**Natural Products**

Deutsche Ausgabe: DOI: 10.1002/ange.201602439
Internationale Ausgabe: DOI: 10.1002/anie.201602439

# Total Syntheses of Periconiasins A–E

*Chong Tian, Xiaoqiang Lei, Yuanhao Wang, Zhen Dong, Gang Liu,* and Yefeng Tang**

*Dedicated to Professor K. C. Nicolaou on the occasion of his 70th birthday*

**Abstract:** *The first and collective total syntheses of periconiasins A–E, a group of naturally occurring cytochalasans, were achieved by a series of rationally designed or bioinspired transformations. Salient features of the syntheses include a tandem aldol condensation/Grob fragmentation to assemble the linear polyketide–amino acid hybrid precursor, a Diels–Alder macrocylization to construct the 9/6/5 tricyclic core of periconiasins A–C, and a transannular carbonyl–ene reaction to forge the polycyclic framework of periconiasins D and E.*

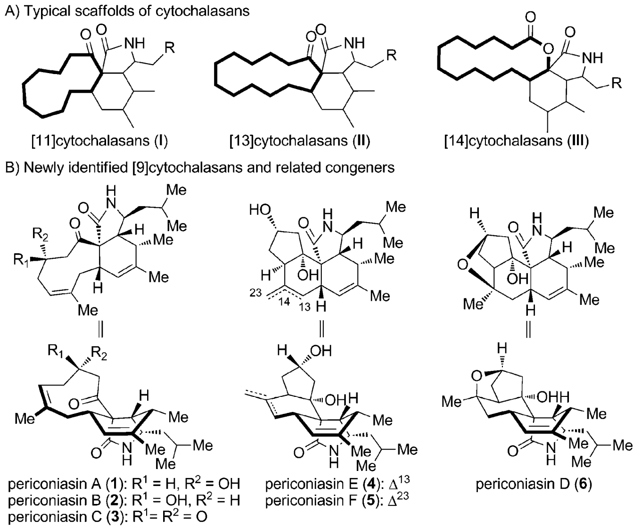


*Figure 1.* Structures of the cytochalasans.

Cytochalasans comprise a growing family of polyketide–amino acid hybrid metabolites with over 200 members having been identified to date.[1,2] Owing to their remarkable structural and biological diversity, they have emerged as ambitious targets for total syntheses and important chemical tools for biomedical studies.[3,4] Structurally, most cytochalasans feature a tricyclic skeleton with a macrocycle fused to an isoindolone moiety, as illustrated by the structures **A**–**C** in Figure 1 A. Notably, the macrocycles presented in the cytochalasans are generally 11/13-membered carbocyclic or 12/14-membered lactone rings. Comparably, cytochalasans bearing a medium-size ring had not been discovered until 2013 when periconiasins A–C (**1**–**3**; Figure 1 B) were identified by Dai and co-workers from the endophytic fungus *periconia sp. F-31*.[5] **1**–**3** possess an unprecedented 9/6/5 tricyclic framework which constitutes a new subclass of cytochalasans. More interestingly, several structurally relevant congeners were also disclosed by the same laboratory in 2015,[6] as exemplified by periconiasins D–F (**4**–**6**). Distinct from previously identified cytochalasans, **4**–**6** possess highly complex polycyclic architectures embracing multiple stereogenic centers, which largely enrich the chemodiversity of the cytochalasan family. Equally noteworthy is the fact that some members of the periconiasins (e.g., **1** and **2**) display selective and potent cytotoxicity against the HCT-8 and BGC-823 cell lines,[5] thus representing excellent lead compounds for anticancer drug development. The intriguing structures of **1**–**6** combined with their promising biological profiles render them attractive but unexplored synthetic targets. Herein, we report the first and collective total syntheses of periconiasins A–E (**1**–**4**, **6** through a highly efficient and biomimetic strategy.

