A Journal of the Gesellschaft Deutscher Chemiker

Angewandte International Edition GDCh Chemie

www.angewandte.org

Accepted Article

Title: Total Synthesis of (−)-Glaucocalyxin A

Authors: Yanxing Jia, Jiuzhou Guo, Bo Li, Weihao Ma, and Mallesham Pitchakuntla

To be cited as: *Angew. Chem. Int. Ed.* 10.1002/anie.202005932

Link to VoR: https://doi.org/10.1002/anie.202005932

WILEY-VCH

10.1002/anie.202005932

WILEY-VCH

COMMUNICATION

Total Synthesis of (−)-Glaucocalyxin A

Jiuzhou Guo, Bo Li, Weihao Ma, Mallesham Pitchakuntla, and Yanxing Jia*

Abstract: A practically useful method for the formation of the highly oxygenated bicyclo[3.2.1]octane ring system by $Mn(OAc)_3$-mediated radical cyclization of alkynyl ketones has been developed, which opens up a new avenue to the total synthesis of a number of highly oxidized diterpenoids. Application of this method allows the first total synthesis of (−)-glaucocalyxin A. Other salient features of the synthesis include a highly enantioselective conjugate addition/ acylation cascade reaction, a Yamamoto aldol reaction, and an intramolecular Diels-Alder reaction to assemble the A/B ring system.

The bicyclo[3.2.1]octane system is the basic subunit of many important biologically active natural products, particularly of compounds in a variety of diterpene families.[1] Accordingly, these diterpenoids have attracted considerable attention from the synthesis community over the past 50 years. A number of elegant syntheses of some target molecules have been achieved based on the evolution of strategies for constructing fused and bridged ring systems.[1,2] And the bicyclo[3.2.1]octane system is generally assembled either in the middle of or the late stage of the synthetic strategy.[2-5]

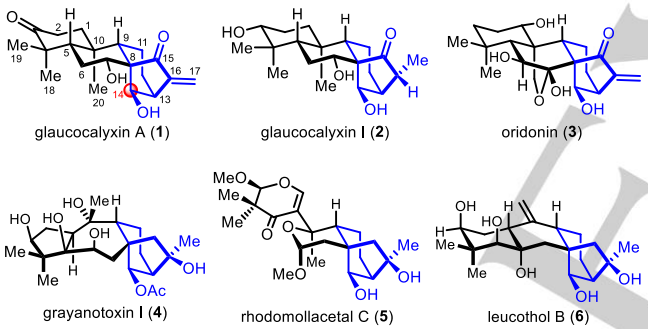
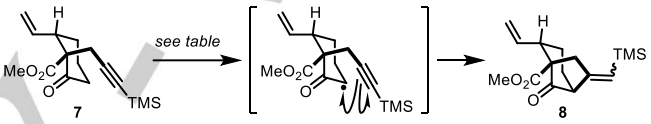


Figure 1. Diterpenoids possessing C14-oxygenated patterns.

Among these diterpenoids, about half contain 14(β)-oxygenation patterns (Figure 1).[6,7] As shown, the 14-oxygenated bicyclo[3.2.1]octane ring system contains four to five continuous stereocenters. Some of these natural products, such as glaucocalyxin A (**1**),[8] oridonin (**3**),[9] and grayanotoxin I (**4**),[7] exhibit a variety of promising therapeutic properties and have been used as leads in drug development. However, synthetic efforts toward these diterpenoids have been especially limited, perhaps because these highly oxygenated diterpenoids present tremendous challenges for chemical synthesis.[3d,3i,5] Furthermore, it is difficult to introduce the C14-OH by employing the previously reported strategies.[5,6] In the course of our investigation on the total synthesis of structurally complex diterpenoids,[10] we are also intrigued by the intricate molecular architecture of these 14-oxygenated diterpenoids. We conceived an opposite sequence for the formation of the ring system to the previously reported approaches, and in our design the 14-oxygenated bicyclo[3.2.1]octane system is formed at the early stage. Herein, we report a practically useful method for the formation of the 14-oxygenated bicyclo[3.2.1]octane system, which enables us to achieve the first total synthesis of (−)-glaucocalyxin A (**1**).

