Total Synthesis of the Depsipeptide FR-901375

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The first total synthesis of FR-901375, a novel bicyclic depsipeptide isolated from the fermentation broth of Pseudomonas chloroaphis No. 2522, has been achieved. The synthetic approach involves 13 reaction steps and is achieved in 12% overall yield. The key points in the successful synthetic strategy are a concise asymmetric synthesis of the key building block (3R,4E)-3-hydroxy-7-mercapto-4-heptenoic acid, a mild Mitsunobu macrolactonization step, and an I₂-mediated deprotection with concomitant disulfide-bridge formation.

Introduction

FR-901375 (1) and FR-901228 (2), discovered by Fujisawa Pharmaceutical Co., Ltd., in the fermentation broth of Pseudomonas chloroaphis (No. 2522) and Chromobacterium violaceum (No. 968), respectively, are members of a rare and structurally elegant family of bicyclic depsipeptide molecules.¹ These natural products possess potent antitumor activity against a range of murine and human solid tumors, and their mechanism of action has been linked to the reversal of prodifferentiation effects of the ras oncogene pathway via blockade of p21 proteinmediated signal transduction. FR-901228 (2) is also a potent Zn-dependent histone deacetylase inhibitor,^{2,3} and recent research has provided evidence that bicyclic depsipeptides that contain a disulfide bridge have potent activity as immunosuppressants.⁴ Finally, phase II clinical trials are underway for the use of 2 as an anticancer agent in the United States.⁵



Examination of FR-901375 (1) reveals several unique structural aspects and challenging molecular motifs present within its structure: (1) a tetrapeptide framework consisting of H_2N -D-Val-D-Val-D-Cys-L-Thr-OH-, (2) a 16-membered ring macrocyclic lactone joined by a union between the carboxy terminus of the tetrapeptide and the hydroxy moiety from (3S,4E)-hydroxy-7-mercapto-4heptenoic acid (5), and (3) a disulfide bond linking the side chain of the D-cysteine residue and the thiol functionality of 5. Clearly, depsipeptide structures such as FR-901375 (1) and FR-901228 (2) present exciting synthetic challenges. Herein, we report the total synthesis of FR-901375.

Simon and co-workers⁶ recently reported the synthesis of FR-901228 (2). By analogy to Simon's synthetic approach, our retrosynthetic strategy to FR-901375 (1) involves an initial disconnection wherein we focus our effort on a simultaneous oxidative deprotection and disulfide bond formation from a preformed macrolactone (Scheme 1). Accordingly, the lactone can be constructed from the acyclic precursor 3 via a mild Mitsunobu macrolactonization reaction.⁷ This step was viewed as a formidable challenge because of the likely possibility for elimination of the allylic alcohol functionality present in 5. The acyclic precursor 3, itself, was envisaged as being formed from building blocks, tetrapeptide 4, and 5.

Results and Discussion

Tetrapeptide **4** was assembled rapidly and efficiently using solution-phase Fmoc-based peptide synthesis methodology⁸ (Scheme 2). Thus, L-threonine methyl ester 7⁹ was reacted with N- Fmoc-D-cysteine-[S-triphenylmethyl (Trt)] using 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride with 1-hydroxybenzotria-

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^{1501.}

SCHEME 1. Retrosynthetic Analysis of FR-901375 (1)



zole, followed by TBS protection to yield protected dipeptide **8** (83% overall yield).¹⁰ The choice of the TBS protecting group was driven by the anticipated requirement for mild deprotection conditions in the later stages of our synthesis. *N*-Fmoc deprotection of **8** (Et₂NH), followed by coupling to *N*-Fmoc-D-valine provided tripeptide **9** (97% yield). A further cycle of *N*-Fmoc deprotection and coupling with D-valine furnished the tetrapeptide **10** in 71% yield. Treatment of **10** with Et₂NH

SCHEME 2. Synthesis of Tetrapeptide 4

effected the removal of the Fmoc protecting group to give **4** in quantitative yield (Scheme 2).

