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Enantioselective Total Synthesis of Diocollettines A

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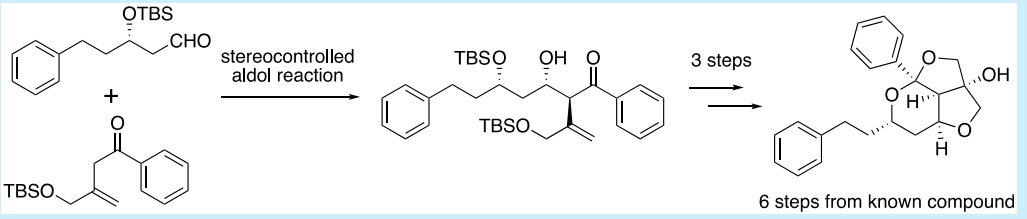
Supporting Information



ABSTRACT: The first enantioselective total synthesis of diocollettines A was accomplished in only six steps from a known compound. A short and practical synthetic route was disclosed, featuring an intensive investigation of the stereoselective aldol reaction as a key step using an easily prepared aldehyde moiety and an enone derivative. The synthetic scheme also includes the efficient stereocontrolled construction of the tricyclic skeleton of diocollettines A by intramolecular acetal formation, stereoselective dihydroxylation, and intramolecular ether cyclization.

A novel tricyclic diarylheptanoid derivative,[1] diocollettine A (**1**), along with known compound **2**−**6** was isolated by Gao and co-workers in 2016 in their search for novel bioactive compounds from the rhizomes *Dioscorea collettii* (Figure 1).[2,3]

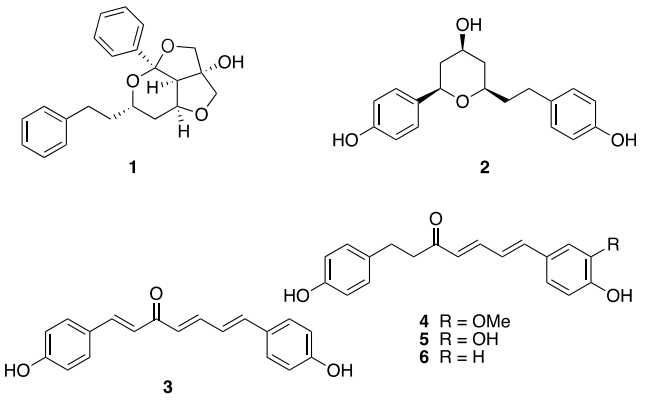


Figure 1. Chemical structures of compounds **1**−**6**.

The structure of diocollettines A was elucidated by extensive NMR spectroscopic analysis in addition to HR-ESI-MS measurements. The absolute configuration of compound **1** was established by electronic circular dichroism (ECD) spectra and X-ray single-crystal diffraction data. Compound **1** possesses a tricyclic skeleton with five stereogenic centers, two tetrahydrofuran rings, and one tetrahydropyran ring fused to construct a complicated heterocyclic structure.

Compounds **1**−**6** were evaluated for their cytotoxicity against human lung cancer NCL-H460 cell lines.[2] Compound **1** displayed moderate activity with an IC_{50} value of 20.15 μM, while compound **4** showed the most potent activity with an IC_{50} value of 0.23 μM. In contrast, compound **2** was less active (IC_{50} value >100 μM). To date, no total synthesis of diocollettines A has been accomplished, and the structural features of compound **1** provided our motivation for this synthetic study. Here, we disclose a short and practical synthetic route to **1** in only six steps from known compounds, featuring an intensive investigation of the stereocontrolled aldol reaction as a key step. Our total synthesis also involves the efficient construction of the tricyclic skeleton of diocollettines A by intramolecular acetal formation and stereoselective dihydroxylation followed by intramolecular ether cyclization.

