Organic LETTERS

Letter

pubs.acs.org/OrgLett

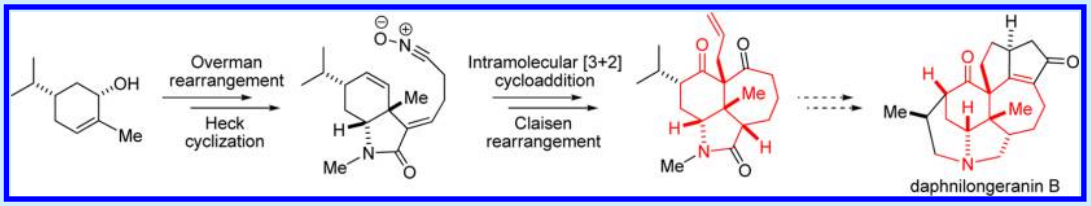
Asymmetric Synthesis of the Tricyclic Core of *Calyciphylline* A-Type Alkaloids via Intramolecular [3 + 2] Cycloaddition

Lu Wang,[†] Chen Xu,[†,§] Li Chen,[†] Xiaojiang Hao,*[,‡] and David Zhigang Wang*[,†]

[†]Laboratory of Chemical Genomics, School of Chemical Biology and Biotechnology, Shenzhen Graduate School of Peking University, Shenzhen 518055, China

[‡]Kunming Institute of Botany, Chinese Academy of Sciences, Kunming 650204, China

Supporting Information



ABSTRACT: Asymmetric synthesis of the [5−6−7] tricyclic system common to the *Calyciphylline* A-type alkaloids is reported, featuring Overman rearrangement, Heck cyclization, intramolecular [3 + 2] cycloaddition, diastereoselective hydrogenation, and Claisen rearrangement as strategic events. The approach is capable of installing the crucial carbonyl functionality as well as multiple stereogenic centers within a congested polycyclic ring skeleton.

Structurally complex natural products continuously serve as a powerful vehicle for the invention of novel synthetic strategies, and in such activities the desired stereochemical controls are frequently achieved through substrate-directed strategies enabled by structural characteristics of a synthetic target of interest. Among the numerous natural products uncovered in recent years, the *Daphniphyllum* alkaloids constitute a fascinating family due to their unusual polycyclic ring skeletons, stereochemical complexities,[1] and demonstrated bioactivities.[2]

Intrigued by their unprecedented structures as well as their scarce natural supply, we are particularly interested in chemical syntheses of the *Calyciphylline* A-type alkaloids within this family.[3] As highlighted in Figure 1, structural hallmarks of these substances are the shared [5−6−7] tricyclic framework possessing a carbonyl group as well as four contiguous stereogenic centers (two of which being quaternary) embedded in a highly congested ring system (in red). In our previous reports, we had described our developed strategies toward the tri- and tetracyclic skeletons of daphnilongeranin B (**1**), featuring sequentially Mannich condensation, [2 + 2] photochemical cycloaddition, and Grob fragmentation for the construction of A−C−D and A−B−C−D ring systems.[3f,k]

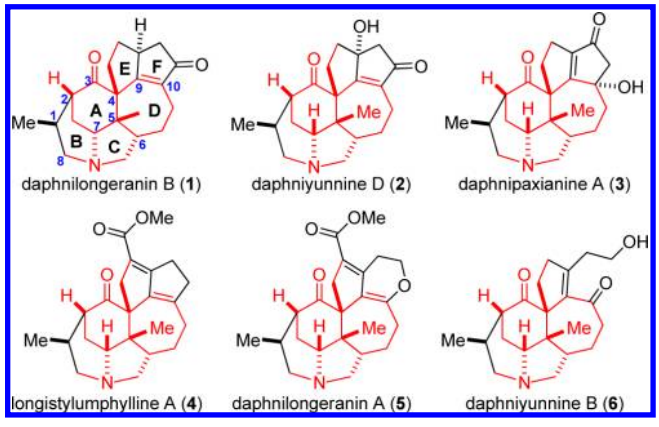


Figure 1. *Calyciphylline* A-class alkaloids featuring a common [5−6−7] tricyclic core and embedded carbonyl functionality.