Table 1: Condition optimization for the formation of the oxygenated Bicyclo[3.2.1]octane System.[a]



Entry	Equiv. of Mn(III)	Solvent	Temp. (°C)	Time	Yield[b]
1	6	EtOH/HOAc (9:1)	100 (heat)	3 d	23%
2	6	EtOH/HOAc (9:1)	100 (MW)	6 h	27%
3	3	HOAc	100 (MW)	30 min	32%
4	3	THF/HOAc (9:1)	100 (MW)	6 h	40%
5	3	THF	110 (MW)	6 h	47%
6	3	DCE	110 (MW)	6 h	58%
7	3	DCE	120 (MW)	3 h	60%
8	**2.5**	**DCE**	**125 (MW)**	**3 h**	**60%**

[a] Reaction conditions: **7** (0.3 mmol), $Mn(OAc)_3$, solvent (3 mL). [b] Isolated yield. TMS = trimethylsilyl, THF = tetrahydrofuran, DCE = 1,2-dichloroethane.

The $Mn(OAc)_3$-mediated radical cyclization of alkynyl ketones for the formation of the bicyclo[3.2.1]octane system developed by Snider attracted our attention due to its short synthetic route and readily available starting materials.[11] In order to verify the feasibility, the alkynyl ketone **7** was prepared in two steps (See SI) and subjected to Snider's reaction conditions (Table 1, entry 1). The desired **8**, a mixture of *E/Z* isomers, was obtained in only 23% yield. The low yield, long reaction time and the use of a large excess of $Mn(OAc)_3$ promoted us to optimize the reaction conditions (Table 1). Microwave conditions can dramatically reduce the reaction time (Table 1, entry 2). Unexpectedly, after a variety of solvents were tested, DCE gave the highest yield (Table 1, entries 2-6). It is worth noting that HOAc and ethanol are the most common solvents in $Mn(OAc)_3$-mediated reactions, and the use of DCE has not been reported.[11b] Further optimizations

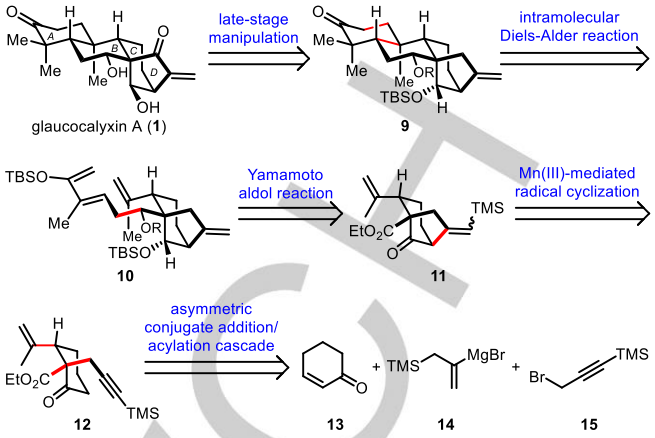
[a] J. Guo,[†] B. Li,[†] W. Ma, Dr. M. Pitchakuntla, and Prof. Y. Jia
State Key Laboratory of Natural and Biomimetic Drugs, School of Pharmaceutical Sciences,
Peking University,
Xue Yuan Rd. 38, Beijing 100191, China
E-mail: yanxingjia@pku.edu.cn
[†] These authors contributed equally to this work.
[b] Supporting information for this article is given via a link at the end of the document.((Please delete this text if not appropriate))

