Communication

Protecting-group-free syntheses of ent-kaurane diterpenoids: [3+2+1] cycloaddition/cycloalkenylation approach

Jin Wang, Benke Hong, Dachao Hu, Yuichiro Kadonaga, Ruyao Tang, and Xiaoguang Lei

J. Am. Chem. Soc., **Just Accepted Manuscript** • DOI: 10.1021/jacs.9b13722 • Publication Date (Web): 22 Jan 2020

Protecting-group-free syntheses of *ent*-kaurane diterpenoids: [3+2+1] cycloaddition/cycloalkenylation approach

Jin Wang,[†,‡,∥] Benke Hong,[†,‡,∥] Dachao Hu,[†,‡] Yuichiro Kadonaga,[†,‡] Ruyao Tang,[†,‡] and Xiaoguang Lei*[,†,‡,§]

[†]Beijing National Laboratory for Molecular Sciences, Key Laboratory of Bioorganic Chemistry and Molecular Engineering of Ministry of Education, College of Chemistry and Molecular Engineering, Peking University, Beijing 100871, China

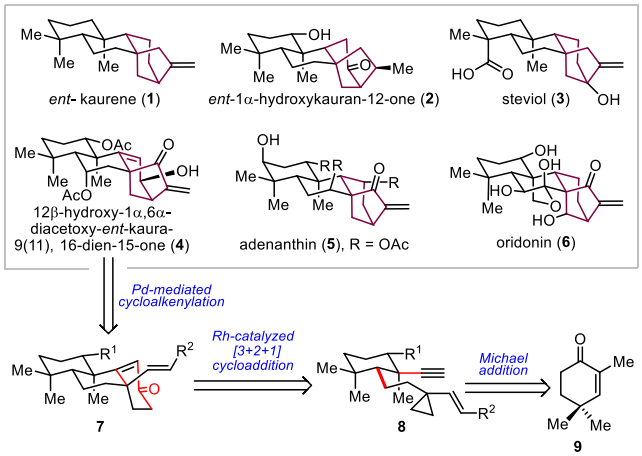
[‡]Department of Chemical Biology, Synthetic and Functional Biomolecules Center, Peking University, Beijing 100871, China

[§]Peking-Tsinghua Center for Life Sciences, Peking University, Beijing 100871, China.

Supporting Information Placeholder

ABSTRACT: The Rh-catalyzed [3+2+1] cycloaddition followed by a Pd-mediated *5-endo* cycloalkenylation is shown to be a general and powerful approach for efficient construction of tetracyclic core structure of *ent*-kaurane diterpenoids. The utility of this strategy was further demonstrated by concise and protecting-group-free total syntheses of *ent*-1α-hydroxykauran-12-one, 12-oxo-9,11-dehydrokaurene and 12α-hydroxy-9,11-dehydrokaurene.

The *ent*-kaurane diterpenoids are a unique family of tetracyclic natural products and more than 1000 members have been isolated to date from different plants species, especially from *Isodon* genus.[1] These natural products including *ent*-kaurene (**1**),[2a] *ent*-1α-hydroxykauran-12-one (**2**),[2b] steviol (**3**),[2c] 12β-hydroxy-1α,6α-diacetoxy-ent-kaura-9(11),16-dien-15-one (**4**),[2d] adenanthin (**5**),[2e] oridonin (**6**),[2f] feature a bicyclo[3.2.1]octene ring system with different oxidation state at the key tetracyclic skeleton (**Scheme 1**). It has been found



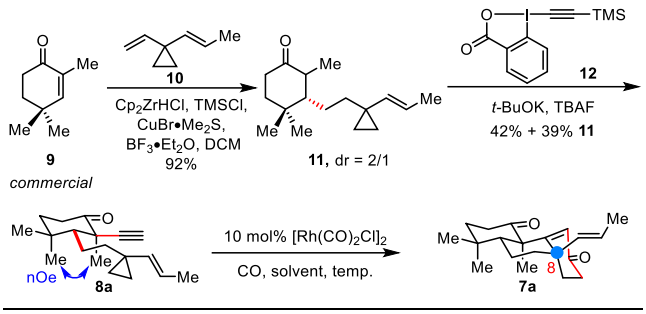
Scheme 1. Representative *ent*-kauranoids and retrosynthetic analysis of the core tetracyclic skeleton

that the *ent*-kaurane diterpenoids possess many promising biological activities such as anticancer, antifungal and antiviral activities.[1] Their intriguing structures as well as potential biological activities have attracted tremendous attention from the synthetic community, culminated in numerous elegant syntheses of their core structures and target molecules.[3-5] Most of the reported methods required multistep reactions to construct the tetracyclic *ent*-kaurene skeleton, especially the [3.2.1] bicyclic moiety.[3]

Herein, we report a concise and general synthetic approach to assemble the *ent*-kaurane diterpenoids skeleton. As demonstrated in **Scheme 1**, we envisaged that the [3.2.1] bicyclic motif of the tetracyclic skeleton of *ent*-kauranoids can be accessed from **7** via a palladium-mediated cycloalkenylation. The 6/6/6 tricyclic ring system of enone **7** could be efficiently accessed using the Rh-catalyzed [3 + 2 + 1] cycloaddition of 1-yne-vinylcyclopropane (VCP) precursor **8** and CO developed by Yu's group.[6] Using this two-step sequence, *ent*-kauranoid skeleton bearing different functional groups could be constructed efficiently from various 1-yne-vinylcyclopropane (VCP) precursors. If successful, this strategy could not only enable the total synthesis of *ent*-kaurane diterpenoids but also facilitate the efficient preparation of diverse natural product analogues for further biological study. The key precursor **8** might be derived from the commercially available enone **9** via Michael addition and alkynylation.

