Tetrahedron Letters 60 (2019) 150992

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Construction of the A/B/C core of mexicanolides via a tandem double-aldol reaction

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ARTICLE INFO

Article history:
Received 17 June 2019
Revised 24 July 2019
Accepted 27 July 2019
Available online 29 July 2019

Keywords:
Limonoid
Mexicanolide
Cascade reaction
Aldol reaction

ABSTRACT

An efficient and concise approach for rapid assembly of the ABC tricyclic carbon skeleton of mexicanolide-type limonoids is described. The acetal/ketal diketoester precursors were prepared from simple starting materials by LiOH-mediated Michael reactions. The ABC tricyclic skeleton bearing multiple stereogenic centers was efficiently constructed by a powerful one-pot cascade reaction, which includes acetal/ketal hydrolysis, double intramolecular aldol condensation, and alkene migration.

Introduction

Limonoids [1], which are also known as tetranortriterpenoids, constitute a large category of terpenoid natural products with a diverse range of structural architectures. Among them, mexicanolides, such as mexicanolide [2], xylomolin C_2 [3], andirolide N [4], and trichinenlide D [5], are B, D-seco limonoids [6] with rigid conformation and congested steric hindrance, which have been isolated from the Meliaceae and Rutaceae families (Fig. 1). These terpenes possess promising biological activities, including defensive activity against insects [7] and a number of pharmacological activities on humans [8], such as anti-HIV [3], anti-inflammatory [9], antiviral [10], neuroprotective [11], and anticancer effects [12]. Structurally, a large number of mexicanolide limonoids share a characteristic cyclohexane-fused bicyclo[3.3.1]nonane core (i.e., ABC skeleton **1**), which is densely functionalized with a bridgehead methyl group and a fused-lactone ring with a distinctive furan group, as well as ester, hydroxyl, ketone, and other substituents. Terpenoids of this structural type also contain multiple contiguous stereogenic centers, which poses a significant challenge for organic synthesis. From a biosynthetic point of view, mexicanolides with the cyclohexane-fused bicyclo[3.3.1]nonane framework are speculated to be precursors of some other types of limonoids, including phragmalin, ecuadorin, dukunolide, and entilin [1a].

The biosynthetic significance and architectural complexity, as well as the notable bioactivities, have rendered mexicanolides highly pursued synthetic targets for decades [13–15]. In 1987, Liu and co-workers reported construction of the CD ring of mexicanolides by Robinson annulation and subsequent oxidative cleavage of the vicinal diol [13]. Williams and co-workers achieved the first enantioselective total syntheses of several mexicanolides (mexicanolide, khayasin, and proceranolide) using a ketal-Claisen rearrangement as the key step, wherein the cyclohexane-fused bicyclo[3.3.1]nonane core was forged by a biomimetic 1,6-conjugate addition [14]. Recently, the Newhouse's group finished the first total synthesis of andirolide N using a divergent strategy, in which the bridged A ring was constructed at the late stage by an intramolecular Michael addition [15]. Despite these successful cases, given the large number of chemically unaccessed members of mexicanolides, development of new and efficient strategies to provide rapid access to the general core structure of mexicanolides is highly demanded.

Cascade reactions, which can rapidly enhance the structural complexity of a specific targeted scaffold by forming several bonds in a one-pot fashion and enable the employment of unstable but versatile intermediates generated in situ, have emerged as a sustainable and powerful tool for synthesis of polycyclic scaffolds [16]. As part of our continued interest in natural product synthesis [17], we report herein our research on construction of the ABC tricyclic framework of mexicanolide-type limonoids from simple building blocks by a cascade reaction, which includes acetal/ketal

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https://doi.org/10.1016/j.tetlet.2019.150992
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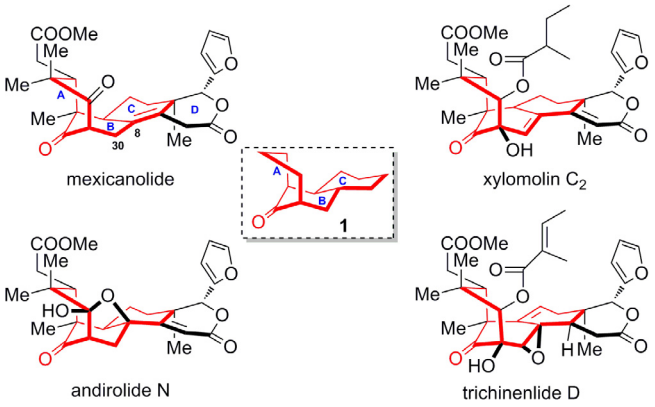