10.1002/anie.202005932

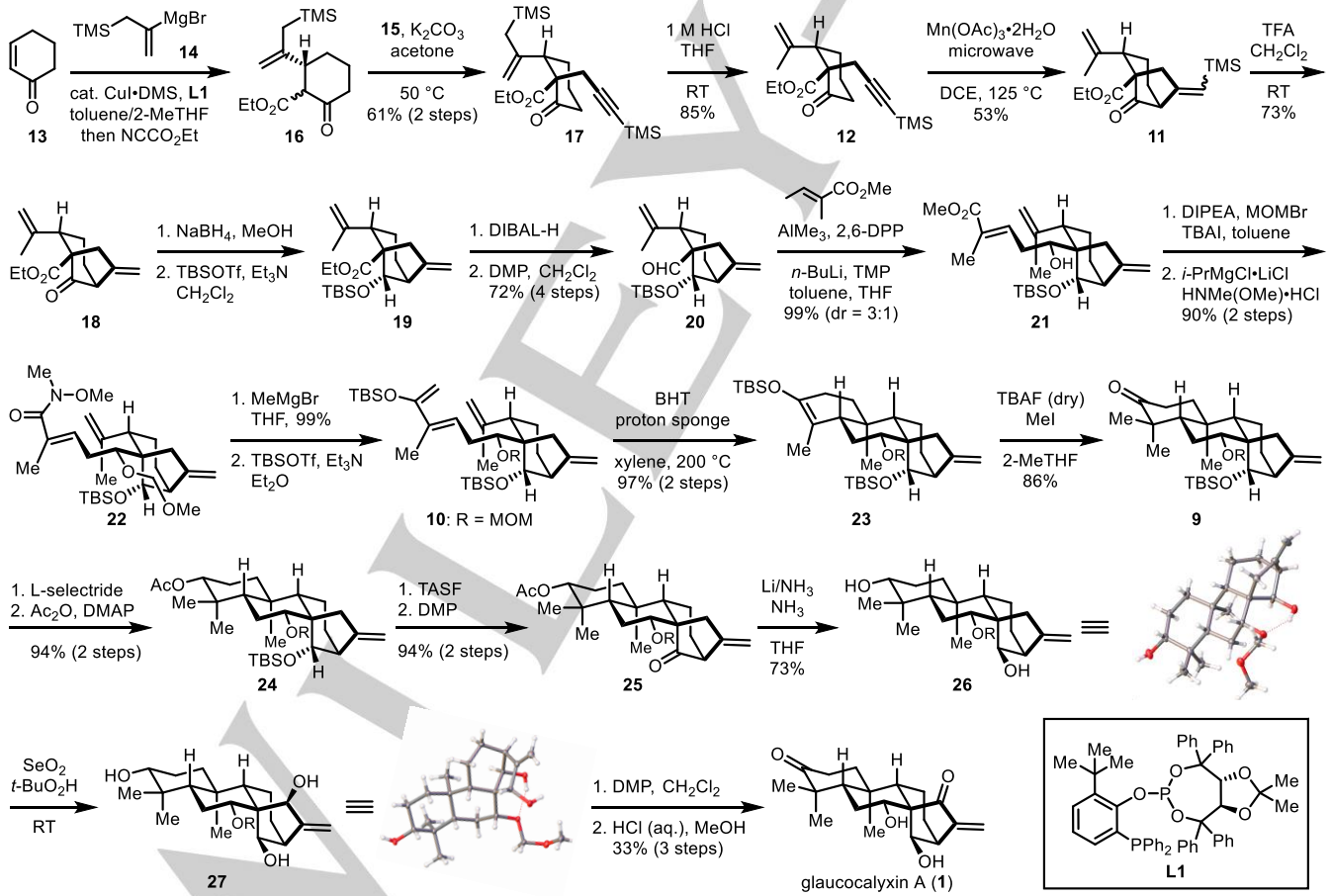
WILEY-VCH

showed that the equivalence of $Mn(OAc)_3$ can be reduced to 2.5 and the reaction temperature can be increased to 125 °C (Table 1, entries 7-8). Thus, the 14-oxygenated bicyclo[3.2.1]octane ring system could be prepared in only three steps from commercially available starting materials.

