JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
Communication
pubs.acs.org/JACS

Enantioselective Total Synthesis of (+)-Psiguadial B

Lauren M. Chapman, Jordan C. Beck, Linglin Wu, and Sarah E. Reisman*

The Warren and Katharine Schlinger Laboratory for Chemistry and Chemical Engineering, Division of Chemistry and Chemical Engineering, California Institute of Technology, Pasadena, California 91125, United States

Supporting Information

ABSTRACT: The first enantioselective total synthesis of the cytotoxic natural product (+)-psiguadial B is reported. Key features of the synthesis include (1) the enantioselective preparation of a key cyclobutane intermediate by a tandem Wolff rearrangement/asymmetric ketene addition, (2) a directed C(sp^3)–H alkenylation reaction to strategically forge the C1–C2 bond, and (3) a ring-closing metathesis to build the bridging bicyclo[4.3.1]decane terpene framework.

(+)-Psiguadial B (**1**) is a diformyl phloroglucinol-containing meroterpenoid recently isolated by Shao and co-workers from the leaves of *Psidium guajava*, a plant that is widely used in traditional Chinese medicine.[1] Biological investigations revealed that **1** exhibits potent antiproliferative activity against human hepatoma cells (HepG2 IC_{50} = 46 nM),[1] although detailed mode-of-action studies have not been disclosed. Biosynthetically, the sesquiterpenoid fragment of **1** can be traced to *β*-caryophyllene;[2] indeed, a number of biomimetic approaches to phloroglucinol meroterpenoids starting from *β*-caryophyllene have been reported.[3,4] However, we recognized that an abiotic synthesis of **1** would allow us to develop new chemistry and strategy concepts that would be useful in broader synthetic contexts. Here we report an enantioselective total synthesis of **1** that was enabled by the development of a catalytic asymmetric addition of 8-aminoquinoline to a photolytically generated ketene.

From a synthetic standpoint, we reasoned that the primary challenge posed by **1** is construction of the central bicyclo[4.3.1]decane, which is *trans*-fused to a cyclobutane. Specifically, we identified the C1–C2 bond (Figure 1), which links the A and C rings through vicinal stereogenic centers, as a strategic disconnection. On the basis of this analysis, we became interested in forming this bond by a Pd-catalyzed C(sp^3)–H alkenylation reaction between cyclobutane **5** and vinyl iodide **6**. Although the direct product of this reaction would be a *cis*-cyclobutane, we envisioned accessing the thermodynamically more stable *trans*-cyclobutane through an epimerization process. C(sp^3)–H functionalization of cyclobutanes has previously been reported[5] and elegantly demonstrated in total synthesis,[6] but there was some uncertainty about whether the proximal methyl C–H bonds would intervene unproductively.

Mapping this strategic bond construction onto a more complete retrosynthesis of **1**, we planned to reserve installation of the two formyl groups and the C1′ phenyl substituent until the final steps of the synthesis, thereby simplifying **1** to **2**. Scission of the aryl C–O bond in **2** revealed bromide **3**; in the forward sense, the chroman substructure would be constructed via intramolecular *O*-arylation. Bromide **3** was then further simplified to ketone **4**, where the strained seven-membered B ring would be formed by a potentially challenging[7] ring-closing metathesis, while the arene functionality could be installed via aldol condensation. In turn, ketone **4** was expected to be accessible in short order from the product of the directed C(sp^3)–H alkenylation reaction joining fragments **5** and **6**.

