A Journal of the Gesellschaft Deutscher Chemiker

Angewandte International Edition

GDCh

Chemie

www.angewandte.org

Accepted Article

Title: Enantioselective Total Synthesis of (+)-Plumisclerin A

Authors: Ming Gao, Ye-Cheng Wang, Kai-Rui Yang, Wei He, Xiao-Liang Yang, and Z.-J. Yao

To be cited as: *Angew. Chem. Int. Ed.* 10.1002/anie.201808517
Angew. Chem. 10.1002/ange.201808517

Link to VoR: http://dx.doi.org/10.1002/anie.201808517
http://dx.doi.org/10.1002/ange.201808517

WILEY-VCH

10.1002/anie.201808517

Accepted Article

WILEY-VCH

Enantioselective Total Synthesis of (+)-Plumisclerin A

Ming Gao,[a] Ye-Cheng Wang,[a] Kai-Rui Yang,[a] Wei He,[b] Xiao-Liang Yang,[a] and Zhu-Jun Yao[a]*

Dedicated to Professor Yu-Lin Wu on the occasion of his 80th birthday

Abstract: The first and enantioselective total synthesis of (+)-plumisclerin A, a novel unique complex cytotoxic marine diterpenoid, has been accomplished. Around the central cyclopentane anchorage, a sequential ring-formation protocol was adopted to generate the characteristic tricycle[4.3.1.$0^{1,5}$]decane and *trans*-fused dihyrdopyran moiety. Scalable enantioselective La(III)-catalyzed Michael reaction, palladium(0)-catalyzed carbonylation and SmI_2-mediated radical conjugate addition were successfully applied in the synthesis, affording multiple grams of the complex and rigid B/C/D-ring system having six continuous stereogenic centers and two all-carbon quaternary centers. The *trans*-fused dihyrdopyran moiety with an *exo* side-chain was furnished in final stage through sequential redox transformations from a lactone precursor, which overcome the largish steric strain of the dense multiring system. The reported total synthesis also confirms the absolute chemistries of natural (+)-plumisclerin A.

Since the isolation of xenicin (Fig. 1, **1**), the first xenicane diterpenoid from the soft coral *Xenia elongate* in 1977,[1] more than a hundred diverse members have been discovered in this family. A cyclononane ring and an isoprenyl side chain, or their diverse modification forms, are characteristic structural features for all the xenicanes.[2] This family of marine products were also reported to display a wide range of biological activities, such as cytotoxic, antibacterial and antitumor activities.[2] Unfortunately, to date, only few total syntheses have been reported.[3] Plumisclerin A, a new unique member of this family, was recently isolated and characterized by Reyes and co-workers from the cytotoxic crude extracts of soft coral *Plumigorgia terminosclera* in 2010, showing low-micromolar cytotoxicity against multiple tumor cells, such as A549 cells (GI_{50} of 4.7 μM), HT29 cells (GI_{50} of 2.1 μM) and MDA-MB-231 cells (GI_{50} of 6.1 μM).[4] Compared to other xenicane members, plumisclerin A is structurally more complex, featuring a compact tetracyclic (6/5/4/6-fused ring) system. This brand-new terpene carbon-skeleton is newly named as plumisclerane (**5**, Fig. 1A). Plumisclerin A was proposed to be biogenetically transformed from cristaxenicin A (6/9-fused ring system, **2**, Fig. 1A), a known xenicane, through an intramolecular [2+2] cycloaddition

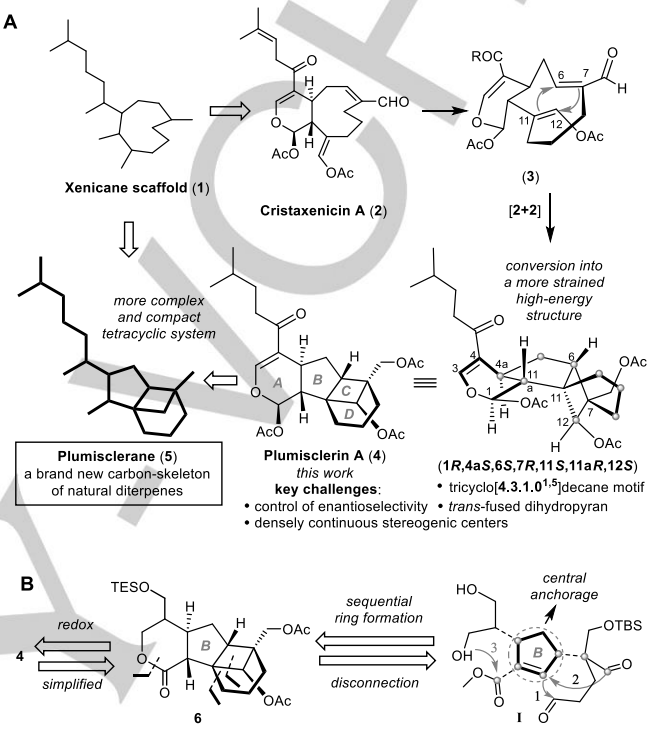


Figure 1. A) Possible biosynthetic pathway to plumisclerin A (**4**); and B) general consideration of sequential ring-formation based on a multi-substituted cyclopentane (ring B) anchorage.