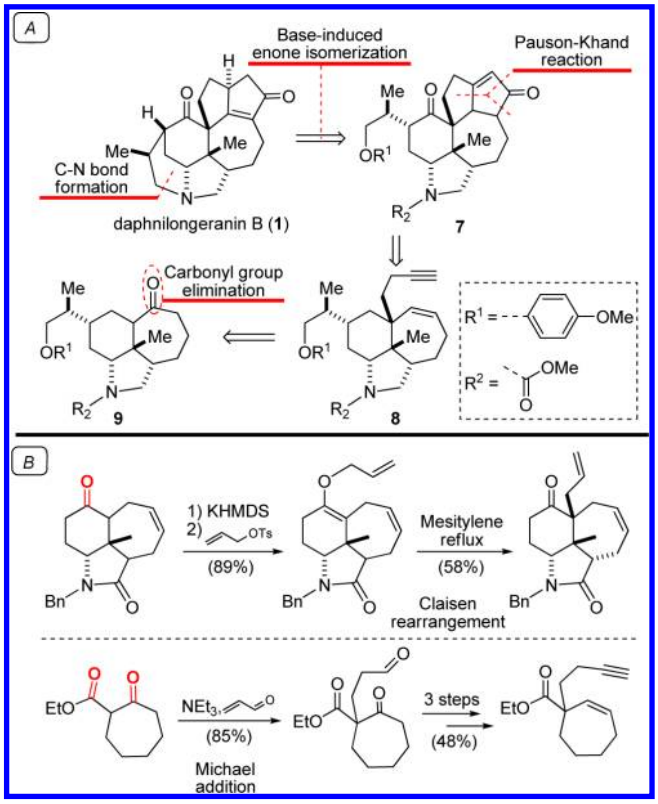
The previous lesson subsequently teaches a revised retrosynthetic analysis outlined herein. With daphnilongeranin B as the exemplary target, as illustrated in Scheme 1A, a sequence involving Pauson−Khand annulation followed by base-mediated enone isomerization[3j,s] and intramolecular S_N2 displacement[3k] would efficiently degrade the target into the tricyclic intermediate **9**, to which we have already established a facile access.[3f,k] Thus, our attention was next focused on installing the requisite carbonyl group on ring A and introducing the all-carbon quaternary functionalities at C_4.

It is notable that while our synthetic explorations are in progress,[3s] Dixon and co-workers described their syntheses of A−C−D and D−E−F tricyclic cores of *Calyciphylline* A-type alkaloids.[3i,j] As shown in Scheme 1B, the Claisen rearrangement[3i] as well as Michael addition[3j] used for installation of the critical functionalities at C_4 position are particularly inspiring for our investigation. Their work demonstrated that the carbonyl groups on ring A and ring D played important roles in construction of the E−F ring system through the intended Pauson−Khand event.

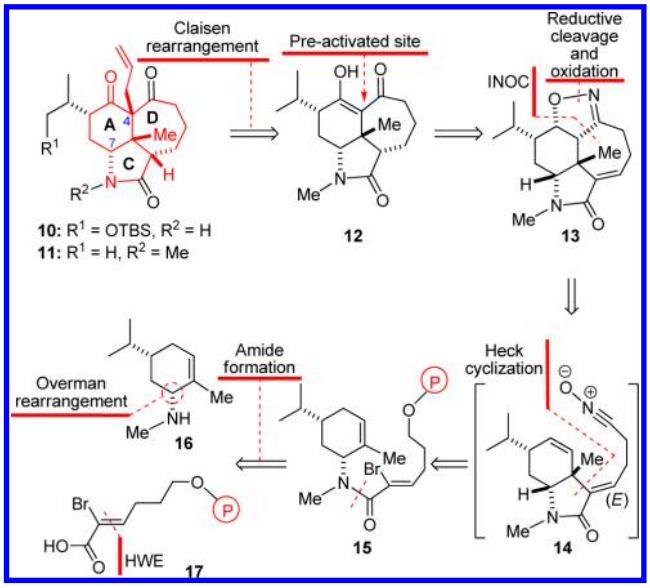
Received: December 13, 2013
Published: February 7, 2014