To explore the feasibility of the proposed Rh-catalyzed [3+2+1] cycloaddition/Pd-mediated alkenylation sequence, **8a** was chosen as a model substrate, which was accessed from commercial enone **9** through Michael addition[7] and alkynylation[8] in 2 steps. To our delight, the key Rh(I)-catalyzed [3+2+1] cycloaddition of **8a** and CO occurred smoothly with 10 mol% rhodium dimer catalyst under 0.2 atm CO atmosphere at 80 °C. The reaction afforded **7a** in 49% combined yield with a diastereomeric ratio of about 2.1:1 (Table 1, entry 1). Single-crystal X-ray diffraction analysis confirmed the desired stereochemistry of the major product (see Supporting Information). A brief screening of solvents indicated that toluene gave the best diastereomeric ratio (Table 1, entries 1, 3, 4). Subsequent screenings revealed that higher CO pressure facilitated the

Table 1. Optimization of Rh-catalyzed [3+2+1] cycloaddition[a]



entry	CO(atm)	solvent	T (°C)	Yield[b] (d.r.[c])
1	0.2	toluene	80	49% (2.1:1)
2[d]	0.2	toluene	80	47% (1.9:1)
3	0.2	dioxane	80	51% (1.2:1)
4	0.2	DCE	80	25% (1.1:1)
5	1	toluene	80	42% (5.0:1)
6	1	toluene	60	28% (10.7:1)
7	1	toluene	100	52% (2.2:1)
8[e]	1	toluene	80	52% (5.8:1)

[a]Unless state otherwise, the reactions were performed with **8a** (0.055 mmol) and 10 mol% $[Rh(CO)_2Cl]_2$ in solvent (1 mL) under a balloon of CO for 18 h. [b]Isolated combined yields. [c]Determined by ^{1}H-NMR analysis. [d]$[Rh(COD)_2Cl]_2$ was used instead of $[Rh(CO)_2Cl]_2$. [e]20 mol% $[Rh(CO)_2Cl]_2$ was used instead of 10 m% $[Rh(CO)_2Cl]_2$

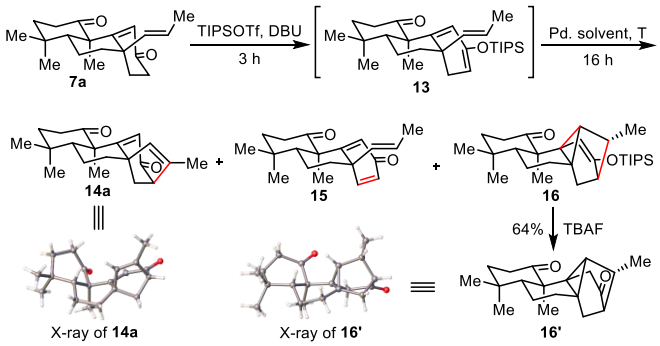
formation of the desired diastereomer (Table 1, entry 5) while changing temperature did not improve the reaction (Table 1, entries 6,7). Upon increasing the catalyst loading, **7a** was generated in 52% combined yield with a diastereomeric ratio of 5.8:1. It is noteworthy that two rings, three carbon-carbon bonds and one quaternary stereogenic center were created in a single operation by this remarkable [3+2+1] cycloaddition.

With **7a** in hand, we then further tested the Pd-mediated cycloalkenylation (**Table 2**). Although this transformation has been well established for 5-allyl silyl enol ether precursors,[9,10,4j] we anticipated that it might be more challenging for **7**: to the best of our knowledge, there were no reported examples of transition metal-mediated *5-endo* oxidative cyclization for 5-vinyl silyl enol ether precursors.[11] Indeed, commonly used TMS and TBS silyl enol ether only led to the removal of silyl group in the presence of $Pd(OAc)_2$. Therefore, the more stable TIPS enol ether **13** was prepared by deprotonation with DBU and trapping with TIPSOTf. Pleasingly, the direct subjection of **13** to stoichiometric $Pd(OAc)_2$ in DMSO at 50 °C furnished tetracycle **14a**, albeit in poor yield (Table 2, entry 1). After careful analysis, we found the byproducts of the reaction were mainly Saegusa oxidation product **15** along with trace intramolecular Diels-Alder product **16**. In an effort to further improve the yield, a thorough survey of reaction parameters was conducted. There was no significant improvement with various palladium sources (Table 2, entries 2, 3). Upon switching the solvent to dioxane, the conversion was improved to 42% due to the inhibition of Saegusa oxidation (Table 2, entry 4). Further improvement was achieved by increasing the equivalents of $Pd(OAc)_2$ to accelerate the alkenylation process while decreasing the reaction temperature to reduce the Diels-Alder product (entries 5, 6). Fortunately, upon treatment of **7a** with DBU and TIPSOTf followed by 5 equivalents $Pd(OAc)_2$ in dioxane at 23 °C, the alkenylation occurred efficiently to give **14a** in 75% isolated yield. The structure of **14a** was unambiguously determined by X-ray crystallographic analysis (see Supporting Information). An attempt to conduct the reaction under catalytic amount of $Pd(OAc)_2$ under O_2 was found to be unsuccessful (Table 2, entry 7). Additionally, control experiment showed $Pd(OAc)_2$ is essential for the formation of **16** (Table 2, entry 8). The structure of **16** was assigned by two-dimensional NMR spectroscopy and further confirmed by single-crystal X-ray diffraction analysis of the TIPS deprotection product **16'** (see Supporting Information). To the best of our knowledge, this is the first example of a Pd-mediated oxidative cyclization of a 5-vinyl silyl enol ether to generate the [3.2.1] ring system.

