Indole Alkaloids

International Edition: DOI: 10.1002/anie.201604754
German Edition: DOI: 10.1002/ange.201604754

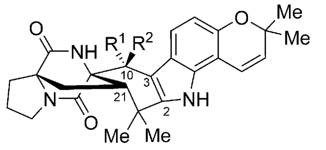
Total Synthesis of Notoamides F, I, and R and Sclerotiamide

Benxiang Zhang[+], Weifeng Zheng[+], Xiaoqing Wang, Deqian Sun, and Chaozhong Li**

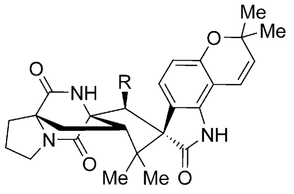
Abstract: *The total synthesis of the natural indole alkaloids (+)-notoamide F, I, and R and (−)-sclerotiamide is described. The four heptacyclic compounds were synthesized in 10–12 steps in a convergent and highly stereoselective manner from the readily available Seebach acetal. Key steps of the synthesis include a stereoselective oxidative aza-Prins cyclization to construct the bicyclo[2.2.2]diazaoctane, and a cobalt-catalyzed radical cycloisomerization to create the cyclohexenyl ring.*

The structural complexity and diverse biological activities of prenylated indole alkaloids continue to encourage the development of new methods for their efficient and rapid synthesis.[1] A number of secondary metabolites produced by various fungi of the genera *Aspergillus* and *Penicillium*, including brevianamide B,[2] the stephacidins,[3–6] notoamide B,[5,6] malbrancheamide B,[7] marcfortine B,[8] and the citrinalins,[9] have been synthetic targets of many research groups. For example, Baran et al. accomplished the first total synthesis of stephacidin A[3] on the basis of a stereoselective intramolecular oxidative ester–amide coupling developed by the same group.[10] Williams and co-workers nicely introduced the biomimetic synthesis of stephacidin A by using an azadiene intramolecular Diels–Alder reaction and also succeeded in the biomimetic oxidation of stephacidin A to notoamide B.[5] More recently, Simpkins et al. also reported the synthesis of stephacidin A with a tandem radical cyclization as the key step.[6]

Notoamides I (**1**), R (**2**), and F (**3**) are three new members of this family isolated from marine-derived *Aspergillus* sp. by the Tsukamoto group.[11] They can be regarded as oxygenated metabolites of stephacidin A (**4**). Notoamide R may also serve as the biosynthetic precursor to sclerotiamide (**5**),[12] another member of the family that was isolated two decades ago but has never been synthesized, despite the significant interest in spirooxindoles of this type,[5–9] such as notoamide B (**6**). Herein we report the first total synthesis of natural (+)-notoamides F, I, and R and (−)-sclerotiamide.

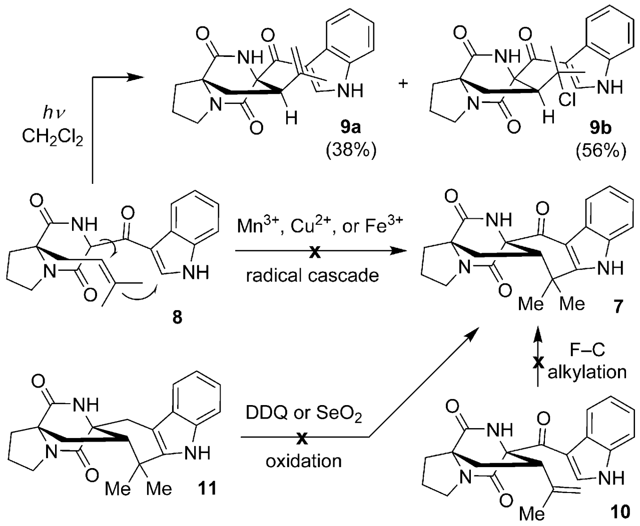


notoamide I (**1**, R^1, R^2 = O)
notoamide R (**2**, R^1 = H, R^2 = OH)
notoamide F (**3**, R^1 = H, R^2 = OMe)
stephacidin A (**4**, R^1 = R^2 = H)



sclerotiamide (**5**, R = OH)
notoamide B (**6**, R = H)

