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JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
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Convergent Route to *ent*-Kaurane Diterpenoids: Total Synthesis of Lungshengenin D and 1α,6α-Diacetoxy-*ent*-kaura-9(11),16-dien-12,15-dione

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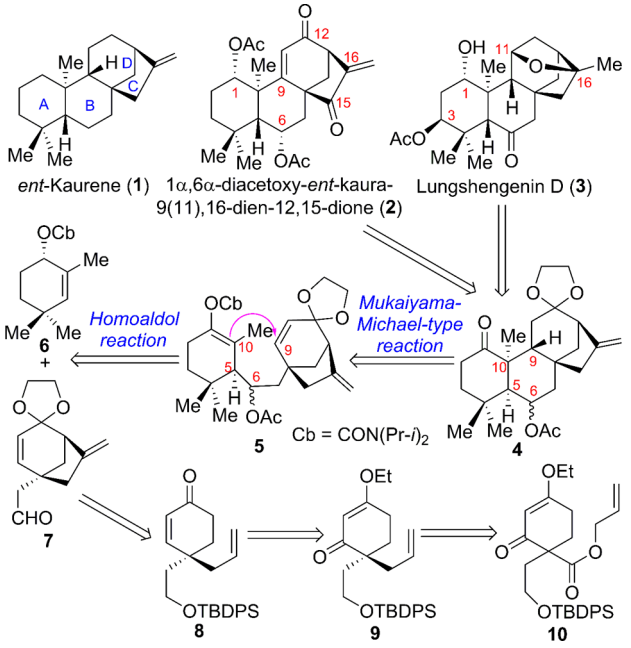
Supporting Information

ABSTRACT: The Hoppe's homoaldol reaction of a cyclo-hexenyl carbamate with an aldehyde followed by an unprecedented $BF_3{\cdot}OEt_2$ mediated intramolecular Mukaiyama−Michael-type reaction affords the tetracyclic core structure of *ent*-kaurane diterpenoids. The usage of this convergent approach for assembling these natural products is demonstrated by the first asymmetric total syntheses of two highly oxidized *ent*-kaurane diterpenoids: Lungshengenin D and 1α,6α-diacetoxy-*ent*-kaura-9(11),16-dien-12,15-dione.

Since the first discovery of *ent*-kaurene (**1**) (Scheme 1) from the leaf essential oil of the New Zealand kauri in 1961,[1] more than a thousand *ent*-kaurane diterpenoids have been isolated and identified from different plants species, especially *Isodon* genus.[2] These natural products are assumed to share the same biogenic precursor, *ent*-kaurene (**1**), and generate through different oxygenations, C−C bond cleavages, or fragmentations.[2,3a] In the preliminary biological studies, these diterpenoids have been found to possess a broad range of bioactivities spanning from antitumor, anti-infective and immunosuppressive actions to inhibition of vascular smooth muscle contraction.[2] During the past half century, their intriguing structures and interesting biological activities have piqued the interest of a number of research groups, whose studies culminated several elegant synthesis of their core structures and target molecules.[3−5] However, more efficient and general strategies for assembling the *ent*-kaurane diterpenoids remain highly desirable to accelerate the process of syntheses and biological studies.

Scheme 1. Structures of Some *ent*-Kaurane Diterpenoids and Their Retrosynthetic Analysis



To date, eight diterpenoids with the basic structure of *ent*-kaurane have been synthesized.[4] Interestingly, the reported synthetic strategies for installing the [3.2.1] bicyclic motif were all set up at late stages, which maximized functional group manipulations and lengthened their overall linear synthetic steps in some cases.[4a−i,l,m,o] This problem prompts us to develop a more convergent protocol to *ent*-kaurane diterpenoids, in which the [3.2.1] bicyclic unit is established at the early stage. The strategy has enabled the first total syntheses of 1α,6α-diacetoxy-*ent*-kaura-9(11),16-dien-12,15-dione (**2**)[6] and Lungshengenin D (**3**).[7]

