A Journal of the Gesellschaft Deutscher Chemiker

Angewandte

GDCh

International Edition

Chemie

www.angewandte.org

Accepted Article

Title: Unified Asymmetric Total Syntheses of Alotaketals A-D and Phorbaketal A

Authors: Hang Cheng, Zhihong Zhang, Hongliang Yao, Wei Zhang, Jingxun Yu, and Rongbiao Tong

This manuscript has been accepted after peer review and appears as an Accepted Article online prior to editing, proofing, and formal publication of the final Version of Record (VoR). This work is currently citable by using the Digital Object Identifier (DOI) given below. The VoR will be published online in Early View as soon as possible and may be different to this Accepted Article as a result of editing. Readers should obtain the VoR from the journal website shown below when it is published to ensure accuracy of information. The authors are responsible for the content of this Accepted Article.

To be cited as: *Angew. Chem. Int. Ed.* 10.1002/anie.201704628
Angew. Chem. 10.1002/ange.201704628

Link to VoR: http://dx.doi.org/10.1002/anie.201704628
http://dx.doi.org/10.1002/ange.201704628

WILEY-VCH

10.1002/anie.201704628

WILEY-VCH

COMMUNICATION

Unified Asymmetric Total Syntheses of Alotaketals A–D and Phorbaketal A

Hang Cheng, Zhihong Zhang, Hongliang Yao, Wei Zhang, Jingxun Yu, and Rongbiao Tong*

Abstract: The novel tricyclic spiroketal alotane-type sesterterpenoids showed strikingly different biological activities and potency with subtle structural alterations. Asymmetric total syntheses of such tricyclic sesterterpenoid alotaketals A-D and phorbaketal A were accomplished (29-31 steps from (–)-malic acid) in a collective way for the first time. The key features of our strategy included (i) the new cascade cyclization of vinyl epoxy δ-keto-alcohol (VEKA) to forge the common tricyclic spiroketal intermediate, (ii) a late-stage allylic C-H oxidation, and (iii) olefin cross metathesis to install the different side chains.

Alotaketals A-D[1] and phorbaketals A-K[2] (Figure 1) were biogenetically related, structurally novel spiroketal sesterterpenoid natural products isolated recently from the marine sponge *Hamigera sp.* and/or *Phorbas sp*. They showed strikingly different biological activities and potency with only subtle structural variations at the C ring and/or the side chain.

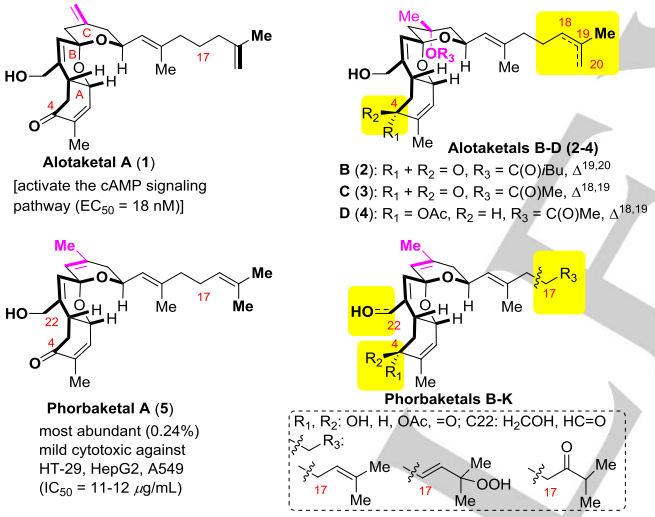
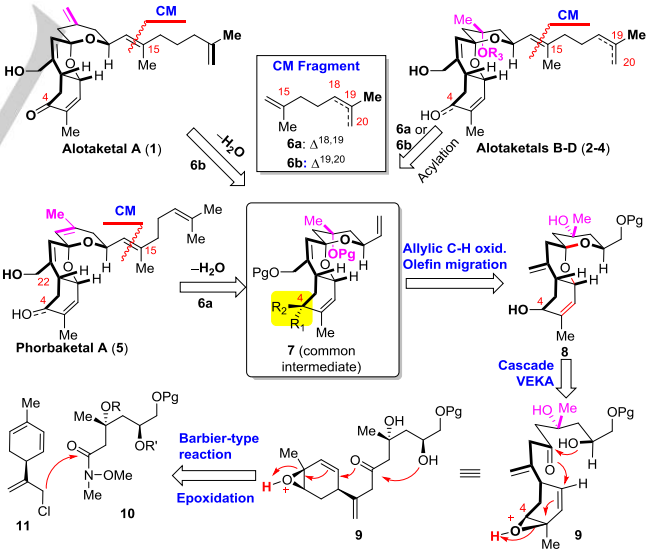


