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Total Synthesis of the Depsipeptide FR-901375

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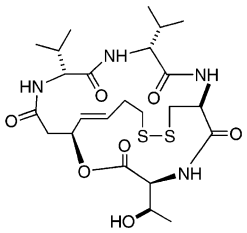
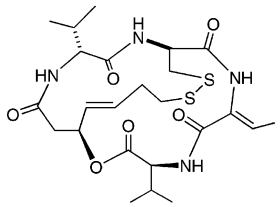
The first total synthesis of FR-901375, a novel bicyclic depsipeptide isolated from the fermentation broth of *Pseudomonas chloroaphis* No. 2522, has been achieved. The synthetic approach involves 13 reaction steps and is achieved in 12% overall yield. The key points in the successful synthetic strategy are a concise asymmetric synthesis of the key building block (3*R*,4*E*)-3-hydroxy-7-mercapto-4-heptenoic acid, a mild Mitsunobu macrolactonization step, and an I_2-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 protein-mediated 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]



FR-901375 (1)



FR-901228 (2)

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 (3*S*,4*E*)-hydroxy-7-mercapto-4-heptenoic 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-workers[6] 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 methodology[8] (Scheme 2). Thus, L-threonine methyl ester **7**[9] 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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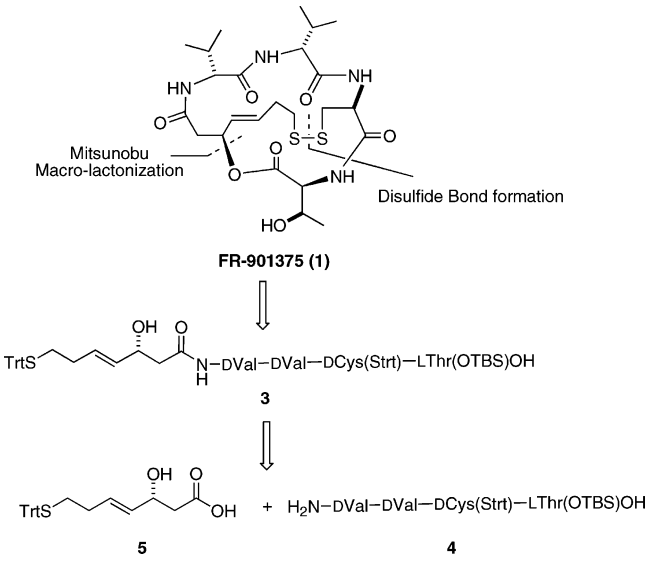
SCHEME 1. Retrosynthetic Analysis of FR-901375 (1)

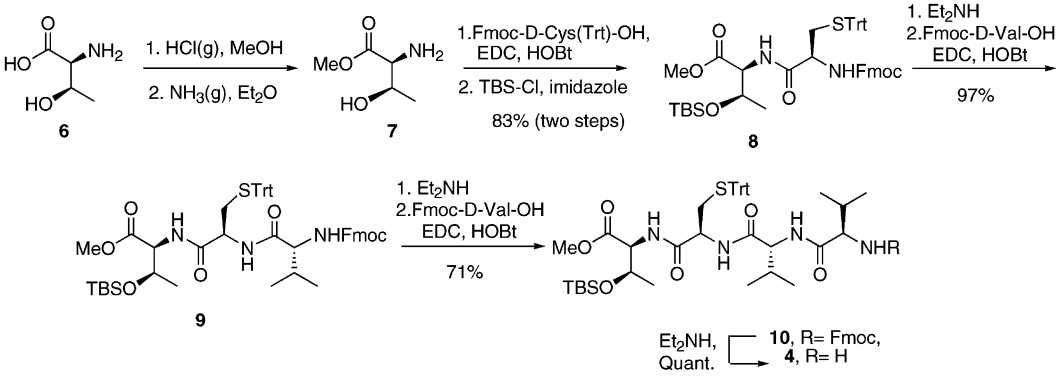


zole, followed by TBS protection to yield protected dipeptide **8** (83% overall yield).[10] The choice of the TBS protecting group was driven by the anticipated requirement for mild deprotection conditions in the later stages of our synthesis. *N*-Fmoc deprotection of **8** (Et_2NH), followed by coupling 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 Et_2NH effected the removal of the Fmoc protecting group to give **4** in quantitative yield (Scheme 2).

