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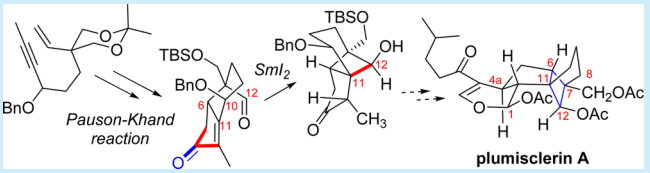
Synthesis of Tricyclo[4,3,1,0^{1,5}]decane Core of Plumisclerin A Using Pauson–Khand Annulation and SmI_2-Mediated Radical Cyclization

Ji-Peng Chen, Wei He, Zhen-Yu Yang, and Zhu-Jun Yao*,†

State Key Laboratory of Bioorganic and Natural Products Chemistry, Collaborative Innovation Center of Chemistry for Life Sciences, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling Road, Shanghai 200032, China

Supporting Information

ABSTRACT: An efficient synthesis of the tricyclo[4,3,1,0^{1,5}]-decane core (B/C/D rings) of plumisclerin A, a unique cytotoxic marine diterpenoid, is described. A Pauson–Khand reaction and a SmI_2-mediated radical 1,4-conjugate addition successfully served as key reactions for construction of the fully functionalized 5,6-fused rings and the highly strained cyclobutanol moiety with correct relative stereochemistries, respectively.



Plumisclerin A (**1**, Figure 1) is a unique marine diterpenoid isolated from the samples of the hitherto uninvestigated

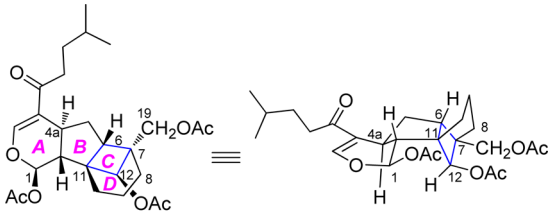


Figure 1. Structure of plumisclerin A (**1**).

soft coral *Plumigorgia terminosclera* collected at Mayotte Island in 2010.[1] Plumisclerin A contains a complex and dense ring system, including a fully substituted cyclobutane (C ring), a bridged cyclohexane (D ring), a multisubstituted cyclopentane (B ring), and a fused dihydropyran ring (A ring). Its unique rigid tricyclo[4,3,1,0^{1,5}]decane skeleton is the first description of such a plumisclerane skeleton in the natural products. Plumisclerin A, whose dihydropyran ring (A ring) is *trans*-fused to the cyclopentane ring (B ring), also differs from many known natural terpenoids having a *cis*-fused dihydropyran ring.[2] Furthermore, seven continuous stereogenic centers including two all-carbon quaternary stereocenters densely distributed in the molecule. Its relative stereochemistries were elucidated as (1*R**,4a*S**,6*S**,7*R**,11*S**,11a*R**,12*S**) by the aid of corresponding HREIMS, COSY, HSQC, HMBC, TOCSY, and NOESY experiments.[1] Besides its challenging structural characters, plumisclerin A displays moderate cytotoxicities against several common tumor cells, such as lung cancer A549 cells (GI_{50} of 4.7 μM), colon cancer HT29 cells (GI_{50} of 2.1 μM) and breast cancer MDA-MB-231 cells (GI_{50} of 6.1 μM).[1] Therefore, plumisclerin A is an attractive and valuable target for both academic and pharmaceutical researches.

As a marine natural product, continuous sample supply of plumisclerin A is considerably difficult through the traditional isolation from natural sources. Organic synthesis is undoubtedly a relatively stable alternative way to acquire plumisclerin A and its interesting derivatives, as well as artificially designed analogues. To date, total synthesis of plumisclerin A, even the synthetic studies, has not appeared in current literatures yet. Herein, we wish to report our efficient synthesis of the B/C/D ring system of plumisclerin A using a Pauson–Khand annulation and a SmI_2-mediated intramolecular conjugate addition.

Our retrosynthesis of plumisclerin A (**1**) is illustrated in Figure 2. As mentioned above, a fully functionalized rigid cyclobutane ring (C ring) is geometrically located at the center of plumisclerin A, which represents one major challenge in the

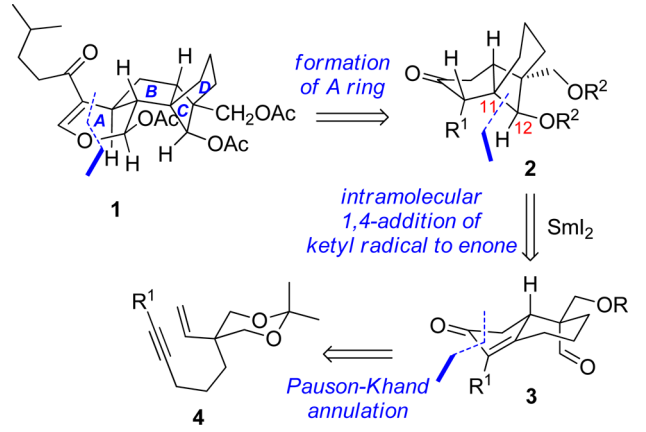


Figure 2. Retrosynthetic analysis of plumisclerin A (**1**).

