A Journal of the Gesellschaft Deutscher Chemiker

Angewandte International Edition GDCh Chemie

www.angewandte.org

Accepted Article

Title: Total Syntheses of Rhodomolleins XX and XXII: A Reductive Epoxide-Opening/Beckwith-Dowd Approach

Authors: Kuan Yu, Zhen-Ning Yang, Chun-Hui Liu, Shao-Qi Wu, Xin Hong, Xiao-Li Zhao, and Hanfeng Ding

To be cited as: *Angew. Chem. Int. Ed.* 10.1002/anie.201903349
Angew. Chem. 10.1002/ange.201903349

Link to VoR: http://dx.doi.org/10.1002/anie.201903349
http://dx.doi.org/10.1002/ange.201903349

WILEY-VCH

10.1002/anie.201903349

WILEY-VCH

COMMUNICATION

Total Syntheses of Rhodomolleins XX and XXII: A Reductive Epoxide-Opening/Beckwith–Dowd Approach

Kuan Yu, Zhen-Ning Yang, Chun-Hui Liu, Shao-Qi Wu, Xin Hong, Xiao-Li Zhao, and Hanfeng Ding*

Abstract: *A new Ti(III)-mediated reductive epoxide-opening/ Beckwith–Dowd rearrangement process efficiently assembles the bicyclo[3.2.1]octane framework of highly oxidized grayanane diterpenoids. By incorporation of a Cu(tbs)$_2$-catalyzed intramolecular cyclopropanation, a diastereoselective ODI-Diels–Alder cycloaddition and a MeReO$_3$-catalyzed Rubottom oxidation, this apporach has enabled the first total syntheses of rhodomolleins XX and XXII in 23 and 22 steps, respectively.*

The Ericaceae species have a long history of being used in traditional herbal folk medicines to treat a variety of diseases due to their curative ability. To date, over 150 grayanane diterpenoids have been isolated from this genus.[1] Besides high toxicities, grayanoids are well known for their broad range of bioactivities, such as sodium channel modulating, analgesic, sedative, insecticidal, and antifeedant activities. The structures of the vast majority of grayanoids feature an unusual [5,7,6,5] tetracyclic carbon framework decorated with 7–10 stereogenic centers, as well as the dense arrangement of hydroxy groups (e.g., **1**–**6**, Figure 1). Biosynthetically, these molecules are assumed to originate from a common *ent*-kaurane skeleton, which contains a characteristic bicyclo[3.2.1]octane (C/D) ring system.[2] The above distinct features rendered grayanoids attractive targets for synthetic studies.[3] However, only two total syntheses have been disclosed, presumably ascribed to the challenges in construction of their highly functionalized tetracyclic skeletons. More than forty years ago, the group of Matsumoto reported a relay total synthesis of grayanotoxin II (**1**) based on a key biomimetic photo-santonin rearrangement (>39 steps, <0.0005% overall yield).[3a,b] In 1994, Shirahama and coworkers achieved an enantioselective total synthesis of (–)-grayanotoxin III (**2**) in 38 steps and 0.05% overall yield, featuring a series of SmI_2-mediated stereoselective cyclizations.[3c] Despite these impressive developments, more efficient and general strategies for assembling grayanoids remain in urgent demand to accelerate the process of their syntheses and biological investigation.

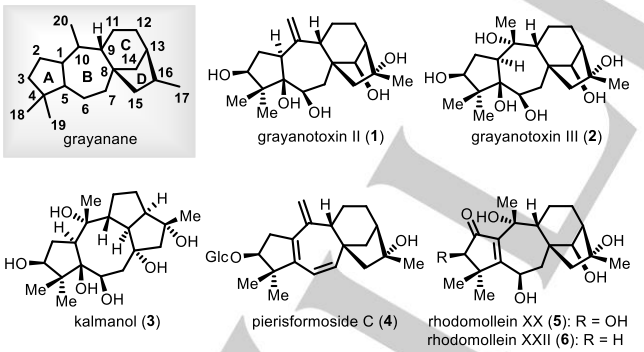
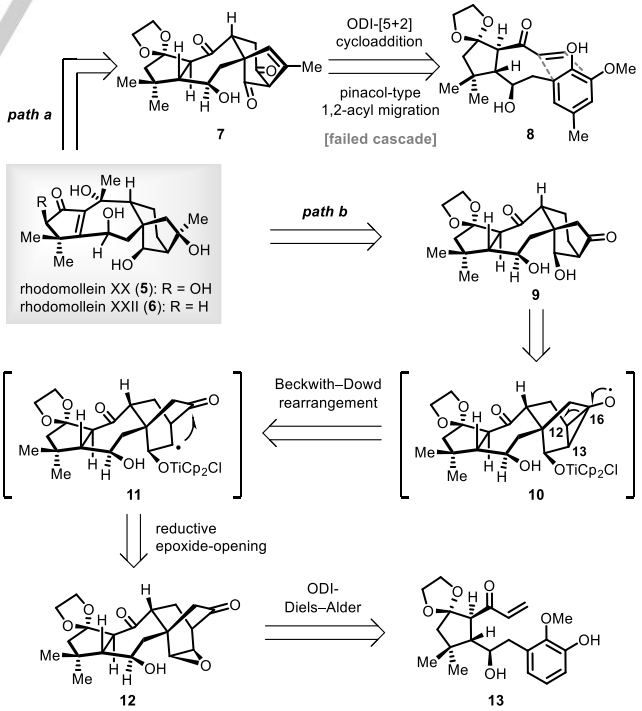