With the optimized protocol in hand, we began to explore the substrate scope of this [3+2+1] cycloaddition/cycloalkenylation approach (**Scheme 2**). We first tested different 1-yne-vinylcyclopropane (VCP) precursors (**Scheme 2b**). The oxidation state of C-1 did not affect the reaction efficiency of the [3+2+1] cycloaddition (**7b**). Various vinylcyclopropanes with different substitutions at vinyl group were converted into the corresponding products in moderate yields with acceptable diastereomeric ratio (**7c-7f**). Substrate **7g** with two free hydroxyl groups was also compatible, which showed this transformation could be applied to the synthesis of highly oxidized skeletons. However, the substrate scope studies also revealed neither electron withdrawing group nor amino group were tolerated for this reaction (**7h, 7i**).

Next, the scope of the Pd-mediated cycloalkenylation wasalso studied (**Scheme 2c**). To our delight, *ent*-kaurane skelet-

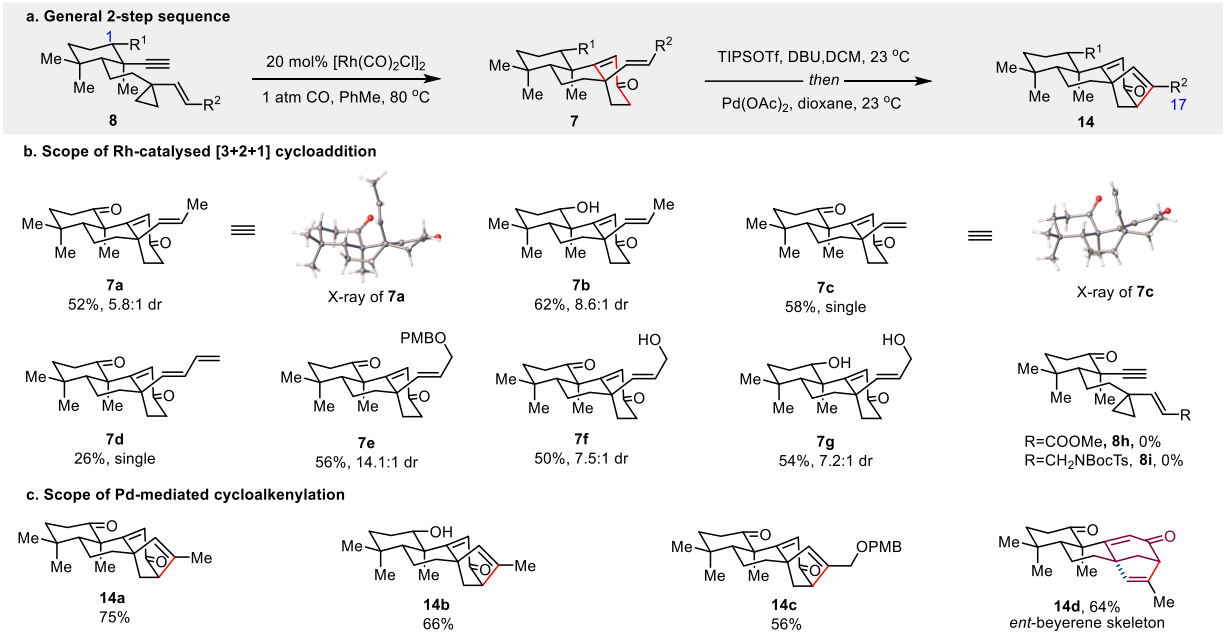
Table 2. Optimization of Pd-mediated cycloalkenylation[a]



entry	Pd source	T (°C)	solvent	conversion[b] 14a	15	16
1	$Pd(OAc)_2$	50	DMSO	24%	65%	8%
2	$PdCl_2$	50	DMSO	11%	89%	0%
3	$Pd(TFA)_2$	50	DMSO	0%	63%	0%
4	$Pd(OAc)_2$	50	Dioxane	42%	12%	33%
5[c]	$Pd(OAc)_2$	50	Dioxane	50%	23%	13%
6[c]	$Pd(OAc)_2$	23	Dioxane	79%	7%	9%
7[d]	$Pd(OAc)_2$	23	Dioxane	0%	0%	0%
8	-	50	Dioxane	0%	0%	0%

Reaction conditions: **7a** (6.7 μmol), DBU (2 equiv), TIPSOTf (1.8 equiv), CH_2Cl_2 (0.3 mL), 3 h then Pd salt (1 equiv), solvent (0.3 mL), 16 h. [b]Determined by ^{1}HNMR analysis. [c]5 equiv $Pd(OAc)_2$ was used instead of 1 equiv $Pd(OAc)_2$. [d]0.2 equiv $Pd(OAc)_2$ was used under a balloon of O_2 instead of 1 equiv $Pd(OAc)_2$.