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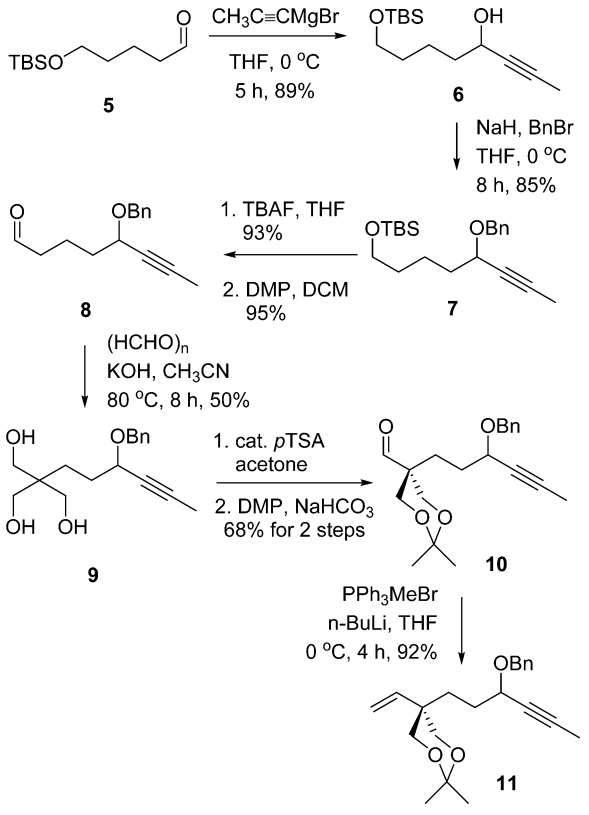
total synthesis. The dihydropyran ring (A ring) was considered to be introduced at late stage to the B/C/D core **2** equipping all the essential stereochemistries. Because SmI_2-mediated free-radical conjugate addition[3] has been proven a practical method for synthesis of natural and unnatural cyclobutanes,[4] the C11−C12 bond of the cyclobutane in core skeleton **2** was decided to be disconnected, resulting in the corresponding B/D-ring intermediate **3**. The cyclopentenone characteristics of intermediate **3** mentioned us that Pauson−Khand annulation[5] of an enyne precursor **4** would be a convenient access.

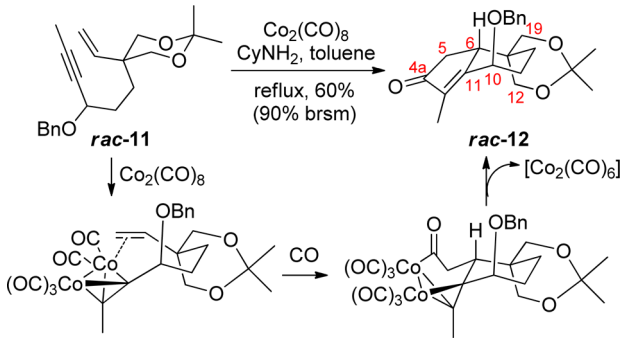
Our synthesis commenced with the preparation of alcohol **6** via an addition of propynyl magnesium to aldehyde **5**.[6] The newly formed hydroxyl group of **6** was then protected as the benzyl ether **7**. It is noteworthy here that introduction of a removable adjacent alkoxyl group to the alkyne functionality was designed to control the stereoselectivity of the key Pauson−Khand reaction[7] (see Scheme 2). Compound **7** was converted into the corresponding aldehyde **8** through removal of TBS group followed by Dess−Martin oxidation.[8] Reaction of aldehyde **8** with excess paraformaldehyde in the presence of KOH afforded triol **9** in moderate yield. Two hydroxyls of the triol **9** were then masked with an acetonide group so that the remaining primary alcohol could be uniquely exposed to the next Dess−Martin oxidation. The resulting aldehyde **10** was converted into the desired enyne precursor **11** by treatment with methyltriphenylphosphonium bromide and *n*-BuLi in THF (Scheme 1).

Pauson−Khand reaction[5,7] of enyne **11** was then explored to construct the designed B/D-ring intermediate containing an α,β-unsaturated cyclopentenone functionality. A variety of combinations of $Co_2(CO)_8$ with various promoters, such as NMO,[9] TMANO[10] and cyclohexylamine ($CyNH_2$)[11] were examined. The desired compound **12** was afforded as the only product in a moderate yield (60% isolated yield, 90% yield based on the recovery of starting material) in the presence of $CyNH_2$. Unfortunately, our further attempts all failed under the conditions with catalytic amount of $Co_2(CO)_8$. According to the NMR experiments of **12**, both C^6−H and C^{10}-OBn was assigned as axial bonds and located in the same face of the molecule. Such a conclusion was further confirmed by the X-ray single crystallographic analysis of compound **17** at a later stage (see below text). The result also confirmed that the C^{10}-OBn of enyne **11** played its perfect roles to stereochemically control the newly born stereogenic center at C6 position when generating the required cyclopentenone ring (Scheme 2).