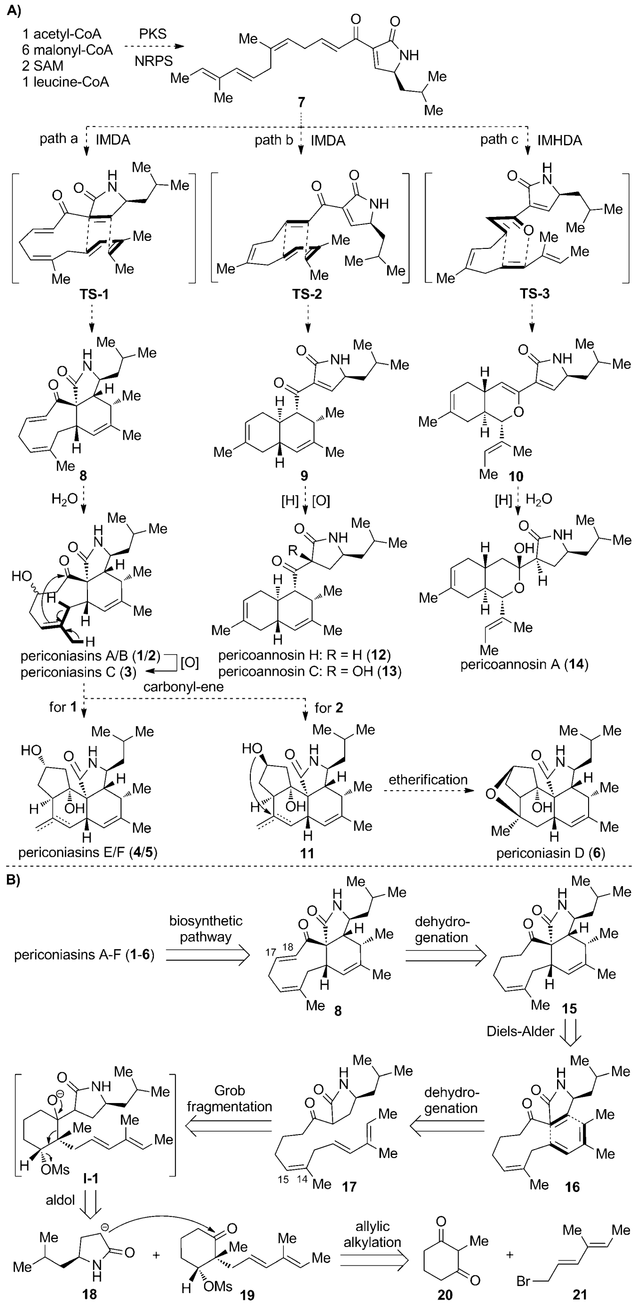
Our synthetic plan for **1**–**6** was inspired by their plausible biosynthetic origin.[5,6] As depicted in Scheme 1 A, it is believed that **1**–**6** should stem from a common linear precursor (**7**) which, in turn, could be assembled from some elementary building blocks by a polyketide synthase/non-ribosomal peptide synthetase (PKS-NRPS) hybrid machinery. Starting from **7**, an intramolecular Diels–Alder (IMDA) reaction could take place via transition-state **TS-1** to afford the tricyclic intermediate **8**, which would then advance to **1** and **2** by oxa-Michael addition (path a). Subsequently, **1** and **2** could be transformed to **3** by oxidation. Besides, they could also undergo a transannular carbonyl–ene reaction to yield **4**/**5** and their C17 epimer (**11**), respectively. Eventually, **11** could be converted into **6** by intramolecular etherification.

Apparently, it is a wise option for synthetic chemists to make the targets **1**–**6** by mimicking nature's synthesis. However, the realization of such a biomimetic synthesis may encounter considerable challenges, particularly in terms of the Diels–Alder reaction leading to the tricyclic compound **8**. Although Diels–Alder macrocyclizations have been applied to the syntheses of some other members of the

