Natural Product Synthesis

International Edition: DOI: 10.1002/anie.201503982
German Edition: DOI: 10.1002/ange.201503982

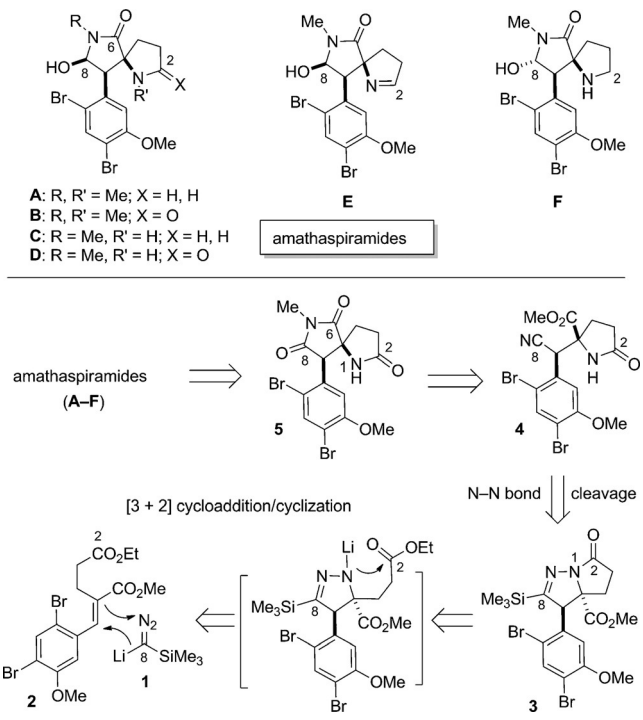
Synthesis of Amathaspiramides by Aminocyanation of Enoates**

*Matthew O'Connor, Chunrui Sun, and Daesung Lee**

Abstract: *Concise routes for the total and formal syntheses of the amathaspiramides were developed through a formal [3+2] cycloaddition between lithium(trimethylsilyl)diazomethane and α,β-unsaturated esters. The effectiveness of this new cycloaddition for the construction of Δ²-pyrazolines containing a α-tert-alkylamino carbon center and subsequent facile protonolytic N–N bond cleavage allows the synthesis of a key intermediate of the amathaspiramides and other α,α-disubstituted amino acid derivatives.*

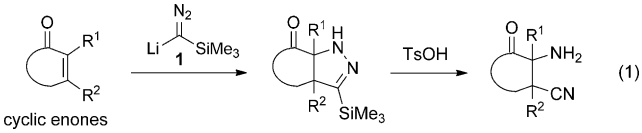
The facile construction of nonproteinogenic amino acid derivatives is of significant value in the fields of medicinal and biological chemistry.[1] These nonproteinogenic amino acids are crucial in the design of proteins, and specifically, α,α-disubstituted α-amino acids (α-*tert*-alkylamino acids) can lead to increased rigidity and stability of these polypeptides.[2] Also, they are often enzyme inhibitors themselves,[3] and serve as useful building blocks for biologically active natural products and pharmaceuticals. One family of natural products containing the α-*tert*-alkylamino carbonyl functionality is the amathaspiramides: spirocyclic alkaloids which exhibit cytotoxic, antiviral and antimicrobrial activity (Scheme 1).[4]

For the synthesis of amathaspiramides or other natural and medicinal compounds (e.g. *N*-methylwelwitindolinone C isothiocyanate,[5] salinosporamide A,[6] BMS-561392[7]), the development an efficient method for the construction of the α-*tert*-alkylamino carbonyl functionality is highly desirable.[8]



Scheme 1. Retrosynthesis of amathaspiramides.

Toward this goal, we recently reported a formal [3+2] cycloaddition between lithium(trimethylsilyl)diazomethane (LTMSD; **1**)[9,10] and α,β-unsaturated cyclic enones [Eq. (1)].[11]



In retrosynthetic planning, the advanced intermediate **5**, a precursor to all members of the amathaspiramide family bearing either different oxidation levels at C2 or different stereochemistry at C8, will be obtained from the lactam **4**, which in turn can be generated through the N–N bond cleavage from the pyrazoline **3** (Scheme 1). This bicyclic pyrazoline is a sequential reaction product formed from an initial cycloaddition (or 1,4-addition-cyclization) of **1**, the source of the C8 carbonyl and N1, with the α,β-unsaturated ester **2** and subsequent ring closure between the resulting lithiumamide and the C2 carboxylate.

