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

Total Synthesis of (−)-Calyciphylline N

Artem Shvartsbart and Amos B. Smith, III*

Department of Chemistry, Laboratory for Research on the Structure of Matter, and Monell Chemical Senses Center, University of Pennsylvania, Philadelphia, Pennsylvania 19104, United States

Supporting Information

ABSTRACT: The total synthesis of the architecturally complex *Daphniphyllum* alkaloid (−)-calyciphylline N has been achieved. Highlights of the synthesis include a Et_2AlCl-promoted, highly stereoselective, susbtrate-controlled intramolecular Diels−Alder reaction, a transannular enolate alkylation, an effective Stille carbonylation/Nazarov cyclization sequence, and a high-risk diastereoselective hydrogenation of a fully substituted conjugated diene ester.

The *Daphniphyllum* alkaloids comprise a large family of complex natural products including more than 180 known members,[1] many with diverse biological activities, that have proven challenging as targets for total synthesis.[2] We in particular became interested in the calyciphylline alkaloids, largely due to their unique frameworks and at the time, limited synthetic studies.[3,4] Calyciphylline N [(−)-**1**, Figure 1], isolated in 2008 by Kobayashi and co-workers,[5] was chosen as our initial target.

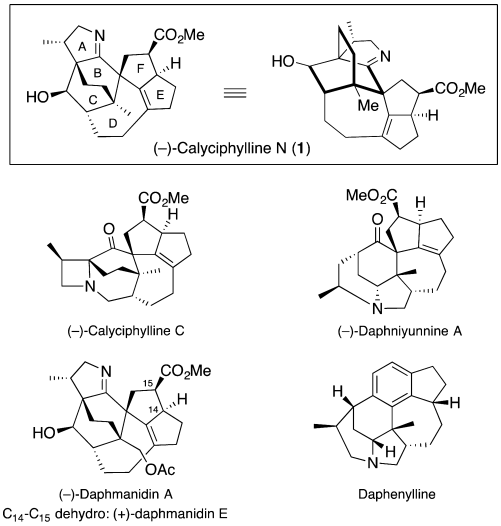


Figure 1. (−)-Calyciphylline N and related congeners.[6]

While the biological activity of (−)-calyciphylline N (**1**) has not been investigated, we reasoned that a synthetic effort toward this alkaloid would not only unveil a wealth of interesting reactivity but also permit access to other congeners of the family. Notable structural features of **1** include six contiguous stereogenic centers, three of which are quaternary bridgehead, a fused A ring dihydropyrrole, and a DEF decahydrocyclopentazulene ring system surrounding a central bicyclo[2.2.2]octane BC core.

Retrosynthetically (Figure 2), we envisioned that the dihydropyrrole A ring could arise via condensation of a primary

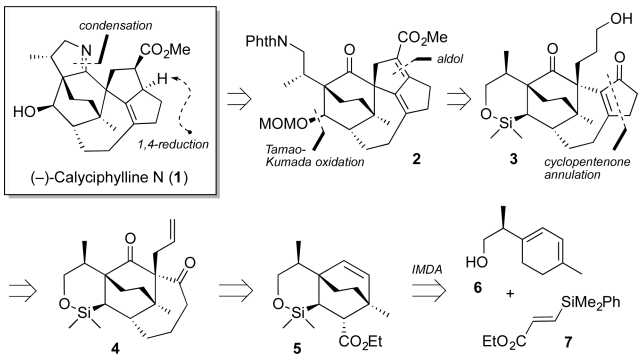


Figure 2. Retrosynthetic analysis.