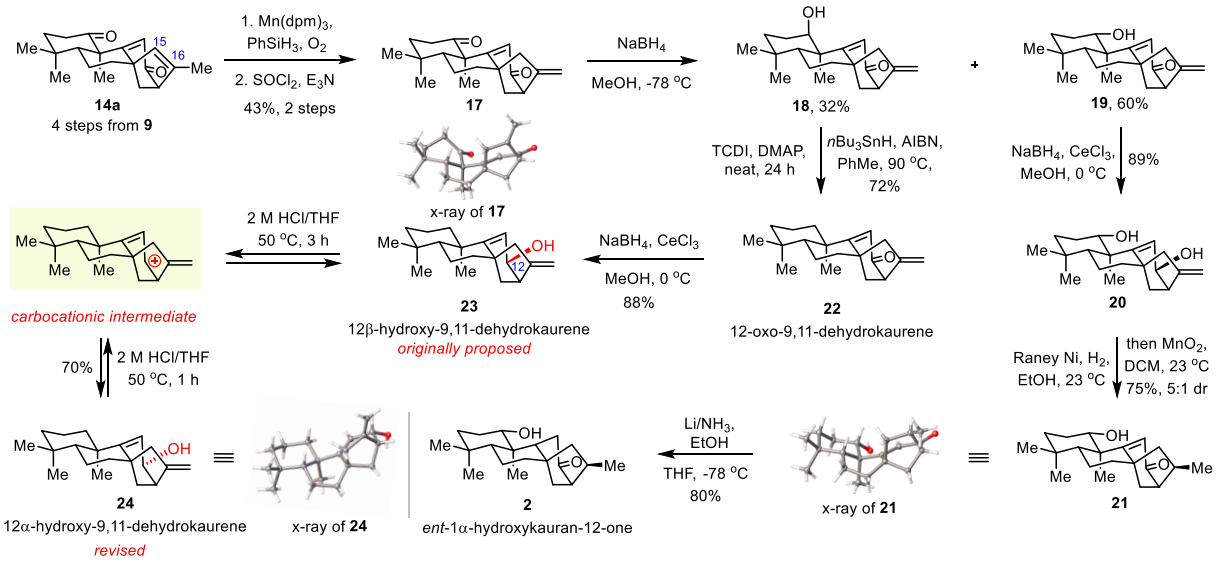
Scheme 2. Evaluation of the substrate scope



on with different oxidation state on the A ring and C-17 could be generated in high yields (**14a-c**). Interestingly, we observed that reaction of the diastereomer of **7a** smoothly afforded the *ent*-beyerene skeleton (**14d**). These results showed that our 2-step sequence could be applied to generate diverse *ent*-kaurane natural product-like skeletons.

With this efficient route to *ent*-kaurane skeletons in hand, we turned our attention to the synthetic utility of our strategy. *ent*-1α-Hydroxykauran-12-one (**2**) was isolated from New Zealand Liverworts *Paraschistochila pinnatifolia* in 1997 and showed anticancer activity.[2b] This natural product could be readily prepared from **14a,** which was synthesized in a 4-step synthetic route (Michael addition, alkynylation, [3+2+1] cycloaddition and cycloalkenylation) (**Scheme 3**). Obviously, the primary challenge of the synthesis is the selective reduction of the C15-C16 double bond to give the desired C16 stereochemistry. Indeed, initial attempts to reduce (hydrogenation) or isomerize (Schenck ene reaction)[4m] the trisubstituted double bond all failed (see Supporting Information). Alternatively, **14a** was subjected to Mukaiyama hydration[12] and dehydration to isomerize the C15-C16 double bond to provide terminal alkene **17** in 43% yield. Reduction of **17** with $NaBH_4$ in MeOH at -78 °C led to the formation of two isomers **18** and **19** in 32% and 60% yield respectively. Unfortunately, hydrogenation of the terminal double bond in **19** only provided the undesired C16 stereochemistry, due to the steric accessibility of the β face.[13] To overcome the substrate-controlled selectivity, hydroxyl directed reduction was investigated. Face-selective 1,2-reduction of **19** with $NaBH_4$ and $CeCl_3$ afforded C12 β-OH **20** as a single diastereomer in 89% yield. Alcohol **20** could also be obtained via one-pot reduction from **17** in 62% yield (See Supporting Information). After extensive condition screenings (see Supporting Information), we were pleased to find that the selective hydroxyl directed reduction of **20** was achieved with Raney Ni and H_2 to afford the desired C16 stereochemistry.[14] Subsequent selective oxidation of the allylic alcohol delivered enone **21** in 75% yield. The structure of **21** was determined by two-dimensional NMR spectroscopy and further confirmed by single-crystal X-ray diffraction analysis. Finally, reduction of **21** using Birch conditions

Scheme 3. Concise total syntheses of *ent*-kaurane diterpenoids and structure revision



(Li/ NH_3, EtOH) enabled the first total synthesis of *ent*-1α-hydroxykauran-12-one (**2**) in 10 steps from commercially available enone **9**.

Moreover, Barton–McCombie deoxygenation[50] of **18** delivered 12-oxo-9,11-dehydrokaurene (**22**), an *ent*-kaurene isolated from *Vellozia caputardeae*.[15] Luche reduction of **22** furnished the reported structure of 12β-hydroxy-9,11-dehydrokaurene **23**.[15] Unfortunately, the proton NMR data of our synthetic sample **23** did not match with the reported data for the natural product. Careful analysis of the NMR data showed significant difference on the chemical shift of H-12 (Δδ = 0.41 ppm), suggesting the stereochemistry of 12-OH in natural product might be α configuration. To our delight, treatment of **23** with 2M HCl at 50 °C gave a mixture of unreacted **23** and the desired 12α-hydroxy-9,11-dehydrokaurene **24** (1:5, 70% isolated yield for **24**). **24** exhibited the same proton NMR data compared with the previously reported data of natural product. The structure of **24** was unambiguously confirmed by single-crystal X-ray diffraction analysis. Therefore, we have revised the structure to be 12α-hydroxy-9,11-dehydrokaurenene for **24**. Additionally, re-subjecting **24** to the same acidic conditions provided the same mixture of **23** and **24** (1:5), which clearly indicated a carbocation intermediate was involved in the stereochemistry inversion.

