Natural Products Synthesis

Tetramic Acid Antibiotics: Stereoselective Synthesis of Streptolic Acid and Tirandalydigin**

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The tetramic acid family of antibiotics have unique chemical structures composed of the 2,6-dioxabicyclononane skeleton and the characteristic dienoyl tetramic acid moiety. They exhibit potent antimicrobial activities and inhibitory activity against bacterial DNA-directed RNA polymerase.[1] The distinctive structural features and potent pharmacological properties render this family of antibiotics worthy targets for synthetic exploration.[2] In the tetramic acid antibiotics, two types of 2,6-dioxabicyclononane structures are known. One is the oxabicyclononane structure with an epoxy ketone moiety, as represented by tirandamycin A and B,[3] and the other is that involving a vinyl epoxide moiety, such as that in streptolydigin (**1**)[4] and tirandalydigin (**2**).[5] Tirandamycin A and B, with the chemically stable 2,6-dioxabicyclononane structure, have been extensively studied and their total syntheses have already established by several groups,[2] whereas synthetic studies of streptolydigin (**1**) and tirandalydigin (**2**), both of which bear the chemically labile vinyl epoxide moiety, are quite few. Indeed, the only synthesis of streptolic acid (**3**), the degradation product from **1** and **2** and the most potent member of the small family of 3-acyltetramic acid antibiotics, has been reported by Ireland and Smith.[2f]

We report herein a new synthetic methodology for streptolydigin (**1**) and tirandalydigin (**2**) that culminates in the first synthesis of the latter antibiotic, as well as a highly stereoselective synthesis of streptolic acid (**3**). Synthetic challenges posed by **1** and **2** include construction of the stereochemically dense 2,6-dioxabicyclononane skeleton, including the extremely acid-labile vinyl epoxide moiety, and synthesis of the distinctive tetramic acid structures. In particular, stereoselective synthesis of the common 2,6-dioxabicyclononane system and construction of the vinyl epoxide moiety are key challenges in the synthesis, since the generally used acid-catalyzed intramolecular acetalization of keto diol precursors has been known not to be effective in the synthesis of the tetramic acid antibiotics.[2d,h]

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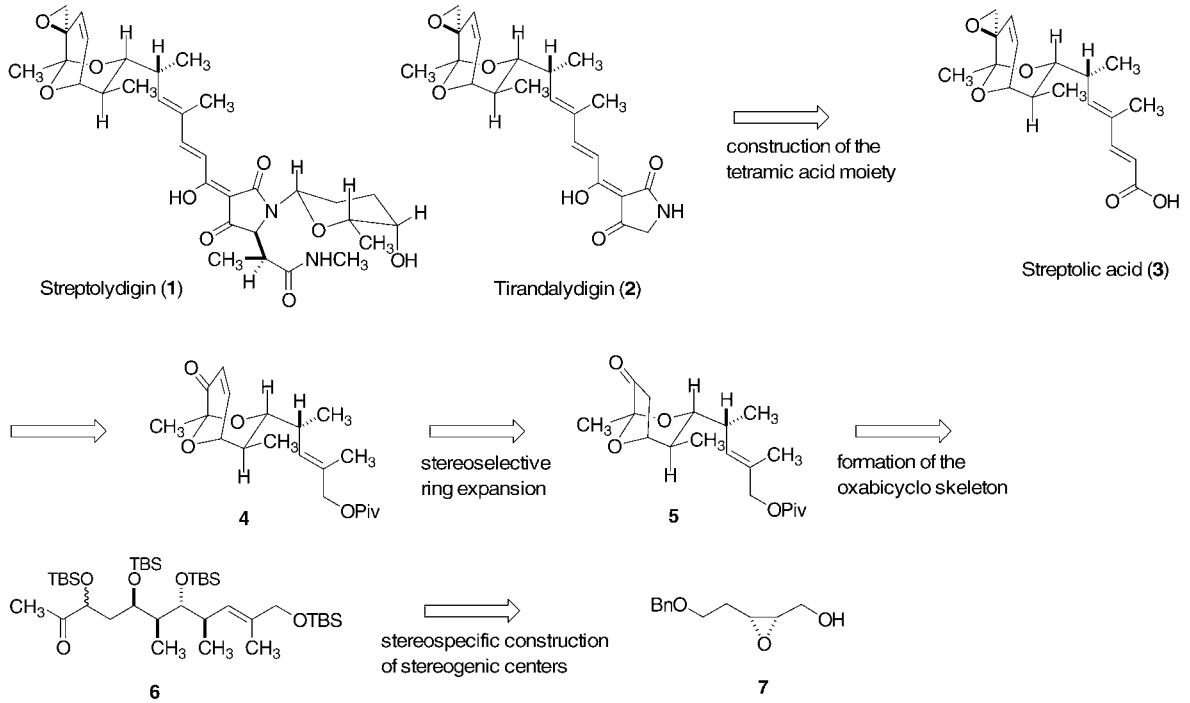
To overcome these difficulties, we designed the synthetic strategy as shown in Scheme 1. This strategy involves a key 2,6-dioxabicyclononen-7-one intermediate **4** that would be derived from a synthetically more accessible dioxabicyclooctanone **5** by a stereoselective ring expansion. We anticipated that the critical intermediate **5** could be efficiently constructed by the acid-catalyzed intramolecular acetalization of the precursor **6**.