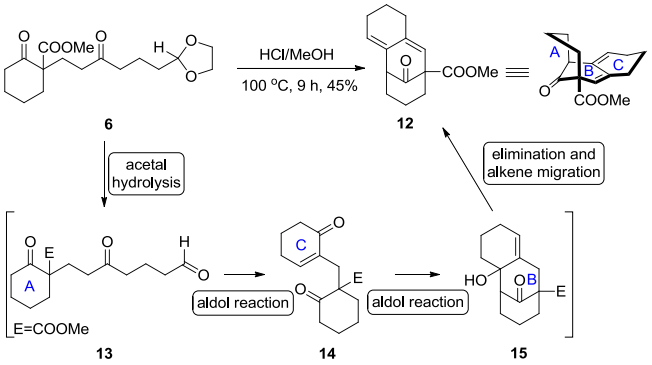
Fig. 1. Representative members of mexicanolide limonoids with the cyclohexane-fused bicyclo[3.3.1]nonane ring system.

hydrolysis, two chemoselective aldol reactions, and alkene migration in one pot.

Results and discussion

The cascade reaction precursors **6** and **11** were prepared from the known compounds **2** [18] and **7** [19], respectively (Scheme 1). Following alkylation with dimethyl malonate, Krapcho decarboxylation [20] of the resulting diester gave rise to monoester **3** in a good yield. Ammonolysis of ester **3** and subsequent Grignard reaction furnished enone **4**, which was subjected to Michael addition with β-ketoester **5** under heterogeneous reaction conditions with solid LiOH as the base and toluene as the solvent to give acetal diketoester **6** in 74% yield [21]. Synthesis of **11** commenced with mono-methyl addition of diamide **7**. Ketal protection of the resultant ketone **8** and subsequent vinyl Grignard reagent addition provided enone **9**. Treatment of **9** with dimethyl β-ketoester **10** under the same conditions for synthesis of acetal **6** afforded ketal **11** in 64% yield. It's worth noting that compound **11** possessing two adjacent quaternary carbon centers can be efficiently accessed under such mild conditions.

With diketoester **6** and **11** in hand, we proceeded to investigate one-pot construction of the tricyclic cyclohexane-fused bicyclo [3.3.1]nonane skeleton. After extensive investigation of various Lewis acids (e.g., $ZnBr_2$, $Sc(OTf)_3$, $Yb(OTf)_3$, $AlCl_3$, and $BF_3{\cdot}OEt_2$) and Brønsted acids (e.g., *p*-TsOH, MsOH, TfOH, H_2SO_4, HCl, and $HClO_4$), solvents (e.g., THF, CH_3CN, toluene, $MeNO_2$, and MeOH), as well as reaction temperatures, we found that the tricyclic framework could be built in a straightforward one-pot reaction of **6** in the presence of HCl in MeOH, affording tricyclic dienone **12** in 45% isolated yield (Scheme 2).

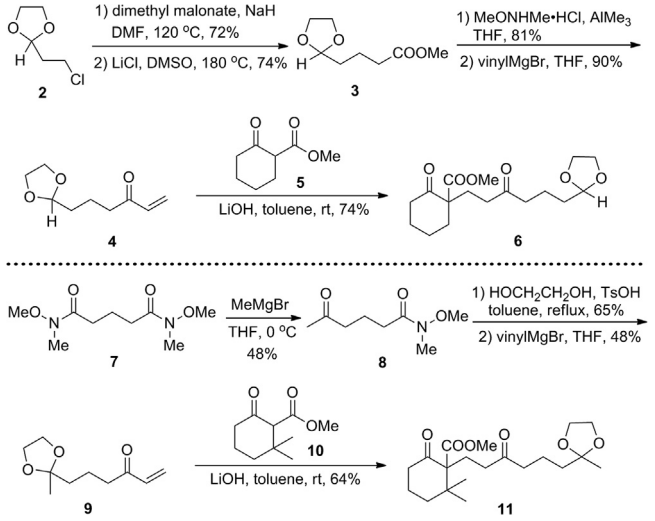


Scheme 2. Cascade reaction of **6** and the proposed reaction pathway.