In conclusion, we have developed a convergent and concise approach for assembling the core structure of *ent*-kaurane diterpenoids. The key elements of our strategy include implementation of a rhodium-catalyzed [3+2+1] cycloaddition to furnish the B ring and C ring in one step as well as a palladium-mediated cycloalkenylation of 5-vinyl silyl enol ether to construct the key [3.2.1] ring system. This synthetic strategy has enabled the first protecting-group free total syntheses of *ent*-1α-hydroxykauran-12-one (**2**) and 12-oxo-9,11-dehydrokaurene (**22**) in 10 and 8 steps from enone **9**, respectively. Total synthesis and structure revision of 12α-hydroxy-9,11-dehydrokaurene (**24**) have also been achieved in 10 steps from enone **9**. The present strategy should be applicable for assembling other *ent*-kaurane diterpenoids by fine tuning the [3+2+1] cycloaddition precursor. These investigations are currently ongoing in our laboratory and will be disclosed in due course.

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.XXXXXXX.
Experimental procedures, product characterization data (PDF)
(CIF)

AUTHOR INFORMATION

Corresponding Author

xglei@pku.edu.cn

Author Contributions

‡These authors contributed equally.

Notes

The authors declare no competing financial interests.

ACKNOWLEDGMENT

We thank Prof. Zhi-Xiang Yu for helpful discussion and suggestion on the rhodium-catalyzed [3+2+1] cycloaddition, Dr. Hiuchun Lam for proofreading the manuscript. We also thank Prof. Jie Su for the assistance with X-ray analysis and Prof. Jiang Zhou for HRMS analysis. Financial support from the National Natural Science Foundation of China (21625201, 21961142010, 91853202, 21661140001 and 21521003); the National Key Research and Development Program of China (2017YFA0505200); and the Beijing Outstanding Young Scientist Program (BJJWZYJH01201910001001) is grateful acknowledged.

REFERENCES

(1) (a) García, P. A.; De Oliveira, A. B.; Batista, R. Occurrence, Biological activities and synthesis of kaurane diterpenes and their glycosides. *Molecules* **2007**, *12*, 455-483. (b) Sun, H.-D.; Huang, S.-X.; Han, Q.-B. Diterpenoids from Isodon species and their biological activities. *Nat. Prod. Rep.* **2006**, *23*, 673-698. (c) Liu, M.; Wang, W.-G.; Sun, H.-D.; Pu, J.-X. Diterpenoids from Isodon species: an update. *Nat. Prod. Rep.* **2017**, *34*, 1090-1140.

(2) (a) Quitt, P.; Mosettig, E.; Cambie, R. C.; Rutledge, P. S.; Briggs, L.H. Optical Rotatory Dispersion Studies. The complete absolute configurations of steviol, kaurene and the diterpene alkaloids of the garryfoline and atisine groups. *J. Am. Chem. Soc.* **1961**, *83*, 3720-3722. (b) Lorimer, S. D.; Perry, N. B.; Burgess, E. J.; Foster, L. M. 1-Hydroxyditerpenes from two New Zealand liverworts, *paraschistochila pinnatifolia* and *trichocolea mollissima*. *J. Nat. Prod.* **1997**, *60*, 421-424. (c) Dolder, F.; Lichti, H.; Mosettig, E.; Quitt, P. The structure and stereochemistry of steviol and isosteviol. *J. Am. Chem. Soc.* **1960**, *82*, 246-247. (d) Qu, J. B.; Zhu, R. L.; Zhang, Y. L.; Guo, H. F.; Wang, X. N.; Xie, C. F.; Yu, W. T.; Ji, M.; Lou, H. X. *ent*-Kaurane diterpenoids from the liverwort *jungermannia atrobrunnea*. *J. Nat. Prod.* **2008**, *71*, 1418-1422. (e) Xu, Y. L.; Sun, H. D.; Wang, D. Z.; Iwashita, T.; Komura, H.; Kozuka, M.; Naya, K.; Kubo, I. Structure of adenanthin. *Tetrahedron Lett.* **1987**, *28*, 499-502. (f) Fujita, E.; Fujita, T.; Katayama, H.; Shibuya, M. Oridonin, a new diterpenoid from *Isodon* species. *Chem. Commun.* **1967**, 252-254.

(3) For reviews of *ent*-kauranoid total synthesis, see: (a) Lazarski, K. E.; Moritz, B. J.; Thomson, R. J. The total synthesis of *Isodon* diterpenes. *Angew. Chem., Int. Ed.* **2014**, *53*, 10588-10599. (b) Zhu, L.; Huang, S.-H.; Yu, J.; Hong, R. Constructive innovation of approaching bicyclo[3.2.1]octane in *ent*-kauranoids. *Tetrahedron Lett.* **2015**, *56*, 23-31. (c) Du, M.; Lei, X. Advanced in the synthesis of kaurane diterpenoids. *Chin. J. Org. Chem.* **2015**, *35*, 2447-2464. (d) Riehl, P. S.; DePorre, Y. C.; Armaly, A. M.; Groso, E. J.; Schindler, C. S. New avenues for the synthesis of *ent*-kaurene diterpenoids. *Tetrahedron* **2015**, *71*, 6629-6650.