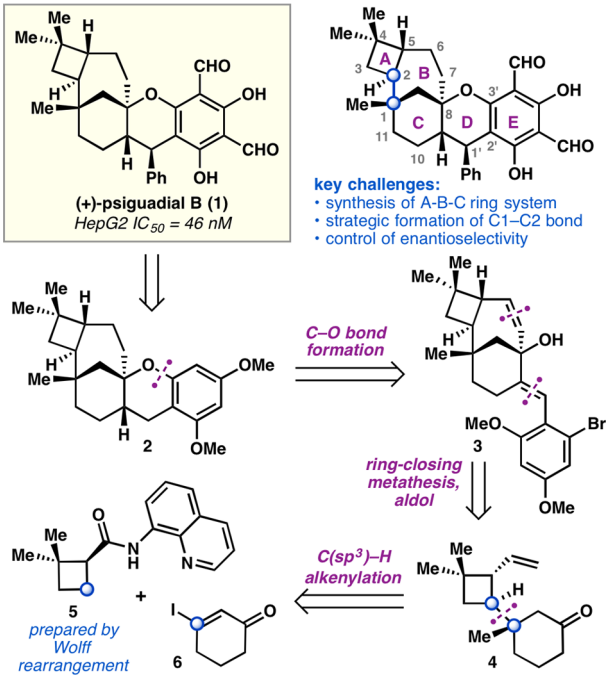


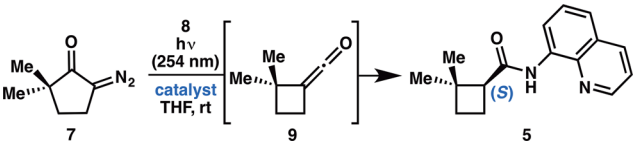
Figure 1. Retrosynthetic analysis.

Having identified an approach to **1** that centered on the coupling between **5** and **6**, we were left to consider how best to synthesize amide **5** in enantioenriched form. The corresponding carboxylic acid had been made previously as a racemate by Wolff rearrangement of diazoketone **7**,[8] which is readily accessible from commercially available 2,2-dimethylcyclopentanone.[9] Inspired by several reports of catalytic asymmetric nucleophilic additions to ketenes,[10] we hypothesized that enantioenriched **5** could be prepared directly by photolysis of **7** in the presence of a chiral catalyst and 8-aminoquinoline (**8**). Thus, we conducted a survey of chiral nucleophilic catalysts known to engage with ketenes (Table 1, **C1**–**C5**)[10,11] and

Received: July 13, 2016
Published: July 24, 2016

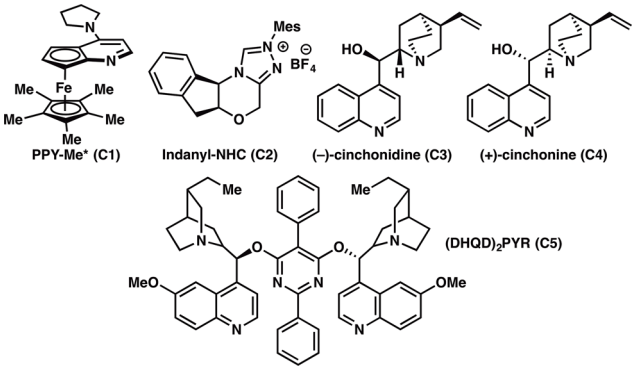
DOI: 10.1021/jacs.6b07229
J. Am. Chem. Soc. 2016, 138, 9803–9806

Table 1. Optimization of the Tandem Wolff Rearrangement/Catalytic Asymmetric Ketene Addition



entry	mmol	cat. (mol %)	equiv of 8	yield of 5 (%)	ee of 5 (%)[a]
1	0.10	0	1	55[b]	0
2	0.10	C1 (50)	1	39[b]	46
3	0.10	C2 (50)	1	32[b]	−66
4	0.10	C3 (50)	1	58[b]	−59
5	0.10	C4 (50)	1	72[b]	77
6	0.10	C5 (50)	1	65[b]	−15
7	0.10	C4 (20)	1	66[c]	81
8	11	C4 (20)	1	37[c]	79
9	15	C4 (20)	3	62[c]	80
10	30	C4 (10)	3	62[c]	79

[a]Determined by supercritical fluid chromatography using a chiral stationary phase. [b]The reaction mixture was irradiated for 24 h, and the yield was determined by ^{1}H NMR analysis versus an added internal standard. [c]Isolated yield.



