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Total Synthesis of (−)-Tirandamycin C

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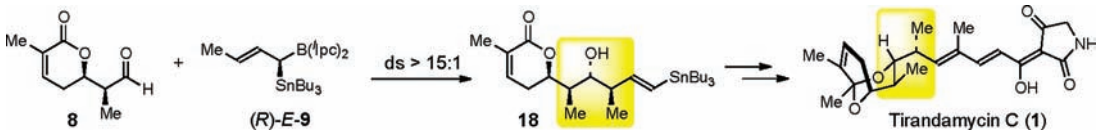
ABSTRACT



Tirandamycin C is a newly isolated member of the tetramic acid family natural products. We described herein the first enantioselective synthesis of natural (−)-tirandamycin C, the postulated biosynthetic precursor of other members of this family. The highly stereoselective (>15:1) mismatched double asymmetric γ-stannylcrotylboration reaction of aldehyde 8 with crotylborane reagent (*R*)-*E*-9 was utilized to access the key *anti,anti*-stereotriad 18.

The naturally occurring tetramic acids are a structurally diverse class of compounds that display a variety of biological activities, including *anti*-HIV-1, antimycotic, antibiotic, and antimicrobial activities.[1] Tirandamycins A (**3**) and B (**4**), two of the more well-known members of this family, were isolated from *Streptomyces* species in the 1970s (Figure 1).[2] Recently, two new tirandamycins, specifically tirandamycins C (**1**) and D (**2**), were isolated from the marine *Streptomyces sp.* 307−9 (Figure 1).[3] It was postulated that tirandamycin C is the biosynthetic precursor of other members of the family, which differ in the oxidation state of the bicyclic ketal moiety.[3] Recent studies identified the biosynthetic gene cluster for this family of natural products, including genes that encode candidate tailoring enzymes for elaboration of the bicyclic ketal system.[4] Because the dienoyl tetramic acid side chains of tirandamycins A−D are identical, the structural variations in the bicyclic unit are responsible for differences in their biological activities and especially for the activity of these compounds against vancomycin-resistant *Enterococcus faecalis*.[4,5]

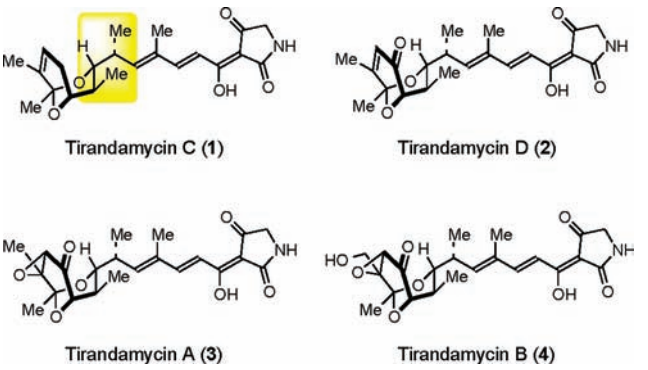


Figure 1. Tetramic acid containing natural products, tirandamycins A−D.

One synthetically challenging structural feature of the tirandamycins is the *anti,anti*-dipropionate stereotriad unit

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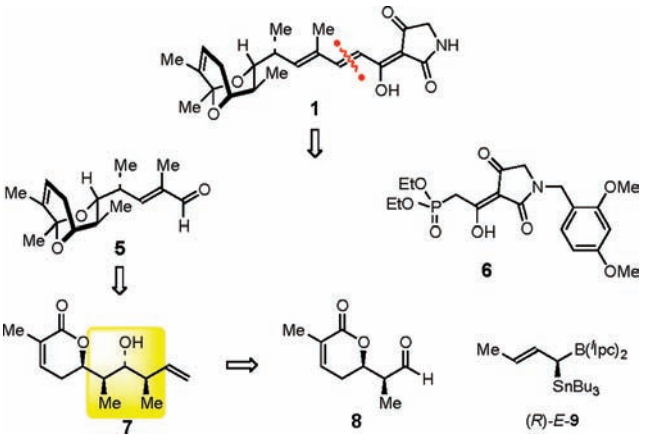
(highlighted in yellow in **1**). The highly stereoselective synthesis of this structural motif remains a significant challenge.[6] Many methods involving asymmetric aldol or crotylboration reactions of highly enantioenriched aldehyde substrates fail to provide synthetically useful selectivities for the desired *anti,anti*-stereotriads. Consequently, multistep, indirect methods have been employed to access this stereotriad unit.[7,8]

