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Synthetic studies on (+)-bucidarasin C: two diastereoselective transannular reactions producing *cis*-decaline derivatives that show reversal selectivity

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ABSTRACT

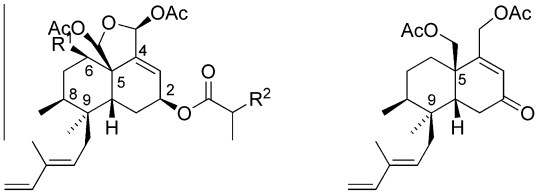
This manuscript describes studies on the construction of the *cis*-decaline core of (+)-bucidarasin C. The transannular Diels–Alder (TADA) reaction of a macrocyclic lactone successfully afforded the desired *cis*-decaline derivative in a stereoselective manner. On the other hand, the stereoselective transannular cascade Michael (TACM) reaction of the parent macrocyclic lactone afforded the diastereomeric *cis*-decaline derivative as the major product.

Bucidarasins (Fig. 1) were isolated in 2001 from an extract of *Bucida buceras*, which is a widely spreading timber and shade evergreen tree found in tropical regions of northern South America.[1] Although (+)-bucidarasin D is inactive, (+)-bucidarasins A–C show significant in vitro cytotoxicity. The IC_{50} values of (+)-bucidarasins A–C range from 0.5 to 1.9 μM against various human tumor cell lines such as KB (nasopharyngeal), A549 (lung), IA9 (ovarian), CAKI (kidney), HCT-8 (ileocecal), MCF-7 (breast), HOS (bone), U87-MG (glioblastoma), and SK-MEL-2 (melanoma). Moreover, their potency of cytotoxicity is retained in the drug-resistant tumor cell lines such as KB-VIN (vincristine resistant), KB-7d (etoposide resistant), KB-CPT (camptothecin resistant), and IA9-PTX10 (paclitaxel resistant), suggesting that they may have a novel mode of action and could become clinical candidates. As (+)-bucidaracin D has no cyctotoxicity, the bis-acetal moiety of (+)-bucidarasins A–C plays a key role in producing the cytotoxicity; however, their mode of action has not been reported so far.

Bucidarasins are a family of *cis*-clerodane diterpenoids, possessing a unique tricyclic ring system incorporating a *cis*-dehydrodecalin core with a fused tetrahydrofuran. The *cis*-dehydrodecalin core has two methyl groups trans to each other at the C8 and C9 positions, and an (*E*)-3-methyl-penta-2,4-dienyl group at the C9 position. The C2 position of bucidarasins is oxygenated, and the C6 position is further oxygenated in (+)-bucidarasins A and B. (+)-Bucidarasin C possesses four successive stereogenic centers on the *cis*-dehydrodecalin core, an isobutyrate at the C2 position, and two acetates as acetals on the tetrahydrofuran ring; hence, (+)-bucidarasin C has seven stereogenic centers in total. The total synthesis of (+)-bucidarasin C has not been reported so far.[2] Therefore, its potent bioactivity as well as unique structural features led us to commence synthetic studies on (+)-bucidarasins C.

Scheme 1 shows our retrosynthetic analysis of (+)-bucidarasins C. We planned to construct the tetrahydrofuran moiety incorporating the acid- and base-sensitive bis-acetal at the late stage of the total synthesis and set compound **1** as the late stage intermediate, which was thought to be obtained from compound **2** via decarboxylation and stereoselective reduction of the C2 ketone. The construction of a stereogenic quaternary all-carbon center is one of the most difficult problems in natural product synthesis. (+)-Bucidarasin C possesses two stereogenic quaternary all-carbon centers at the C5 and C9 positions in the four contiguous stereogenic carbon centers, thus presenting a synthetic challenge.