Figure 1. Structures of grayanane diterpenoids **1**–**6**.

On the other hand, apart from few examples of cascade strategies,[4] the construction of the [3.2.1] bicyclic skeletons in total syntheses of tetracyclic diterpenoids required multistep reaction sequences,[5] which inevitably maximized functional group manipulations and resulted in lengthier synthetic routes. Prompted by this problem, we sought to develop versatile protocols by establishing the [3.2.1] bicyclic motif in a more straightforward manner. Recently, inspired by the oxidative dearomatization-induced (ODI) cycloaddition/ring distortion approaches toward the syntheses of diterpenoid alkaloids,[6] we reported an ODI-[5+2] cycloaddition/pinacol-type 1,2-acyl migration cascade reaction, leading to the concise total syntheses of several highly oxidized *ent*-kauranoids.[7] In continuation of our interest in this area, we herein describe the first total syntheses of rhodomolleins XX (**5**) and XXII (**6**), two congeners of the grayanoid family that isolated from *Rhododendron molle* G. Don (Ericaceae),[8] through a new titanium(III)-mediated reductive epoxide-opening/Beckwith–Dowd rearrangement process.

Our retrosynthetic analysis toward rhodomolleins XX (**5**) and



Scheme 1. Retrosynthetic analysis of rhodomolleins XX (**5**) and XXII (**6**).

[*] K. Yu, Z.-N. Yang, C.-H. Liu, S.-Q. Wu, Prof. Dr. X. Hong, Prof. Dr. H. Ding
Department of Chemistry
Zhejiang University, Hangzhou 310058 (China)
E-mail: hfding@zju.edu.cn
Prof. Dr. X.-L. Zhao
Shanghai Key Laboratory of Green Chemistry and Chemical Processes, Department of Chemistry
East China Normal University, Shanghai 200062 (China)

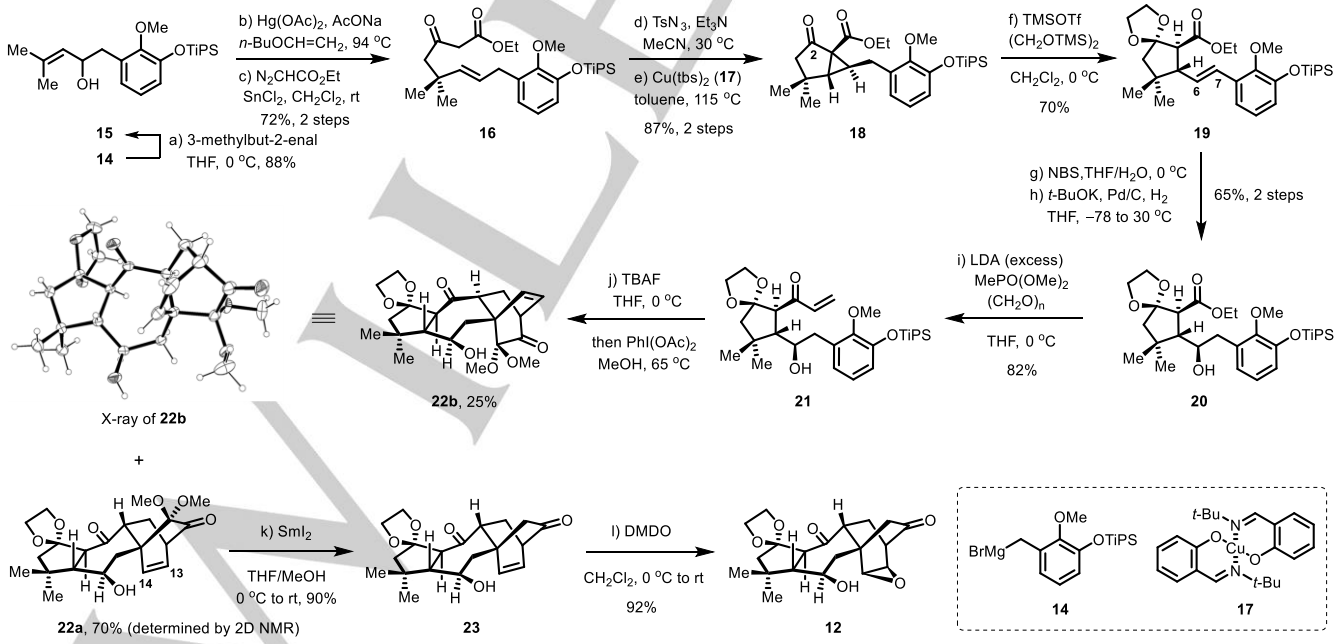
Supporting information for this article is given via a link at the end of the document.

