Towards the total synthesis of FD-838: modular enantioselective assembly of the core†

Arturo Orellana‡ and Tomislav Rovis*

Received (in Cambridge, UK) 25th October 2007, Accepted 22nd November 2007
First published as an Advance Article on the web 4th December 2007
DOI: 10.1039/b716445a

A rapid assembly of the tetracyclic core of FD-838, featuring a catalytic asymmetric Stetter reaction, is described.

The antibiotic FD-838[1a] (Fig. 1) belongs to a family of natural products that share a densely functionalized spirofuranone-lactam core. Minor structural modifications of the substituents around this core result in markedly different biological activity profiles. For example, azaspirene[1b] is a potent anti-angiogenic agent, synerazol[1c] is an antifungal antibiotic, and cephalimysin A[1d] is cytotoxic towards p388 and HL-60 cells. Not surprisingly, these natural products have attracted attention from the synthetic community in recent years.[2]

Intrigued by the densely functionalized spirocyclic core of these natural products and by their diverse biological activities, we initiated a synthesis program with FD-838 as our primary target. Central to our synthesis plan was the rapid construction of the spirobicyclic core common to all these natural products using the catalytic asymmetric Stetter reaction[3] recently developed in our laboratory (Scheme 1).[4] This functionalized core would serve as a platform for a modular synthesis of FD-838 and should also prove useful in the synthesis of other congeners of this family.

To test the viability of the proposed Stetter reaction, we undertook the synthesis of an aldehyde bearing an *N*-benzyl substituted maleimide (Scheme 2). Dibromination and elimination provides the bromomaleimide, and addition–elimination of

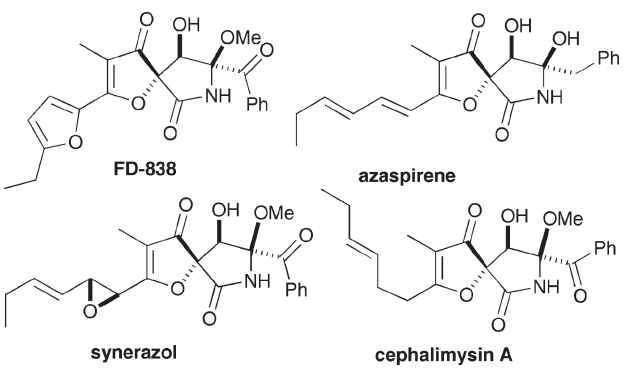
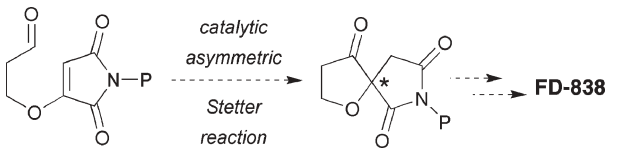


Fig. 1 Selected spirofuranone-lactam natural products.

Department of Chemistry, Colorado State University, Fort Collins, CO, USA. E-mail: rovis@lamar.colostate.edu; Fax: +1 970-491-1801; Tel: +1 970-491-7208

† Electronic supplementary information (ESI) available: Experimental details and characterization of **2**, **3**, **5**, **7**, **8**, **9** and **10**. See DOI: 10.1039/b716445a

‡ Current address: Department of Chemistry, York University, 4700 Keele Street, Toronto, ON, Canada M3J 1P3. E-mail: aorellan@yorku.ca; Fax: +1 416-736-5936; Tel: +1 416-736-5246 x 70760

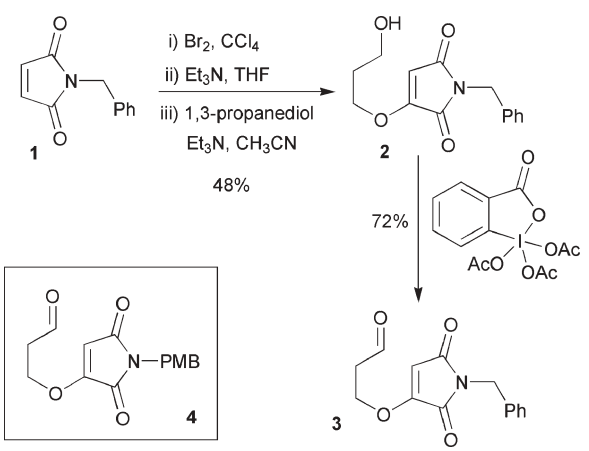


Scheme 1 General synthesis plan for FD-838 and the spirofuranone-lactam family of natural products.

