A Journal of the Gesellschaft Deutscher Chemiker

Angewandte International Edition

GDCh

Chemie

www.angewandte.org

Accepted Article

Title: Enantioselective Total Synthesis of Berkeleyone A and Preaustinoids

Authors: Houhua Li, Yang Zhang, Yunpeng Ji, Ivan Franzoni, Chuning Guo, Hongli Jia, and Benke Hong

To be cited as: *Angew. Chem. Int. Ed.* 10.1002/anie.202104014

Link to VoR: https://doi.org/10.1002/anie.202104014

WILEY-VCH

10.1002/anie.202104014

WILEY-VCH

COMMUNICATION

Enantioselective Total Synthesis of Berkeleyone A and Preaustinoids

Yang Zhang,[a] Yunpeng Ji,[a] Ivan Franzoni,[b] Chuning Guo,[a] Hongli Jia,[a] Benke Hong,[a] and Houhua Li*[a]

This paper is dedicated to Prof. Herbert Waldmann and Prof. Xiaoguang Lei

[a] Dr. Y. Zhang,† Y. Ji,† C. Guo, Dr. H. Jia, Dr. B. Hong, Prof. Dr. H. Li
State Key Laboratory of Natural and Biomimetic Drugs, School of Pharmaceutical Sciences
Peking University
Xue Yuan Road No. 38, Beijing 100191, China
E-mail: lihouhua@pku.edu.cn
[b] Dr. I. Franzoni
NuChem Sciences
2350 rue Cohen Suite 201, Saint-Laurent, Quebec, Canada H4R 2N6
[†] These authors contributed equally to this work

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

Abstract: Herein we report the first enantioselective total synthesis of 3,5-dimethylorsellinic acid-derived meroterpenoids (–)-berkeleyone A and its five congeners ((−)-preaustinoids A, A1, B, B1 and B2) in 12-15 steps, respectively, starting from commercially available 2,4,6-trihydroxybenzoic acid hydrate. Based upon the recognition of latent symmetry within D-ring, our convergent synthesis features two critical reactions: (1) a symmetry-breaking, diastereoselective dearomative alkylation to assemble the entire carbon core, and (2) a $Sc(OTf)_3$-mediated sequential Krapcho dealkoxycarbonylation/carbonyl α-*tert*-alkylation to forge the intricate bicyclo[3.3.1]nonane framework. We also conducted our preliminary biomimetic investigations and uncovered a series of rearrangements (α-ketol, α-hydroxyl-β-diketone, *etc*) responsible for the biomimetic diversification of (−)-berkeleyone A into its five preaustinoid congeners.

Fungal meroterpenoids derived from a simple aromatic polyketide 3,5-dimethylorsellinic acid (DMOA) are a large series of hybrid natural products with huge structural diversity and impressive bioactivities.[1] Since the isolation of their first congener in 1976, over 100 compounds have been described. From a biosynthetic point of view, (–)-berkeleyone A (**1**) stands as a potential gateway compound through the union of a polyketide fragment DMOA with farnesyl pyrophosphate (Figure 1).[2,3] Thereon, diversification at A-ring generates (–)-preaustinoid A (**2**) and (–)-preaustinoid A1 (**3**), where contraction of D-ring produces (–)-preaustinoid B (**4**), (–)-preaustinoid B1 (**5**), and (+)-preaustinoid B2 (**6**).[2] Interestingly, **1**-**3** also possess anti-inflammatory properties by inhibiting the signaling enzyme caspase-1.[2d] To further unveil the biological function and therapeutic potential of DOMA-derived meroterpenoids, both biological and chemical synthetic studies have been done extensively in the past decade.[3-5]

From a chemical synthesis perspective,[4,5] DMOA-derived meroterpenoids present an exceedingly challenge, as exemplified by (–)-berkeleyone A (**1**), which possess a dense tetracyclic framework with a hallmark bicyclo[3.3.1]nonane core, three quaternary carbon centers within C-ring, and a highly oxidized D-ring without any hydrogen atom substituents. Hitherto two elegant racemic total synthesis of **1** and select andrastin/terretonin congeners have been reported by Maimone and Newhouse groups, where oxidative ring expansion and an isomerization−cyclization cascade have been independently applied for the installation of bicyclo[3.3.1]nonane core.[5] En route to polycyclic terpenoids and terpenoid hybrids,[6] we also initiated our investigations into DMOA-derived meroterpenoids. Herein we report our synthetic endeavors, which ultimately accumulate into the first enantioselective total synthesis of **1**-**6** in 12-15 steps, respectively.