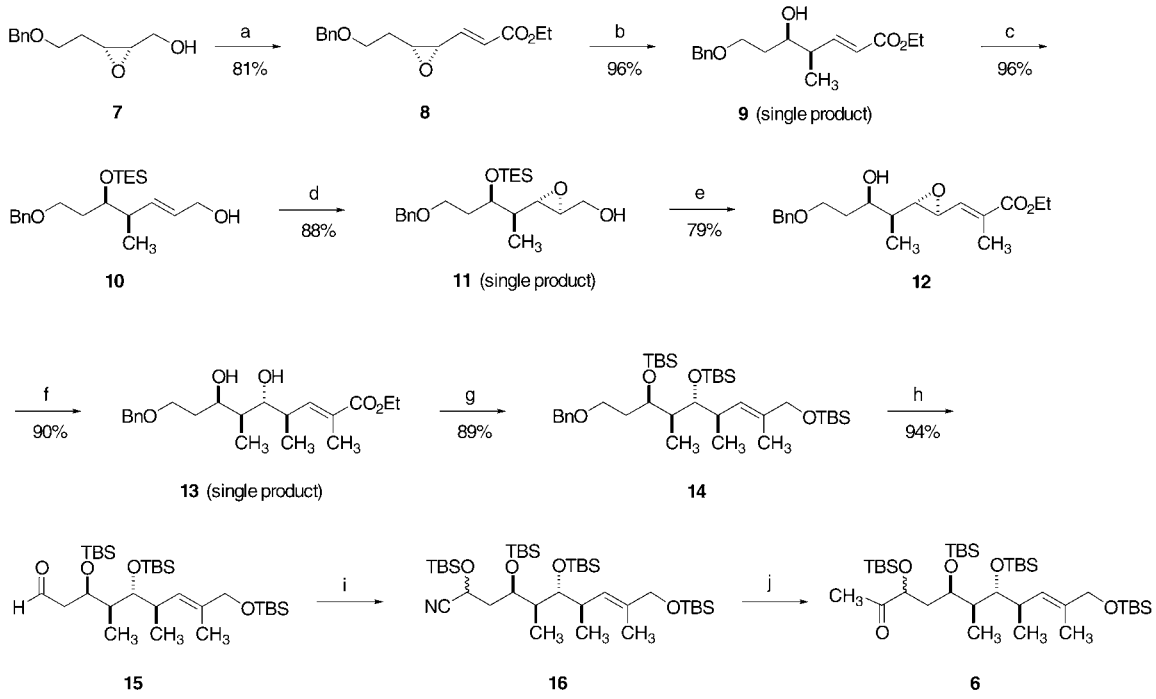
Our first objective focused on the stereoselective synthesis of the key precursor **5** for construction of the 2,6-dioxabicyclononane skeleton. At first, the requisite acyclic compound **6** with four contiguous stereogenic centers was synthesized from the known chiral compound **7** in a highly stereoselective manner according to the method shown in Scheme 2. Thus, the epoxy alcohol **7** was converted into epoxy unsaturated ester **8** in 81% yield by a Swern oxidation followed by a Horner–Wadsworth–Emmons reaction. The crucial methylation reaction of **8** occurred stereospecifically with a Me_3Al/water system developed in our laboratory[6] to give rise to a single product, **9**, in 96% yield. Protection of the hydroxy group in **9** with TESCl and subsequent reduction of the ester with DIBAL-H in THF furnished allyl alcohol **10** in high yield. When **10** was treated with *m*CPBA in CH_2Cl_2, the single α-epoxy alcohol **11** was obtained as expected in 88% yield.[7] The epoxy alcohol **11** was then transformed into epoxy unsaturated ester **12** by a three-step reaction sequence involving oxidation with PDC in $ClCH_2CH_2Cl$ to form the corresponding aldehyde, followed by a Wittig reaction in a one-pot operation, and then removal of the TES group with TBAF in THF (79% yield over three steps). The next key methylation reaction of **12** also proceeded stereospecifically upon treatment with a Me_3Al/water system,[6] to give rise to a single product, **13**, in 90% yield. Thus, fragment **13** with four contiguous stereogenic centers was synthesized in a straightforward and highly stereoselective manner by our original strategy and methodology.