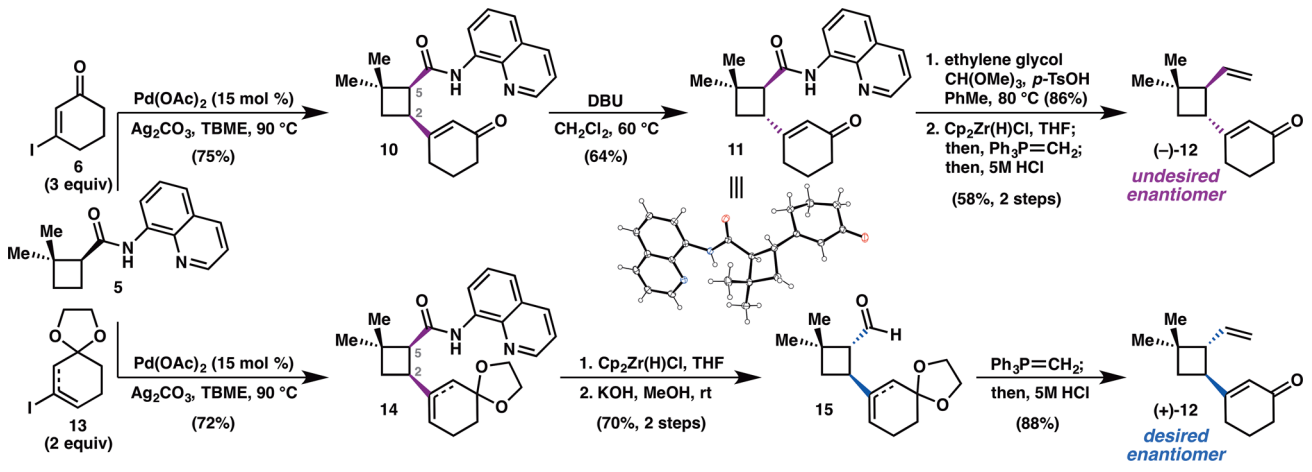
discovered that **5** could indeed be obtained with promising levels of enantioinduction (15−77% ee; entries 2−6). The enantioselectivity is striking given the substantial rate of background reaction observed in the absence of catalyst (entry 1).

Following an investigation of several reaction parameters,[12] irradiation of **7** with 254 nm light in the presence of 1 equiv of **8** and 20 mol % (+)-cinchonine (**C4**) in tetrahydrofuran (THF) was determined to be optimal when conducting the reaction on a small scale in a sealed tube (entry 7). Unfortunately, the yield dropped when the reaction was performed on a preparative scale in a standard photochemical reaction vessel (entry 8). After detecting the evolution of carbon monoxide, we hypothesized that the decreased yield results from decomposition of ketene **9** by photodecarbonylation.[13] In order to drive the product distribution toward nucleophilic trapping, we increased the concentration of **8**, which restored the desired reactivity and afforded **5** in 62% yield with 80% ee on a 15 mmol scale (entry 9). Moreover, the catalyst loading could be reduced to 10 mol % using this protocol, which reliably produced **5** in 62% yield with 79% ee on a 30 mmol scale (entry 10). Although **5** is obtained with modest ee directly from the reaction, a single recrystallization by layer diffusion provided this key intermediate in enantiomerically pure form. To our knowledge, this is the first example of a tandem Wolff rearrangement/catalytic asymmetric ketene addition.

