ORGANIC LETTERS

2011
Vol. 13, No. 24
6592–6595

De Novo Asymmetric Synthesis of Fridamycin E

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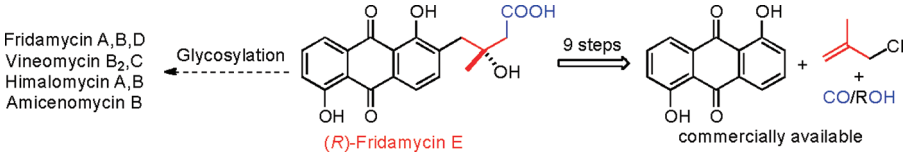
Received November 10, 2011

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 μM).

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 monoglycosylated the mono-, di-, and trisaccharide 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-aculose-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**).[1−3,5−8] Its existence also

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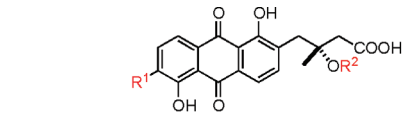
10.1021/ol203041b
Published on Web 11/22/2011



Fridamycin E, **1**: $R^1 = R^2 = H$
Fridamycin A, **2**: R^1 = sugar **a**, $R^2 = H$
Fridamycin B, **3**: R^1 = sugar **b**, $R^2 = H$
Fridamycin D, **4**: R^1 = sugar **c**, $R^2 = H$
Vineomycin B_2, **5**: R^1 = sugar **h**, R^2 = sugar **e**
Vineomycin C, **6**: R^1 = sugar **h**, $R^2 = H$
Himalomycin A, **7**: R^1 = sugar **c**, R^2 = sugar **f**
Himalomycin B, **8**: R^1 = sugar **g**, R^2 = sugar **f**
Amicenomycin B, **9**: R^1 = sugar **d**, R^2 = sugar **i**

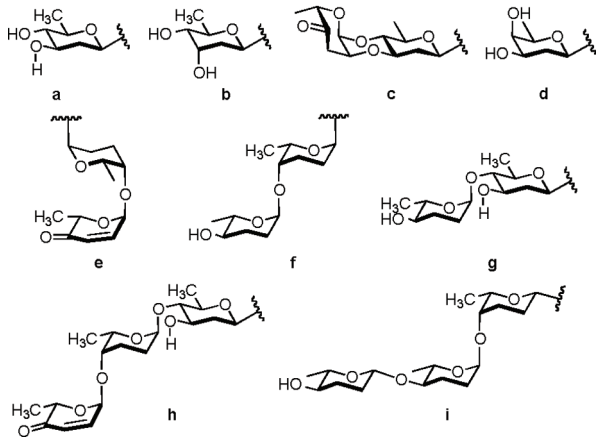


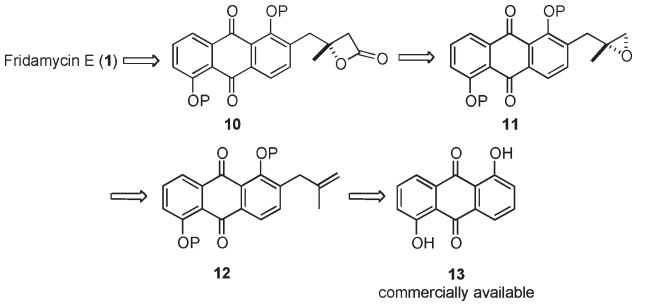
Figure 1. Sample angucyclines with a (*R*)-fridamycin E nucleus.

suggests the existence of a biosynthetic *C*-glycosylation and the potential for a synthetic variant.[4]

The total syntheses of fridamycin E, and 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 varied from the use of chiral starting materials ((*S*)-lactic acid)[3b] and auxiliaries (menthol based titanium enolate)[9a,b] to the use of enzyme-(lipase and hydrolase)[3c,9c] catalyzed kinetic resolutions. The most recent and arguably most successful of these routes was 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 and 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 as 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 Co-catalyzed epoxide to β-lactone carbonylation reaction.[10]

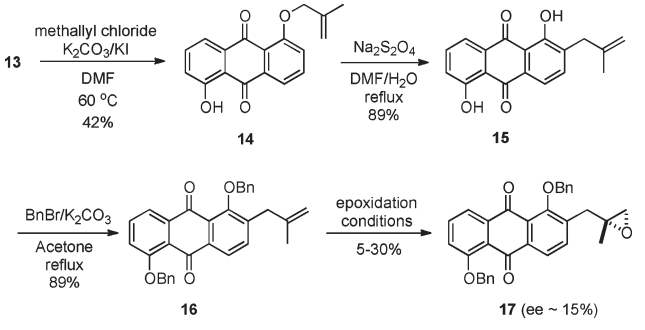
Our approach to fridamycin E (**1**) is depicted in Scheme 1. We envisioned that **1** could be accessed from β-lactone **10**, which in turn could be prepared via a Co-catalyzed carbonylation of epoxide **11**. An asymmetric epoxidation of a disubstituted alkene **12** could be used to install the desired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

