The Taumycin A Macrocycle: Asymmetric Total Synthesis and Revision of Relative Stereochemistry

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Supporting Information

ABSTRACT: The first asymmetric total synthesis and revision of the relative configuration of the 12-membered taumycin A macrocycle is described. Key to the success of this work was a novel α-keto ketene macrocyclization that provided an efficient means by which to access two diastereomers of the desired macrolide without the need to employ additional coupling agents or unnecessary oxidation state adjustments.

The symbiotic association of marine microorganisms with their host sponges continues to be an extraordinary source of hybrid polyketide/nonribosomal secondary metabolites that often possess unique structures in conjunction with interesting biological activity.1 Recently, taumycins A and B (1−2, Figure 1) were isolated by Kashman and co-workers, in extremely small amounts, from a Madagascar sponge of genus Fascaplysinopsis.2a Of particular note, taumycin A (1) was shown to inhibit UT-7 cell growth in the micromolar range, whereas taumycin B (2), which lacks the terminal oxazole moiety at C(12), is completely devoid of this activity.2a,b To date, extensive biological evaluation has not been performed on either metabolite, and the mechanism of action of 1 remains unknown.2a,b

The relative configuration of the macrolide common to 1 and 2 was assigned using both detailed multidimensional NMR analyses and degradation studies (cf. 3); however, due to its remote location, the configuration about the side chain C(9) methyl remains undefined. As determined by Kashman,2a,b the taumycin macrolide contains one L- and one D-isoleucine residue (Figure 1) which, in the absence of an X-ray quality crystal, made it difficult to establish absolute stereochemistry due to what was perceived to be potential ambiguity surrounding the correct sequence of amino acid subunits within the macrocycle.

With this in mind, the relative stereochemistry as drawn by Kashman in the isolation report is somewhat unclear, as it does not adequately address the two stereocenters in each isoleucine residue (cf. Kashman vs. Expanded Stereochemistry, Figure 1).3 The presence of a D-amino acid is usually regarded as the empirical evidence that allows one to claim the source of a natural product to be bacterial derived, as it has been well established that certain bacteria are able to epimerize L-amino acids to their D-form.4 In the case of isoleucine, however, α-epimerization would only affect the amino center, leaving the β-methyl center unchanged. Using this reasoning, L-isoleucine (4) can only be converted to its diastereomer, D-α-epimere (7), and not its enantiomer, D-isoleucine (6). This is further supported by the fact that D-α-isoleucine has been found previously in natural products,3 while secondary metabolites which feature either D-isoleucine, or its α-epimer (7), are relatively uncommon in the literature.5 We therefore believed that the taumycin macrolide was more likely to feature one L- and one D-α-epimere (Figure 1).

At the onset of our synthetic campaign, we believed that the prudent approach might be to first target aldehyde 3, a compound initially accessed by Kashman2a via reductive ozonolysis of 1, as a means to address both the unknown

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relative and absolute stereochemistry of the taumycin macrocycle. Once stereochemistry had been established, our plan was to then transition to the total syntheses of 1 and 2, targeting both combinations of the undefined stereocenter at C(9).

From a retrosynthetic perspective (Scheme 1), we envisioned construction of the desired aldehyde in two sequential operations involving (1) macrocyclization followed by (2) alkene ozonolysis. Rather than rely on the use of unnecessary coupling reagents, we thought that a reasonable method would be cyclization exploiting an α-keto ketene (cf. 8), which could be generated via the thermal rearrangement of β-keto tert-butylester 9.9 While similar approaches9 have been documented for the synthesis of macrocycles, to the best of our knowledge there has been no reported use of this strategy for depsipeptide cyclization.9 Our rationale for pursuing this strategy came as a result of studying several reports on related depsipeptides, some noting difficulty in their macrocyclization steps; for example, the macrocyclization of a similar substrate was recently reported by Gosh and Xu9 and required oxidation state adjustments to the 1,3-carbonyl moiety in order to cyclize. Ester 9 could in turn be synthesized via the stepwise union of amino acids 11 and 12 with alcohol 10.

