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Asymmetric synthesis of the core of AMPTD, the key amino acid of microsclerodermins F-I

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ABSTRACT

We report a stereoselective synthesis of the five consecutive stereocenters of AMPTD in seven steps. Highlights include an Evans glycolate aldol reaction, the use of a Weinreb amide as an aldehyde masking group, and a Mannich reaction with an Ellman-type chiral sulfimine.

Microsclerodermins F-I (**1**–**4**, Fig. 1), members of a family of antitumor and antifungal cyclic peptides, were isolated in 2000 from a deep-water species of the marine sponge *Microscleroderma*.[1] A biological assay of **1** revealed cytotoxicity against the human carcinoma cell line HCT-116 (IC_{50} = 2.7 μM for **2**) and antifungal activity against *Candida albicans*. The biological activity of these molecules, coupled with their poor availability from natural sources (0.001 wt % from the sponge), attracted our synthetic interest.

Microsclerodermins F and H contain a D-tryptophan residue, while G and I feature a dehydrotryptophan residue. The molecules offer several synthetic challenges, including a pyrrolidinone with a β-amido hemiaminal and a γ-amino-β-hydroxy amino acid; however, the most intimidating is 3-amino-6-methyl-12-phenyl-2,4,5-trihydroxydodeca-7,9,11-trienoic acid (AMPTD, **5**, Fig. 2). AMPTD is a polyhydroxylated β-amino acid with five contiguous stereogenic centers and an all-*trans* phenyltriene; **3** and **4** also feature a methyl substituent on the triene portion. Shioiri reported a synthesis of AMMTD, a constituent of microsclerodermins A and B with the same stereochemistry as AMPTD but a different side chain, in 17 steps without the side chain[2] and 31 steps with the side chain.[3] We report herein a concise synthesis of the stereochemical core of **5** adaptable to the synthesis of **1**–**4**.

Our retrosynthesis of the protected AMPTD moiety **5** introduces four stereogenic centers via aldol methodology (Fig. 2). We envisioned preparation of **5** by condensation of the known diene phosphonate **6**[4] and aldehyde **7**, prepared by replacement of the chiral auxiliary in **8** with the methyl ester, followed by a deprotection–oxidation sequence. The amino alcohol **8** would come from a *syn*-selective aldol reaction between a chiral glycolate equivalent and imine **9**, which in turn could be prepared from alcohol **10** by protection of the 1,2-diol and conversion of the chiral auxiliary to the corresponding imine. The alcohol **10** would come from another *syn*-selective aldol reaction between a chiral glycolate and an α-chiral aldehyde **11**, prepared in two steps from the commercially available Roche ester.

We first explored aldol reaction of the *cis*-lactone **13**; Andrus had previously synthesized the trans diastereomer.[5] We found that treatment of the open form **12** with TFA in the presence of triethylsilane as a cation scavenger yielded *cis* O-lactone **13** in much

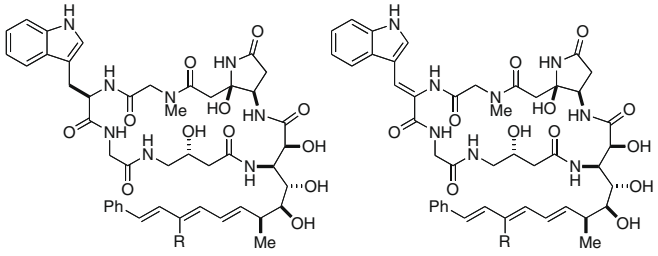

Figure 1. Structures of microsclerodermins F-I (**1**–**4**).

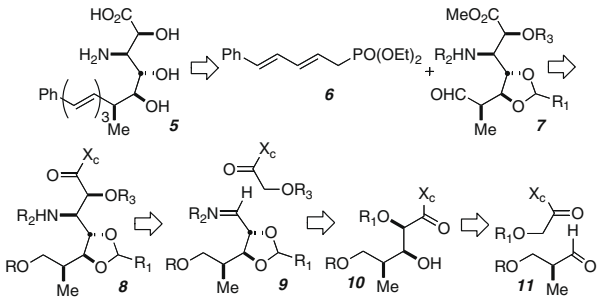

Figure 2. Retrosynthetic analysis of **5**.