dx.doi.org/10.1021/ol403609c | *Org. Lett.* 2014, 16, 1076−1079

Scheme 1



Scheme 2. Retrosynthetic Analysis of the New Strategy



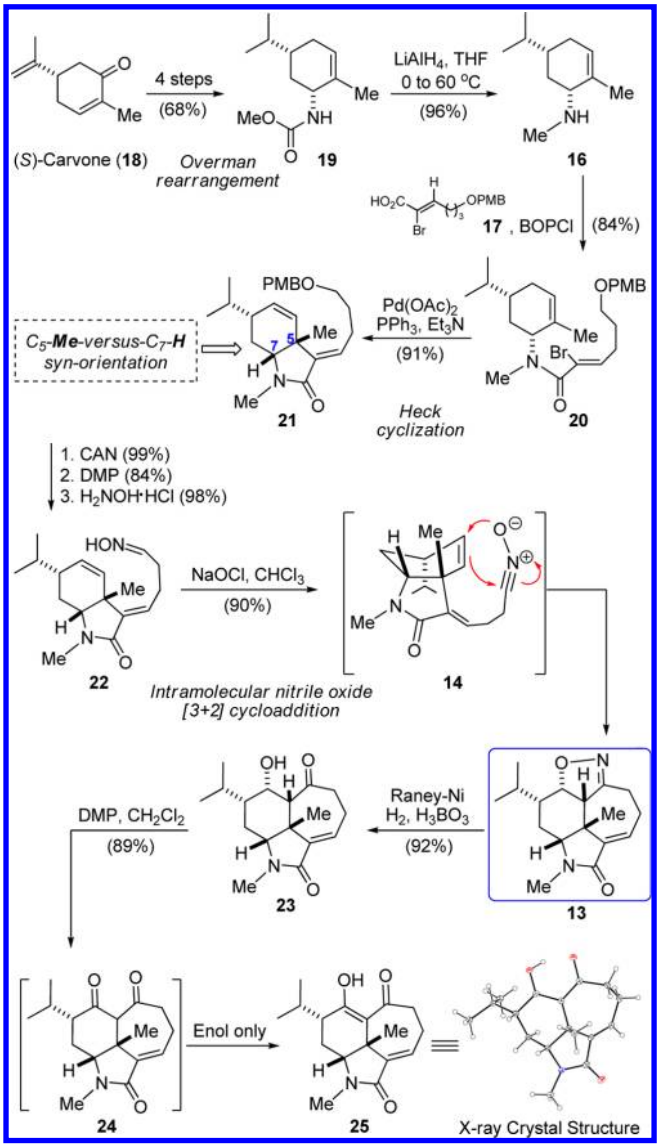
After numerous unsuccessful attempts to construct the C_4 quaternary center as well as exploring carbonyl-directed C−H oxidations at C_3,[4] we elected to proceed through a revised new scenario for *simultaneous entries to both of the ring skeleton and the embedded carbonyl functionality*. For this purpose, a tricyclic diketone **10** and its simplified analogue **11** thus constituted an ideal platform for examining the feasibility of the proposed strategies. We envisioned that the terminal alkene could be transformed into the requisite alkyne[5,3j,p] and the carbonyl group on ring D could be selectively converted to an olefin,[6] which would set the stage for Pauson−Khand annulation to furnish the E−F ring system (Scheme 1A).

As shown in Scheme 2, we envisioned that the stereogenicity at C_4 could be installed via a substrate-directed Claisen rearrangement.[5,3i] The seven-membered ring D and both of the carbonyl groups in **11** could be accessed with an intramolecular nitrile oxide cycloaddition (INOC)[7] followed by reductive cleavage of the N−O bond and oxidation of the resulting secondary alcohol. With C_7 chirality as a critical stereochemical control element, the five-membered C ring as well as the C_5 all-carbon quaternary center could be established by a stereoselective Heck reaction of bromide **15**, from which the released double bond moiety would provide the needed alkenyl partner to engage on the subsequent INOC process. The precursor **15** would next be assembled by an amide formation event between enantiopure allylic amine **16** and unsaturated carboxylic acid **17**. Finally, the key C_7-chirality in **16** could be introduced by an Overman rearrangement established in our previous synthetic routes and, through a series of substrate-directed stereochemical controls, it would serve as the foundation for securing all of the rest stereogenicities present in the target compound **1**.[3f,k] Notably, within this scenario, a (*Z*)-conjugated carboxylic acid **17** must be employed for the delivery of (*E*)-*exo*-trisubstituted double bond in **14** that should facilitate the intended INOC event.[8]