Figure 1. Selected Alotaketals and Phorbaketals

For example, alotaketals A-C (**1-3**) exhibited different potency in activating the cAMP cell signaling pathway[3] (EC_{50}: 18 nM–6.5 μM). Notably, alotaketal A is 170 times more potent than the widely used forskolin (EC_{50} = 3 μM) in cell biology.[4] Recent study by Andersen[1c] *et al* showed that alotaketal C was an agonist of protein kinase C (PKC) and able to activate latent HIV-1 reservoirs at a concentration substantially lower (*ca.* 30 folds) than the positive control prostratin. The structurally related alotane-type phorbaketals A-K exhibited mild cytotoxicity (IC_{50} ≥ 4.9 μM), while phorbaketal A (**5**) was found to significantly stimulate osteoblast differentiation and to considerably inhibit adipogenic differentiation.[5]

The potent and wide array of biological activities of alotaketals and phorbaketals have attracted considerable synthetic interest. Yang[6a,b] and Dalby[6c] accomplished the elegant total synthesis of alotaketal A by the similar strategy that was tactically orchestrated for the late-stage C-ring construction through the Barbier-type reaction and spiroketalization. Recently, Brimble[7a] and Bray[7b] disclosed two efficient strategies for the tricyclic spiroketal core, which unfortunately could not be elaborated to the natural products. To date, it remains an unmet challenge to synthesize two or more members of this family with the reported strategies that could not address the structural variations at both the C ring and the side chains. Herein, we report a new synthetic strategy that leads to collective total syntheses of alotaketals A-D (**1-4**) and phorbaketal A (**5**), featuring a new cascade cyclization of vinyl epoxy δ-keto-alcohol (VEKA) to forge the common tricyclic spiroketal core (Scheme 1).



Scheme 1. Unified synthetic strategy for alotaketals A-D and phorbaketal A

Retrosynthetically (Scheme 1), we planned to install the different side chain at the final stage of synthesis via olefin cross metathesis of the linear diene (**6a** or **6b**) and the common tricyclic spiroketal core **7**, which might be derived from allylic C-H oxidation[8] of **8** with the double bond migration and an unprecedented cascade cyclization[9] of VEKA (**9** → **8**).[10] Preparation of **9** could be achieved by a Barbier-type reaction of

[*] Dr. H. Cheng, Z. Zhang, Dr. H. Yao, Dr. W. Zhang, J. Yu, Prof. Dr. R. Tong*
Department of Chemistry
The Hong Kong University of Science and Technology
Clear Water Bay, Kowloon, HK (China)
E-mail: rtong@ust.hk

Supporting information for this article is available on the WWW under http:

Accepted Manuscript

This article is protected by copyright. All rights reserved.

10.1002/anie.201704628

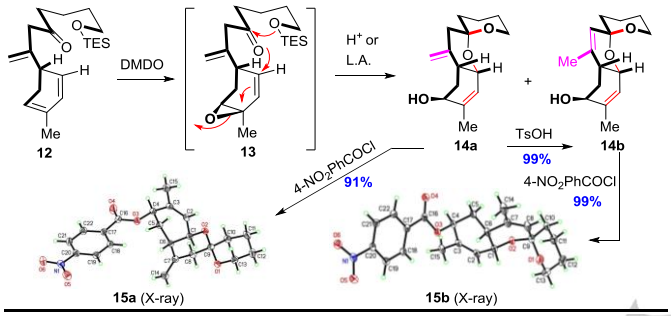
WILEY-VCH

COMMUNICATION

the allyl Grignard of **11**[10] and Weinreb amide **10** followed by regioselective epoxidation. The two biggest challenges for implementing this strategy are (i) the efficiency, regioselectivity,[11] stereochemical outcome of the previously unknown cascade reaction of VEKA and (ii) practicability of the chemoselective allylic C-H oxidation (**8** → **7**) in the context of the complex tricyclic substrates.

