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Synthesis of (+)-Bullatacin via the Highly Diastereoselective [3+2] Annulation Reaction of a Racemic Aldehyde and a Nonracemic Allylsilane

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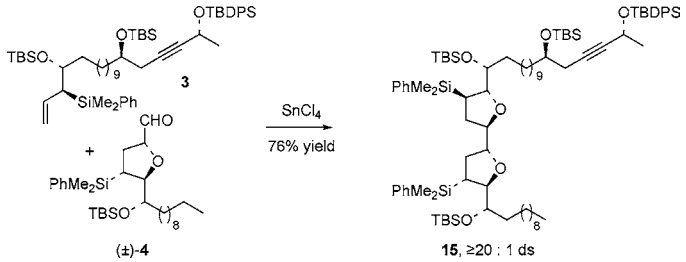
ABSTRACT



A total synthesis of (+)-bullatacin has been accomplished via a diastereoselective [3+2] annulation reaction of the highly enantiomerically enriched allylsilane 3 and racemic aldehyde 4, which provides the key bis-tetrahydrofuran fragment 15 with ≥20:1 ds.

(+)-Bullatacin (**1**) is one of more than 350 Annonaceous acetogenins isolated from the tropical plant family Annonaceae (Figure 1). Many members of this structurally diverse family of natural products exhibit impressive antitumor activity in human tumor cell lines.[1] The acetogenins contain a long aliphatic backbone bearing a terminal butenolide unit and one or more tetrahydrofuran rings and hydroxyl groups at internal positions of the aliphatic chain. These compounds are intriguing synthetic targets owing to the variation of stereochemistry around the tetrahydrofuran rings and at the sites bearing additional hydroxyl groups.[2,3]

The [3+2] annulation reaction of aldehydes and chiral allylsilanes is an important method for the stereocontrolled synthesis of substituted tetrahydrofurans.[4,5] β-Silyloxy-substituted allylsilanes undergo [3+2] annulation reactions with aldehydes and certain electrophilic ketones to give either 2,5-*trans* or 2,5-*cis* substituted tetrahydrofurans with excellent selectivity, depending on the use of chelating or nonchelating Lewis acids, respectively.[6] We have recently utilized this methodology in a highly stereoselective total synthesis of asimicin (**2**).[7]

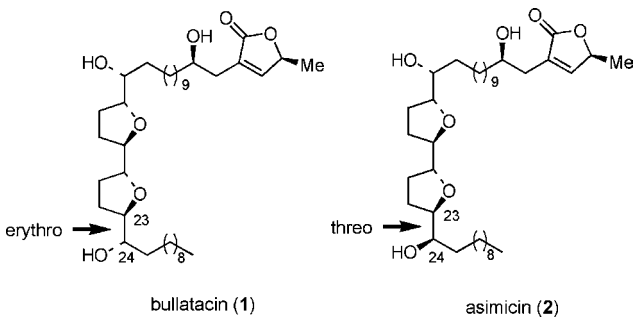


Figure 1. Structures of bullatacin and asimicin.

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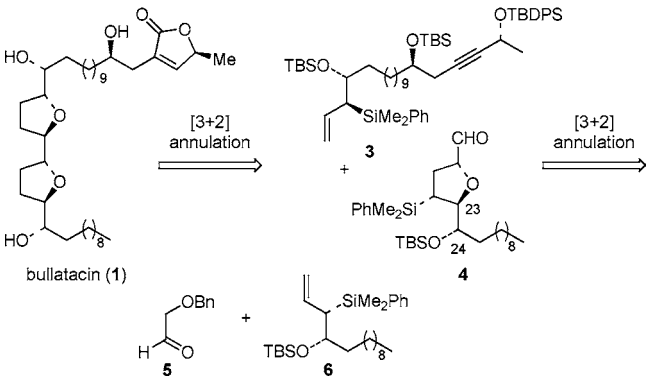
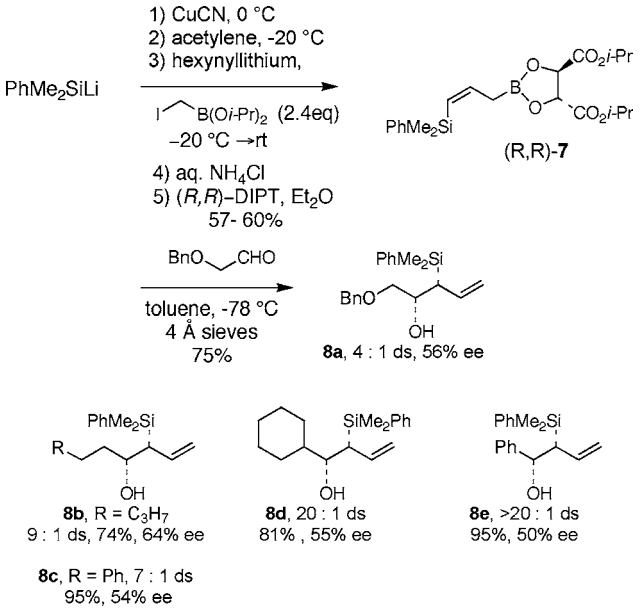


