Organic LETTERS

Letter

pubs.acs.org/OrgLett

Total Synthesis of Herbimycin A

Rui Yan, Chuancai Bian, and Xiaoming Yu*

State Key Laboratory of Bioactive Substance and Function of Natural Medicine, Institute of Materia Medica, Peking Union Medical College & Chinese Academy of Medical Sciences, No. 1 Xiannongtan Street, Beijing 100050, China

Supporting Information

ABSTRACT: Benzoquinone ansamycin antibiotic herbimycin A was synthesized in 19 linear steps and 4.2% yield. Highlighted is the design of a chiral γ-lactone as the C11−C15 synthon that enabled a facile catalytic asymmetric synthesis of the challenging C8−C20 fragment of the target molecule. The easy access to the stereogenic centers and high overall yield made the strategy applicable in the molecular editing of benzoquinone ansamycins.

Benzoquinone ansamycins are polyketide antibiotics isolated from bacterial species *S. hygroscopicus*.[1] Geldanamycin (**1**),[2] macbecin I (**2**),[3] and herbimycin A (**3**)[4] are among the typical members of this natural product family (Figure 1) that

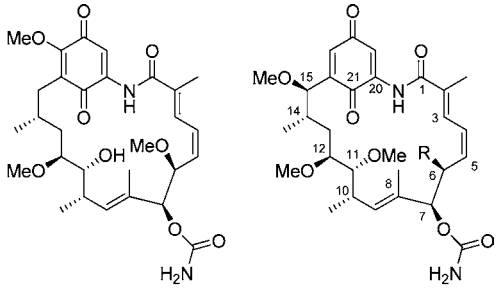


Figure 1. Selected structures of benzoquinone ansamycins.

bear in common a 19-membered macrolactam skeleton, accommodating six or seven stereogenic carbons, three geometrically defined C=C double bonds, and a *p*-benzoquinone subunit. Compounds **1**−**3** were observed to exhibit potent anticancer activities upon their isolation, yet the real fascination lies in their mechanism of action revealed later. With geldanamycin being the first, all the compounds were found to be potent inhibitors of heat shock protein 90 (hsp90),[5] a newly validated anticancer drug target.[6] Benzoquinone ansamycins are therefore thought to be valuable lead structures in seeking novel anticancer drugs,[7] and in our view, an ideal subject for implementation of the "molecular editing" strategy that might give rise to a deep-seated SAR understanding.[8]

Since the first report in 1989, nearly a dozen successful total syntheses had been contributed to **1**−**3** by a number of teams worldwide,[9−11] with each distinguished from others by their access to the challenging chiral centers, in particular, the tertiary C10 and C14. For example, Baker, Evans, and Andrus finished the total synthesis of **2** and **1**, respectively, using easily available chiral auxiliaries; Panek accomplished all three natural products using varied chiral crotylsilanes developed in their own laboratory, and in other elegant cases, Roush and Brown asymmetric crotylations as well as Marshall asymmetric propargylation also played critical roles. In this context, an asymmetric catalysis based approach to benzoquinone ansamycin, which is of considerable significance from the perspective of either academia or practice, is still awaiting development.

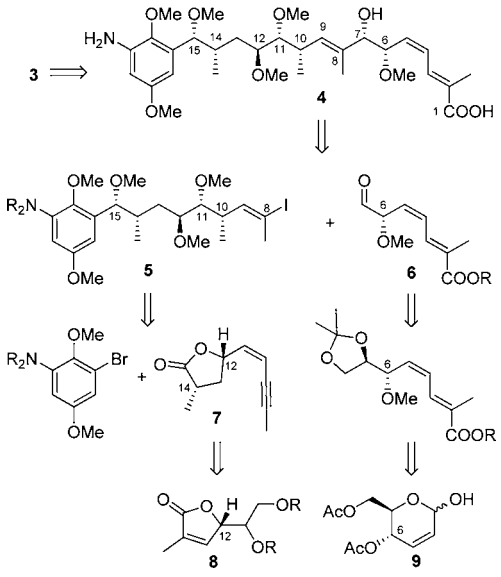
We recently found an L-glutamic acid derived chiral γ-lactone to be a practically useful C11−C14 synthon for reblastatin, a compound closely related to **1**.[12] We also found that, as demonstrated in the total synthesis of **3** reported herein, a more sophisticated application of this "γ-lactone" tactic would help bridge the gap between asymmetric catalysis and chemical synthesis of benzoquinone ansamycins.