(**3**, Fig. 1A).[4,5] However, the absolute stereochemistry of plumisclerin A remains unconfirmed yet.

Existence of an unusual tricyclo[4.3.1.$0^{1,5}$]decane with high congestion and rigidity makes plumisclerin A an attractive synthetic target. The complex 5/4/6-ring system including a fully substituted and two quaternary carbon centers bridged cyclobutane (C ring) and seven continuous stereocenters renders it many predictable and unpredictable challenges for chemical synthesis. An additional synthetic difficulty lies in the dihydropyran ring (ring A) with an *exo*-side chain, which is *trans*-fused to the central cyclopentane. For the sp^2 hybrid nature of both C3 and C4 will make the whole skeleton to be further rigid and higher tension. In the past four decades, the synthesis of xenicane diterpenoid having such a *trans*-fused unsaturated pyranoside moiety has proven to be difficult and has not been realized yet.[2,3,6] Herein, we report the first and enantioselective total synthesis of natural (+)-plumisclerin A, as well as confirmation of the absolute stereochemistry.

Structural perspective of plumisclerin A reveals that cyclopentane (ring B) is located at the center of the molecule. Therefore, the common cyclopentane could be devised as an anchorage to support sequential formation of other rings (I, Fig 1B), such as construction of the complex 6/5/4/6- tetracyclic framework (**6**, Fig 1B) and generation of *trans*-fused dihydropyran

[a] M. Gao, Y.-C. Wang, K.-R. Yang, Dr. W. He, Prof. Dr. X.-L. Yang, and Prof. Dr. Z.-J. Yao
State Key Laboratory of Coordination Chemistry, and Jiangsu Key Laboratory of Advanced Organic Materials
School of Chemistry and Chemical Engineering
Nanjing University
163 Xianlin Avenue, Nanjing, Jiangsu 210023, CHINA
E-mail: yaoz@nju.edu.cn

[b] Dr. W. He
STA Pharmaceutical Co. Ltd.
90 Delin Road, Waigaoqiao, Shanghai, China

Supporting information for this article is given via a link at the end of the document.((Please delete this text if not appropriate))

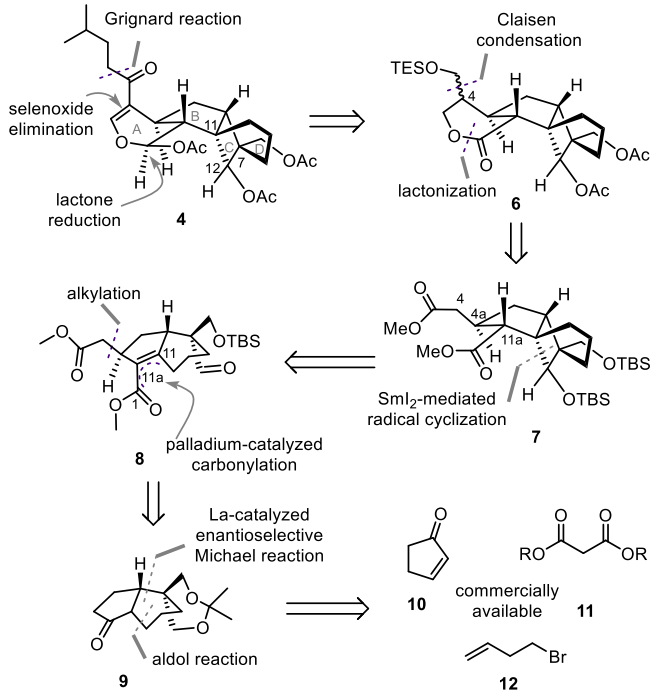
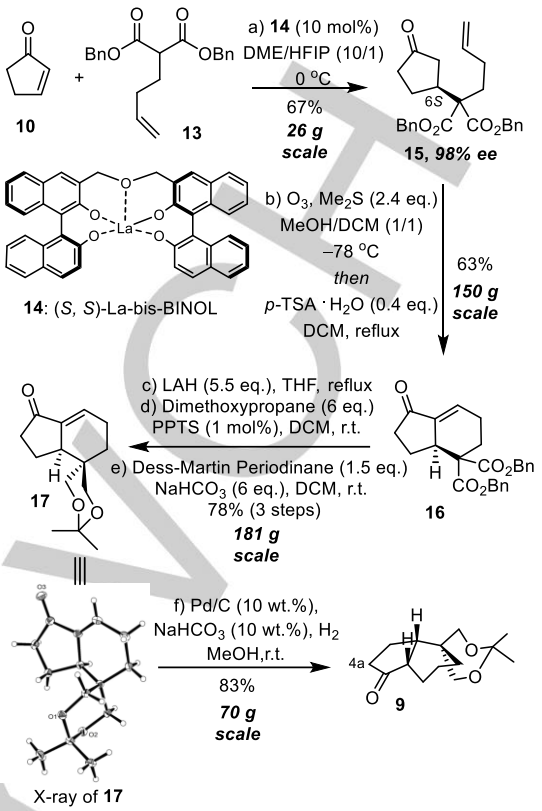


Figure 2. Retrosynthetic analysis of plumisclerin A (**4**).