We recently disclosed the synthesis of the chiral crotylborylating reagent (*R*)-*E*-**9** via the enantioconvergent enantioselective hydroboration of racemic 1-tributylstannyl-1,2-butadiene (±)-**17**.[9] To demonstrate the potential of this reagent in the synthesis of stereochemically complex natural products and, equally, to gain further insight into the structure−activity relationships of the tirandamycins, we report herein the enantioselective synthesis of natural (−)-tirandamycin C (**1**) by a route featuring the highly stereoselective synthesis of the requisite *anti,anti*-stereotriad **7** via the mismatched double asymmetric γ-stannylcrotylboration of aldehyde **8** and reagent (*R*)-*E*-**9** (Scheme 1).[10]

Scheme 1. Tirandamycin C, Retrosynthetic Analysis



We envisioned that tirandamycin C (**1**) could be assembled from the bicyclic aldehyde **5** and the phosphonate reagent **6**[7c] via Horner−Wadsworth−Emmons olefination (Scheme 1). Aldehyde **5** would be accessed by elaboration of lactone **7**, which in turn would be obtained from the mismatched double asymmetric stannyl-crotylboration of aldehyde **8** with reagent (*R*)-*E*-**9**.[9]

Homoallylic alcohol **11** was synthesized in three steps according to known procedures, starting from the commercially available ester **10** (Scheme 2).[11] Acylation of homoallylic alcohol **11** with methacryloyl chloride (**12**) gave ester **13** in 86% yield. Ring closing metathesis of ester **13** using Grubbs' second generation catalyst **14** (10% catalyst loading) at 60 °C in the presence of 10% tetrafluoro-1,4-benzoquinone (TFBQ)[12] provided lactone **15** in 76% yield.[13] It is worth noting that without the addition of tetrafluoro-1,4-benzoquinone, significant amounts of a five-membered ring lactone product were obtained. Deprotection of the primary TBDPS ether of lactone **15** using TBAF (buffered with HOAc) gave alcohol **16** in near-quantitative yield. Subsequent oxidation of alcohol **16** with Dess−Martin periodinane[14] provided aldehyde **8** in 95% yield.

The mismatched double asymmetric crotylboration of aldehyde **8** was initiated by the synthesis of crotylborane (*R*)-*E*-**9** via the enantioconvergent hydroboration of racemic allenylstannane (±)-**17** with diisopinocampheylborane [(^{t}Ipc)$_2$BH] in diethyl ether, as previously described.[9] An Et_2O solution of aldehyde **8** was added to reagent (*R*)-*E*-**9** at −78 °C, and the solution was allowed to warm to ambient temperature and was stirred for 24 h. Gratifyingly, the desired *anti*,*anti*-stereotriad **18** was obtained with excellent stereoselectivity (> 15:1). This is a highly significant result, since the intrinsic diastereofacial selectivity of **8**, as determined by reactions with the achiral pinacol (*E*)-crotylboronate, favors production of the 3,4-*anti*-4,5-*syn* homoallylic alcohol by an 89:11 ratio (with the *anti, anti* stereoisomer **7** as the minor reaction product; see Supporting Information). In general, it is exceedingly difficult to overcome this level of intrinsic aldehyde face selectivity by using a chiral reagent.[6] Subsequent protodestannylation of vinylstannane **18** under acidic conditions (TsOH•H_2O)[15] gave lactone **7** in 72% yield (over two steps from aldehyde **8**). The stereochemistry of **7** was assigned as detailed in the Supporting Information.

Treatment of lactone **7** with MeLi (2 equiv)[16] at −78 °C provided the lactol intermediate **19**, which was used directly in the subsequent ketalization without purification. Exposure of lactol **19** to a catalytic amount of *p*PTS in

