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A photoisomerization-coupled asymmetric Stetter reaction: application to the total synthesis of three diastereomers of (–)-cephalimysin A

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Abstract

The total synthesis of 8-*epi*, 8,9-*epi*, and 9-*epi*-(–)-cephalimysin A is described. Our catalytic enantioselective synthesis takes advantage of a novel tandem photoisomerization/Stetter reaction. The approach provides rapid access to the desired spirofuranone lactam core in good yield and excellent enantioselectivity. A late stage oxidation strategy allows for flexible access to three of the four diastereomers of cephalimysin A. Access to the epimers provides further support for the correction of the initially proposed relative stereochemistry of cephalimysin A.

Introduction

In 2007 cephalimysin A (**1**) was isolated by Yamada and coworkers¹ from the culture broth of *Aspergillus fumigatus* initially isolated from the marine fish *Mugil cephalus*. Cephalimysin A belongs to a family of natural products containing a unique 1-oxa-7-azaspiro[4.4]non-2-ene-4,6-dione core structure (Figure 1). This group of natural products is characterized by their highly substituted spirocyclic core and wide range of biological activities.² Specifically, cephalimysin A has exhibited significant cytotoxicity against the murine P388 leukemia cell line (IC₅₀ = 15.0 nM) and the human HL-60 leukemia cell line (IC₅₀ = 9.5 nM).¹ Several total syntheses of members of this family of natural products have been described in the literature.³ To date, there are no known syntheses of cephalimysin A (**1**).

Interestingly, the structure of cephalimysin A was initially proposed to possess a *trans* relationship between the C-8 methoxy group and C-9 alcohol (**1a**), a relationship unique within this family of natural products (Figure 1). In 2010 Yamada and co-workers published a report on the CD Cotton effect and the absolute stereochemistry of FD-838 (**2a**) and its seven stereoisomers.⁴ In their report the structure of cephalimysin A is corrected (see **1b**, Figure 1). This correction of the structure is in agreement with observed ¹H nmr splitting of the hydrogen at C-8 (*vide infra*). Intrigued by the densely functionalized stereochemically challenging core and the apparent disparity between it and its congeners, in 2008 we initiated a program directed at the total synthesis of cephalimysin A.

Recently, *N*-heterocyclic carbene organocatalyzed transformations have received increased attention in organic chemistry.⁵ Of these reactions the carbene catalyzed Stetter reaction⁶ has become an efficient method for the asymmetric formation of C-C bonds. Our group's

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implementation of amino-indanol and pyrrolidine derived triazolium *N*-heterocyclic carbenes (NHCs)⁷ has been integral for the development of a variety of highly stereoselective intra-⁸ and intermolecular⁹ asymmetric Stetter reactions. In an effort to showcase the power of this newly developed stereoselective umpolung reactivity in the context of natural product synthesis, we became interested in the structurally unique and biologically active spirofuranone lactam containing natural products.

We recently disclosed the application of the intramolecular Stetter reaction for the asymmetric synthesis of spirocycle **5** in good yield and enantioselectivity (Figure 2).¹⁰ This process allowed rapid and selective access to the desired spirocyclic core of this family of natural products. Spirocycle **5** was further functionalized to an advanced intermediate but did not allow access to the target, FD-838 (**2a**). One of the difficulties in accessing the desired natural product was installation of the methyl group at C-3. We sought to overcome this problem by conducting the Stetter reaction with enal **6**. Use of aldehyde **6** would not only circumvent the need for a late state installation of the methyl group but also produce the furanone oxidation state which is set for installation of the desired side chain at C-2.

Three potential complications were considered when proposing the desired Stetter reaction. First, the olefin geometry of the enal would be crucial to the success of the Stetter reaction with the (*Z*) isomer needed for the reaction to proceed. Second, we have previously shown that aldehydes bearing substitution generally yield Stetter products with low enantioselectivity.¹¹ Third, the possibility of carbene catalyzed redox⁵ pathways could inhibit the desired C-C bond formation. However, we believed that the potential utility of this kind of Stetter reaction warranted further investigation as synthesis of spirofuranone **7** could potentially allow access to a number of members of the spirofuranone lactam containing natural products.