The extra functionality at the C10 position in **1**–**3** causes unexpected difficulties in their synthesis, and the reported strategies for the synthesis of stephacidin A are not readily applicable to **1**–**3**, as demonstrated by our initial endeavors to construct the hexacyclic skeleton, namely, compound **7**, as a simplified model of notoamide I (Scheme 1). An oxidative tandem radical cyclization pathway similar to the strategy used by Simpkins and co-workers[6] was first tested. Unfortunately, under various conditions, the attempted Mn^{III}-, Cu^{II}-, Fe^{III}-, or Ce^{IV}-mediated oxidative radical cyclization[13] of β-ketoamide **8** failed to give any of the desired product (see below and Table S1 in the Supporting Information).[14] Instead, we found that direct UV photolysis of **8** in CH_2Cl_2 led to the monocyclization products **9a** and **9b**, both with the *R* rather than the desired *S* configuration at C21. Furthermore, formation of the C2−C22 bond through intramolecular Friedel–Crafts alkylation or a formal ene reaction of alkene **10** (the strategy described by Baran et al.)[3] was also



Scheme 1. Attempts to synthesize **7** as a simplified model of notoamide I. DDQ = 2,3-dichloro-5,6-dicyano-*p*-benzoquinone.

---

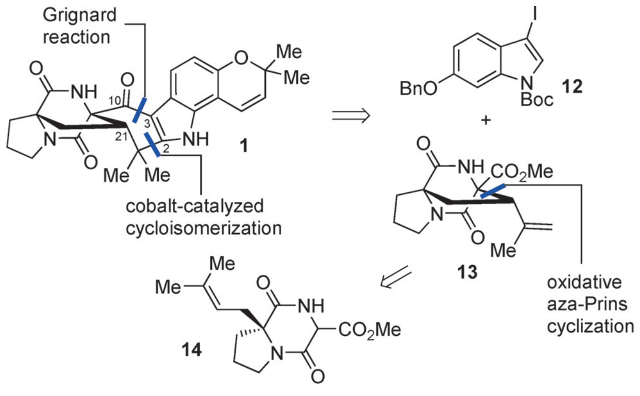
[*] B. Zhang,[+] Dr. W. Zheng,[+] Dr. X. Wang, Dr. D. Sun, Prof. Dr. C. Li
Key Laboratory of Organofluorine Chemistry and Collaborative Innovation Center of Chemistry for Life Sciences
Shanghai Institute of Organic Chemistry
Chinese Academy of Sciences
345 Lingling Road, Shanghai 200032 (P.R. China)
E-mail: sundeqian@sioc.ac.cn
clig@mail.sioc.ac.cn
Prof. Dr. C. Li
School of Chemical Engineering, Ningbo University of Technology
89 Cuibai Road, Ningbo 315016 (P.R. China)

[+] These authors contributed equally.

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.201604754.

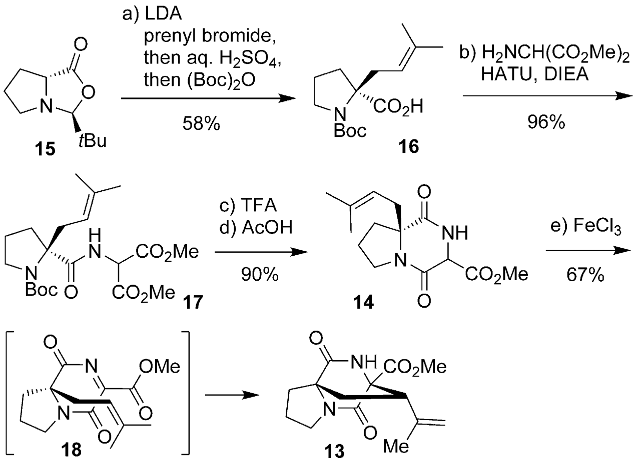
unsuccessful, probably because of the conjugation of the electron-withdrawing carbonyl group (see Table S3). The attempted introduction of the carbonyl moiety by the oxidation of compound **11**[5c] with DDQ or SeO_2 also failed: The starting material either remained unchanged or underwent rupture of the skeleton (see Table S4).