10.1002/anie.201903349

XXII (**6**) is depicted in Scheme 1. Initially, we assumed that the bicyclo[3.2.1]octane carbon frameworks of **5** and **6** could be built up from vinylphenol **8** according to our previously developed ODI-[5+2] cascade (path a).[7] However, attempts to access the cycloheptane-fused cycloadduct **7** were met with disappointing results (for details, see the Supporting Information). Based on the elegant works of Baran[9a] and Mori,[9b] an alternative strategy relying on the regioselective fragmentation of an excessively functionalized intermediate[10] was proposed (path b). Therefore, we rationalized that both **5** and **6** could be synthesized from tetracycle **7** through a late-stage core modification. For the construction of **9**, an unprecedented ring distortion cascade was devised. Accordingly, a titanium(III)-mediated reductive ring-opening of [2.2.2] bicyclic keto-epoxide **12** generates **11**,[11] which would undergo successive Beckwith–Dowd rearrangement[12] through the intermediacy of cyclopropoxy radical **10** to forge the desired bicyclo[3.2.1]octane ring of the molecules. The realization of this cascade would require a preferential cleavage of the C12-C16 bond over the C13-C16 bond in **10**. Although control of such a fragmentation was estimated to be challenging since these two bonds appear to be nearly indistinguishable,[13] we envisioned that the β-titanoxy group in **11** might be capable of retarding the rate of radical quenching at C-13, thus allowing for reversible formation of the exocyclic β-keto radical leading to **9**.[14] Finally, the preparation of **12** could be traced back to vinylphenol **13** by taking advantage of a diastereoselective ODI-Diels–Alder cycloaddition.[15]

Our synthesis commenced with construction of the keto-epoxide **12** (Scheme 2). The 1,2-addition of Grignard reagent **14,** prepared in four steps from commercially available 3-hydroxy-2-methoxybenzaldehyde (for details, see the Supporting Information),[16] to 3-methylbut-2-enal afforded alcohol **15** in 88% yield. The latter underwent a Claisen rearrangement with *n*-butyl vinyl ether[17] followed by Roskamp homologation of the resultant aldehyde in the presence of catalytic $SnCl_2$ and ethyl diazoacetate to give β-keto ester **16** in 72% yield over two steps. After being converted to the corresponding diazo compound, different metal catalysts were screened for the following intramolecular cyclopropanation to forge the A ring. Pleasingly, by treatment with $Cu(tbs)_2$ (**17**, 5 mol%),[18] the expected 5,3-fused bicycle **18** was generated in 87% yield over two steps. To our disappointment, initial attempts on the direct introduction of the hydroxy group at C6 through oxy-homo-Michael additions of various oxygen nucleophiles[19] to **18** proved futile. As an alternative, the ring-opening of the cyclopropane accompanied by acetal protection of the ketone at C2 was achieved upon exposure to TMSOTf/$(CH_2OTMS)_2$, affording **19** in 70% yield. A substrate-controlled epoxidation of the $\Delta^{6,7}$ olefin exclusively gave the β-isomer, which underwent further hydrogenative ring-opening of the epoxide at benzylic position to provide **20** in 65% yield over two steps. Subsequently, a tandem β-keto phosphonate formation/Horner–Wadsworth–Emmons olefination took place smoothly in the presence of excess LDA and afforded enone **21** in 82% yield. Desilylation of **21** produced intermediate vinylphenol **13**, which was then engaged in an intramolecular ODI-Diels–Alder cycloaddition upon exposure to $PhI(OAc)_2$ in methanol, delivering a 2.8:1 mixture of **22a** and **22b** (ORTEP drawing, Scheme 2)[20] in 95% combined yield.[21,22] After SmI_2-mediated reductive demethoxylation of **22a** to gave **23**, the epoxidation of the $\Delta^{13,14}$ olefin proceeded from the convex face of the bicyclo[2.2.2]octane framework and provided **12** as a single diastereomer in 83% yield over two steps.