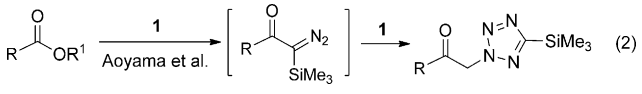
One immediate concern of this plan is the uncertainty regarding the undesired 1,2-addition versus the desired 1,4-addition/cyclization (a formal cycloaddition), given the report

[*] M. O'Connor, Prof. D. Lee
Department of Chemistry, University of Illinois at Chicago
845 West Taylor Street, Chicago, IL (USA)
E-mail: dsunglee@uic.edu
C. Sun
Merck Discovery Chemistry
2000 Galloping Hill Road, Kenilworth, NJ 07033 (USA)

[**] We thank UIC (LAS Science Award), NSF (CHE 0955972), and the donors of the Petroleum Research Fund for financial support. We also acknowledge Furong Sun of the mass spectrometry facility at UIUC for mass spectrometry data and Prof. Neal Mankad for his help in obtaining X-ray structures.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201503982.

by Aoyama and Shioiri on a facile 1,2-addition of **1** with alkyl carboxylates to form a diazo ketone followed by its subsequent reaction with another molecule of **1**, thus generating a tetrazole derivative [Eq. (2)].[13]

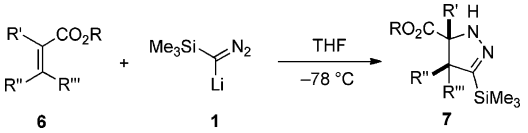


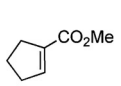
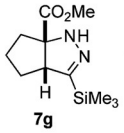
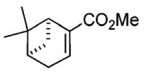
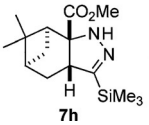
(2)

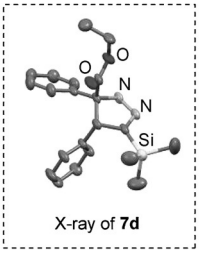
To check this critical chemoselectivity and general reactivity of α,β-unsaturated esters toward **1**, we examined the structure-dependent reaction profiles of α,β-unsaturated esters (Table 1). Methyl methacrylate (**6a**) reacted cleanly with **1**, thus delivering the Δ^2-pyrazoline **7a** as the sole product in 91% yield (entry 1). Ethyl tiglate (**6b**) produced the Δ^2-pyrazoline **7b** in 82% yield as a 4:1 mixture of diastereomers based on ^{1}H NMR analysis of the crude reaction mixture (entry 2). For β,β-disubstituted esters, 1,2-addition becomes a more favored mode of reaction if typical methyl and ethyl esters are employed. To suppress the 1,2-addition of **1** with β,β-disubstituted esters, a *tert*-butyl ester was found to be suitable. When subjected to the typical reaction conditions, the *tert*-butyl ester **6c** reacted cleanly with **1**, thus producing the Δ^2-pyrazoline **7c**, containing an all-carbon quaternary center, as the sole product in 75% yield (entry 3). To further probe the stereoselectivity of the reaction, *E*- and *Z*-ethyl cinnamate derivatives, **6d** and **6e**, respectively, were subjected to the standard reaction conditions. The reaction of **6d** produced the pyrazoline **7d** as a 10:1 mixture of diastereomers whose structure was confirmed unambiguously by X-ray diffraction analysis,[14] whereas **6e** produced a 1:1 mixture of diastereomers. The tetrasubstituted enone **6f** was not a suitable substrate under the standard reaction conditions, and the starting material was recovered intact. Cyclic esters are also viable substrates for cycloadditions, as the methyl cyclopentene carboxylate **6g** produced the bicyclic pyrazoline **7g** in 71% yield (entry 7). Other cyclic carboxylates such as methyl myrtenate (**6h**) produced the corresponding pyrazoline **7h** as a single diastereomer (entry 8).