Our successful retrosynthetic design of notoamide I is outlined in Scheme 2. We decided to construct the 2*H*-pyranyl ring last to avoid any possible complication in the early stages of the synthesis. We envisioned that the C2–C22 linkage could be created by cobalt-catalyzed radical cycloisomerization as described by Shenvi and co-workers,[15] and that the C3–C10 bond could be formed by a Grignard reaction between iodide **12** and ester **13**. The bicyclo[2.2.2]diazaoctane ring of **13** could in turn be generated by an oxidative aza-Prins cyclization[16] of dipeptide **14**.



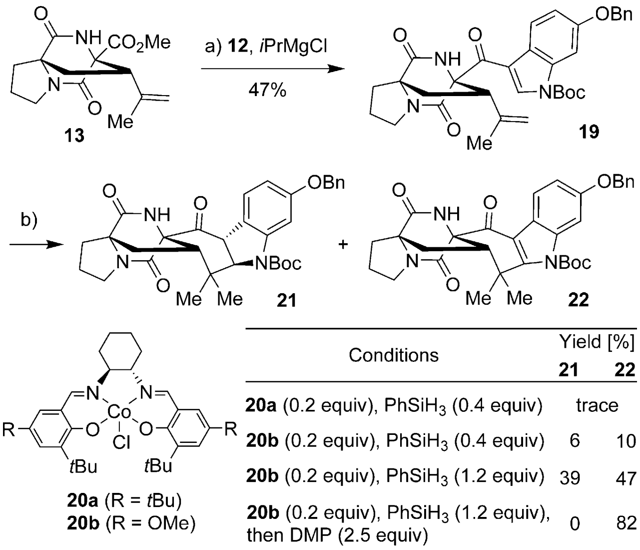
Scheme 2. Retrosynthesis of notoamide I. Bn = benzyl, Boc = *tert*-butoxycarbonyl.

Thus, our synthetic route to **1**–**3** and **5** started with the known and readily available Seebach acetal[17] **15** (Scheme 3). The prenylation of **15**, followed by acid quenching and subsequent N-Boc-protection, gave acid **16** in 58% overall yield. Compound **16** underwent condensation with dimethyl 2-aminomalonate to give the corresponding amide **17** in nearly quantitative yield. The deprotection of **17** with trifluoroacetic acid, followed by treatment with acetic acid, afforded the expected cyclic dipeptide **14**. Various conditions for the oxidative cyclization of **14** were then screened (see below and Table S5). Gratifyingly, the reaction of **14** with $FeCl_3$ in a CH_3CN/CH_2Cl_2 solvent mixture at room temperature furnished bicyclo[2.2.2]diazaoctane **13** in 67% yield as the only stereoisomer. Note that the $Mn(OAc)_3$-mediated[13a] radical reaction of **14** failed to give any cyclization products; instead the substrate underwent decomposition. On the other hand, the copper(II)-promoted reaction of **14** in MeOH produced the α-methoxylated product in 65% yield, presumably through oxidation (to give imine **18**) followed by the addition of methanol to the imine. Upon treatment with $BF_3{\cdot}Et_2O$ and $FeCl_3$, the methoxylated compound could be converted into **13** in a highly stereoselective manner, albeit in low yield (30%). These results in combination with the experiments with ketoamide **8** (see above) indicate that the above $FeCl_3$-mediated reaction of **14** is better classified as an oxidative aza-Prins cyclization via imine **18**.