Our retrosynthesis of **3** (Scheme 1) started from *seco*-amino acid **4**, a three-step precursor Cossy had synthesized.[11d] This secondary target was expected to be obtained in its protected form through a halogen−metal exchange mediated coupling between **5** and **6** since the Cram chelation model prediction pointed to the correct configuration at C7.[12] We then intended to build the stereogenic C15 in the C8−C20 fragment **5** through a catalytic asymmetric reduction. To address the C10 and C11 chirality in **5**, we assumed a two-step protocol comprising an asymmetric epoxidation of *Z*-enyne substituted γ-lactone **7** and a methyl carbanion effected regioselective nucleophilic epoxide ring-opening. Owing to the 1,3-*cis* geometry of **7** that is accessible by regular hydrogenation, furanone **8**, presumably an easy target of Sharpless AD, arose as a good starting point for the total synthesis. The synthesis of C1−C7 aldehyde **6**, on the other hand, could be achieved by following the approach adapted from our previous study using inexpensive compound **9**.

Received: May 6, 2014
Published: June 9, 2014

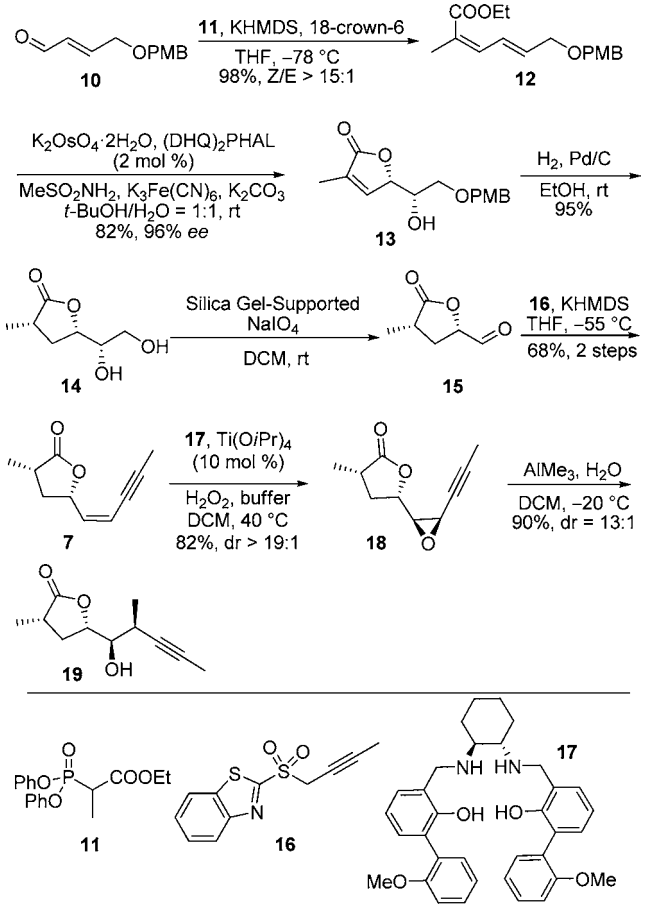
   dx.doi.org/10.1021/ol5012899 | *Org. Lett.* 2014, 16, 3280−3283

Scheme 1. Retrosynthesis of Herbimycin A (3)



Sharpless AD mediated preparation of the chiral furanone equivalence of **8** proved easy (Scheme 2). The known aldehyde **10**[13] reacted readily with Ando-modified HWE reagent **11**[14] to give Z,E-dienoate **12** in 98% yield (Z/E > 15/1). With the O-PMB acting as both regio- and enantioselectivity enhancer,[15] dihydroxylation of this dienoate using AD-mix-α delivered spontaneously cyclized furanone **13** in 82% yield and 96% ee.