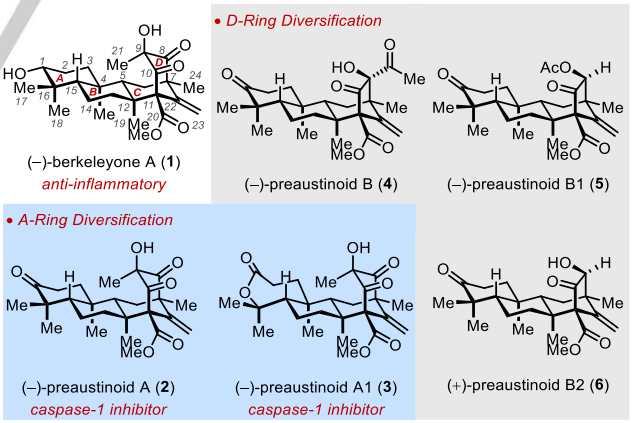


Figure 1. Representative structures of 3,5-dimethylorsellinic acid (DMOA)-derived meroterpenoids.

At the outset of our investigations, the recognition of a hidden symmetry within the D-ring of (–)-berkeleyone A (**1**) proved to be essential to our synthetic plan. As has already been constantly recognized in many landmark total syntheses, the recognition of latent symmetry in a target molecule would drastically simplify the task at hand.[7] Depicted in Figure 2A, upon replacement of CH_2 with O at C23 position, the highly oxidized D-ring can therefore be

10.1002/anie.202104014

extracted to a symmetrical methyl 4-methoxy-3,5-dimethyl phloroglucinol carboxylate (**7**). Thus, (–)-berkeleyone A (**1**), a common precursor to preaustinoids **2**-**6** through biomimetic diversification, were retrosynthetically reduced to the tetracyclic intermediate **8** (Figure 2B). The challenging C11-C12 linkage of **8** can be forged through an intramolecular carbonyl α-*tert*-alkylation of keto-ester **9**,[8-11] which also simultaneously installs two adjacent quaternary carbon centers C11 and C12.[12] To achieve a convergent synthesis, intermediate **9** was assembled through a symmetry-breaking dearomative alkylation of **7** with bicyclic fragment **10**.[13] Finally, carboxylate **7** would be easily obtained through a successive *ortho*-methylation sequence, starting from commercially available 2,4,6-trihydroxybenzoic acid hydrate (**11**).[14]

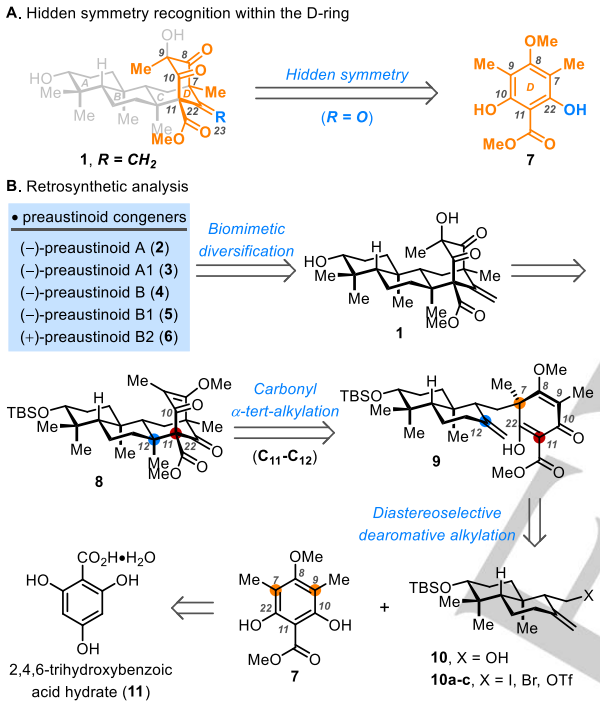


Figure 2. Retrosynthetic analysis of **1**-**6** based on hidden symmetry recognition.

As shown in Scheme 1, we commenced our studies by synthesizing aldehyde **12** following a known 4-step protocol (see Scheme S1).[14] Subsequent reduction afforded carboxylate **7**. In addition, using a modified Sharpless asymmetric dihydroxylation of commercially available farnesyl acetate followed by a reductive cyclization, enantioenriched bicyclic fragment **10** could also be easily prepared through a modified 5-step protocol (see Scheme S2).[15] With **7** and **10** in hand, we embarked on our investigation into symmetry-breaking dearomative alkylation.[13] Whereas dearomative alkylation of acylphloroglucinols have previously been well explored by Porco and George groups,[13] currently this annulative method is limited to acyclic electrophiles, with always poor diastereoselectivity in all cases owing to the lack of remote stereocontrol. In our case, we initially observed decomposition with iodide **10a** or bromide **10b** derived from **10** due to their inner instability. Later on, upon treatment of **7** with in-situ formed **10c** under basic conditions (LHMDS), two inseparable tautomers **9a** and **9b** were isolated in 69% yield on a gram scale, with excellent diastereoselectivity (>20:1). To the best of our knowledge, this is the first diastereoselective dearomative alkylation of acylphloroglucinols with cyclic electrophiles.