As shown in Scheme 1, we envisaged that some highly oxidized *ent*-kaurane diterpenoids like **2** and **3** could be elaborated from the same intermediate **4** via late-stage functional group manipulations. A unique retrosynthetic design of the core **4** was to forge the central B ring featuring two key strategic connections at the C5/C6 and C9/10 junctures with two relatively simple fragments **6** and **7**. We assumed that the preparation of **4** could be achieved through generation of the C9−C10 bond by an unprecedented Mukaiyama−Michael-type reaction of **5**,[8] which could be installed by a signature Hoppe's homoaldol reaction[9] of cyclohexenyl carbamate **6** and aldehyde **7** to forge C5−C6 bond. If these two C−C bond formation reactions work well, we would be able to develop a convergent and efficient route to the core structure of a number of *ent*-kaurane diterpenoids. The required building block **6** could be easily obtained from 2,4,4-trimethyl-2-cyclohenen-1-one, while the [3.2.1] bicyclic motif **7** could be assembled using Toyota's Pd-catalyzed cycloalkenylation[10] of a silyl enol ether generated

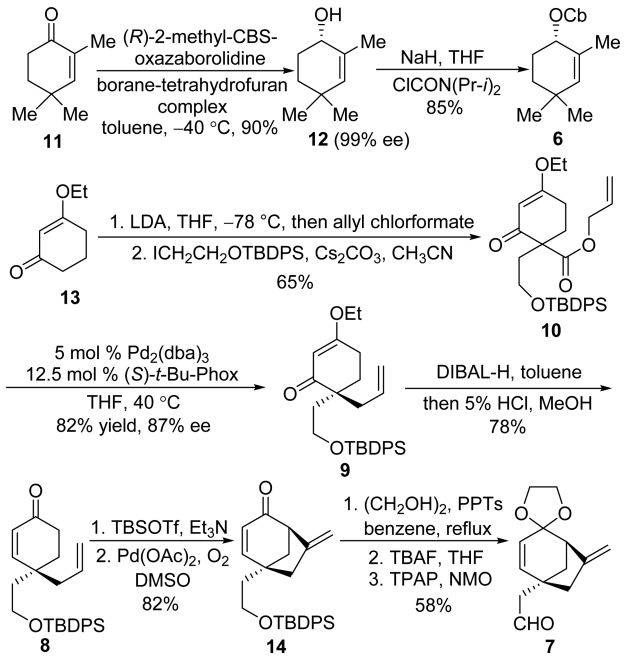
Received: January 7, 2017
Published: February 10, 2017

DOI: 10.1021/jacs.7b00140
J. Am. Chem. Soc. 2017, 139, 2932−2935

from olefin **8** and Stoltz's Pd-catalyzed asymmetric allylic alkylation reaction[11,12] of **10** as the key steps.

With the idea in mind, we started our investigation by preparing two building blocks **6** and **7** (Scheme 2). Asymmetric