Results and discussion

Stetter reaction optimization

The synthesis of the desired Stetter reaction precursor bearing either a *para*-methoxybenzyl (PMB) or 2-(trimethylsilyl)-ethoxyethyl (SEM) protection group was carried out in two steps from known bromomaleimide **8** (Scheme 1).¹² Mitsunobu protection¹³ of maleimide **8** affords the protected bromomaleimide **9a**. Treatment of maleimide **9a** with the potassium salt of dialdehyde **10**¹⁴ in a mixture of acetonitrile and dimethylsulfoxide affords the desired aldehyde-tethered maleimide **11a** in moderate yield. A similar sequence allows for the synthesis of the SEM protected maleimide **11b**.¹⁵ However, in both cases the aldehydes **11a** and **11b** were formed exclusively as the undesired (*E*) isomer.

Although the undesired olefin isomer was obtained we believed that in situ isomerization of the olefin in the presence of the carbene catalyst could potentially allow for the desired Stetter reaction to proceed. Of the various methods for olefin isomerization, photoisomerization seemed to be the most attractive since it would not require the addition of any additional reagents that could interfere with the carbene catalyst. However, the stability and reactivity of the carbene upon exposure to high energy light (UV) radiation, typically necessary for isomerization, was not clear.¹⁶

We were encouraged to find that UV irradiation of a mixture of the aldehyde **11a** in the presence of triazolium **13a** and sodium acetate delivered the desired product, albeit in low yield (35%) and enantioselectivity (28%) (Table 1, entry 1). An investigation of amino-indanol derived precatalysts showed that trichlorophenyl triazolium **13b** delivers the desired spirocycle with increased yield and enantioselectivity (entry 2). The bis(trifluoromethyl)-phenyl catalyst¹⁷ **13c** delivers the product with further increase in yield (46%) (entry 3).

Interestingly catalyst **13c** yields the opposite major enantiomer of spirocycle **12a** in a good 87% ee.¹⁸ Encouraged by these results, a series of phenyl-alanine derived catalysts were screened under the reaction conditions but no improvement of yield and enantioselectivity was observed (entries 4–6). It is worth noting that unlike catalyst **13c** the phenyl-alanine derived bis(trifluoromethyl)-phenyl catalyst **14c** did not afford the opposite enantiomer of product **12a** (entry 6).¹⁹ Having identified catalyst **13c** as delivering the best selectivity a brief screen of solvents was conducted (entries 7–9). It was found that benzene affords the product in an acceptable 64% yield and excellent 94% ee.²⁰ The same conditions could be applied to the SEM protected aldehyde **11b** to afford the product with similar results (62% yield, 95% ee, entry 10).^{21,22} Importantly, the Stetter reaction could be carried out on 2.50 g scale with no change in the yield or enantioselectivity.²³

Retrosynthetic analysis

Having established an efficient enantioselective synthesis of key spirocycle **12b** we aimed to develop a strategy for the synthesis of cephalimysin A, due to both the ambiguity surrounding the C-8 stereochemistry and its high biological activity. Indeed, at the time the program was initiated we were under the impression that the stereochemistry at C-8 was as initially proposed. However, we were leery of this assignment based on the known stereochemistry of all other members of this family of natural products. With this in mind we knew our approach must be flexible in installing the methoxy group at C-8 and would ideally do so at a late stage. We hoped that this strategy would allow for further confirmation of relative stereochemistry of cephalimysin A.

Our retrosynthetic plan is outlined in Scheme 2. We envisioned a late stage oxidation of spirocycle **17** to afford the natural product **1**. The enone **17** would arise from oxidation and elimination of the benzylidene lactam **16**. We would arrive at benzylidene lactam **16** via a Barbier coupling between spirocyclic succinimide **15** and benzyl bromide followed by oxidation of the enol ether to the desired furanone. In turn succinimide **15** would be delivered via conjugate addition followed by enolate trapping of the spirocyclic furanone **12b**, which is easily accessed on gram scale from previously described asymmetric Stetter reaction. We believed that this route should allow for late stage functionalization of the C-8 position with the possibility of accessing multiple diastereomers of cephalimysin A for comparison to the natural isolate.

