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Highly Stereoselective and Modular Syntheses of 10-Hydroxytrilobacin and Three Diastereomers via Stereodivergent [3 + 2]-Annulation Reactions

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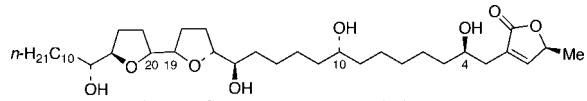
ABSTRACT



(19*R*, 20*S*) : 10-hydroxytrilobacin (**4a**)
(19*S*, 20*S*) : 4,10-dihydroxysquamocin-N (**4b**)
(19*R*, 20*R*) : 10-hydroxyasimicin (**4c**)
(19*S*, 20*R*) : an unnatural acetogenin (**4d**)

A convergent synthesis of the annonaceous acetogenin, 10-hydroxytrilobacin (4a), was accomplished by using the [3 + 2]-annulation reaction of tetrahydrofuranyl carboxaldehyde 2a and allylsilane 3. The stereodivergency of the [3 + 2]-annulation reaction made it possible to achieve modular, highly stereoselective syntheses of three 10-hydroxytrilobacin diastereomers from the same precursors by using simple modifications of reaction conditions.

The annonaceous acetogenins are fatty acid derived natural products isolated from *Annonaceae* species (custard apple).[1] As of 2005, more than 400 acetogenins had been reported.[1a] The acetogenins are characterized by their ability to inhibit mitochondria complex I of the mammalian and insect mitochondrial electron transport system.[1a]

Among the numerous natural acetogenins, the stereochemically diverse group of adjacent bis-THF acetogenins (especially those with hydroxyl groups flanking both ends of the bis-THF unit) have attracted the attention of many synthetic laboratories[2] because of their significant biological activity against various human cancer cell lines.[1b]

While it has been stated in a review that the stereochemistry of the bis-THF core is not as important as the number of THF units and the number of hydroxyl groups in determining the biological potency of the various acetogenins,[1b] it is readily apparent from comparison of the activity of diastereomeric bis-THF acetogenins that the stereochemistry of the bis-THF unit contributes substantially to their biological profiles. For example, the LC_{50}'s for bullatacin and asimicin (which differ at a single stereocenter) against MCF-7 are $<10^{-12}$ μg/mL and 8.5×10^{-1} μg/mL, respectively.[3] However, the factors that govern the relationship of acetogenin stereochemistry to biological activity are unknown at present. Thus, generation of all possible diastereomers of the bis-THF acetogenins would enable this question to be addressed. Development of a modular and stereochemically general synthesis of adjacent bis-THF acetogenins amenable to SAR studies remains a major

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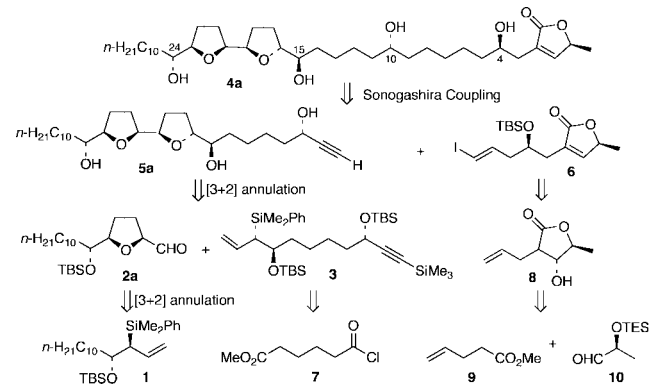
challenge.[4] Current approaches to the synthesis of libraries of bis-THF acetogenin analogues require use of multiple complex starting materials[5] or additional steps to install flanking hydroxyl groups after establishment of the bis-THF core.[6]

