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Stereoselective Construction of the Methylcyclopentane Core of Pedititthins B−H with Five Continuous Stereocenters

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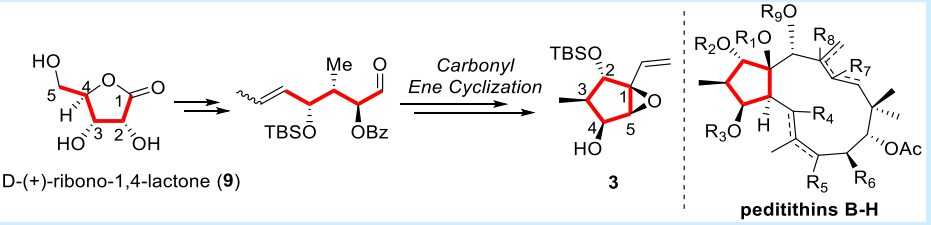

ABSTRACT: A stereoselective construction of the methylcyclopentane core (**3**) of jatrophane diterpenoids pedititthins B−H was achieved in 14 steps from commercially available D-(+)-ribono-1,4-lactone (**9**). The linear 5-ene-heptanal derived from **9** was cyclized to the five-membered ring by an intramolecular carbonyl ene reaction, and five continuous stereocenters on **3** were stereoselectively introduced via a successive substrate-controlled manner, involving diastereoselective 1,4-addition, MoOPH-induced hydroxylation, and stereospecific epoxidation.

Diterpenoids featuring a highly functionalized methylcyclopentane core (ring A) are mainly found in plants of the family Euphorbiaceae. So far, more than 900 of such Euphorbiaceae diterpenoids, incorporating more than 10 scaffolds (Figure 1), have been isolated.[1] Their fascinating structures and significant biological activities have made this class a promising feedstock in drug discovery, as exemplified by picato[2] (ingenane-type), resiniferatoxin[3] (daphnane-type), and prostratin[4] (tigliane-type) in cancer or HIV therapy.

Spurred by their impressive structures and bioactivities, the synthetic endeavors toward these Euphorbiaceae diterpenoids have continued unabated over the past several decades, leading to the elaborate chemical syntheses of several natural products or their partial motifs.[5] In these syntheses, the inaugural construction of the common methylcyclopentane segment is quite challenging, often involving lengthy and tedious synthetic steps, especially when the five-membered ring was highly functionalized. For instance, Rinner and co-workers reported the synthesis of two diastereomeric cyclopentane segments via a ring-closing metathesis (RCM) reaction of functionalized 1,6-diene using a precious Grubbs second-generation catalyst.[6] Hiersemann et al. constructed the nonnatural 17-norjatrophane diterpene 3-propionyl-15-acetyl-17-norcharaciol through the thermal intramolecular carbonyl ene reaction of the activated enone substrate.[7] Mulzer et al. synthesized the cyclopentanyl vinyl triflate in a total yield of 1.8% in 18 steps from a furfuryl alcohol.[8] However, these efforts achieved the synthesis of methylcyclopentane containing only three or four stereocenters. So far, the synthesis involving five continuous stereocenters has never been reported.

In our continuing efforts toward discovering structurally intriguing and biologically significant metabolites from Euphorbiaceae species,[9] a series of new jatrophane diterpenoids, pedititthins B−H, were isolated from *Pedilanthus tithymaloides*.[10] These pedititthins and their derivatives turned out to be the most potent natural P-glycoprotein (Pgp) inhibitors reported so far, exhibiting pronounced multidrug resistance (MDR) reversal ability on adiamycin resistant cancer cell lines *in vitro* and *in vivo*.[10] Structurally, pedititthins B−H represent a group of complex jatrophane diterpenoids (*trans* 5/12 ring system) containing a fully functionalized methylcyclopentane core (ring A). The five continuous stereocenters on ring A were considered as the essential elements for the activity of this class. Thus, efficient construction of this common motif not only constitutes a synthetic pathway to a specific pedititthin but also provides access to a group of medicinally important jatrophane analogues in future.

