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Assembly of the Limonoid Architecture by a Divergent Approach: Total Synthesis of (±)-Andirolide N via (±)-8α-Hydroxycarapin

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Supporting Information

ABSTRACT: We report the first total synthesis of the limonoid andirolide N using a 12-step sequence from commercially available materials. The final step of this route demonstrates the chemical feasibility of our biosynthetic proposal that andirolide N arises from 8α-hydroxycarapin. The strategic use of a degraded limonoid as a platform for the synthesis of more structurally complex congeners may be a general approach to obtain limonoids with diverse functional properties.

Andirolide N (**5**), a limonoid tetranortriterpenoid natural product isolated from the flowers of a mahogany tree indigenous to the Amazonian rainforest (*Carapa guianensis*), possesses a synthetically demanding bicyclo[3.3.1]nonane ring system with a bridging tetrahydrofuran ring appended.[1,2] Decades of limonoid synthetic investigations[3] have been motivated by the wide range of their biological properties,[4] including antimalarial,[1] anticancer,[5] and anti-inflammatory activities.[6] Recent reports have also demonstrated exciting neuroprotective and regenerative properties.[7] Herein, the first total synthesis of the limonoid andirolide N (**5**) is reported by chemical conversion from the limonoid 8α-hydroxycarapin (**6**), which demonstrates the chemical feasibility of this pathway as a possible mode of biosynthesis (Figure 1). To generate these limonoids, as well as to allow access to a multitude of limonoids with differing A-ring structures, this approach utilizes a late-stage introduction of the limonoid A-ring: a location of great chemical diversity in this class of natural products as exemplified by compounds **1**–**6**.[8]

While many limonoids, including andirolide N (**5**), are trace isolates from threatened rainforest environments, availability from citrus and neem fruits has allowed for investigations of some members of the limonoid class through the use of semisynthesis and relay synthesis.[9] Independent, contemporaneous studies in the early 1970s by the groups of Connolly and Ekong[10] examined the biomimetic oxidative fragmentation of the limonoid B-ring and reassembly through a 1,6-conjugate addition to form mexicanolide (**3**). Williams and co-workers recently completed a total synthesis of mexicanolide (**3**) through employment of an analogous 1,6-conjugate addition strategy.[11] Additionally, a relay synthesis of azadirachtin reported by Ley took advantage of the availability of this natural product from neem oil.[12]

A landmark total synthesis of azadiradione was reported by Corey and Hahl that used a polyene cyclization to form the skeleton of azadiradione in a stereocontrolled manner.[13] An alternative polycyclization strategy was developed for the groundbreaking synthesis of limonin (**1**) by Yamashita, Hayashi, Hirama and co-workers.[14] Additionally, Corey and Behenna reported the synthesis of a protolimonoid by polyolefin cyclization; the protolimonoid was suggested to be a precursor to all known limonoids through systematic biomimetic oxidation and rearrangement reactions.[15]