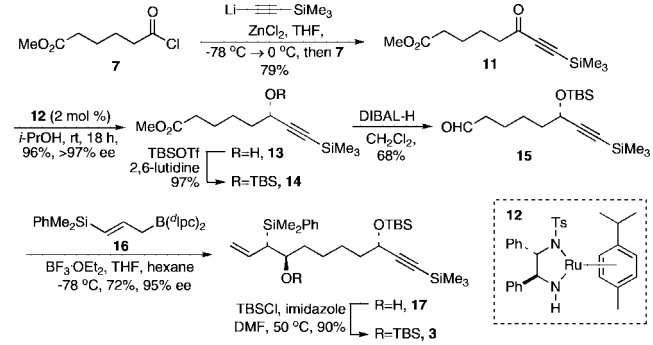
Preliminary studies in our laboratory demonstrated the potential for use of the [3 + 2]-annulation reaction[7] for synthesis of adjacent bis-THF acetogenin analogues.[8] The stereochemistry of the two THF rings is set by using either a nonchelate (BF_3•OEt_2 catalyzed) or a chelate controlled ($SnCl_4$ catalyzed) [3 + 2]-annulation reaction of a chiral allylsilane with the appropriate aldehyde coupling partner. Although we previously reported syntheses of asimicin and bullatacin using the [3 + 2]-annulation reaction,[2a,b] these syntheses were too linear and correspondingly lengthy. This prevented us from using these routes to capitalize on the implicit stereodivergency of the [3 + 2]-annulation reaction for generation of stereochemically diverse bis-THF acetogenin analogues. Therefore, we have developed and report herein a convergent, highly stereoselective and stereodivergent synthesis of four representative adjacent bis-THF acetogenins using [3 + 2]-annulation reactions of chiral, nonracemic β-alkoxy allylsilanes **1** and **3**.

We targeted the synthesis of 10-hydroxytrilobacin[3] (**4a**), a natural acetogenin with a *cis*/*erythro*/*trans* bis-THF core unit which displays high cytotoxicity toward two human cancer cell lines, A-549 ($LC_{50} = 1.0 \times 10^{-8}$ μg/mL) and MCF-7 ($LC_{50} = 1.9 \times 10^{-8}$ μg/mL).[3] We anticipated 10-hydroxytrilobacin (**4a**) could be generated by Sonogashira coupling[9] of the bis-THF alkyne fragment **5a** and the butenolide-containing vinyl iodide **6** (Scheme 1). The bis-THF unit of **5a** would be accessed by a nonchelate-controlled [3 + 2]-annulation of *cis*-THF aldehyde **2a** and allylsilane **3**. On the basis of earlier studies, it was anticipated that this [3 + 2]-annulation would be stereochemically mismatched[8] and therefore synthetically challenging. The *cis*-THF aldehyde **2a** would be derived from allylsilane **1** by a nonchelate-controlled [3 + 2]-annulation.[7c] The allylsilane subunit of **3** would be introduced by using an asymmetric γ-silylallylboration reaction,[10] whereas the chiral propargyl alcohol center of **3** would be generated by transfer hydrogenation of a propargyl ketone precursor.[11] We anticipated that the butenolide **6** could be obtained from the β-hydroxy-γ-lactone **8**, which in turn would be assembled via the aldol reaction of ester **9** and aldehyde **10**.

Scheme 1. Retrosynthetic Analysis of 10-Hydroxytrilobacin (**4a**)



Scheme 2. Synthesis of the Allylsilane Fragment **3**



The synthesis of allylsilane **3** began with nucleophilic addition of trimethylsilylethynyl lithium to methyl adipoyl chloride (**7**),[12] followed by a Noyori asymmetric transfer hydrogenation using chiral catalyst **12**[13] which provided propargyl alcohol **13** with 97% ee and 76% yield for two steps (Scheme 2). After protection of **13** as the TBS ether (97%), the ester unit of **14** was reduced by treatment with DIBAL-H to yield aldehyde **15** (68%). Asymmetric allylation of **15** with γ-silylallylborane **16**[10] and then protection of the new hydroxyl group as a TBS ether afforded **3** in 65% yield for the two steps, and with 95% ee.