Figure 2. Retrosynthetic analysis of bullatacin.

As part of ongoing studies focusing on the development of a stereochemically general synthesis of members of the acetogenin family, we have developed and report herein a highly stereoselective synthesis of bullatacin (**1**),[8] which differs from asimicin (**2**) at a single stereocenter (C-24). We envisaged that the bis-tetrahydrofuran core unit of bullatacin could be synthesized from sequential chelate-controlled [3+2] annulation reactions of allylsilanes **3** and **6** (Figure 2). The proposed [3+2] annulation of **3** and **4** is expected to be a stereochemically matched double asymmetric reaction under chelate-controlled conditions, by analogy with the corresponding reaction in our asimicin synthesis that proceeded with ≥20:1 ds.[7]

The *erythro* stereochemistry of C(23)−C(24) of aldehyde **4** requires that a *syn*-*β*-silyloxy allylsilane **6** be used in a chelate-controlled [3+2] annulation reaction with α-benzyloxy acetaldehyde (**5**). Initial attempts to develop an enantioselective synthesis of *syn*-*β*-silyloxy allylsilanes related to **6** focused on asymmetric allylboration reactions using (*Z*)-*γ*-dimethylphenylsilyallylboronate **7** (Scheme 1). Thus, si-

Scheme 1. Synthesis of *syn*-*β*-Hydroxyallylsilanes via Asymmetric Allylboration



lylcupration[9] of acetylene, addition of the intermediate vinylcopper species to diisopropyl iodomethylboronate,[10] hydrolysis of the crude alkylation product, and then esterification of the intermediate allylic boronic acid with diisopropyl (*R*,*R*)-tartrate provided (*R*,*R*)-**7** in 57−60% yield. This reagent underwent the expected[11] *syn*-selective allylboration reaction of achiral aldehydes in 74−95% yield. However, the *syn*-*β*-hydroxyallylsilanes **8** were obtained with only 50−64% ee. Because the synthesis of **7** proved difficult to scale-up, alternative strategies for synthesis of the targeted allylsilanes was pursued.

A more convenient route to (racemic) *syn*-*β*-hydroxyallylsilanes **8** involves the *γ*-silylallylstannation of aldehydes using *γ*-(dimethylphenylsilyl)allylstannane **9**.[12] Treatment of cyclohexanecarboxaldehyde with **9** at −78 °C in CH_2Cl_2 in the presence of $BF_3{\cdot}OEt_2$ provided **8d** in 51% yield, along

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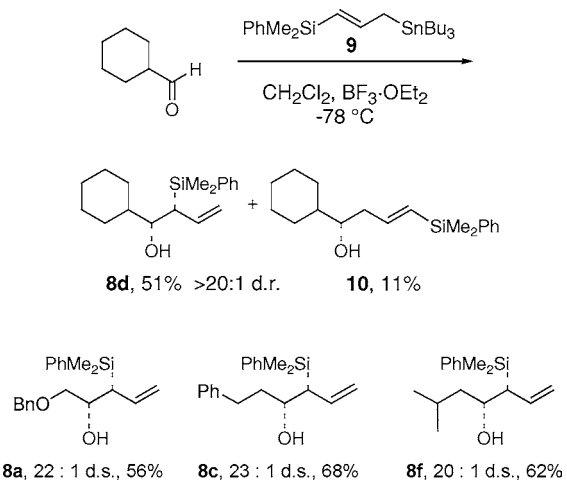
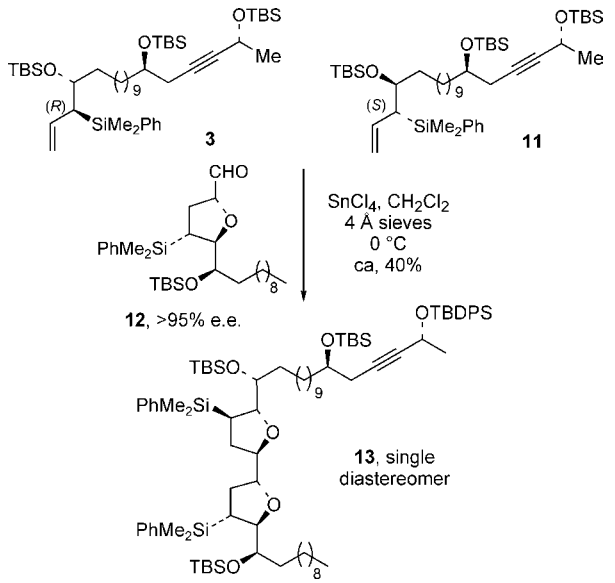
Scheme 2. Synthesis of Racemic *syn*-β-Hydroxyallylsilanes via γ-Silylallylstannation