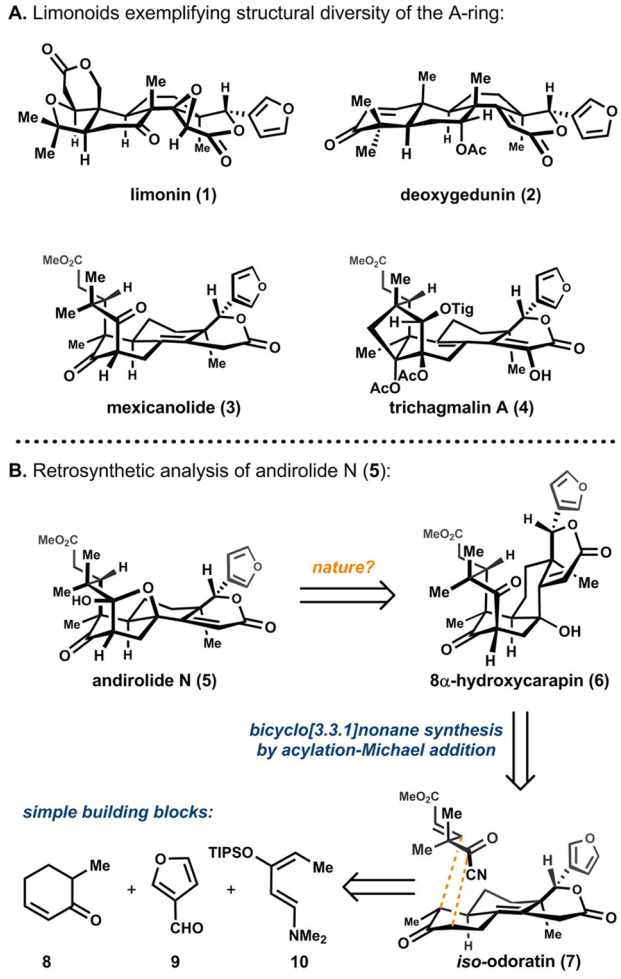

Figure 1. Synthetic approach to andirolide N (**5**) via *iso*-odoratin (**7**).

We developed a general synthetic approach to access limonoids with differing A-ring structures, such as those in Figure 1, by envisioning that these materials might arise from the degraded limonoid *iso*-odoratin (**7**),[16] the $\Delta^{8(14)}$ isomer of the natural

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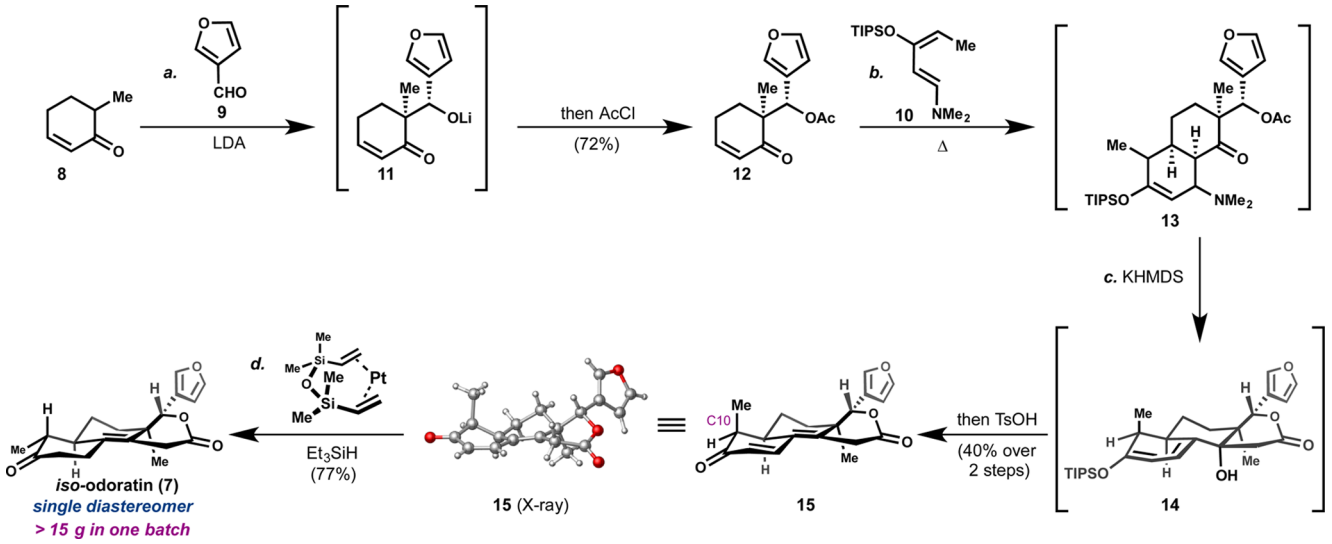
Scheme 1. Scalable Synthesis of *iso*-Odoratin (7)[a]