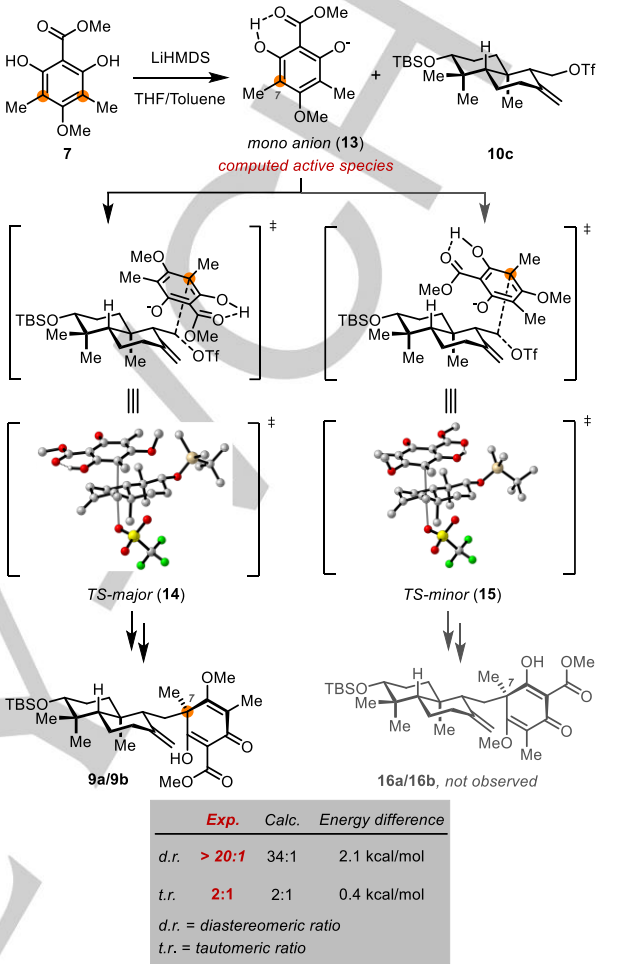


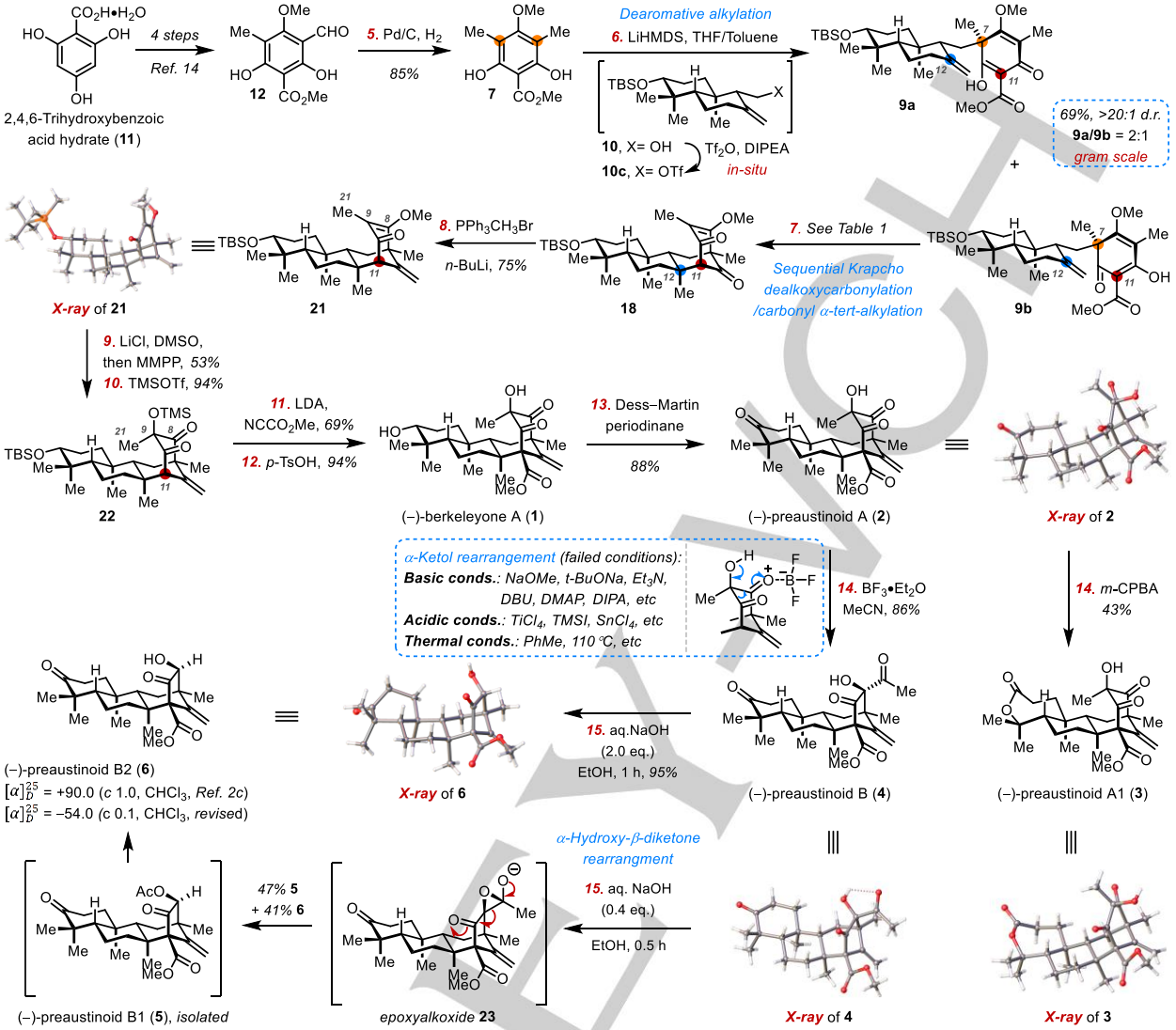
Figure 3. Diastereoselectivity rationale based on DFT calculations. Diastereoselective determined transition state calculation at the M06-2X/6-31+G(d,p)//B3LYP-D3BJ/6-31G(d) level in THF (SMD solvation model).