We decided to employ the transannular Diels–Alder (TADA) reaction of **3** to synthesize **2** because it could generate the requisite *cis*-fused decaline core with four contiguous stereogenic centers that include the C5 stereogenic quaternary all-carbon center.[3] Compound **3** was expected to be prepared via the macrolactone formation of **4**, which would be prepared from **5**. Compound **5** would be obtained by the oxidative ring-opening reaction of **6**, which was expected to be derived from **7**. Finally, compound **7** was envisioned to be prepared from **8**, a chiral building block



(+)-bucidarasin A: R^1=OH, R^2=CH_3
(+)-bucidarasin B: R^1=OH, R^2=C_2H_5
(+)-bucidarasin C: R^1=H, R^2=CH_3

(+)-bucidarasin D

Figure 1. Structures of (+)-bucirarasin A–D.

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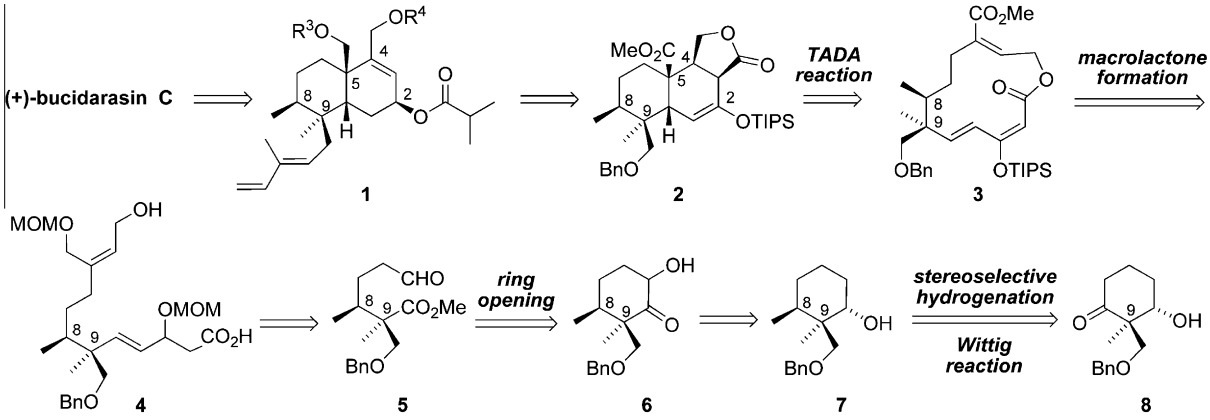
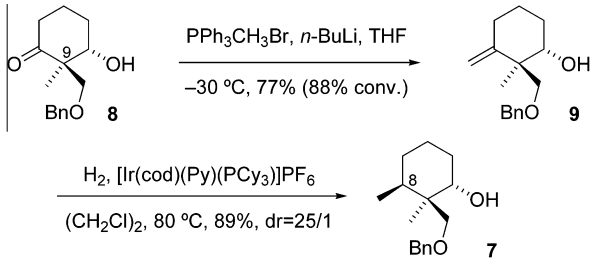


Scheme 1. Retrosynthetic analysis of (+)-bucidarasin C.

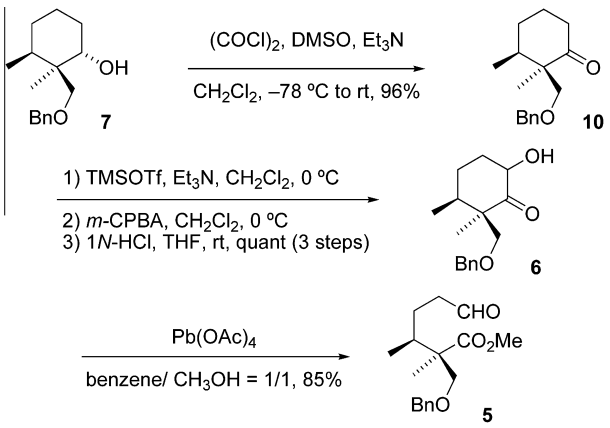


Scheme 2. Stereoselective synthesis of **7** from **8**.

prepared by us,[4] by the Wittig reaction and stereoselective hydrogenation.