In this study, we designed a (1*S*,2*S*,3*R*,4*S*,5*S*)-3-methyl-1-vinyl-6-oxabicyclo[3.1.0]hexane-2,4-diol derivative (**3**) as the target, as it could serve as an advanced intermediate that condenses with a series of alkenyl halides (**2**) by transition-metal-mediated epoxide-opening reaction and subsequent

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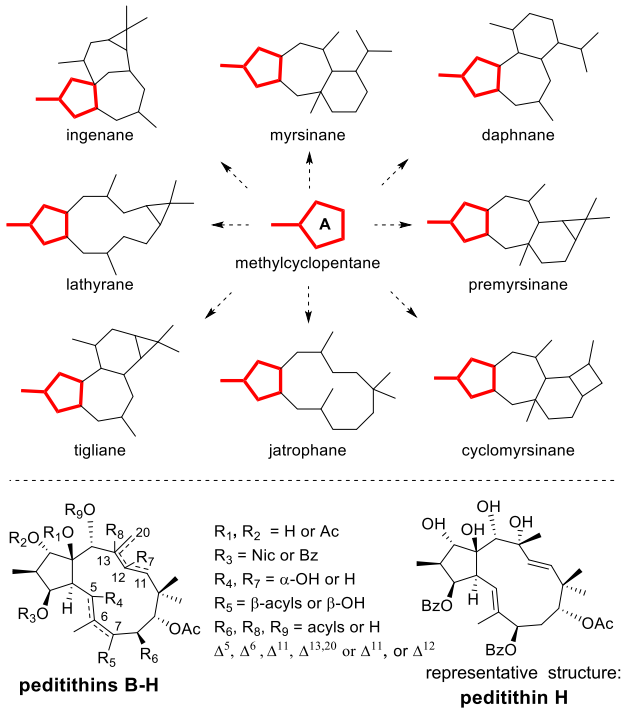
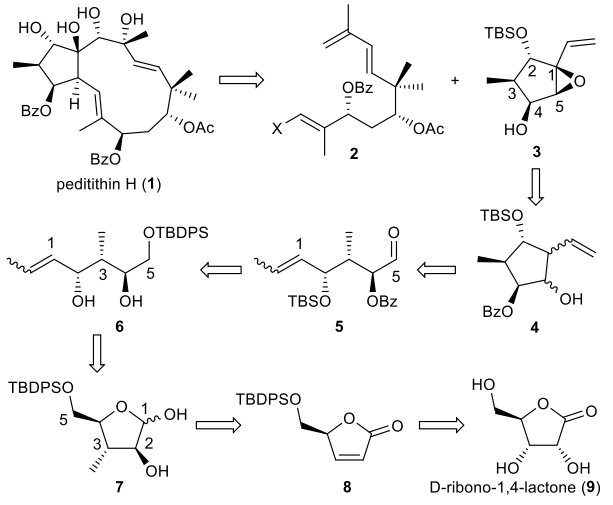


Figure 1. Some representative skeletons of methylcyclopentane-containing Euphorbiaceae diterpenoids and the structures of peditithins.

RCM reaction to generate the 5/12 ring skeleton of diverse peditithins. As exemplified by the retrosynthetic analysis of peditithin H (Scheme 1), **3** was envisaged to be prepared by

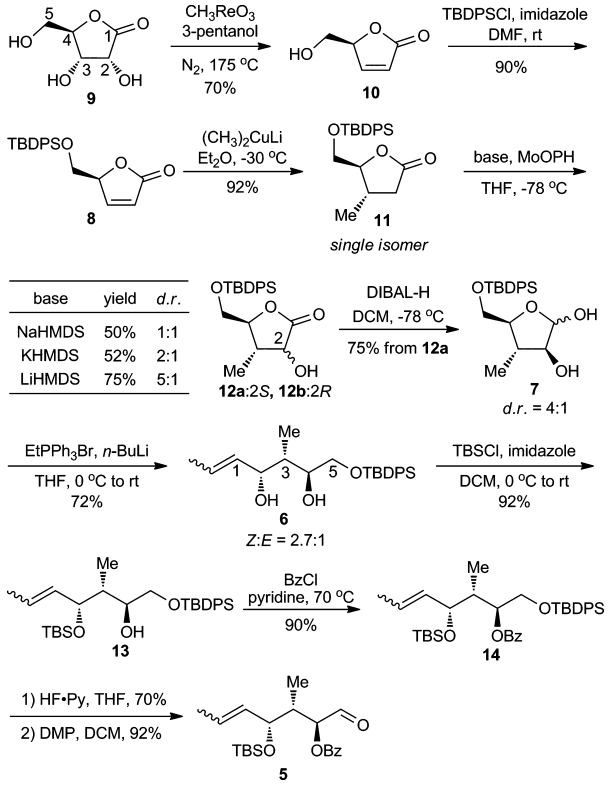
Scheme 1. Retrosynthetic Analysis of Peditithin H (1)



C4-OH-induced stereospecific epoxidation of the diene intermediate derived from homoallyl alcohol **4**. The cyclopentane core of **4** could be established by intramolecular carbonyl ene reaction of the linear 5-ene-heptanal **5**, which is readily accessible from **6** through a selective protection and oxidation sequence. The double bond on **6** could be formed by an *in situ* Wittig olefination of hemiacetal **7**. To introduce in a stereocontrolled manner the substituents on C2 and C3 in **7**, butenolide **8** was used as the chiral template, which successively underwent conjugate addition with lithium dimethylcuprate, stereoselective MoOPH-induced oxidation of C2, and partial reduction of C1 to afford **7**. Butenolide **8** would be obtained by deoxydehydration of the commercially available D-(+)-ribono-1,4-lactone **9**.