With this encouraging result, we selected glaucocalyxin A (**1**),[8] a highly oxygenated *ent*-kaurene diterpenoid with promising therapeutic properties, as the target molecule to prove our concept. Retrosynthetically, we envisioned that **1** could be generated from the tetracycle **9** via late-stage functional group manipulations (Scheme 1). The key tetracycle **9** possessing the kaurene skeleton could be assembled by an intramolecular Diels-Alder (IMDA) reaction of **10**. Accordingly, **10** could be prepared from the 14-oxygenated bicyclo[3.2.1]octane compound **11** which could be constructed by a $Mn(OAc)_3$-mediated cyclization of **12**. In turn, **12** could be obtained from readily available compounds **13**-**15**.



Scheme 1. Retrosynthetic analysis of glaucocalyxin A (**1**). TBS = *tert*-butyldimethylsilyl.

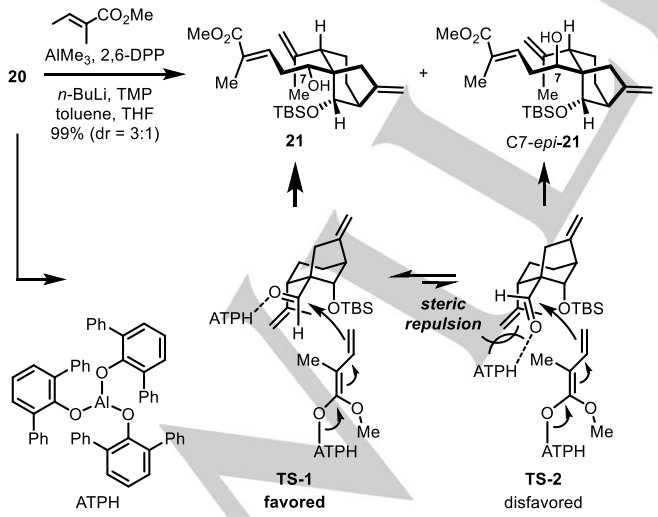


Scheme 2. Total synthesis of (−)-glaucocalyxin A (**1**). TFA = trifluoroacetic acid, DIBAL-H = diisobutylaluminium hydride, DMP = Dess-Martin periodinane, 2,6-DPP = 2,6-diphenylphenol, TMP = 2,2,6,6-tetramethylpiperidine, DIPEA = *N*,*N*-diisopropylethylamine, MOM = methoxymethyl, TBAI = tetra-*n*-butylammonium iodide, BHT = butylated hydroxytoluene, TBAF = tetra-*n*-butylammonium fluoride, DMAP = 4-dimethylaminopyridine, TASF = tris(dimethylamino)sulfanium.

10.1002/anie.202005932

Our synthesis commenced with the scalable preparation of the chiral cyclization precursor **12** (Scheme 2). Baran had developed a highly enantioselective conjugate addition of **14** with cyclohexenone (**13**) by modification of Schmalz' procedure.[12,13] We thought that trapping the resulting enolate at the carbon terminus could afford **16**. After several trials, the stereoselective conjugate addition−acylation cascade reaction with ethyl cyanoformate (Mander's reagent) proceeded smoothly to provide **16** as an inconsequential mixture of ketone and enol. Diastereoselective alkylation of **16** with **15** provided the desired β-ketoester **17**. Selective removal of the allyl TMS group on **17** gave cyclization precursor **12** in 85% yield. Oxidative cyclization of **12** under our optimized condition gave the desired **11** in 53% yield.

Having constructed the crucial 14-oxygenated bicyclo[3.2.1]octane system **11**, we turned our attention to the Intramolecular Diels-Alder reaction (IMDA) to assemble the AB rings. Desilylation of **11** with TFA afforded **18** in 73% yield. Reduction of **18** with a variety of reducing agents afforded only the undesired C14-α-OH. After a series of failures to invert the C-14 configuration, we protected the alcohol with TBS and moved the inversion to a later step. Reduction of **19** with DIBAL-H followed by oxidation of the resulting alcohol with Dess-Martin periodinance (DMP) afforded aldehyde **20**. Vinylogous aldol reaction of **20** according to the Yamamoto protocol provided the desired product **21** and its C7-epimer (C7-*epi*-**21**) in 99% combined yield as a mixture of two separable diastereoisomers (*dr* = 3:1) in favour of **21**.[14] The diastereo-selectivity could be explained as depicted in Scheme 3. Firstly, the bulky aluminium tris(2,6-diphenylphenoxide) (ATPH) coordinated to the aldehyde, and two possible transition states (**TS-1** & **TS-2**) could be considered to lead to **21** and C7-*epi*-**21**, respectively. Due to the enhanced steric repulsion between ATPH and isopropenyl group in **TS-2**, the less hindered **TS-1** should be favored, allowing the formation of **21** as the main product.