The Wittig reaction of **8** afforded **9** (Scheme 2), but the epimerization at the C9 position of **8** occurred after a prolonged reaction time because the concomitant retro-aldol reaction of **8** occurred.[5] Therefore, the Wittig reaction was stopped at an 88% conversion to avoid epimerization. The hydroxyl-directed hydrogenation of **9** with the Crabtree's catalyst ($[Ir(cod)(Py)(PCy_3)]PF_6$)[6] stereoselectively afforded the desired compound **7**. Because the diol, which was obtained by the hydrogenation of **7**, was a known compound, its structure was confirmed by a comparison of NMR data.[7]

Swern oxidation of **7** afforded **10** (Scheme 3), followed by trimethylsilyl enol ether formation and Rubottom oxidation to give **6** quantitatively, which was treated with a lead tetraacetate in the presence of methanol to afford methyl ester **5**.



Scheme 3. Transformation of **7** to **5**.

Next, **5** was converted into seco-acid **4** to achieve macrocyclization (Scheme 4). The reaction of **5** with Ohira–Bestman's reagent,[8] subsequent reaction with $LiAlH_4$, and then, Swern oxidation afforded aldehyde **11**. The Horner–Wadsworth–Emmons reaction of **11** afforded the corresponding enal, which was converted into 1,3-dioxane **12**. The terminal alkyne of **12** was formylated, and the subsequent one-pot reduction of the aldehyde and alkyne with Red-Al, followed by treatment with iodine, afforded the allylic alcohol. The allylic alcohol was protected as *t*-butyldiphenylsilyl (TBDPS) ether, followed by the palladium-mediated carbonylation to afford methyl ester **13**.

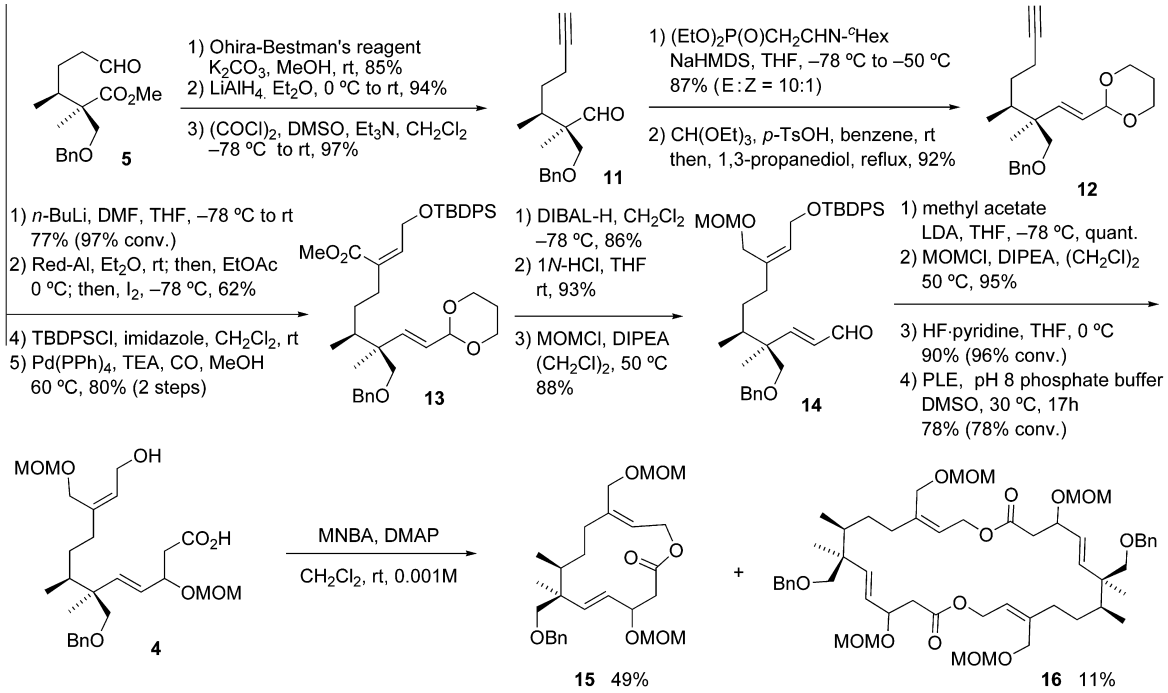
The diisobutylaluminum hydride (DIBAL-H) reduction of **13** and the subsequent deprotection of the 1,3-dioxane, and the protection of the allylic alcohol as methoxymethyl (MOM) ether gave **14**. The aldol reaction of **14** with methyl acetate and subsequent protection of the resultant secondary hydroxyl as MOM ether, and deprotection of the TBDPS group with HF-pyridine, afforded a methyl ester of **4**.