Scheme 2. Preparation of C8−C15 Fragment 15

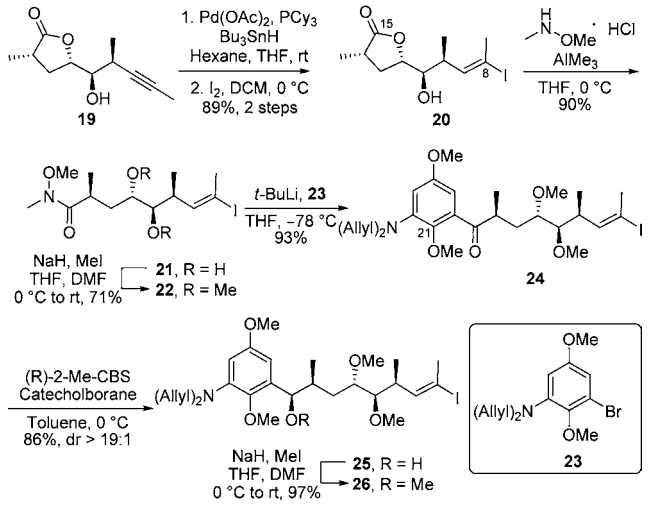


As expected, regular hydrogenation of **13** at ambient pressure and temperature proceeded with high facial selectivity and smooth removal of the PMB group, giving *cis*-lactone **14** in 95% yield. Upon further vicinal diol cleavage using Shing's silica gel supported $NaIO_4$,[16] aldehyde **15** was obtained and directly subjected to the Julia−Kocienski reaction with **16**[17] to give the desired *Z*-enyne lactone **7** in 68% yield over two steps. It is noteworthy that the use of Shing's reagent is necessary because **15** is highly aqueous soluble, and this reagent helped circumvent aqueous workup.

The titanium−salan-catalyzed asymmetric epoxidation developed by Katsuki was then applied.[18] With 10 mol % of catalyst loading, oxidation of **7** using 30% H_2O_2 gave **18** in 82% yield without detecting stereoisomers. With this material in hand, two different methylaluminum-derived reagents, i.e., Me_3Al/H_2O, discovered by Maruoka et al.,[19] and $LiAlMe_4$, reported by Kishi,[20] were utilized to realize the regioselective S_N2 epoxide ring-opening of **18**. Our results indicated that the former was superior, giving rise to the isolation of expected **19** in 90% yield accompanied by 7% of an unidentified isomer, whereas the latter led to complicated reactions.

After successful establishment of the four chiral centers in **19**, we turned our attention to the introduction of the aromatic moiety, yet prior to that the vinyl iodide function had to be installed (Scheme 3). Hydrozirconation of the triple bond in **19**

Scheme 3. Introduction of the Aromatic Subunit



using Schwartz reagent[21] was ineffective due to the preferential reduction of lactone. Hydrostannylation using the $Pd(PPh_3)_2Cl_2/Bu_3SnH$ system,[22] on the other hand, was chemoselective but lacked regioselectivity. This problem was finally solved by changing the ligand and counteranion to the palladium catalyst. The $Pd(PCy_3)_2(OAc)_2/Bu_3SnH$ system[23] exclusively produced C8 stannylated product from **19**, and by treating the resulting vinylstannane with iodine, compound **20** was obtained in excellent yield. Notably, the free hydroxyl in **20** actually offered an opportunity for further derivatization at C11, but in this study we went on to the trimethylalane-promoted lactone ring-opening of **20** with *N*-methoxymethylamine to afford Weinreb amide **21**. After global O-methylation of **21**, resultant **22** was subjected to the Weinreb reaction with the phenyllithium species generated from **23**[11d] to give ketone **24** in 93% yield.

dx.doi.org/10.1021/ol5012899 | *Org. Lett.* 2014, 16, 3280−3283

As such, the aromatic ring was introduced at a relatively late stage, in favor of a diverted synthesis that aims at altering the benzoquinone substructure. However, the success of such design still owes much to the subsequent reduction of **24**.