Once the scope of the formal cycloaddition (1,4-addition-cyclization) of α,β-unsaturated esters, including the β,β-disubstituted ester **6c**, was successfully demonstrated to generate structurally diverse Δ^2-pyrazolines, we then pursued a total synthesis of amathspiramide C (Scheme 2). The ester **8** and aldehyde **9** were merged by a Peterson olefination with subsequent deprotection and tosylation to deliver the cinnamates **10** ($E/Z = 1:1$). The formal [3+2] cycloaddition between **10** and **1** led to mixtures of the bicyclic pyrazolines **11**. The N–N bond cleavage in the pyrazolines **11** (TsOH, CH_2Cl_2, reflux) generated the epimers **12a**,**b**, which were converted into the imide **13** under known reaction conditions.[15] Gratifyingly, **12b** was epimerized under basic conditions. Methylation of N7 under Mitsunobu conditions provided the penultimate intermediate **14**, which was expected to provide amathaspiramide C by reducing the C8

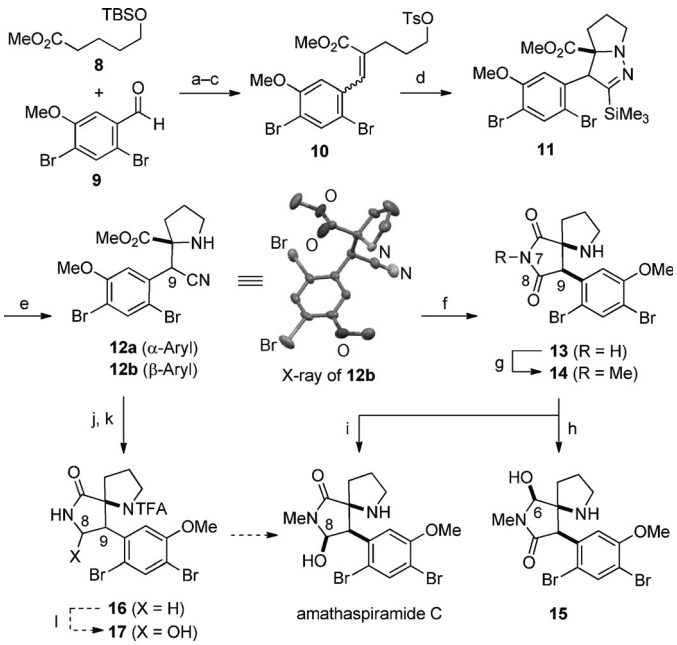
Table 1: [3+2] cycloaddition of **1** with α,β-unsaturated esters.



Entry	α,β-Unsaturated ester (**6**)	Pyrazoline (**7**)	Yield [%][a]	d.r.
1	**6a**, R = Me, R' = R'' = R''' = H	**7a**	91	–
2	**6b**, R = Et, R' = Me, R'' = H, R''' = Me	**7b**	82	4:1
3	**6c**, R = *t*Bu, R' = H, R'' = R''' = Me	**7c**	75	–
4	**6d**, R = Et, R' = Ph, R'' = Ph, R''' = H	**7d**	85	10:1
5	**6e**, R = Et, R' = Ph, R'' = H, R''' = Ph	**7e**	80	1:1
6	**6f**, R = *t*Bu, R' = Ph, R'' = Ph, R''' = Ph	**7f**	n.r.[b]	–
7	 **6g**	 **7g**	71	1:0
8	 **6h**	 **7h**	65	1:0



[a] Yield of the isolated product. [b] No reaction under the standard reaction conditions.