Hydrolysis of the methyl ester under commonly used conditions was difficult to achieve, causing β-elimination to afford α,β-unsaturated ester as the major product. However, this difficulty was solved using the enzyme-mediated hydrolysis. Thus, the methyl ester was successfully hydrolyzed with pig liver esterase to afford **4** in KPB8 buffer using dimethyl sulfoxide (DMSO) as the additive.[9]

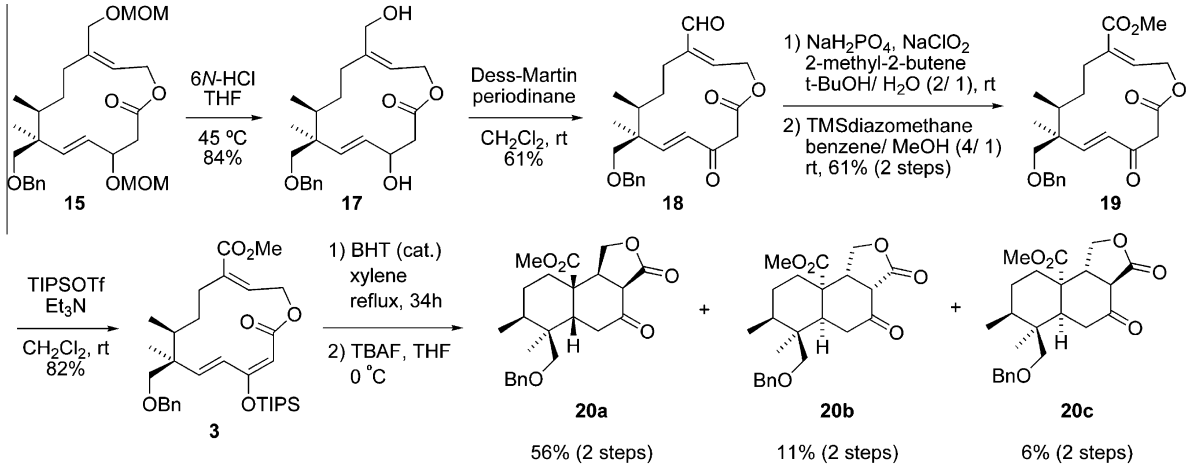
With seco-acid **4** in hand, the macrolactonization of **4** was examined. Gradual addition of a solution of **4** in CH_2Cl_2 using a syringe pump to a solution of 2-methyl-6-nitrobenzoic anhydride (MNBA)[10] and 4-*N*,*N*-dimethylaminopyridine (DMAP) in CH_2Cl_2 under high dilution conditions at room temperature afforded macrolactone **15**. The major by-product was the dimer **16**, which was formed in an 11% yield.