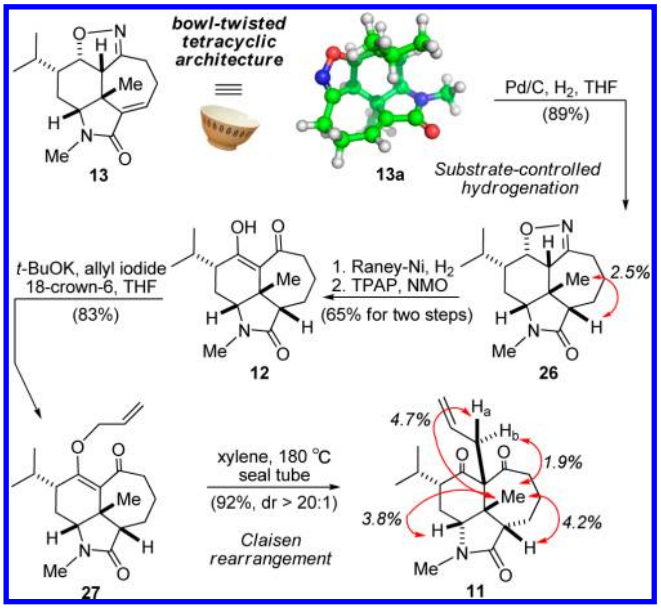
As summarized in Scheme 3, (*S*)-carvone was converted into carbamate **19** with a series of known procedures involving an Overman rearrangement,[3f] thus establishing the original chirality in the target, in a combined yield of 68% over the four-step sequence. $LiAlH_4$ reduction of **19** then gave allylic amine **16** in nearly quantitative yield. Condensation of amine **16** with unsaturated acid **17** afforded amide **20**, the precursor for the key Heck cyclization, in 84% isolated yield. The initial reaction condition screenings involving the use of 10 mol % of $Pd(OAc)_2$ as precatalyst, 20 mol % of BINAP as ligand, and 5 equiv of Et_3N as base and revealed a significant solvent effect: while the use of MeOH, EtOH, toluene, or THF led to low product yields (0−37%), the use of CH_3CN and DMF promoted a remarkable improvement (78% and 83% yield, respectively). The use of simpler PPh_3 in place of bidentate BINAP enhanced further the yield of **21** to 91% when the Heck cyclization was performed at 100 °C in DMF. The C_5-**Me** and C_7-**H** were confirmed to adopt spatially a *syn*-orientation (NOESY). Compound **21** was next transformed into oxime **22** in very high yield by sequential oxidative removal of the PMB group, oxidation of the alcohol, and condensation with hydroxylamine. Delightfully, upon exposure to the oxidant NaOCl, **22** underwent smoothly intramolecular 1,3-dipolar cycloaddition via the nitrile oxide intermediate **14** to afford the tetracyclic isoxazoline **13** as a single diastereomer[12] and in excellent isolated yield (90%). The facile formation of **13** laid the foundation for not only constructing the seven-membered D ring but also site-specific functionalization on the C_3-carbon in the six-membered A ring. With **13** in hand, an appropriate reaction condition for effecting the N−O bond cleavage was then investigated. The use of activated zinc,[7a] molybdenum hexacarbonyl,[9a] Fe/NH_4Cl,[9b] and samarium diiodide[9c] all failed to produce the desired product. A notable improvement while using Raney nickel/H_3BO_3[10] in place of Pd/C[9d] was next observed, leading to the hydroxy ketone **23** in 92% yield upon hydrogenolysis at 45 °C for 8 h in an optimal solvent mixture of MeOH and H_2O (in 5:1 volume ratio). Compound **23** was readily oxidized by Dess−Martin periodinane via a 1,3-diketone intermediate **24** to exclusively generate enol **25**, whose

dx.doi.org/10.1021/ol403609c | *Org. Lett.* 2014, 16, 1076−1079

Scheme 3. Synthesis of the [5−6−7] Tricyclic Skeleton 25



Scheme 4. Synthesis of the Tricyclic Skeleton 11



structure and stereochemistry were established by X-ray crystallographic analysis.[11]

The above success prompted us to progress further to the synthesis of the tricyclic system **11** (Scheme 4).

