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Total Synthesis of (−)-Bucidarasin A Starting from an Original Chiral Building Block

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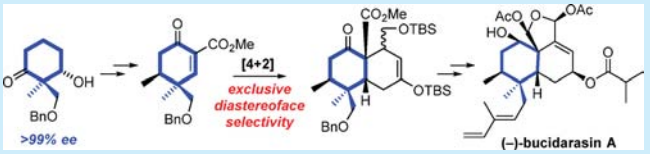
Supporting Information

ABSTRACT: The highly stereoselective total synthesis of (−)-bucidarasin A, which also elucidated the absolute structure of its natural form, is described. The total synthesis features effective use of the original chiral building block prepared by us and a series of highly stereoselective reactions, i.e., hydroxy-directed hydrogenation, [4 + 2] cycloaddition of a sterically hindered dienophile, reduction of ketones, formation of the C9 side-chain diene, and formation of the THF moiety bearing two acetyloxy groups.



Bucidarasins A−D (Figure 1), isolated from a crude extract of *Bucida-buceras*,[1] belong to clerodane diterpene, a large family that consists of *cis*- and *trans*-fused members in addition to *ent*-members.[2] Clerodane diterpenes possess the characteristic scaffold shown in Figure 1, and bucidarasins A−C feature

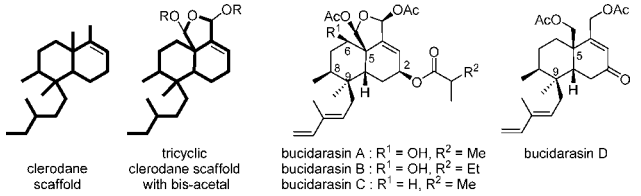


Figure 1. Structures of clerodane and tricyclic clerodane scaffolds, and (−)-bucidarasins A−D.

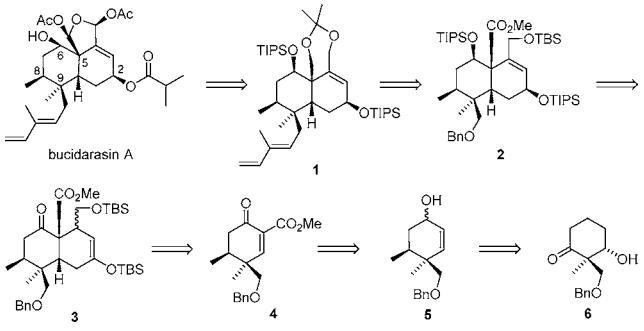
the tricyclic scaffold composed of *cis*-dehydrodecalin fused with a tetrahydrofuran (THF) ring bearing two acetyloxy groups at the C18 and C19 positions. The tricyclic scaffold contains up to eight stereogenic centers, six of which are contiguous and include two all-carbon quaternary stereogenic centers. A series of similar tricyclic *cis*-clerodane diterpenes has been isolated chiefly from the tropical genus Casearia,[3,4] and many compounds have been shown to exhibit a wide range of bioactivities[1,3a,f,h,l−u,w−y,4a,b,e,h,i,k−p] including cytotoxicity.[1,3a,f,h,n−r,t,u,w−y,4a,b,e,h,i,k−p] Specifically, recent studies revealed that some members of this subfamily showed apoptotic activity[5] and synergistic effects with TRAIL (tumor necrosis factor-α-related apoptosis-inducing ligand), leading to cell death.[4m]

Bucidarasins A−C show potent and wide spectrum activity as inhibitors of human tumor cell replication. The IC_{50} values range from 0.5 to 1.9 μM against nine human tumor cell lines, and the potency is retained in drug resistant lines. Interestingly, bucidarasin D is biologically inactive, suggesting that the acetal moiety is essential for cytotoxic activity.[1]

The potent bioactivity and complex structure make bucidarasins A−C and related compounds attractive synthetic targets, but the total synthesis of these fascinating compounds has not yet been reported though a number of clerodane diterpenes have been synthesized.[6] Hence, in pursuit of the development of a chemical approach toward bucidarasins and related compounds to elucidate their structure−activity relationships as well as their modes of action, we began synthetic studies regarding bucidarasins. Herein, we report the total synthesis and structure elucidation of (−)-bucidarasin A.