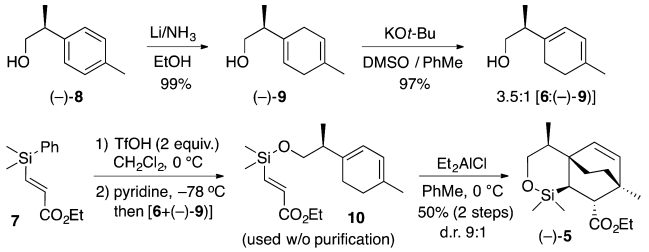
amine with the carbonyl group in ring B, while the stereochemistry of the EF ring system could be installed by a challenging/critical late-stage α,β-reduction of an exceptionally hindered diene ester (**2**). The secondary hydroxyl in ring C could in turn be generated via a Tamao−Kumada[7] oxidation of the siloxane ring, while construction of ring F would entail an aldol condensation, simplifying the structure to **3**, the latter accessible from **4** via a cyclopentenone annulation involving a Stille carbonylation[8]/Nazarov cyclization[9] sequence. Continuing with this analysis, tetracycle **4** could be accessed through elaboration of bicyclic ester **5**, anticipated to be the product of an intramolecular Diels−Alder (IMDA) reaction.[10] The requisite IMDA triene, in turn, would arise via union of enantiomerically pure homoallylic alcohol **6** and known silyl acrylate **7**.[11]

The synthesis of (−)-calyciphylline N (**1**) began with alcohol (−)-**8** (Scheme 1), prepared in three steps from commercially available *p*-tolylacetic acid.[12] Birch reduction[13] readily furnished the desired cyclohexadiene; olefin isomerization with KO*t*-Bu in DMSO[14] then provided an inseparable mixture (3.5:1) of the 1,3- and 1,4-dienes **6** and (−)-**9**, respectively, in excellent yield. Silyl acrylate **7**, obtained via oxidative hydrosilylation of ethyl acrylate with phenyldimethylsilane,[11] was subsequently appended, employing a method introduced by Sieburth.[15] To this end, treatment of **7** with TfOH at 0 °C, followed by sequential

Received: November 12, 2013
Published: December 9, 2013

   dx.doi.org/10.1021/ja411539w | *J. Am. Chem. Soc.* 2014, 136, 870−873

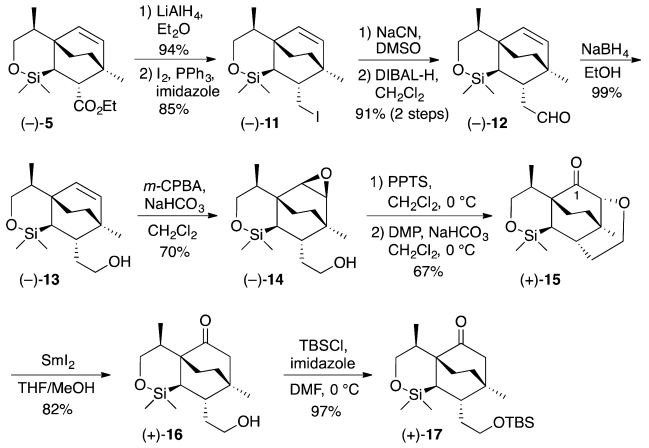
Scheme 1



addition of pyridine and the mixture of the alcohols **6** and (−)-**9** at −78 °C, led to the requisite triene **10** for the IMDA reaction. However, due to the instability of **10** toward silica gel chromatography, the mixture was carried forward without purification. Interestingly, while the thermal Diels−Alder reaction led to a mixture of all possible diastereomers (as determined by ^{1}H NMR), we were pleased to discover that the Et_2AlCl-promoted cyclization provided a 9:1 mixture of diastereomers in favor of the desired cycloadduct (−)-**5**.