Compound **13** was readily transformed into **14** in three steps: 1) protection of the secondary hydroxy groups with TBSOTf, 2) reduction of the ester with DIBAL-H, and 3) protection of the primary alcohol with TBSCl (89% yield over three steps). When **14** was treated with LDBB in THF and then with Dess–Martin periodinane in the presence of pyridine in CH_2Cl_2, the desired aldehyde **15** was obtained in 94% yield. The crucial acyclic precursor **6** was successfully derived from aldehyde **15** by treatment with TBSCN and ZnI_2,[8] which led to cyanohydrin **16**, followed by an addition of MeLi to the nitrile group in THF. The product **6** was a diastereomeric mixture with respect to the configuration of the silyloxy group.

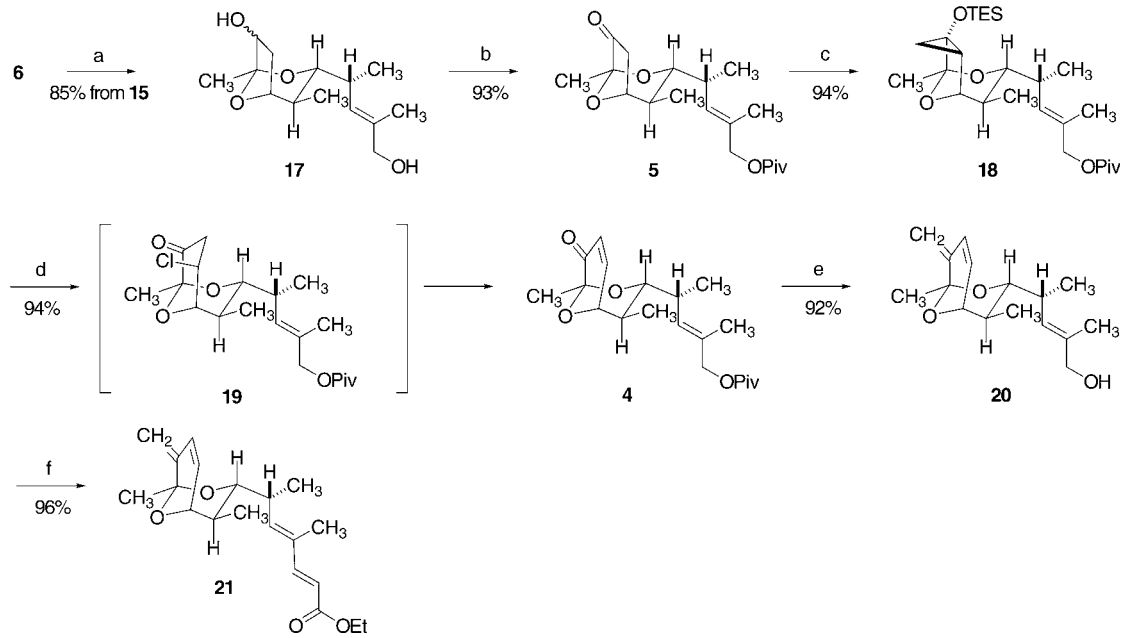
The acid-catalyzed intramolecular acetalization of **6** to form the crucial 2,6-dioxabicylooctane skeleton proceeded very efficiently as we expected (Scheme 3). Thus, when **6** was treated with aqueous HF in CH_3CN at room temperature, the intramolecular acetalization occurred smoothly and cleanly, to give rise to **17** in 85% overall yield from **15**. After protection of the primary alcohol in **17** as a pivalate moiety, oxidation of the secondary alcohol with Dess–Martin periodinane furnished the desired 2,6-dioxabicyclooctanone **5** in 93% yield. With the critical precursor in hand, we next focused on the ring expansion of **5** to form the dioxabicyclononane skeleton **4**, the key step in the present synthesis. The key transformation was efficiently and highly stereoselectively performed by using the Ito–Saegusa method,[9] which involves the following three-step reaction sequence: 1) preparation of the silyl enol ether by treatment of **5** with KHMDS and TESCl, 2) cyclopropanation with Et_2Zn and CH_2I_2 to form **18**, and 3) subsequent treatment of **18** with $FeCl_3$ (88% yield over three steps). Thus, the targeted 2,6-dioxabicyclo-