[a]Reagents and conditions: (a) *i*-Pr_2NH (1.25 equiv), *n*-BuLi (1.1 equiv), 3-furaldehyde (**9**) (1.05 equiv), −78 °C, THF, 0.5 h, then AcCl (1.3 equiv), −78 to −30 °C, 72%; (b) **10** (2.5 equiv), $PhCF_3$, 120 °C, 14 h; (c) KHMDS (2.0 equiv), −78 °C, 1.5 h, then TsOH (1.0 equiv), 1 h, 23 °C, 40% over 2 steps; (d) Karstedt's Catalyst (0.3 mol %), Et_3SiH (2.0 equiv), PhMe, 90 °C, 2.5 h, 77%.

product odoratin.[17] For the synthesis of 8α-hydroxycarapin (**6**), the bicyclo[3.3.1]nonane could be forged through an acylation−Michael addition strategy using a suitable electrophile. Retrosynthetic design via 8α-hydroxycarapin (**6**) would provide a means to test our hypothesis that this material can lead to andirolide N (**5**). To study the feasibility of this biosynthetic relationship and forming a bicyclo[3.3.1]nonane by this approach, we developed a route to *iso*-odoratin through the assembly of three simple building blocks (**8**−**10**).

The synthesis of *iso*-odoratin (**7**) is described in Scheme 1 and begins with a diastereoselective aldol reaction with 3-furaldehyde (**9**) and 6-methylcyclohexenone (**8**), the latter prepared from commercially available dihydrocarvone in one step,[18] to provide **12** in 72% yield after the intermediate alkoxide, **11**, was treated with AcCl. Use of a Rawal-type diene (**10**)[19] elicited a thermal Diels−Alder reaction with **12** to form the adduct **13**, as an uncharacterized mixture of diastereomers. An intramolecular acetate aldol and β-elimination of the dimethylamino group was performed with KHMDS to form the intermediate **14**. Upon treatment of the organic extracts with TsOH, **15** was formed by desilylation and dehydration. The conversion of **12** to **15** over two steps proceeds in an excellent 40% overall yield to provide **15** as an inconsequential mixture of diastereomers at C10 (1:1 dr). The structures of **15** and *epi*-**15** were confirmed by X-ray crystallography and NOESY NMR experiments, respectively.

This mixture of diastereomers was subjected to Karstedt's catalyst (tris(tetramethyldivinyldisiloxane)diplatinum)[20] and Et_3SiH, which cleanly afforded *iso*-odoratin (**7**) as a single diastereomer in 77% yield after acidic aqueous workup. The use of Et_3SiH was more efficient than the use of other silanes (TIPSiH, DMPSiH, TMDS, or PMHS), which correlates with previously observed differences in rates of hydrosilylation with Karstedt's catalyst.[20,21] It is noteworthy that commonly employed conditions for enone reduction were not successful for reducing the doubly vinylogous 1,7-dicarbonyl compound, in part owing to the propensity for many reagents to deprotonate this substrate (**15**), rather than effect an alkene reduction. Formation of the extended enolate of **15** was confirmed by quenching purple reaction mixtures with deuterated solvent resulting in loss of color and incorporation of deuterium. The four-step sequence to convert 6-methylcyclohexenone (**8**) to *iso*-odoratin (**7**) proceeds in 22% overall yield and can produce decagram quantities of **7** per batch.

The regio- and stereoselective hydroxylation of C8 of the limonoid framework is a well-established problem in the semisynthesis literature.[22] Specifically, the oxidation of odoratin is known to lead to aromatization of the leftmost ring of odoratin, the limonoid B-ring. This established challenge guided us to employ *iso*-odoratin (**7**) as an alternative synthetic intermediate. Detailed, empirical studies established that the C8 hydroxyl group could be installed directly by treating the crude reduction mixture that contains *iso*-odoratin (**7**) with O_2, $P(OMe)_3$, and DBU (Scheme 2). This formal alkene hydration results in the formation of **16** as a single regioisomer and diastereomer after TMS ether formation. The product of hydroxylation to form the *cis*-decalin arrangement present in 8α-hydroxycarapin (**6**) was confirmed by analysis of NOESY and X-ray diffraction data.