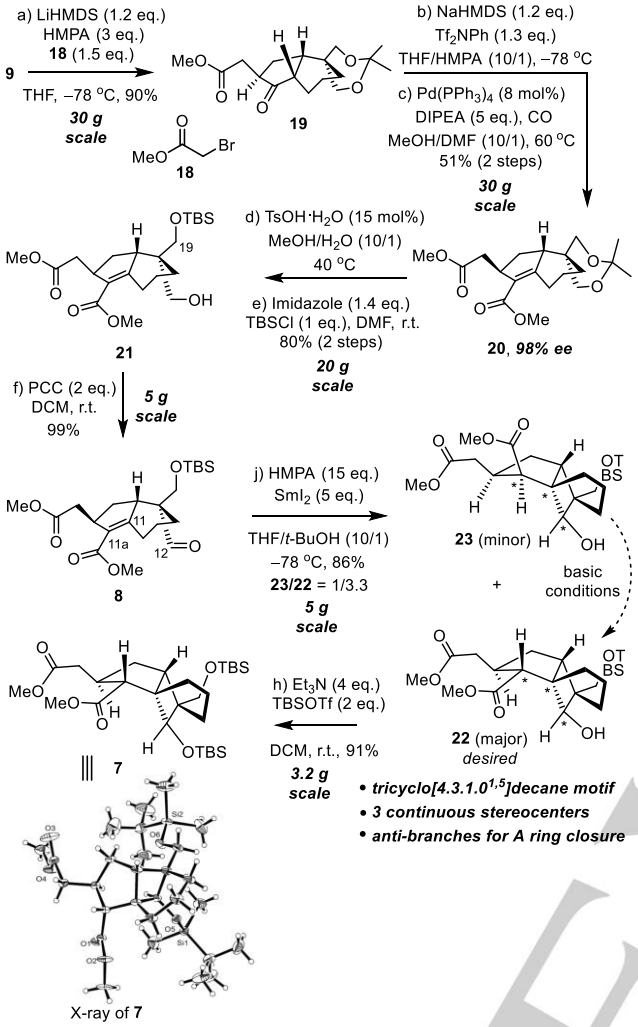


Scheme 1. Scalable enantioselective synthesis of *cis*-bicyclic ketone **9**.

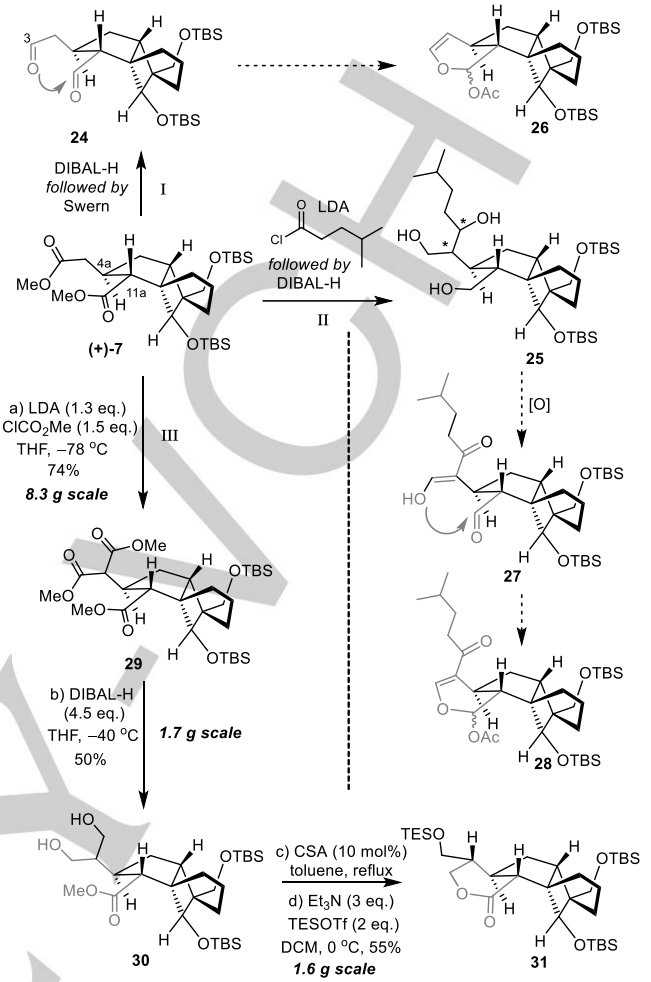
moiety via proper redox sequence.[7,8,9] Based on such considerations, plumisclerin A (**4**) can be retrosynthetically simplified to a *trans*-lactone **6** (including all rings) by functional group manipulations (Fig 2). Lactone **6** is then disassembled into tricyclo[4.3.1.$0^{1,5}$]decane system **7**. A SmI_2-mediated intramolecular radical conjugate addition could be exploited to form cyclobutanol **7**.[6] Compound **8** could be prepared from the corresponding ketone precursor **9** through introduction of the two-carbon substituent at the C4a position, and Pd-catalyzed carbonylation. Cyclic ketone **9** is traced back to cyclopent-2-en-1-one **10** (origin of the cyclopentane anchorage), malonate **11** and bromide **12** by enantioselective La-catalyzed Michael reaction[10] and intramolecular aldol reaction. We hypothesized that the absolute configuration of the C6 of plumisclerin A is *S*, based on its biogenetic relationship with cristaxenicin A (Fig 1A).[5a]