Scheme 1 shows the retrosynthetic analysis of bucidarasin A. The bis-hemiacylal in the THF ring moiety has been reported to

Scheme 1. Retrosynthetic Analysis of (−)-Bucidarasin A



be unstable under acidic conditions and readily degrade to form the corresponding dialdehyde.[4e,o] Hence, we chose to form this moiety during the final stage of the synthesis, and compound **1** was set as the advanced intermediate, which was to be prepared from compound **2**, with the side chain scheduled to be introduced during the late stage of the synthesis. The *cis*-

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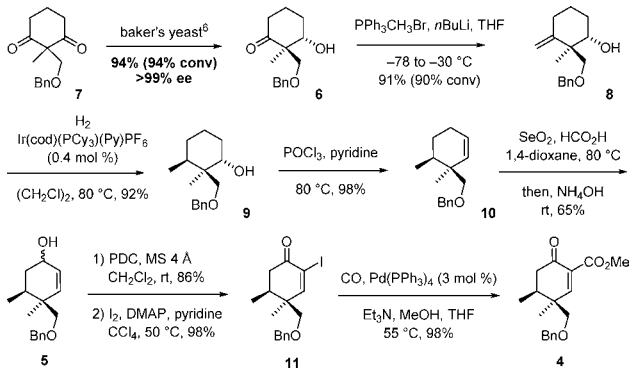
dehydrodecaline scaffold in **2** could be formed by a [4 + 2] cycloaddition because [4 + 2] cycloadditions of α-alkylidene β-keto esters have been reported to afford cycloadducts with an all-carbon quaternary center in high yields.[7] Hence, we planned to obtain **2** from **3**, which could be prepared by the [4 + 2] cycloaddition of **4**, which would be obtained from **5** via oxidation and introduction of a methyl ester.

We reported the highly enantio- and stereoselective preparation of chiral building block **6** (94% (94% conv), >99% ee, Scheme 2) by the baker's yeast reduction of **7**,[8] which

Scheme 2. Preparation of 4



was easily obtained from commercially available methyl 2,6-dimethoxybenzoate. Compound **6** was suitable for the preparation of **5** because it possesses an all-carbon quaternary stereogenic center, which could become the C9 stereogenic center of bucidarasin A. Consequently, we began the total synthesis of bucidarasin A from compound **6**.

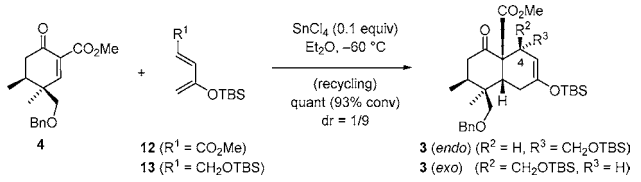
The formation of the C8 tertiary stereogenic center in compound **9** was envisioned to proceed through the hydroxy-directed hydrogenation of compound **8**. Hence, the conversion of compound **6** to **8** was first examined. The Wittig reaction of **6** with methylidene triphenylphosphorane at −30 °C successfully proceeded without epimerization which was induced by the retro-aldol reaction. The hydrogenation of **8** using Crabtree's catalyst[9] at 80 °C afforded compound **9** as a sole product in 92% yield. Dehydration of **9** with $POCl_3$ required heating, but afforded **10** in 98% yield.

Next, we examined the allylic oxidation[10] of **10** and found that the use of SeO_2 with formic acid in 1,4-dioxane[11] gave the best results. PDC oxidation of the resultant allylic alcohol **5** generated the corresponding ketone, followed by iodination to afford compound **11**. The Pd-catalyzed methoxycarbonylation of **11** using $Pd(OAc)_2$, dppp (diphenylphosphinopropane), and 2,6-lutidine under an atmosphere of carbon monoxide[12] was sluggish and irreproducible. However, the use of a catalytic amount of $Pd(PPh_3)_4$ and triethylamine solved this problem and improved the yield to 98%.

The [4 + 2] cycloaddition of **4** and diene **12**[13] (Scheme 3) was first examined because the expected product would possess two esters which could be converted simultaneously. However, the reaction of **4** and **12** did not take place with heat or in the presence of a Lewis acid. Moreover, the reaction with a Lewis acid at elevated temperature caused decomposition of **4**.

To suppress the aforementioned decomposition, a more reactive diene **13**[13] was employed. After surveying various reaction conditions, the [4 + 2] cycloaddition in the presence of a catalytic amount of $SnCl_4$ (0.1 equiv) in Et_2O at −60 °C afforded compound **3** in a stereoselective manner. However, a

Scheme 3. [4 + 2] Cycloaddition of 4



certain amount (ca. 20%) of both **4** and **13** remained unreacted. Hence, a mixture of starting materials and products, which was obtained after workup, was treated again with $SnCl_4$ (0.1 equiv) in Et_2O at −60 °C to afford an inseparable mixture of diastereomers (quant (93% conv), dr = 1/9).[14]

As described below, the major product of **3** was found to be the *exo*-adduct and the minor product was the *endo*-adduct, both of which were formed by the reaction at the *Re*-face of **4**. Generally, the *endo*-adduct is favorable in [4 + 2] cycloadditions because secondary orbital interactions stabilize the transition state. However, the *exo*-adduct was favored in the [4 + 2] cycloaddition of **4**, because sterically hindered **4** destabilized the *endo*-mode transition state.