Scheme 3. Synthesis of the key intermediate **13**. Reagents and conditions: a) LDA (1.2 equiv), prenyl bromide (1.8 equiv), THF, −78 °C, 1.5 h; then aqueous H_2SO_4, 25 °C, 24 h; then $(Boc)_2O$ (5 equiv), NaOH (30 equiv), 1,4-dioxane, 25 °C, 24 h, 58% overall; b) $ClH_3NCH(CO_2Me)_2$ (1.1 equiv), HATU (1.1 equiv), DIEA (2.5 equiv), CH_3CN, 25 °C, 12 h, 96%; c) TFA/CH_2Cl_2 (1:5), 0 °C, 5 h; d) AcOH/toluene (1:9), reflux, 5 h, 90% overall; e) $FeCl_3$ (3 equiv), CH_2Cl_2/CH_3CN (1:4), 25 °C, 3 h, 67%. LDA = lithium diisopropylamide, HATU = *N*,*N*,*N*′,*N*′-tetramethyl-*O*-(7-azabenzotriazol-1-yl)uronium hexafluorophosphate, DIEA = diisopropylethylamine, TFA = trifluoroacetic acid.

The reaction of **13** with the Grignard reagent derived from 3-iodoindole **12** and *i*PrMgCl provided ketone **19** in 47% yield, thus setting the stage for the desired cycloisomerization (Scheme 4). The treatment of **19** with catalytic amounts of the cobalt–salen complex **20a** and phenylsilane according to the method described by Shenvi and co-workers[15] did not give

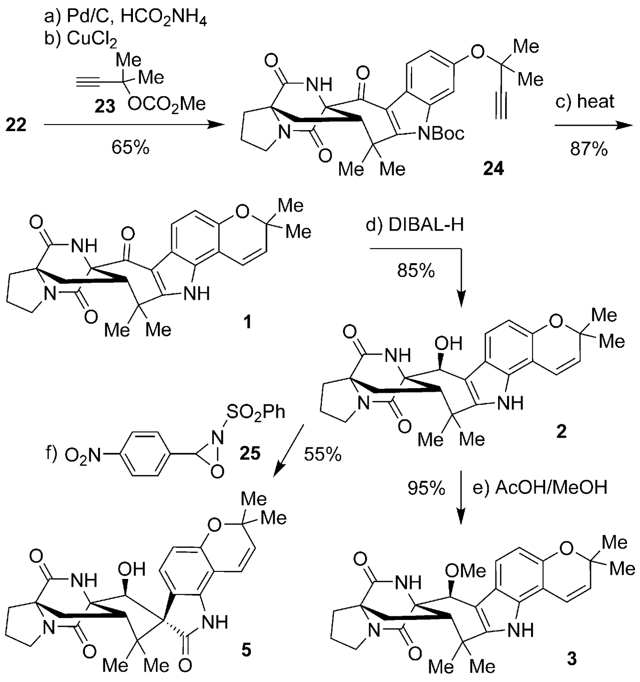


Conditions	Yield [%] 21	Yield [%] 22
20a (0.2 equiv), $PhSiH_3$ (0.4 equiv)	trace	
20b (0.2 equiv), $PhSiH_3$ (0.4 equiv)	6	10
20b (0.2 equiv), $PhSiH_3$ (1.2 equiv)	39	47
20b (0.2 equiv), $PhSiH_3$ (1.2 equiv), then DMP (2.5 equiv)	0	82

Scheme 4. Cobalt-catalyzed radical cyclization. Reagents and conditions: a) **12** (2.0 equiv), *i*PrMgCl (2.2 equiv), THF, 0 °C, 30 min, 47%; b) **20b** (0.2 equiv), $PhSiH_3$ (1.2 equiv), C_6H_6, 60 °C, 5 h; then DMP (2.5 equiv), 25 °C, 5 h, 82%. DMP = 1,1,1-tris(acetyloxy)-1,1-dihydro-1,2-benziodoxol-3-(1*H*)-one.