The first task of this total synthesis is to achieve and scale up the asymmetric synthesis of tricyclo[4.3.1.$0^{1,5}$]decane core **22** (Schemes 1 and 2). As shown in scheme 1, based on the work of Shibasaki,[10] the first stereogenic center was enantioselectively introduced by catalytic asymmetric conjugate addition of malonate **13**[11] to cyclopentenone **10** with the catalysis of (*S,S*)-La-bis-BINOL **14** (10 mol%).[10] Our procedure could reliably provide the adduct (*S*)-**15** on a reasonably large scale (26 g of **10**/batch, 67% yield, and >98% ee by HPLC). It is noteworthy that the rare-earth catalyst, (*S,S*)-La-bis-BINOL **14**, could be recovered and re-applied to the same reaction for two additional times (totally three times), providing (*S*)-**15** with comparable enantiomeric purity (see Supporting Information for more details). Ozonolysis of the terminal olefin **15** followed by intramolecular aldol reaction and dehydration in the presence of catalytic amount of *p*-TSA•H_2O furnished enone **16** in 63% yield, in which the newly formed six-membered ring is the first ring docked to the central cyclopentane. Complete reduction of the diester **16** was carried out with $LiAlH_4$, and the resulting 1,3-diol was selectively protected with 2,2-dimethoxypropane. Dess-Martin oxidation of the remaining alcohol provided enone **17** (78% overall yield, 3 steps from **16**), whose absolute stereochemistry was confirmed by the corresponding X-ray single crystallographic analysis. Catalytic hydrogenation of **17** was carried out in the presence of 10% Pd/C and $NaHCO_3$ in MeOH, affording the *cis*-bicyclic ketone **9** in 83% yield.

Diastereoselectivity of the C4a-alkylation of ketone **9** is crucial to late-stage establishment of the *trans*-fused dihyrdopyran ring. To our delight, reaction of the enolate prepared from bicyclic ketone **9** with methyl bromoacetate **18** afforded ketone **19** in 90% yield, as a single diastereoisomer with desired stereochemistry (Scheme 2). Treatment of sodium enolate derived from **19** with $PhNTf_2$ followed by Pd(0)-catalyzed carbonylation (cat. $Pd(PPh_3)_4$, CO, MeOH, DMF)[12] provided α,β–unsaturated esters **20** (51% yield for 2 steps; 98% ee by chiral HPLC). Comparison to that with NaHMDS, use of either LiHMDS or KHMDS in this reaction resulted in poor regioselectivities in the enolization of ketone **19**. Then, the *O,O*-acetonide protecting group of **20** was removed under acidic conditions, and one primary alcohol at C19 was regioselectively protected with TBSCl, giving mono-silyl ether **21** (80% yield for 2 steps). Oxidation of the remaining alcohol **21** with pyridinium chlorochromate (PCC) provided aldehyde **8** (99% yield), the precursor for constructing the rigid tricyclodecane system. A SmI_2-mediated ketyl radical 1,4-addition[6,13] was



Scheme 2. Gram-scale synthesis of tricyclo[4,3,1,$0^{1,5}$]decane intermediate **22**.