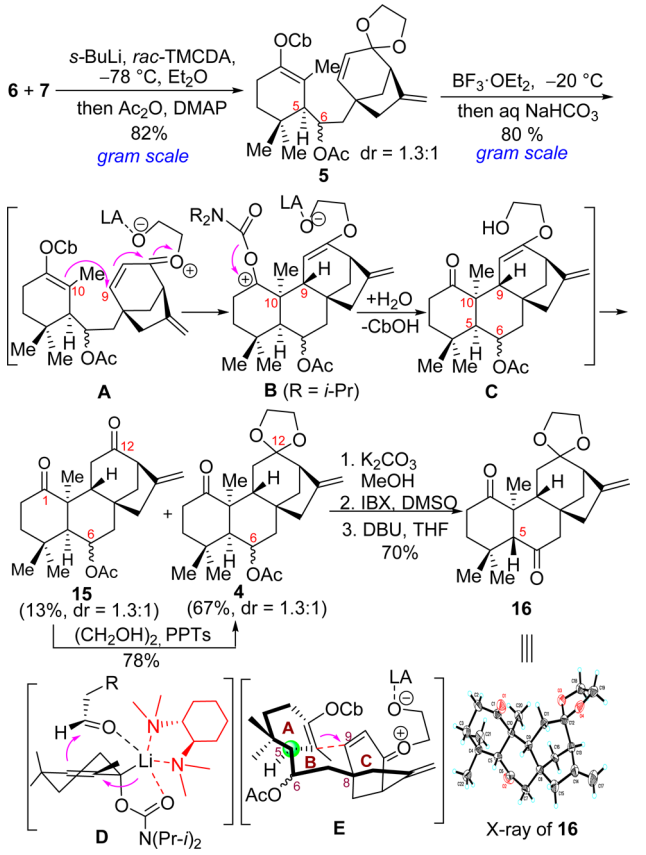
Scheme 2. Synthesis of Building Blocks 6 and 7



reduction of enone **11** under the typical Corey–Bakshi–Shibata's conditions[13] provided alcohol **12** in 90% yield with 99% ee, which was treated with NaH in THF and then trapped the resultant sodium alkoxide with *N*,*N*-diisopropyl chloroformamide to afford the carbamate **6**. In a parallel procedure, deprotonation of enone **13** followed by carbamoylation delivered a *β*-keto ester, which was subjected to alkylation with an iodide to give **10**. Under the catalysis of $Pd_2(dba)_3$ and (*S*)-*t*-Bu-Phox,[14] intramolecular allylation proceeded smoothly in an enantioselective manner to furnish enol ether **9** in 82% yield with 87% ee. Next, DIBAL-H reduction of **9** and subsequent hydrolysis with 5% HCl produce enone **8** upon elimination of the resultant hydroxyl group. After **8** was converted to the corresponding enol silyl ether, Pd-catalyzed cycloalkenylation was conducted to give bicyclic enone **14**.[10a] Finally, protection the ketone moiety in **14** followed by cleavage of the silyl ether and oxidation with TPAP and NMO yielded the aldehyde **7**.

With the cyclohexenyl carbamate **6** and the aldehyde **7** in hand, we attempted their homoaldol reaction under Hoppe's conditions (Scheme 3). Accordingly, stereospecific deprotonation of **6** with the retention of the configuration[15] in the presence of *s*-BuLi and racemic *trans*-*N*,*N*,*N*′,*N*′-tetramethyl 1,2-diamino-cyclohexane (TMCDA) followed by addition of **7** produced an alcohol, which was trapped with acetic anhydride to give the ester **5**. In the homoaldol reaction, the stereochemistry of C5 in **5** was fully controlled by configurationally stable allyllithiums, proceeding in a strict suprafacial manner through a possible transition state **D**,[15a,b] in which the lithiated species attacked the aldehyde **7** from the back side of the carbamate group. However, another newly created stereogenic center C6 in **5** was poorly induced so that a diastereomeric mixture of 1.3:1 was obtained. Since this stereogenic center

Scheme 3. Homoaldol Reaction of 6 and 7 and Subsequent Cyclization



would be inconsequential in the subsequent transformation, we decided to use this mixture **5** to carry out the crucial cyclization through an unprecedented Mukaiyama–Michael-type reaction.