the expected product, but instead most of **19** was recovered. Switching of the cobalt catalyst to complex **20b** resulted in the formation of the desired product **22** along with 2,3-dihydroindole product **21**, both in low yields. However, when the reaction was carried out with a slight excess of phenylsilane, the yields of **21** and **22** were both significantly increased. The concurrent formation of **21** and **22** indicate that reductive cyclization[18] competes well with cycloisomerization. Nevertheless, it was envisioned that **21** could be further converted into **22** by oxidation. Thus, **19** was treated with phenylsilane under the catalysis of cobalt complex **20b**, and the reaction was then quenched with Dess–Martin periodinane (DMP). Compound **22** was obtained cleanly in 82 % yield by this one-pot procedure.

With intermediate **22** in hand, we went on to complete the total synthesis of **1**–**3** and **5** (Scheme 5). The debenzylation of **22**, followed by copper-catalyzed propargylation[19] with propargyl carbonate **23**, afforded ether **24** in 65 % yield over two steps. Allenyl Claisen rearrangement[20] with simultaneous deprotection furnished (+)-notoamide I (**1**) in 87 % yield with a measured $[\alpha]_D^{25}$ value of +39.0 (c = 0.12, MeOH/$CHCl_3$ 1:1), in agreement with the previously reported $[\alpha]_D^{29}$ value of +31.0 (c = 0.1, MeOH/$CHCl_3$ 1:1).[11a] Thus, starting from Seebach acetal **15**, (+)-notoamide I was synthesized in only 10 steps in 7.3 % overall yield. This convergent route is not only efficient and highly stereoselective, but also much shorter than any reported route towards stephacidin A (≥ 13 steps).



Scheme 5. Completion of the synthesis of **1**–**3** and **5**. Reagents and conditions: a) 10% Pd/C, HCO_2NH_4 (18 equiv), CH_2Cl_2/MeOH (1:1), 25 °C, 1 h, 93 %; b) $CuCl_2$ (0.05 equiv), **23** (9 equiv), DBU (3 equiv), CH_3CN, 25 °C, 24 h, 65 %; c) 1,2-dichlorobenzene, 180 °C, 20 min, 87%; d) DIBAL-H (1.5 equiv), THF, 0 °C, 1 h, 85 %; e) AcOH/MeOH (1:20), 25 °C, 24 h, 95 %; f) **25** (1.2 equiv), CH_2Cl_2, 25 °C, 8 h, 55 %. DIBAL-H = diisobutylaluminum hydride.

The reduction of **1** with DIBAL-H gave (+)-notoamide R (**2**) as the only stereoisomer in 85 % yield with an $[\alpha]_D^{22}$ value of +39.1 (c = 0.23, MeOH), consistent with the reported value of +38.0 (c = 0.50, MeOH).[11b] Further treatment of **2** with AcOH in methanol produced (+)-notoamide F (**3**) exclusively with complete retention of configuration. The $[\alpha]_D^{22}$ value of **3** was found to be +4.7 (c = 0.23, MeOH), which is comparable with the previously reported value ($[\alpha]_D^{21}$ = +1.9 (c = 0.27, MeOH)).[11a] Finally, the conversion of **2** into (−)-sclerotiamide (**5**) with oxaziridines[5,21] was investigated. We screened a number of oxaziridines (see Table S6) and found that, with oxaziridine **25** as the oxidant, the rearrangement of **2** proceeded smoothly at room temperature to furnish **5** in 55 % yield. The measured $[\alpha]_D^{22}$ value of −57.4 (c = 0.073, MeOH) matches the reported value[12] well ($[\alpha]_D$ = −55.1 (c = 0.1, MeOH)). The ^1H and ^{13}C spectra of **1**–**3** and **5** thus synthesized were identical to those reported previously.