A variety of catalytic asymmetric reducing agents were screened for the diastereoselective reduction of **24** into desired **25**. The combination of (*R*)-B-Me-CBS catalyst with catechol−borane[24] was finally found to be a good option. Under fully optimized conditions, catecholborane was slowly added to premixed **24** and 20 mol % of catalyst over 10 h through a syringe pump at 0 °C, leading to the isolation of **25** as single diastereomer. Compound **25** was then O-methylated to furnish **26**. Lower CBS catalyst loading (10 mol %) in the reduction also led to a satisfying result if the addition rate of catecholborane was lowered further.

The sense of selectivity of the CBS catalyst in this case was inconsistent with regular prediction model, but easily rationalized by the two possible catalyst−reactant complexes, **A** and **B** (Figure 2). As has been noted by Corey,[25] the *o*-OMe

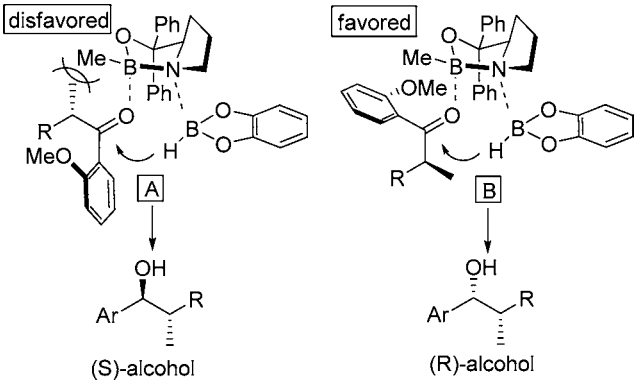


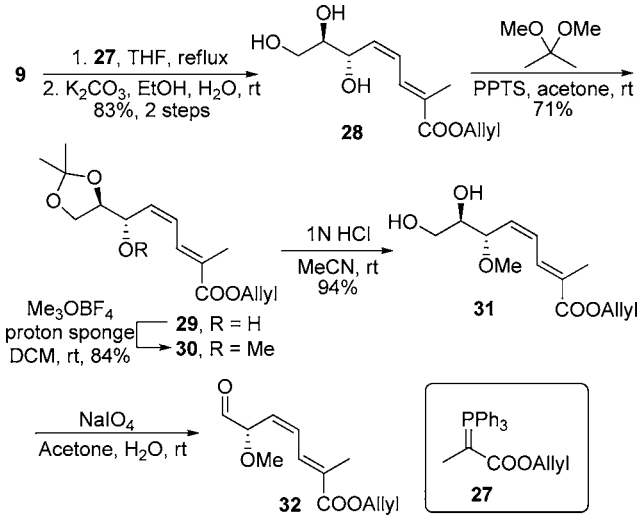
Figure 2. Proposed catalyst−reactant complexes for the reduction of **24**.

(C21-OMe) in **24** tends to keep the phenyl ring perpendicular to the carbonyl plane; therefore, the *B*−*Me* in complex **B** only feels a face-on interaction from the substituted phenyl whereas that in complex **A** has to overcome a strong spherical repulsion.