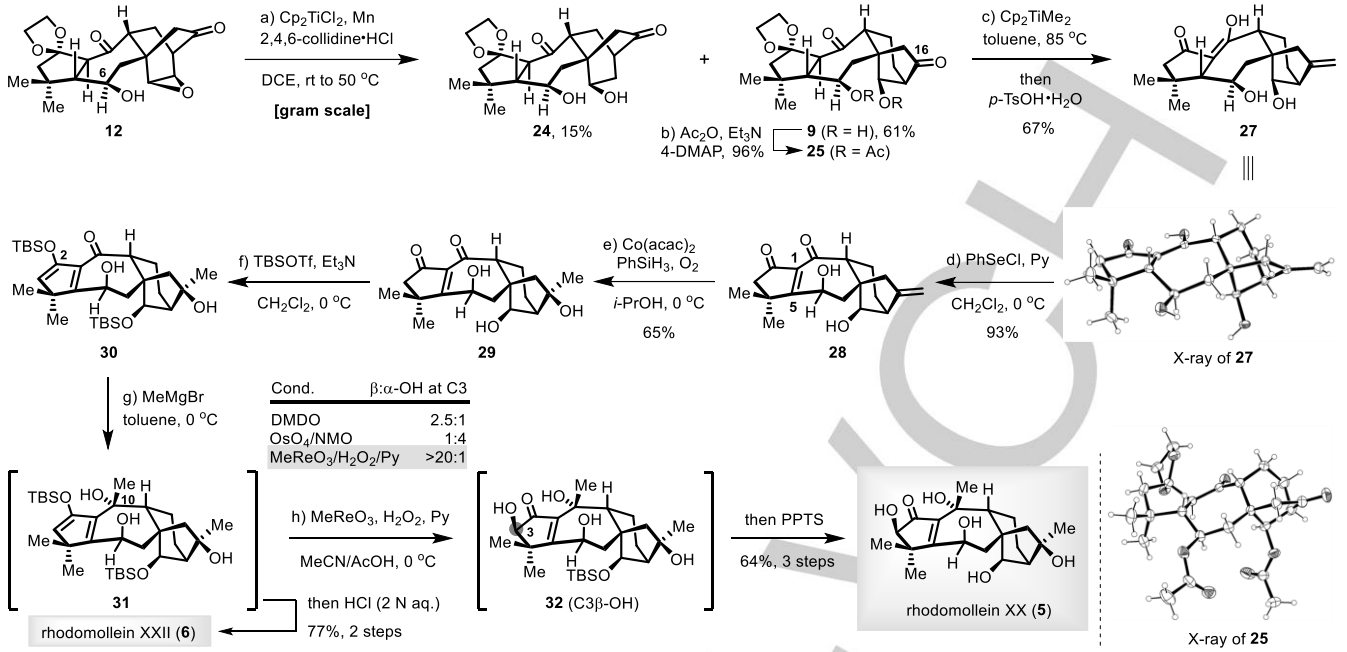
Having secured **12**, we turned our attention to investigating the proposed reductive epoxide-opening/Beckwith–Dowd rearrangement reaction (Scheme 3). After extensive optimization, we were pleased to find that by subjection of **12** to catalytic



Scheme 2. Construction of keto-epoxide **12**. DMDO = dimethyldioxirane, LDA= lithium diisopropylamide, NBS = *N*-bromosuccinimide, TBAF = tetra-*n*-butylammonium fluoride, tbs = *N*-*tert*-butylsalicylaldiminato, THF = tetrahydrofuran, TiPS = triisopropylsilyl, TMSOTf = trimethylsilyl trifluoromethanesulfonate,Ts = 4-toluenesulfonyl.

10.1002/anie.201903349

WILEY-VCH



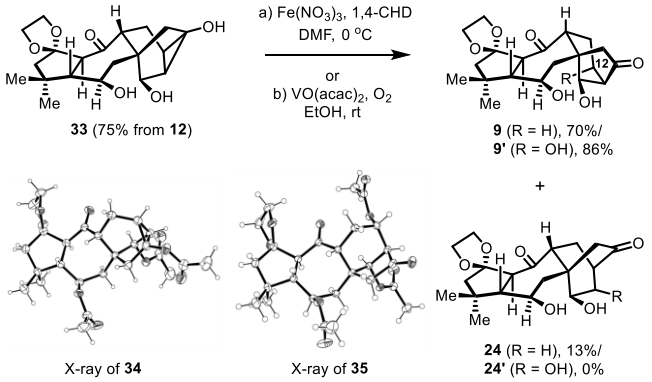
Scheme 3. Late-stage syntheses of rhodomolleins XX (**5**) and XXII (**6**). acac = acetylacetonate, collidine = trimethylpyridine, Cp = cyclopentadiene, DCE = 1,2-dichloroethane, DMAP= *N,N'*-dimethylaminopyridine. NMO = *N*-methylmorpholine *N*-oxide, PPTS = pyridinium 4-toluenesulfonate, Py = pyridine, TBSOTf = *tert*-butyldimethylsilyl trifluoromethanesulfonate.