Scheme 1. Retrosynthetic analysis of streptolic acid (**3**) and tirandalydigin (**2**). Piv = pivaloyl, TBS = *tert*-butyldimethylsilyl, Bn = benzyl.



Scheme 2. Highly stereoselective synthesis of the acyclic precursor **6**. Reagents and conditions: a) 1. Swern oxidation; 2. $(EtO)_2P(O)CH_2CO_2Et$, NaH, THF, 0 °C, 81 % (2 steps); b) Me_3Al, D_2O, CH_2Cl_2, −30→−10 °C, 96 %; c) 1. TESCl, imidazole, DMAP, CH_2Cl_2, room temperature; 2. DIBAL-H, THF, 0 °C, 96 % (2 steps); d) *m*CPBA, CH_2Cl_2, 0 °C, 88 %; e) 1. PDC, MS4A, $ClCH_2CH_2Cl$, 60 °C, then $Ph_3P{=}C(CH_3)CO_2Et$, 0 °C, 79 %; 2. TBAF, THF, 0 °C, 100 %; f) Me_3Al, D_2O, CH_2Cl_2, −30→−10 °C, 90 %; g) 1. TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 93 %; 2. DIBAL-H, THF, 0 °C, 98 %; 3) TBSCl, imidazole, DMAP, CH_2Cl_2, 0 °C, 98 %; h) 1. LDBB, THF, −78→−45 °C, 99 %; 2. Dess–Martin periodinane, pyridine, CH_2Cl_2, room temperature, 95 %; i) TBSCN, ZnI_2, room temperature; j) MeLi, THF, −78 °C, then aq. HCl. THF = tetrahydrofuran, TES = triethylsilyl, DMAP = 4-(dimethylamino)pyridine, DIBAL-H = diisobutylaluminum hydride, *m*CPBA = 3-chloroperoxybenzoic acid, PDC = pyridinium dichromate, MS4A = molecular sieves (4 Å), $ClCH_2CH_2Cl$ = dichloroethane, TBAF = tetrabutylammonium fluoride, OTf = trifluoromethanesulfonate, LDBB = lithium di-*tert*-butylbiphenylide.

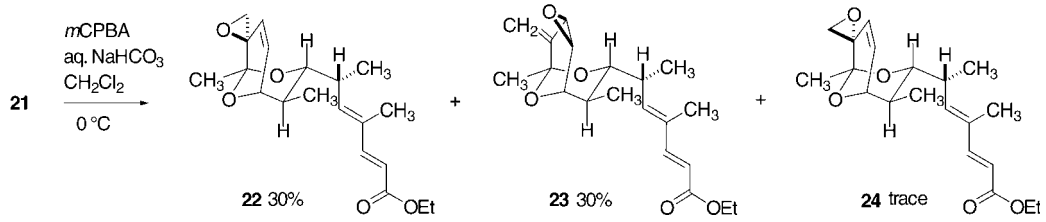


Scheme 3. Stereoselective ring expansion leading to the key dioxabicyclo compound, **4**. Reagents and conditions: a) aq. HF, CH_3CN, room temperature, 85 % from **15**; b) 1. PivCl, pyridine, CH_2Cl_2, 0 °C; 2. Dess–Martin periodinane, H_2O, pyridine, CH_2Cl_2, room temperature, 93 % (2 steps); c) 1. KHMDS, TESCl, THF, −78 °C; 2. Et_2Zn, CH_2I_2, Et_2O, reflux, 94 % (2 steps); d) 1. $FeCl_3$, pyridine, DMF, 100 °C, 94 %; e) 1. Bu_3SnCH_2Li, THF, −78 °C, then MeLi; 2. aq. HF, CH_3CN, room temperature, 92 % (2 steps); f) 1. MnO_2, CH_2Cl_2, room temperature; 2. $(EtO)_2P(O)CH_2CO_2Et$, NaH, THF, room temperature, 96 % (2 steps). Piv = pivaloyl, KHMDS = potassium hexamethyldisilazide, DMF = *N*,*N*-dimethylformamide, Bu_3SnCH_2Li = (tributylstannyl)methyllithium.