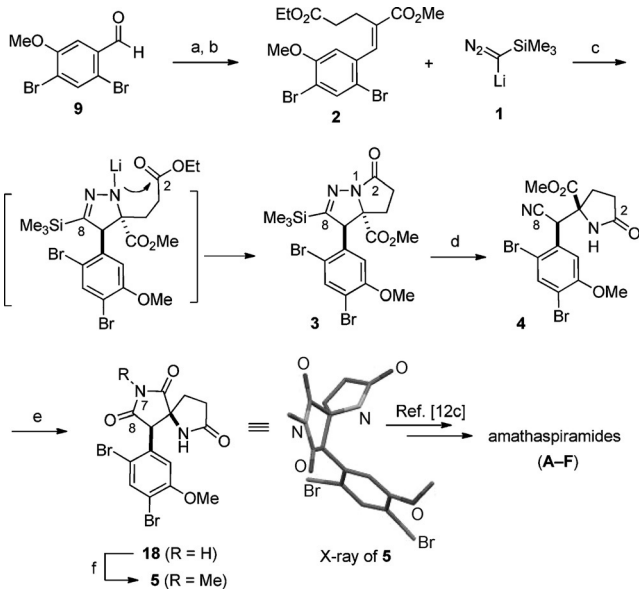


Scheme 2. Total synthesis of amathaspiramide C: a) LDA, $ClSiPh_2Me$; b) LDA, **9**, −78 °C; then $HCl_{(aq)}$; c) TsCl, Et_3N; d) $TMSCLiN_2$, −78 °C; e) TsOH, EtOH; f) HOOH, NaOH, EtOH, RT, 50%; g) MeOH, PPh_3, DIAD, THF, RT, 85%; h) $NaBH_4$, MeOH or $LiAlH_4$, THF; i) DIBAL, CH_2Cl_2, −78 °C, 31% of amathaspiramide C and 45% of **15**; j) $(F_3CCO)_2O$, pyridine; k) $[Cp_2Zr(H)Cl]$ (3 equiv) CH_2Cl_2; l) Ag^{II} picolinate (3 equiv), TFA/H_2O (1:9), RT. Cp = cyclopentadiene, DIAD = diisopropyl azodicarboxylate, DIBAL = diisobutylaluminum hydride, LDA = lithiumdiisopropylamide, TFA = trifluoroacetic acid, THF = tetrahydrofuran, Ts = 4-toluenesulfonyl.

carbonyl group. Treating **14** with various reducing reagents, however, afforded either the C6-carbonyl-reduced product **15** ($NaBH_4$/MeOH, $LiAlH_4$) or no reaction (2 equivalents K-Selectride). It was found that an excess of DIBAL (2.5 equivalents) provided a C8-carbonyl-reduced compound, the NMR signals of which matched those of authentic amathaspiramide C (31%), along with the C6-carbonyl-reduced product **15** (43%) in a 1:1.5 ratio.[16,17] To avoid this late-stage differentiation of the similar imide carbonyl groups, an alternative route involving selective reduction of the CN functionality was examined. First, N1 (pyrrolidine nitrogen atom) of **12a**,**b** was protected as the trifluoroacetamide and the resulting compound was treated with $[Cp_2Zr(H)Cl]$, which, however, provided only the pyrolidinone **16** without an imine or its C8-hemiaminal **17**. Oxidation of **15** at C8 to form **17** under known reaction conditions[18] was unsuccessful.

The synthetic route in Scheme 2 successfully implemented the new cycloaddition between **1** and α,β-unsaturated esters in a short synthesis of amathaspiramide C. However, it is limited to the synthesis of only amathaspiramides C and F. The versatile cycloaddition-based strategy would be further extended to the synthesis of all members of the the amathaspiramide family if the α,β-unsaturated ester **2**, containing a tethered ester, is employed (see Scheme 3). Although racemic, this new route provides not only rapid access to an advanced intermediate, **5**, from which all members of amathaspiramides were synthesized enantioselectively by Fukuyama and co-workers,[12c] but also results in a significantly shortened synthetic sequence compared to that needed for the tosylate-containing cinnamate derivative **10**.