Our retrosynthetic analysis for the total synthesis of diocollettines A is shown in Scheme 1. From a retrosynthetic perspective, the C ring of the core framework could be constructed by stereoselective dihydroxylation of compound **7** and selective tosylation of the resultant primary alcohol followed by ether cyclization. The A and B rings of compound **7** could be built by deprotection and subsequent intramolecular acetal formation of compound **8**, which would in turn be synthesized from aldehyde **9** and enone **10** using the intermolecular aldol reaction in a stereoselective manner.

The synthesis commenced with the preparation of aldehyde **9** and enone **10**, precursors for the key aldol reaction, as shown in Scheme 2. The requisite aldehyde **9** was formed through a three-step sequence involving asymmetric allylation, silylation of the resultant alcohol, and oxidative cleavage of the double bond. The asymmetric allylation was performed by employing diisopinocampheylallylborane in 73% yield and 91% ee.[4,5] After TBS protection, Lemieux−Johnson condition afforded the desired aldehyde **14**.[6] Enones **16** and **17** were derived from

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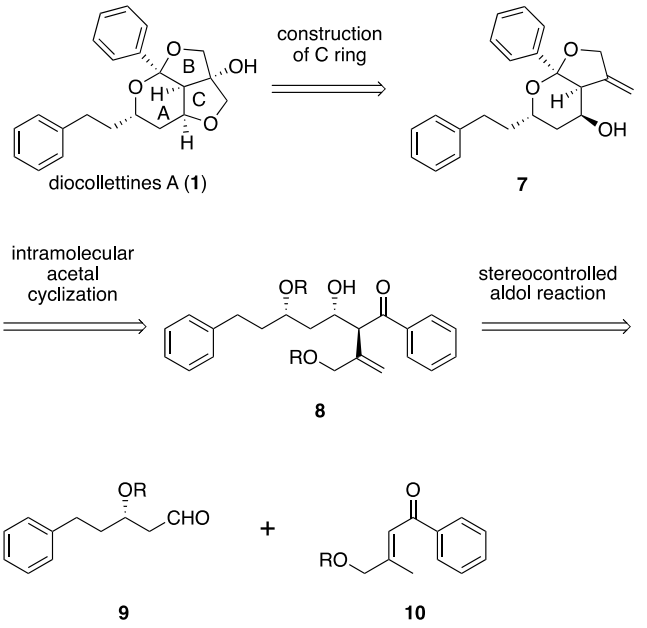
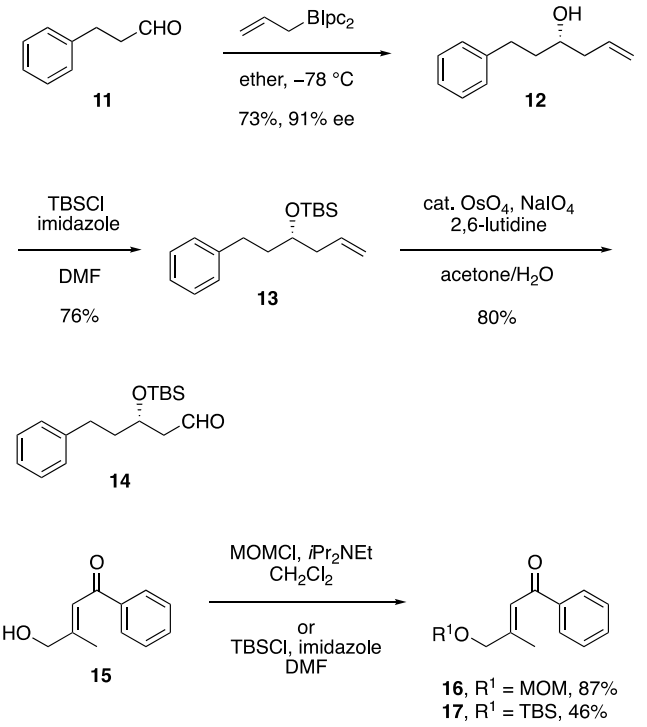
Scheme 1. Retrosynthetic Analysis of 1