To rationalize the unprecedented high level of diastereoselectivity observed in the crucial triflate nucleophilic displacement step, we carried out DFT calculations at the SMD(THF)/M06-2X/6-31+G(d,p)//B3LYP-D3BJ/6-31G(d) level of theory (Figure 3 and see Supporting Information (SI) for details). The inclusion of the dispersion correction term was found to be pivotal in computationally rationalizing our experimental results. Detailedly, among the diverse, plausible forms of the nucleophilic partner **7** (*i.e.* bisdeprotonated, lithium ion adducts), mono anion **13** was firstly identified as computed active species.[16] This intermediate is characterized by a stable intramolecular H-bond interaction between the hydroxyl and carbonyl groups. In the computed transition states, mono anion **13** approaches **10c** from the most accessible face while maximizing the contact between the aromatic π-system of **13** and the lipophilic surface of the 6,6-fused bicyclic framework of **10c**. The computed relative energy difference between two transition states TS-major **14** and TS-minor **15** is 2.1 kcal/mol, corresponding to a predicted

10.1002/anie.202104014

WILEY-VCH

COMMUNICATION



Scheme 1. Enantioselective total synthesis of **1**-**6**. THF = tetrahydrofuran, DIPEA = *N,N*-diisopropylethylamine, MMPP = magnesium monoperoxyphthalate, TMSOTf = trimethylsilyl trifluoromethanesulfonate, LDA = lithium diisopropylamide, *m*-CPBA = 3-chloroperbenzoic acid.

diastereoisomeric ratio of 34:1 in favor of **9a/9b** over **16a/16b**. This result fully matches with the experimental ratio (>20:1). The relative energy difference between transition states **14** and **15** presumably stems from a balance between attractive dispersion forces and steric repulsion between **13** and **10c**.[17] Overall, the rigidity of 6,6-fused bicyclic scaffold defines better the interaction between electrophile and aryl nucleophile, thereby inducing high diastereoselectivity, while in the case of an acyclic electrophile, its conformational flexibility is expected to significantly reduce the diastereo-outcome of the reaction. Of note, the computed energy difference for two tautomers **9a** and **9b** is 0.4 kcal/mol, responsible for a predicted ratio of 2:1 in favor of **9a**, which also fully matched with the ratio observed (2:1).

With access to **9a/9b** secured, we proceeded to the intramolecular carbonyl α-*tert*-alkylation (Table 1). At this stage, we considered three distinct tactics to achieve this challenging transformation: (i) Brønsted or Lewis acid-mediated cationic cyclization;[8,9] (ii) photocatalyzed radical cyclization;[10] (iii) $Mn(OAc)_3$-mediated oxidative cyclization.[11] Disappointedly, numerous studies with **9a/9b** proved unfruitful and mainly led to decomposition into unidentified side products (entries 1-4). With a hope that the removal of methyl ester at C11 position might drastically reduce steric crowding during carbonyl *C11*-α-*tert*-alkylation, we conducted Krapcho dealkoxycarbonylation of **9a/9b** using 10 mol% of $Sc(OTf)_3$ and **17** was generated smoothly.[18]

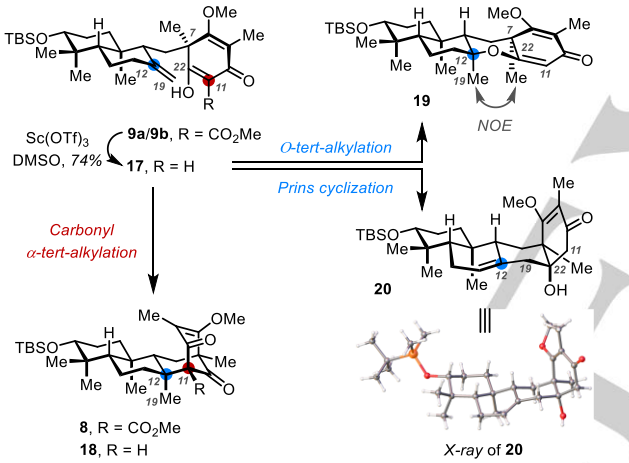
Diketone **17** was then engaged into different intramolecular carbonyl α-*tert*-alkylation conditions. Initial treatment of **17** with various Brønsted acids again resulted in decomposition (entry 5). Pleasingly, the desired carbonyl α-*tert*-alkylation product **18** was firstly obtained by using $SnCl_4$ (entry 6), albeit contaminated with *O*-*tert*-alkylation product **19** as the main product (27% yield). Further screening of various Lewis acids identified $Sc(OTf)_3$ as an optimal catalyst which promoted **17** to preferentially undergo carbonyl *C11*-α-*tert*-alkylation and delivered **18** in 50% yield (entry 7).[9c] Of interesting note, Et_2AlCl promoted a novel Prins cyclization to afford **20** (entry 8).[19] Finally, starting from