Cp_2TiCl_2, Mn and 2,4,6-collidine•HCl in DCE at 50 °C over a period of 12 h, the desired bicyclo[3.2.1]octane **9** could be formed in 61% yield on gram scale, accompanied by the generation of **24** in 15% yield.[23] The structure of **9** was verified by X-ray crystallographic analysis of its corresponding diacetate **25** (ORTEP drawing, Scheme 3).[20] Of note, the nonpolar solvent was pivotal to the success of this cascade, and the free alcohol at C6 of **12** was found to play an important role in regioselective control of the reductive epoxide-opening step.[24] With suitable quantities of **9** in hand, we next focused on the late-stage syntheses of rhodomolleins XX (**5**) and XXII (**6**). Regioselective methylenation of the ketone at C16 was achieved using Petasis reagent. By following a deacetalization in one pot, enol **27** was formed in 67% yield (ORTEP drawing, Scheme 3).[20] Surprisingly, through treatment of **27** with PhSeCl and pyridine for a prolonged reaction time, a slow but spontaneous elimination of the resultant selenide was observed to forge the desired $\Delta^{1,5}$ double bond, providing **28** in 93% yield. The above outcome indicates the involvement of an exclusive α-facial selenation,[25] which could also be supported by the fact that addition of extraneous oxidants (*m*-CPBA, H_2O_2, $NaIO_4$, etc.) to accelerate the elimination through selenoxide intermediate led to messy reaction mixtures. As expected, Mukaiyama hydration of the more reactive $\Delta^{15,16}$ olefin occurred from the convex face of the bicyclo[3.2.1]octane skeleton and delivered triol **29** in 65% yield as a single diastereomer. After tentative protection of the ketone at C2 as a silyl dienol ether (**30**), the Grignard addition to the C10-ketone, which was presumably directed by the *pseudo*-axial C6-OH, gave **31** as the solely detectable isomer. Without isolation, the latter was further transformed into rhodomollein XXII (**6**) via an acid-promoted desilylation in 77% yield over two steps. On the other hand, the α-hydroxylation at C3 of **31** proved to be problematic (Table S1). Although Rubottom oxidation with DMDO provided a promising diastereoselectivity (2.5:1 at C3), an unsatisfactory yield (ca. 20%) was observed. However, replacement with other oxidants such as *m*-CPBA, Davis' oxaziridine and Cu/TBHP caused desilylation of the enol ether, and the dihydroxylation of **31** afforded **32** and its C3-epimer in 81% yield as a 1:4 mixture. Probably due to steric hindrance around A ring, the attempted [4+2] cycloaddition between the silyl dienol ether moiety and in situ generated singlet oxygen from triphenyl phosphite ozonide (TPPO)[26] led only to the recovery of **31**. Fortunately, with the aid of catalytic $MeReO_3$, H_2O_2 and pyridine,[27] **32** was formed with excellent d.r. (>20:1). Further deprotection in the presence of PPTS furnished rhodomollein XX (**5**) in 64% yield over three steps. Synthetic **5** and **6** exhibited ^1H and ^{13}C NMR spectra identical in all respects to those reported for the natural products.[8]

To further extend the generality of this reductive epoxide-opening/Beckwith–Dowd rearrangement process, the regio-selective fragmentation of cyclopropanol **33**, which could be prepared from **12** in 75% yield following Fernández-Mateos' procedure,[28] was also conducted (Scheme 4).[29] On the basis of seminal works by DePuy, Saegusa and Narasaka,[30] it was found that the cleavage of C13-C16 bond could be significantly inhibited in the presence of $Fe(NO_3)_3$ and 1,4-cyclohexadiene in DMF,[31] affording a 5.4:1 mixture of **9** and **24** in 83% yield (cond. a). More importantly, triol **9'**, a viable advanced intermediate enroute to the C12-oxygenated grayanane diterpenoids of biological importance (such as grayanotoxin XI and rhodomollein XXVIII),[32] was obtained as well in an even higher yield upon treatment of **33** with catalytic $VO(acac)_3$ under oxygen atmosphere (cond. b).[33] The structures of **33** and **9'** were unambiguously determined by X-ray

10.1002/anie.201903349

crystallographic analysis of their corresponding triacetates **34** and **35**, respectively (ORTEP drawings, Scheme 4).[20]



Scheme 4. Regioselective fragmentation of cyclopropanol **33**. CHD = cyclohexadiene, DMF = *N*,*N*-dimethylformamide.

In summary, we have developed a new titanium(III)-mediated reductive epoxide-opening/Beckwith–Dowd rearrangement process, in an either cascade or stepwise fashion for the construction of functionalized bicyclo[3.2.1]octane core structures of grayanane diterpenoids. Taken together with a $Cu(tbs)_2$-catalyzed intramolecular cyclopropanation, a diastereoselective ODI-Diels–Alder cycloaddition and a $MeReO_3$-catalyzed Rubottom oxidation, the employment of this efficient approach for assembling highly oxidized grayanoids is demonstrated by the first total syntheses of rhodomolleins XX and XXII in 23 and 22 steps, respectively. Moreover, the asymmetric syntheses could also be realized through the enantioselective preparation of (–)-**17**.[34] With high efficiency in building structural complexity, the described strategy and methodologies should be readily applied to the total syntheses of other members of grayanoids as well as other related diterpenoids and alkaloids, and allow further exploration of their biological properties.