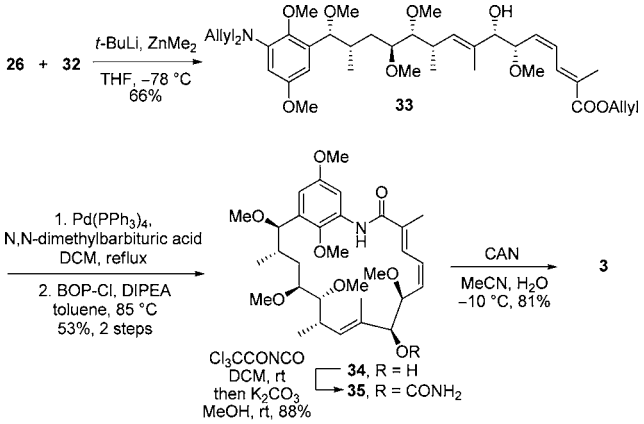
By finishing the aforementioned chemistry, which essentially constitutes the first example of *catalytic asymmetric* synthesis of the challenging C8−C20 fragment of both **2** and **3**, we set out to prepare the C1−C7 fragment (equivalence of **6**). Similar to that reported in our synthesis of reblastatin,[12b] the known compound **9** was subjected to a Wittig reaction with stable ylide **27** and then deacetylated with K_2CO_3/EtOH to provide triol **28** in 83% yield over two steps (Scheme 4). After regioselective acetonide protection of **28** under standard condition, the resultant compound **29** was O-methylated with Meerwein's salt to give **30**. Subsequent acidic hydrolysis of **30** followed by an oxidative 1,2-diol cleavage successfully delivered aldehyde **32**, a compound that is directly submitted to the next reaction.

To finish the final assembly (Scheme 5), a zincate-mediated coupling of **26** with **32** was performed using *tert*-butyllithium and dimethylzinc[26] and resulted in the isolation of **33** in an optimal yield of 66%. Concomitant O- and N-deallylation of **33** then provided the *seco*-amino acid **4**, the secondary target of this study. Unfortunately, the compound was not stable enough to be fully characterized. We therefore directly moved on to the macrocyclization effected by BOPCl and DIPEA. Upon isolation of macrolactam **34**, installation of the C7-carbamate

Scheme 4. Preparation of C1−C7 Fragment 32



Scheme 5. Finale of Herbimycin A (3) Synthesis



and oxidative unmasking of the *p*-benzoquinone were carried out as previously described by both Cossy[11c] and Panek[11d] to complete the total synthesis. The optical rotation of our sample ($[\alpha]_D^{20}$ +222 (*c* = 0.17, $CHCl_3$)) matched the value reported by Cossy ($[\alpha]_D^{20}$ +223 (*c* = 0.14, $CHCl_3$)), and spectral data was consistent with previous reports in the literature.

In summary, we described a straightforward total synthesis of herbimycin A. The synthesis took 19 longest linear steps from readily available achiral starting materials and a cheap chiral-pool substance with an overall yield up to 4.2%. The key to success is the employment of chiral γ-lactone **15** as the C11−C15 synthon that links the total synthesis to three well-established catalytic asymmetric reactions. With this achievement as steping stone, we are now tackling an "edited" collection of natural and unnatural benzoquinone ansamycin analogues, and results will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details, characterization data, and copies of the NMR spectra of compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

dx.doi.org/10.1021/ol5012899 | Org. Lett. 2014, 16, 3280−3283

AUTHOR INFORMATION

Corresponding Author

*E-mail: mingxyu@imm.ac.cn.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

This project received financial support from the National Natural Science Foundation of China (21272279).