10.1002/anie.202104014

inseparable **9a/9b**, we maneuvered to operate a $Sc(OTf)_3$-mediated sequential Krapcho dealkoxycarbonylation/carbonyl α-*tert*-alkylation and **18** was isolated in 41% yields (entry 9). The structures of three cyclization products **18**, **19**, and **20** described above were determined based on 2D-NMR spectroscopy or confirmed by X-ray crystallographic analysis.[20]

Now in possession of key intermediate **18**, we focused our next efforts on the elaboration of highly oxidized D-ring (Scheme 1). Wittig olefination of **18** delivered **21** in 75% yield. The absolute configurations were also secured at this stage by X-ray crystallographic analysis of **21**.[21] Subsequent C11 acylation of either **18** or **21** under various basic conditions (LDA, LTMP, *etc*) turned out to be problematic, presumably due to the interference of C21 allylic methyl group within **18** or **21**. Therefore, we performed a sequential Krapcho-type demethylation/stereoselective oxidation with magnesium monoperoxyphthalate (MMPP).[5c] Subsequent TMS protection delivered diketone **22**, which underwent C11 acylation smoothly using Mander's reagent.[22] Acidic removal of silyl groups (TBS, TMS) afforded the natural product (–)-berkeleyone A (**1**).

Table 1. $Sc(OTf)_3$-mediated sequential Krapcho dealkoxycarbonylation/carbonyl α-*tert*-alkylation[a].



Entry	Conditions	18[b]	19[b]	20[b]
1	**9a/9b**, Brønsted acids (formic acid, TFA, *p*-TsOH, *etc*)	100% cons.[c] unidentified decomposed side products		
2	**9a/9b**, Lewis acids ($SnCl_4$, Et_2AlCl, BF_3•Et_2O, *etc*)			
3	**9a/9b**, LED 390 nm, MeCN			
4	**9a/9b**, $Mn(OAc)_3$, $Cu(OAc)_2$, AcOH			
5	**17**, Brønsted acids (formic acid, TFA, *etc*)	0	-	-
6	**17**, $SnCl_4$, CH_2Cl_2, 23°C	19%	27%	10%
7	**17**, $Sc(OTf)_3$, CH_2Cl_2, 23°C	50%	13%	23%
8	**17**, Et_2AlCl, CH_2Cl_2, 23°C	5%	-	67%
9	**9a/9b**, $Sc(OTf)_3$, DMSO, 100°C, then CH_2Cl_2, 23°C	41%	6%	9%

[a] See Table S19 for details. [b] Isolated yield. [c] cons. = consumption.

Finally, we turned our attention to biomimetic diversification of **1**. Therefrom, oxidation with Dess–Martin periodinane delivered (–)-preaustinoid A (**2**) in 88% yield. Further Baeyer–Villiger oxidation of **2** generated (–)-preaustinoid A1 (**3**) in 43% yield.[23] Meanwhile, we resorted to α-ketol rearrangement for D-ring contraction.[24] Whereas the reaction did not take place under various acidic, basic and thermal conditions, pleasingly, upon treatment with BF_3•Et_2O, α-ketol rearrangement of **2** occurred smoothly to afford (–)-preaustinoid B (**4**) as a sole ring contraction product. Later on, treating **4** with 2.0 equivalent of aqueous NaOH in EtOH afforded (–)-preaustinoid B2 (**6**) in 95% yield. Interestingly, by using 0.4 equivalent of aqueous NaOH, we obtained a mixture of (–)-preaustinoid B1 (**5**) and (–)-preaustinoid B2 (**6**). Thus, an α-hydroxyl-β-diketone rearrangement through in-situ generated epoxyalkoxide (**23**) intermediate followed by basic hydrolysis was most likely responsible for this deacylation process.[25] All physical and spectroscopic data of synthetic **1**-**6** were in good accordance with those reported.[2] Moreover, the structures of **2**, **3**, **4** and **6** were elucidated unambiguously by X-ray crystallographic analysis.[26] Of note, we also corrected the optical rotation of **6** as –54.0, which was originally reported as +90.0.[2c]