These two challenges were first addressed with our model studies (Table 1 and Scheme 2). Compound **12** (see Supporting Information for details on its synthesis) was used to examine the key cascade cyclization. Epoxidation of **12** with freshly prepared dimethyldioxirane (DMDO) provided the clean but unstable epoxide **13** (see SI for NMR spectra of the crude product). This

Table 1. Selected conditions for the cascade cyclization of vinyl epoxy δ-keto-alcohol (VEKA, **12**).[a]

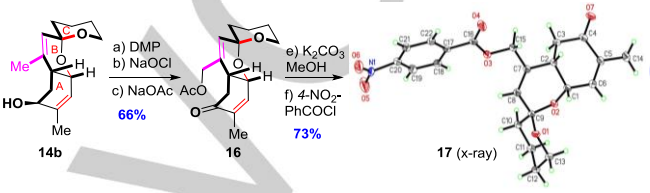


entry	reagent (equiv)	solvent	time	temp	yield[b] (%, **14a**/**14b**)
1	BF_3-Et_2O (1.0)	CH_2Cl_2	1 h	-78 °C	50 (1/0)
2	TESOTf (0.1)	CH_2Cl_2	1 h	-78 °C	40 (1/0)
3	$AgSbF_6$ (1.0)	CH_2Cl_2	1 h	0 °C→rt	54 (1/0)
4	$Yb(OTf)_3$ (1.0)	CH_2Cl_2	1 h	0 °C	35 (1/0)
5	PPTS (1.0)	CH_2Cl_2	2 h	rt	71 (0/1)
6	TFA (1.0)	CH_2Cl_2	2 h	0 °C→rt	0
7	CSA (1.0)	CH_2Cl_2	5 min	rt	20 (0/1)
8	**TfOH (0.5)**	**CH_2Cl_2**	**2 h**	**0 °C**	**80 (0/1)**

[a]Conditions: **12** (17.4 mg, 0.005 mmol) in CH_2Cl_2 (0.5 mL) was treated with the acidic promoter. [b]yield was based on ^{1}H-NMR of the crude mixture. DMDO = dimethyl dioxirane, TES = triethylsilyl, TsOH = *p*-toluenesulfonic acid, PPTS = pyridinium *p*-toluenesulfonate, TFA = trifluoroacetic acid, CSA = camphorsulfonic acid, TfOH = triflic acid. Thermal ellipsoids shown at 40% probability.[30]

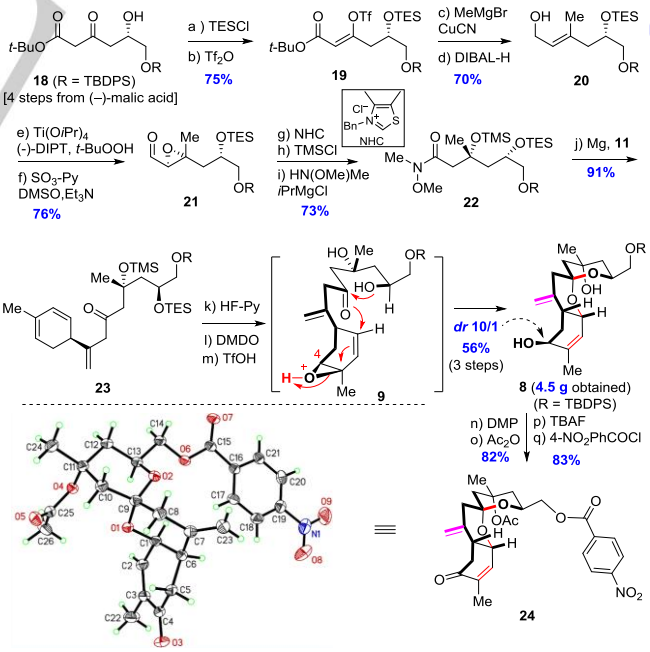
epoxide **13** was then treated with a variety of promoters and Table 1 listed selected conditions from >50 different runs. Clearly, triflic acid (TfOH) was superior to other acidic promoters for the cascade reaction on scales ranging from 17 mg to 100 mg. Interestingly, Lewis acid (entries 1-4) effected only the cyclization to afford the tricyclic product **14a** in moderate yields, while Brønsted acids (entries 5-8) promoted both the cyclization and double bond isomerization to provide the **14b** as the only product with better overall yields (2 steps). Notably, the alkene isomerization occurred in a nearly quantitative yield when **14a** was treated with *p*-TsOH. The molecular structure of both **14a** and **14b** was substantiated by X-ray crystallography of their benzoyl derivatives (**15a** and **15b**).