---

[*] C. Tian, X. Lei, Y. Wang, Z. Dong, Prof. Dr. G. Liu, Prof. Dr. Y. Tang
School of Pharmaceutical Sciences & Comprehensive AIDS Research Center, Tsinghua University, Beijing 100084 (China)
E-mail: gangliu27@tsinghua.edu.cn
yefengtang@tsinghua.edu.cn
C. Tian, Prof. Dr. G. Liu
Tsinghua-Peking Center for Life Sciences, School of Life Sciences, Tsinghua University, Beijing 100084 (P.R. China)
Prof. Dr. Y. Tang
Collaborative Innovation Center for Biotherapy, State Key Laboratory of Biotherapy and Cancer Center, West China Hospital, West China Medical School, Sichuan University, Chengdu 610041 (China)

Supporting information and the ORCID identification number(s) for the author(s) of this article can be found under http://dx.doi.org/10.1002/anie.201602439.

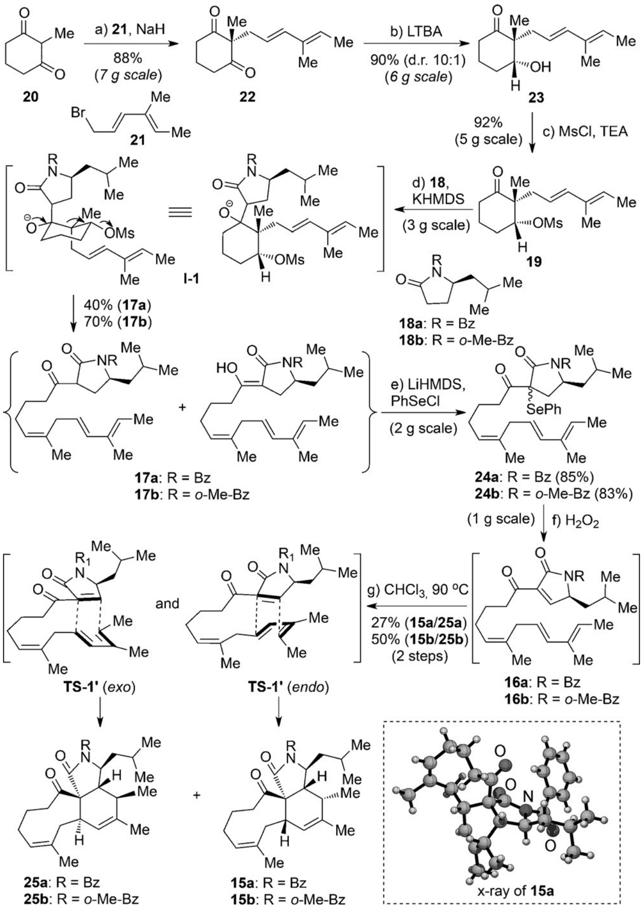


*Scheme 1.* A) Proposed biogenesis of periconiasins. B) Retrosynthetic analysis of periconiasins.

cytochalasans,[4b,k–m] the current approach has two competitive pathways as shown in paths b and c (Scheme 1 A). Indeed, as a versatile precursor, **7** could also evolve into the 6/6 bicyclic compounds **9** and **10** by two other Diels–Alder reactions. These processes may account for the biogenesis of pericoannosins, a group of natural products identified along with periconiasins from the same species.[6,7] While nature elegantly makes periconiasins and pericoannosins from a common precursor by divergent Diels–Alder reactions, presumably by means of enzyme catalysis, controlling the chemoselectivity of such processes poses a formidable challenge for synthetic chemists.

Keeping the above concern in minds, our retrosynthetic analysis for **1**–**6** is shown in Scheme 1 B. We envisioned that **1**–**6** could be derived from the common tricyclic precursor **8** following the biosynthetic proposal. Since direct access of **8** from **7** by a Diels–Alder reaction might suffer from the underlying selectivity issue, we intended to achieve this goal through an alternative way, wherein **8** could be first traced back to **15** by dehydrogenation, and the latter would then arise from **16** by a Diels–Alder reaction. As a continuation of the retrosynthesis, **16** could be obtained from the fragments **18** and **19** by tandem aldol condensation/Grob fragmentation[8] followed by dehydrogenation. Finally, both **18** and **19** could be prepared from readily accessible material according to known methods.