One-carbon homologation of (−)-**5** to alcohol (−)-**13** (Scheme 2) was next achieved by $LiAlH_4$ reduction and

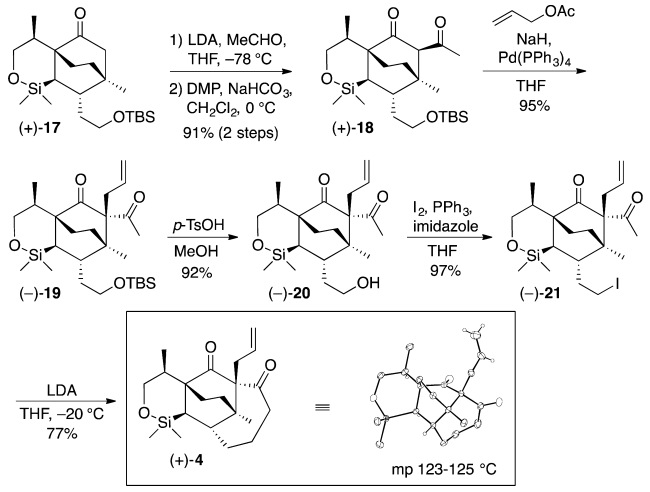
Scheme 2



conversion to the corresponding iodide (−)-**11**, followed by cyanide displacement and a two-step reduction of the resulting nitrile. The overall yield for the five steps was 65%. Epoxidation of the olefin in (−)-**13** with *m*-CPBA then led to (−)-**14** as a single diastereomer in 70% yield. Installation of the C_1 ketone was next achieved in two steps and 67% yield via an acid-promoted epoxide opening and oxidation of the resulting secondary alcohol, employing Dess−Martin periodinane (DMP),[16] to deliver (+)-**15**. Reductive cleavage of the tetrahydropyran ring with SmI_2 in a mixture of THF/MeOH then led to hydroxy ketone (+)-**16** in 82% yield,[17] the primary alcohol of which was protected as the TBS ether (TBSCl/imidazole in DMF) to provide (+)-**17**.

Elaboration of the requisite side chain for eventual construction of ring D called for introduction of disubstitution α to the carbonyl in ketone (+)-**17** (Scheme 3). Initially, (+)-**17** proved unreactive toward standard acylating agents (EtOAc, Ac_2O, 1-acetyl-imidazole, etc.) employing the lithium, potassium, or sodium enolates, with the exception of AcCl, which led to complex mixtures of C- and O-acylated products. However, an LDA-mediated aldol reaction with acetaldehyde, followed without purification by DMP oxidation of the β-

Scheme 3



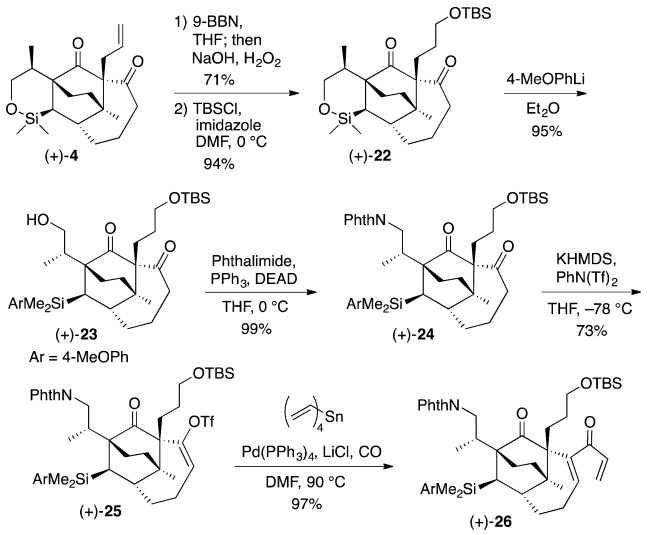
hydroxy ketone, provided diketone (+)-**18** in 91% yield for the two steps.[18] Introduction of the allyl group via the Tsuji−Trost allylation[19] then furnished (−)-**19** as a single diastereomer (95%), which upon exposure to catalytic *p*-TsOH in MeOH cleanly led to the corresponding alcohol (−)-**20**; the latter converted to primary iodide (−)-**21** in 97% yield. Pleasingly, transannular cyclization utilizing LDA delivered tetracycle (+)-**4** as a crystalline solid (mp 123−125 °C), completing the construction of ring D. Interestingly, use of NaHMDS led only to elimination of the iodide. Single-crystal X-ray analysis of (+)-**4** confirmed the structure, as well as the relative and absolute configurations.