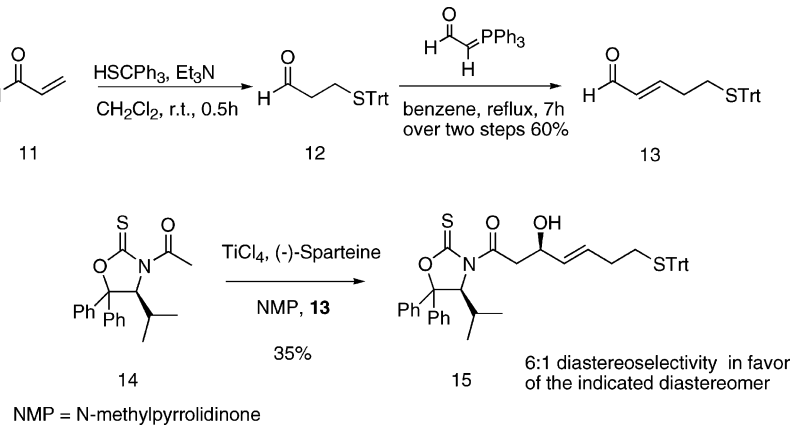
In Simon's approach to FR-901228, synthon **5** was generated from an initial three-step synthesis of (2*E*)-5-[(triphenylmethyl)thio]-2-pentenal (**13**). There then followed the preparation of a chiral ligand, *R*-(+)-binaphthyl amino alcohol, necessary for a transition-metal-catalyzed chiral aldol 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 simple-looking 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 yielded 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-workers[13] reported a highly diastereoselective acetate

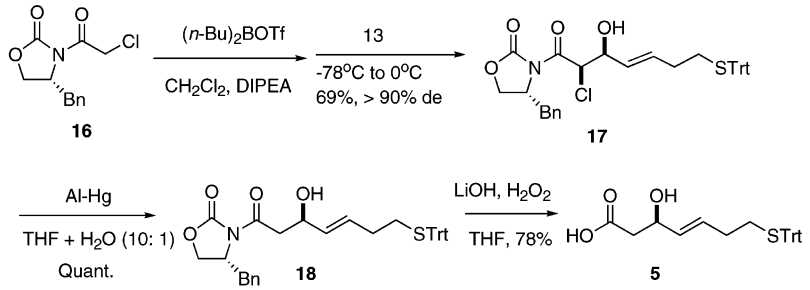
SCHEME 2. Synthesis of Tetrapeptide 4



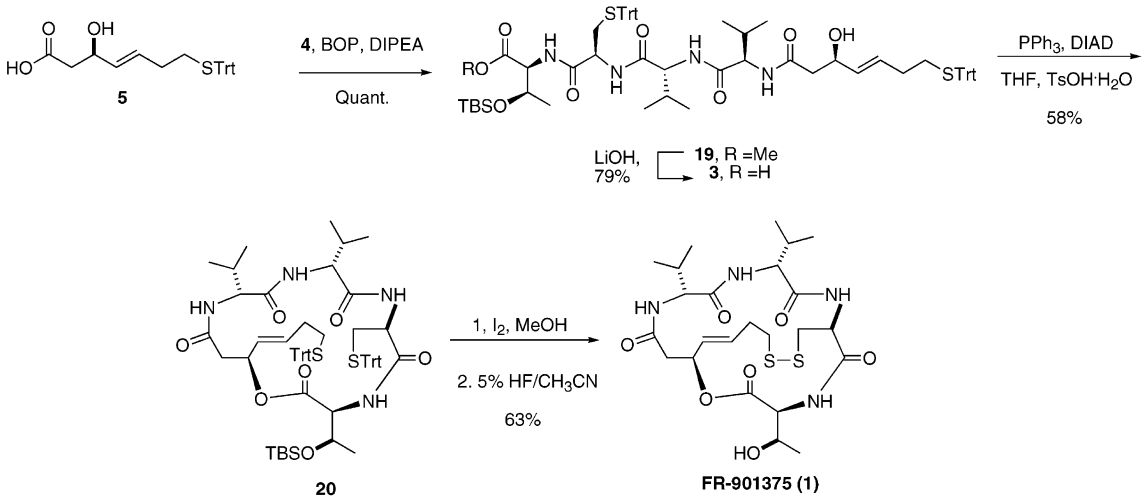
SCHEME 3. Aldol Reaction Based on an Oxazolidinethione Auxiliary



SCHEME 4. Asymmetric Synthesis of Chiral Acid 5



SCHEME 5. Latter Stage Assembly of FR-901375 (1)



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 ^{1}H 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/NH_4Cl were not applicable methods for this transformation. However, dechlorination of **17** was achieved with Al−Hg[17] to give **18** in quantitative yield. 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 solution[19] and HF/CH_3CN[20] afforded FR-901375 (**1**) in 63% yield over two steps (Scheme 5). This synthetic material gave ^{1}H and ^{13}C 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 (3*R*,4*E*)-

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3-hydroxy-7-mercapto-4-heptenoic acid **5** on the gram scale, a mild Mitsunobu macrolactonization step, and a simultaneous I_2-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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