Our study commenced from the synthesis of **19** (Scheme 2). Alkylation of 2-methylcyclohexane-1,3-dione

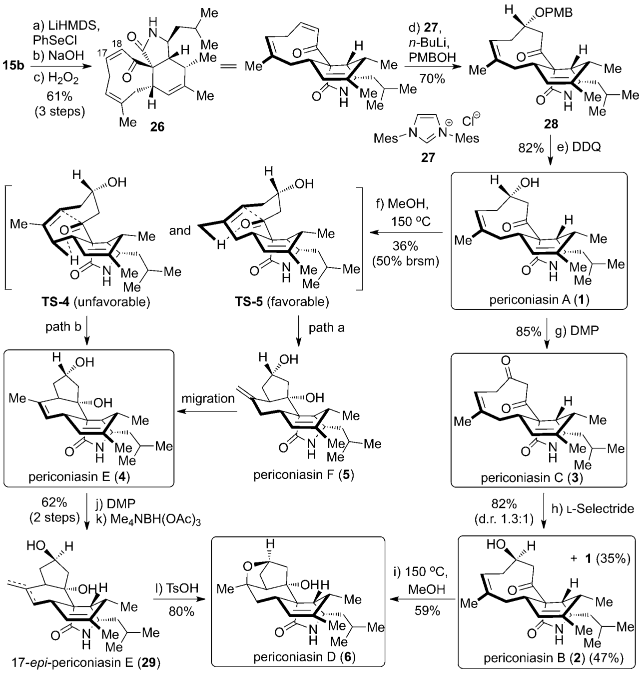


*Scheme 2.* Synthesis of the 9/6/5 tricyclic core of the periconiasins. Reagents and conditions: a) NaH (1.1 equiv), DMF, 0 °C to RT; then **21** (1.4 equiv), 88 %; b) LTBA (1.5 equiv), THF, −60 °C, 90 % (d.r. 10:1); c) MsCl (1.3 equiv), $Et_3N$ (1.5 equiv), DCM, 0 °C, 92 %; d) KHMDS (3.3 equiv), **18** (3.0 equiv), THF, −78 °C to RT, 40 % for **17a** and 70 % for **17b**; e) LiHMDS (1.3 equiv), PhSeCl (1.3 equiv), THF, −78 °C, 85 % for **24a** and 83 % for **24b**; f) 30 % $H_2O_2$/$H_2O$ (1:1), DCM, 0 °C; g) $CHCl_3$, BHT, 90 °C, **15a** (20 %) + **25a** (7 %) from **24a**; **15b** (38 %) + **25b** (12 %) from **24b**. BHT = butylated hydroxytoluene, DMF = *N*, *N*-dimethylformamide, KHMDS = potassium bis(trimethylsilyl)amide, LiHMDS = lithium bis(trimethylsilyl)amide, LTBA = lithium tri-*tert*-butoxyaluminum hydride, Ms = methanesulfonyl, THF = tetrahydrofuran.

(**20**) with the bromide derivative **21**[9] afforded **22** in 88% yield. Partial reduction of **22** with LTBA gave **23** in excellent yield and diastereoselectivity (d.r. 10:1),[10] and after mesylation, furnished the key precursor **19**. At this point, an extensive survey of reaction conditions was undertaken to explore the tandem aldol condensation/Grob fragmentation. Initially, the lactam **18a**[11] was used in the reaction. Deprotonation of **18a** with KHMDS followed by quenching the resulting enolate with **19** led to the formation of the intermediate **I-1** which spontaneously underwent Grob fragmentation to provide **17a** as a mixture of ketone/enol tautomers in 40% yield. Notably, another product (structure not shown) resulted from the self-condensation of **18a** was also isolated in about 30% yield. To avoid the side-reaction, we evaluated several reaction parameters, including the base, reaction temperature, and equivalents of **18a** used. However, no significant improvement could be attained (see Table S1 in the Supporting Information). Fortunately, we found that the N-protecting group on the lactam fragment exerted profound influence on the reaction. When the lactam **18b**[12] was used, the corresponding by-product was largely inhibited, thus delivering **17b** in 70% yield. It is worth noting that the preparation of such a polyketide–amino acid hybrid precursor generally requires stepwise chain extension manipulations, as witnessed in the literature.[4b,i–k] Comparably, our method enables expedient access to the linear backbone of the periconiasins from three readily accessible fragments (**20**, **21**, and **18b**) in a modular manner. Moreover, the stereospecific nature of the Grob fragmentation ideally secured the requisite *Z* configuration of the resulting C14–C15 double bond.