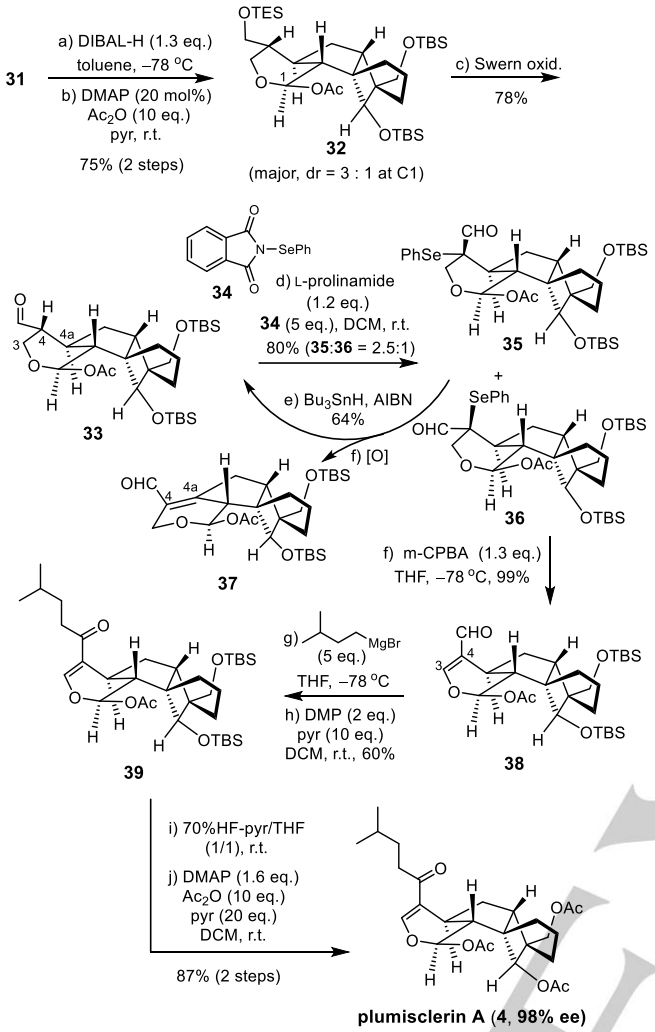


Scheme 3. Protocols to construct dihydropyran ring *trans*-fused to the central cyclopentane.

employed to establish the tricyclodecane system**,** and the final optimized ratio of **22** and **23** (dr at C11a) was improved up to 3.3:1 on a multi-gram scale, using SmI_2 (5 equiv.) and HMPA (15 equiv.) in THF and *t*-BuOH (10:1, v/v) at −78 °C. This reaction generated three new continuous stereogenic centers at C11a, C11 and C12. It is believed that the diastereoselectivity at C11a would be influenced by temperature and proton source (see Supporting Information for more details). In addition, formation of the cyclobutane pushes the D-ring to adopt a high-energy boat conformation, according to the X-ray analysis of a following intermediate **7** (Scheme 2). Unfortunately, our attempts to convert the undesired diastereomer **23** into **22** all failed under a variety of alkaline conditions, leading to some kinds of unclear fragmentations. The newly born hydroxyl group at C12 of **22** was then protected with TBSOTf and Et_3N, affording diester **7** in 91% yield.

With multiple-gram quantity of diester **7** in hand, we began to investigate the final ring formation, a dihydropyran *trans*-fused to the cyclopentane. Several protocols were attempted based on intermediate **7** (protocols I, II, III, Scheme 3). Though protocols I and II seem to be more direct, formation of the strained *trans*-dihydropyran moiety (A ring) is exceptionally challenging under non-biogenetic conditions.[8,9] The X-ray analysis of diester intermediate **7** (Scheme 2) also showed that the torsion angle of the two adjacent branches (at C4a and C11a positions, respectively) was spatially unfavorable for the expected ring-closure. Indeed, we failed to convert diester **7** to the corresponding dihydropyrans either by protocol I or II. To resolve the above obstacle, an indirect approach based on a lactonization (protocol III) was then taken into our consideration. Treatment of **7** with LDA and methyl bromoacetate afforded malonate **29** (74% yield) chemoselectively.[14] Selective reduction of malonate **29** was accomplished with DIBAL-H at −40 °C.[15] The favorable feature of diol **30** is that one alcohol can be applied to construct A ring, and the other can be employed to install the side-chain branch later. Following this idea, diol **30** was converted into the corresponding lactone with a catalytic amount of CSA,[16] and the remaining hydroxyl group was protected with TESOTf to provide stable tetracyclic lactone **31** in 55% yield (2 steps). Sequential redox transformation of lactone **31** into plumisclerin A was then executed (Scheme 4).

10.1002/anie.201808517



Scheme 4. Completion of the total synthesis of (+)-plumisclerin A.