Installation of the bicyclo[3.3.1]nonane was initiated by acylation of the lithium enolate derived from **16** and the acyl cyanide **17**[23] to provide **18** in 76% yield. The use of an acylation strategy[24] rather than an aldol and oxidation approach allowed for a redox-neutral[25] installation of the 1,3-dicarbonyl functionality, as well as preclusion of retro-aldol and aldol condensation side reactions. Before the Michael addition to construct the bicyclo[3.3.1]nonane could be performed, the 1,3-diketone group required a blocked α-position, such that the γ-position (C10) could be deprotonated and subsequently engage the pendant enoate. Although numerous conventional blocking groups were investigated (e.g., −OR, −SR, or −X),[26] it was eventually found that a carbon-based blocking group allowed for formation of the bicycle. Thus, α-allylation with allyl iodide and Cs_2CO_3 provided the intermediate **19** as a single diastereomer, where allylation occurred from the less hindered convex face, enforcing the necessary geometry for the bicyclo[3.3.1]nonane synthesis. The allylation product **19** underwent palladium-catalyzed carbome-

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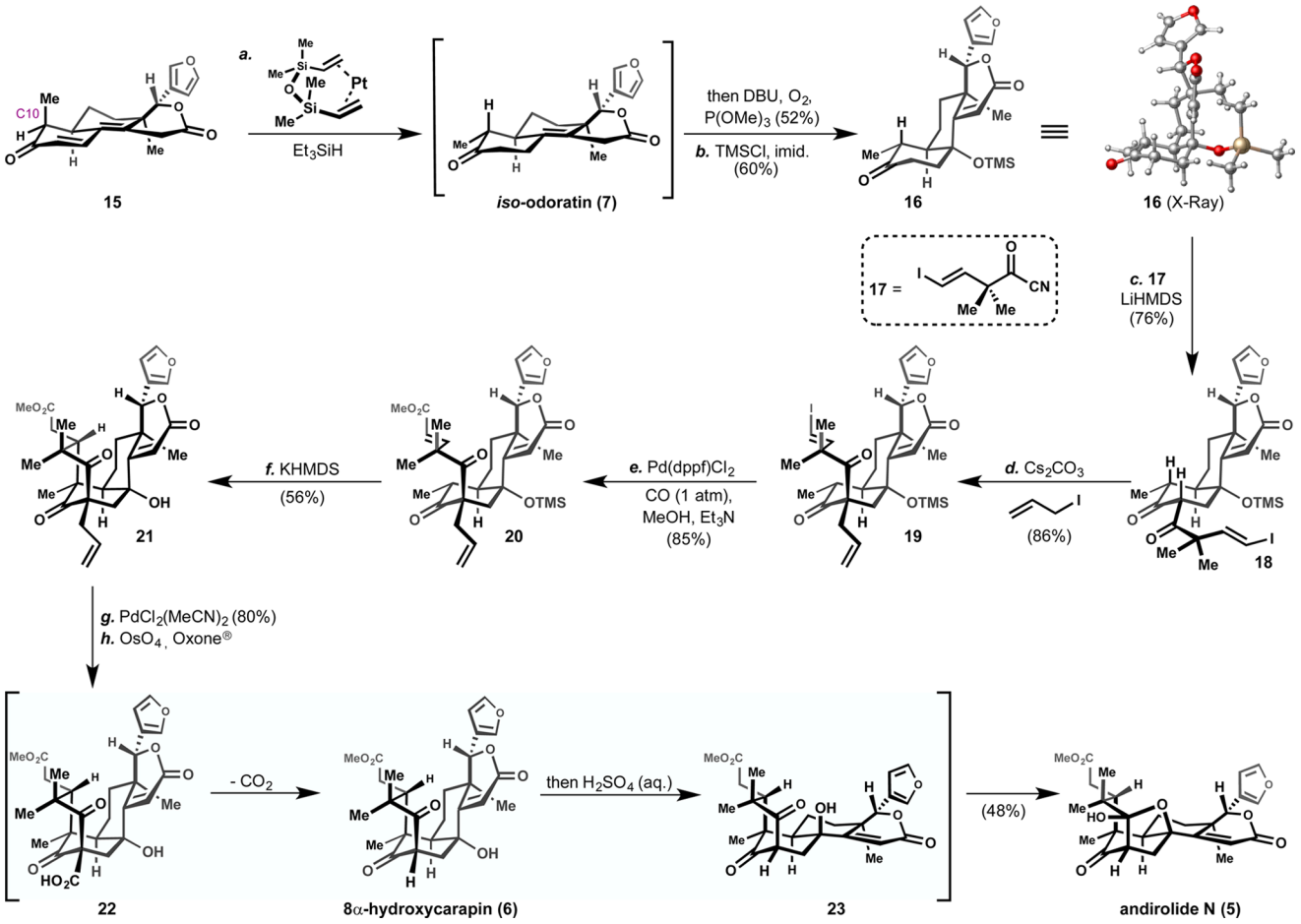
Scheme 2. Total Synthesis of Andirolide N (5) via the Presumed Biosynthetic Precursor 8α-Hydroxycarapin (6)[a]