To address the second challenge, we employed **14b** to explore the allylic C-H oxidation. After some experimentations, we found that Dess-Martin periodinane (DMP) oxidation of **14b** produced the enone that electronically differentiated the trisubstituted alkenes in A and B rings and allowed successful chemoselective allylic C-H chlorination[12] at B ring. S_N2 substitution with NaOAc provided allyl acetate **16**, which relative configuration was confirmed by the X-ray diffraction analysis of its 4-nitrobenzoate **17**.



Scheme 2. Model study on the allylic C-H oxidation. DMP = Dess-Martin periodinane. Thermal ellipsoids shown at 40% probability.[30]

Overcoming these two potential synthetic challenges with the model studies convinced us to undertake our planned unified total syntheses (Scheme 1) of alotaketals A-D and phorbaketal A, which represent major structural variations at the C ring and the side chains within the alotane family (Figure 1). As depicted in Scheme 3, our synthesis began with the preparation of allylic alcohol **20** from the known β-keto ester **18**[13] (four steps from (–)-malic acid in 51% yield) through TES protection, triflation, CuCN



Scheme 3. Synthesis of the tricyclic Core **8**. DIBAL-H = diisobutylaluminum hydride, DIPT = diisopropyl tartrate, DMSO = dimethyl sulfoxide, NHC = *N*-heterocyclic carbene, TMS = trimethylsilyl, TBDPS = *tert*-butyldiphenylsilyl, DMDO = dimethyl dioxirane, TBAF = tetra-*n*-butylammonium fluoride, DMP = Dess-Martin periodinane. Thermal ellipsoids shown at 40% probability.[30]

Accepted Manuscript

This article is protected by copyright. All rights reserved.