REFERENCES

(1) Rascher, A.; Hu, Z.; Buchanan, G. O.; Reid, R.; Hutchinson, C. R. *Appl. Environ. Microbiol.* **2005**, *71*, 4862−4871.
(2) DeBoer, C.; Meulman, P.; Wnuk, R.; Peterson, D. *J. Antibiot.* **1970**, *23*, 442.
(3) Tanida, S.; Hasegawa, T.; Higashide, E. *J. Antibiot.* **1980**, *33*, 199−204.
(4) Omura, S.; Iwai, Y.; Takahashi, Y.; Sadakane, N.; Nakagawa, A.; Oiwa, H.; Hasegawa, Y.; Ikai, T. *J. Antibiot.* **1979**, *32*, 255−261.
(5) (a) Martin, C. J.; Gaisser, S.; Challis, I. R.; Carletti, I.; Wilkinson, B.; Gregory, M.; Prodromou, C.; Roe, S. M.; Pearl, L. H.; Boyd, S. M. *J. Med. Chem.* **2008**, *51*, 2853−2857. (b) Whitesell, L.; Mimnaugh, E. G.; De Costa, B.; Myers, C. E.; Neckers, L. M. *Proc. Natl. Acad. Sci. U.S.A.* **1994**, *91*, 8324−8328.
(6) For recent review, see: Garcia-Carbonero, R.; Carnero, A.; Paz-Ares, L. *Lancet Oncol.* **2013**, *14*, 358−369.
(7) For recent reviews, see: (a) Kim, T.; Keum, G.; Pae, A. N. *Expert Opin. Ther. Pat.* **2013**, *23*, 919−943. (b) Franke, J.; Eichner, S.; Zeilinger, C.; Kirschning, A. *Nat. Prod. Rep.* **2013**, *30*, 1299−1323. (c) Kitson, R. R.; Moody, C. J. *J. Org. Chem.* **2013**, *78*, 5117−5141.
(8) For reviews, see: (a) Wilson, R. M.; Danishefsky, S. J. *J. Org. Chem.* **2006**, *71*, 8329−8351. (b) Szpilman, A. M.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2010**, *49*, 9592−9628.
(9) For total synthesis of geldanamycin, see: (a) Andrus, M. B.; Meredith, E. L.; Simmons, B. L.; Soma Sekhar, B.; Hicken, E. J. *Org. Lett.* **2002**, *4*, 3549−3552. (b) Andrus, M. B.; Meredith, E. L.; Hicken, E. J.; Simmons, B. L.; Glancey, R. R.; Ma, W. *J. Org. Chem.* **2003**, *68*, 8162−8169. (c) Qin, H. L.; Panek, J. S. *Org. Lett.* **2008**, *10*, 2477−2479. (d) Hampel, T.; Neubauer, T.; van Leeuwen, T.; Bach, T. *Chem.—Eur. J.* **2012**, *18*, 10382−10392 (a two-step precursor).
(10) For the total synthesis of macbecin I, see: (a) Baker, R.; Castro, J. L. *J. Chem. Soc., Chem. Commun.* **1989**, 378−381. (b) Baker, R.; Castro, J. L. *J. Chem. Soc., Perkin Trans. 1* **1990**, 47−65. (c) Evans, D. A.; Miller, S. J.; Ennis, M. D.; Ornstein, P. L. *J. Org. Chem.* **1992**, *57*, 1067−1069. (d) Panek, J. S.; Xu, F. *J. Am. Chem. Soc.* **1995**, *117*, 10587−10588. (e) Belardi, J. K.; Micalizio, G. C. *Angew. Chem., Int. Ed.* **2008**, *47*, 4005−4008.
(11) For total synthesis of herbimycin A, see: (a) Nakata, M.; Osumi, T.; Ueno, A.; Kimura, T.; Tamai, T.; Tatsuta, K. *Tetrahedron Lett.* **1991**, *32*, 6015−6018. (b) Nakata, M.; Osumi, T.; Ueno, A.; Kimura, T.; Tamai, T.; Tatsuta, K. *Bull. Chem. Soc. Jpn.* **1992**, *65*, 2974−2991. (c) Carter, K. D.; Panek, J. S. *Org. Lett.* **2004**, *6*, 55−57. (d) Canova, S.; Bellosta, V.; Bigot, A.; Mailliet, P.; Mignani, S.; Cossy, J. *Org. Lett.* **2007**, *9*, 145−148.