Scheme 3. Proposed mechanism of vinylogous aldol condensation.

MOM protection of alcohol **21** followed by conversion of the ester group to Weinreb amide yielded **22**.[15] Treatment of amide **22** with excess MeMgBr followed by silyl enolization produced compound **10**. Tetraene **10** was then subjected to intramolecular Diels-Alder reaction to provide the desired tetracyclic silyl enol ether **23** as a single product in 97% yield. The high stereoselectivity observed may be attributed to a chair-like conformation in the transition state. It is worthy to note that the stereochemistry of C7-OH has a significant effect on the Diels-Alder reaction.

The only thing left to assemble the *ent*-kaurene skeleton was the introduction of the geminal dimethyl group at C4. In similar structures, the methyl group was introduced by cyclopropanation followed by opening the cyclopropane ring. However, attempts to cyclopropanation of **23** failed.[16] We decided to employ a direct methylation method with MeI and TBAF that is rarely used.[17] After several trials, we found that treatment of **23** with high concentrations of MeI and pre-dehydrated TBAF (dried with $LiAlH_4$) in 2-MeTHF afforded the desired product **9** in 86% yield. Thus, we have successfully constructed the tetracyclic skeleton of *ent*-kaurenoids.

With ketone **9** in hand, all that remained to complete the synthesis of **1** was the inversion of C14 configuration and the installation of the ketone group at C15. Attempts to remove the TBS group of **9** resulted in decomposition of the starting material. After several trials, we found that C3 ketone had a significant effect on C14-OH desilylation. To overcome this issue, ketone **9** was selectively reduced to the corresponding alcohol which was subsequently protected with Ac_2O to provide the acetate **24**. Removal of the TBS group of **24** with TASF proceeded smoothly to produce the corresponding alcohol which was then oxidized by DMP to yield ketone **25**.[18] Reduction of the ketone **25** with Li in liquid NH_3 gave the desired diol **26** in 73% yield.[19] The structure of diol **26** was confirmed by X-ray crystallography analysis.[20] Allylic oxidation with 4 equiv. of *t*-BuO_2H (TBHP) in the presence of 1 equiv of SeO_2 provided the allylic alcohol **27** as the sole stereoisomer, and its structure was confirmed by X-ray crystallography analysis.[21] It was noteworthy that the amount of SeO_2 is critical to the reaction yield. Finally, chemoselective oxidation of C3 and C15 hydroxyl groups followed by removal of MOM protecting group provided **1** in 33% yield (3 steps). The physical data of our synthesized (−)-glaucocalyxin A (**1**) was identical to those reported in the literature.[8c]

In conclusion, we have developed a practically useful method for the formation of the highly oxygenated bicyclo[3.2.1]octane ring system by $Mn(OAc)_3$-mediated oxidative cyclization of alkynyl ketones. By application of this method, we have achieved the first total synthesis of (−)-glaucocalyxin A (**1**). Our synthetic approach offers the possibility for flexible and deep-seated structural changes inaccessible by semi-synthesis. The present method could also be applied to the synthesis of other natural products containing the highly oxygenated bicyclo[3.2.1]octane system. These studies are now in progress in our laboratory and will be reported in due course.

Acknowledgements

This research was supported by the National Natural Science Foundation of China (Nos. 21925101 and 21871013), the Drug

Innovation Major Project (Grant No. 2018ZX09711-001-005-005), and PKU-Baidu Fund (Grant No. 2019BD015).