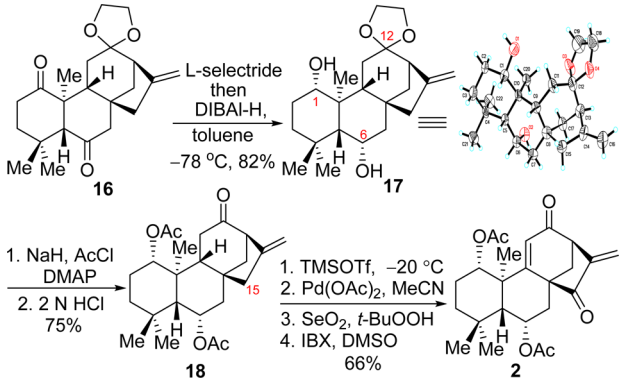
Since the discovery of Hoppe's homoaldol reaction, further transformations of its alkenyl cabamate products mainly focused on the formation of polysubstituted tetrahydrofurans through an intramolecular addition of the carbamoyl-protected enolate unit to the oxonium moiety that was *in situ* formed by condensation of the alcohol part with an aldehyde.[8,15] We speculated that the ketal moiety in our homoaldol product **5** might deliver an vinylogous oxonium intermediate **A** upon treatment with a Lewis acid, in which the alkenylcabamates unit might attack the extremely polar C–C double bond at C9 and therefore produce Mukaiyama–Michael-type reaction intermediate **B**. Treatment of **B** with water would cleave its carbamate part to form ketone intermediate **C**, which would undergo hydrolysis or cyclization to afford **15** and **4**, respectively. On the basis of this consideration, we explored the reaction of the ketal **5** under the action of different Lewis acids, and were pleased to find that $BF_3{\cdot}OEt_2$ mediated reaction proceeded well at −20 °C to provide a mixture of **15** and **4** with a ratio of 13:67 by quenching the reaction with aqueous $NaHCO_3$. When aqueous NH_4Cl was added to quench the reaction, 15 was isolated as a single product. Interestingly, the dione **15** could be selectively protected to give **4**, presumably because of the relative steric hindrance of the carbonyl at the C1 position. As we expected, the cyclization took place in a highly stereoselective manner and only the formation of two isomers **15** and **4** was observed. This result can be rationalized that the cyclization proceeded via a favored transition state **E**, in

DOI: 10.1021/jacs.7b00140
J. Am. Chem. Soc. 2017, 139, 2932–2935

which the C10 stereochemistry was fully controlled by the C5 stereogenic center, while the alkenylcabamate unit attacked the vinylogous oxonium moiety from the sterically less hindered convex face of the [3.2.1] bicyclic unit to give the desired C9 stereochemistry. At this moment, only the C5 stereochemistry was undesired for the synthesis of the target molecules.[16] We planned to epimerize the compound at this position after oxidation of the liberated alcohol to ketone. To this end, deprotection of **4** followed by oxidation with IBX reagent produced a dione, which was treated with DBU in THF to deliver the desired dione **16** exclusively.

Having completed the assembly of the core structure **16**, we turned our attention to its further conversion to the highly oxidized *ent*-kaurane diterpenes. In 2008, Lou group discovered diterpene **2**[6] from Chinese liverwort, an aquatic habituated liverwort *Jungermannia atrobrunnea*. Structurally, **2** has close oxygenation pattern with **16**, and therefore was chosen as the first target molecule. The conversion of **16** to **2** is depicted in Scheme 4. We found that the C1 ketone part is sterically less

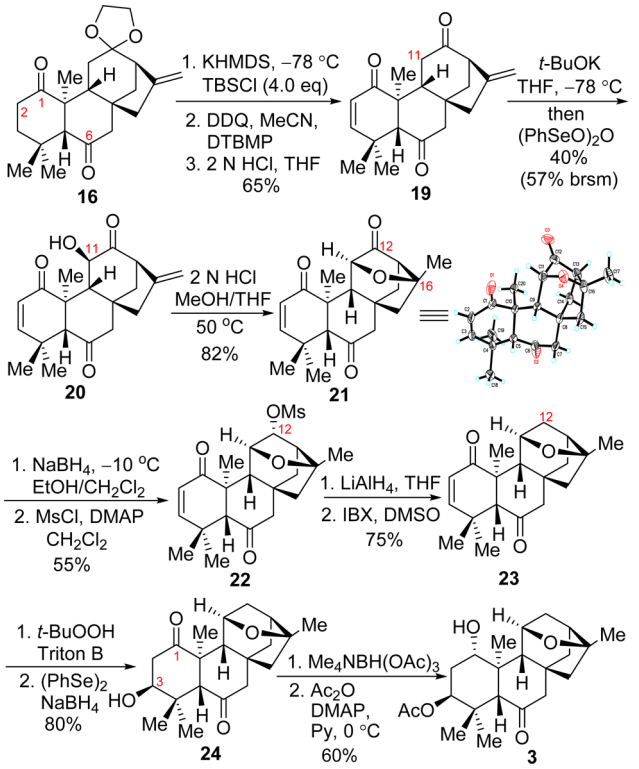
Scheme 4. Total Synthesis of *ent*-Kaurane Diterpenoid 2



