the desired alkene **16** in hand, we then focused on its direct asymmetric epoxidation, which proved problematic. For instance, when alkene **16** was subjected to the typical Jacobsen epoxidation conditions (5 mol % of (*S,S*)-Mn-salen catalyst and buffered NaOCl_(aq) in CH₂Cl₂ at 0 °C)¹² only trace amounts of epoxide **17** were detected. Improved yields of epoxide **17** were found for the Shi epoxidation of **16** (30% yield at ~33% conversion), however the relatively low levels of asymmetric induction dampened our enthusiasm for this direct approach (~15% *ee*).¹³

We eventually resorted to the Sharpless dihydroxylation of **16** to install asymmetry (Table 1).¹⁴ This was done begrudgingly because of the recognition of the additional steps required and the precedent from Rutledge and Woodgate, which suggested the dihydroxylation would occur with less than ideal enantioexcesses (< 70% *ee*).¹⁵ For instance, when (DHQD)₂PHAL was used as the ligand for the dihydroxylation (entry 1), diol **18** (*S*) was produced in excellent yield but only moderate enantiopurity (70% *ee*). Using the pseudo-enantiomeric ligand system (entry 6, (DHQ)₂PHAL), the (*R*)-diol **18** was obtained (98%, 75% *ee*). To our surprise, the configuration of diols obtained using these PHAL-ligands were the opposite from what is predicted by the Sharpless mnemonic.¹⁴ This reversal in facial selectivity suggested to us that other linkers might give different and/or improved facial selectivities. Several ligand systems and conditions were screened (entries 2–5 and 7–10) and various selectivities were found. To our delight, we found that when alkene **16** was dihydroxylated with the Sharpless DPP-linker ligand systems, diols with more than satisfactory enantiopurity were afforded. For instance, asymmetric dihydroxylation of **16** with (DHQD)₂DPP formed (*S*)-diol (*ent*)-**18** in 98% yield with 90% *ee* (entry 5). Similarly, the (DHQ)₂DPP ligand gave the (*R*)-diol **18** in 98% yield with 88% *ee* (entry 10).¹⁶

With the desired stereochemistry installed, we then turned our attention to the conversion of diol **18** into the desired epoxide **17** for a subsequent cobalt-catalyzed epoxide to β -lactone carbonylation reaction (**17** to **20**, Scheme 3). While we had a high degree of confidence in the outcome of this transformation, we were concerned with the possibility of catalyst oxidation by the anthraquinone functional group or competing Lewis acid catalyzed isomerization of the epoxide substrate to an allylic alcohol.

Treatment of (*R*)-diol **18** with TsCl in the presence of Bu₂SnO and Et₃N in CH₂Cl₂ afforded tosylate **19** in 91% yield. Subsequent deprotonation of **19** with NaH smoothly converted it into epoxide **17** in 92%. To our delight, similar success was found when we turned to the proposed Co(–I)-catalyzed carbonylation.¹⁷ Thus, when epoxide **17** was treated with 10 mol % of [CITPPAl]⁺[Co(CO)₄][–] (CITPP = *meso*-tetra(4-chlorophenyl)porphyrinato) in THF under a carbon monoxide atmosphere (900 psi) at 40 °C, the desired β -lactone **20** was obtained in 70% yield. Despite our concerns to the contrary, we found this Co(–I)-catalyzed carbonylation at 40 °C proceeded cleanly without any signs of competing reaction pathways. However, when the reaction was carried at higher temperature (60 °C) a significant amount (~20%) of alkene **16** was also detected.

The synthesis of fridamycin E was completed by a two sequence as outlined in Scheme 4. This began with hydrolysis of β -lactone **20** (NaOH_(aq)/THF) to afford β -hydroxyl carboxylic acid **21** in 97% yield. Finally, debenzylation with 1,4-cyclohexadiene and Pd/C in ethanol gave (*R*)-fridamycin E in 88% yield.¹⁸ This synthetic (*R*)-fridamycin E material had physical and spectroscopic data in good agreement with literature values (*e.g.*, $[\alpha]_D^{21}=+8.3$ (*c* = 1.0, dioxane) ($[\alpha]_D^{27}=+8.9$)).^{3c}

With the success of the (*R*)-fridamycin E synthesis, we then turned to synthesize its enantiomer (Scheme 5). Following a nearly identical procedure (switching (DHQ)₂DPP to (DHQD)₂DPP), (*S*)-fridamycin E (*ent*)-**1** was enantioselectively prepared in 47% overall yield (6 steps) from alkene **16**.

With adequate supplies of both enantiomers of fridamycin E in hand, we began our analysis of the antibacterial Structure Activity Relationship (SAR) using the two different strains of *E. coli*. The first is a wild-type *E. coli* (K-12 MG1655) which served as a Gram(–) model organism and the second a genetically modified *E. coli imp* (K-12 BAS901) which served as a Gram(+)-like model organism. *E. coli imp* has a mutation (*imp*-4213) that increases the permeability of the outer membrane.¹⁹ Minimal inhibitory concentrations (MIC) were determined for both fridamycin E enantiomers (Table 2). Interestingly, while both enantiomers showed no activity (>64 μ M) against the wild-type *E. coli* (Gram(–)), the natural enantiomer **1** was significantly more active (8 μ M) than the unnatural enantiomer (*ent*)-**1** (64 μ M) against the Gram(+)-like *E. coli imp* mutant. The lack of antibacterial activity against the wild type *E. coli* suggests poor cell wall permeability of the natural product. In contrast, the 8-fold difference in activity for the two enantiomeric forms suggests the importance of the tertiary alcohol on the mechanism of action against the Gram(+)-like *E. coli imp* mutant.