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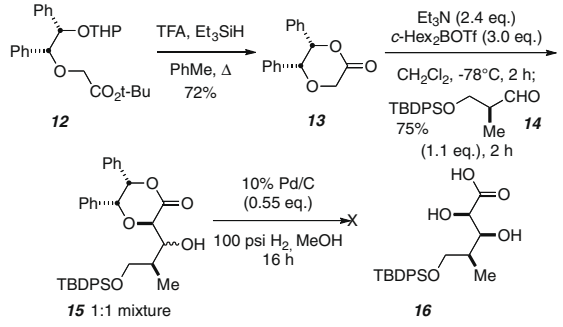
higher yield than our previously reported two-step procedure from **12**.[6] Aldol reaction of **13** with aldehyde **14** (obtained by reduction of the corresponding ester in situ to avoid epimerization of the methyl group upon standing)[2] gave the desired adduct **15** in good yield; unfortunately, we obtained **15** as a 1:1 mixture of diastereomers (Scheme 1). Our attempts to remove the biphenyl failed to yield diol **16**, and we were thus unable to ascertain the stereochemistry of the product mixture; we anticipate that the use of higher hydrogen pressure would allow template removal. Studies toward the use of **13** as a template for the synthesis of chiral α-substituted-α-hydroxyacids (via alkylation) and β-substituted-α,β-dihydroxyacids (via aldol reaction) are ongoing.

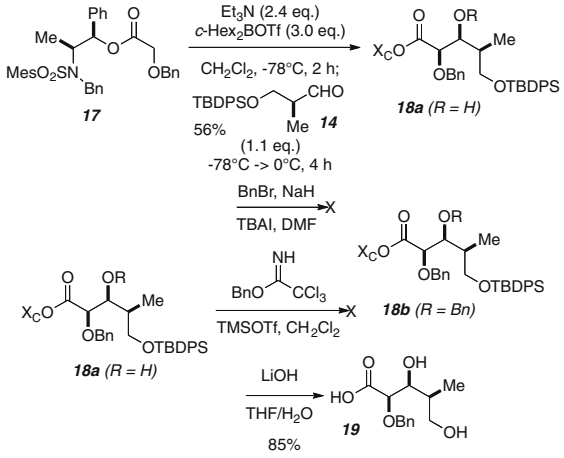
We next probed aldol reactions of Andrus' modified Masamune norephedrine template **17** (Scheme 2)[7] with **14**. Compound **17** gave a moderate yield of addition product **18a**, but attempted benzylation of the secondary alcohol returned **18a** unchanged. Basic hydrolysis of the chiral template removed the TBDPS ether to give alcohol **19**.

Crimmins' oxazolidinethione **20** (Scheme 3)[8] gave a moderate yield of and diastereoselectivity for the corresponding aldol product **21a**. We wished to produce the diol and form the acetonide; unfortunately, the sulfur prevented hydrogenolysis to **21b**. Removal of the chiral template gave diol **22a** quantitatively, but hydrogenation again failed, presumably due to traces of sulfur contamination. Birch debenzylation was not pursued, as the resultant triol would be difficult to purify from the reaction.

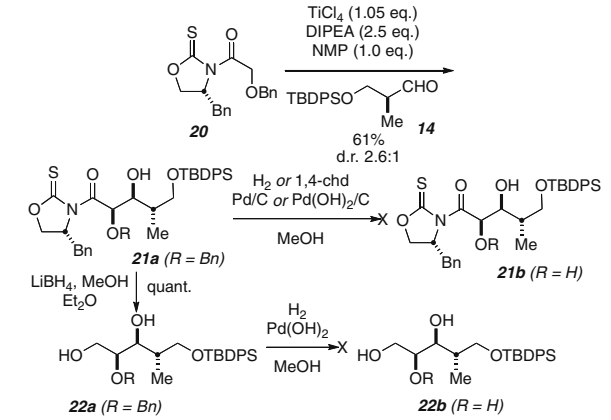
We next turned to Evans' chiral oxazolidinone **23a**,[9] which underwent *syn*-aldol reaction with **14** to give adduct **24**. The reaction was not clean at room temperature, but we obtained a single diastereomer of **24** at 0 °C (Scheme 4). Hydrogenation of the benzyl



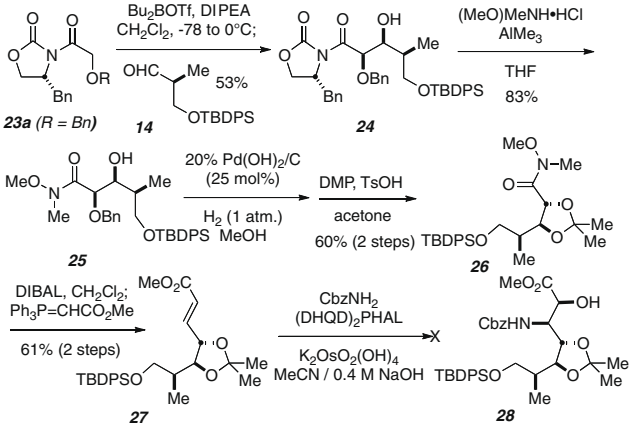
Scheme 1. Application of O-lactone **13**.