hindered and could be regioselectively and stereoselectively reduced with L-selectride at −78 °C to give a monoalcohol, which was further reduced with DIBAL-H in one-pot to afford diol **17**. It is notable that direct reduction of two ketone units with DIBAL-H was possible, but gave two isomers because of poor seteroselectivity at the C1 position. Esterification of **17** with NaH/AcCl followed by deprotection of the ketal moiety with HCl provided ketone **18**. After **18** was transformed into the corresponding enone according to Saegusa's procedure,[17] SeO_2-oxidation of the C15 methylene and subsequent oxidation of the resultant allyl alcohol were conducted to furnish **2**.

Lungshengenin D is a pentacyclic *ent*-kaurane diterpenoid that was isolated from a medicinal herb for treatment of hepatitis.[7] It contains an ether link between C11 and C16. We planned to install this unit by creating a hydroxyl group at the C11 position of **16**. Before it more reactive C2 position must be blocked, and we therefore decided to increase the oxygenation state of the A-ring first. As depicted in Scheme 5, after **16** was converted into disilyl enol ether, selective oxidation of the less sterically hindered A-ring with DDQ and DTBMP produced an enone,[18] which was treated with HCl to cleavage the remained silyl enol ether unit and the ketal moiety to provide enone **19** in 65% yield. Selective deprotonation at C11 was achieved by treatment of **19** with *t*-BuOK at −78 °C, and the resulting carbanion was oxidized to afford alcohol **20** as a single isomer in 40% yield, along with the recovery of **19** in 30% yield.[19] Attempts to push this reaction to full conversion failed (see SI);

Scheme 5. Total Synthesis of Lungshengenin D



mainly because overoxidation of the product to the C11/12 enone was observed. After exposing of **20** on 2 N HCl in mixed methanol and THF, intramolecular ether formation occurred directly to provide **21** in 82% yield.

After installation of the requisite ether linkage, our next challenging task was reduction of C12 carbonyl group in the presence two other carbonyl groups. After some attempts, we found that C12 ketone moiety was still more reactive than the other two ketone units, and could be selectively reduced with $NaBH_4$ in ethanol. The resultant alcohol was reacted with mesyl chloride to provide **22**. Next, $LiAlH_4$-reduction of **22** to remove the mesylate group and subsequent reoxidation of two resultant hydroxyl groups with IBX produced enone **23** in 75% yield. Finally, stereoselective epoxidation of **23** with *t*-BuO_2H followed by reduction of the resultant epoxide with NaSePh furnished alcohol **24** as a single product.[20] After hydroxyl-directed reduction of **24** with $Me_4NBH(OAc)_3$ to control the C1 stereochemistry, regioselective acetylation of the resultant diol delivered **3** in 60% yield.