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



Our synthesis of fridamycin E began with the monomethallylation of anthrarufin (methallylCl, KI/K_2CO_3) 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 ($BnBr/K_2CO_3$, 89% yield).[11]

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



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

(9) (a) Pausler, G. M.; Rutledge, P. S. *Tetrahedron Lett.* **1994**, *35*, 3345–3348. (b) Pausler, M. G.; Rutledge, P. S. *Aust. J. Chem.* **1994**, *47*, 2135–2147. (c) Ueberbacher, B. J.; Osprian, I.; Mayer, S. F.; Faber, K. *Eur. J. Org. Chem.* **2005**, 1266–1270.

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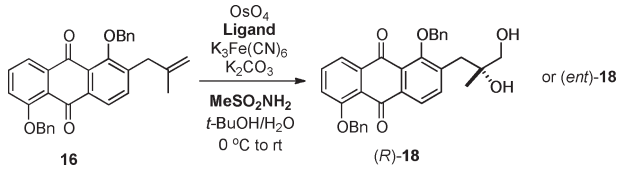
typical Jacobsen epoxidation conditions (5 mol % of (*S,S*)-Mn-salen catalyst and buffered $NaOCl_{(aq)}$ in CH_2Cl_2 at 0 °C)[12] only trace amounts of epoxide **17** were detected. Improved yields of epoxide **17** were found for the Shi epoxidation of **16** (30% yield at ~33% conversion), however 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 pseudoenantiomeric 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]

Table 1. Optimization of Asymmetric Dihydroxylation of **16**[a]

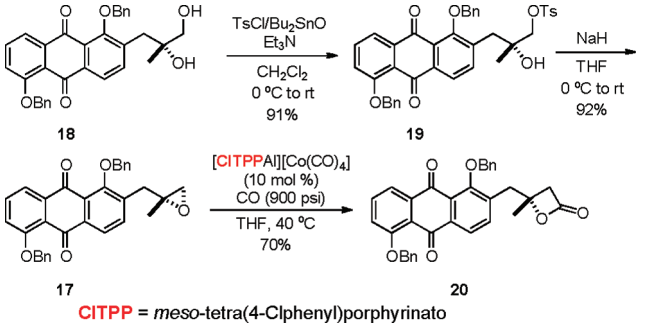


entry	ligand	yield[b]	$[\alpha]_D$[c]	ee %[d]	conf.
1	$(DHQD)_2PHAL$	98%	−5.0	70	*S*
2	$(DHQD)_2AQN$	96%	−5.2	66[e]	*S*
3	$(DHQD)_2PYR$	96%	+2.4	30[e]	*R*
4	(DHQD)PHN	94%	+4.6	59[e]	*R*
5	**$(DHQD)_2DPP$**	**98%**	**−7.2**	**90**	*S*
6	$(DHQ)_2PHAL$	98%	+5.9	75[e]	*R*
7	$(DHQ)_2PYDZ$	94%	+2.1	27[e]	*R*
8	DHQ-4-Me-2-Quin	94%	−1.1	14[e]	*S*
9	$(DHQ)_2DPP$	98%	+6.5	83[e]	*R*
10[f]	**$(DHQ)_2DPP$**	**98%**	**+6.9**	**88**	*R*

[a] Reaction conditions: **16** (0.1 mmol), OsO_4 (0.004 mmol), ligand (0.02 mmol), $K_3Fe(CN)_6$ (0.3 mmol), K_2CO_3 (0.3 mmol), $MeSO_2NH_2$ (0.11 mmol), *t*-BuOH/H_2O (1 mL/1 mL), 0 °C to rt. [b] Isolated yield based on **16**. [c] All rotations were taken in CH_2Cl_2. [d] The ee values were determined by the use of Mosher's reagent. [e] The ee values were determined by comparison of their optical rotations. [f] No $MeSO_2NH_2$ was used.

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.

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



Treatment of (*R*)-diol **18** with TsCl in the presence of Bu_2SnO and Et_3N in CH_2Cl_2 afforded tosylate **19** in 91% yield. Subsequent deprotonation of **19** with NaH smoothly converted it into epoxide **17** in 92% yield. To our delight, similar success was found when we turned to the proposed Co(−I)-catalyzed carbonylation.[17] Thus, when **17** was treated with 10 mol % of $[ClTPPAl]^+[Co(CO)_4]^-$ (ClTPP = *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. Yet, when the reaction was carried out at a higher temperature (60 °C) a significant amount (~20%) of alkene **16** was also detected.