Synthesis

Our synthesis of key enone **17** began with conjugate addition of Grignard **18** in the presence of copper(I) bromide to furanone **12b** followed by *in situ* enolate trapping with tert-butyldimethylsilyl chloride (TBSCl) to afford silylenol ether **19** in 74% yield as a 10:1 mixture of diastereomers. Under our previously developed conditions,^{10,24} treatment of succinimide **19** with benzyl bromide and samarium diiodide followed by mild acidic work-up gives the benzylidene lactam **20** in good yield as a 5:1 mixture of *E/Z* olefins. Oxidation of the silylenol ether with DDQ²⁵ followed by deprotection of the SEM group affords the unprotected lactam **16**. Treatment of benzylidene lactam **16** with dimethyldioxirane (DMDO) generates the diol **21** as an inconsequential mixture of diastereomers.²⁶ Surprisingly, exposure of diol **21** to Martin-sulfurane (2.2 equiv.) mediates both oxidation of the secondary alcohol as well as elimination of the tertiary alcohol to yield the desired enone **17**. Although unexpected, oxidation of activated secondary alcohols by Martin-sulfurane has been previously reported.²⁷ With the desired enone in hand we were set to explore our planned late stage oxidation of enone **17** to afford cephalimysin A.

Initial attempts at oxidation of the enone **17** with electrophilic oxidants such as *m*-chloroperoxybenzoic acid (*m*-CPBA), DMDO, trifluoroperoxyacetic acid, and osmium

tetroxide led to either epoxidation of the distal alkene with no observed oxidation of the desired olefin or no reaction. Nucleophilic epoxidation conditions generally led to decomposition of the molecule again failing to deliver any of the desired oxidized product. Having found the selective electrophilic epoxidation of the enamide double bond to be problematic we turned our attention to an alternate strategy to functionalize the lactam.

We predicted that halo etherification may allow for a selective functionalization of the desired alkene due to the reversible nature of halonium formation.²⁸ In this case halonium opening would now be the product determining step. We postulated that the enamide alkene should be more prone to halonium opening due to donation of the nitrogen lone pair into the π^* orbital of the halonium ion. Indeed, treatment of spirocycle **17** with *N*-iodosuccinimide (NIS) in methanol affords the desired iodoether **22a** as a 7:1 mixture of diastereomers.²⁹ Notably, oxidation of the distal alkene was not observed under these conditions. Dehalogenative hydroxylation of the alkyl iodide **22a** using modified Nakamura conditions³⁰ affords the desired diastereomeric alcohols **1c** and **1a** as a 1.5:1 mixture in 65% combined yield. The relative stereochemistry of the products was determined by comparison of the ^1H nmr to the natural product cephalimysin A,¹ and to the three diastereomers of related natural product FD-838⁴ *vide infra*.

Compound **1c** was determined to contain a *cis* relationship between C-9 alcohol and C-8 methoxy group based on the 12.6 Hz coupling observed for the C-9 proton. This rather large coupling constant is indicative of an intramolecular hydrogen bond only accessible via a *cis* relationship and is consistent with other members of this family of natural products (Figure 2). However, the ^1H and ^{13}C nmr signals of **1c** did not match that of the natural isolate. Thus we determine we have accessed 8,9-epi-cephalimysin A (**1c**). Spirocycle **1a** was determined to possess a *trans* relationship between C-9 alcohol and C-8 methoxy group based on the much smaller 4.1 Hz coupling observed for the C-9 proton. This relatively small coupling is consistent with a lack of intramolecular hydrogen bonding and therefore a *trans* relationship. The stereochemistry at C-8 should be conserved during the hydroxylation and the two resulting alcohols should be epimeric at C-9; thus the stereochemistry of **1a** is as shown. This structure matches the originally proposed structure of cephalimysin A, but the ^1H and ^{13}C nmr do not match that of the natural isolate.