The synthesis of β-keto ester 10 commenced with the known non-Evans-syn aldol union between crotonaldehyde and 4-benzyl-3-propionyl-2-thiazolidine-2-thione, following the literature procedure of Crimmins,10 to furnish (+)-13 in good yield and high diastereoselectivity (Scheme 2). We chose to employ this titanium-mediated aldol method for several reasons: first, the ability to access both the Evans-syn and non-Evans-syn product from the same thiazolidinethione enantiomer by simply modulating the equivalents of base10b,c was extremely appealing, since at the onset of our work it was still unclear which syn diastereomer of the southern hemisphere was needed for the natural product;11 also of note, the ease with which the aldon product could be purified using silica gel chromatography, simply by collecting the bright yellow band as it elutes off the column, ensured that we could process decagram batches of pure material in an extremely time efficient manner; the most attractive feature, however, of the thiazolidinethione relative to other chiral auxiliaries (e.g., the Evans oxazolidinone) is its ability to be efficiently displaced by a variety of nucleophiles employing relatively mild reaction conditions.12

Initially, we thought that rapid access to β-keto ester 10 could be achieved through direct replacement of the thiazolidinethione using the potassium salt of mono-tert-butyl malonate and MgCl2 (Scheme 2), similar to the elegant studies by Smith and co-workers employing the potassium salt of monoethyl malonate.12a,b Unfortunately, while we did observe auxiliary displacement, we could not prevent the in situ hydrolysis of the tert-butyl group under these conditions and any attempt led directly to the carboxylic acid derivative of 10. Pleadingly, recourse to thiazolidinethione cleavage employing N,O-dimethylhydroxyl amine12c allowed efficient access to Weinreb amide (−)-14 (Scheme 2). Alcohol protection followed by enolate displacement13 and cleavage of the trimethylsilyl group upon workup afforded the desired C(1)−C(6) fragment [(−)-10] in good overall yield (58%). It should be noted that enolate displacement directly on nonprotected (−)-14 gave good, but somewhat inferior, results compared to those in Scheme 2.

At this stage, we began our fragment union studies en route to synthetic taumycin A aldehyde. We knew that, in order to establish the correct relative configuration of 3, it would be necessary to synthesize several macrocycles in which the order of amino acids would be varied (Scheme 3). We would also discover that the most efficient approach would not be the most convergent [i.e., uniting (−)-10 with both dipeptide combinations].14 Rather, we quickly determined that the iterative, three-step15 addition of Fmoc protected amino acids18 to sequentially install both combinations of the requisite dipeptide unit allowed for a more efficient route to access precyclization products (−)-15 and (−)-16 (Scheme 3). Notably, utilizing this strategy, the dipeptide unit can be installed in a single day, inclusive of intermediate purifications.17,18

With these compounds in hand, we next explored the viability of macrocyclization exploiting the thermal β-keto tert-butylester rearrangement. Based on the elegant studies of Witzeman and Nottingham4a regarding transacetoacetylations using tert-butylacetoacetate, as well as the seminal work by Boeckman7a−c and others7d−f on dioxinone rearrangements to form acylketene intermediates, we believed that thermal rearrangement in the presence of a primary amine [e.g., derived after the Fmoc cleavage of either (−)-15 or (−)-16], under high dilution conditions, should lead directly to the desired depsipeptide macrocycles. To the best of our knowledge, there has been no reported use of the Witzeman method to effect macrocyclization, although the Boeckman method is a commonly employed tactic for ring closure.7

In the event, after Fmoc cleavage and gentle refluxing of the resultant amines for 2 h in toluene, macrocyclization to form amides (−)-17 and (+)-18 could be effected with excellent selectivity (mono vs poly) and in serviceable yield. Based on related observations by Hoye during his elegant synthesis of
callipeltoside, we believe the transition from α-keto ketene to macrolide likely involves (1) carbonyl–N–H precoordination, followed by (2) the concerted movement of 6 π-electrons (cf. 8, Scheme 4). In the final step, reductive ozonolysis of either (+)-17 or (+)-18 allowed access to aldehydes (+)-19 and (+)-3, respectively.

Pleasingly, there was a 1H and 13C NMR match between one of our synthetic derivatives and natural taumycin aldehyde [cf. (+)-3, Scheme 3]; this work has allowed us to confirm that the correct amino acid sequence is in the order L-isoleucine followed by D-isoleucine. Our findings also contradict the initial claim that a D-isoleucine residue is present within the taumycin family to be made. Unfortunately, however, in the absence of a known optical rotation value for 3, we are not able to definitively claim an absolute stereassignment.

In conclusion, the relative stereochemistry of the taumycin macrolide has been confirmed via the first total synthesis of taumycin aldehyde (longest linear sequence is 10 steps from crotonaldehyde, 21% overall yield). Key to the success of this work was a novel macrocyclization tactic initiated by the β-keto tert-butylester. Full documentation of additional taumycin aldehyde diastereomers, including the D-isoleucine series, and studies directed toward the syntheses of taumycins A and B are ongoing and will be reported in due course.

ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures as well as scans of 1H and 13C NMR spectra are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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