Reduction of lactone **31** followed by O-acylation afforded acetal **32** (75% yield, 3:1 dr at C1). Removal of TES group followed by Swern oxidation[17] of the resulting alcohol (at C13) furnished aldehyde **33** in 78% yield in one pot. The subsequent introduction of a C=C bond to aldehyde **33**, between C3 and C4, was proven to be very troublesome. Because of its highly rigid structure, such an operation upon **33** has to overcome much higher energy barrier. Indeed, formation of the double bond failed by direct oxidations such as IBX oxidation[18] and Saegusa oxidation.[19] Meanwhile, it also failed to form α-seleno product using classical conditions (M^+HMDS with PhSeX, silyl enol ether with PhSeX and piperidine with PhSeX).[20] Finally, L-prolinamide-promoted α-selenenylation of aldehyde **33** was found to work well when N-(phenylseleno)phthalimide **34** was used as the seleno reagent.[21] The reaction was carried out with L-prolinamide (1.2 eq.) and **34** (5 eq.), affording two separable seleno diastereomers **35** and **36** (80% yield, 2.5:1 dr). To our surprise, alternative use of D-prolinamide gave a similar diastereoselectivity for the two seleno-products. The diastereoselectivity of this reaction seems to be highly controlled by the spatial environment of **33**. Oxidative elimination of seleno compound **36** furnished the desired α,β-unsaturated aldehyde **38**, which bears a further strained molecule skeleton. While, the parallel oxidative elimination of the other seleno product **35** delivered **37** only, whose double bond is located between C4 and C4a by following general oxidative *syn*-elimination mechanism.[22] In order to save the material, the undesired seleno-product **35** was recycled back to aldehyde **33** (64% yield) by reduction with tributyltin hydride in the presence of azobisisobutyronitrile (AIBN) in toluene at 110 °C.[23]

Introduction of the isopentyl group into enal **38** failed when the moderately reactive isopentyl cerium reagents was employed.[24] After a number of screenings, the 1,2-addition to enal **38** was smoothly carried out with isopentyl Grignard reagents at −78 °C. The resulting allylic alcohol was oxidized with Dess-Martin periodinane to yield α,β-unsaturated ketone **39**. Finally, complete removal of O-silyl ethers of **39** with 70% HF-pyridine[25] followed by full O-acylation with acetic anhydride and DMAP delivered (+)-plumisclerin A (**4**) in 87% yield (98% ee by chiral HPLC). The NMRs, HRMS, IR, and optical rotation (synthetic: $[\alpha]_D$ 105.3; natural: $[\alpha]_D$ 125.0) of our synthetic sample were in well agreement with those reported for natural product.[4] Completion of the first catalytic enantioselective total synthesis of (+)-plumisclerin A also enabled us to unambiguously confirm the absolute chemistry of natural compound as (1*R*,4a*S*,6*S*,7*R*,11*S*,11a*R*,12*S*). It's noteworthy here that this synthesis is also the first example for plumisclerane marine diterpenoids (Fig 1, **5**).

In summary, the first and enantioselective total synthesis of (+)-plumisclerin A, a challenging cytotoxic marine diterpenoid containing a novel rigid multiring carbon-skeleton, has been achieved in 27 longest linear steps. A sequential ring-construction protocol geometrically supported by the central cyclopentane was performed in the total synthesis. Successful application of scalable La(III)-catalyzed enantioselective Michael reaction and diastereoselective intramolecular SmI_2-mediated ketyl radical conjugate addition enabled multiple gram preparation of the complex rigid tricyclo[4,3,1,$0^{1,5}$]decane core. Internal lactionization provided a practical way to furnish the *trans*-fused dihydropyran moiety, leading to final completion of the total synthesis. The reported total synthesis is believed to provide an entrance to novel medicinally interesting complex derivatives of marine xenicanes, and opens new opportunities for the related biological investigations.

Acknowledgements

This project is financially supported by National Key Research and Development Program of China (No. 2018YFC0310900), National Natural Science Foundation of China (No. 21532002, 21761142001), and the Fundamental Research Funds for the Central Universities (No. 020514380131). The authors also thank Drs. Zhenyu Yang and Ji-Peng Chen (SIOC), and Prof. Shaozhong Wang (NJU) for their early efforts and helpful discussions to this work.

Keywords: plumisclerin A • total synthesis • conjugate addition • samarium diiodide • scalable enantioselective synthesis

[1] D. J. Vanderah, P. A. Steudler, L. S. Ciereszko, F. J. Schmitz, J. D. Ekstrand, D. van der Helm, *J. Am. Chem. Soc.* **1977**, *99*, 5780.

[2] Review on *Xenia* diterpenoids: (a) L. Betschatr, K.-H. Altmann, *Current Pharm. Design*, **2015**, *21*, 5467. (b) T. Huber, L. Weisheit, T. Magauer, *Beilsten J. Org. Chem*. **2015**, *11*, 2521.

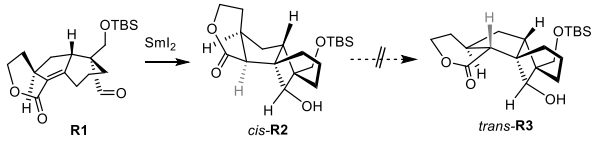
[3] Total syntheses of Xenia diterpenoids: (a) L. A. Paquette, T.-Z. Wang. E. P inard, *J. Am. Chem. Soc.* **1995**, *117*, 1455. (b) D. Renneberg, H. Pfander, C. J. Leumann, *J. Org. Chem.* **2000**, *65*, 9069. (c) O. V. Larionov, E. J. Corey, *J. Am. Chem. Soc.* **2008**, *130*, 2954. (d) C. Hamel, E. V. Prusov, J. Gertsch, W. B. Schweizer, K.-H. Altmann, *Angew. Chem., Int. Ed.* **2008**, *47*, 10081. (e) D. R. Williams, M. J. Walsh, N. A. Miller, *J. Am. Chem. Soc.* **2009**, *131*, 9038.