Having accessed two diastereomers of the natural cephalimysin A we sought to synthesize the correct diastereomer. We concluded that inversion of the diastereoselectivity of the haloetherification should allow access to the desired natural product. We were delighted to find that addition of trifluoroacetic acid to our previously developed conditions for haloetherification results in a reversal in diastereoselectivity to give **22b** as the major diastereomer in a 4:1 ratio. We propose two possible explanations for this observed reversal in diastereoselectivity. First, addition of acid may prevent the Lewis basic carbonyl of the furanone from stabilizing the iodonium from the top face of the molecule. Second, acidic reaction conditions may disrupt hydrogen bonding between the nucleophile and the substrate. In particular hydrogen bonding between the furanone oxygen and methanol in a six-membered ring transition state would deliver the nucleophile from the bottom face of the molecule. Interruption of this hydrogen bonding interaction could lead to the observed diastereoselectivity.

With the desired diastereomer **22b** we were poised to execute the dehalogenative hydroxylation. However exposure of **22b** to same conditions described previously failed to deliver the desired product; the minor diastereomer **22a** was consumed but the major diastereomer **22b** failed to react. We circumvented this problem by carrying out a two step process with TEMPO³¹ as the terminal oxidant to form the desired oxygenated species. Subsequent cleavage of the N-O bond with zinc metal in the presence of acetic acid

delivered **1d**. A single diastereomer was isolated and the 3.6 Hz coupling observed for the proton at C-9 indicated a *trans* relationship between the alcohol and methoxy group. Therefore 9-*epi*-cephalimysin A (**1d**) represents the third diastereomer of cephalimysin A (**1b**) synthesized from common spirocycle **17**.

Our ability to rapidly access three diastereomers of cephalimysin A (**1a, c–d**) has allowed the comparison of the spectroscopic information of naturally isolated cephalimysin A to our synthetic samples. This data (*vide supra*) strongly suggests that the originally proposed structure of cephalimysin A (**1a**) is in error and that the revised structure as first reported by Yamada⁴ (**1b**) possesses the correct relative stereochemistry.

Conclusions

In conclusion, we have described an efficient method for the enantioselective synthesis of the core of spirocyclic furanone containing natural products via a novel photoisomerization intramolecular asymmetric Stetter reaction. This approach allows for a rapid entry to the cephalimysin A framework. Our late stage oxidation strategy has allowed for the synthesis of three diastereomers of cephalimysin A (**1a, c–d**). Access to these epimers give further credence for the correction of the structure of cephalimysin A (**1b**) and will allow for further biological testing of these unnatural stereoisomers.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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21. Conducting the reaction in the absence of UV radiation at 60 °C only returned starting material ruling out the possibility of carbene catalyzed or thermal enal isomerization.
22. Absolute stereochemistry was determined by X-ray crystallography of a related compound. See Supporting Information for details.
23. The moderate yield of the Stetter reaction is attributed to the relative instability of the starting aldehydes **11a** and **11b**. Storage of the aldehydes on the bench top open to the air leads to significant decomposition after a few days indicating its sensitive nature. The presumed mode of decomposition is through conjugate addition to the enal followed by elimination of 3-hydroxymaleimide. This process is presumably exacerbated under the reaction conditions via conjugate addition by either the base or NHC followed by elimination.
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Fig. 1.
Representative spirofuranone containing natural products.

Previous Approach: **New Approach:**

Fig. 2.
Planned approach towards spirofuranone containing natural products.

synthetic samples

8,9-*epi*-cephalimysin A
4.50 ppm, 12.6 Hz

8-*epi*-cephalimysin A
4.78 ppm, 4.1 Hz

natural isolates

cephalimysin D
4.90 ppm, 4.1 Hz

cephalimysin B
4.87 ppm, 3.9 Hz

cephalimysin C
4.59 ppm, 12.4 Hz

cephalimysin A
4.59 ppm, 12.5 Hz

Fig. 3. Comparison of C-9 ^1H NMR data of synthetic compounds **1a** and **1c** to natural isolates cephalimysin A–D (**1b**, **2b–2d**).