The synthesis of the butenolide fragment **6** was initiated by *B*-iododicyclohexylborane-mediated aldol reaction[14] of ester **9** and chiral aldehyde **10**,[15] followed by lactonization triggered by treatment of the aldol mixture with HF (Scheme 3). Lactone **8** was obtained as the major component of a mixture of diastereomers (4.7:1, ratio of **8** to the sum of three

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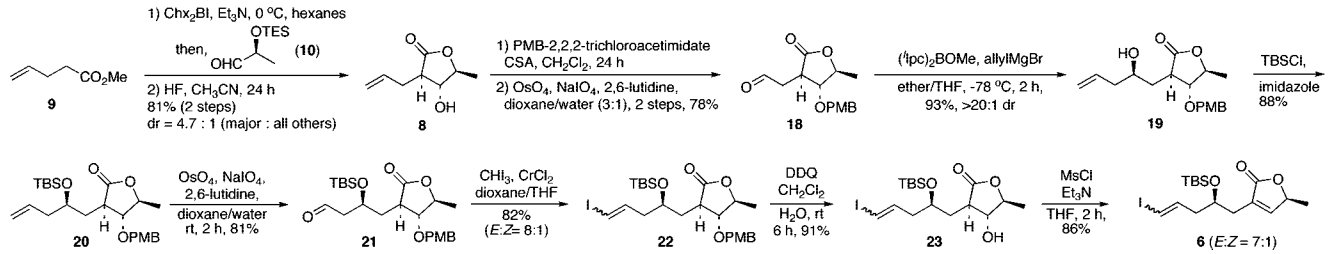
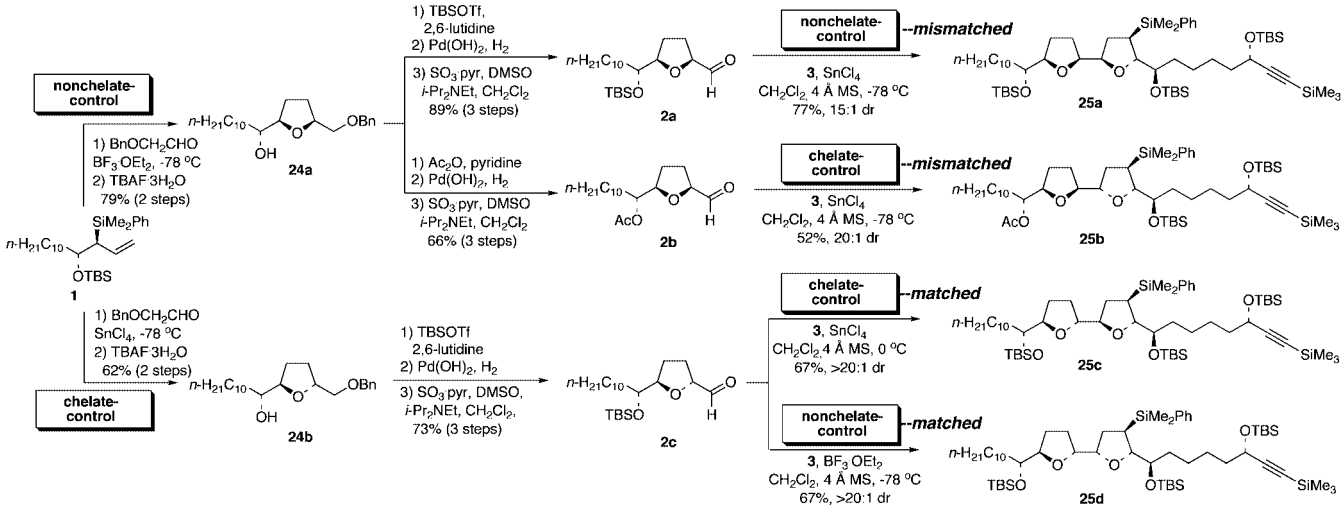
Scheme 3. Synthesis of Vinyl Iodide Fragment **6**