Acknowledgements

Financial support from Zhejiang Natural Science Fund for Distinguished Young Scholars (LR16B020001) and National Natural Science Foundation of China (21871230, 21622205 for H.D.; 21873081, 21702182 for X.H.) are gratefully acknowledged.

Keywords: cyclopropanation • Diels–Alder • radical reactions • terpenoids • total synthesis

[1] For reviews, see: a) T. Kaiya, J. Sakakibara, *Nagoya Shiritsu Daigaku Yakugakubu Kenkyu Nenpo* **1982**, *30*, 1; b) L. Wang, G. Qin, *Nat. Prod. Res. Dev.* **1997**, *9*, 82; c) Y. Li, Y.-B. Liu, S.-S. Yu, *Phytochem. Rev.* **2013**, *12*, 305.

[2] T. Masutani, M. Hamada, E. Kawano, J. Iwasa, Z. Kumazawa, H. Ueda, *Agric. Biol. Chem.* **1981**, *45*, 1281.

[3] For total syntheses, 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; for synthetic studies, see: d) M. Shiozaki, K. Mori, M. Matsui, T. Hiraoka, *Tetrahedron Lett.* **1972**, *13*, 657; e) T. Kan, F. Matsuda, M. Yanagiya, H. Shirahama, *Synlett* **1991**, 391; f) L. A. Paquette, S. Borrelly, *J. Org. Chem.* **1995**, *60*, 6912; g) S. Borrelly, L. A. Paquette, *J. Am. Chem. Soc.* **1996**, *118*, 727; h) S. Chow, C. Kreß, N. Albæk, C. Jessen, C. M. Williams, *Org. Lett.* **2011**, *13*, 5286.

[4] a) D. J. Kucera, S. J. O'Connor, L. E. Overman, *J. Org. Chem.* **1993**, *58*, 5304; b) L. E. Overman, D. J. Ricca, V. D. Tran, *J. Am. Chem. Soc.* **1997**, *119*, 12031; c) M. E. Fox, C. Li, Marino, J. P. Marino, Jr., L. E. Overman, *J. Am. Chem. Soc.* **1999**, *121,* 5467; d) B. B. Snider, J. Y. Kiselgof, B. M. Foxman, *J. Org. Chem.* **1998**, *63,* 7945; e) L. Zhu, C. Zhou, W. Yang, S. He, G.-J. Cheng, X. Zhang, C.-S. Lee, *J. Org. Chem.* **2013**, *78*, 7912; f) L. Zhu, W. Ma, M. Zhang, M. M.-L. Lee, W.-Y. Wong, B. D. Chan, Q. Yang, W.-T. Wang, W. C.-S. Tai, C.-S. Lee, *Nat. Commun.* **2018**, *9*, 1283.

[5] For reviews on the syntheses of bicyclo[3.2.1]octanes, see: a) M.-H. Filippini, J. Rodriguez, *Chem. Rev.* **1999**, *99*, 27; b) M. Presset, Y. Coquerel, J. Rodriguez, *Chem. Rev.* **2013**, *113*, 525; c) L. Zhu, S.-H. Huang, J. Yu, R. Hong, *Tetrahedron Lett.* **2015**, *56*, 23.

[6] For selected examples toward the syntheses of diterpenoid alkaloids, see: a) H. Cheng, L. Xu, D.-L. Chen, Q.-H. Chen, F.-P. Wang, *Tetrahedron* **2012**, *68*, 1171; b) C. J. Marth, G. M. Gallego, J. C. Lee, T. P. Lebold, S. Kulyk, K. G. M. Kou, J. Qin, R. Lilien, R. Sarpong, *Nature* **2015**, *528*, 493; c) K. G. M. Kou, S. Kulyk, C. J. Marth, J. C. Lee, N. A. Doering, B. X. Li, G. M. Gallego, T. P. Lebold, R. Sarpong, *J. Am. Chem. Soc.* **2017**, *139*, 13882; d) Y. Nishiyama, S. Yokoshima, T. Fukuyama, *Org. Lett.* **2016**, *18*, 2359; e) Y. Nishiyama, S. Yokoshima, T. Fukuyama, *Org. Lett.* **2017**, *19*, 5833; for other examples toward the syntheses of diterpenoids, see: f) P. Lu, A. Mailyan, Z. Gu, D. M. Guptill, H. Wang, H. M. L. Davies, A. Zakarian, *J. Am. Chem. Soc.* **2014**, *136*, 17738; g) L. Song, G. Zhu, Y. Liu, B. Liu, S. Qin, *J. Am. Chem. Soc.* **2015**, *137*, 13706.