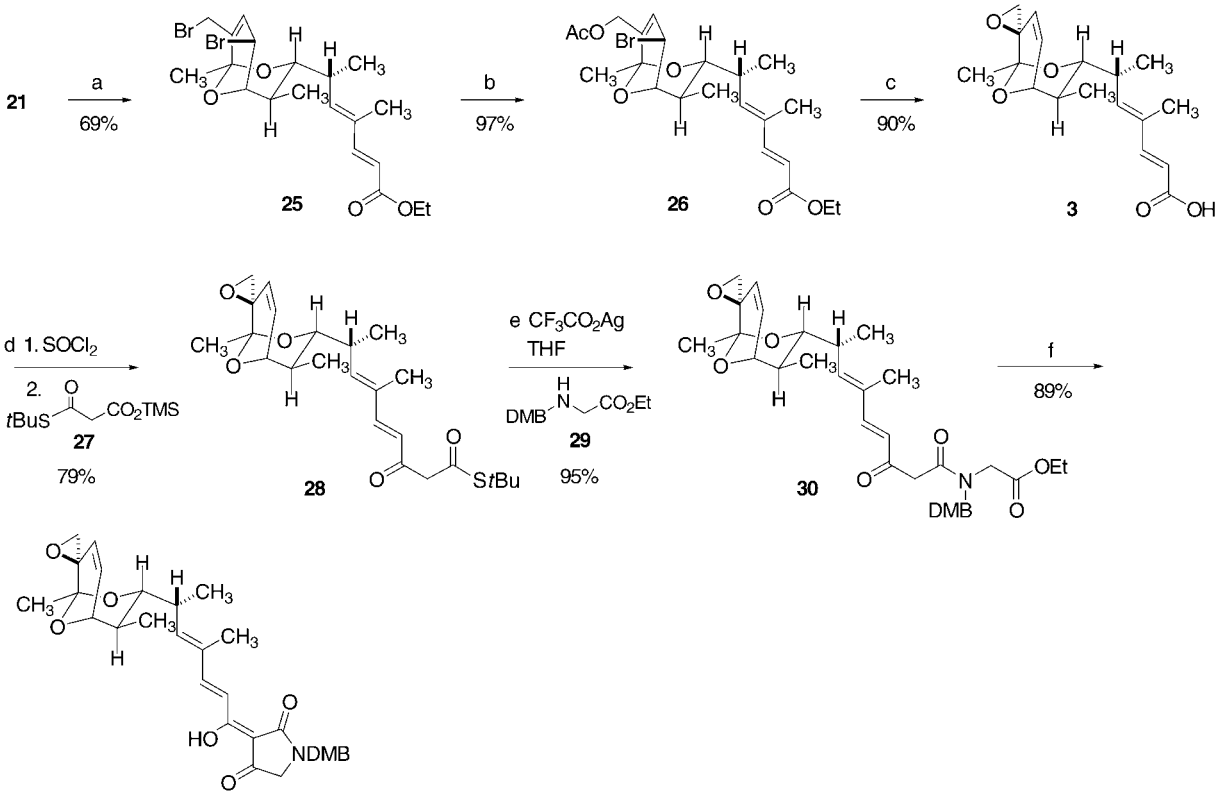
nonane skeleton **4** could be highly efficiently and stereoselectively secured by the ring-expansion strategy. The next task was introduction of the vinyl epoxide moiety. For this purpose, the enone **4** was initially transformed into diene **20** in three steps: 1) treatment with (tributylstannyl)methyllithium[10] in THF, 2) then treatment with MeLi to remove the pivaloyl group, and 3) formation of the *exo* methylene group by treatment with HF in CH_3CN (92% over three steps). Compound **20** was routinely converted into **21** in 96% yield by MnO_2 oxidation followed by a Horner–Wadsworth–Emmons reaction. Notably, every step depicted in Scheme 3 proceeded with excellent (more than 90%) yields.