Keywords: terpenoids • total synthesis • oxidative cyclization • asymmetric synthesis • natural products

[1] a) M.-H. Filippini, J. Rodriguez, *Chem. Rev.* **1999**, *99*, 27; b) M. Presset, Y. Coquerel, J. Rodriguez, *Chem. Rev.* **2013**, *113*, 525.

[2] For recent reviews, see: a) K. E. Lazarski, B. J. Moritz, R. J. Thomson, *Angew. Chem. Int. Ed.* **2014**, *53*, 10588; *Angew. Chem.* **2014**, *126*, 10762; b) L. Zhu, S.-H. Huang, J. Yu, R. Hong, *Tetrahedron Lett.* **2015**, *56*, 23; c) M.-J. Du, X.-G. Lei, *Youji Huaxue* **2015**, *35*, 2447; d) P. S. Riehl, Y. C. DePorre, A. M. Armaly, E. J. Groso, C. S. Schindler, *Tetrahedron* **2015**, *71*, 6629.

[3] For selected recent syntheses of *ent*-kaurenoids with the bicyclo[3.2.1]octane system, see: a) E. C. Cherney, J. C. Green, P. S. Baran, *Angew. Chem. Int. Ed.* **2013**, *52*, 9019; *Angew. Chem.* **2013**, *125*, 9189; b) L. Zhu, J. Luo, R. Hong, *Org. Lett.* **2014**, *16*, 2162; c) X. Zhao, W. Li, J. Wang, D. Ma, *J. Am. Chem. Soc.* **2017**, *139*, 2932; d) C. He, J. Hu, Y. Wu, H. Ding, *J. Am. Chem. Soc.* **2017**, *139*, 6098; e) F. Su, Y. Lu, L. Kong, J. Liu, T. Luo, *Angew. Chem. Int. Ed.* **2018**, *57*, 760; *Angew. Chem.* **2018**, *130*, 768; f) L. Zhu, W. Ma, M. Zhang, M. M.-L. Lee, W.-Y. Wong, B. D. Chan, Q. Yang, W.-T. Wong, W. C.-S. Tai, C.-S. Lee, *Nat. Commun.* **2018**, *9*, 1283; g) B. Hong, W. Liu, J. Wang, J. Wu, Y. Kadonaga, P.-J. Cai, H.-X. Lou, Z.-X. Yu, H. Li, X. Lei, *Chem* **2019**, *5*, 1671; h) J. Wang, D. Ma, *Angew. Chem. Int. Ed.* **2019**, *58*, 15731; *Angew. Chem.* **2019**, *131*, 15878; i) L. Kong, F. Su, H. Yu, Z. Jiang, Y. Lu, T. Luo, *J. Am. Chem. Soc.* **2019**, *141*, 20048; j) J. Wang, B. Hong, D. Hu, Y. Kadonaga, R. Tang, X. Lei. *J. Am. Chem. Soc.* **2020**, *142*, 2238.