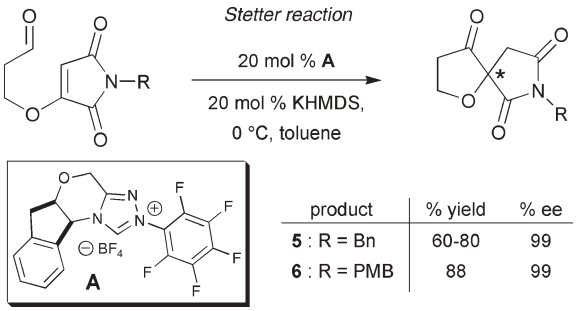
1,3-propanediol under basic conditions generates the expected alcohol.[5] A number of oxidation methods were screened, and although aldehyde **3** could be observed in crude reaction mixtures, attempts to isolate it resulted in its decomposition. We speculate that this material decomposes *via* a β-elimination process, releasing an oxymaleimide leaving group. Gratifyingly, Dess–Martin oxidation, followed by a careful work-up and purification procedure, provides aldehyde **3** in good yield. The analogous PMB-protected maleimide **4** can also be prepared using this protocol.

With access to aldehydes **3** and **4**, we evaluated the key catalytic asymmetric Stetter reaction under a variety of conditions. We were delighted to find that the use of aminoindanol derived precatalyst **A** under the optimized conditions[6] resulted in formation of the desired product in excellent yield and enantiomeric excess (Scheme 3).

Conversion of spirocyclic compound **5** into a Michael acceptor is achieved using a two-step process. Generation of the triethylsilyl enol ether **7** proceeds efficiently under soft enolization conditions. Oxidation of **7** to furanone **8** is achieved through a hydride abstraction using the trityl cation in the presence of a hindered base.[7]



Scheme 2 Synthesis of substrates for the Stetter reaction.



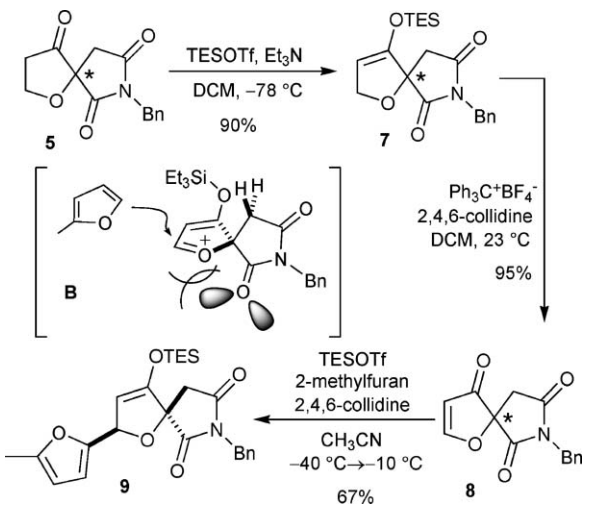
product	% yield	% ee
5 : R = Bn	60-80	99
6 : R = PMB	88	99

Scheme 3 Key catalytic asymmetric Stetter reaction.

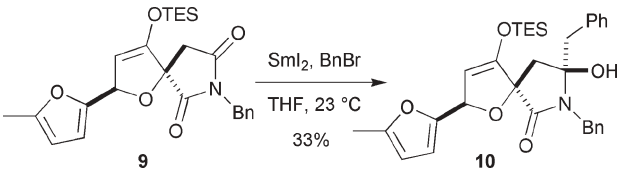
Next our attention turned to the installation of the pendant furan ring. This is carried out by treating furanone **8** with a strong Lewis acid in the presence of methylfuran.[8] This reaction is thought to proceed *via* formation of a resonance-stabilized oxocarbenium ion which is trapped by furan, followed by rearomatization. Notably, this reaction fails completely in DCM and nitromethane, which leads us to speculate that the oxocarbenium ion formed is stabilized by reversible addition of acetonitrile to form the corresponding nitrilium ion[9] until trapping by furan can occur. The stereochemistry of the trapping event may be rationalized by considering model **B**, Scheme 4. The bottom face of the oxocarbenium ion is shielded by the proximal carbonyl on the succinimide ring while the top face has the methylene.[10]

With tricyclic compound **9** as a platform, we have begun to explore end-game strategies for the synthesis of FD-838. The Barbier-type alkylation of succinimides reported by Farcas and Namy seemed well-suited for this task.[11] Indeed, treatment of compound **9** with samarium diiodide in the presence of benzyl bromide provides hemiaminal **10** in 33% unoptimized yield as a single regioisomer (Scheme 5).[12] The illustrated stereochemistry is likely inconsequential since the hemiaminal may undergo facile ring-opening.