In conclusion, we have developed a convergent and concise approach for assembling the core structure of some *ent*-kaurane diterpenoids. The key elements of this synthesis include implementation of a Hoppe's homoaldol reaction to connect two conveniently accessible building blocks as well as an unprecedented intramolecular Mukaiyama-Michael-type reaction to install the B-ring. By using this strategy, we have accomplished the first total syntheses of 1α,6α-diacetoxy-*ent*-kaura-9(11),16-dien-12,15-dione and Lungshengenin D. In late-stage functional group manipulations, several regioselective and stereospecific transformations were applied to establish the densely functionalized structure. The present strategy should be applicable for assembling more *ent*-kaurane diterpenoids by finely tuning the homoaldol condensation partners. These

DOI: 10.1021/jacs.7b00140
J. Am. Chem. Soc. 2017, 139, 2932−2935

investigations are actively pursued in our laboratory and will be disclosed in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.7b00140.

Experimental procedures and compound characterization (PDF)
Data for $C_{22}H_{30}O_4$ (CIF)
Data for $C_{22}H_{30}O_4$ (CIF)
Data for $C_{23}H_{32}Cl_2O_4$ (CIF)
Data for $C_{22}H_{34}O_4$ (CIF)
Data for $C_{20}H_{24}O_4$ (CIF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors are grateful to Chinese Academy of Sciences (supported by the Strategic Priority Research Program, grant XDB20020200 & QYZDJ-SSW-SLH029) and the National Natural Science Foundation of China (grant 21132008) for their financial support.

■ REFERENCES

(1) Quitt, P.; Mosettig, E.; Cambie, R. C.; Rutledge, P. S.; Briggs, L. H. *J. Am. Chem. Soc.* **1961**, *83*, 3720.

(2) (a) García, P. A.; De Oliveira, A. B.; Batista, R. *Molecules* **2007**, *12*, 455. (b) Sun, H.-D.; Huang, S.-X.; Han, Q.-B. *Nat. Prod. Rep.* **2006**, *23*, 673.

(3) For reviews, see: (a) Lazarski, K. E.; Moritz, B. J.; Thomson, R. J. *Angew. Chem., Int. Ed.* **2014**, *53*, 10588. (b) Zhu, L.; Huang, S.-H.; Yu, J.; Hong, R. *Tetrahedron Lett.* **2015**, *56*, 23. (c) Du, M.-J.; Lei, X.-G. *Youji Huaxue* **2015**, *35*, 2447.

(4) For synthesis of *ent*-kauranoids with the parent *ent*-kaurene carbon skeleton, see: (a) Bell, R. A.; Ireland, R. E.; Pastyka, R. A. *J. Org. Chem.* **1962**, *47*, 3741. (b) Church, R. F.; Ireland, R. E.; Marshall, J. A. *Tetrahedron Lett.* **1960**, *1*, l. (c) Bell, R. A.; Ireland, R. E.; Partyka, R. A. *J. Org. Chem.* **1966**, *31*, 2530. (d) Church, R. F.; Ireland, R. E.; Marshall, J. A. *J. Org. Chem.* **1966**, *31*, 2526. (e) Mori, K.; Matsui, M. *Tetrahedron Lett.* **1966**, *7*, 175. (f) Mori, K.; Matsui, M.; Ikekawa, N.; Sumiki, Y. *Tetrahedron Lett.* **1966**, *7*, 3395. (g) Mori, K.; Nakahara, Y.; Matsui, M. *Tetrahedron Lett.* **1970**, *11*, 2411. (h) Nakahara, Y.; Mori, K.; Matsui, M. *Agric. Biol. Chem.* **1971**, *35*, 918. (i) Mori, K.; Nakahara, Y.; Matsui, M. *Tetrahedron* **1972**, *28*, 3217. (j) Ziegler, F. E.; Kloek, J. A. *Tetrahedron* **1977**, *33*, 373. (k) Ziegler, F. E.; Kloek, J. A. *Tetrahedron Lett.* **1971**, *12*, 2201. (l) Cherney, E. C.; Green, J. C.; Baran, P. S. *Angew. Chem., Int. Ed.* **2013**, *52*, 9019. (m) Corey, E. J.; Liu, K. *J. Am. Chem. Soc.* **1997**, *119*, 9929. (n) Corey, E. J.; Wess, G.; Xiang, Y. B.; Singh, A. K. *J. Am. Chem. Soc.* **1987**, *109*, 4717. (o) Zhu, L.; Luo, J.; Hong, R. *Org. Lett.* **2014**, *16*, 2162. (p) Singh, A. K.; Bakshi, R. K.; Corey, E. J. *J. Am. Chem. Soc.* **1987**, *109*, 6187. (q) Backhaus, D.; Paquette, L. A. *Tetrahedron Lett.* **1997**, *38*, 29. (r) Paquette, L. A.; Backhaus, D.; Braun, R. *J. Am. Chem. Soc.* **1996**, *118*, 11990. (s) Paquette, L. A.; Ladouceur, G. *J. Org. Chem.* **1989**, *54*, 4278. (t) Yeoman, J. T. S.; Mak, V. W.; Reisman, S. E. *J. Am. Chem. Soc.* **2013**, *135*, 11764. (u) Yeoman, J. T. S.; Cha, J. Y.; Mak, V. W.; Reisman, S. E. *Tetrahedron* **2014**, *70*, 4070.