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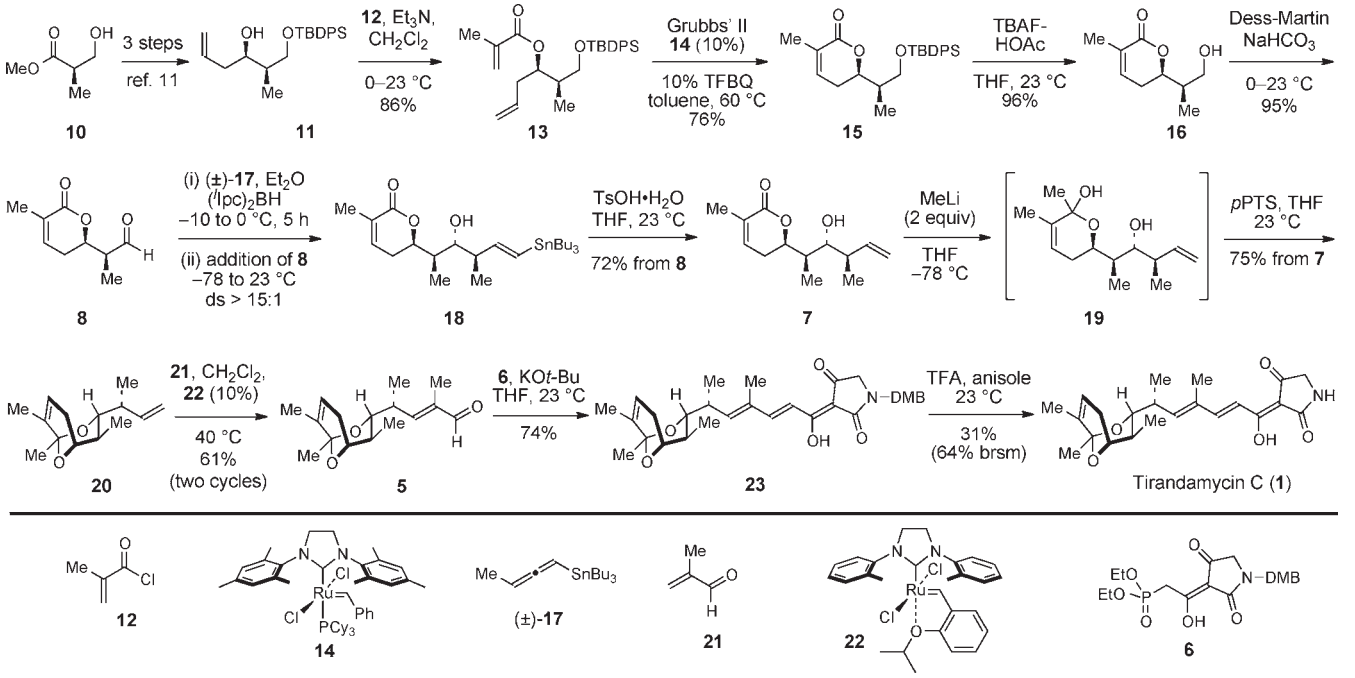
Scheme 2. Total Synthesis of (−)-Tirandamycin C (**1**)



THF provided bicyclic ketal **20** in 75% yield from alcohol **7**. Cross metathesis of bicyclic ketal **20** with methacrolein (**21**) using 10% Grubbs–Hoveyda catalyst **22**[17] in refluxing CH_2Cl_2 gave aldehyde **5** with excellent selectivity (> 20:1). Although the conversion of this cross metathesis reaction was moderate, recovered spiroketal **20** can be recycled. In this way, aldehyde **5** was obtained in 61% yield over two reaction cycles (93% based on recovered starting material). Treatment of phosphonate **6**[7c] with KO*t*-Bu in THF followed by addition of aldehyde **5** gave *N*-dimethoxybenzyl (DMB) protected tirandamycin C (**23**) in 74% yield. Finally, deprotection of **23** by treatment with TFA[7] provided synthetic (−)-tirandamycin C (**1**) in 31% yield (64% based on recovered starting material). The spectroscopic data (^{1}H NMR, ^{13}C NMR, $[\alpha]_D$) of synthetic (−)-tirandamycin C were in excellent agreement with the data previously reported for the natural product.[3]

In summary, the enantioselective total synthesis of natural (−)-tirandamycin C has been accomplished in 14 steps starting from ester **10**. Most importantly, the mismatched double asymmetric γ-stannylcrotylboration of aldehyde **8** with crotylborane reagent (*R*)-*E*-**9** proceeded with excellent selectivity (> 15:1) to give the requisite *anti*, *anti*-stereotriad **18**. Application of this methodology to the synthesis of other members of tirandamycin family will be reported in due course.

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Supporting Information Available. Experimental procedures and spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org