In conclusion, we have constructed the spirobicyclic core of FD-838 using a high yielding and highly enantioselective catalytic Stetter reaction. In addition, we have developed a protocol for the installation of the furan ring and alkylation of the succinimide ring. We continue to study these advanced intermediates and will



Scheme 4 Synthesis of tricycle **9**.



Scheme 5 Barbier-type alkylation of tricycle **9**.

report on the synthesis of FD-838 and other congeners of this family in due course.

Financial support has been provided by the National Institute of General Medical Sciences (GM72586). We thank Eli Lilly and Boehringer-Ingelheim for unrestricted support, and Donald Gauthier (Merck Research Laboratories) for a generous gift of aminoindanol. T. R. is a fellow of the Alfred P. Sloan Foundation and thanks the Monfort Family Foundation for a Monfort Professorship.

Notes and references

1 (*a*) K. Mizoue, T. Okazaki, K. Hanada, T. Amamoto, M. Yamagashi and S. Omura, *Eur. Pat. Appl.* EP 216607, *J. P. Appl.* 205278, 1987; Chem. Abstr., 1987, **107**, 132627x; (*b*) Y. Asami, H. Kakeya, R. Onose, A. Yoshida, H. Matsuzaki and H. Osada, *Org. Lett.*, 2002, **4**, 2845; (*c*) O. Ando, H. Satake, M. Nakajina, A. Sato, T. Nakamura, T. Kinoshita, K. Furuya and T. Haneishi, *J. Antibiot.*, 1991, **44**, 382; (*d*) T. Yamada, E. Imai, K. Nakatuji, A. Numata and R. Tanaka, *Tetrahedron Lett.*, 2007, **48**, 6294.

2 Reported syntheses: (*a*) Y. Hayashi, M. Shoji, J. Yamaguchi, K. Sato, S. Yamaguchi, T. Mukaiyama, K. Sakai, Y. Asami, H. Kakeya and H. Osada, *J. Am. Chem. Soc.*, 2002, **124**, 12078; (*b*) Y. Hayashi, M. Shoji, S. Yamaguchi, T. Mukaiyama, J. Yamaguchi, H. Kakeya and H. Osada, *Org. Lett.*, 2003, **5**, 2287; (*c*) S. Aoki, T. Oi, K. Shimizu, R. Shiraki, K. Takao and K. Tadano, *Heterocycles*, 2004, **62**, 161; (*d*) S. Aoki, T. Oi, K. Shimizu, R. Shiraki, K. Takao and K. Tadano, *Bull. Chem. Soc. Jpn.*, 2004, **77**, 1703; (*e*) Y. Hayashi, M. Shoji, T. Mukaiyama, H. Gotoh, S. Yamaguchi, M. Nakata, H. Kakeya and H. Osada, *J. Org. Chem.*, 2005, **70**, 5643. Synthetic Studies: (*f*) Z. Su and C. Tamm, *Tetrahedron*, 1995, **51**, 11177; (*g*) J. M. Mitchell and N. S. Finney, *Org. Biomol. Chem.*, 2005, **3**, 4274. Biosynthetic studies: (*h*) Y. Igarashi, Y. Yabuta, A. Sekine, K. Fujii, K. Harada, T. Oikawa, M. Sato, T. Furumai and T. Oki, *J. Antibiot.*, 2004, **57**, 748.

3 (*a*) H. Stetter and H. Kuhlmann, *Organic Reactions*, ed. L. A. Paquette, Wiley, New York, 1991, vol. 40, p. 407; (*b*) H. Stetter and H. Kuhlmann, *Chem. Ber.*, 1976, **109**, 2890; (*c*) H. Stetter, *Angew. Chem., Int. Ed. Engl.*, 1976, **15**, 639.