[a]Reagents and conditions: (a) Karstedt's Catalyst (0.3 mol %), Et_3SiH (2.0 equiv), PhMe, 90 °C, 2.5 h, then DBU (2.0 equiv), $P(OMe)_3$ (1.5 equiv), O_2 (1 atm), MeCN, 35 °C, 2 h, 52%; (b) TMSCl (1.5 equiv), imid. (3.5 equiv), CH_2Cl_2, 23 °C, 3 h, 60%; (c) LiHMDS (1.5 equiv), **17** (1.1 equiv), Et_2O–THF (4:1), −78 to 0 °C, 1 h, 76%; (d) Cs_2CO_3 (2.5 equiv), allyl iodide (1.7 equiv), acetone, 56 °C, 12 h, 86%; (e) $Pd(dppf)Cl_2$ (6 mol %), Et_3N (1.5 equiv), CO (1 atm), MeOH–DMF (5:1), 60 °C, 0.5 h, 85%; (f) KHMDS (2.0 equiv), PhMe–THF (1:3), −78 to 23 °C, 0.5 h, 56%; (g) $PdCl_2(MeCN)_2$ (15 mol %), PhH, 60 °C, 2 h, 80%; (h) OsO_4 (5 mol %), Oxone (2.5 equiv), 23 °C, 7 h, then aq. H_2SO_4, 0.5 h, 48%.

thoxylation with $Pd(dppf)Cl_2$, CO, and methanol to afford the precursor to the Michael addition (**20**).

In addition to the challenge associated with forming a quaternary center at C10, the Michael addition is further impeded by the presence of *syn*-pentane interactions with the axially disposed B-ring substituents. However, the reactive potassium enolate proved to be effective for forming the sterically congested bicyclo[3.3.1]nonane: the bridgehead allylated analog of 8α-hydroxycarapin (**21**) was obtained in 56% yield by treatment of **20** with KHMDS. Additionally, this protocol conveniently resulted in concomitant TMS deprotection. Removal of the allyl group present in **21** was planned through alkene isomerization, oxidative cleavage, and Barton decarboxylation to reach 8α-hydroxycarapin. The alkene isomerization reaction was performed using $PdCl_2(MeCN)_2$ in benzene to provide the internal alkene isomer, ***iso*-21**.[27,28]