Considering both reactivity and stereoselectivity in the bowl-shaped architecture disclosed in our previous work,[3k] we believed that the tetracyclic core **13** (see the 3D structure of **13a** in Scheme 4) was the appropriate substrate for installing the correct chiral center at C_6. To our delight, upon exposure to simple Pd/C hydrogenation conditions, **26** was obtained in 89% yield as a single isomer.[12] Treatment of **26** with Raney nickel protocol followed by oxidation with TPAP exclusively afforded enol **12**. The enolic double bond was determined to reside within the six-membered ring A on the basis of 2D NMR spectroscopic analysis, which was consistent with the structure of **25**.[12] The resulting enol **12** was subjected to allylation with *t*-BuOK, [18]crown-6,[13] and allyl iodide to give the corresponding allyl enol ether **27** (83%), which in turn underwent Claisen rearrangement at 180 °C in xylene to afford ketone **11** in excellent selectivity and yield (dr >20:1, 92%). The stereochemistry of compound **11** was clearly manifested via 2D-NMR study and their nuclear Overhauser effect (NOE) correlations.[12]

In summary, a concise and fully stereochemically controlled synthetic route to the [5−6−7] tricyclic framework of the *Daphniphyllum* subclass *Calyciphylline* A-type alkaloids has been demonstrated. Success hinged on such key events as Heck cyclization to install a congested quaternary stereogenic center, an intramolecular nitrile oxide [3 + 2] cycloaddition to deliver both seven-membered ring and the crucial carbonyl functionalities, diastereoselective hydrogenation to furnish a *cis*-[5−7] ring junction, and a late-stage Claisen rearrangement to yield allyl-substituted 1,3-diketone amendable for further structural editing toward Pauson−Khand annulation. Further studies directed toward enantioselective total synthesis of certain members of these alkaloids are currently underway in our laboratories.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, X-ray crystallographic analysis, and ^{1}H and ^{13}C NMR spectra for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: haoxj@mail.kib.ac.cn.
*E-mail: dzw@pkusz.edu.cn.

Present Address

[§]Division of Chemistry and Chemical Engineering, California Institute of Technology, Mail Code 101-20, 1200 E California Blvd, Pasadena, CA 91125.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the National Science Foundation of China (Grant Nos. 21290183, 21272014, and 20972008 to D.Z.W. and 20672160 to X.J.H.), the national "973 Project" of the State

Ministry of Science and Technology (Grant Nos. 2012CB722602 and 2010CB833200), and the Shenzhen Bureau of Science and Technology for financial support. We also thank Mr. Bo Zhang (Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, Shanghai) for helpful discussions.