4 (*a*) M. S. Kerr, J. Read de Alaniz and T. Rovis, *J. Am. Chem. Soc.*, 2002, **124**, 10298; (*b*) M. S. Kerr and T. Rovis, *Synlett*, 2003, 1934; (*c*) M. S. Kerr and T. Rovis, *J. Am. Chem. Soc.*, 2004, **126**, 8876; (*d*) J. Read de Alaniz and T. Rovis, *J. Am. Chem. Soc.*, 2005, **127**, 6284; (*e*) N. T. Reynolds and T. Rovis, *Tetrahedron*, 2005, **61**, 6368; (*f*) Q. Liu and T. Rovis, *J. Am. Chem. Soc.*, 2006, **128**, 2552; (*g*) J. L. Moore, M. S. Kerr and T. Rovis, *Tetrahedron*, 2006, **62**, 11477; (*h*) Q. Liu and T. Rovis, *Org. Process Res. Dev.*, 2007, **11**, 598.

5 M. J. Sahoo, S. B. Mhaske and N. P. Argade, *Synthesis*, 2003, 346.

6 Larger scale reactions proceed with lower catalyst loading. Representative experimental procedure for the catalytic asymmetric Stetter reaction: to a cooled (0 °C) suspension of triazolium carbene precatalyst **A** (10 mol%, 73 mg, 0.16 mmol) in toluene (12 mL) under Ar is added *via* a cannula a freshly prepared, cooled (0 °C) solution of KHMDS (10 mol%, 32 mg in toluene). After this mixture has been stirred for 10 minutes, a cooled (0 °C) solution of aldehyde **3** (409 mg, 1.58 mmol) in toluene (12 mL) is added *via* a cannula. Consumption of the aldehyde is monitored by TLC and once the reaction is deemed complete the mixture is filtered through a pad of silica gel to remove the solids. The filtrate is concentrated and the crude product purified by flash column chromatography (1 : 1 EtOAc : Hex) to give spirocycle **5** (279 mg, 1.07 mmol, 68% yield) as a pale yellow solid. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 2.61–2.72 (ddd, 1 H, J = 8.5, 8.5, 18.5 Hz), 2.70–2.75 (d, 1 H, J = 18.1 Hz), 2.76–2.84 (ddd, 1 H, J = 18.5, 7.9, 4.5 Hz),

2.91–2.96 (d, 1 H, J = 18.1 Hz), 4.37–4.44 (ddd, 1 H, J = 9.0, 8.5, 4.5 Hz), 4.62–4.69 (ddd, 1 H, J = 7.9, 8.5, 9.0 Hz), 4.66 (s, 2 H), 7.25–7.31 (m, 5 H). **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 35.7, 38.2, 42.9, 66.1, 82.3, 128.3, 128.6, 129.0, 135.0, 172.8, 174.0, 210.2. **HRMS**: $[M + H]^+$ *calculated*: 260.0917, *found*: 260.0915.

7 (*a*) M. E. Jung, Y.-G. Pan, M. W. Rathke, D. F. Sullivan and R. P. Woodbury, *J. Org. Chem.*, 1977, **42**, 3961; (*b*) I. Fleming and I. Paterson, *Synthesis*, 1979, 736.

8 M. A. Grundl, A. Kaster, E. D. Beaulieu and D. Trauner, *Org. Lett.*, 2006, **8**, 5429.

9 (*a*) J.-R. Pougny and P. Sinaÿ, *Tetrahedron Lett.*, 1976, **17**, 4073; (*b*) A. J. Ratcliffe and B. Fraser-Reid, *J. Chem. Soc., Perkin Trans. 1*, 1990, 747; (*c*) A. Marra, J. Esnault, A. Veyrieres and P. Sinaÿ, *J. Am. Chem. Soc.*, 1992, **114**, 6354.

10 Stereochemistry was assigned on the basis of extensive NOE experiments on an analogue bearing a vinyl group in place of the furan. Further support for this assignment was provided by a partially solved crystal structure of compound **10** (a fully solved structure proved unattainable presumably due to crystal twinning).

11 S. Farcas and J.-L. Namy, *Tetrahedron Lett.*, 2001, **42**, 879.

12 Observed by-products invariably involved dihydrofuran ring opening. In no case did we observe formation of regioisomers.