(4) For selected total syntheses of *ent*-kaurane diterpenoids with an intact *ent*-kaurane skeleton, see: (a) Bell, R. A.; Ireland, R. E.; Partyka, R. A. The total synthesis of *dl*-kaurene. *J. Org. Chem.* **1962**, *27*, 3741-3742. (b) Bell, R. A.; Ireland, R. E.; Partyka, R. A. Experiments directed toward the total synthesis of terpenes. Ⅷ. The total synthesis of (±)-kaurene and (±)-atisirene. *J. Org. Chem.* **1966**, *31*, 2530-2536. (c) Mori, K.; Nakahara, Y.; Matsui, M. Diterpenoid total synthesis XIX: (±)-steviol and erythroxydiol A: rearrangements in bicyclooctane compounds. *Tetrahedron* **1972**, *28*, 3217-3226. (d) Ziegler, F. E.; Kloek, J. A. The stereocontrolled photoaddition of allene to cyclopent-1-ene-1-carboxaldehydes. A total synthesis of (±) steviol methyl ester and isosteviol methyl ester. *Tetrahedron* **1977**, *33*, 373-380. (e) Corey, E. J.; Wess, G.; Xiang, Y. B.; Singh, A. K. Stereospecific total synthesis of (±)-cafestol. *J. Am. Chem. Soc.* **1987**, *109*, 4717-4718. (f) Singh, A. K.; Bakshi, R. K.; Corey, E. J. Total synthesis of (±)-atractyligenin. *J. Am. Chem. Soc.* **1987**, *109*, 6187-6189. (g) Corey, E. J.; Liu, K. Enantioselective total synthesis of the potent anti-HIV agent neotripterifordin. Reassignment of stereochemistry at C(16). *J. Am. Chem. Soc.* **1997**, *119*, 9929-9930. (h) Abad, A.; Agulló, C.; Cuñat, A. C.; de Alfonso Marzal, I.; Navarro, I.; Gris, A. A unified synthetic approach to trachylobane-, beyerane-, atisane- and kauranetype diterpenes. *Tetrahedron* **2006**, *62*, 3266–3283. (i) Cherney, E. C.; Green, J. C.; Baran, P. S. Synthesis of *ent*-kaurane and beyerane diterpenoids by controlled fragmentations of overbred intermediates. *Angew. Chem., Int. Ed.* **2013**, *52*, 9019-9022. (j) Yeoman, J. T. S.; Mark, V. W.; Reisman, S. E. A unified strategy to *ent*-kauranoid natural products: total syntheses of (−)-trichorabdal A and (−)-longikaurin E. *J. Am. Chem. Soc.* **2013**, *135*, 11764–11767. (k) Zhu, L.; Luo, J.; Hong, R. Total synthesis of (±)-cafestol: a late-stage construction of the furan ring inspired by a biosynthesis strategy. *Org. Lett.* **2014**, *16*, 2162-2165. (l) Zhao, X.; Li, W.; Wang, J.; Ma, D. Convergent route to *ent*-kaurane diterpenoids: total synthesis of

lungshengenin D and 1α,6α-diacetoxy-*ent*-kaura-9(11),16-dien-12,15-dione. *J. Am. Chem. Soc.* **2017**, *139*, 2932-2935. (m) He, C.; Hu, J.; Wu, Y.; Ding, H. Total syntheses of highly oxidized *ent*-kaurenoids pharicin A, pharicinin B, 7-O-acetylpseurata C, and pseurata C: a [5 + 2] cascade approach. *J. Am. Chem. Soc.* **2017**, *139*, 6098-6101. (n) Su, F.; Lu, Y.; Kong, L.; Liu, J.; Luo, T. Total synthesis of maoecrystal P: application of a strained bicyclic synthon. *Angew. Chem., Int. Ed.* **2018**, *57*, 760-764. (o) Zhu, L.; Ma, W.; Zhang, M.; Lee, M. M.-L.; Wong, W.-Y.; Chan, B. D.; Yang, Q.; Wong, W.-T.; Tai, W. C.-S.; Lee, C.-S. Scalable synthesis enabling multilevel bio-evaluations of natural products for discovery of lead compounds. *Nat. Commun.* **2018**, *9*, 1283-1292. (p) Hong, B.; Liu, W.; Wang, J.; Wu, J.; Kadonaga, Y.; Cai, P.; Lou, H.; Yu, Z.; Li, H.; Lei, X. Photoinduced skeletal rearrangements reveal radical-mediated synthesis of terpenoids. *Chem* **2019**, *5*, 1671-1681. (q) Wang, J.; Ma, D. 6-Methylenebicyclo[3.2.1]oct-1-en-3-one: a twisted olefin as Diels-Alder dienophile for expedited syntheses of four kaurane diterpenoids. *Angew. Chem., Int. Ed.* **2019**, 58, 15731-15735. (r) Kong, L.; Su, F.; Yu, H.; Jiang, Z.; Lu, Y.; Luo, T. Total synthesis of (−)-oridonin: an interrupted Nazarov approach. *J. Am. Chem. Soc*. **2019**, *141*, 20048-20052.