To conclude, benefited from the recognition of a hidden symmetry within the D-ring, we have accomplished the first enantioselective total synthesis of **1**-**6** in 12-15 steps, respectively, starting from commercially available 2,4,6-trihydroxybenzoic acid hydrate. In the course of our synthetic studies, we devised a highly convergent route relied upon a diastereoselective dearomative alkylation. Meanwhile, a $Sc(OTf)_3$-mediated sequential Krapcho dealkoxycarbonylation/carbonyl α-*tert*-alkylation have been developed to forge bicyclo[3.3.1]nonane core. At last, we also disclosed our preliminary biomimetic investigations, which generated five additional preaustinoid congeners through a series of rearrangements (α-ketol rearrangement, α-hydroxyl-β-diketone rearrangement, *etc*). Overall, our convergent route is highly modular, thereby should be amenable to access structurally diverse DMOA-derived meroterpenoids, as well as other bicyclo[3.3.1]nonane-containing meroterpenoids, which are currently underway and will be reported in due course.

Acknowledgements

We thank Prof. Chao Li (NIBS) and Prof. Yu-Ming Zhao (SNNU) for helpful discussion. The computational study presented in this paper was carried out on facilities provided by WestGrid (https://www.westgrid.ca/) and Compute Canada (www.computecanada.ca). Financial support from National Natural Science Foundation of China (Grant No. 22071006), Clinical Medicine Plus X-Young Scholars Project (Grant No. PKU2020LCXQ003), Peking University, and National 1000-Youth Talents Program is gratefully acknowledged.

Keywords: hidden symmetry • biomimetic rearrangements • meroterpenoids • natural products • total synthesis

[1] a) R. Geris, T. Simpson, J. *Nat. Prod. Rep*. **2009**, *26*, 1063-1094; b) Y. Matsuda, I. Abe, *Nat. Prod. Rep*. **2016**, *33*, 26-53; c) Y. Matsuda, T. Awakawa, T. Mori, I. Abe, *Curr. Opin. Chem. Biol*. **2016**, *31*, 1-7.

[2] a) R. M. Geris dos Santos, E. Rodrigues-Fo, *Phytochemistry* **2002**, *61*, 907-912; b) R. M. Geris dos Santos, E. Rodrigues-Fo, *Z. Naturforsch.* **2003**, *58c*, 663-669; c) T. P. Fill, G. K. Pereira, R. M. Geris dos Santos, E. Rodrigues-Fo, *Z. Naturforsch*. **2007**, *62b*, 1035-1044; d) D. B. Stierle,

A. A. Stierle, B. Patacini, K. McIntyre, T. Girtsman, E. Bolstad, *J. Nat. Prod*. **2011**, *74*, 2273-2277.

[3] For selected biosynthetic studies towards DMOA-derived meroterpenoids, see: a) H.-C. Lo, R. Entwistle, C.-J. Guo, M. Ahuja, E. Szewczyk, J.-H. Hung, Y.-M. Chiang, B. R. Oakley, C. C. C. Wang, *J. Am. Chem. Soc*. **2012**, *134*, 4709-4720; b) C.-J. Guo, B. P. Knox, Y.-M. Chiang, H.-C. Lo, J. F. Sanchez, K.-H. Lee, B. R. Oakley, K. S. Bruno, C. C. C. Wang, *Org. Lett*. **2012**, *14*, 5684-5687; c) T. Itoh, K. Tokunaga, E. K. Radhakrishnan, I. Fujii, I. Abe, Y. Ebizuka, T. Kushiro, *ChemBioChem* **2012**, *13*, 1132-1135; d) Y. Matsuda, T. Awakawa, T. Itoh, T. Wakimoto, T. Kushiro, I. Fujii, Y. Ebizuka, I. Abe, *ChemBioChem* **2012**, *13*, 1738-1741; e) Y. Matsuda, T. Awakawa, I. Abe, *Tetrahedron* **2013**, *69*, 8199-8204; f) T. Mitsuhashi, L. Barra, Z. Powers, V. Kojasoy, A. Cheng, F. Yang, Y. Taniguchi, T. Kikuchi, M. Fujita, D. J. Tantillo, J. A. Porco, Jr., I. Abe, *Angew. Chem.* **2020**, *132*, 23980-23989; *Angew. Chem. Int. Ed*. **2020**, *59*, 23772-23781.

[4] For previous synthetic studies towards DMOA-derived meroterpenoids, see: a) J. E. Spangler, E. J. Sorensen, *Tetrahedron* **2009**, *65*, 6739-6745; b) J. E. Spangler, Ph.D. Dissertation, Princeton University, 2011; c) J. W. Lockner, Ph.D. Dissertation, The Scripps Research Institute, 2011; d) R. Okamoto, K. Takeda, H. Tokuyama, Ihara, M.; Toyota, M. *J. Org. Chem*. **2013**, *78*, 93-103; e) K. Suzuki, H. Yamakoshi, S. Nakamura, *Chem. Eur. J*. **2015**, *21*, 17605-17609; f) G. Zhu, C. Zhou, S. Chen, S. Fu, B. Liu, *Org. Lett*. **2019**, *21*, 7809-7812; g) Z. Powers, A. Scharf, A. Cheng, F. Yang, M. Himmelbauer, T. Mitsuhashi, L. Barra, Y. Taniguchi, T. Kikuchi, M. Fujita, I. Abe, J. A. Porco, Jr., *Angew. Chem.* **2019**, *131*, 16287-16292; *Angew. Chem. Int. Ed.* **2019**, *58*, 16141-16146.