In Simon's approach to FR-901228, synthon **5** was generated from an initial three-step synthesis of (2*E*)-5-[(triphenylmethyl)thio]-2-pentenal (**13**). There then followed the preparation of a chiral ligand, *R*-(+)-binaphthyl amino alcohol, necessary for a transition-metal-catalyzed chiral aldol approach to β -hydroxy acid **5**.^{6,11} However, in our hands, we were unable to reproduce the 98% *ee* in the Ti(IV)-catalyzed aldolization reaction that Simon observed in his synthetic approach to **5**. Therefore, at this point in our synthesis of FR-901375, we moved away from Simon's synthetic route in an attempt to establish a practical and scaleable synthetic approach to the key synthon **5**.

The crucial intermediate, 5, is a deceptively simplelooking molecule that exposes two major limitations of current asymmetric synthesis methodologies, namely, lack of effective asymmetric aldol reactions with unsubstituted, acetate-derived enolates and the inability to carry out asymmetric ketone reductions on γ , δ -unsaturated β -keto esters. We rapidly assembled aldehyde **13** in a two-step, one-pot procedure involving an initial conjugate addition of triphenylmethanethiol to acrolein 11 to afford aldehyde **12**.¹² Subsequent treatment of **12** with commercially available (triphenylphosphoranylidene)acetaldehyde in refluxing benzene vielded the α,β unsaturated aldehyde 13 (overall 60% yield, two steps. Scheme 3). With the requisite aldehyde 13 in hand, the asymmetric aldol reaction was investigated. Phillips and co-workers¹³ reported a highly diastereoselective acetate







NMP = N-methylpyrrolidinone

SCHEME 4. Asymmetric Synthesis of Chiral Acid 5







aldol reaction based on an oxazolidinethione auxiliary. Unfortunately, the reaction between oxazolidinethione **14** and aldehyde **13** provided the aldol product **15** in poor yield (35%) and moderate diastereoselectivity (Scheme 3).¹⁴

The use of Evans' auxiliary-based aldolization reactions of haloacetyloxazolidinones, as masked chiral acetate enolate equivalents, has proven reproducibly reliable.¹⁵ Thus and to our delight, the asymmetric aldol reaction between the dibutylboron enolate derivative of chloroacetyl-oxazolidinone **16** and aldehyde **13** provided the desired chlorohydrin **17** (69%) with excellent diastereoselectivity (>90% *de* as judged by ¹H NMR, Scheme 4).¹⁶ The subsequent dechlorination of **17** was complicated by the acid sensitivity of the *S*-trityl protecting group. Thus Zn/HOAc and Zn/NH₄Cl were not applicable methods for this transformation. However, dechlorination of **17** was achieved with Al–Hg¹⁷ to give **18** in quantitative yield.

configuration is based on Evans' model.

Subsequent hydrolysis of the chiral auxiliary of **18**, with $LiOH/H_2O_2$, furnished **5** in 78% yield (Scheme 4).¹⁸ Thus, while our approach to **5** is longer, in terms of synthetic steps, than Simon's approach, our methodology allows us to routinely prepare **5** on a multigram scale and in essentially enantiomerically pure form.

With chiral acid **5** conveniently accessible, the coupling of **4** and **5** with BOP reagent ((benzotriazol-1-yloxy)tris-(dimethylamino)phosphonium hexafluorophosphate) proceeded smoothly to grant the hydroxy methyl ester **19**. Basic hydrolysis (LiOH/THF) afforded **3** (79% yield over two steps). The stage was now set for the Mitsunobu macrolactonization of **3**; gratifyingly, this reaction proceeded quite well to afford lactone **20** in 59% yield. Final oxidative deprotection of the bis(*S*-triphenyl)lactone with iodine in dilute MeOH solution¹⁹ and HF/CH₃CN²⁰ afforded FR-901375 (**1**) in 63% yield over two steps (Scheme 5). This synthetic material gave ¹H and ¹³C NMR spectral data, which matched perfectly those for the natural product.

We have developed an efficient total synthesis of FR-901375 that involves 13 linear steps, with an overall yield of 12.4%. Our synthetic effort features a concise asymmetric synthesis of the quintessential synthon (3R, 4E)-

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3-hydroxy-7-mercapto-4-heptenoic acid **5** on the gram scale, a mild Mitsunobu macrolactonization step, and a simultaneous I₂-mediated deprotection/disulfide bridge formation. This synthetic approach should provide a readily accessible route to bicyclic depsipeptide libraries and thus facilitate SAR profiling of these interesting structures. Explorations along these lines will be reported in due course.

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Supporting Information Available: All experimental details and analytical data. This material is available free of charge via the Internet at http://pubs.acs.org.

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