The synthesis of key linear intermediate **5** for subsequent ring closure reaction is shown in Scheme 2. According to the

Scheme 2. Preparation of 5-Ene-heptanal 5



standard conditions reported by Toste,[11] the methyltrioxorhenium (MTO)-catalyzed deoxydehydration of commercially available D-(+)-ribono-1,4-lactone **9** led to the desired butenolide **10** on a gram scale in 70% yield. Protection of the primary alcohol by using TBDPSCl/imidazole afforded **8** in 90% yield. Conjugate addition of Gilman reagent[12] $(CH_3)_2CuLi$ to α,β-unsaturated lactone **8** gave γ-lactone **11** as a single stereoisomer in 92% yield. Substrate-directed α-hydroxylation of **11** with classic Davis reagent[13] under various base conditions led to **12** but in a poor yield and poor stereoselectivity. Gratifyingly, Vedejs reagent,[14] oxodiperoxymolybdenum (pyridine) (hexamethylphosphoric triamide) (MoOPH), was proven to be effective for this transformation. It is worth mentioning that the base played an important role in the control of both yield and stereoselectivity in this reaction, probably due to their different counterion effects.[15] Among different bases, lithium hexamethyldisilazide (LiHMDS) turned out to be the best, under which the desired product **12a** was smoothly afforded in 75% yield with a diastereomeric ratio of 5:1. The resulting mixture could be separated by column chromatography. DIBAL-H reduction of lactone **12** gave hemiacetal **7** as inseparable diastereomers, which further underwent an *in situ* Wittig olefination[16] to afford **6** in 72% yield as a 2.7:1 mixture of *Z* and *E* isomers. Sequential protection of the allyl alcohol and C4-OH in **6** by using TBSCl/imidazole and BzCl/Py, respectively, furnished fully protected **14** in 83% overall yield. Selective removal of the TBDPS group in **14** followed by Dess-Martin periodinane

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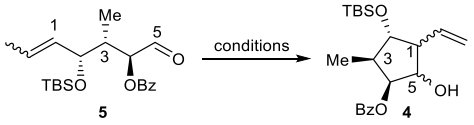
(DMP) oxidation[17] finally yielded linear 5-ene-heptanal **5** in 64% overall yield.

With enal **5** in hand, the stage is now set for the crucial intramolecular carbonyl ene cyclization.[7,18] To optimize the reaction conditions, a variety of reaction parameters such as the additive, solvent, and temperature were examined, and some of the representative results are listed in Table 1. With

Table 1. Screening for Intramolecular Carbonyl Ene Reaction of Unactivated 5-Ene-heptanal 5[a]



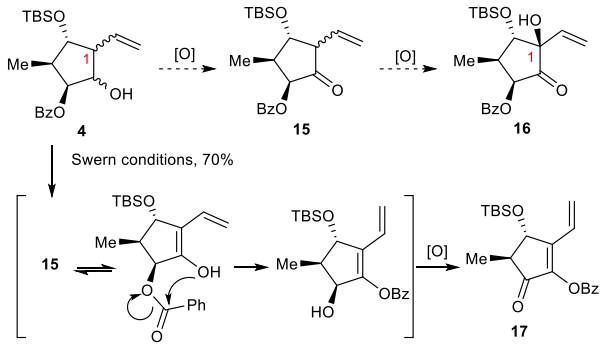
entry	Lewis acid	solvent	temperature	yield[b]
1	$BF_3{\cdot}Et_2O$	Et_2O	0 °C to rt	NR
2	$BF_3{\cdot}Et_2O$	DCM	−78 °C	15%
3	Et_2AlCl	DCM	0 °C to rt	NR
4	TMSOTf	DCM	0 °C	messy
5	$ZnCl_2$	toluene	100 °C	messy
6	Et_2AlCl	toluene	100 °C	messy
7[c]	–	toluene	180−190 °C	47%

[a]General reaction conditions: **5** (0.1 mmol) in solvent (5 mL), Lewis acid (1.0 equiv), under Ar. [b]Isolated yield of **4**. [c]A sealed tube was used.

Lewis acid $BF_3{\cdot}Et_2O$ as the promoter, no reaction occurred in Et_2O, while in dichloromethane, the desired homoallyl alcohol **4** was obtained in 15% yield as diastereoisomers. Other Lewis acids such as Et_2AlCl, TMSOTf, and $ZnCl_2$ were found to be ineffective for the cyclization. To our delight, **4** could be directly generated at a higher temperature (180−190 °C) in toluene (47% yield), without the addition of Lewis acid.