Subjection of the alkene isomer of **21** to oxidative cleavage conditions developed by Borhan and co-workers[29] resulted in smooth conversion of the starting material, which after acidic aqueous workup provided andirolide N (**5**) directly in 48% yield. Although several mechanistic explanations could be advanced for the preceding observation, we propose that decarboxylation of **22** occurs spontaneously under the reaction conditions to give 8α-hydroxycarapin (**6**), which upon workup with aqueous 3 M H_2SO_4 undergoes a stereochemical inversion via a stabilized carbocation conjugated to the neighboring enoate to lead to the diastereomeric alcohol of 8α-hydroxycarapin, **23**. The diastereomeric alcohol **23** may then undergo ketalization to form the thermodynamically favored ketal isomer.

Support for this hypothesis derives from a series of experimental observations. Aqueous workup of the oxidative cleavage reaction with saturated aqueous $NaHCO_3$ provided 8α-hydroxycarapin (**6**), demonstrating the intermediacy of this natural product. When 8α-hydroxycarapin (**6**) was subjected to conditions analogous to the aqueous workup of the oxidative cleavage reaction, andirolide N (**5**) was produced as the major product. As an alternative possibility, the opposite order of events could occur, wherein hydration of the ketone precedes the inversion of configuration of the C8 stereocenter. However, further studies are required to distinguish between these mechanistic pathways.

In conclusion we have developed a 12-step synthesis of the limonoid andirolide N (**5**) from commercially available dihydrocarvone through employment of an acylation-Michael strategy for bicyclo[3.3.1]nonane construction from the degraded limonoid *iso*-odoratin (**7**). The unique tetrahydrofuran

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appended to the bicyclic structure of the carbocyclic skeleton of andirolide N was installed via an acid-mediated reorganization of 8α-hydroxycarapin (**6**). While these studies demonstrate the chemical feasibility that 8α-hydroxycarapin could be the biosynthetic precursor to andirolide N, whether or not the polycyclic structure of andirolide N is formed in nature by this pathway remains unknown.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b12268.

Experimental procedures, X-ray diffraction, spectroscopic data for all new compounds including ^{1}H and ^{13}C NMR spectra (PDF)

Crystallographic data (CIF, CIF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) For the isolation of andirolide N, see: Tanaka, Y.; Sakamoto, A.; Inoue, T.; Yamada, T.; Kikuchi, T.; Kajimoto, T.; Muraoka, O.; Sato, A.; Wataya, Y.; Kim, H.-S.; Tanaka, R. *Tetrahedron* **2012**, *68*, 3669−3677.

(2) For the isolation of 8α-hydroxycarapin, see: (a) Adesogan, E. K.; MacLachlan, L. K.; Taylor, D. A. H. *S. Afr. J. Chem.* **1987**, *40*, 25−29. (b) Lin, B.-D.; Yuan, T.; Zhang, C.-R.; Dong, L.; Zhang, B.; Wu, Y.; Yue, J.-M. *J. Nat. Prod.* **2009**, *72*, 2084−2090.

(3) For a review on limonoid total synthesis, see: Heasley, B. *Eur. J. Org. Chem.* **2011**, *2011*, 19−46.

(4) For reviews on limonoid biological activity, see: (a) Champagne, D. E.; Koul, O.; Isman, M. B.; Scudder, G. G. E.; Towers, G. H. N. *Phytochemistry* **1992**, *31*, 377−394. (b) Saraf, S.; Roy, A. *Biol. Pharm. Bull.* **2006**, *29*, 191−201.

(5) For reviews on limonoid anticancer activity, see: (a) Miller, E. G.; Porter, J. L.; Binnie, W. H.; Guo, Y. I.; Hasegawa, S. *J. Agric. Food Chem.* **2004**, *52*, 4908−4912. (b) Subapriya, R.; Nagini, S. *Curr. Med. Chem. − Anti-Cancer Agents* **2005**, *5*, 1−7. (c) Ejaz, S.; Ejaz, A.; Matsuda, K.; Lim, C. W. *J. Sci. Food Agric.* **2006**, *86*, 339−345.