The new synthetic sequence commenced with a Baylis–Hillman reaction of methyl acrylate with known aldehyde **9** and subsequent orthoester Claisen rearrangement of the resulting adduct, which provided the cinnamate derivative **2** in good yield (Scheme 3).[19] Although there is a possibility that the extra unconjugated ester moiety might undergo 1,2-addition with **1** to preclude the implementation of the plan, gratifyingly treatment of **2** with **1** exclusively provided the bicyclic pyrazoline **3** in 80% yield as the sole diastereomer. This result clearly suggests that even cinnamate derivatives deactivated by electronic and steric factors can undergo cycloaddition more favorably over 1,2-addition on a typical ester moiety. Starting from **3**, Fukuyama's advanced intermediate **5** was generated efficiently through a three-step sequence. First, the protonolytic N–N bond cleavage was accomplished by treating **3** with *p*-TsOH in EtOH, thus affording the C9 cyano lactam **4** in excellent yield. Subsequently, the cyano group of **4** was selectively hydrolyzed by treatment with hydrogen peroxide and K_2CO_3 in DMSO,[20] thus delivering the imide **18** as a single diastereomer. Under these reaction conditions, the pyrrolidinone moiety remained intact. Methylation of N7 turned out to be much more challenging than that of **12**. After extensive experimentation, it was found that a Mitsunobu reaction employing polymer-supported triphenylphosphine effected the methylation, thus delivering **5** in 62% (2 steps).[21] Since **5** serves as a precursor to all the amathaspiramides in Fukuyama's synthesis, this synthetic route resulted in an formal synthesis of amathaspiramides A–F.



Scheme 3. Concise route for the synthesis of all members of amathaspiramides: a) methyl acrylate, DABCO, DMSO, RT, 85%; b) $(EtO)_3CCH_3$, propionic acid, reflux, 65%; c) **1**, THF, −78°C, 80%; d) *p*-TsOH, EtOH, reflux; K_2CO_3, 95%; e) HOOH, K_2CO_3, DMSO, 0°C to RT, 66%; f) MeOH, DBAD, PS-PPh_3, THF, sonication, 58%. DABCO = 1,4-diazabicyclo[2.2.2]octane, DBAD = di-*tert*-butyl azodicarboxylate, DMSO = dimethylsulfoxide, PS-PPh_3 = polymer-bound triphenylphosphine.

In summary, a concise total synthesis of amathaspiramide C as well as a formal synthesis of all members of the amathaspiramide family has been achieved. The key feature of these syntheses is the cycloaddition between lithium(trimethylsilyl)diazomethane (**1**) with α,β-unsaturated esters followed by a facile protonolytic N–N bond cleavage to install the necessary functional groups. This synthetic endeavor resulted in the development of an efficient new synthetic method for structurally diverse α,α-disubstituted α-amino acid (α-*tert*-alkylamino acid) derivatives from readily available α,β-unsaturated esters and **1**. The utility and effectiveness of this synthetic method toward other natural products is under active investigation.

Keywords: amino acid · cycloaddition · diazo compounds · natural products · total synthesis

How to cite: *Angew. Chem. Int. Ed.* **2015**, *54*, 9963–9966
Angew. Chem. **2015**, *127*, 10101–10104

[1] For recent reviews, see: a) T. Heck, B. Geueke, H. P. E. Kohler, *Chem. Biodiversity* **2012**, *9*, 2388; b) A. G. Jamieson, N. Boutard, D. Sabatino, W. D. Lubell, *Chem. Biol. Drug Des.* **2013**, *81*, 148; c) I. Kwon, S. I. Lim, *Macromol. Chem. Phys.* **2013**, *214*, 1295; d) P. G. Vasudev, S. Chatterjee, N. Shamala, P. Balaram, *Chem. Rev.* **2011**, *111*, 657.