With rapid access to multigram quantities of **5**, we turned our attention to its coupling with vinyl iodide **6** (Scheme 1). To our delight, subjecting a mixture of **5** and **6** to $Pd(OAc)_2$ and Ag_2CO_3 at 90 °C provided *cis*-cyclobutane **10** in 75% yield. The requisite *trans*-cyclobutane was obtained by selective epimerization[14] at C2, as determined by deuterium-labeling studies. Ketalization of **11** enabled clean reductive cleavage of the directing group, and the corresponding aldehyde was telescoped through Wittig olefination and hydrolysis to afford vinyl enone (−)-**12** in 58% yield over the two steps. It was at this stage that we were able to obtain single crystals of *trans*-cyclobutane **11** suitable for X-ray diffraction. Unfortunately, **11** was found to be in the incorrect enantiomeric series for elaboration to natural **1**. To our dismay, we could not circumvent this problem by simply employing (−)-cinchonidine (**C3**) in the tandem Wolff rearrangement/asymmetric ketene addition, as this *pseudoenantiomeric* catalyst afforded *ent*-**5** in lower yield with only 59% ee (Table 1, entry 4).

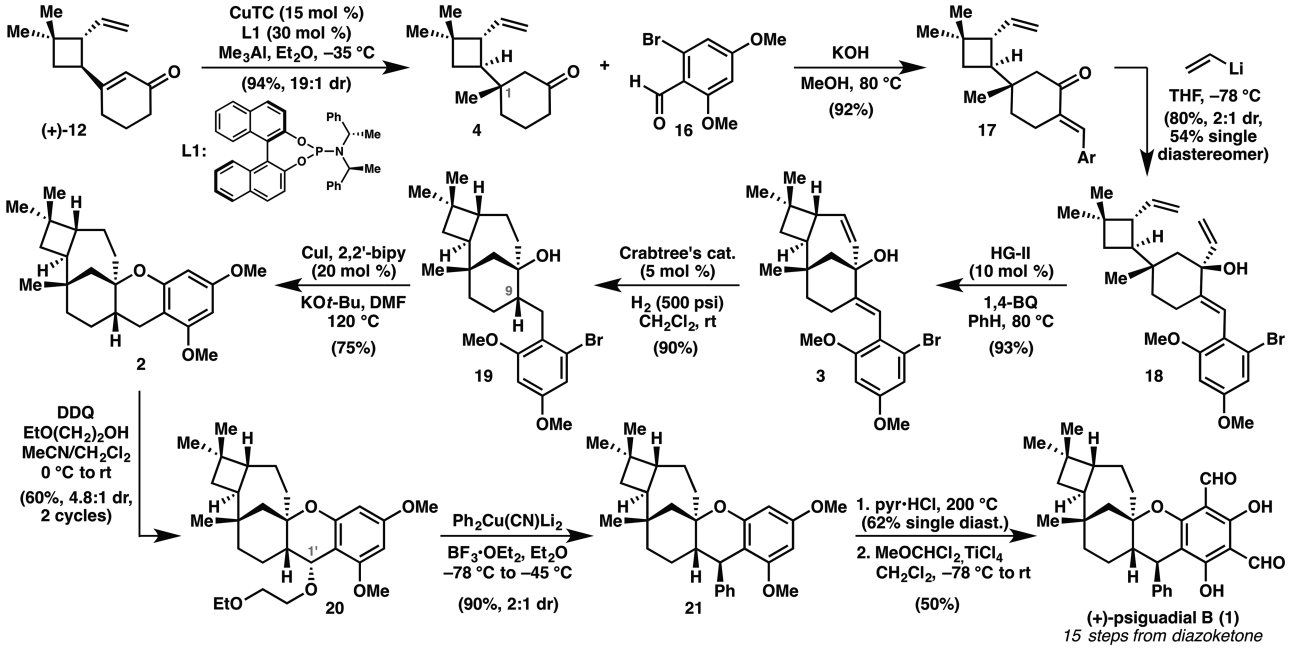
We recognized that the desired enantiomer of **12** could potentially be generated from **5** through an alternate sequence involving epimerization at C5 instead of C2. To this end, iodide **13** (isolated as an 8:1 mixture of olefin isomers) was prepared and subjected to the cross-coupling conditions, furnishing **14** in 72% yield on a gram scale. Reduction of the amide provided the