Scheme 4. Stereodivergent Syntheses of Bis-THF Fragments **25a**−**d**



minor isomers, 81% combined yield). The β-hydroxyl group of **8** was protected as a *p*-methoxybenzyl ether (PMB) by using *p*-methoxylbenzyl 2,2,2-trichloroacetimidate and catalytic CSA.[16] One-pot oxidative cleavage[17] of the terminal vinyl group then afforded aldehyde **18** in 78% yield for the two steps. Asymmetric allylation[18] of **18** provided allylation product **19** with >20:1 ds (93% yield). Homoallylic alcohol **19** was then protected as a TBS ether, and the terminal vinyl group was subsequently oxidatively cleaved[17] to furnish aldehyde **21** (81% yield). The vinyl iodide was then installed under modified Takai alkenylation conditions,[19] and the PMB ether was removed using DDQ to give alcohol **23** (74% for two steps). Finally, β-elimination of the hydroxyl group of **23** by treatment with MsCl and Et_3N afforded butenolide fragment **6** (86%).[20]

The bis-THF fragment **25a**, needed for synthesis of 10-hydroxytrilobacin, was synthesized as summarized in Scheme 4. *Cis*-THF aldehyde **2a** was obtained from allylsilane **1** via a known five-step sequence.[8] The stereochemically mismatched[8] [3 + 2]-annulation reaction of **2a** and allylsilane **3** mediated by $SnCl_4$ provided *cis*/*erythro*/*trans* bis-THF **25a** in 77% yield and with 15:1 diastereoselectivity. It was previously determined that the bulky TBS ether side chain in *cis*-THF aldehyde **2a** prevents the chelation with $SnCl_4$ in the stereochemically mismatched [3 + 2]-annulation reaction of **2a** with chiral, nonracemic allylsilanes homochirally related to **3**.[8]

We synthesized the three additional bis-THF diastereomers by simple modification of the conditions for the two [3 + 2]-annulation reactions summarized in Scheme 4. Use of an acetyl protecting group in **2b** allows chelation of **2b** and $SnCl_4$ in the stereochemically mismatched double asymmetric [3 + 2]-annulation reaction with allylsilane **3**,[8] from which the *cis*/*threo*/*cis* bis-THF **25b** was obtained in 52% yield and with 20:1 diastereoselectivity.

Allylsilane **1** was also used in the modular synthesis of *trans*-THF **24b** by the chelate-controlled [3 + 2]-annulation with α-benzyloxyacetaldehyde, followed by protiodesilyla-

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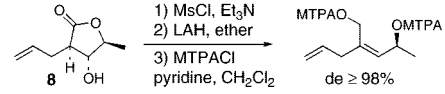
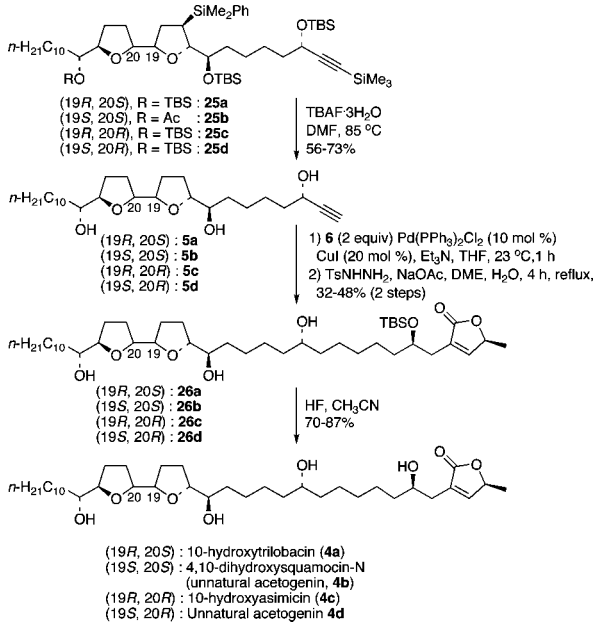
(20) The dehydration of **8** by treatment with MsCl and Et_3N was studied to determine if epimerization of the butenolide occurs under the mildly basic elimination conditions. As shown below, the dehydration of **8** via mesylate elimination proceeds without detectable racemization.