[4] M. J. Martín, R. Fernández, A. Francesch, P. Amade, S. S. de Matos-Pita, F. Reyes, C. Cuevas, *Org. Lett.* **2010**, *12*, 912.

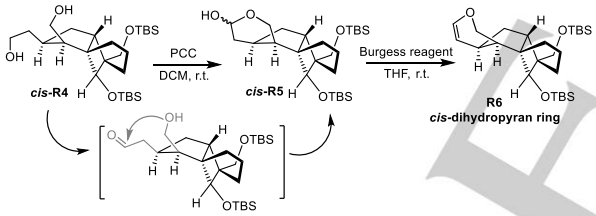
[5] (a) S.-T. Ishigami, Y. Goto, N. Inoue, S.-I. Kawazu, Y. Matsumoto, Y. Imahara, M. Tarumi, H. Nakai, N. Fusetani, Y. Nakao, *J. Org. Chem*. **2012**, *77*, 10962. (b) V. Sio, J. G. Harrison, D. Tantillo, *Tetrahedron Letters,* **2012**, *53*, 6919.

[6] J.-P. Chen, W. He, Z.-Y. Yang, Z.-J Yao, *Org. Lett.* **2015**, *17*, 3379.

[7] Our experiments showed that, the SmI_2-based free-radical cyclization of an unstaturated lactone **R1** only gave a cis-fused product **R2**, which was unable to convert into **R3** under alkaline conditions.



[8] Compared to that of *trans*-fused dihydropyran*,* our experiment showed that the *cis*-fused dihydropyran ring could be formed easily. For example, *cis*-diol **R4** was converted into **R6** by oxidation with PCC and dehydration with Burgess reagent under mild conditions.



[9] As shown in Scheme 3, intramolecular cyclization of dialdehyde **24** was firstly tried to deliver unsaturated pyranoside **26** in one step (protocol I). However, inefficient generation of the enol derived from the aldehyde (C3 position) and the rigid tricyclodecane architecture blocked such a cyclization under various conditions, including those using different bases, Bronsted acids and Lewis acids. In order to stabilize the enol intermediate, 1,3-dicarbonyl compound **27** was designed for the cyclization step (protocol II). However, oxidation of the diasteromeric mixture of triol **25** did not afford **27** as a stable compound or useful intermediate for further transformation.

[10] (a) R. Takita, T. Ohshima, M. Shibaski, *Tetrahedron Lett.* **2002**, *43*, 4661. (b) S. Matsunaga, J. Das, J. Roels, E. M. Vogl, N. Yamamoto, T. Iida, K. Yamaguchi, M. Shibasaki, *J. Am. Chem. Soc.* **2000**, *122*, 2252.

[11] T. Connolly, Z. Wang, M. A. Walker, I. M. McDonald, K. M. Peese, *Org. Lett.* **2014**, *16*, 4444.

[12] (a) S. Cacchi, E. Morera, G. Ortar, *Tetrahedron Lett.* **1985**, *26*, 1109. (b) H. Sun, J. Yang, K. E. Amaral, B. A. Horenstein, *Tetrahedron Lett.* **2001**, *42*, 2451. (c) T. Magauer, J. Mulzer, K. Tiefenbacher, *Org. Lett.* **2009**, *11*, 5306.

[13] (a) D. J. Edmonds, D. Johnston, D. J. Procter, *Chem. Rev.* **2004**, *104*, 3371. (b) H.-J. Gong, X.-S. Jia, H.-B. Di, *Chinese. J. Org. Chem.* **2010**, *30*, 939. (c) H.-Y. Chuang, M. Isobe, *Org. Lett.* **2014**, *16*, 4166. (d) N. Zhao, S. Yin, S. Xie, H. Yan, P. Ren, G. Chen, F. Chen, J. Xu, *Angew. Chem., Int. Ed.* **2018**, *57*, 3386. (e) E. P. Farney, S. S. Feng, F. Schäfers, S. E. Reisman, *J. Am. Chem. Soc.* **2018**, *140*, 1267.

[14] T. R. Kelly, X. Cai, B. Tu, E. L. Elliott, G. Grossmann, P. Laurent, *Org. Lett.* **2004**, *6*, 4953.

[15] M. Tercel, W. A. Denny, *J. Chem. Soc., Perkin Trans. 1* **1998**, *3*, 509.

[16] M. Ihara, T. Suzuki, M. Katogi, N. Taniguchi, K. Fukumoto, *J. Chem. Soc., Chem. Commun.* **1991**, 646.