(5) For selected syntheses of *ent*-kaurane diterpenoids with a rearranged or cleaved *ent*-kaurane skeleton, see: (a) Fujita, E.; Shibuya, M.; Nakamura, S.; Okada, Y.; Fujita, T. Terpenoids. Part XXVIII. Total synthesis of enmein. *J. Chem. Soc., Perkin Trans. 1* **1974**, 165-177. (b) Paquette, L. A.; Backhaus, D.; Braun, R.; Underiner, T. L.; Fuchs, K. Total synthesis of (-)-O-Methylshikoccin and (+)-O-(methylepoxy)shikoccin. *J. Am. Chem. Soc.* **1996**, *118*, 11990-11991. (c) Gong, J.; Lin, G.; Sun, W.; Li, C.-C.; Yang, Z. Total synthesis of (±) maoecrystal V. *J. Am. Chem. Soc.* **2010**, *132*, 16745-16746. (d) Cha, J. Y.; Yeoman, J. T. S.; Reisman, S. E. A concise total synthesis of (-)-maoecrystal Z. *J. Am. Chem. Soc.* **2011**, 133, 14964-14967. (e) Peng, F.; Danishefsky, S. J. Total synthesis of (±) maoecrystal V. *J. Am. Chem. Soc.* **2012**, *134*, 18860-18867. (f) Lu, P.; Gu, Z.; Zakarian, A. Total synthesis of maoecrystal V: early-stage C–H functionalization and lactone assembly by radical cyclization. *J. Am. Chem. Soc.* **2013**, *135*, 14552-14555. (g) Breitler, S.; Carreira, E. M. Total synthesis of (+)-crotogoudin. *Angew. Chem., Int. Ed.* **2013**, 52, 11168-11171. (h) Lu, P.; Mailyan, A.; Gu, Z.; Guptill, D. M.; Wang, H.; Davies, H. M. L.; Zakarian, A. Enantioselective synthesis of (−)-maoecrystal V by enantiodetermining C−H functionalization. *J. Am. Chem. Soc.* **2014**, *136*, 17738-17749. (i) Zheng, C.; Dubovyk, I.; Lazarski, K. E.; Thomson, R. J. Enantioselective total synthesis of (−)-maoecrystal V. *J. Am. Chem. Soc.* **2014**, *136*, 17750-17756. (j) Moritz, B. J.; Mack, D. J.; Tong, L.; Thomson, R. J. Total synthesis of the *Isodon* diterpene sculponeatin N. *Angew. Chem., Int. Ed.* **2014**, *53*, 2988-2991. (k) Pan, Z.; Zheng, C.; Wang, H.; Chen, Y.; Li, Y.; Cheng, B.; Zhai, H. Total synthesis of (±)-sculponeatin N. *Org. Lett.* **2014**, *16*, 216-219. (l) Song, L.; Zhu, G.; Liu, Y.; Liu, B.; Qin, S. Total synthesis of atisane-type diterpenoids: application of Diels-Alder cycloadditions of podocarpane-type unmasked *ortho*-benzoquinones. *J. Am. Chem. Soc.* **2015,** *137*, 13706-13714. (m) Cheng, H.; Zeng, F.-H.; Yang, X.; Meng, Y.-J.; Xu, L.; Wang, F.-P. Collective total syntheses of atisane-type diterpenes and atisine-type diterpenoid alkaloids: (±)-spiramilactone B, (±)-spiraminol, (±)-dihydroajaconine, and (±)-spiramines C and D. *Angew. Chem., Int. Ed.* **2016**, *55*, 392-396. (n) Cernijenko, A.; Risgaard, R.; Baran, P. S. 11-Step total synthesis of (−)-maoecrystal V. *J. Am. Chem. Soc.* **2016**, *138*, 9425-9428. (o) Liu, W.; Li, H.; Cai P.-J.; Wang, Z.; Yu, Z.-X.; Lei, X. Scalable total synthesis of rac-jungermannenones B and C. *Angew. Chem., Int. Ed.* **2016**, 55, 3112-3116, (p) Lv, Z.; Chen, B.; Zhang, C.; Liang, G. Total syntheses of trichorabdal A and maoecrystal Z. *Chem. - Eur. J.* **2018**, *24*, 9773–9777. (q) Wu, J.; Kadonaga, Y.; Hong, B.; Wang, J.; Lei, X. Enantioselective total synthesis of (+)-jungermatrobrunin A. *Angew. Chem., Int. Ed.* **2019**, 58, 10879–10883. (r) Zhang, J.; Li, Z.; Zhuo, J.; Cui, Y.; Han, T.; Li, C. Tandem decarboxylative cyclization/alkenylation strategy for total syntheses of (+)-longirabdiol, (−)-longirabdolactone, and (−)-effusin. *J. Am. Chem. Soc.* **2019**, *141*, 8372–8380. (s) Wein, L. A.; Wurst, K.; Angyal, P.; Weisheit, L.; Magauer, T. Synthesis of (−)-mitrephorone A via a bioinspired late stage C-H oxidation of (−)-mitrephorone B. *J. Am. Chem. Soc.* **2019**, *141*, 19589-19593.

(6) (a) Jiao, L.; Lin, M.; Zhuo, L.-G.; Yu, Z.-X. Rh(I)-catalyzed [(3 + 2) + 1] cycloaddition of 1-yne/ene-vinylcyclopropanes and CO: homologous Pauson-Khand reaction and total synthesis of (±)-α-agarofuran. *Org. Lett.* **2010**, *12*, 2528-2531. (b) Lin, M.; Li, F.; Jiao, L.; Yu, Z.-X. Rh(I)-catalyzed formal [5 + 1]/[2 + 2 + 1] cycloaddition of 1-yne-vinylcyclopropanes and two CO units: one-step construction of multifunctional angular tricyclic 5/5/6 compounds. *J. Am. Chem. Soc.* **2011**, *133*, 1690-1693. (c) Feng, Y.; Yu, Z.-X. Formal synthesis of (±)-galanthamine and (±)-lycoramine using Rh(I)-catalyzed [(3 + 2) + 1] cycloaddition of 1-ene-vinylcyclopropane and CO. *J. Org. Chem.* **2015**, *80*, 1952-1956. (d) Bose, S.; Yang, J.; Yu, Z.-X. Formal synthesis of gracilamine using Rh(I)-catalyzed [3 + 2 + 1] cycloaddition of 1-yne-vinylcyclopropanes and CO. *J. Org. Chem.* **2016**, *81*, 6757-6765. (f) Yang, J.; Xu, W.; Cui, Q.; Fan, X.; Wang, L.-N.; Yu, Z.-X. Asymmetric Total Synthesis of (-)-Clovan-2,9-dione Using Rh(I)-Catalyzed [3 + 2 + 1] Cycloaddition of 1-Yne-vinylcyclopropane and CO. *Org. Lett.* **2017**, *19*, 6040-6043.