After sequential selenylation and oxidative elimination, **17a/b** is converted into the enones **16a/b** smoothly. Of the two, **16a** was unstable and had to be immediately submitted to an elevated temperature (CHCl$_3$, 90°C) to effect the Diels–Alder reaction. Pleasingly, the desired *endo*-adduct **15a** was isolated in 20% yield after two steps, and was unambiguously confirmed by the X-ray crystallographic study.[13] Meanwhile, a small amount of the *exo*-adduct **25a** (7%) was also detected (for structural assignment see Figure S1). This outcome seemed to be encouraging, however, the reaction yield was unsatisfactory because of the severe decomposition of **16a** as a result of its fragile nature.[14] Fortunately, we found that **16b** was relatively stable and proved to be a superior precursor for the Diels–Alder reaction. As a result, the corresponding products were obtained in notably improved yields (**15b**: 38%; **25b**: 12%).

With the pivotal tricyclic intermediate **15b** secured in a concise and scalable manner (7 steps, gram-scale synthesis), we proceeded to complete the total syntheses of **1**–**6** (Scheme 3). To this end, **15b** underwent sequential selenylation, deprotection, and oxidative elimination to afford **26** as a single *Z* isomer. Next, introduction of the C17 group by oxa-Michael addition was attempted. While the direct use of H$_2$O as a nucleophile[15] failed to deliver promising results (see Table S2), a novel N-heterocyclic carbene promoted 1,4-conjugate addition of an alcohol was successful.[16] Indeed, the desired reaction worked smoothly with PMBOH as the nucleophile, thus furnishing **28** as a single diastereoisomer in 70% yield.[17] Cleavage of the PMB group from **28** with DDQ afforded periconiasin A (**1**) in 82% yield. Furthermore, the proposed biomimetic transannular carbonyl–ene reaction[18] of **1** could be effected under thermal conditions (MeOH, seal tube, 150°C), and furnished periconiasin E (**4**) in 36% yield (50% brsm). Notably, periconiasin F (**5**) was not detected in this reaction. Mechanistically, we speculate that although the direct formation of **4** via the transition-state **TS-4** (path b; Scheme 3) could not be excluded completely, it is more likely that **1** first converts into **5** via the favorable transition-state **TS-5** (path a), and the latter would then undergo double migration to afford the thermodynamically more stable **4**.



***Scheme 3.*** Collective total syntheses of the periconiasins A–E. Reagents and conditions: a) LiHMDS (1.2 equiv), PhSeCl (1.2 equiv), THF, −78°C, 78%; b) NaOH (21.0 equiv), MeOH/H$_2$O (20:1), RT; c) 30% H$_2$O$_2$/H$_2$O (1:1), pyridine (10.0 equiv), DCM, RT, 78% two steps; d) **27** (2.0 equiv), LiCl (2.0 equiv), *n*BuLi (2.0 equiv), THF, −78°C to RT, then PMBOH (3.0 equiv), **26** (1.0 equiv), toluene, RT, 70%; e) DDQ (1.5 equiv), DCM/H$_2$O (19:1), RT, 82%; f) MeOH, seal tube, 150°C, 36% (50% brsm); g) DMP (1.5 equiv), DCM, RT, 85%; h) L-Selectride (2.0 equiv), THF, −78°C, **1** (35%) + **2** (47%); i) MeOH, seal tube, 150°C, 59%; j) DMP (1.5 equiv), DCM, RT, 83%; k) Me$_4$NBH(OAc)$_3$ (10.0 equiv), MeCN/AcOH (10:1), RT, 75%; l) TsOH, DCM, RT, 80%. brsm = based on recovered starting material, DCM = dichloromethane, DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, DMP = Dess–Martin periodinane, L-Selectride = lithium tri-*sec*-butyl(hydrido)borate, PMB = *p*-methoxybenzyl, Ts = *p*-toluenesulfonyl.