(5) For synthesis of *ent*-kauranoids with oxidatively cleaved or rearranged ring system, see: (a) Fujita, E.; Shibuya, M.; Nakamura, S.; Okada, Y.; Fujita, T. *J. Chem. Soc., Perkin Trans. 1* **1974**, 165. (b) Shibuya, M.; Fujita, E. *J. Chem. Soc., Perkin Trans. 1* **1974**, 178. (c) Kenny, M. J.; Mander, L. N.; Sethi, S. P. *Tetrahedron Lett.* **1986**, *27*, 3923. (d) Kenny, M. J.; Mander, L. N.; Sethi, S. P. *Tetrahedron Lett.* **1986**, *27*, 3927. (e) Cha, J. Y.; Yeoman, J. T. S.; Reisman, S. E. *J. Am. Chem. Soc.* **2011**, *133*, 14964. (f) Pan, Z.-Q.; Zheng, C.-Y.; Wang, H.-Y.; Chen, Y.-H.; Li, Y.; Cheng, B.; Zhai, H.-B. *Org. Lett.* **2013**, *16*, 216. (g) Moritz, B. J.; Mack, D. J.; Tong, L.; Thomson, R. J. *Angew. Chem., Int. Ed.* **2014**, *53*, 2988. (h) Gong, J.; Lin, G.; Sun, W.; Li, C.-C.; Yang, Z. *J. Am. Chem. Soc.* **2010**, *132*, 16745. (i) Peng, F.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2012**, *134*, 18860. (j) Lu, P.; Gu, Z.; Zakarian, A. *J. Am. Chem. Soc.* **2013**, *135*, 14552. (k) Lu, P.; Mailyan, A.; Gu, Z.; Guptill, D. M.; Wang, H.; Davies, H. M. L.; Zakarian, A. *J. Am. Chem. Soc.* **2014**, *136*, 17738. (l) Zheng, C.; Dubovyk, I.; Lazarski, K. E.; Thomson, R. J. *J. Am. Chem. Soc.* **2014**, *136*, 17750. (m) Zhang, W.-B.; Shao, W.-B.; Li, F.-Z.; Gong, J.-X.; Yang, Z. *Chem. - Asian J.* **2015**, *10*, 1874. (n) Cernijenko, C.; Risgaard, R.; Baran, P. S. *J. Am. Chem. Soc.* **2016**, *138*, 9425.

(6) 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. *J. Nat. Prod.* **2008**, *71*, 1418.

(7) Jiang, B.; Lub, Z.-Q.; Sun, H.-D. *Nat. Prod. Lett.* **1998**, *12*, 281.