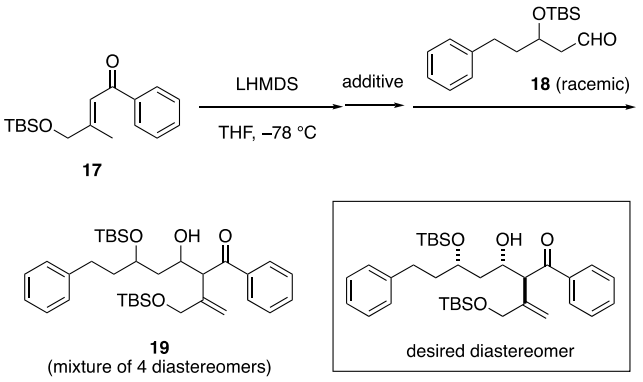
Scheme 2. Synthesis of Aldol Reaction Precursors



the alcohol **15**[7] through protection with MOM and TBS groups.

With the desired aldehyde **14** and enones **16** and **17** in hand, we next focused on the key aldol reaction. At first, vinyl lithium enolate generated from the enone **17** by LHMDS was reacted with aldehyde **18** (racemic) to give the aldol adduct **19** in 77% yield (Scheme 3). The diastereoselectivity was very poor, although the *anti*-aldol adducts were obtained as major diastereomers. This low selectivity is probably due to the weak chelation ability of lithium atom. Thus, zinc, which has a strong chelation ability, was added to form a vinyl zinc enolate after preparation of the vinyl lithium enolate. Unfortunately,

Scheme 3. Attempts at Aldol Reaction Using Vinyl Lithium Enolate



additive	yield (mixture of 4 diastereomers)	aldol selectivity (**anti**/syn)	1,3-diol selectivity (anti/**syn**)
free	77%	2 : 1	1 : 1
$ZnCl_2$	72%	8 : 5	1 : 1

the resulting diastereoselectivity was almost the same. The unsatisfactory outcome of the zinc enolate is because of inadequate control of the geometric isomers, furnishing a mixture of *E*/*Z* isomers. Therefore, a boron enolate was employed to control the isomers.

Thus, enone **16** was directly subjected to the aldol conditions using Cy_2BCl and Et_3N, which has been reported to generate *E*-enolate selectively,[8] followed by addition of aldehyde **21**. Regrettably, only starting material **16** was recovered. This suggested that the boron enolate was not produced from **16**.

Therefore, compound **20**, in which the double bond is migrated to the terminal olefin, was synthesized via deprotonation and protonation of enone **16** by treatment with LHMDS and subsequent quenching by aqueous NH_4Cl (Scheme 4). The aldol reaction of the *E* boron enolate and aldehyde **21** was performed to obtain adduct **22** in 91% yield in an exclusively *anti*-selective fashion. However, the stereochemical outcome regarding the 1,3-diol moiety was unsatisfactory (undesired *anti* vs desired *syn* = 2:3). This result encouraged us to add a metal additive to chelate the carbonyl oxygen of the aldehyde and the MOM oxygen depicted in Scheme 4. After many attempts including $ZnCl_2$, $AlCl_3$, $MgClO_4$, and $ZnEt_2$, LiCl gave the best result, forming *anti* and *syn* adducts in a 1:2 ratio. With access to stereocontrolled aldol adduct **22** achieved, the next challenge was to construct the AB rings. To accomplish this, cleavage of the MOM groups followed by acetal cyclization was attempted under several acidic conditions. However, all efforts (HCl, TFA, TMSI,[9] catechol boron bromide[10]) provided only decomposition of the starting material. This failure to remove the MOM groups prompted us to change the protective groups (Scheme 5).