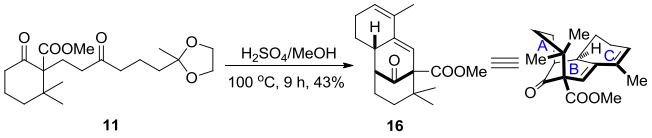
To understand the reaction process of this transformation, a plausible reaction mechanism was proposed. Firstly, acid-mediated acetal hydrolysis generates δ-oxo aldehyde **13**. Secondly, the first intramolecular aldol condensation of **13** produces **14** with the formation of C ring. Thirdly, the second intramolecular aldol reaction between the ketone and the enone chemoselectively generates tricyclic intermediate **15**, which undergoes dehydration and alkene migration to give the desired tricyclic ketone **12**. To support the proposed reaction mechanism, preliminary mechanistic studies were conducted. Bicyclic intermediate **14** was isolated as a stable compound in 41% yield from the HCl-mediated reaction of **6** by lowering the reaction temperature and shortening the reaction time. **14** could be smoothly converted to **12** under the typical cascade reaction conditions (see the Supporting Information for details). Those results are consistent with our proposed reaction pathway involving enone **14** as the key intermediate.

To investigate the influence of additional substituents on this cascade reaction, ketal **11** with a gem-dimethyl group was subjected to the typical cascade reaction conditions (i.e., HCl/MeOH). However, no desired tricyclic product was observed. Further screening of the acids revealed that H_2SO_4 was an efficient acid to promote the cascade reaction of **11**, affording multi-substituted tricyclic dienone **16** in 43% isolated yield (Scheme 3).

The structures and stereochemistry of **12** and **16** were unambiguously determined by X-ray crystallographic analysis (Fig. 2) [22]. It is noteworthy that the double bond locations on the C rings of products **12** and **16** are different. Vysotskaya and co-workers reported that the dehydration of 2-hydroxy tricyclo-[7.3.1.$0^{2,7}$] tridecan-13-one derivatives, which are saturated equivalents of tentative intermediate **15**, would lead to products with double bonds located at different sites using different acids as the promoters [23]. In our case, **12** and **16** with different double bond locations were speculated to be generated respectively as the thermodynamic products under the conditions of heating and strong acids. Additionally, the double bonds located on B rings of



Scheme 1. Preparation of precursors **6** and **11**.



Scheme 3. Cascade reaction of **11**–**16**.

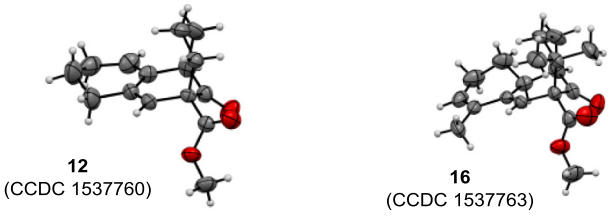


Fig. 2. X-ray structures of **12** and **16**.

both products coincide with the ubiquitous C8–C30 double bond in natural limonoids.

Conclusion

We have developed a novel and efficient tandem process of acetal/ketal hydrolysis/double aldol condensation for one-pot construction of the cyclohexane-fused bicyclo[3.3.1]nonane skeleton, core structure of the widespread mexicanolide-type limonoids. This strategy is operationally simple and allows rapid access to complex tricyclic compounds in acceptable yields from readily available starting materials.

Acknowledgments

We are grateful for the financial support from the National Natural Science Foundation of China (21672029, 21871033, and 21702023), Chongqing Science and Technology Commission (cstc2018jcyjAX0421), and Sharing Fund of Large-Scale Equipment (201903150122, 201903150123, 201903150124) of Chongqing University. We thank Mr Xiangnan Gong (CQU) for X-ray crystallographic analysis.

Appendix A. Supplementary data

Supplementary data (experimental procedures, mass and NMR spectral data for compounds) to this article can be found online at https://doi.org/10.1016/j.tetlet.2019.150992.

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