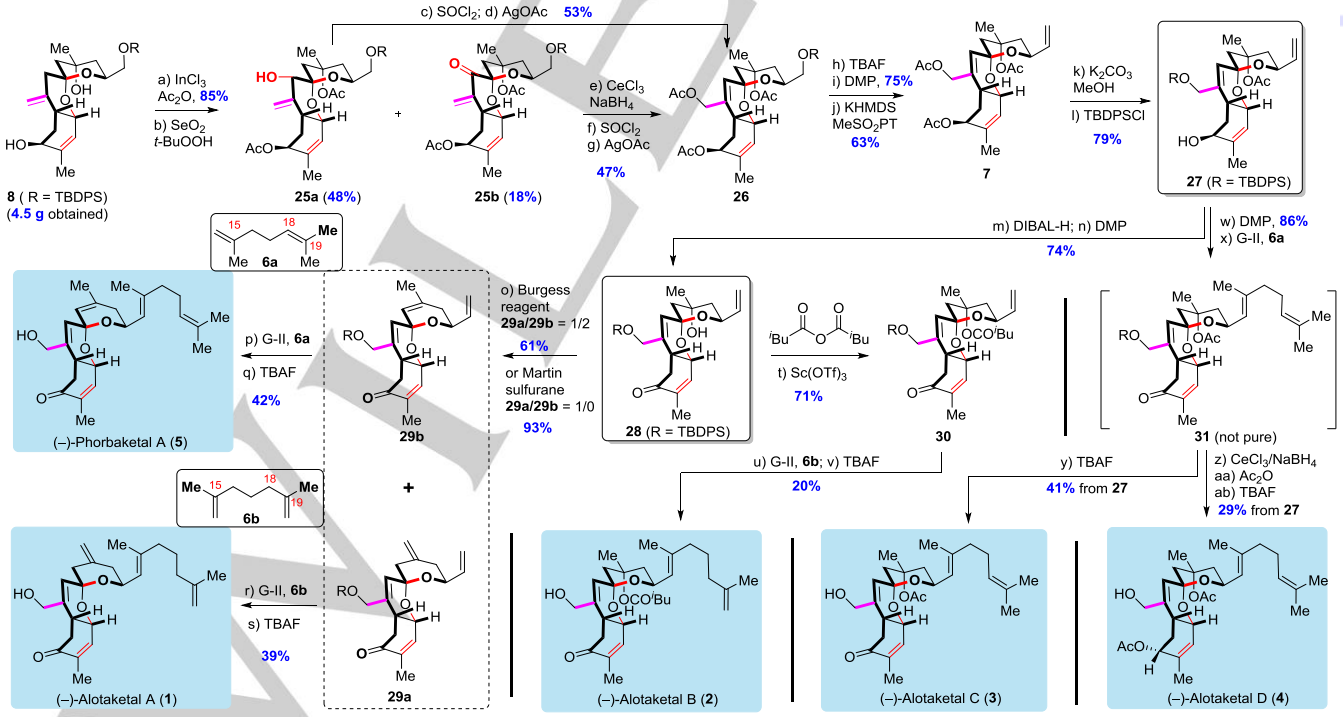
10.1002/anie.201704628

WILEY-VCH

COMMUNICATION

-mediated methylation[14] of (*Z*)-enol triflate, and DIBAL-H reduction. Sharpless asymmetric epoxidation of **20** followed by Parikh-Doering oxidation provided epoxy aldehyde **21**, which was converted to Weinreb amide **22** through a 3-step sequence involving NHC-catalyzed redox esterification,[15] TMS protection and amidation. Reaction of Weinreb amide **12** and the freshly-prepared Grignard reagent of the allylic chloride **11**[10] gave the ketone **23** in a reproducibly excellent yield on decagram scales. The key cascade cyclization was carried out by sequential treatments of **23** with HF-py (chemoselective removal of TMS and TES), DMDO (stereoselective epoxidation) and TfOH (cascade reaction of VEKA) to provide the desired tricyclic spiroketal **8** in 56% yield (4.5 g obtained!) as a mixture of 10/1 diastereomers at C4. Interestingly, we did not observe the *exo*-methylene isomerization, which was different from our model study. The relative and absolute configuration of **8** was confirmed by X-ray diffraction analysis of its 4-nitrobenzoate derivative **24**.

With 4.5 grams of the key tricyclic spiroketal core **8** in hand, we set out to undertake the collective total synthesis (Scheme 4). After double $InCl_3$-mediated acetylation[16] of **8** (other procedures gave poor yields), Riley (SeO_2) oxidation[17] that gave a very poor yield for our model substrates **14a/b** was found to proceed effectively and provide the allylic alcohol **25a** (48% yield) and over-oxidation product **25b** (18.5% yield). Other allylic C-H oxidation methods such as Kharasch-Sosnovsky,[18] NaOCl/$CeCl_3$,[12] Br_2/$FeCl_3$[19] and NBS[20] resulted in decomposition of **8**. Fortunately, both of **25a** and **25b** could be readily and efficiently converted to the allylic acetate **26** in 2 and 3 steps, respectively, by using Wender's procedure.[21] Although direct installation of the long side chain on **26** through various aldehyde olefinations (with 8-carbon ylide[22]) including Wittig,[23] Julia-Kocienski,[24] and Horner-Wadsworth-Emmons failed, the terminal alkene for olefin cross metathesis was successfully introduced on **26** in three steps: desilylation with TBAF, DMP oxidation in the presence of pyridine (other classical oxidation procedures including Swern, Parikh-Doering, TPAP/NMO, PCC, IBX gave <40% yield) and Julia-Kocienski methylenation (**26** → **7**). Double desilylation of **7** followed by regioselective protection of the primary alcohol as *tert*-butyldiphenylsilyl (TBDPS) ether provided the advanced common intermediate **27** for all alotane natural products. We first targeted alotaketal A and phorbaketal A and therefore tertiary acetate of **27** was removed by DIBAL-H reduction (poor conversion by K_2CO_3/MeOH) for dehydration. After DMP oxidation of the secondary alcohol to the enone **28**, dehydration of the tertiary alcohol of **28** with Burgess reagent[25] gave a 1/2 mixture of **29a**/**29b** favoring **29b** in 61% combined yield while dehydration with Martin sulfurance[26] produced exclusive thermodynamically more stable **29b** in 93% yield. Grubbs-II-catalyzed olefin cross metathesis of **29a** and **29b** with 1,6-diene **6b**[27] and 1,5-diene **6a**,[28] respectively, followed by desilylation completed the total syntheses of (–)-alotaketal A (**1**) and (–)-phorbaketal A (**5**).[28] $Sc(OTf)_3$-promoted acylation[29] of the tertiary alcohol of **28** with isovaleric anhydride provided **30**, which underwent olefin cross metathesis with 1,6-diene **6b** and desilylation to furnish (–)-alotaketal B (**2**). On the other hand, the tertiary acetate of the common intermediate **7**, corresponding to alotaketals C and D, could retain while regioselective deacetylation, silylation and DMP oxidation (**7** → **27**). Cross metathesis of **27** with 1,5-diene **6a** to provide the crude **29a/b**, which was treated either with TBAF to complete the total synthesis of alotaketal C in 41% yield over 2 steps or sequentially with $CeCl_3$/$NaBH_4$, acetic anhydride and TBAF to furnish alotaketal D