(8) (a) Hoppe, D.; Krämer, T.; Freire Erdbrügger, C.; Egert, E. *Tetrahedron Lett.* **1989**, *30*, 1233. (b) Paulsen, H.; Graeve, C.; Fröhlich, R.; Hoppe, D. *Synthesis* **1996**, *1996*, 145. (c) Ünaldi, S.; Özlügedik, M.; Fröhlich, R.; Hoppe, D. *Adv. Synth. Catal.* **2005**, *347*, 1621.

(9) For reviews, see: (a) Hoppe, D.; Hense, T. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2282. (b) Hoppe, D. *Synthesis* **2009**, *2009*, 43.

(10) (a) Toyota, M.; Wada, T.; Fukumoto, K.; Ihara, M. *J. Am. Chem. Soc.* **1998**, *120*, 4916. (b) Toyota, M.; Rudyanto, M.; Ihara, M. *J. Org. Chem.* **2002**, *67*, 3374. (c) Toyota, M.; Ihara, M. *Synlett* **2002**, 1211.

(11) (a) Levine, S. R.; Krout, M. R.; Stoltz, B. M. *Org. Lett.* **2009**, *11*, 289. (b) Mohr, J. T. D.; Behenna, C.; Harned, A. M.; Stoltz, B. M. *Angew. Chem., Int. Ed.* **2005**, *44*, 6924. (c) Behenna, D. C.; Stoltz, B. M. *J. Am. Chem. Soc.* **2004**, *126*, 15044. For a review, see: (d) Hong, A. Y.; Stoltz, B. M. *Eur. J. Org. Chem.* **2013**, *2013*, 2745.

(12) Trost, B. M.; Bream, R. N.; Xu, J. *Angew. Chem., Int. Ed.* **2006**, *45*, 3109.

(13) (a) Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 5551.

(14) Liu, Y. Y.; Liniger, M.; McFadden, R. M.; Roizen, J. L.; Malette, J.; Reeves, C. M.; Behenna, D. C.; Seto, M.; Kim, J.; Mohr, J. T.; Virgil, S. C.; Stoltz, B. M. *Beilstein J. Org. Chem.* **2014**, *10*, 2501.

(15) (a) Becker, J.; Fröhlich, R.; Salorinne, K.; Hoppe, D. *Eur. J. Org. Chem.* **2007**, *2007*, 3337. (b) Becker, J.; Grimme, S.; Fröhlich, R.; Hoppe, D. *Angew. Chem., Int. Ed.* **2007**, *46*, 1645. (c) Becker, J.; Bergander, K.; Fröhlich, R.; Hoppe, D. *Angew. Chem., Int. Ed.* **2008**, *47*, 1654.

(16) It is notable that homoaldol reaction of **7** with the enantiomer of **6** and subsequent cyclization gave an intermediate with the desired stereochemistry at C5, but undesired stereochemistry at C10.

(17) Ito, Y.; Hirao, T.; Saegusa, T. *J. Org. Chem.* **1978**, *43*, 1011.

(18) (a) Jung, M. E.; Pan, Y.-G.; Rathke, M. W.; Sullivan, D. F.; Woodbury, R. P. *J. Org. Chem.* **1977**, *42*, 3961. (b) Zhang, H.; Reddy, M. S.; Phoenix, S.; Deslongchamps, P. *Angew. Chem., Int. Ed.* **2008**, *47*, 1272.

(19) (a) Masters, J. J.; Link, J. T.; Snyder, L. B.; Young, W. B.; Danishefsky, S. J. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1723. (b) Yuan, C.-X; Jin, Y.-H.; Wilde, N. C.; Baran, P. S. *Angew. Chem., Int. Ed.* **2016**, *55*, 8280.

(20) (a) Miyashita, M.; Suzuki, T.; Yoshikoshi, A. *Tetrahedron Lett.* **1987**, *28*, 4293. (b) Nicolaou, K. C.; Sasmal, P. K.; Roecker, A. J.; Sun, X.-W.; Mandal, S.; Converso, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 3443.

DOI: 10.1021/jacs.7b00140
J. Am. Chem. Soc. 2017, 139, 2932−2935