In summary, the first total synthesis of **1**–**3** and **5** from the Seebach acetal **15** was completed in only 10–12 steps. The synthesis is efficient and highly stereoselective, and features an oxidative aza-Prins cyclization to construct the bicyclo[2.2.2]diazaoctane in a highly stereoselective manner, and a cobalt-catalyzed radical cycloisomerization to generate the cyclohexenyl ring.

Acknowledgements

This project was supported by the NSFC (Grants 21272259, 21290180, 21421002, 21472220, 21502210, 21532008, and 21361140377) and by the CAS (Grant XDB20020000).

Keywords: cyclization · indole alkaloids · natural products · radicals · total synthesis

How to cite: *Angew. Chem. Int. Ed.* **2016**, *55*, 10435–10438
Angew. Chem. **2016**, *128*, 10591–10594

---

[1] K. A. Miller, R. M. Williams, *Chem. Soc. Rev.* **2009**, *38*, 3160–3174.

[2] a) R. M. Williams, T. Glinka, E. Kwast, *J. Am. Chem. Soc.* **1988**, *110*, 5927–5929; b) R. M. Williams, T. Glinka, E. Kwast, H. Coffman, J. K. Stille, *J. Am. Chem. Soc.* **1990**, *112*, 808–821; c) L. A. Adams, M. W. N. Valente, R. M. Williams, *Tetrahedron* **2006**, *62*, 5195–5200.

[3] a) P. S. Baran, C. A. Guerrero, N. B. Ambhaikar, B. D. Hafensteiner, *Angew. Chem. Int. Ed.* **2005**, *44*, 606–609; *Angew. Chem.* **2005**, *117*, 612–615; b) P. S. Baran, B. D. Hafensteiner, N. B. Ambhaikar, C. A. Guerrero, J. D. Gallagher, *J. Am. Chem. Soc.* **2006**, *128*, 8678–8693.

[4] S. B. Herzon, A. G. Myers, *J. Am. Chem. Soc.* **2005**, *127*, 5342–5344.

[5] a) T. J. Greshock, A. W. Grubbs, S. Tsukamoto, R. M. Williams, *Angew. Chem. Int. Ed.* **2007**, *46*, 2262–2265; *Angew. Chem.* **2007**, *119*, 2312–2315; b) G. D. Artman III, A. W. Grubbs, R. M. Williams, *J. Am. Chem. Soc.* **2007**, *129*, 6336–6342; c) T. J. Greshock, R. M. Williams, *Org. Lett.* **2007**, *9*, 4255–4258; d) J. D. Sunderhaus, T. J. McAfoos, J. M. Finefield, H. Kato, S. Li, S. Tsukamoto, D. H. Sherman, R. M. Williams, *Org. Lett.* **2013**, *15*, 22–25.

[6] a) N. S. Simpkins, I. Pavlakos, M. D. Weller, L. Male, *Org. Biomol. Chem.* **2013**, *11*, 4957 – 4970; b) N. Simpkins, I. Pavlakos, L. Male, *Chem. Commun.* **2012**, *48*, 1958 – 1960.

[7] a) K. A. Miller, T. R. Welch, T. J. Greshock, Y. Ding, D. H. Sherman, R. M. Williams, *J. Org. Chem.* **2008**, *73*, 3116 – 3119; b) F. Frebault, N. S. Simpkins, A. Fenwick, *J. Am. Chem. Soc.* **2009**, *131*, 4214 – 4215; c) S. W. Laws, J. R. Scheerer, *J. Org. Chem.* **2013**, *78*, 2422 – 2429.

[8] B. M. Trost, N. Cramer, H. Bernsmann, *J. Am. Chem. Soc.* **2007**, *129*, 3086 – 3087.