Scheme 4. Collective total syntheses of alotaketals A-D and phorbaketal A. KHMDS = Potassium bis(trimethylsilyl)amide, G-II = Grubbs catalyst 2nd generation, TBAF = tetra-*n*-butylammonium fluoride, DMP = Dess-Martin periodinane, DIBAL-H = diisobutylaluminum hydride, $MeSO_2PT$ = methyl 1-phenyl-1*H*-tetrazol-5-yl sulfone.

This article is protected by copyright. All rights reserved.

in 29% yield over 4 steps. All spectroscopic data of our synthetic samples were in good agreement with those reported for the corresponding natural products.[28]

In conclusion, we developed a new cascade cyclization of vinyl epoxy δ-keto-alcohol (VEKA), which enabled us to achieve unified asymmetric total syntheses of alotaketals A-D and phorbaketal A. Notably, alotaketals B-D and phorbaketal A were totally synthesized for the first time. Additional key reactions employed in this new strategy include (1) allylic C-H oxidation and alkene isomerization on the complex tricyclic spiroketal substrates and (2) olefin cross metathesis to install the different side chain. Extension of this strategy to other members of alotane-type sesterterpenoids (phorbaketals B-K) and biological activity study are undergoing in our lab and will be reported in due course.

Acknowledgements

This research was financially supported by Research Grant Council of Hong Kong (GRF 605113, GRF 16305314, and GRF 16311716). We are very grateful to Prof. Ian Williams (HKUST) and Dr. Herman Sung (HKUST) for single-crystal diffraction analysis and Prof. Guang Zhu (HKUST) for providing assistance in NMR data collection.

Keywords: sesterterpenoid • alotaketal • phorbaketal • cascade cyclization• vinyl epoxide opening

[1] a) R. Forestieri, C. E. Merchant, N. J. de Voogd, T. Matainaho, T. J. Kieffer, R. J. Andersen, *Org. Lett.* **2009**, *11*, 5166-5169. b) J. Daoust, M. Chen, M. Wang, D. Williams, M. Garcia Chavez, Y. Wang, C. Merchant, A. Fontana, T. Kieffer, R. Andersen, *J. Org. Chem.* **2013**, *78*, 8267-8273. c) M. Wang, I. Tietjen, M. Chen, D. E. Williams, J. Daoust, M. A. Brockman, R. J. Andersen, *J. Org. Chem.* **2016**, *81*, 11324-11334.

[2] a) J.-R. Rho, B. S. Hwang, C. J. Sim, S. Joung, H. Y. Lee, H.-J. Kim, *Org. Lett.* **2009**, *11*, 5590-5593 . (b) W. Wang, B. Mun, Y. Lee, M. V. Reddy, Y.Park, J. Lee, H. Kim, D. Hahn, J. Chin, M. Ekins, S.-J. Nam, H. Kang, *J. Nat. Prod*. **2013**, *76*, 170-177. (c) Y. Lee, W. Wang, H. Kim, A. G. Giri, D. H. Won, D. Hahn, K. R. Baek, J. Lee, I. Yang, H. Choi, S.-J. Nam, H. Kang, *Bioorg. Med. Chem. Lett.* **2014**, *24*, 4095-4098.

[3] J. A. Beavo, L. L. Brunton, *Nat. Rev. Mol. Cell. Biol.* **2002**, *3*, 710-718.

[4] a) S. V. Bhat, B. S. Bajwa, H. Dornauer, N. J. de Souza, H. W. Fehlhaber, *Tetrahedron Lett.* **1977**, 1669-1672. b) K. B. Seamon, W. Padgett, J. W. Daly, *Proc. Natl. Acad. Sci. U.S.A.* **1981**, *78*, 3363-3367.

[5] a) M. R. Byun, A. R. Kim, J.-H. Hwang, M. K. Sung, Y. K. Lee, B. S. Hwang, J.-R. Rho, E. S. Hwang, J.-H. Hong, *FEBS Lett.* **2012**, *586*, 1086-1092. b) M. R. Byun, C. H. Lee, J.-H. Hwang, A. R. Kim, S. A. Moon, M. K. Sung, J.-R. Roh, E. S. Hwang, J.-H. Hong, *Eur. J. Pharmacol.* **2013**, *718*, 181-187.