Before turning to elaboration of the eastern hemisphere, we investigated the proposed Tamao−Kumada[7] oxidation of the siloxane ring in (+)-**4**. Unfortunately, the siloxane was found to be completely inert to the oxidation. Standard conditions (various fluoride sources, H_2O_2, and bicarbonate salts)[7,20] led only to the recovery of starting material, while strongly basic conditions[21] resulted in decomposition. Curiously, the use of TBAF (with or without oxidant) resulted in desilylation rather than oxidation.[22] Attempts to transform the siloxane to a more reactive silane (e.g., silyl halide or hydride)[23] prior to oxidation also proved unrewarding. Earlier studies, however, had demonstrated that a similar siloxane was a substrate for nucleophilic ring-opening at the Si−O bond upon treatment with aryllithium reagents. Such reactivity was recently employed for the development of siloxanes as recoverable transfer agents in Pd-catalyzed cross-coupling reactions.[24] We surmised that an arylsilane could be converted to the corresponding alcohol via the Fleming modification[26] of the Tamao−Kumada oxidation.

With these earlier observations in mind, attempted siloxane opening in (+)-**4** resulted in partial isomerization of the terminal alkene (not shown). We therefore functionalized the allyl group before moving forward (Scheme 4). Brown hydroboration (9-BBN) and oxidation (NaOH and H_2O_2)[25] delivered the expected primary alcohol in 71% yield. Protection of the alcohol with TBSCl then furnished (+)-**22** in 94% yield. Pleasingly, the siloxane could now be converted to arylsilane (+)-**23** in excellent yield by treatment with 4-methoxyphenyl-lithium at room temperature. Selection of the methoxyphenyl substituent was in anticipation of greater reactivity toward the protodesilylation step of the Fleming−Tamao oxidation.[26] Notably, both hindered carbonyls in (+)-**22** remained

dx.doi.org/10.1021/ja411539w | J. Am. Chem. Soc. 2014, 136, 870−873

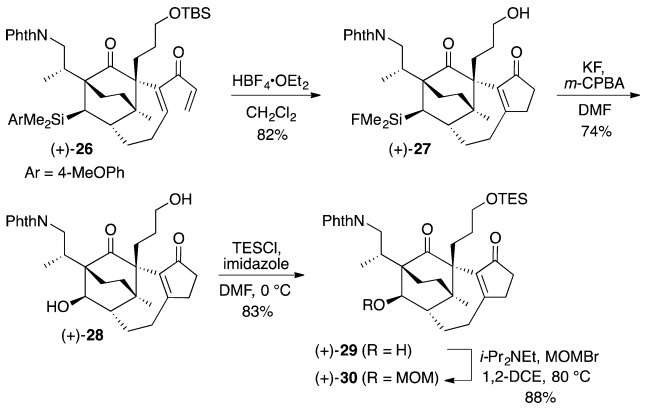
Scheme 4



completely inert to nucleophilic addition. Moving forward, rather than protect the newly generated primary alcohol, we introduced the requisite nitrogen with protection via treatment of (+)-**23** with phthalimide under Mitsunobu conditions[27] to provide (+)-**24** in 99% yield.