[2] a) P. Balaram, *Curr. Opin. Struct. Biol.* **1992**, *2*, 845; b) E. Benedetti, E. Gavuzzo, A. Santini, D. R. Kent, Y.-F. Zhu, Q. Zhu, C. Mahr, M. Goodman, *J. Pept. Sci.* **1995**, *1*, 349; c) O. Déry, H. Josien, J. Grassi, G. Chassaing, J. Y. Couraud, S. Lavielle, *Biopolymers* **1996**, *39*, 67; d) C. Cativiela, M. D. Díaz-de-

Villegas, *Tetrahedron: Asymmetry* **1998**, *9*, 3517; e) C. Toniolo, M. Crisma, F. Formaggio, C. Peggion, *Biopolymers* **2001**, *60*, 396; f) P. Maity, B. König, *Biopolymers* **2008**, *90*, 8.

[3] a) T. L. Sourkes, *Arch. Biochem. Biophys.* **1954**, *51*, 444; b) D. K. Zhelyaskov, M. Levitt, S. Uddenfriend, *Mol. Pharmacol.* **1968**, *4*, 445; c) R. Pellicciari, R. Luneia, G. Costantino, M. Marinozzi, B. Natalini, P. Jakobsen, A. Kanstrup, G. Lombardi, F. Moroni, C. Thomsen, *J. Med. Chem.* **1995**, *38*, 3717; d) D. D. Schoepp, D. E. Jane, J. A. Monn, *Neuropharmacology* **1999**, *38*, 1431.

[4] B. D. Morris, M. R. Prinsep, *J. Nat. Prod.* **1999**, *62*, 688.

[5] a) K. Stratmann, R. E. Moore, R. Bonjouklian, J. B. Deeter, G. M. L. Patterson, S. Shaffer, C. D. Smith, T. A. Smitka, *J. Am. Chem. Soc.* **1994**, *116*, 9935; b) J. I. Jimenez, U. Huber, R. E. Moore, G. M. L. Patterson, *J. Nat. Prod.* **1999**, *62*, 569.

[6] R. H. Feling, G. O. Buchanan, T. J. Mincer, C. A. Kauffman, P. R. Jensen, W. Fenical, *Angew. Chem. Int. Ed.* **2003**, *42*, 355; *Angew. Chem.* **2003**, *115*, 369.

[7] M. Grootveld, M. F. McDermott, *Curr. Opin. Invest. Drugs* **2003**, *4*, 598.

[8] For the installation of α-*tert*-alkylamino functionality: a) S. H. Kang, S. Y. Kang, H.-S. Lee, A. J. Buglass, *Chem. Rev.* **2005**, *105*, 4537; b) Y. Ohfune, T. Shinada, *Eur. J. Org. Chem.* **2005**, 5127; c) C. Cativiela, M. D. Diaz-de-Villegas, *Tetrahedron: Asymmetry* **2007**, *18*, 569; d) H. Vogt, S. Bräse, *Org. Biomol. Chem.* **2007**, *5*, 406; e) G. Frey, H.-T. Luu, P. Bichovski, M. Feurer, J. Streuff, *Angew. Chem. Int. Ed.* **2013**, *52*, 7131; *Angew. Chem.* **2013**, *125*, 7271; f) K. Li, G. Tan, J. Huang, F. Song, J. You, *Angew. Chem. Int. Ed.* **2013**, *52*, 12942; *Angew. Chem.* **2013**, *125*, 13180; g) F.-g. Sun, S. Ye, *Org. Biomol. Chem.* **2011**, *9*, 3632; h) K.-J. Wu, G.-Q. Li, Y. Li, L.-X. Dai, S.-L. You, *Chem. Commun.* **2011**, *47*, 493; for asymmetric α-aminations: i) C. Greck, B. Drouillat, C. Thomassigny, *Eur. J. Org. Chem.* **2004**, 1377; j) J. M. Janey, *Angew. Chem. Int. Ed.* **2005**, *44*, 4292; *Angew. Chem.* **2005**, *117*, 4364; For other methods: k) G. Guillena, D. J. Ramon, *Tetrahedron: Asymmetry* **2006**, *17*, 1465; l) A. Russo, C. D. Fusco, A. Lattanzi, *RSC Adv.* **2012**, *2*, 385; for reviews: m) C. Nájera, J. M. Sansano, *Chem. Rev.* **2007**, *107*, 4584; n) A. M. R. Smith, K. K. Hii, *Chem. Rev.* **2011**, *111*, 1637.