Scheme 2. Application of chiral template **17**.



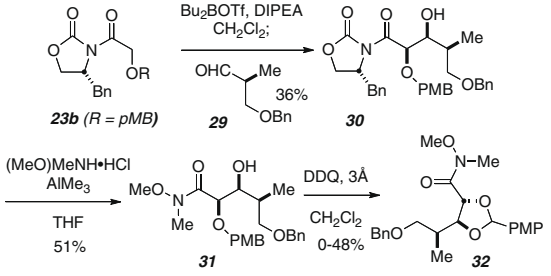
Scheme 3. Application of chiral template **20**.



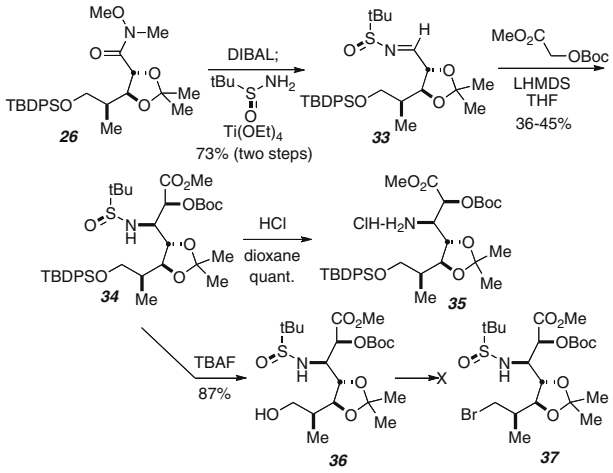
Scheme 4. Synthesis and attempted amino-hydroxylation of **27**.

ether was blocked by the bulky oxazolidinone and TBDPS group; thus we converted the oxazolidinone to Weinreb amide **25**. With the steric hindrance reduced, the diol was obtained and protected as acetonide **26**. Reduction of the Weinreb amide to the aldehyde and Wittig reaction produced *trans*-α,β-unsaturated ester **27**; attempted Sharpless amino-hydroxylation of **27** (in analogy with a previous synthesis of ours)[10] failed, yielding not the desired amino alcohol (**28**) but only loss of the TBDPS residue.

We then switched protecting groups: aldol reaction of the corresponding *para*-methoxybenzyl (PMB) glycolate **23b** and benzyl-protected aldehyde **29** gave adduct **30** in moderate yield, and conversion to the Weinreb amide **31** allowed direct oxidation to the *p*-methoxyphenyl acetal **32** (Scheme 5). While we preferred this protecting-group scheme, both the aldol reaction and acetal formation proved to be capricious, so we abandoned this route.



Scheme 5. Use of alternate protecting groups to give **32**.



Scheme 6. Completion of the five chiral centers and deprotection.

Returning to our original route, we converted acetonide **26** via reduction and condensation to the chiral sulfimine **33** (Scheme 6).[11] Addition of Boc-protected methyl glycolate according to Aitken's procedure gave ester **34**, bearing all of the stereogenic centers of AMPTD. While the published work did not discuss deprotection of the adduct, we discovered that treatment of **34** with a dry solution of HCl in dioxane allowed selective removal of the sulfimine group to yield amine salt **35**. TBAF-mediated removal of the TBDPS group from **34** also proceeded smoothly to give **36**; conversion of the alcohol to bromide **37** was unsuccessful under various conditions, presumably due to deprotection of the acetonide by HBr formed in the course of the reaction. (Our original retrosynthesis envisioned conversion of **37** to a phosphonate and reaction with the corresponding aldehyde analogue of **6**.) Studies on the oxidation of **36** to **7** and reaction with **6** are ongoing.

In summary, we have synthesized **34**, containing the stereochemical core of AMPTD, in seven steps from known starting materials. We are exploring use of the alcohol of **36** as a key intermediate for the total synthesis of the microsclerodermins. We have also shown that the protecting groups can be selectively manipulated, thus allowing us to explore structure–activity relationships of the phenyltriene side chain in microsclerodermins F-I. Studies toward the total synthesis of **1**–**4** are ongoing in our laboratories.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.06.144.

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