Having synthesized the requisite ketone **23** bearing a TBS-protected primary alcohol and the desired aldehydes **24** or **25**[11] bearing a PMB- or SEM-protected secondary alcohol, the aldol reaction was carried out again. The PMB or SEM group was chosen not only because they could have the ability to chelate the metal additive, and likewise the MOM group, but

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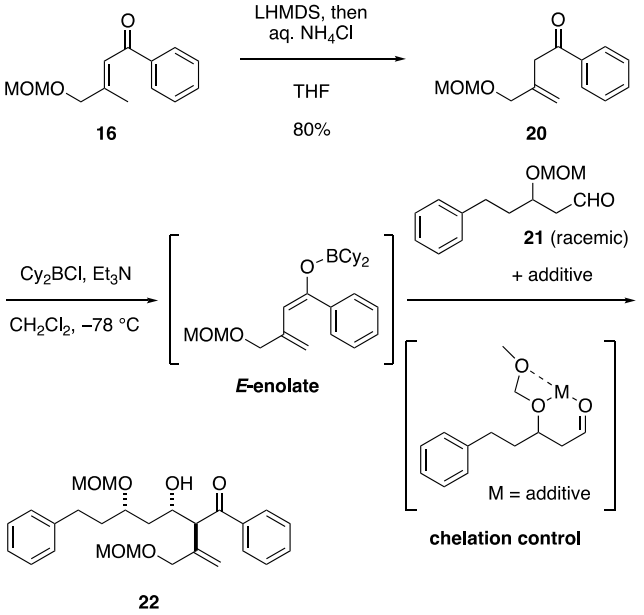
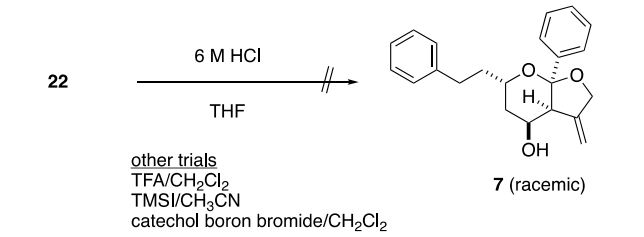
Scheme 4. Attempts at Aldol Reaction Using Vinyl Boron Enolate



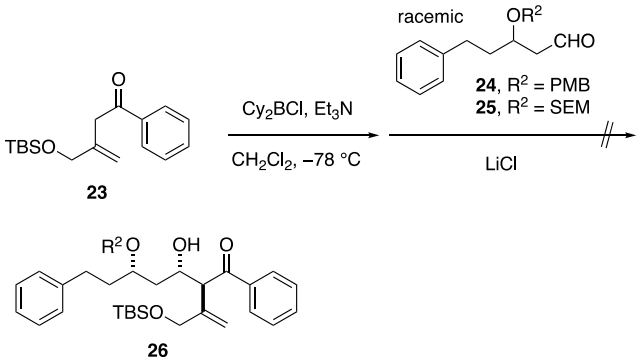
additive	yield (aldol anti products)	aldol selectivity (**anti**/syn)	1,3-diol selectivity (anti/**syn**)
free	91%	> 95 : 5	2 : 3
LiCl	55%	> 95 : 5	1 : 2