with 11% of homoallylic alcohol **10**. The latter compound presumably arises from a secondary reaction of **8d** with cyclohexanecarboxaldehyde via an oxonia-Cope process.[13] Production of the vinylsilane byproducts can be minimized by using an excess of **9** (tyically 2 equiv) in the allylstannation reaction, and by maintaining the reaction temperature at −78 °C. This method consistently provides the targeted (racemic) *syn*-β-hydroxyallylsilanes **8** in 51−68% yield with ≥20:1 ds (Scheme 2). Efforts to accomplish these reactions by using a chiral Lewis acid catalyst are in progress.

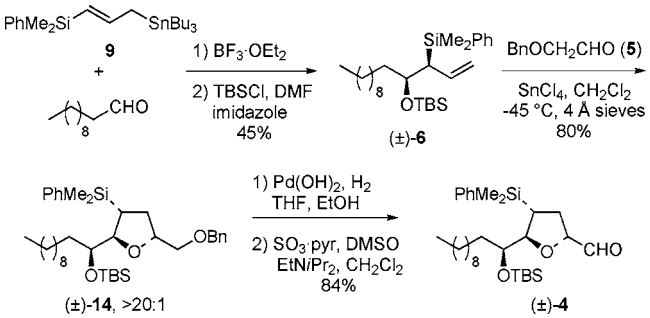
Scheme 3. Kinetic Diastereomer Resolution in the Asimicin Synthesis



We decided to pursue a kinetic resolution strategy in the bullatacin synthesis based on observations made in our asimicin synthesis.[7,14] Specifically, initial batches of allylsilane **3** were prepared that contained significant amounts of the diastereomer **11** (Scheme 3). When these mixtures were subjected to the [3+2] annulation reaction with *trans*-tetrahydrofuran aldehyde **12** (>95% ee), only one diastereomeric bis-tetrahydrofuran **13** was obtained. This result implied that the reaction of the (*R*)-allylsilane **3** with **12** is stereochemically matched and that the reaction of these two components is substantially faster and/or chemically more efficient than the mismatched reaction of the diastereomeric (*S*)-allylsilane **11** with **12**.[15] This conclusion is supported by studies in our laboratory on double asymmetric reactions of chiral tetrahydrofuran aldehydes and chiral allylsilanes.[16]

The synthesis of bullatacin commenced with the synthesis of racemic tetrahydrofuran carboxaldehyde **4** (Scheme 4).

Scheme 4. Synthesis of *Erythro* (±)-Tetrahydrofuryl Carboxaldehyde **4**



Allylsilane **6** was readily prepared from the $BF_3{\cdot}OEt_2$ catalyzed reaction of silylallylstannane **9** and undecanal, followed by protection of the resulting secondary alcohol as a TBS ether.[17] The chelate controlled [3+2] annulation reaction of allylsilane (±)-**6** and α-benzyloxy acetaldehyde (**5**) in the presence of $SnCl_4$ at −45 °C afforded the 2,5-*trans* tetrahydrofuran (±)-**14** in 80% yield and ≥20:1 diastereoselectivity. Hydrogenolysis of the benzyl ether using $Pd(OH)_2$ and subsequent oxidation of the alcohol with SO_3-pyridine and DMSO provided (±)-**4**.[18]

Treatment of highly enantiomerically enriched allylsilane **3**[7] with 1 equiv of racemic aldehyde **4** in the presence of $SnCl_4$ (1 equiv) at 0 °C provided the bis-tetrahydrofuran **15** as a single diastereomer in 25% yield (Scheme 5).[19] When 2 equiv of the aldehyde were used in the annulation reaction, the yield of **15** increased to 50%, and a 76% yield was obtained when 3 equiv of (±)-**4** was employed. In each case, bis-tetrahydrofuran **15** was obtained as a single diastereomer.