In conclusion, the *de novo* asymmetric synthesis of both the natural (*R*)- and the unnatural (*S*)-fridamycin E was accomplished in 9 steps and 16% overall yield. This stereodivergent strategy shows the importance of ligand choice in the Sharpless asymmetric dihydroxylation for control of absolute stereochemistry. The route also shows the efficiency and functional group compatibility of the cobalt-catalyzed epoxide to β -lactone carbonylation for the synthesis of tertiary β -hydroxyl carboxylic acids. The antibacterial activity of both enantiomers of fridamycin E showed the importance of stereochemistry to its antibacterial

structure activity relationship. Further synthetic/biological investigations along these lines are ongoing and will be reported in due course.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We are grateful to NIH (GAO, GM090259 and GM088839), NSF (GAO, CHE-0749451; PJB MCB-0845033) and DOE (GWC, DE-FG02-05ER15687) for their financial support of this research. PJB is a Cottrell Scholar of the Research Corporation for Science Advancement.

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Fridamycin E, **1**: $R^1 = R^2 = H$

Fridamycin A, **2**: $R^1 = \text{sugar a}$, $R^2 = H$

Fridamycin B, **3**: $R^1 = \text{sugar b}$, $R^2 = H$

Fridamycin D, **4**: $R^1 = \text{sugar c}$, $R^2 = H$

Vineomycin B₂, **5**: $R^1 = \text{sugar h}$, $R^2 = \text{sugar e}$

Vineomycin C, **6**: $R^1 = \text{sugar h}$, $R^2 = H$

Himalomycin A, **7**: $R^1 = \text{sugar c}$, $R^2 = \text{sugar f}$

Himalomycin B, **8**: $R^1 = \text{sugar g}$, $R^2 = \text{sugar f}$

Amicenomycin B, **9**: $R^1 = \text{sugar d}$, $R^2 = \text{sugar i}$

Figure 1.
Sample Angucyclines with a (*R*)-Fridamycin E Nucleus

Scheme 1.
De Novo Retrosynthesis of (*R*)-Fridamycin E

Scheme 2.
De Novo Asymmetric Synthesis of Epoxide **17**

Scheme 3.
Synthesis of β -Lactone **20**

Scheme 4.
Synthesis of (*R*)-Fridamycin E (**1**)

Scheme 5.
Synthesis of (*S*)-Fridamycin E (*ent*)-1

Table 1

Optimization of Asymmetric Dihydroxylation of **16**^a

entry	ligand	yield ^b	[α] _D ^c	ee % ^d	conf.
1	(DHQD) ₂ PHAL	98%	-5.0	70	<i>S</i>
2	(DHQD) ₂ AQN	96%	-5.2	66 ^e	<i>S</i>
3	(DHQD) ₂ PYR	96%	+2.4	30 ^e	<i>R</i>
4	(DHQD)PHN	94%	+4.6	59 ^e	<i>R</i>
5	(DHQD)₂DPP	98%	-7.2	90	<i>S</i>
6	(DHQ) ₂ PHAL	98%	+5.9	75 ^e	<i>R</i>
7	(DHQ) ₂ PYDZ	94%	+2.1	27 ^e	<i>R</i>
8	DHQ-4-Me-2-Quin	94%	-1.1	14 ^e	<i>S</i>
9	(DHQ) ₂ DPP	98%	+6.5	83 ^e	<i>R</i>
10^f	(DHQ)₂DPP	98%	+6.9	88	<i>R</i>

^aReaction conditions: **16** (0.1 mmol), OsO₄ (0.004 mmol), ligand (0.02 mmol), K₃Fe(CN)₆ (0.3 mmol), K₂CO₃ (0.3 mmol), MeSO₂NH₂ (0.11 mmol), *t*-BuOH/H₂O (1 mL/1 mL), 0 °C to room temperature.

^bIsolated yield based on **16**.

^cAll rotations were taken in CH₂Cl₂.

^dThe ee values were determined by the use of Mosher's reagent.

^eThe ee values were determined by comparison of their optical rotations.

^fNo MeSO₂NH₂ was used.

Table 2MIC Values for (*R/S*)-Fridamycin E^a

	MIC (μ M)	
	<i>imp</i>	MG1655
(<i>R</i>)-Fridamycin E	8	>64
(<i>S</i>)-Fridamycin E	64	>64

^aOvernight bacterial cultures were diluted 10-fold into fresh LB medium and grown to the desired OD₆₀₀ value (depending on strain used). The cell cultures were again diluted by 1000-fold into fresh LB medium containing serial dilutions (2-fold) of the fridamycin E, then grown at 37 °C in agitated 96-well microtiter plates and incubated for 20 h (100 μ L/well). Cell densities (OD₆₀₀) were recorded on an automated plate reader. MG1655 and BAS901 (*imp*-4213) were gifts from Prof. Kim Lewis (NEU). Data are reported for the average of at least three independent sets of experiments.