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Total Synthesis of (−)-Tirandamycin C

Ming Chen and William R. Roush*

Department of Chemistry, Scripps Florida, Jupiter, Florida 33458, United States

roush@scripps.edu

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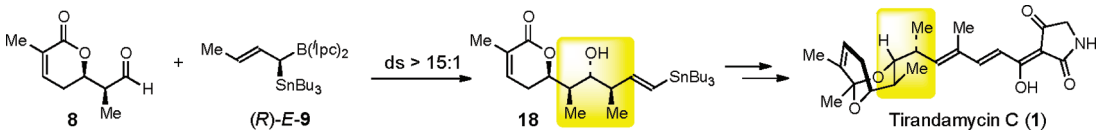
ABSTRACT



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]

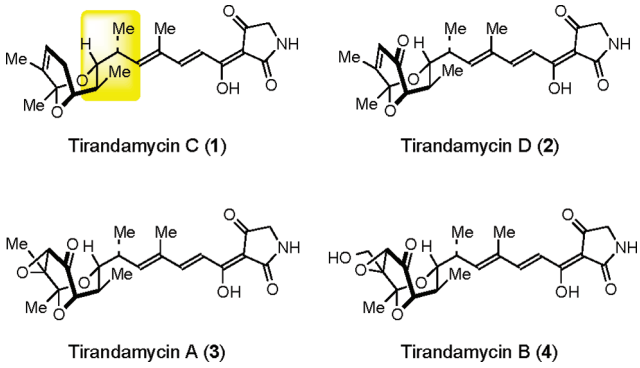


Figure 1. Tetramic acid containing natural products, tirandamycins A−D.

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

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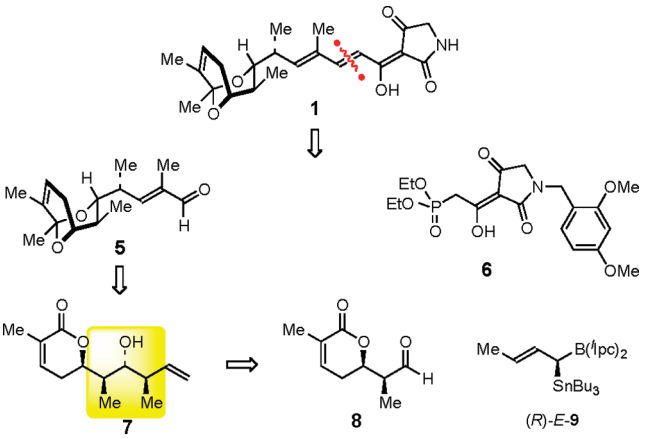
(highlighted in yellow in **1**). The highly stereoselective synthesis of this structural motif remains a significant challenge.[6] Many methods involving asymmetric aldol or crotylboration reactions of highly enantioenriched aldehyde substrates fail to provide synthetically useful selectivities for 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 [(^{i}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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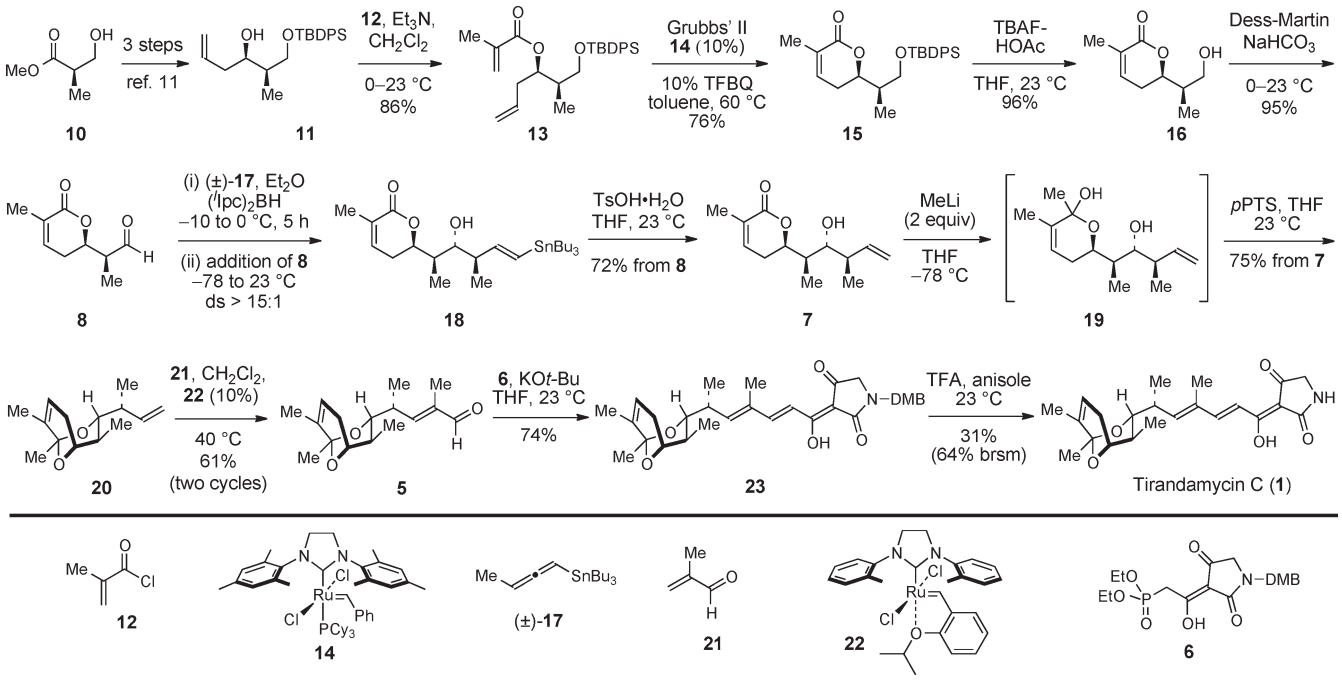
Scheme 2. Total Synthesis of (−)-Tirandamycin C (**1**)



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