The deprotection of MOM ethers of **15** under acidic conditions (Scheme 5) gave diol **17**, which was subjected to Dess–Martin oxidation to afford keto-aldehyde **18**. The Pinnick oxidation of **18**, and subsequent reaction with diazomethane afforded methyl ester **19**. Treatment of **19** with triisopropylsilyltrifluoromethane sulfonate (TIPSOTf) and triethylamine afforded triisopropylsilyl (TIPS) ether **3**, which was subjected to the TADA reaction. The TADA reaction of **3** did not occur in the presence of Lewis acid at low temperature and decomposition of the substrate occurred at room temperature. Hence, the TADA reaction of **3** was carried out at the reflux temperature of xylene to produce a mixture of three products, which was then treated with tetrabutylammonium fluoride (TBAF) to afford **20a** (56%, 2 steps), **20b** (11%, 2 steps), and **20c** (6%, 2 steps).

Analysis by nuclear Overhauser effect (NOE) experiments of the products (Scheme 6) suggested that the structures of **20a** and **20b**



Scheme 4. Preparation of macrolactone **15**.

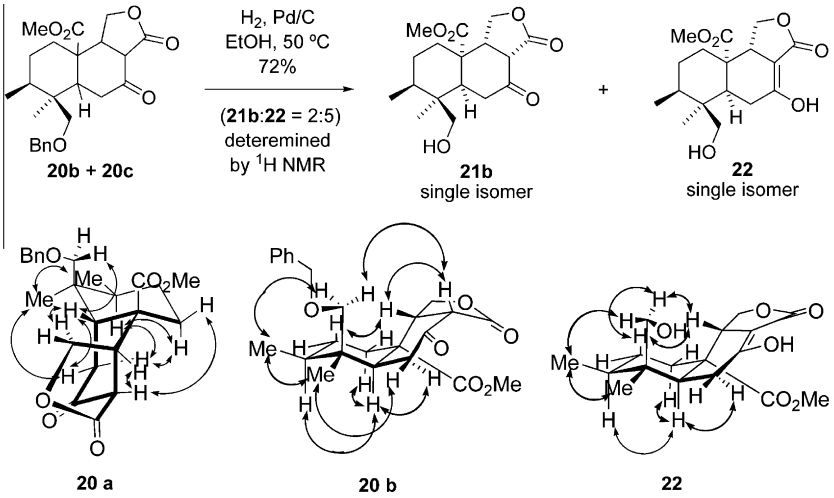


Scheme 5. Preparation of **3** and the TADA reaction.

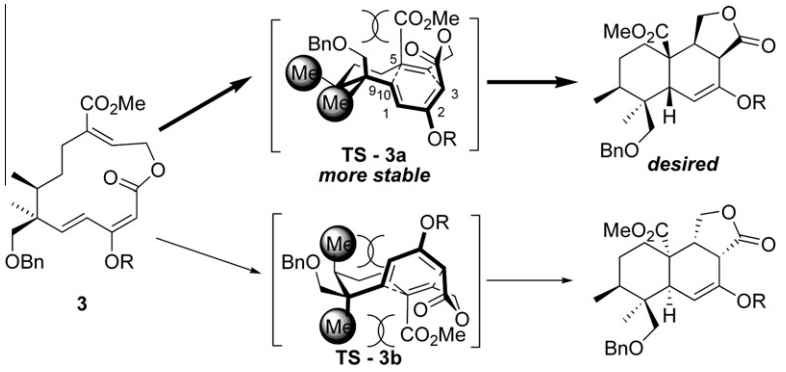
were as shown in Scheme 5. Compound **20c** was found to be the epimer of **20b** because the hydrogenation of a mixture of **20b** and **20c** (Scheme 6) afforded a separable mixture of **21b** and **22**, and the structure of **22** was suggested to be as shown in Scheme 6 by NOE analysis. The major product **20a** had the desired configuration, indicating that the TADA reaction of **3** successfully constructed the *cis*-decaline core of (+)-busidaracins in a stereoselective manner.