At the end of our synthetic campaign, we attempted the most challenging target, periconiasin D (**6**). At first, the proposed biosynthetic process (Scheme 1A) was attempted. To this end, **1** was oxidized to periconiasin C (**3**) by Dess–Martin oxidation, which, as we envisaged, might be converted into **2** by regio- and diastereoselective reduction of the C17 ketone. However, we found that although a wide range of reducing regents such as NaBH$_4$, DIBAL-H, LTBA, and L-Selectride could effect the reduction with excellent regioselectivities, they provided only poor diastereoselectivities (d.r.

1:0.6 to 1:1.3; see Table S3). Without further optimization, **2** was submitted to the reaction conditions employed for the synthesis of **4,** and resulted in the direct formation of **6** by tandem transannular carbonyl–ene reaction/etherification (Scheme 3). Meanwhile, an alternative approach was also established to access **6** in a diastereoselective manner. Thus, oxidation of **4** with DMP produced the corresponding β-hydroxy ketone in 83 % yield, and then underwent a 1,3-directed reduction in the presence of $Me_4NBH(OAc)_3$ to yield 17-*epi*-periconiasin E (**29**) as a single diastereoisomer. Upon treatment with TsOH, **29** readily converted into **6** by etherification in 80 % yield.

In summary, we have achieved the first and collective total syntheses of periconiasins A–E, a group of newly identified cytochalasans, through an efficient biomimetic strategy. An array of rationally designed or bioinspired transformations, including a tandem aldol condensation/Grob fragmentation, a Diels–Alder macrocyclization, and a transannular carbonyl–ene reaction, led to rapid access of all representative members of periconiasins from readily accessible fragments. We anticipate that the unified strategy, particularly the tactic to assemble the linear polyketide–amino acid hybrid precursor, can be extended to the synthesis of other valuable cytochalasans bearing different macrocycle and amino-acid residue, the implementation of which is underway in our laboratory.

## Acknowledgements

We gratefully acknowledge financial support from the National Science Foundation of China (21272133, 21572112). We also thank Prof. Jungui Dai (IMM, PUMC) for providing authentic samples of periconiasins A and B, and Mr. Yuanhe Li (Peking University) for helpful discussions.

**Keywords:** biomimetic synthesis · cycloaddition · natural products · polyketides · total synthesis

**How to cite:** *Angew. Chem. Int. Ed.* **2016**, *55*, 6992–6996
*Angew. Chem.* **2016**, *128*, 7106–7110

---

[1] For reviews, see: a) K. Scherlach, D. Boettger, N. Remme, C. Hertweck, *Nat. Prod. Rep.* **2010**, *27*, 869; b) S. Bräse, A. Encinas, J. Keck, C. F. Nising, *Chem. Rev.* **2009**, *109*, 3903; c) M. Binder, C. Tamm, *Angew. Chem. Int. Ed. Engl.* **1973**, *12*, 370; *Angew. Chem.* **1973**, *85*, 369.

[2] For selected recent isolations of cytochalasans, see: a) R. Liu, Z. Lin, T. Zhu, Y. Fang, Q. Gu, W. Zhu, *J. Nat. Prod.* **2008**, *71*, 1127; b) Z. Lin, T. Zhu, H. Wei, G. Zhang, H. Wang, Q. Gu, *Eur. J. Org. Chem.* **2009**, 3045; c) G. Ding, H. L. Wang, L. Li, A. J. Chen, L. Chen, H. Chen, H. W. Zhang, X. Z. Liu, Z. M. Zou, *Eur. J. Org. Chem.* **2012**, 2516; d) H. Zhu, C. Chen, Y. Xue, Q. Tong, X. N. Li, X. Chen, J. Wang, G. Yao, Z. Luo, Y. Zhang, *Angew. Chem. Int. Ed.* **2015**, *54*, 13374; *Angew. Chem.* **2015**, *127*, 13572; e) H. Zhu, C. Chen, Q. Tong, X. N. Li, J. Yang, Y. Xue, Z. Luo, J. Wang, G. Yao, Y. Zhang, *Angew. Chem. Int. Ed.* **2016**, *55*, 3486; *Angew. Chem.* **2016**, *128*, 3547.