[17] (a) A. Rodríguez, M. Nomen, B. W. Spur, J. J. Godfroid, *Tetrahedron Lett.* **1999**, *40*, 5161. (b) M. T. Crimmins, M. W. Haley, E. A. O'Bryan, *Org. Lett.* **2011**, *13*, 4712.

[18] (a) K. C. Nicolaou, T. Montagnon, P. S. Baran, *Angew. Chem. Int. Ed.* **2002**, *41*, 993. (b) K. C. Nicolaou, D. L. F. Gray, T. Montagnon, S. T. Harrison, *Angew. Chem. Int. Ed.* **2002**, *41*, 996.

[19] Y. Ito, T. Hirao, T. Saegusa, *J. Org. Chem.* **1978**, *43*, 1011.

[20] (a) A. B. Smith III, T. Bosanac, K. Basu, *J. Am. Chem. Soc.* **2009**, *131*, 2348. (b) D. R. Williams, K. Nishitani, *Tetrahedron Lett.* **1980**, *21*, 4417. (c) L. A. Paquette, X. Wang, *J. Org. Chem.* **1994**, *59*, 2052. (d) S. A. Ramachandran, R. K. Kharul, S. Marque, P. Soucy, F. Jacques, R. Chênevert, P. Deslongchamps, *J. Org. Chem.* **2006**, *71,* 6149. (e) J. Li, W. Zhang, F. Zhang, Y. Chen, A. Li, *J. Am. Chem. Soc.* **2017,** *139*, 14893.

[21] (a) J. Wang, H. Li, Y. Mei, B. Lou, D. Xu, D. Xie, H. Guo, W. Wang, *J. Org. Chem.* **2005**, *70*, 5678. (b) W. Wang, J. Wang, H. Li, *Org. Lett.* **2004**, *6*, 2817.

[22] H. J. Reich, Organic Reactions, *Vol. 44,* Wiley: New York, **1993**, Chapter 1.

[23] (a) D. L. J. Clive, G. J. Chittattu, V. Farina, W. A. Kiel, S. M. Menchen, C. G. Russell, A. Singh, C. K. Wong, N. J. Curtis, *J. Am. Chem. Soc.* **1980**, *102*, 4438. (b) K. C. Nicolaou, J. Pastor, S. Barluenga, N. Winssinger, *Chem. Commun.* **1998**, 1947. (c) M. A. Corsello, J. Kim, N. K. Garg, *Nat. Chem.* **2017**, *9*, 944.

[24] A. Krasovskiy, F. Kopp, P. Knochel, *Angew. Chem. Int. Ed.* **2006**, *45*, 497.

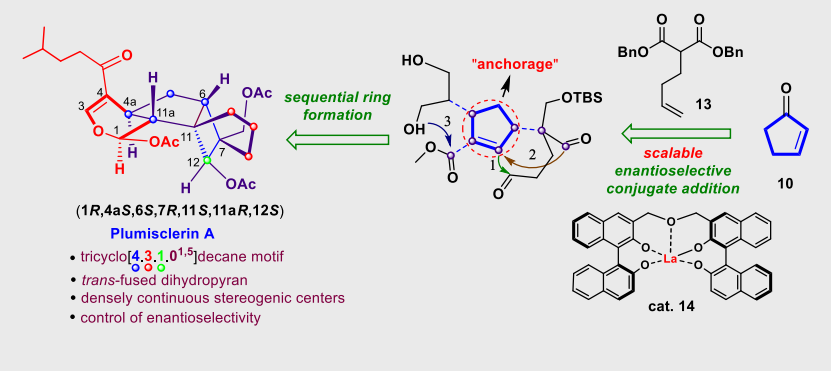
[25] P. A. Wender, C. T. Hardman, S. Ho, M. S. Jeffreys, J. K. Maclaren, R. Quiroz, S. M. Ryckbosch, A. J. Shimizu, J. L. Sloane, M. C. Stevens, *Science*. **2017**, *358*, 218.

10.1002/anie.201808517

WILEY-VCH

Entry for the Table of Contents (Please choose one layout)

COMMUNICATION



*Ming Gao, Ye-Cheng Wang, Kai-Rui Yang, Wei He, Xiao-Liang Yang, and Zhu-Jun Yao**

Page No. – Page No.

Enantioselective Total Synthesis of (+)-Plumisclerin A

The first and enantioselective total synthesis of (+)-plumisclerin A, a cytotoxic complex marine diterpenoid featuring with a brand-new unique carbon-skeleton of highly strained tricycle[4.3.1.0^{1,5}]decane, has been accomplished. A sequential ring-formation protocol was employed using the central cyclopentane as the anchorage, and scalable enantioselective La(III)-catalyzed Michael addition, Pd(0)-catalyzed carbonylation and SmI_2-mediated intramolecular radical conjugate addition successfully served as the key reactions in this synthesis.