Scheme 1. Synthesis of the Enyne Precursor 11

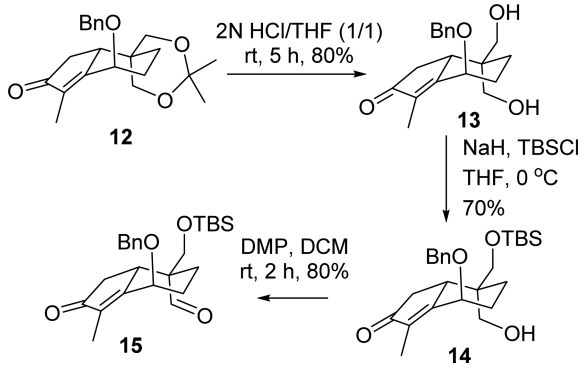


Scheme 2. Pauson−Khand Cyclization of Enyne 11



Removal of the acetonide group was smoothly carried out under acidic conditions at room temperature, affording diol **13** (80% yield) (Scheme 3). Chemoselective protection of the top primary alcohol of diol **13** was successfully achieved with TBSCl in the presence of NaH in THF at 0 °C, affording mono-*O*-TBS ether **14** in 70% yield. The remaining primary alcohol of **14** was then oxidized with Dess−Martin periodinane in DCM at room temperature to give the corresponding aldehyde **15** (80% yield) containing all the essential functionalities for the next free-radical cyclization.

Scheme 3. Synthesis of Aldehyde 15



With enone-aldehyde **15** in hand, formation of the cyclobutane-ring was explored, and it was finally proven to be a smooth process. Treatment of **15** with SmI_2 in mixed solvents of THF and *t*-BuOH (4:1, v/v) at 0 °C afforded the expected bridged-compound **16** in 60% yield[12] (Scheme 4). In order to confirm the relative stereochemical assignment, compound **16** was further converted into the corresponding tri-*p*-nitrobenzoate **17** in three simple steps (Scheme 4). The X-ray

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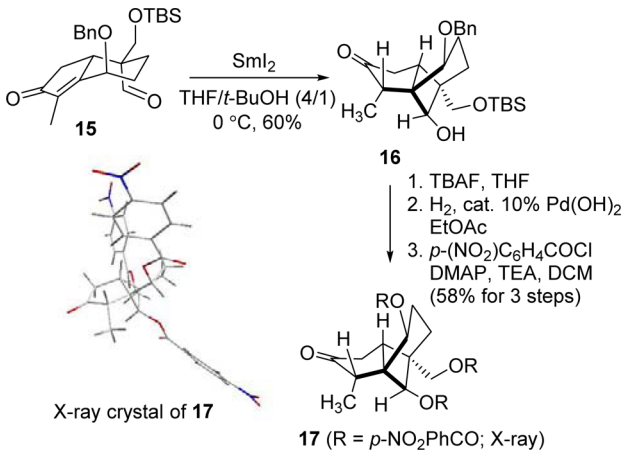
Scheme 4. SmI_2-Mediated Free-Radical Cyclization and Confirmation of the Relative Configurations



single crystallographic analysis of **17** unambiguously indicated that all the stereochemistries in the synthetic B/C/D-ring intermediate **16** matched those in the natural skeleton of plumisclerin A, and also confirmed our previous stereochemical assignment of compound **12** (see Scheme 2).

In summary, a highly diastereoselective synthesis of the tricyclo[4,3,1,$0^{1,5}$]decane core of cytotoxic marine diterpenoid plumisclerin A has been accomplished in 12 steps from the readily available ω-hydroxypentanal. Successful application of SmI_2-mediated intramolecular aldehyde/enone conjugate addition (to generate the functionalized rigid cyclobutanol moiety) and Pauson–Khand annulation (to furnish the fused cyclopentenone with perfect stereochemical controls) featured the whole synthesis with satisfactory efficiency. Further optimization of the reported route to an enantioselective version and completion of the total synthesis of plumisclerin A are currently in progress.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details and characterizations of new compounds, NMR copies of new compounds (PDF), single crystal data of compound **17** (CIF). The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01563.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: yaoz@sioc.ac.cn, yaoz@nju.edu.cn.

Present Address

[†]School of Chemistry and Chemical Engineering, Nanjing University, 22 Hankou Road, Nanjing 210093, China.

Notes

The authors declare no competing financial interest.

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