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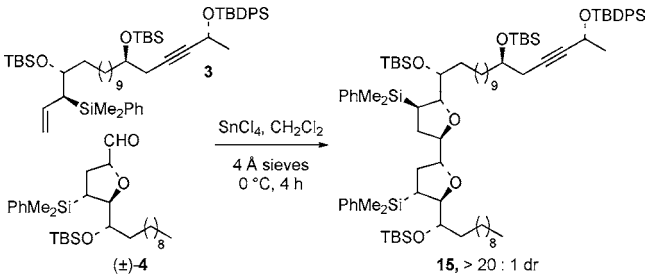
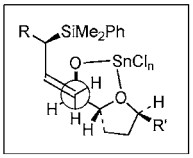
(19) Aldehyde **4** recovered from this reaction was reduced with $NaBH_4$ to give the corresponding primary alcohol. Moster ester analysis of this intermediate indicated that the recovered **4** had an enantiomeric purity of ca. 20% ee.

Scheme 5. Kinetic Resolution in the [3+2] Annulation Reaction of **3** and (±)-**4**

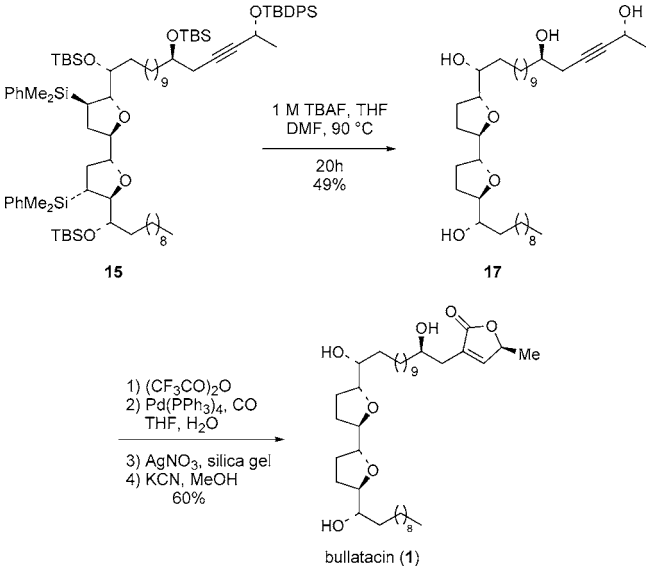




16, *syn-synclinal Transition State*

equiv of **4**	yield of **15** (%)
1	25
2	50
3	76

Scheme 6. Completion of the Total Synthesis of Bullatacin



The high selectivity of this reaction is attributed to the matched facial selectivity of the chiral allylsilane and the (*2R*,*4R*,*5S*)-enantiomer of the $SnCl_4$-chelated chiral aldehyde in the favored *syn*-synclinal transition state **16**.[6,16,20]

Woerpel and co-workers have previously described a kinetic resolution in a double asymmetric [3+2] annulation reaction of a racemic allylsilane and a chiral auxiliary-bearing α-keto ester to prepare highly substituted tetrahydrofurans as single enantiomers.[21] Our methodology is complementary in that it takes advantage of the stereochemistry inherent in the annulation substrates. In principle, our approach may be expanded to other reaction partners.

Protiodesilylation of the bis-tetrahydrofuran **15** was accomplished by treatment with TBAF in a 1:1 mixture of THF and DMF at 90 °C;[22] this provided tetraol **17** in 49% yield (Scheme 6). The butenolide ring was then installed by using a procedure developed by Marshall and co-workers.[7,23] Thus, per-trifluoroacetylation of **17** followed by Pd(0)-catalyzed hydroxycarbonylation and Ag(I)-promoted cyclization of the intermediate allenyl carboxylic acid gave the tris-trifluoroacetate ester of bullatacin. Deprotection of the three trifluoroacetates by treatment of the tri-ester with KCN in MeOH then provided synthetic (+)-bullatacin (**1**) in 60% yield for this four-step sequence. The spectroscopic properties of synthetic (+)-bullatacin were in excellent agreement with literature data (see the Supporting Information).

In summary, the total synthesis of (+)-bullatacin has been accomplished via a highly diastereoselective [3+2] annulation reaction of allylsilane **3** and racemic aldehyde **4** in the kinetic resolution manifold. Applications of the [3+2] annulation sequence to the synthesis of other members of the Annonaceous acetogenin family will be reported in due course.

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

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