[9] a) E. V. Mercado-Martin, P. Garcia-Reynaga, S. Romminger, E. F. Pimenta, D. K. Rommey, M. W. Lodewyk, D. E. Williams, R. J. Andersen, S. J. Miller, D. J. Tantillo, R. G. S. Berlinck, R. Sarpong, *Nature* **2014**, *509*, 318 – 324; b) Z. Bian, C. C. Marvin, S. F. Martin, *J. Am. Chem. Soc.* **2013**, *135*, 10886 – 10889; c) K. Kong, J. A. Enquist, Jr., M. E. McCallum, G. M. Smith, T. Matsumaru, E. Menhaji-Klotz, J. L. Wood, *J. Am. Chem. Soc.* **2013**, *135*, 10890 – 10893.

[10] P. S. Baran, M. P. DeMartino, *Angew. Chem. Int. Ed.* **2006**, *45*, 7083 – 7086; *Angew. Chem.* **2006**, *118*, 7241 – 7244.

[11] a) S. Tsukamoto, H. Kato, M. Samizo, Y. Nojiri, H. Onuki, H. Hirota, T. Ohta, *J. Nat. Prod.* **2008**, *71*, 2064 – 2067; b) S. Tsukamoto, H. Umaoka, K. Yoshikawa, T. Ikeda, H. Hirota, *J. Nat. Prod.* **2010**, *73*, 1438 – 1440.

[12] A. C. Whyte, J. B. Gloer, D. T. Wicklow, P. F. Dowd, *J. Nat. Prod.* **1996**, *59*, 1093 – 1095.

[13] a) B. B. Snider, *Chem. Rev.* **1996**, *96*, 339 – 363; b) B. B. Snider in *Radicals in Organic Synthesis*, *Vol. 1* (Eds.: P. Renaud, M. P. Sibi), Wiley-VCH, Weinheim, **2001**, pp. 198 – 218; c) T. Linker in *Radicals in Organic Synthesis*, *Vol. 1* (Eds.: P. Renaud, M. P. Sibi), Wiley-VCH, Weinheim, **2001**, pp. 219 – 228; d) J. W. Burton in *Encyclopedia of Radicals in Chemistry*, *Biology and Materials* (Eds.: C. Chatgilialoglu, A. Studer), Wiley, Chichester, **2012**, pp. 902 – 942.

[14] An intramolecular Diels–Alder (IMDA) reaction of **8** was also attempted, but failed (see Table S2 for details). A similar IMDA reaction was reported to be unsuccessful by Baran et al. (see Ref. [3b]).

[15] S. W. M. Crossley, F. Barabe, R. A. Shenvi, *J. Am. Chem. Soc.* **2014**, *136*, 16788 – 16791.

[16] R. B. Ruggeri, M. M. Hansen, C. H. Heathcock, *J. Am. Chem. Soc.* **1988**, *110*, 8734 – 8736.

[17] D. Seebach, M. Boes, R. Naef, W. B. Schweizer, *J. Am. Chem. Soc.* **1983**, *105*, 5390 – 5398.

[18] a) G. Li, A. Han, M. E. Pulling, D. P. Estes, J. R. Norton, *J. Am. Chem. Soc.* **2012**, *134*, 14662 – 14665; b) A. Han, T. Spataru, J. Hartung, G. Li, J. R. Norton, *J. Org. Chem.* **2014**, *79*, 1938 – 1946.

[19] E. J. Tisdale, B. G. Vong, H. Li, S. H. Kim, C. Chowdhury, E. A. Theodorakis, *Tetrahedron* **2003**, *59*, 6873 – 6887.

[20] R. J. Cox, R. M. Williams, *Tetrahedron Lett.* **2002**, *43*, 2149 – 2152.

[21] a) F. A. Davis, J. C. Towson, D. B. Vashi, R. ThimmaReady, J. P. McCauley, M. E. Harakal, D. J. Gosciniak, *J. Org. Chem.* **1990**, *55*, 1254 – 1261; b) B. B. Snider, H. Zeng, *J. Org. Chem.* **2003**, *68*, 545 – 563.

Received: May 16, 2016