REFERENCES

(1) Kobayashi, J.; Kubota, T. *Nat. Prod. Rep.* **2009**, *26*, 936.
(2) (a) Zhang, Y.; He, H.; Di, Y.; Mu, S.; Wang, Y.; Wang, J.; Li, C.; Kong, N.; Gao, S.; Hao, X. *Tetrahedron Lett.* **2007**, *48*, 9104. (b) Yamamura, S.; Hirata, Y. *Tetrahedron Lett.* **1974**, *15*, 2849. (c) Saito, S.; Yahata, H.; Kubota, T.; Obara, Y.; Nakahata, N.; Kobayashi, J. *Tetrahedron* **2008**, *64*, 1901.
(3) For recent synthetic approaches to daphniphyllum alkaloids, see: (a) Solé, D.; Urbaneja, X.; Bonjoch, J. *Org. Lett.* **2005**, *7*, 5461. (b) Denmark, S. E.; Baiazitov, R. Y. *J. Org. Chem.* **2006**, *71*, 593. (c) Ikeda, S.; Shibuya, M.; Kanoh, N.; Iwabuchi, Y. *Org. Lett.* **2009**, *11*, 1833. (d) Dunn, T. B.; Ellis, J. M.; Kofink, C. C.; Manning, J. R.; Overman, L. E. *Org. Lett.* **2009**, *11*, 5658. (e) Coldham, I.; Burrell, A. J. M.; Guerrand, H. D. S.; Oram, N. *Org. Lett.* **2011**, *13*, 1267. (f) Xu, C.; Liu, Z.; Wang, H.; Zhang, B.; Xiang, Z.; Hao, X.; Wang, D. Z. *Org. Lett.* **2011**, *13*, 1812. (g) Bélanger, G.; Boudreault, J.; Lévesque, F. *Org. Lett.* **2011**, *13*, 6204. (h) Coldham, I.; Watson, L.; Adams, H.; Martin, N. G. *J. Org. Chem.* **2011**, *76*, 2360. (i) Sladojevich, F.; Michaelides, I. N.; Darses, B.; Ward, J. W.; Dixon, D. J. *Org. Lett.* **2011**, *13*, 5132. (j) Darses, B.; Michaelides, I. N.; Sladojevich, F.; Ward, J. W.; Rzepa, P. R.; Dixon, D. J. *Org. Lett.* **2012**, *14*, 1684. (k) Xu, C.; Wang, L.; Hao, X.; Wang, D. Z. *J. Org. Chem.* **2012**, *77*, 6307. (l) Feng, B.; Zheng, H.; Zhao, C.; Jing, P.; Li, H.; Xie, X.; She, X. *J. Org. Chem.* **2012**, *77*, 8367. (m) Yang, M.; Wang, L.; He, Z.; Wang, S.; Zhang, S.; Tu, Y.; Zhang, F. *Org. Lett.* **2012**, *14*, 5114. (n) Yao, Y.; Liang, G. *Org. Lett.* **2012**, *14*, 5499. (o) Hanessian, S.; Dorich, S.; Menz, H. *Org. Lett.* **2013**, *15*, 4134. For the total syntheses of these alkaloids, see: (p) Weiss, M. E.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2011**, *50*, 11501. (q) Lu, Z.; Li, Y.; Deng, J.; Li, A. *Nature Chem* **2013**, *5*, 679. (r) Shvartsbart, A.; Smith, A. B. *J. Am. Chem. Soc.* **2014**, *136*, 870. (s) Liu, Z.; Xu, C.; Zhang, B.; Wang, H.; Xiang, Z.; Hao, X.; Wang, D. Z. *The 241st Anaheim ACS National Meeting*, 2011, poster number 18339. (t) Xiong, X.; Li, Y.; Lu, Z.; Wan, M.; Deng, J.; Wu, S.; Shao, H.; Li, A. *Chem. Commun.* **2013**, DOI: 10.1039/C3CC47873D.
(4) Details of such attempts are compiled in the Supporting Information.
(5) Shimizu, Y.; Kuramochi, A.; Usuda, H.; Kanai, M.; Shibasaki, M. *Tetrahedron Lett.* **2007**, *48*, 4173.
(6) (a) Peese, K. M.; Gin, D. Y. *Org. Lett.* **2005**, *7*, 3323. (b) Shimada, N.; Hanari, T.; Kurosaki, Y.; Takeda, K.; Anada, M.; Nambu, H.; Shiro, M.; Hashimoto, S. *J. Org. Chem.* **2010**, *75*, 6039.
(7) For some selected reports on INOC, see: (a) Yokoshima, S.; Ueda, T.; Kobayashi, S.; Sato, A.; Kuboyama, T.; Tokuyama, H.; Fukuyama, T. *J. Am. Chem. Soc.* **2002**, *124*, 2137. (b) Bode, J. W.; Fraefel, N.; Muri, D.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2001**, *40*, 2082. (c) Kozikowski, A. P.; Stein, P. D. *J. Am. Chem. Soc.* **1982**, *104*, 4023. (d) Muri, D.; Carreira, E. M. *J. Org. Chem.* **2009**, *74*, 8695. (e) Wollenberg, R. H.; Goldstein, J. E. *Synthesis* **1980**, 757. (f) Cheng, G.; Wang, X.; Zhu, R.; Shao, C.; Xu, J.; Hu, Y. *J. Org. Chem.* **2011**, *76*, 2694. (g) Bode, J. W.; Carreira, E. M. *J. Am. Chem. Soc.* **2001**, *123*, 3611. For use of a carbonyl-conjugated alkene to construct a seven-membered ring, see: (h) Frie, J.; Jeffrey, C. S.; Sorensen, E. J. *Org. Lett.* **2009**, *11*, 5394.
(8) For details of the synthetic explorations of (*Z*)-type acid **17** and its analogues, see theSupporting Information.
(9) (a) Baraldi, P. G.; Barco, A.; Benetti, S.; Manfredini, S.; Simoni, D. *Synthesis* **1987**, 276. (b) Jiang, D.; Chen, Y. *J. Org. Chem.* **2008**, *73*, 9181. (c) Bode, J. W.; Carreira, E. M. *Org. Lett.* **2001**, *3*, 1587. (d) Cheng, G.; Wang, X.; Bao, H.; Cheng, C.; Liu, N.; Hu, Y. *Org. Lett.* **2012**, *14*, 1062.
(10) (a) Curran, D. P. *J. Am. Chem. Soc.* **1982**, *104*, 4024. (b) Curran, D. P. *J. Am. Chem. Soc.* **1983**, *105*, 5826.
(11) The crystal structure of **25** was deposited at the Cambridge Crystallographic Data Centre (tracking no. 951031).
(12) For detailed NMR spectroscopic analysis, see the Supporting Information.
(13) 18-Crown-6 was obtained from Adamas-beta Chemical Company (Switzerland).