[3] For selected biological studies on cytochalasans, see: a) S. B. Carter, *Nature* **1967**, *213*, 261; b) N. K. Wessells, B. S. Spooner, J. F. Ash, M. O. Bradley, M. A. Luduena, E. L. Taylor, J. T. Wrenn, K. M. Yamada, *Science* **1971**, *171*, 135; c) J. A. Cooper, *J. Cell Biol.* **1987**, *105*, 1473; d) R. E. Fournier, A. B. Pardee, *Proc. Natl. Acad. Sci. USA* **1975**, *72*, 869; e) J. R. Peterson, T. J. Mitchison, *Chem. Biol.* **2002**, *9*, 1275.

[4] For syntheses of cytochalasans, see: a) G. Stork, E. Nakamura, Y. Nakahara, W. J. Greenlee, *J. Am. Chem. Soc.* **1978**, *100*, 7775; b) G. Stork, E. Nakamura, *J. Am. Chem. Soc.* **1983**, *105*, 5510; c) E. Vedejs, J. G. Reid, *J. Am. Chem. Soc.* **1984**, *106*, 4617; d) B. M. Trost, M. Ohmori, S. A. Boyd, H. Okawara, S. J. Brickner, *J. Am. Chem. Soc.* **1989**, *111*, 8281; e) E. Vedejs, J. G. Reid, J. D. Rodgers, S. J. Wittenberger, *J. Am. Chem. Soc.* **1990**, *112*, 4351; f) E. Vedejs, S. J. Wittenberger, *J. Am. Chem. Soc.* **1990**, *112*, 4357; g) E. J. Thomas, J. W. F. Whitehead, *J. Chem. Soc. Chem. Commun.* **1986**, 727; h) H. Dyke, R. Sauter, P. Steel, E. J. Thomas, *J. Chem. Soc. Chem. Commun.* **1986**, 1447; i) E. Merifield, E. J. Thomas, *J. Chem. Soc. Chem. Commun.* **1990**, 464; j) E. J. Thomas, *Acc. Chem. Res.* **1991**, *24*, 229; k) E. Merifield, E. J. Thomas, *J. Chem. Soc. Perkin Trans. 1* **1999**, 3269; l) A. M. Haidle, A. G. Myers, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 12048; m) S. M. Canham, L. E. Overman, P. S. Tanis, *Tetrahedron* **2011**, *67*, 9837.

[5] D. Zhang, H. Ge, D. Xie, R. Chen, J. H. Zou, X. Tao, J. Dai, *Org. Lett.* **2013**, *15*, 1674.

[6] D. Zhang, X. Tao, R. Chen, J. Liu, L. Li, X. Fang, L. Yu, J. Dai, *Org. Lett.* **2015**, *17*, 4304.

[7] D. W. Zhang, *Chemical Constituents from Endophytic Fungus Periconia Sp. F-31 Isolated from Annona Muricata.* Ph.D. Thesis, Chinese Academy of Medical Sciences and Peking Union Medical College, **2013**.