[5] a) C. P. Ting, G. Xu, X. Zeng, T. J. Maimone, *J. Am. Chem. Soc*. **2016**, *138*, 14868-14871; b) M. Elkin, S. M. Szewczyk, A. C. Scruse, T. R. Newhouse, *J. Am. Chem. Soc*. **2017**, *139*, 1790-1793; c) G. Xu, M. Elkin, D. J. Tantillo, T. R. Newhouse, T. J. Maimone, *Angew. Chem.* **2017**, *129*, 12672-12676; *Angew. Chem. Int. Ed*. **2017**, *56*, 12498-12502.

[6] a) B. Hong, C. Li, Z. Wang, J. Chen, H. Li, X. Lei, *J. Am. Chem. Soc*. **2015**, *137*, 11946-11949; b) 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*, 1671-1681.

[7] For recent reviews, see: a) J. K. Kisunzu, R. Sarpong, *Angew. Chem.* **2013**, *125*, 10890-10892; *Angew. Chem. Int. Ed.* **2013**, *52*, 10694-10696; b) W.-J. Bai, X. Wang, *Nat. Prod. Rep*. **2017**, *34*, 1345-1358. For selected recent examples, see: c) S. Mahapatra, R. G. Carter, *Angew. Chem.* **2012**, *124*, 8072-8075; *Angew. Chem. Int. Ed.* **2012**, *51*, 7948-7951; d) S. Mahapatra, R. G. Carter, *J. Am. Chem. Soc*. **2013**, *135*, 10792-10803; e) J. T. Malinowski, R. J. Sharpe, J. S. Johnson, *Science* **2013**, *340*, 180-182; f) M. Nagatomo, M. Koshimizu, K. Masuda, T. Tabuchi, D. Urabe, M. Inoue, *J. Am. Chem. Soc*. **2014**, *136*, 5916-5919; g) M. Yang, J. Li, A. Li, *Nat. Commun*. **2015**, *6*, 6445.

[8] For Brønsted acid-mediated cationic carbonyl α-*tert*-alkylation, see: a) J. H. Boyce, J. A. Porco, Jr., *Angew. Chem.* **2014**, *126*, 7966-7971; *Angew. Chem. Int. Ed*. **2014**, *53*, 7832-7837; b) J. H. Boyce, V. Eschenbrenner-Lux, J. A. Porco, Jr., *J. Am. Chem. Soc*. **2016**, *138*, 14789-14797.

[9] For Lewis acid-mediated cationic carbonyl α-*tert*-alkylation, see: a) E. E. van Tamelen, J. R. Hwu, T. M. Leiden, *J. Chem. Soc. Chem. Commun*. **1983**, 62-63; b) E. Fillion, D. Fishlock, *J. Am. Chem. Soc*. **2005**, *127*, 13144-13145; c) C. C. McAtee, D. C. Ellinwood, R. C. McAtee, C. S. Schindler, *Tetrahedron* **2018**, *74*, 3306-3313.

[10] For photocatalyzed radical carbonyl α-*tert*-alkylation, see: S. Wen, J. H. Boyce, S. K. Kandappa, J. Sivaguru, J. A. Porco, Jr., *J. Am. Chem. Soc*. **2019**, *141*, 11315-11321.

[11] For $Mn(OAc)_3$-mediated oxidative carbonyl α-*tert*-alkylation, see: a) B. B. Snider, *Chem. Rev*. **1996**, *96*, 339-363; b) B. Mitasev, J. A. Porco, Jr., *Org. Lett*. **2009**, *11*, 2285-2288; c) H. P. Pepper, H. C. Lam, W. M. Bloch, J. H. George, *Org. Lett*. **2012**, *14*, 5162-5164; d) H. P. Pepper, S. J. Tulip, Y. Nakano, J. H. George, *J. Org. Chem*. **2014**, *79*, 2564-2573.

[12] For recent reviews, see: a) R. Long, J. Huang, J. Gong, Z. Yang, *Nat. Prod. Rep*. **2015**, *32*, 1584-1601; b) M. Büschleb, S. Dorich, S. Hanessian, D. Tao, K. B. Schenthal, L. E. Overman, *Angew. Chem.* **2016**, *128*, 4226-4258; *Angew. Chem. Int. Ed.* **2016**, *55*, 4156-4186.