Although **4** is sterically hindered owing to the C9 all-carbon quaternary center, the two electron-withdrawing groups, the keto and ester groups, activate the alkene to afford products in high yields. The energetically favorable transition state of the [4 + 2] cycloaddition would be derived from the half-chair-like conformer **4a** (Figure 2), in which two methyl groups are

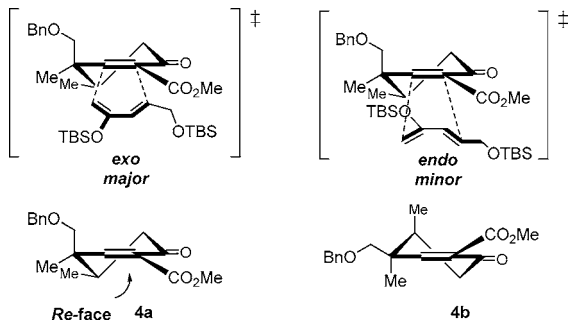


Figure 2. Proposed transition state models.

pseudoequatorial and the benzyloxymethyl group is pseudoaxial. Thus, the reaction at the less-hindered *Re*-face of **4** would be favorable and would lead to the exclusive formation of the desired products. Other transition states derived from the half-chair-like conformer **4b**, which includes two pseudoaxial methyl groups and the pseudoequatrial benzyloxymethyl group, would be energetically unfavorable because both alkene faces are sterically hindered by the axial methyl groups.

Reduction of the products **3** in the [4 + 2] cycloaddition with DIBAL-H in CH_2Cl_2 at −78 °C proceeded stereoselectively (dr = 1/0 (β-OH/α-OH) for **3** (*endo*), dr = 4/1 (β-OH/α-OH) for **3** (*exo*)) (Scheme 4).[15] The configuration of all the products was confirmed by NOESY studies. The products with the β-C6 hydroxy (76%)[15] in the DIBAL-H reduction were treated with DDQ[16] to afford enone **14** in 85% yield. The reduction of the C2 ketone in **14** afforded only the undesired isomer probably because the reaction occurred at the less hindered convex face. However, the inversion using DIAD and chloroacetic acid afforded the desired product. Hydrolysis of the resulting chloroacetate, and subsequent formation of TIPS ethers afforded compound **2**.

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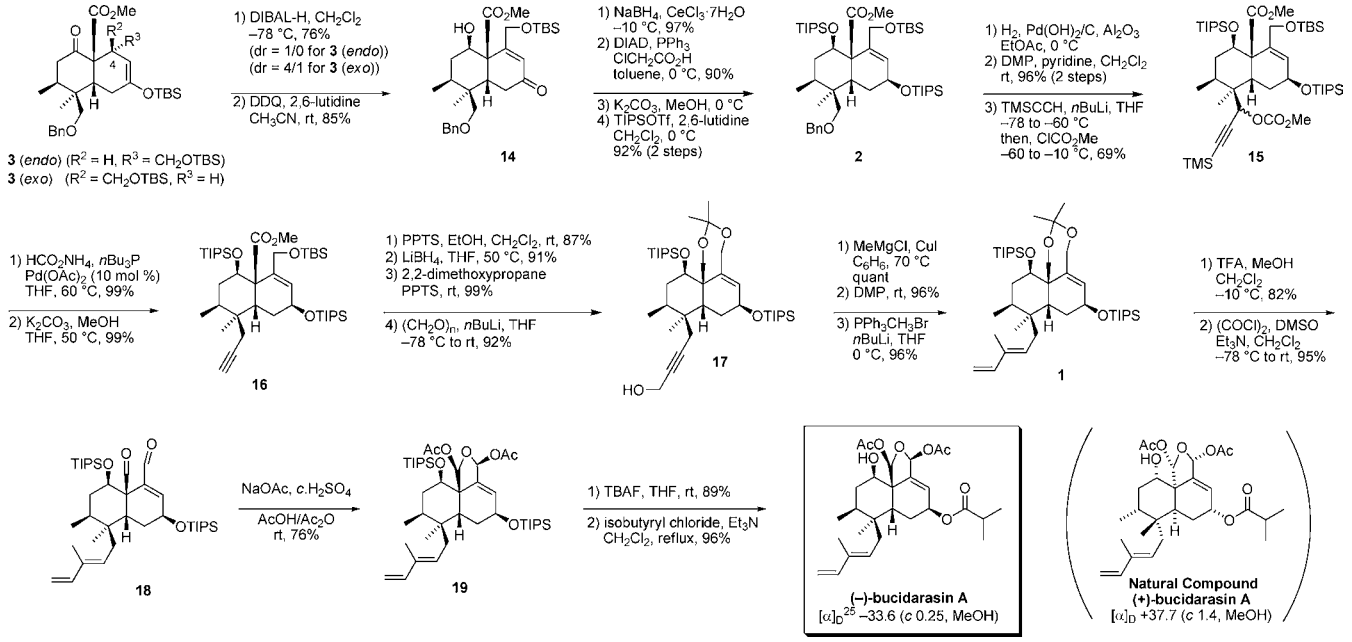
Scheme 4. Total Synthesis and Elucidation of the Absolute Structure of Bucidarasin A