[4] For selected recent syntheses of oxidatively cleaved or rearranged *ent*-kaurenoids with the bicyclo[3.2.1]octane system, see: a) J. T. S. Yeoman, V. W. Mak, S. E. Reisman, *J. Am. Chem. Soc.* **2013**, *135*, 11764; b) B. J. Moritz, D. J. Mack, L. Tong, R. J. Thomson, *Angew. Chem. Int. Ed.* **2014**, *53*, 2988; *Angew. Chem.* **2014**, *126*, 3032; c) Z. Pan, C. Zheng, H. Wang, Y. Chen, Y. Li, B. Cheng, H. Zhai, *Org. Lett.* **2014**, *16*, 216; d) S. Pan, S. Chen, G. Dong, *Angew. Chem. Int. Ed.* **2018**, *57*, 6333; *Angew. Chem.* **2018**, *130*, 6441; e) Z. Lv, B. Chen, C. Zhang, G. Liang, *Chem. Eur. J.* **2018**, *24*, 9773; f) M. J. R. Richter, M. Schneider, M. Brandstätter, S. Krautwald, E. M. Carreira, *J. Am. Chem. Soc.* **2018**, *140*, 16704; g) J. Wu, Y. Kadonaga, B. Hong, J. Wang, X. Lei, *Angew. Chem. Int. Ed.* **2019**, *58*, 10879; *Angew. Chem.* **2019**, *131*, 10995; h) J. Zhang, Z. Li, J. Zhuo, Y. Cui, T. Han, C. Li, *J. Am. Chem. Soc.* **2019**, *141*, 8372; i) L. A. Wein, K. Wurst, P. Angyal, L. Weisheit, T. Magauer, *J. Am. Chem. Soc*. **2019**, *141*, 19589; j) Y. Que, H. Shao, H. He, S. Gao, *Angew. Chem. Int. Ed.* **2020**, *59*, 7444; *Angew. Chem.* **2020**, *132*, 7514.

[5] For selected references on synthesis of grayanoids, see: a) N. Hamanaka, T. Matsumoto, *Tetrahedron Lett.* **1972**, *13*, 3087; b) S. Gasa, N. Hamanaka, S. Matsunaga, T. Okuno, N. Takeda, T. Matsumoto, *Tetrahedron Lett.* **1976**, *17*, 553; c) T. Kan, S. Hosokawa, S. Nara, M. Oikawa, S. Ito, F. Matsuda, H. Shirahama, *J. Org. Chem.* **1994**, *59*, 5532; d) A. Turlik, Y. Chen, A. C. Scruse, T. R. Newhouse, *J. Am. Chem. Soc.* **2019**, *141*, 8088; e) K. Yu, Z.-N. Yang, C.-H. Liu, S.-Q. Wu, X. Hong, X.-Li. Zhao, H. Ding, *Angew. Chem. Int. Ed.* **2019**, *58*, 8556; *Angew. Chem.* **2019**, *131*, 8644.

[6] a) H.-D. Sun, S.-X. Huang, Q.-B. Han, *Nat. Prod. Rep.* **2006**, *23*, 673; b) P. A. García, A. B. De Oliveira, R. Batista, *Molecules* **2007**, *12*, 455; c) M. Liu, W.-G. Wang, H.-D. Sun, J.-X. Pu, *Nat. Prod. Rep.* **2017**, *34*, 1090.

[7] For reviews on grayanoids, see: a) Y. Li, Y.-B. Liu, S.-S. Yu, *Phytochem. Rev.* **2013**, *12*, 305; b) C.-H. Li, J.-Y. Zhang, X.-Y. Zhang, S.-H. Li, J.-M. Gao, *Eur. J. Med. Chem.* **2019**, *166*, 400.

[8] For isolation of glaucocalyxin A, see: a) Y. Takeda, T. Fujita, A. Ueno, *Chem. Lett.* **1981**, 1229; b) Y. L. Xu, X. C. Sun, H. D. Sun, Z. W. Lin, Z. D. Wang, *Acta Bot Yunnanica.* **1981**, *3*, 283; c) X.-D. Shen, B. Wang, X. Li, C.-Y. Liu, J. Zhang, *Zhongcaoyao* **2009**, *40*, 1883. For drug development of glaucocalyxin A, see: d) M. Rahman, L. Zhang, L. Wu, Y. Xie, C. Li, J. Cao, *Drug Des. Dev. Ther* **2017,** 11, 2431.

[9] For isolation of oridonin, see: E. Fujita, T. Fujita, H. Katayama, M. Shibuya, *Chem. Commun.* **1967**, 252; For drug development of oridonin, see: a) J. Xu, E. A. Wold, Y. Ding, Q. Shen, J. Zhou, *Molecules* **2018**, *23*, 474; b) S. Xu, H. Yao, S. Luo, Y.-K. Zhang, D.-H. Yang, D. Li, G. Wang, M. Hu, Y. Qiu, X. Wu, H. Yao, W. Xie, Z.-S. Chen, J. Xu, *J. Med. Chem.* **2017,** *60*, 1449.