[8] For leading reviews, see: a) C. A. Grob, P. W. Schiess, *Angew. Chem. Int. Ed. Engl.* **1967**, *6*, 1; *Angew. Chem.* **1967**, *79*, 1; b) C. A. Grob, *Angew. Chem. Int. Ed. Engl.* **1969**, *8*, 535; *Angew. Chem.* **1969**, *81*, 543; c) K. Prantz, J. Mulzer, *Chem. Rev.* **2010**, *110*, 3741; d) M. A. Drahl, M. Manpadi, L. J. Williams, *Angew. Chem. Int. Ed.* **2013**, *52*, 11222; *Angew. Chem.* **2013**, *125*, 11430; For some inspiring examples, see: e) D. A. Clark, P. L. Fuchs, *J. Am. Chem. Soc.* **1979**, *101*, 3567; f) A. E. Imai, Y. Sato, M. Nishida, M. Mori, *J. Am. Chem. Soc.* **1999**, *121*, 1217; g) B. M. Trost, M. J. Bogdanowicz, W. J. Frazee, T. N. Salzmann, *J. Am. Chem. Soc.* **1978**, *100*, 5512; h) C. Fehr, J. Galindo, O. Etter, W. Thommen, *Angew. Chem. Int. Ed.* **2002**, *41*, 4523; *Angew. Chem.* **2002**, *114*, 4705; i) T. J. Maimone, A.-F. Voica, P. S. Baran, *Angew. Chem. Int. Ed.* **2008**, *47*, 3054; *Angew. Chem.* **2008**, *120*, 3097.

[9] The bromide derivative **21** was prepared in 3 steps from commercially available material according to the following reference. D. Enders, G. Geibel, S. Osborne, *Chem. Eur. J.* **2000**, *6*, 1302.

[10] J. M. Carr, T. S. Snowden, *Tetrahedron* **2008**, *64*, 2897.

[11] S. M. Canham, L. E. Overman, P. S. Tanis, *Tetrahedron* **2011**, *67*, 9837.

[12] For the preparation of **18b**, see the Supporting Information.

[13] For the crystallographic data of **15a**, refer to CCDC 1455037 and the CIF in the Supporting Information.

[14] It has been documented that 3-acetylpyrrol-2(5*H*)-one derivatives were unstable and readily underwent polymerization upon isolation. For related reference, see Refs. [4c] and [4g–k].

[15] For leading reviews on hetero-Michael additions, see: a) C. F. Nising, S. Bräse, *Chem. Soc. Rev.* **2008**, *37*, 1218; b) C. F. Nising, S. Bräse, *Chem. Soc. Rev.* **2012**, *41*, 988; c) E. Hartmann, D. J. Vyas, M. Oestreich, *Chem. Commun.* **2011**, *47*, 7917; For selected examples of using $H_2O$ as a Michael donor, see: d) I. C. Stewart, R. G. Bergman, F. D. Toste, *J. Am. Chem. Soc.* **2003**, *125*, 8696; e) A. J. Boersma, D. Coquière, D. Geerdink, F. Rosati, B. L. Feringa, G. Roelfes, *Nat. Chem.* **2010**, *2*, 991; f) C. Li, L. Dian, W. Zhang, X. Lei, *J. Am. Chem. Soc.* **2012**, *134*, 12414; g) V. Resch, C. Seidler, B. S. Chen, I. Degeling, U. Hanefeld, *Eur. J. Org. Chem.* **2013**, *2013*, 7697.

[16] E. M. Phillips, M. Riedrich, K. A. Scheidt, *J. Am. Chem. Soc.* **2010**, *132*, 13179. Of note, because of the existence of an unprotected amide moiety in **26**, stoichiometric amounts of **27** were used in the current case to secure good conversion for the reaction.

[17] The exceptional diastereoselectivity of the 1,4-conjugate addition might be attributed to the underlying chelation effect. For details of conformational analysis, see the Supporting Information (see Figure S2).

[18] For leading reviews on carbonyl–ene reactions see: a) K. Mikami, M. Shimizu, *Chem. Rev.* **1992**, *92*, 1021; b) B. B. Snider, *Acc. Chem. Res.* **1980**, *13*, 426; For inspiring cases, see: c) L. Barriault, D. H. Deon, *Org. Lett.* **2001**, *3*, 1925; d) E. L. O. Sauer, J. Hooper, T. Woo, L. Barriault, *J. Am. Chem. Soc.* **2007**, *129*, 2112.

Received: March 9, 2016