In the TADA reaction of **3**, the *exo*-addition would be favored because the *endo*-addition is energetically unfavored due to the severe strains arising from the mode of transannular reaction. Indeed, only *exo*-adducts were formed by the TADA reaction of **3** (Scheme 5). Two transition states including a chair-structure, **TS-3a,** and **TS-3b** are surmised to be energetically favored for the TADA reaction of **3**, but **TS-3b** would be unfavorable due to the steric strains derived from 1,3-diaxial interactions when compared with **TS-3a**. Consequently, the desired product **20a** would be formed as the major product. The TADA reaction of **3** was surmised to afford products with the *cis*-fused γ-lactone as shown in Scheme 7. Hence, **20c** was thought to be kinetically formed by the protonation of the enolate generated from the thermodynamically more stable **20b** during the reaction with basic TBAF.

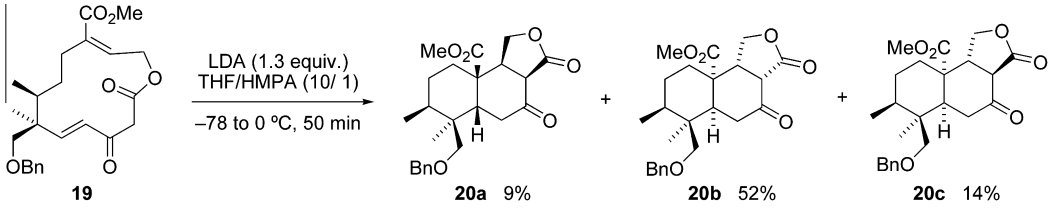
On the other hand, compound **19**, which is a parent compound of **3**, possessed a β-keto ester, an α,β-unsaturated ester, and an α,β-unsaturated ketone at the positions suitable for the transannular cascade Michael (TACM) reaction. Hence, the treatment of **19** with an appropriate base was expected to produce **20a**–**c**. Therefore, the reactions of **19** under basic conditions were examined, and we found that the reaction of **19** with lithium diisopropylamide (LDA) under optimized conditions shown in Scheme 8 afforded **20a** (9%), **20b** (52%), and **20c** (14%). Interestingly, the major product was **20b** and the diastereoselectivity was 9:66 (1:7.3) because



Scheme 6. Conversion of **20b** and **20c** to **21b** and **22**, and NOE correlations in **20a**, **20b**, and **22**.



Scheme 7. Plausible transition states of the TADA reaction of 3 (R = TIPS).



Scheme 8. The transannnular cascade Michael (TACM) reaction of **19**.

20c is the epimer of **20b**. On the other hand, the diastereoselectivity of the TADA reaction of **3** was 56:17 (3.3:1); that is, the diastereoselectivity of the two reactions was reversed.

The reversal of the diastereoselectivity is surmised to arise from the different reaction mechanism between the TADA reaction and the TACM reaction. TADA reactions require *s*-cis conformation of the diene for the concerted reaction with the dienophile. On the other hand, the TACM reaction of **19** proceeded by step-wise C–C bond formations. Thus, the first intramolecular Michael reaction of **19** generated the γ-butyrolactone and the subsequent intramolecular Michael reaction constructed the tricyclic carbon skeleton. Therefore, the first C–C bond-forming reaction did not require *s*-cis conformation of the dienolate that formed from **19**. That is, the dienolate could take the *s*-trans conformation to undergo the first reaction. The difference described above suggests that the diastereoselectivity-determining transition states of the two reactions are different, thereby leading to the observed reversal.

In summary, the *cis*-decaline derivative, which would be a key intermediate for the total synthesis of (+)-bucidarasin C, was successfully prepared by the stereoselective TADA reaction of a mactocyclic lactone. Moreover, the stereoselective TACM reaction of the parent macrocyclic lactone was found to afford the diastereomeric *cis*-decaline derivative as the major product. These two stereoselective transannular reactions that show reversal diastereoselectivity would be useful for the synthesis of natural products that include a *cis*-decaline core.

Acknowledgments

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