The synthesis of fridamycin E was completed by a two-step sequence as outlined in Scheme 4. This began with

(12) (a) Jacobsen, E. N.; Zhang, W.; Muci, A. R.; Ecker, J. R.; Deng, L. *J. Am. Chem. Soc.* **1991**, *113*, 7063–7064. (b) Brandes, B. D.; Jacobsen, E. N. *J. Org. Chem.* **1994**, *59*, 4378–4380.

(13) Wang, Z.-X.; Tu, Y.; Frohn, M.; Zhang, J.-R.; Shi, Y. *J. Am. Chem. Soc.* **1997**, *119*, 11224–11235.

(14) For a review, see: Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483–2547.

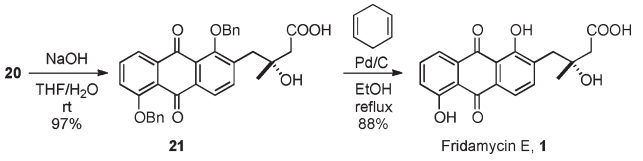
(15) Related substrates to **16** gave diols with moderate %ee's (< 70%), see: Beauregard, D. A.; Cambie, R. C.; Dansted, P. C.; Rutledge, P. S.; Woodgate, P. D. *Aust. J. Chem.* **1995**, *48*, 669–676.

(16) While not perfect, the crystalline nature of this class of compounds provided ideal opportunities to improve the product enantioexcess.

(17) (a) Getzler, Y. D. Y. L.; Mahadevan, V.; Lobkovsky, E. B.; Coates, G. W. *J. Am. Chem. Soc.* **2002**, *124*, 1174–1175. (b) Rowley, J. M.; Lobkovsky, E. B.; Coates, G. W. *J. Am. Chem. Soc.* **2007**, *129*, 4948–4960.

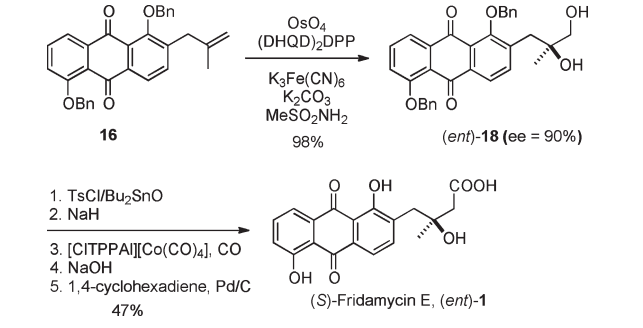
hydrolysis of β-lactone **20** ($NaOH_{(aq)}$/THF) to afford β-hydroxyl carboxylic acid **21** in 97% yield. Finally, debenzylation with 1,4-cyclohexadiene and Pd/C in ethanol gave (*R*)-fridamycin E in 88% yield.[18] This synthetic (*R*)-fridamycin E material had physical and spectroscopic data in good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

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



With the success of the (*R*)-fridamycin E synthesis, we then turned to synthesize its enantiomer (Scheme 5). Following a nearly identical procedure (switching $(DHQ)_2$-DPP to $(DHQD)_2DPP$), (*S*)-fridamycin E (*ent*)-**1** was enantioselectively prepared in 47% overall yield (6 steps) from alkene **16**.

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



With adequate supplies of both enantiomers of fridamycin E in hand, we began our analysis of the antibacterial Structure Activity Relationship (SAR) using 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 ($> 64\ \mu$M) against the wild-type *E. coli* (Gram-(−)), the natural enantiomer **1** was significantly more active (8 μM) than the unnatural enantiomer (*ent*)-**1** (64 μM) 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.

Table 2. MIC Values for (*R*/*S*)-Fridamycin E[a]

	MIC (μM)	
	imp	MG1655
(*R*)-Fridamycin E	8	>64
(*S*)-Fridamycin E	64	>64

[a] Overnight bacterial cultures were diluted 10-fold into fresh LB medium and grown to the desired OD_{600} 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. Cell densities (OD_{600}) 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.

In summary, the *de novo* asymmetric synthesis of both natural (*R*)- and 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 Co-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 SAR. Further synthetic/biological investigations are ongoing and will be reported in due course.

Acknowledgment. We are grateful to NIH (G.A.O., GM090259 and GM088839), NSF (G.A.O., CHE-0749451; P.J.B., MCB-0845033) and DOE (G.W.C., DE-FG02-05ER15687) for their financial support of this research. P.J.B. is a Cottrell Scholar of the Research Corporation for Science Advancement.

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.

(18) Evidence of the anthraquinone sensitivity to reducing conditions can be seen by the fact that when **21** is reduced under typical hydrogenolysis conditions (Pd/C, H_2 (1 atm), EtOH, rt) products with B-ring reduction were produced.

(19) Sampson, B. A.; Misr, R.; Benson, S. A. *Genetics* **1989**, *122*, 491–501.