[6] a) J. Huang, J. R. Yang, J. Zhang, J. Yang, *J. Am. Chem. Soc.* **2012**, *134*, 8806-8809. b) J. Huang, J. R. Yang, J. Zhang, J. Yang, *Org. Biomol. Chem.* **2013**, *11*, 3212-3222. c) M. Xuan, I. Paterson, S. M. Dalby, *Org. Lett.* **2012**, *14*, 5492-5495.

[7] a) J. G. Hubert, D. P. Furkert, M. A. Brimble, *J. Org. Chem.* **2015**, *80*, 2715-2723. (b) H. J. Shirley, C. D. Bray, *Eur. J. Org. Chem.* **2016**, 1504-1507.

[8] For selected reviews, see: a) A. Nakamura, M. Nakata, *Synthesis* **2013**, *45*, 1421-1451. b) V. Weidmann, W. Maison, *Synthesis* **2013**, *45*, 2201-2221. For selected examples of allylic C-H oxidation in synthesis complex molecules, see: c) E. J. Horn, B. R. Rosen, Y. Chen, J. Tang, K. Chen, M. D. Eastgate, P. S. Baran, *Nature* **2016**, *533*, 77-81. d) Y. Jin, C.-H. Yeh, C. A. Kuttruff, L. Jørgensen, G. Dünstl, J. Felding, S. R. Natarajan, P. S. Baran, *Angew. Chem. Int. Ed.* **2015**, *54*, 14044-14048. e) C. Yuan, Y. Jin, N. C. Wilde, P. S. Baran, *Angew. Chem. Int. Ed.* **2016**, *55*, 8280-8284. f) H. Chu, J. M. Smith, J. Felding, P. S. Baran, *ACS Cent. Sci.* **2017**, *3*, 47-51. g) K. J. Fraunhoffer, N. Prabagaran, L. E. Sirois, M. C. White, *J. Am. Chem. Soc.* **2006**, *128*, 9032-9033. h) E. M. Stang, M. C. White, *Nat. Chem.* **2009**, *1*, 547-551.

[9] The only related process is the PIFA-mediated cyclization of 4-(7-hydroxy-3-keto) phenols for the total synthesis of aculeatins. For a recent review, see: a) L. Song, H. Yao, Y. Dai, M. Wu, R. Tong, *Tetrahedron Lett.* **2016**, *57*, 4257-4263. For approaches using a ketone to open the epoxide, see: b) R. L. Mulholland, Jr., A. R. Chamberlin, *J. Org. Chem*. **1988**, *53*, 1082-1085. c) C. H. Fotsch, A. R. Chamberlin, *J. Org. Chem.* **1991**, *56*, 4141-4147. d) S. D. Rychnovsky, V. H. Dahanukar, *Tetrahedron Lett*. **1996**, *37*, 339-342. e) Y. Xie, P. E. Floreancig, *Angew. Chem. Int. Ed*, **2013**, *52*, 625-628

[10] W. Zhang, H. Yao, J. Yu, Z. Zhang, R. Tong, *Angew. Chem. Int. Ed.* **2017**, 56, 4787-4791.

[11] Ring opening of vinyl epoxides with internal alcohol nucleophiles usually proceeds in 1,2-addition manner (S_N2), not favoring our designed 1,4-addition (S_N2'). J. He, J. Ling, P. Chiu, *Chem. Rev.* **2014**, *114*, 8037-8128

[12] a) F. J. Moreno-Dorado, F. M. Guerra, F. L. Manzano, F. J. Aladro, Z. D. Jorge, G. M. Massanet, *Tetrahedron Lett.* **2003**, *44*, 6691-6693. b) M. Blair, C. M. Forsyth, K. L. Tuck, *Tetrahedron Lett.* **2010**, *51*, 4808-4811.

[13] Y. Su, Y. Xu, J. Han, J. Zheng, J. Qi, T. Jiang, X. Pan, X. She, *J. Org. Chem.* **2009**, *74*, 2743-2749.

[14] T. J. Zahn, C. Weinbaum, R. A. Gibbs, *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1763-1766.

[15] K. Y.-K. Chow, J. W. Bode, *J. Am. Chem. Soc.* **2004**, *126*, 8126-8127.