Turning to construction of ring E via the proposed Stille carbonylation[8]/Nazarov[9] cyclization sequence, exposure of (+)-**24** to KHMDS in the presence of $PhN(Tf)_2$ at −78 °C furnished vinyl triflate (+)-**25**, which underwent a highly efficient Stille carbonylation in DMF at 90 °C, employing only 1 atm. of CO, to provide dienone (+)-**26** in 97% yield. Given that both Nazarov cyclizations and protodesilylations can be achieved with protic acid,[9,26] we reasoned that both transformations could be accomplished in the same flask. Indeed, treatment of (+)-**26** with $HBF_4{\cdot}OEt_2$ at ambient temperature directly furnished silyl fluoride (+)-**27** in 82% overall yield (Scheme 5). Under these conditions, the primary TBS group

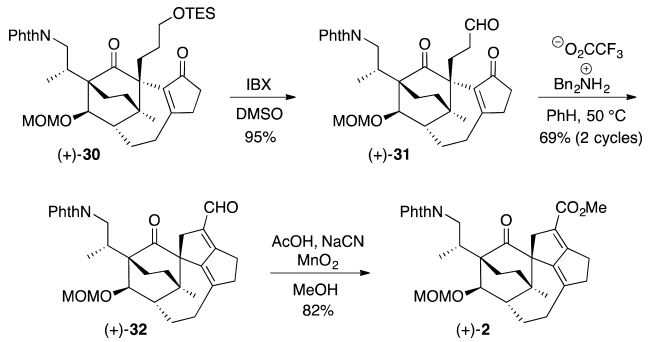
Scheme 5



was also removed. We were also pleased to discover that treatment of (+)-**27** with KF and *m*-CPBA in DMF resulted in the successful Fleming−Tamao oxidation to diol (+)-**28** in 74% yield. Differentiation of the alcohols was then realized via chemoselective protection of the primary alcohol as the TES ether, followed by MOM protection of the secondary alcohol to afford protected diol (+)-**30**.

Next, oxidative removal of the TES ether with IBX (Scheme 6) directly provided aldehyde (+)-**31** in excellent yield.[28] The

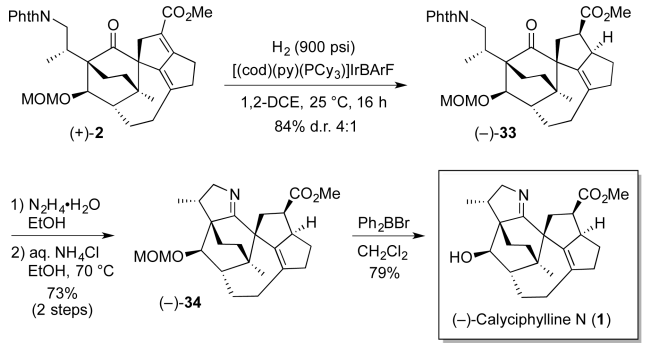
Scheme 6



requisite aldol condensation to prepare (+)-**32** was then achieved employing the conditions reported by Weiss and Carreira ($Bn_2NH_2O_2CCF_3$, PhH, 50 °C) in their synthesis of (+)−daphmanidin E.[3]

Turning to the critical 1,4-reduction of the conjugated diene in (+)-**32**, extensive experimentation on a less advanced aldehyde revealed a set of conditions involving the combination of $ZnCl_2$, Ph_2SiH_2, and catalytic $Pd(PPh_3)_4$[29] as uniquely effective (see Supporting Information). Unfortunately, when applied to (+)-**32**, this reduction protocol resulted only in decomposition. Undeterred, aldehyde (+)-**32** was oxidized to methyl ester (+)-**2** (AcOH, NaCN, MeOH, then MnO_2) via the method of Corey.[30] A screen of cationic hydrogenation catalysts was next explored with the intent of directing the hydrogenation to the α,β-olefinic bond. Pleasingly, the BArF analogue of the Crabtree catalyst,[31] developed by Wuestenberg and Pfaltz,[32] employing 900 psi of H_2 pressure, proved effective in reducing (+)-**2** to furnish a mixture (4:1) of diastereomers in 84% yield (Scheme 7). Detailed 2D NMR analysis revealed the

Scheme 7



major diastereomer to be (−)-**33**. This transformation, possibly directed by the C_1 carbonyl in (+)-**2**, should prove useful in accessing natural congeners bearing the same monounsaturated DEF ring system (Figure 1).