Scheme 1. C(sp^3)−H Alkenylation and Epimerization Strategies



DOI: 10.1021/jacs.6b07229
J. Am. Chem. Soc. 2016, 138, 9803−9806

Scheme 2. Completion of the Synthesis of (+)-Psiguadial B (1)



cis-aldehyde (not shown), which was epimerized at C5 by treatment with KOH in methanol to give **15**. Gratifyingly, methylenation and hydrolysis under the previously developed conditions provided (+)-**12**, the desired enantiomer. Thus, utilization of **13** as a coupling partner eliminated a linear protection step and substantially improved the material throughput. Moreover, it is notable that either enantiomer of **12** can be prepared using a single enantiomer of organocatalyst.

With the desired enantiomer of vinyl enone **12** in hand, we turned our attention to installation of the methyl group at the C1 quaternary center (Scheme 2). Reaction of **12** with Gilman's reagent furnished ketone **4** in only moderate yield with 3:1 dr. Fortunately, the yield and diastereoselectivity of the conjugate addition were enhanced by employing the copper-catalyzed asymmetric method developed by Alexakis and co-workers,[15] which provided **4** in 94% yield with 19:1 dr. Subsequent aldol condensation between **4** and aldehyde **16** afforded *exo*-enone **17** in excellent yield. However, 1,2-addition into this hindered ketone proved challenging. Allylic alcohol **18** was obtained in good yield with serviceable dr by employing vinyllithium in THF at −78 °C; extensive experimentation aimed at improving the dr proved unfruitful. Finally, the key ring-closing metathesis proceeded with excellent efficiency using the second-generation Hoveyda−Grubbs catalyst (HG-II), delivering the fully assembled A−B−C ring system in 93% yield.

With the strained sesquiterpene framework secured, both the di- and trisubstituted olefins in **3** were hydrogenated in the presence of Crabtree's catalyst, thus establishing the C9 stereogenic center with 16:1 dr and providing **19** in 90% isolated yield. The final ring of the psiguadial framework was constructed by a Cu-catalyzed intramolecular *O*-arylation reaction, which furnished pentacycle **2** in 75% yield.[16]

Completion of the synthesis required installation of the phenyl group at C1′ and formylation of the E ring. To this end, treatment of **2** with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in the presence of ethoxyethanol[17] effected benzylic oxidation to give **20** in 60% yield over two cycles. Addition of $BF_3{\cdot}OEt_2$ to a mixture of **20** and lithium diphenylcyanocuprate[18] delivered **21** in 90% yield as an inseparable 2:1 mixture of diastereomers, favoring the desired configuration. Double demethylation was achieved with pyridine hydrochloride at 200 °C; at this stage the diastereomeric resorcinols were readily separable by column chromatography. Finally, the two aryl aldehydes were installed simultaneously using Rieche formylation conditions,[19] delivering **1** in 50% yield. Synthetic **1** was found to be spectroscopically identical in all respects to the natural sample reported by Shao et al.[1,10]

In summary, the total synthesis of the cytotoxic natural product (+)-psiguadial B (**1**) was completed in 15 steps from diazoketone **7**. The synthetic strategy was enabled by de novo construction of the *trans*-fused cyclobutane ring via a tandem Wolff rearrangement/asymmetric ketene addition followed by a Pd-catalyzed C(sp^3)−H alkenylation reaction. Notably, both enantiomers of the natural product are accessible from a single enantiomer of organocatalyst. Efforts to expand the scope of these key transformations and apply this sequence in the synthesis of other *trans*-cyclobutane-containing natural products are ongoing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b07229.

Crystallographic data for **11** (CIF)

Experimental procedures and characterization and spectral data for all compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*reisman@caltech.edu

Notes

The authors declare no competing financial interest.