Scheme 1.

Synthesis of aldehydes **11a** and **11b**. Reagents and conditions: (a) DIAD, PPh₃, *para*-methoxybenzyl alcohol, neopentyl alcohol, THF, -78 to 22 °C (67% of **9a**); (b) SEMCl, DIPEA, CH₂Cl₂, -40 °C (86% of **9b**); (c) **10**, MeCN/DMSO, 22 °C (60% of **11a** and 62% of **11b**); DIAD = diisopropyl azodicarboxylate, SEMCl = 2-(trimethylsilyl)ethoxymethyl chloride, DIPEA = *N,N*-diisopropylethylamine, DMSO = dimethyl sulfoxide.

Scheme 2.
Retrosynthetic analysis of cephalimysin A.

Scheme 3.

Synthesis of spirocyclic enone **17**. Reagents and conditions: (a) **18**, CuBr•SMe₂, THF, −78 °C, then TBSCl, HMPA, −78 °C to 0 °C (74%, 10:1 dr); (b) SmI₂, benzyl bromide, THF, 22 °C then 0.05 M HCl (aq) (77%, 5:1 *E/Z*); (c) DDQ, H₂O/CH₂Cl₂, 22 °C (68%); (d) i) TFA, CH₂Cl₂, 0 °C to 22 °C; ii) ethylene diamine, 10 M NaOH, MeOH, 23 °C (65%); (e) DMDO, acetone, −40 °C (70%); (f) Martin-sulfurane (2.2 equiv.), CH₂Cl₂, 23 °C (67%); TBSCl = tertbutyldimethylsilyl chloride, HMPA = hexamethylphosphoramide, TFA = trifluoroacetic acid, DMDO = dimethyldioxirane.

Scheme 4.

Synthesis of 8-*epi*-cephalimysin A (**1a**) and 8,9-*epi*-cephalimysin A (**1c**). Reagents and conditions: (a) NIS, MeOH, 0 °C (80%, 7:1 dr); (b) ((CH₃)₃SiH, AIBN, air, toluene 80 °C (65%, 1.5:1 dr); NIS = *N*-iodosuccinimide, AIBN = azobisisobutyronitrile.

Scheme 5.

Synthesis of 9-*epi*-cephalimysin A (**1d**). Reagents and conditions: (a) NIS, TFA, MeOH, (71%, 4:1 dr); (b) i) TEMPO, tributyltin hydride, toluene, 70 °C; ii) Zn, AcOH/THF/H₂O, 70 °C (38%); TEMPO = 2,2,6,6-tetramethyl-1-piperidinyloxy free radical.

Table 1

Optimization of photoinduced isomerization asymmetric Stetter reaction.^a

Entry	Aldehyde	Cat.	Solvent	Yield (%) ^b	ee (%) ^c
1	11a	13a	CHCl ₃	35	28
2	11a	13b	CHCl ₃	40	60
3	11a	13c	CHCl ₃	47	-87
4	11a	14a	CHCl ₃	37	50
5	11a	14b	CHCl ₃	20	72
6	11a	14c	CHCl ₃	32	44
7	11a	13c	DCE	40	-92
8	11a	13c	PhMe	43	-94
9	11a	13c	PhH	58	-94
10 ^d	11b	<i>ent</i> - 13c	PhH	62 ^e	95

^a Reagents and conditions unless otherwise noted: triazolium salt (30 mol %), sodium acetate (1.0 equiv.), benzene (0.05 M), 45 °C, UV irradiation (300 < λ < 400), 24 h.^b Isolated yield of spirocycle **12a** or **12b**.^c Enantiomeric excess was determined by HPLC analysis on a chiral stationary phase.

d 20 mol % triazolium salt, 48 h.

e 2.50 g scale.