Exposure of (−)-**33** to hydrazine in EtOH led cleanly to removal of the phthalimide. Ring A construction involving imine formation was then readily achieved by heating the resulting amine with aqueous NH_4Cl (sat.) in EtOH at 70 °C.[3] Completion of the total synthesis of (−)-calyciphylline N entailed treatment of (−)-**34** with Ph_2BBr[33] to remove the MOM acetal. Totally synthetic (−)-calyciphylline N displayed

dx.doi.org/10.1021/ja411539w | J. Am. Chem. Soc. 2014, 136, 870−873

spectral properties in excellent agreement with those derived from the natural product [i.e., ^{1}H and ^{13}C NMR (500 and 125 MHz, respectively), HRMS parent ion identification, and chiroptic properties].

In summary, the first total synthesis of a member of the calyciphylline alkaloids, (−)-calyciphylline N (**1**), has been achieved with a longest linear sequence of 37 steps from known alcohol (−)-**8**. Application of the strategies presented herein for the synthesis of other members of the *Daphniphyllum* alkaloids continues in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details, spectra, and X-ray crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

smithab@sas.upenn.edu

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Financial support was provided by the National Institutes of Health (National Cancer Institute) through CA-19033. We also thank Drs. George Furst, Rakesh Kohli, and Patrick Carroll for help in obtaining high-resolution NMR, mass spectral, and X-ray crystallographic data, respectively.

■ REFERENCES

(1) Kobayashi, J.; Kubota, T. *Nat. Prod. Rep.* **2009**, *26*, 936.

(2) For recent synthetic studies, see: (a) Coldham, I.; Watson, L.; Adams, H.; Martin, N. G. *J. Org. Chem.* **2011**, *76*, 2360. (b) Darses, B.; Michaelides, I. N.; Sladojevich, F.; Ward, J. W.; Rzepa, P. R.; Dixon, D. J. *Org. Lett.* **2012**, *14*, 1684.

(3) For an elegant total synthesis of the closely related congener, (+)-daphmanidin E (Figure 1), see: Weiss, M. E.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2011**, *50*, 11501.

(4) For a very recent total synthesis of the *Daphniphyllum* alkaloid, daphenylline (Figure 1), see: Lu, Z. Y.; Li, Y.; Deng, J.; Li, A. *Nat. Chem.* **2013**, *5*, 679.

(5) Yahata, H.; Kubota, T.; Kobayashi, J. *J. Nat. Prod.* **2008**, *72*, 148.

(6) (a) daphmanidin A: Kobayashi, J.; Ueno, S.; Morita, H. *J. Org. Chem.* **2002**, *67*, 6546. (b) daphmanidin E: Morita, H.; Ishioka, N.; Takatsu, H.; Iizuka, T.; Kobayashi, J. *J. Nat. Prod.* **2006**, *69*, 418. (c) calyciphylline C: Saito, S.; Kubota, T.; Fukushi, E.; Kawabata, J.; Zhang, H.-P.; Kobayashi, J. *Tetrahedron Lett.* **2007**, *48*, 1587. (d) daphniyunnine A: Zhang, H.; Yang, S.-P.; Fan, C.-Q.; Ding, J.; Yue, J.-M. *J. Nat. Prod.* **2006**, *69*, 553. (e) daphenylline: Zhang, Q.; Di, Y.-T.; Li, C.-S.; Fang, X.; Tan, C.-J.; Zhang, Z.; Zhang, Y.; He, H.-P.; Li, S.-L.; Hao, X.-J. *Org. Lett.* **2009**, *11*, 2357.

(7) Tamao, K.; Ishida, N.; Tanaka, T.; Kumada, M. *Organometallics* **1983**, *2*, 1694.