Introduction of the C9 side chain was first attempted via a coupling reaction, but fruitless results were obtained. Hence, the addition reaction of the aldehyde derived from **2** was examined. The alcohol obtained by the hydrogenolysis was oxidized by Dess-Martin periodinane, and the resultant aldehyde was reacted with trimethylsilylacetylide, followed by the *in situ* reaction with methyl chloroformate to form **15**. The Pd-catalyzed reduction of **15** with formic acid[17] and subsequent removal of the TMS group under typical reaction conditions successfully afforded **16**, which was subsequently transformed to **17** via the removal of the TBS group, reduction of the methyl ester, acetonide formation, and hydroxymethylation of the alkyne terminal.

The reaction of propargyl alcohol **17** with MeMgCl in the presence of CuI[18] quantitatively afforded the desired (*E*)-trisubstituted allyl alcohol as a single isomer. Subsequent Dess-Martin oxidation and Wittig reaction successfully furnished the C9 side chain to afford **1**.

The final problem to be solved was the formation of the oxygenated THF moiety. To this end, the acetonide in **1** was removed under acidic conditions, and Swern oxidation of the resultant diol afforded the desired dialdehyde **18** in 95% yield. We envisioned that the transformation of **18** could begin from the addition of an acetate anion to the less hindered allylic aldehyde, followed by formation of the THF ring. Finally, the acetylation of the resultant hemiacetal would give compound **19** bearing two *cis*-oriented acetyloxy groups, which were expected to be energetically favorable, as the two acetyloxy groups in other isomers would cause steric strain.

Consequently, the reaction conditions were set for the thermodynamically controlled reaction; i.e., **18** was treated with sodium acetate in acetic acid and acetic anhydride. The reaction proceeded slowly in the presence of a catalytic amount of concentrated H_2SO_4 to afford **19** as a single isomer in 76% yield.[19] The two acetyloxy groups were *β*-oriented, as confirmed by extensive ^{1}H NMR studies.

The two TIPS groups in **19** were simultaneously removed with TBAF, and subsequent acylation afforded the final product with an isobutyrate only at the C2 position probably owing to the steric hindrance. The final product proved to be identical to bucidarasin A in all respects (^{1}H and ^{13}C NMR, IR, and HRMS) with the exception of the sign of specific rotation;[1] i.e., the synthetic product had the minus sign while the natural product was reported to have the plus sign. Because the absolute structure of the starting material **6** had been established,[6a] the absolute structure of bucidarasin A was elucidated, as shown in Scheme 4.

In summary, we accomplished the first highly stereoselective total synthesis of (−)-bucidarasin A, which also elucidated the absolute structure of its natural form. The total synthesis features the effective use of the original chiral building block prepared via the highly enantio- and stereoselective baker's yeast reduction, and a series of highly stereoselective reactions, i.e., hydroxy-directed hydrogenation, [4 + 2] cycloaddition of a sterically hindered dienophile, reduction of ketones, formation of the C9 side-chain diene, and formation of the THF moiety bearing two acetyloxy groups. To accomplish the total synthesis of natural (+)-bucidarasin A by this approach, the enantiomeric starting material is required, but cannot be prepared via baker's yeast reduction. However, we reported CBS (Corey–Bakshi–Shibata) reduction as an alternative method to prepare similar chiral building blocks,[8b] which will facilitate an enantioselective approach to (+)-bucidarasin A. Further synthetic studies are now underway and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and copies of the NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(14) The dr = 1/9 was determined by ^{1}H NMR.

(15) The DIBAL-H reduction of **3** afforded two products with the *β*-C6 hydroxy, **3a** (67%) and **3b** (9%), and a product with *α*-C6 hydroxy **3c** (16%). Oxidation of **3a** and **3c** afforded the major product of **3**. The dr = 1/9 in the [4 + 2] cycloaddition of **4** well corresponds to the ratio of **3b**/(**3a** + **3c**) = 9/83.

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