[9] Caution! See the Supporting Information and: J. Kemsley, *Chem. Eng. News* **2011**, *89*(19), 15.

[10] a) K. Miwa, T. Aoyama, T. Shioiri, *Synlett* **1994**, 107; b) T. Shioiri, T. Aoyama, *Advances in the Use of Synthons in Organic Chemistry*, *Vol. 1* (Ed.: A. Dondoni), JAI, London, **1993**, pp. 55–101; c) J. Podlech, *J. Prakt. Chem.* **1998**, *340*, 679.

[11] C. Sun, M. J. O'Connor, D. Lee, D. J. Wink, R. D. Milligan, *Angew. Chem. Int. Ed.* **2014**, *53*, 3197; *Angew. Chem.* **2014**, *126*, 3261.

[12] a) C. C. Hughes, D. Trauner, *Angew. Chem. Int. Ed.* **2002**, *41*, 4556; *Angew. Chem.* **2002**, *114*, 4738; b) K. Sakaguchi, M. Ayabe, Y. Watanabe, T. Okada, K. Kawamura, T. Shiada, Y. Ohfune, *Org. Lett.* **2008**, *10*, 5449; c) K. Chiyoda, J. Shimokawa, T. Fukuyama, *Angew. Chem. Int. Ed.* **2012**, *51*, 2505; *Angew. Chem.* **2012**, *124*, 2555; d) A. Soheili, U. K. Tambar, *Org. Lett.* **2013**, *15*, 5138.

[13] T. Aoyama, T. Shioiri, *Chem. Pharm. Bull.* **1982**, *30*, 3450.

[14] CCDC 1044098 (**7d**), 1044017 (**12b**), and 1044018 (**5**) contain the supplementary crystallographic data for this paper. These data are provided free of charge by The Cambridge Crystallographic Data Centre.

[15] C. R. Noller, *Org. Syn. Coll.* **1943**, *2*, 586.

[16] Contrary to the selective reduction of **5** to amathaspiramide D (Ref. [12c]), reduction of the compound **14** with DIBAL is not chemoselective for the C8 carbonyl group. Thus, the C6-carbonyl-reduced compound **15** was generated as a major product along with amathaspiramide C in a 1.5:1 ratio. This result implies that the C2 carbonyl group on compound **5** plays an important role for selective reduction of its C8 carbonyl group over that at C6.

[17] The ^{1}H and ^{13}C NMR signals of **15** clearly indicate that one of the carbonyl groups is reduced. Because these NMR signals do not match those of amathaspiramide F, **15** must be reduced at the C6 carbonyl group. The configuration of the hydroxy group at C6 is confirmed by nOe experiment.

[18] I. B. Seiple, S. Su, I. S. Young, A. Nakamura, J. Yamaguchi, L. Jørgensen, R. A. Rodrigues, D. P. O'Malley, T. Gaich, M. Köck, P. S. Baran, *J. Am. Chem. Soc.* **2011**, *133*, 14710.

[19] For a recent reviews of the Baylis–Hillman reaction, see: a) D. Basavaiah, A. J. Rao, T. Satyanarayana, *Chem. Rev.* **2003**, *103*, 811; b) D. Basavaiah, P. D. Rao, R. S. Hyma, *Tetrahedron* **1996**, *52*, 8001; for the Johnson–Claisen rearrangement of Baylis–Hillman adducts, see c) D. Basavaiah, S. Pandiaraju, *Tetrahedron Lett.* **1995**, *36*, 757; d) D. Basavaiah, S. Pandiaraju, M. Krishnamacharyulu, *Synlett* **1996**, 747.

[20] K. Nagata, D. Sano, Y. Shimizu, M. Miyazaki, T. Kanemitsu, T. Itoh, *Tetrahedron: Asymmetry* **2009**, *20*, 2530.

[21] M. Kiankarimi, R. Lowe, J. R. McCarthy, J. P. Whitten, *Tetrahedron Lett.* **1999**, *40*, 4497.

Received: April 30, 2015
Published online: June 30, 2015