DOI: 10.1021/jacs.6b07229
J. Am. Chem. Soc. 2016, 138, 9803−9806

■ ACKNOWLEDGMENTS

Prof. Greg Fu is gratefully acknowledged for insightful discussions. We thank Dr. Allen Oliver and Dr. Nathan Schley for X-ray crystallographic structure determination, Dr. David VanderVelde for assistance with NMR structure determination, Dr. Scott Virgil and the Caltech Center for Catalysis and Chemical Synthesis for access to analytical equipment, and Materia, Inc. for a donation of HG-II catalyst. Fellowship support was provided by the NSF (L.M.C., Grant DGE-1144469) and SNF (L.W., Grant PBZHP2-147311). S.E.R. is an American Cancer Society Research Scholar and a Heritage Medical Research Foundation Investigator. Financial support from the California Institute of Technology, the NSF (CHE 1057143), the American Cancer Society, the Research Corporation Cottrell Scholars Program, and DuPont is gratefully acknowledged.

■ REFERENCES

(1) For psiguadial A and B, see: Shao, M.; Wang, Y.; Liu, Z.; Zhang, D.-M.; Cao, H.-H.; Jiang, R.-W.; Fan, C.-L.; Zhang, X.-Q.; Chen, H.-R.; Yao, X.-S.; Ye, W.-C. *Org. Lett.* **2010**, *12*, 5040.

(2) For psiguadial C and D and proposed biosynthesis, see: Shao, M.; Wang, Y.; Jian, Y.-Q.; Huang, X.-J.; Zhang, D.-M.; Tang, Q.-F.; Jiang, R.-W.; Sun, X.-G.; Lv, Z.-P.; Zhang, X.-Q.; Ye, W.-C. *Org. Lett.* **2012**, *14*, 5262.

(3) (a) Tran, D. N. Rhodium-Catalyzed Imine-Directed C−H Bond Activation and Biomimetic Synthesis of Sesquiterpenoids. Ph.D. Thesis, ETH Zürich, Zürich, Switzerland, 2014. (b) For semisyntheses of guajadial and psidial A, see: Lawrence, A. L.; Adlington, R. M.; Baldwin, J. E.; Lee, V.; Kershaw, J. A.; Thompson, A. L. *Org. Lett.* **2010**, *12*, 1676. (c) For a semisynthesis of caryolanemagnolol, see: Cheng, X.; Harzdorf, N. L.; Shaw, T.; Siegel, D. *Org. Lett.* **2010**, *12*, 1304.

(4) Biomimetic syntheses of several related meroterpenoids from bicyclogermacrene have also been reported. See: Tran, D. N.; Cramer, N. *Chem. - Eur. J.* **2014**, *20*, 10654.

(5) (a) Zhang, S.-Y.; Li, Q.; He, G.; Nack, W. A.; Chen, G. *J. Am. Chem. Soc.* **2013**, *135*, 12135. (b) Wang, B.; Lu, C.; Zhang, S.-Y.; He, G.; Nack, W. A.; Chen, G. *Org. Lett.* **2014**, *16*, 6260. (c) Xiao, K.-J.; Lin, D. W.; Miura, M.; Zhu, R.-Y.; Gong, W.; Wasa, M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2014**, *136*, 8138. For seminal studies, see: (d) Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.* **2010**, *132*, 3965. (e) Zaitsev, V. G.; Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.* **2005**, *127*, 13154. For a review, see: (f) Yamaguchi, J.; Itami, K.; Yamaguchi, A. D. *Angew. Chem., Int. Ed.* **2012**, *51*, 8960.