(6) Yu, J.; Wang, L.; Walzem, R. L.; Miller, E. G.; Pike, L. M.; Patil, B. S. *J. Agric. Food Chem.* **2005**, *53*, 2009−2014.

(7) For recent reports on neurologically active limonoids, see: (a) Jang, S. W.; Liu, X.; Chan, C. B.; France, S. A.; Sayeed, I.; Tang, W.; Lin, X.; Xiao, G.; Andero, R.; Chang, Q.; Ressler, K. J.; Ye, K. *PLoS One* **2010**, *5*, e11528. (b) Hett, E. C.; Slater, L. H.; Mark, K. G.; Kawate, T.; Monks, B. G.; Stutz, A.; Latz, E.; Hung, D. T. *Nat. Chem. Biol.* **2013**, *9*, 398−405. (c) English, A. W.; Liu, K.; Nicolini, J. F.; Mulligan, A. M.; Ye, K. *Proc. Natl. Acad. Sci. U. S. A.* **2013**, *110*, 16217−16222. (f) Li, H.; Li, Y.; Wang, X.; Pang, T.; Zhang, L.; Luo, J.; Kong, L. *RSC Adv.* **2015**, *5*, 40465−40474.

(8) Tan, Q.; Luo, X. *Chem. Rev.* **2011**, *111*, 7437−7522.

(9) (a) Connolly, J. D.; McCrindle, R.; Overton, K. H. *Chem. Commun.* **1965**, 162−163. (b) Bevan, C. W. L.; Powell, J. W.; Taylor, D. A. H.; Halsall, T. G.; Toft, P.; Welford, M. *J. Chem. Soc. C* **1967**, 163−170. (b) Connolly, J. D.; McCrindle, R.; Overton, K. H. *Tetrahedron* **1968**, *24*, 1489−1495. (c) Connolly, J. D.; Thornton, I. M. S.; Taylor, D. A. H. *J. Chem. Soc. D* **1970**, 1205. (d) Connolly, J. D.; Overton, K. H.; Polonsky, J. *Progress in Phytochemistry*; Reinhold, L., Liwschitz, Y., Eds.; Interscience Publishers: New York, 1970; Vol. 2, pp 385−455. (e) Kehrli, A. R. H.; Taylor, D. A. H.; Niven, M. *J. Chem. Soc., Perkin Trans. 1* **1990**, 2057−2065. (f) Kehrli, A. R. H; Taylor, D. A. H. *J. Chem. Soc., Perkin Trans. 1* **1990**, 2067−2070. (g) Grigorjeva, L.; Liepinsh, E.; Razafimahefa, S.; Yahorau, A.; Yahorava, S.; Rasoanaivo, P.; Jirgensons, A.; Wikberg, J. E. S. *J. Org. Chem.* **2014**, *79*, 4148−4153.

(10) (a) Connolly, J. D.; Thornton, I. M. S.; Taylor, D. A. H. *J. Chem. Soc. D* **1971**, 17−18. (b) Obasi, M. E.; Okogun, J. I.; Ekong, D. E. U. *J. Chem. Soc., Perkin Trans. 1* **1972**, 1943−1946. (c) Connolly, J. D.; Thornton, I. M. S.; Taylor, D. A. H. *J. Chem. Soc., Perkin Trans. 1* **1973**, 2407−2413.

(11) (a) Faber, J. M.; Williams, C. M. *Chem. Commun.* **2011**, *47*, 2258−2260. (b) Schuster, H.; Martinez, R.; Bruss, H.; Antonchick, A. P.; Kaiser, M.; Schurmann, M.; Waldmann, H. *Chem. Commun.* **2011**, *47*, 6545−6547. (c) Faber, J. M.; Eger, W. A.; Williams, C. M. *J. Org. Chem.* **2012**, *77*, 8913−8921.