Scheme 5. Failure To Remove MOM Groups



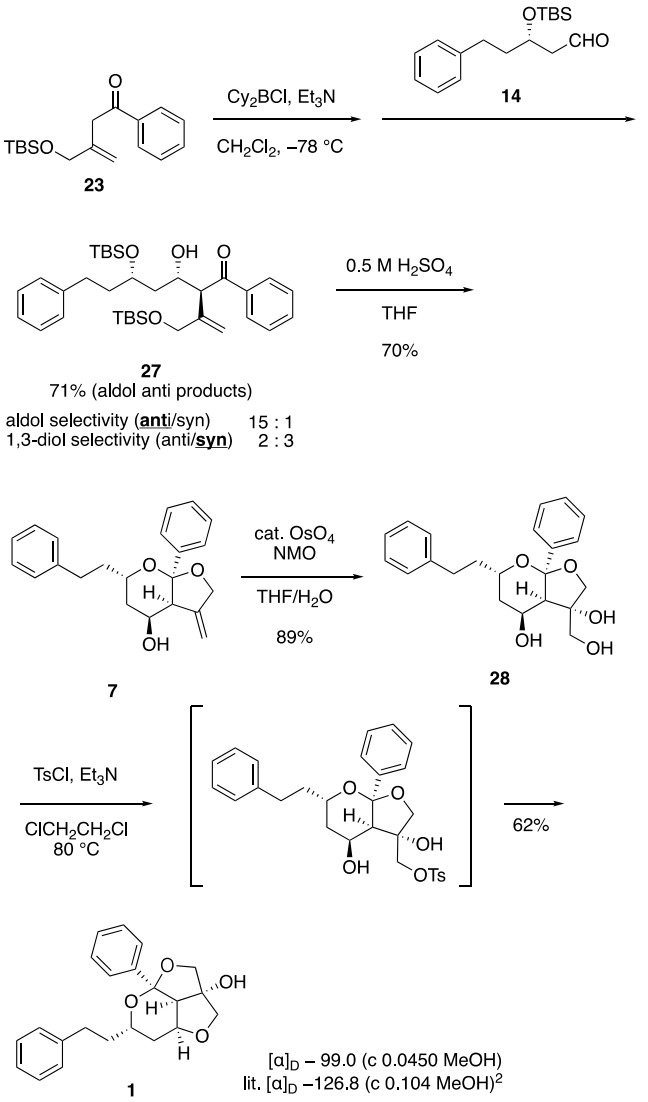
because they are easier to remove than the MOM group under nonacidic conditions. However, the desired reaction did not proceed (Scheme 6).

Scheme 6. Attempts at Aldol Reaction Using Other Protective Groups



Finally, we executed the aldol reaction utilizing only TBS group (Scheme 7). Addition of the boron enolate generated

Scheme 7. Completion of Enantioselective Total Synthesis



from **23** to aldehyde **14** with a secondary alcohol silylated by a TBS group smoothly took place to produce adduct **27** in a selective manner. Since the stereochemical control of the 1,3-diol moiety was not satisfactory, some additives ($ZnCl_2$, $AlCl_3$, LiCl) for chelation were employed as in the case of the MOM group, but the selectivity was not improved. After HPLC separation of the diastereomers, we turned our attention to construction of the tricyclic skeleton. Treatment of **27** with 0.5 M H_2SO_4 triggered removal of the TBS groups followed by intramolecular acetal cyclization to yield compound **7** possessing the AB rings. The stereochemistry of **7** was confirmed by NOESY experiments (see the Supporting Information). The phenyl group was located at the more stable α face, the equatorial position. With the AB rings constructed, the remaining task was to form the C ring in a two-step procedure. Stereoselective dihydroxylation occurred exclusively from the convex face to afford triol **28**. Furthermore, TsCl and Et_3N induced the selective tosylation of the primary alcohol, and the resultant tosylate was attacked by the secondary alcohol to build the C ring, completing the

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total synthesis of the target molecule. Both the ^{1}H and ^{13}C NMR spectra of synthetic diocollettines A (**1**) were identical with those reported in the literature. The value of $[\alpha]_D$ slightly differs from the original one in the literature probably because compound **12**, which compound **1** was derived from, does not have perfect ee (91% ee).

In conclusion, the first enantioselective total synthesis of diocollettines A (**1**) was achieved in only six steps from the known compound. The synthetic method involved a stereocontrolled aldol reaction and efficient construction of the tricyclic structure, including intramolecular acetal cyclization, stereoselective dihydroxylation, and intramolecular ether formation. This short and practical synthetic strategy could be applied to structure and activity relationship studies of the bioactive compounds.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b01776.

Experimental procedure, spectral data (PDF)

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Notes

The authors declare no competing financial interest.

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(11) Aldehydes **24** and **25** were synthesized like aldehyde **14** (see the Supporting Information). Compound **24** is known compound.

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