[16] A. K. Chakraborti, R. Gulhane, *Tetrahedron Lett.* **2003**, *44*, 6749-6753.

[17] a) M. A. Umbreit, K. B. Sharpless, *J. Am. Chem. Soc.* **1977**, *99*, 5526-5528. b) M. Furber, L. N. Mander, *J. Am. Chem. Soc.* **1987**, *109*, 6389-6396. c) K. M. Peese, D. Y. Gin, *J. Am. Chem. Soc.* **2006**, *128*, 8734-8735. For a recent review, see: d) J. Młochowski, H. Wójtowicz-Młochowska, *Molecules* **2015**, *20*, 10205-10243.

[18] a) M. S. Kharasch, G. Sosnovsky, *J. Am. Chem. Soc*. **1958**, *80*, 756-756.

[19] M. E. Maier, A. Bayer, *Eur. J. Org. Chem*. **2006**, 4034-4043.

[20] A. Abad, C. Agulló, A. C. Cuñat, D. Pardo, *Tetrahedron Lett.* **2003**, *44*, 1899-1902.

[21] P. A. Wender, C. D. Jesudason, H. Nakahira, N. Tamura, A. L. Tebbe, Y. Ueno, *J. Am. Chem. Soc.* **1997**, *119*, 12976-12977.

[22] A. Fukuzawa, H. Sato, T. Masamune, *Tetrahedron Lett.* **1987**, *28*, 4303-4306.

[23] S. A. Snyder, Z.-Y. Tang, R. Gupta, *J. Am. Chem. Soc.* **2009**, *131*, 5744-5745.

[24] H. Huang, J. S. Panek, *Org. Lett.* **2004**, *6*, 4383-4385.

[25] G. M. Atkins, E. M. Burgess, *J. Am. Chem. Soc.* **1968**, *90*, 4744-4745.

[26] J. C. Martin, R. J. Arhart, *J. Am. Chem. Soc.* **1971**, *93*, 4327-4329.

[27] W. F. Berkowitz, Y. Wu, *J. Org. Chem.* **1997**, *62*, 1536-1539.

[28] See Supporting Information.

[29] a) K. Ishihara, M. Kubota, H. Kurihara, H. Yamamoto, *J. Am. Chem. Soc.* **1995**, *117*, 4413-4414. b) K. Ishihara, M. Kubota, H. Kurihara, H. Yamamoto, *J. Org. Chem.* **1996**, *61*, 4560-4567.

[30] CCDC 1544104 (**15a**), CCDC 1544105 (**15b**), CCDC 1544106 (**17**), and CCDC 1544499 (**24**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

Accepted Manuscript

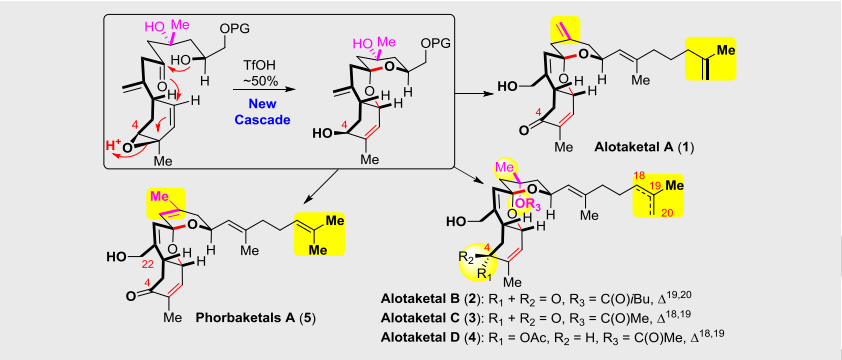
This article is protected by copyright. All rights reserved.

10.1002/anie.201704628

WILEY-VCH

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

COMMUNICATION



*Hang Cheng, Zhihong Zhang, Hongliang Yao, Wei Zhang, Jingxun Yu, and Rongbiao Tong**

Page No. – Page No.

Unified Asymmetric Total Syntheses of Alotaketals A–D and Phorbaketal A

All-in-one: Unified total syntheses of tricyclic sesterterpenoid alotaketals A-D and phorbaketal A were accomplished (29-31 steps from (–)-malic acid) in a collective way for the first time, featuring a new cascade cyclization of vinyl epoxy δ-keto-alcohol (VEKA), late-stage C-H oxidation, and olefin cross metathesis.

WILEY-VCH Accepted Manuscript

This article is protected by copyright. All rights reserved.