[7] C. He, J. Hu, Y. Wu, H. Ding, *J. Am. Chem. Soc.* **2017**, *139*, 6098.

[8] a) C.-J. Li, H. Liu, L.-Q. Wang, M.-W. Jin, S.-N. Chen, G.-H. Bao, G.-W. Qin, *Acta Chim. Sinica* **2003**, *61*, 1153; b) S.-Z. Zhou, S. Yao, C. Tang, C. Ke, L. Li, G. Lin, Y. Ye, *J. Nat. Prod.* **2014**, *77*, 1185.

[9] a) E. C. Cherney, J. C. Green, P. S. Baran, *Angew. Chem., Int. Ed.* **2013**, *52*, 9019; *Angew. Chem.* **2013**, *125*, 9189; b) K. Mori, Y. Nakahara, M. Matsui, *Tetrahedron Lett.* **1970**, *11*, 2411.

[10] R. W. Hoffmann, *Elements of Synthesis Planning*, Springer, Berlin, **2009**, pp. 106, and references therein.

[11] a) T. V. RajanBabu, W. A. Nugent, *J. Am. Chem. Soc.* **1994**, *116*, 986; for reviews, see: b) A. Gansäuer, T. Lauterbach, S. Narayan, *Angew. Chem., Int. Ed.* **2003**, *42*, 5556; *Angew. Chem.* **2003**, *115*, 5714; c) J. M. Cuerva, J. Justicia, J. L. Oller-López, J. E. Oltra, *Top. Curr. Chem.* **2006**, *264*, 63; d) S. P. Morcillo, D. Miguel, A. G. Campaña, L. Á. de Cienfuegos, J. Justicia, J. M. Cuerva, *Org. Chem. Front.* **2014**, *1*, 15.

[12] P. Dowd, W. Zhang, *Chem. Rev.* **1993**, *93*, 2091.

[13] A. Abad, C. Agulló, A. C. Cuñat, I. de Alfonso Marzal, I. Navarro, A. Gris, *Tetrahedron* **2006**, *62*, 3266.

[14] a) A. J. Blake, A. J. Highton, T. N. Majid, N. S. Simpkins, *Org. Lett.* **1999**, *1*, 1787; b) A. Highton, R. Volpicelli, N. S. Simpkins, *Tetrahedron Lett.* **2004**, *45*, 6679.

[15] For reviews, see: a) K. C. Nicolaou, S. A. Snyder, T. Montagnon, G. Vassilikogiannakis, *Angew. Chem., Int. Ed.* **2002**, *41*, 1668; *Angew. Chem.* **2002**, *114*, 1742; b) C.-C. Liao, *Pure Appl. Chem.* **2005**, *77*, 1221; c) S. P. Roche, J. A. Porco, Jr., *Angew. Chem., Int. Ed.* **2011**, *50*, 4068; *Angew. Chem.* **2011**, *123*, 4154.

[16] a) K. Surendra, E. J. Corey, *J. Am. Chem. Soc.* **2009**, *131*, 13928; b) H. Sekita, K. Adachi, I. Kobayashi, Y. Sato, M. Nakada, *Org. Lett.* **2017**, *19*, 2390.

[17] H. Tokuyama, T. Makido, T. Ueda, T. Fukuyama, *Synth. Commun.* **2002**, *32*, 869.

[18] E. J. Corey, A. G. Myers, *Tetrahedron Lett.* **1984**, *25*, 3559.

[19] S. Takada, K. Iwata, T. Yubune, Y. Nishii, *Tetrahedron Lett.* **2016**, *57*, 2422.

[20] CCDC 1902519–1902523 (**22b**, **25**–**27** and **34**), 1903788 (**35**) and 1897977 (**S-7**) contain the supplementary crystallographic data for this

10.1002/anie.201903349

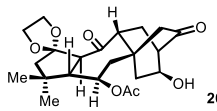
paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[21] Addition of various Lewis acids to improve the diastereoselectivity failed to give any amounts of the desired adducts. It should also be noted that previous Diels–Alder reactions of masked *o*-benzoquinones (MOBs) to form seven membered ring-annulated cycloadducts were reported with low efficiency: a) Y.-K. Chen, R. K. Peddinti, C.-C. Liao, *Chem. Commun.* **2001**, 1340; for other applications of *o*-MOB cycloaddition in natural product synthesis, see: b) C.-D. Lu, A. Zakarian, *Angew. Chem. Int. Ed.* **2008**, *47*, 6829; *Angew. Chem.* **2008**, *120*, 6935; c) P. Lu, Z. Gu, A. Zakarian, *J. Am. Chem. Soc.* **2013**, *135*, 14552; d) Z. Gu, A. Zakarian, *Org. Lett.* **2011**, *13*, 1080.

[22] DFT calculations were performed to support the observed diastereoselectivity; see the Supporting Information for details.