(12) Veitch, G. E.; Beckmann, E.; Burke, B. J.; Boyer, A.; Maslen, S. L.; Ley, S. V. *Angew. Chem., Int. Ed.* **2007**, *46*, 7629−7632.

(13) (a) Corey, E. J.; Reid, J. G.; Myers, A. G.; Hahl, R. W. *J. Am. Chem. Soc.* **1987**, *109*, 918−919. (b) Corey, E. J.; Hahl, R. H. *Tetrahedron Lett.* **1989**, *30*, 3023−3026.

(14) Yamashita, S.; Naruko, A.; Nakazawa, Y.; Zhao, L.; Hayashi, Y.; Hirama, M. *Angew. Chem., Int. Ed.* **2015**, *54*, 8538−8541.

(15) Behenna, D. C.; Corey, E. J. *J. Am. Chem. Soc.* **2008**, *130*, 6720−6721.

(16) For a description of structure-goal strategies, see: Corey, E. J.; Cheng, X.-M. *The Logic of Chemical Synthesis*; Wiley: New York, 1989.

(17) Chan, W. R.; Taylor, D. R.; Aplin, R. T. *Chem. Commun.* **1966**, 576−577.

(18) For a scalable procedure of 6-methylcyclohexenone (**8**) synthesized from dihydrocarvone in one step, see: Huang, D.; Schuppe, A. W.; Liang, M. Z.; Newhouse, T. R. *Org. Biomol. Chem.* **2016**, *14*, 6197−6200.

(19) Compound **10** was prepared in two steps. See the Supporting Information for details.

(20) Johnson, C. R.; Raheja, R. K. *J. Org. Chem.* **1994**, *59*, 2287−2288.

(21) Stein, J.; Lewis, L. N.; Gao, Y.; Scott, R. A. *J. Am. Chem. Soc.* **1999**, *121*, 3693−3703.

(22) Chan, W. R.; Taylor, D. R.; Aplin, R. T. *Tetrahedron* **1972**, *28*, 431−437.

(23) Compound **17** was prepared in five steps. See the Supporting Information for details.

(24) (a) Mander, L. N.; Sethi, S. P. *Tetrahedron Lett.* **1983**, *24*, 5425−5428. (b) Tang, Q.; Sen, S. E. *Tetrahedron Lett.* **1998**, *39*, 2249−2252.

(25) Burns, N. Z.; Baran, P. S.; Hoffmann, R. W. *Angew. Chem., Int. Ed.* **2009**, *48*, 2854−2867.

(26) For an example of blocking the α-position of a 1,3-dicarbonyl compound in total synthesis, see: Corey, E. J.; Li, W.; Nagamitsu, T. *Angew. Chem., Int. Ed.* **1998**, *37*, 1676−1679.

(27) (a) Sen, A.; Lai, T.-W. *Inorg. Chem.* **1981**, *20*, 4036−4038. (b) Yu, J.; Gaunt, M. J.; Spencer, J. B. *J. Org. Chem.* **2002**, *67*, 4627−4629. (c) Petrova, K. V.; Mohr, J. T.; Stoltz, B. M. *Org. Lett.* **2009**, *11*, 293−295.

(28) For mechanistic studies involving $PdCl_2(RCN)_2$ catalyzed alkene isomerization, see: Schmidt, A.; Nödling, A. R.; Hilt, G. *Angew. Chem., Int. Ed.* **2015**, *54*, 801−804. For alternative Pd-catalyzed alkene isomerization conditions attempted and a comprehensive review, see: Lim, H. J.; Smith, C. R.; RajanBabu, T. V. *J. Org. Chem.* **2009**, *74*, 4565−4572.

(29) Travis, B. R.; Narayan, R. S.; Borhan, B. *J. Am. Chem. Soc.* **2002**, *124*, 3824−3825.

DOI: 10.1021/jacs.6b12268
J. Am. Chem. Soc. 2017, 139, 631−634