[10] a) B. Huang, L. Guo, Y. Jia, *Angew. Chem. Int. Ed.* **2015**, *54*, 13599; *Angew. Chem.* **2015**, *127*, 13803; b) X. Zhang, X. Cai, B. Huang, L. Guo, Z, Guo, Y. Jia, *Angew. Chem. Int. Ed.* **2019**, *58*, 13380; *Angew. Chem.* **2019**, *131*, 13514.

[11] a) S. V. O'Neil, C. A. Quickley, B. B. Snider, *J. Org. Chem.* **1997**, *62*, 1970; b) For reviews of Mn(III)-promoted radical cyclization, see: b) B. B. Snider, *Chem. Rev.* **1996**, *96*, 339; c) G. G. Melikyan, *Org. React.* **1997**, *49*, 427.

[12] A. Cernijenko, R. Risgaard, P. S. Baran, *J. Am. Chem. Soc.* **2016,** *138*, 9425.

[13] T. Robert, J. Velder, H.-G. Schmalz, *Angew. Chem. Int. Ed.* **2008**, *47*, 7718; *Angew. Chem.* **2008**, *120*, 7832.

[14] a) S. Saito, M. Shiozawa and H. Yamamoto, *Angew. Chem. Int. Ed.* **1999**, *38*, 1769; *Angew. Chem.* **1999**, *111*, 1884; b) S. Saito and H. Yamamoto, *Chem. Commun.* **1997**, 1585.

[15] a) S. Nahm, S. M. Weinreb, *Tetrahedron Lett.* **1981,** *22*, 3815. b) F. Weber, R. Brückner, *Eur. J. Org. Chem.* **2015,** 2428.

[16] a) A. Gris, N. Cabedo, I. Navarro, I, de Alfonso, C. Agulló, A. Abad-Somovilla, *J. Org. Chem.* **2012**, *77*, 5664; b) R. Okamoto, K. Takeda, H. Tokuyama, M. Ihara, M. Toyota. *J. Org. Chem.* **2013**, *78*, 93.

[17] a) I. Kuwajima, E. Nakamura, M. Shimizu, *J. Am. Chem. Soc.* **1982,** *104*, 1025; b) R. Noyori, I. Nishida, J. Sakata, *Tetrahedron Lett.* **1980**, *21*, 2085; Only one reported in total synthesis: c) Y. Lee, Y. Utsumi, K. Ohkata, K. Akiba, *Heterocycles* **1990**, *30*, 813.

[18] A. Pitaval, D. Leboeuf, J. Ceccon, A. M. Echavarren, *Org. Lett.* **2013,** *15*, 4580.

[19] a) H. B. Henbest, R. A. L. Wilson, *J. Chem. Soc.* **1956**, 3289; b) L. A. Paquette, F. Geng, *Org. Lett.* **2002,** *4*, 4547.

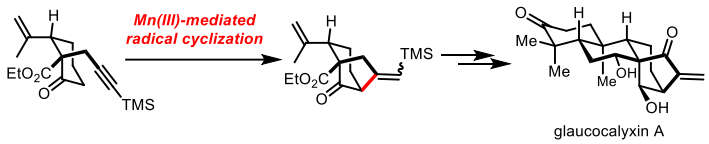
[20] CCDC 1995362 (**26**) and CCDC 1995363 (**27**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

10.1002/anie.202005932

WILEY-VCH

Layout 2:

COMMUNICATION



The first total synthesis of (−)-glaucocalyxin A, a highly oxygenated *ent*-kaurene diterpenoid, was achieved by using a $Mn(OAc)_3$-mediated radical cyclization of alkynyl ketones for the formation of the bicyclo[3.2.1]octane system.

*Jiuzhou Guo, Bo Li, Weihao Ma, Mallesham Pitchakuntla, and Yanxing Jia**

Page No. – Page No.

Total Synthesis of (−)-Glaucocalyxin A