[23] Recycle of **24** was realized by conversion to **23** through a Chugaev elimination in 73% yield over two steps.

[24] As a comparison, the corresponding acetate C6-OAc-**12** afforded C6-OAc-**9**, C6-OAc-**24** and **26** in 32%, 9% and 38% yield, respectively.



26 [X-ray]

[25] a) M. R. Roberts, R. H. Schlessinger, *J. Am. Chem. Soc.* **1981**, *103*, 724; b) D. Liotta, C. Barnum, R. Puleo, G. Zima, C. Bayer, H. S. Kezar, III., *J. Org. Chem.* **1981**, *46*, 2920.

[26] C. Iwata, Y. Takemoto, A. Nakamura, T. Imanishi, *Tetrahedron Lett.* **1985**, *26*, 3227.

[27] S. Stanković, J. H. Espenson, *J. Org. Chem.* **1998**, *63,* 4129.

[28] A. Fernández-Mateos, E. M. de la Nava, G. P. Coca, A. R. Silvo, R. R. González, *Org. Lett.* **1999**, *1*, 607.

[29] For reviews on fragmentation of cyclopropanols, see: a) O. G. Kulinkovich, *Chem. Rev.* **2003**, *103*, 2597; b) A. Nikolaev, A. Orellana, *Synthesis* **2016**, *48*, 1741; c) L. R. Mills, S. Rousseaux, *Eur. J. Org. Chem.* **2019**, 8; d) X. Cai, W. Liang, M. Dai, *Tetrahedron* **2019**, *75*, 193.

[30] a) C. H. DePuy, R. J. Van Lanen, *J. Org. Chem*. **1974**, *39*, 3360; b) Y. Ito, S. Fujii, T. Saegusa, *J. Org. Chem.* **1976**, *41*, 2073; c) N. Iwasawa, S. Hayakawa, K. Isobe, K. Narasaka, *Chem. Lett.* **1991**, *20*, 1193; d) N. Iwasawa, S. Hayakawa, M. Funahashi, K. Isobe, K. Narasaka, *Bull. Chem. Soc. Jpn.* **1993**, *66*, 819; e) S. Chiba, Z. Cao, S. A. A. E. Bialy, K. Narasaka, *Chem. Lett.* **2006**, *35*, 18.

[31] K. I. Booker-Milburn, A. Barker, W. Brailsford, B. Cox, T. E. Mansley, *Tetrahedron* **1998**, *54*, 15321.

[32] a) H. Hikino, T. Ohta, S. Koriyama, Y. Hikino, T. Takemoto, *Chem. Pharm. Bull.* **1971**, *19*, 1289; b) Y. Li, Y.-B. Liu, J.-J. Zhang, Y. Liu, S.-G. Ma, J. Qu, H.-N. Lv, S.-S. Yu, *J. Nat. Prod.* **2015**, *78*, 2887.

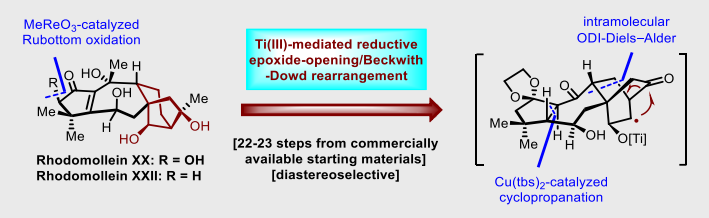
[33] a) M. Kirihara, M. Ichinose, S. Takizawa, T. Momose, *Chem. Commun.* **1998**, 1691; b) M. Kirihara, H. Kakuda, M. Ichinose, Y. Ochiai, S. Takizawa, A. Mokuya, K. Okubo, A. Hatanoa, M. Shiro, *Tetrahedron* **2005**, *61*, 4831.

[34] The optically active (–)-**17** was obtained through a diastereoselective cyclopropanation under chiral bisoxazoline-Cu(I) catalysis (ca. 17:1 d.r., 93% ee); see the Supporting Information for details.

10.1002/anie.201903349

WILEY-VCH

COMMUNICATION



A new Ti(III)-mediated reductive epoxide-opening/Beckwith–Dowd rearrangement process efficiently assembles the bicyclo[3.2.1]octane framework of highly oxidized grayanane diterpenoids. By incorporation of a Cu(tbs)$_2$-catalyzed intramolecular cyclopropanation, a diastereoselective ODI-Diels–Alder cycloaddition and a MeReO$_3$-catalyzed Rubottom oxidation, this apporach has enabled the first total syntheses of rhodomolleins XX and XXII in 23 and 22 steps, respectively.

*K. Yu, Z.-N. Yang, C.-H. Liu, S.-Q. Wu, X. Hong, X.-L. Zhao, H. Ding**

Page No. – Page No.

Total Syntheses of Rhodomolleins XX and XXII: A Reductive Epoxide-Opening/Beckwith–Dowd Approach