Scheme 5. Synthesis of 10-Hydroxytrilobacin and Three Diastereomeric Acetogenins



tion.[21] Further elaboration of *trans*-THF **24b** to aldehyde **2c** followed by stereochemically matched double asymmetric [3 + 2]-annulation reactions with **3** led to the *trans*/*threo*/*trans* (**25c**) and the *trans*/*erythro*/*cis* (**25d**) bistetrahydrofurans via $SnCl_4$-mediated chelate-controlled and $BF_3{\cdot}OEt_2$-mediated nonchelate-controlled annulations, respectively, both with >20:1 dr.

With four diastereomeric bis-THF fragments (**25a**−**d**) in hand, their conversion to natural and unnatural acetogenins **4a**−**d** was completed (Scheme 5). First, bis-THF **25a**, the precursor to 10-hydroxytrilobacin, was subjected to protiodesilylation conditions (TBAF, DMF, 80−85 °C).[21] These conditions effected removal of the *C*-phenyldimethylsilyl group as well as the three TBS ethers and the alkynyl silane and gave alkyne **5a** in 64% yield. Sonogashira coupling[9] of alkyne **5a** and butenolide **6**[22] was followed by enyne reduction using a large excess of $TsNHNH_2$ and NaOAc.[23] Finally, removal of the TBS ether of **26a** by treatment with HF provided 10-hydroxy-trilobacin (**4a**). The enantiomeric purity of the butenolide unit of **4a** was determined to be ≥98% ee by NMR analysis on the bis-Mosher ester species derived from the 2′,4-diol obtained by protection of **4a** as the tetra-TBS ether followed by $LiAlH_4$ reduction.[24] The spectroscopic properties of synthetic 10-hydroxytrilobacin, as well as of the tetra-Mosher esters prepared from **4a**, were in complete agreement with literature values.[3] The longest linear sequence of this synthesis of 10-hydroxytrilobacin was 13 steps, originating from commercially available methyl-4-pentenoate (**9**).

The diastereomeric bis-THF fragments **25b**−**d** were subjected to the same synthetic sequence as described for **25a**, leading to the successful synthesis of three analogues of 10-hydroxytrilobacin: unnatural 4,10-dihydroxysquamocin-*N* (**4b**),[25] 10-hydroxyasimicin (**4c**),[3] and the unnatural acetogenin **4d**. Spectroscopic properties for **4c** were in excellent agreement with literature values.[3] Results of biological evaluation of these compounds will be reported elsewhere.

In conclusion, we have developed a convergent and highly stereoselective synthesis of 10-hydroxytrilobacin (**4a**). By utilizing nonchelate- and chelate-controlled [3 + 2]-annulation reaction conditions, we also achieved the modular synthesis of three diastereomers of 10-hydroxytrilobacin from the same precursors **1**, **3**, and **6**. We anticipate that this strategy for synthesis of adjacent bis-THF acetogenins can be expanded to include use of the enantiomer **1**, both enantiomers of the *syn* diastereomer of **1**,[26] and allylsilane diastereomers of **3**. This chemistry has the potential to provide a stereochemically diverse library of bis-THF acetogenins. Studies along these lines 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.

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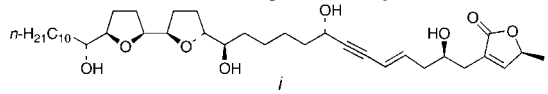
(22) Our original plan was to deprotect the C(4)-OTBS ether of **6** prior to the Sonogashira reaction with **5a**. This sequence provided ***i*** uneventfully (55% yield). However, reduction of the enyne unit of ***i*** provided 10-hydroxytrilobacin contaminated with an inseparable impurity. This problem required that we use the TBS ether protected vinyl iodide **6** in Scheme 5.



i

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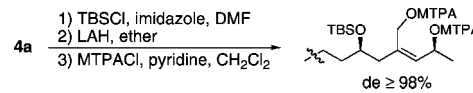

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