(12) (a) Bian, C. C.; Yan, R.; Yu, X. M. *Tetrahedron* **2014**, *70*, 2982−2991. For the original total synthesis of reblastatin, see: (b) Wrona, I. E.; Gabarda, A. E.; Evano, G.; Panek, J. S. *J. Am. Chem. Soc.* **2005**, *127*, 15026−15027. (c) Wrona, I. E.; Gozman, A.; Taldone, T.; Chiosis, G.; Panek, J. S. *J. Org. Chem.* **2010**, *75*, 2820−2835.
(13) García-Fortanet, J.; Murga, J.; Carda, M.; Marco, J. A.; Matesanz, R.; Díaz, J. F.; Barasoain, I. *Chem.—Eur. J.* **2007**, *13*, 5060−5074.
(14) (a) Ando, K. *J. Org. Chem.* **1998**, *63*, 8411−8416. (b) Ando, K. *J. Org. Chem.* **1997**, *62*, 1934−1939.
(15) Guzman-Perez, A.; Corey, E. J. *Tetrahedron Lett.* **1997**, *38*, 5941−5944.
(16) Zhong, Y. L.; Shing, T. K. M. *J. Org. Chem.* **1997**, *62*, 2622−2624.
(17) (a) Bonini, C.; Chiummiento, L.; Videtta, V. *Synlett* **2006**, *2006*, 2079−2082. (b) Micoine, K.; Fürstner, A. *J. Am. Chem. Soc.* **2010**, *132*, 14064−14066.
(18) (a) Shimada, Y.; Kondo, S.; Ohara, Y.; Matsumoto, K.; Katsuki, T. *Synlett* **2007**, *2007*, 2445−2447. (b) Sawada, Y.; Matsumoto, K.; Kondo, S.; Watanabe, H.; Ozawa, T.; Suzuki, K.; Saito, B.; Katsuki, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 3478−3480.
(19) Abe, N.; Hanawa, H.; Maruoka, K.; Sasaki, M.; Miyashita, M. *Tetrahedron lett.* **1999**, *40*, 5369−5372.
(20) Jackson, K. L.; Li, W.; Chen, C. L.; Kishi, Y. *Tetrahedron* **2010**, *66*, 2263−2272.
(21) (a) Pischl, M. C.; Weise, C. F.; Müller, M. A.; Pfaltz, A.; Schneider, C. *Angew. Chem., Int. Ed.* **2013**, *52*, 8968−8972. (b) Hu, T.; Panek, J. S. *J. Am. Chem. Soc.* **2002**, *124*, 11368−11378.
(22) (a) Smith, A. B.; Verhoest, P. R.; Minbiole, K. P.; Schelhaas, M. *J. Am. Chem. Soc.* **2001**, *123*, 4834−4836. (b) Geist, J. G.; Barth, R.; Roush, W. R. *Org. Lett.* **2012**, *15*, 58−61.
(23) (a) Semmelhack, M.; Hooley, R. J. *Tetrahedron lett.* **2003**, *44*, 5737−5739. (b) Yuan, Y.; Men, H.; Lee, C. *J. Am. Chem. Soc.* **2004**, *126*, 14720−14721.
(24) (a) Corey, E. J.; Link, J. O. *Tetrahedron Lett.* **1989**, *30*, 6275−6278. (b) Corey, E. J.; Bakshi, R. K. *Tetrahedron Lett.* **1990**, *31*, 611−614.
(25) (a) Corey, E. J.; Helal, C. J. *Tetrahedron Lett.* **1996**, *37*, 5675−5678. (b) Corey, E. J.; Helal, C. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 1986−2012.
(26) Hayashi, Y.; Shoji, M.; Ishikawa, H.; Yamaguchi, J.; Tamura, T.; Imai, H.; Nishigaya, Y.; Takabe, K.; Kakeya, H.; Osada, H. *Angew. Chem., Int. Ed.* **2008**, *47*, 6657−6660.