(8) Merrifield, J. H.; Godschalx, J. P.; Stille, J. K. *Organometallics* **1984**, *3*, 1108.

(9) (a) Nazarov, I. N.; Zaretskaya, I. I.; Sorkina, T. I. *Zh. Obshch. Khim.* **1960**, *30*, 746. (b) Frontier, A. J.; Collison, C. *Tetrahedron* **2005**, *61*, 7577.

(10) (a) Roush, W. R. *J. Am. Chem. Soc.* **1978**, *100*, 3599. Also see: (b) Roush, W. R. *Comp. Org. Synth.*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991.

(11) Takeshita, K.; Seki, Y.; Kawamoto, K.; Murai, S.; Sonoda, N. *J. Org. Chem.* **1987**, *52*, 4864.

(12) (a) Mori, K. *Tetrahedron: Asymmetry* **2005**, *16*, 1721. (b) Yadav, J. S.; Basak, A. K.; Srihari, P. *Tetrahedron Lett.* **2007**, *48*, 2841.

(13) Birch, A. J. *J. Chem. Soc.* **1944**, 430.

(14) Pearson, D. E.; Buehler, C. A. *Chem. Rev.* **1974**, *74*, 45.

(15) Sieburth, S. M.; Lang, J. *J. Org. Chem.* **1999**, *64*, 1780.

(16) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277.

(17) Molander, G. A.; Hahn, G. *J. Org. Chem.* **1986**, *51*, 1135.

(18) Smith, A. B.; Levenberg, P. A. *Synthesis* **1981**, 567.

(19) (a) Trost, B. M.; Fullerton, T. J. *J. Am. Chem. Soc.* **1973**, *95*, 292. (b) Tsuji, J.; Takahash, H.; Morikawa, M. *Tetrahedron Lett.* **1965**, 4387.

(20) Tamao, K. *J. Syn. Org. Chem. Jpn.* **1988**, *46*, 861.

(21) Smitrovich, J. H.; Woerpel, K. A. *J. Org. Chem.* **1996**, *61*, 6044.

(22) A similar observation was noted in a recent total synthesis of Maoecrystal V: Lu, P.; Gu, Z.; Zakarian, A. *J. Am. Chem. Soc.* **2013**, *135*, 14552.

(23) Tamao, K.; Yamauchi, T.; Ito, Y. *Chem. Lett.* **1987**, 171.

(24) Smith, A. B.; Hoye, A. T.; Martinez-Solorio, D.; Kim, W. S.; Tong, R. B. A. *J. Am. Chem. Soc.* **2012**, *134*, 4533.

(25) Brown, H. C.; Knights, E. F.; Scouten, C. G. *J. Am. Chem. Soc.* **1974**, *96*, 7765.

(26) Fleming, I.; Henning, R.; Plaut, H. *J. Chem. Soc. Chem. Commun.* **1984**, 29.

(27) (a) Mitsunobu, O. *Synthesis* **1981**, 1. (b) Mitsunobu, O.; Yamada, M. *Bull. Chem. Soc. Jpn.* **1967**, *40*, 2380.

(28) Wu, Y. K.; Huang, J. H.; Shen, X.; Hu, Q.; Tang, C. J.; Li, L. *Org. Lett.* **2002**, *4*, 2141.

(29) Keinan, E.; Greenspoon, N. *J. Am. Chem. Soc.* **1986**, *108*, 7314.

(30) Corey, E. J.; Gilman, N. W.; Ganem, B. E. *J. Am. Chem. Soc.* **1968**, *90*, 5616.

(31) Crabtree, R. *Acc. Chem. Res.* **1979**, *12*, 331.

(32) Wuestenberg, B.; Pfaltz, A. *Adv. Synth. Catal.* **2008**, *350*, 174.

(33) Guindon, Y.; Yoakim, C.; Morton, H. E. *J. Org. Chem.* **1984**, *49*, 3912.