(7) (a) Maksymowicz, R. M.; Roth, P. M. C.; Fletcher, S. P. Catalytic asymmetric carbon–carbon bond formation using alkenes as alkylmetal equivalents *Nat. Chem.* **2012**, *4*, 649-654. (b) Catalytic asymmetric conjugate addition was attempted, the yield and *ee* value was very low, see Supporting Information for details.

(8) Utaka, A.; Cavalcanti L. N.; Silva, Jr, L. F. Electrophilic alkynylation of ketones using hypervalent iodine. *Chem*. *Commun*. **2014**, *50*, 3810-3813.

(9) Seminal reports of stoichiometric $Pd^{(II)}$-mediated silyl enol ether oxidative cyclizations: (a) Ito, Y.; Aoyama, H.; Hirao, T.; Mochizuki, A.; Saegusa, T. Cyclization reactions via oxo-π-allylpalladium(II) intermediates. *J. Am. Chem. Soc.* **1979**, *101*, 494-496. (b) Kende, A. S.; Roth, B.; Sanfilippo, P. J. Facile, palladium(II)-mediated synthesis of bridged and spirocyclic bicycloalkenones. *J. Am. Chem. Soc.* **1982**, *104*, 1784-1785. For the development of Pd^{II}-catalyzed cyclizations, see: (c) Toyota, M.; Wada, T.; Fukumoto, K.; Ihara, M. Total synthesis of (±)-methyl atis-16-en-19-oate via homoallyl–homoallyl radical rearrangement. *J. Am. Chem. Soc.* **1998**, *120*, 4916-4925. (d) Toyota, M.; Rudyanto, M.; Ihara, M. Some aspects of palladium-catalyzed cycloalkenylation: developments of environmentally benign catalytic conditions and demonstration of tandem cycloalkenylation. *J. Org. Chem.* **2002**, *67*, 3374-3386.

(10) Selected synthetic applications for palladium-mediated cycloalkenylation: (a) Kende, A. S.; Roth, B.; Sanfilippo, P. J.; Blacklock, T. J. Mechanism and regioisomeric control in palladium(II)-mediated cycloalkenylations. A novel total synthesis of (±)-quadrone. *J. Am. Chem. Soc.* **1982**, *104*, 5808-5810. (b) Kende, A. S.; Sanfilippo, P. J. Palladium(II)-mediated cycloalkenylation. A simple total synthesis of (±)-phyllocladene. *Synth. Commun.* **1983**, *13*, 715-719. (c) Toyota, M.; Odashima, T.; Wada, T.; Ihara, M. Application of palladium-catalyzed cycloalkenylation reaction to C_{20} gibberellin synthesis: formal syntheses of GA12, GA111, and GA112 *J. Am. Chem. Soc.* **2000**, *122*, 9036-9037. (d) Toyota, M.; Sasaki, M.; Ihara, M. Diastereoselective formal total synthesis of the DNA polymerase alpha inhibitor, aphidicolin, using palladium-catalyzed cycloalkenylation and intramolecular Diels-Alder reactions. *Org. Lett.* **2003**, *5*, 1193-1195. (e) Nicolaou, K.C.; Tria, G. S.; Edmonds, D. J.; Kar, M. Total syntheses of (±)-platencin and (-)-platencin. *J. Am. Chem. Soc.* **2009**, *131*, 15909-15917. (f) Varseev, G. N.; Maier, M. E. Formal total synthesis of platencin. *Angew. Chem., Int. Ed.* **2009**, *48*, 3685-3688. (g) Huang, B.; Guo, L.; Jia, Y. Protecting-group-free enantioselective synthesis of (-)-pallavicinin and (+)-neopallavicinin. *Angew. Chem., Int. Ed.* **2015**, *54*, 13599-13603. For a review, see: (h) Toyota, M.; Ihara, M. Development of palladium-catalyzed cycloalkenylation and its application to natural product synthesis. *Synlett* **2002**, 1211-1222.

(11) The only reported example of palladium-catalyzed 5-endo oxidative cyclization for silyl enol ether precursor: Jeker, O. F.; Carreira, E. M. Total synthesis and stereochemical reassignment of (±)-indoxamycin B. *Angew. Chem., Int. Ed.* **2012**, *51*, 3474-3477.

(12) (a) Isayama, S.; Mukaiyama, T. A new method for preparation of alco-hols from olefins with molecular oxygen and phenylsilane by the use of bis(acetylacetonato)cobalt(II). *Chem. Lett.* **1990**, *18*, 1071-1074. (b) Inoki, S.; Kato, K.; Isayama, S.; Mukaiyama, T. A new and facile method for the direct preparation of α-hydroxycarboxylic acid esters from α,β-unsaturated carboxylic acid esters with molecular oxygen and phenylsilane catalyzed by bis(dipivaloylmethanato)manganese(II) complex. Chem. Lett. **1990**, *19*, 1869-1872.

(13) Herz, W.; and Sharma, R. P. New Hydroxylated ent-Kauranoic Acids Prom Eupatorium album. *J. Org. Chem.* **1976**, *41*, 1021-1026.

(14) Zhou, Q.; Chen, X.; Ma, D. Asymmetric, Protecting-Group-Free Total Synthesis of (-)-Englerin A. *Angew. Chem. Int. Ed.* **2010**, *49*, 3513 –3516.

(15) Pinto, A. C.; Prado, S. K.; Pinchin, R. Two kaurenes from *Vellozia caput-ardeae*. *Phytochemistry* **1981**, *20*, 520-521.

Table of Contents