We had reached a critical stage in the total synthesis of streptolic acid (**3**) and tirandalydigin (**2**), that is, the stereoselective epoxidation of the exo double bond and installation of the tetramic acid moiety. To this end, we examined direct epoxidation of **21** to form **22**; however, as shown in Scheme 4, the epoxidation of **21** with *m*CPBA only formed the desired streptolic acid ethyl ester (**22**) in low yield.

To overcome this difficulty and to secure the synthesis of **22**, we designed the synthetic route shown in Scheme 5. Thus, upon treatment of **21** with Bu_4NBr_3 and 2,6-lutidine in $ClCH_2CH_2Cl$, allyl dibromide **25** was produced stereoselectively in 69% yield; this compound was then transformed into acetate **26** by treatment with CsOAc in DMF in 97% yield. When compound **26** was treated with K_2CO_3 in MeOH and then with NaH in THF, streptolic acid ethyl ester (**22**) was formed almost quantitatively. Subsequent hydrolysis of **22** with aqueous NaOH in MeOH furnished streptolic acid (**3**) in 92% yield. The product was identical to natural streptolic acid in all respects, including melting point (m.p. = 163–164 °C; literature value: m.p. = 168–169 °C[2f]), specific rotation ($[\alpha]_D^{24} = +139°$ ($c = 1.18$, 95% EtOH); literature value:



Scheme 4. Unsuccessful epoxidation of **21** with *m*CPBA.



N-2,4-Dimethoxybenzyl tirandalydigin (**31**)

Scheme 5. Synthesis of streptolic acid (**3**) and *N*-2,4-dimethoxybenzyl tirandalydigin (**31**). Reagents and conditions: a) Bu_4NBr_3, 2,6-lutidine, $ClCH_2CH_2Cl$, room temperature, 69%; b) CsOAc, DMF, room temperature, 97%; c) 1. K_2CO_3, MeOH, 0 °C; 2. NaH, THF, room temperature, 98% (2 steps); 3. aq. NaOH, MeOH, room temperature, 92%; d) 1. $SOCl_2$, 2,6-lutidine, CH_2Cl_2, room temperature; 2. NaH, **27**, THF, room temperature, 79% (2 steps); e) **29**, CF_3CO_2Ag, Et_3N, MS4A, THF, room temperature, 95%; f) TBAF, THF, room temperature, 89%. DMB = 2,4-dimethoxybenzyl, Bu_4NBr_3 = tetrabutylammonium tribromide, CsOAc = cesium acetate.

$[\alpha]_D^{22} = +138°$ ($c = 0.55$, 95% EtOH)[2f]), and ^1H and ^{13}C NMR, IR, and mass spectra.[2f]

The crucial construction of the tetramic acid moiety for the total synthesis of tirandalydigin was performed by employing the protocol of Ley et al.[11] Thus, initially, streptolic acid (**3**) was converted into keto thiolester **28** in two steps: 1) treatment with $SOCl_2$ leading to the acid chloride and 2) condensation of the acid chloride with **27** by the use of NaH in THF (79% for two steps). Upon treatment of **28** with *N*-2,4-dimethoxybenzyl glycine ethyl ester (**29**), Et_3N, and silver trifluoroacetate in THF, the desired product **30** was obtained in 95% yield; this product was then treated with TBAF in THF to afford the target compound, *N*-2,4-dimethoxybenzyl tirandalydigin (**31**), in 89% yield.[12] The synthesis of **31** was unambiguously confirmed by its spectral data, including the ^1H and ^{13}C NMR, IR, and mass spectra. The total yield of **31** was 9.8% (an average of 94% yield for each step) in 37 steps from the starting material **7**.

In summary, we have developed a new and promising synthetic methodology for the synthesis of the tetramic acid family of antibiotics and have completed the first synthesis of *N*-2,4-dimethoxybenzyl tirandalydigin (**31**), as well as the synthesis of streptolic acid (**3**), in a highly stereoselective manner.

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[12] Although removal of the *N*-2,4-dimethoxybenzyl group in **31**, leading to tirandalydigin (**2**), was examined under various conditions, this transformation has not been successful so far because of the susceptibility of the vinyl epoxide moiety to acidic conditions. We will discuss the removal of the protective group in detail in a full paper.