[13] For examples of dearomative alkylation of acylphloroglucinols, see: a) J. Qi, J. A. Porco, Jr., *J. Am. Chem. Soc*. **2007**, *129*, 12682-12683; b) Q. Zhang, B. Mitasev, J. Qi, J. A. Porco, Jr., *J. Am. Chem. Soc.* **2010**, *132*, 14212-14215; c) A. J. Grenning, J. H. Boyce, J. A. Porco, Jr., *J. Am. Chem. Soc*. **2014**, *136*, 11799-11804; d) M. Hayashi, L. E. Brown, J. A. Porco, Jr., *Eur. J. Org. Chem*. **2016**, 4800-4804. and Ref.s [3f], [4g], [8], [10], [11b-d].

[14] M. Schmid, D. Trauner, *Angew. Chem.* **2017**, *129*, 12500-12504; *Angew. Chem. Int. Ed*. **2017**, *56*, 12332-12335.

[15] a) A. F. Barrero, M. Mar Herrador, J. F. Quílez del Moral, P. Arteaga, J. F. Arteaga, M. Piedra, E. M. Sánchez, *Org. Lett*. **2005**, *7*, 2301-2304; b) V. Domingo, L. Silva, H. R. Diéguez, J. F. Arteaga, J. F. Quílez del Moral, A. F. Barrero, *J. Org. Chem*. **2009**, *74*, 6151-6156.

[16] Attempts to experimentally identify active species mono anion **13** was unsuccessful due to the formation of a heterogeneous reaction mixture during the deprotonation step.

[17] a) G. Lu, R. Y. Liu, Y. Yang, C. Fang, D. S. Lambrecht, S. L. Buchwald, P. Liu, *J. Am. Chem. Soc*. **2017**, *139*, 16548-16555; b) A. A. Thomas, K. Speck, I. Kevlishvili, Z. Lu, P. Liu, S. L. Buchwald, *J. Am. Chem. Soc*. **2018**, *140*, 13976-13984; c) U. Dhawa, R. Connon, J. C. A. Oliveira, R. Steinbock, L. Ackermann, *Org. Lett*. **2021**, DOI: 10.1021/acs.orglett.1c00615.

[18] For a review, see: A. P. Krapcho, E. Ciganek, *Org. React*. **2013**, *81*, 1-535.

[19] For a review, see: X. Han, G. Peh, P. E. Floreancig, *Eur. J. Org. Chem*. **2013**, 1193-1208.

[20] CCDC 2042296 (**20**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

[21] CCDC 2042297 (**21**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

[22] L. N. Mander, S. P. Sethi, *Tetrahedron Lett*. **1983**, *24*, 5425-5428.

[23] T.-K. Ma, P. J. Parsons, A. G. M. Barrett, *J. Org. Chem*. **2019**, *84*, 4961-4970.

[24] For a review, see: a) L. A. Paquette, J. E. Hofferberth, *Org. React.* **2003**, *62*, 477-567. For selected examples, see: b) L. A. M. Murray, S. M. K. McKinnie, H. P. Pepper, R. Erni, Z. D. Miles, M. C. Cruickshank, B. López-Pérez, B. S. Moore, J. H. George, *Angew. Chem.* **2018**, *130*, 11175-11180; *Angew. Chem. Int. Ed*. **2018**, *57*, 11009-11014. (c) H. Wu, R. Andres, Q. Wang, J. Zhu, *Angew. Chem.* **2019**, *131*, 509-513; *Angew. Chem. Int. Ed.* **2019**, *58*, 499-503.

[25] a) M. B. Rubin, S. Inbar, *Tetrahedron Lett*. **1979**, *52*, 5021-5024; b) M. B. Rubin, S. Inbar, *J. Org. Chem*. **1988**, *53*, 3355-3358; c) M. Kawamura, S. Kamo, S. Azuma, K. Kubo, T. Sasamori, N. Tokitoh, K. Kuramochi, K. Tsubaki, *Org. Lett*. **2017**, *19*, 301-303.

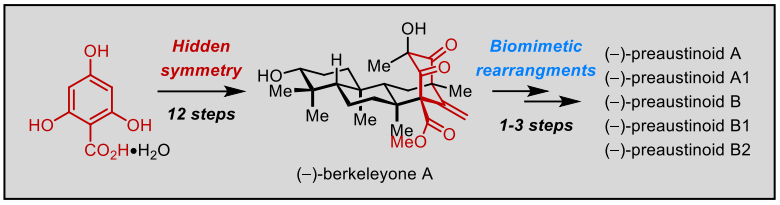
[26] CCDC 2042298, 2042313, 2053783 and 2053785 [**2**, **3**, **4**, **6**] contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

10.1002/anie.202104014

WILEY-VCH

COMMUNICATION

Entry for the Table of Contents



Based upon the recognition of latent symmetry within D-ring, we accomplished the first enantioselective total synthesis of (–)-berkeleyone A and its five preaustinoid congeners. Meanwhile, we also uncovered a series of biomimetic rearrangements that would lend credence to the proposed biosynthetic sequence of DMOA-derived meroterpenoids.