After the successful construction of the methylcyclopentane ring, we initially designed a C1-OH intermediate **16** as the alternative buiding block for **3** (Scheme 3). The C1-OH of **16**

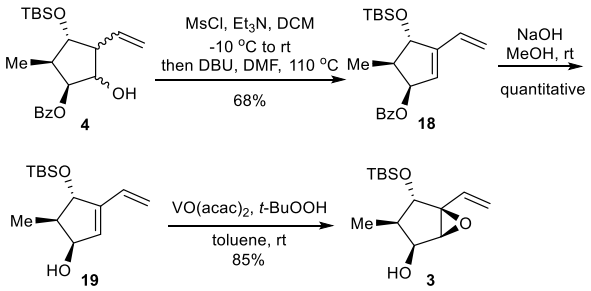
Scheme 3. Attempt to Introduce a Hydroxyl Group at the C1 Position of Homoallyl Alcohol 4



was supposed to be stereoselectively introduced by oxidation of ketone **15**. However, attempts to oxidize **4** to **15** under various oxidation conditions were unsuccessful (see page S17 of the Supporting Information). Instead, a benzoyl-migrated product **17** was isolated as the sole product in 70% yield under Swern reaction conditions,[19] which seemed to be formed from the corresponding enol intermediate via ester exchange and further oxidation.

Thus, we realized that 1,5-epoxide **3** was the more suitable building block, which could introduce the chiralities of both C1 and C5 simultaniously in later synthesis of pedititihins (Scheme 1). As shown in Scheme 4, mesylation of **4** followed

Scheme 4. Synthesis of Epoxide 3 from 4



by heating with DBU in DMF generated diene **18** in 68% yield. Removal of the benzoyl group in **18** employing NaOH in CH_3OH provided cyclopentanol **19** in quantitative yield, which upon hydroxyl-induced chemoselective and stereospecific epoxidation with $VO(acac)_2$ and *tert*-butyl hydroperoxide gave the desired methylcyclopentane core **3** with five continuous stereocenters in 85% yield.[20]

Theoretically, the substrate-controlled manner from a chiral starting material will warrant the correctness of all of the chiralities in **3**. However, to avoid the misassignment due to some unexpected reaction pathways, we validate the structure of **3** by two-dimensional NMR analysis combined with the computational method. As shown in Figure 2, with the

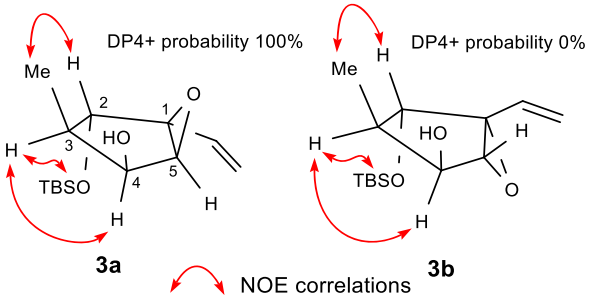


Figure 2. Key NOE correlations of **3** and its two possible epoxy isomers, **3a** and **3b**.

untouched stereochemistry of C-3 in hand, the strong NOE correlations of H-2/Me-3, H-3/TBS, and H-4/H-3 suggested that C2, C3, and C4 adopted 2*S*, 3*R*, and 4*S* configurations, respectively. As the NOE signals regarding the epoxy area are not helpful, two isomers, **3a** and **3b**, with different epoxy orientations were predicted by gauge-independent atomic orbital (GIAO) calculation of its ^1H and ^{13}C NMR chemical shifts (see page S18 of the Supporting Information). The experimental and calculated data were compared by the improved probability DP4+ method,[21] which showed a DP4+ probability score at 100% for *β*-oriented isomer **3a**, indicating that the absolute configuration of **3** was unambiguously assigned as 1*S*,2*S*,3*R*,4*S*,5*S*.

In summary, the methylcyclopentane core containing five consecutive stereocenters present in jatrophane diterpenoids was first constructed in 14 steps via a facile and stereoselective approach. This method may also be applicable to the construction of a general class of a methylcyclopentane core

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with fewer stereocenters, by replacement of the relatively simple raw materials. The densely functionalized methylcyclopentane core obtained in this study may not only serve as a versatile building block for the synthesis of a specific peditithin but also provide access to a group of medicinally important jatrophane analogues in the future. These investigations are continuing.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c03615.

Detailed experimental procedures, spectroscopic characterization of all reported compounds, and ^{1}H and ^{13}C NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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