(6) (a) Gutekunst, W. R.; Baran, P. S. *J. Am. Chem. Soc.* **2011**, *133*, 19076. (b) Gutekunst, W. R.; Gianatassio, R.; Baran, P. S. *Angew. Chem., Int. Ed.* **2012**, *51*, 7507. (c) Gutekunst, W. R.; Baran, P. S. *J. Org. Chem.* **2014**, *79*, 2430. (d) Panish, R. A.; Chintala, S. R.; Fox, J. M. *Angew. Chem., Int. Ed.* **2016**, *55*, 4983. For other relevant examples in synthesis, see: (e) Feng, Y.; Chen, G. *Angew. Chem., Int. Ed.* **2010**, *49*, 958. (f) Ting, C. P.; Maimone, T. J. *Angew. Chem., Int. Ed.* **2014**, *53*, 3115.

(7) We were aware of unsuccessful efforts to prepare β-caryophyllene by ring-closing metathesis. See: Dowling, M. S.; Vanderwal, C. D. *J. Org. Chem.* **2010**, *75*, 6908.

(8) Ghosh, A.; Banerjee, U. K.; Venkateswaran, R. V. *Tetrahedron* **1990**, *46*, 3077.

(9) This starting material can also be prepared according to the following procedure: Caille, S.; Crockett, R.; Ranganathan, K.; Wang, X.; Woo, J. C. S.; Walker, S. D. *J. Org. Chem.* **2011**, *76*, 5198.

(10) (a) Hodous, B. L.; Fu, G. C. *J. Am. Chem. Soc.* **2002**, *124*, 10006. (b) Wiskur, S. L.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 6176.

(11) (a) Pracejus, H. *Justus Liebigs Ann. Chem.* **1960**, *634*, 9. (b) Zhang, Y.-R.; He, L.; Wu, X.; Shao, P.-L.; Ye, S. *Org. Lett.* **2008**, *10*, 277. For a review of catalytic asymmetric additions to ketenes, see: (c) Paull, D. H.; Weatherwax, A.; Lectka, T. *Tetrahedron* **2009**, *65*, 6771.

(12) See the Supporting Information (SI).

(13) Tidwell, T. T. *Ketenes*, 2nd ed.; John Wiley & Sons: Hoboken, NJ, 2006; pp 443−447.

(14) The major side product in this reaction is spirocyclic lactam **S1** (see the SI), which presumably arises via aza-Michael addition of the amide to the pendant enone. This material could be partially converted to **11** by resubjection to the epimerization conditions. For related examples, see: (a) Wasa, M.; Engle, K. M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2010**, *132*, 3680. (b) Stowers, K. j.; Fortner, K. C.; Sanford, M. S. *J. Am. Chem. Soc.* **2011**, *133*, 6541.

(15) (a) d'Augustin, M.; Palais, L. T.; Alexakis, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 1376. (b) Vuagnoux-d'Augustin, M.; Alexakis, A. *Chem. - Eur. J.* **2007**, *13*, 9647.

(16) Suchand, B.; Krishna, J.; Mritunjoy, K.; Satyanarayana, G. *RSC Adv.* **2014**, *4* (27), 13941.

(17) (a) Saito, A.; Nakajima, N.; Tanaka, A.; Ubukata, M. *Tetrahedron* **2002**, *58*, 7829. (b) Dennis, E. G.; Jeffery, D. W.; Johnston, M. R.; Perkins, M. V.; Smith, P. A. *Tetrahedron* **2012**, *68*, 340.

(18) (a) Lipshutz, B. H.; Wilhelm, R. S.; Kozlowski, J. A. *J. Org. Chem.* **1984**, *49*, 3938. (b) Lipshutz, B. H.; Parker, D. A.; Kozlowski, J. A.; Nguyen, S. M. *Tetrahedron Lett.* **1984**, *25*, 5959.

(19) (a) Rieche, A.; Gross, H.; Höft, E. *Chem. Ber.* **1960**, *93*, 88. (b) Aukrust, I. R.; Skattebol, L. *Acta Chem. Scand.* **1996**, *50*, 132. (c) Kraus, G. A.; Mengwasser, J.; Maury, W.; Oh, C. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 1399.

DOI: 10.1021/jacs.6b07229
J. Am. Chem. Soc. 2016, 138, 9803−9806