

Natural Products

International Edition: DOI: 10.1002/anie.201600632
German Edition: DOI: 10.1002/ange.201600632

Stereodivergent and Protecting-Group-Free Synthesis of the Helicascolide Family: A Rhodium-Catalyzed Atom-Economical Lactonization Strategy

Alexander M. Haydl, Dino Berthold, Pierre A. Spreider, and Bernhard Breit*

Abstract: Natural products of polyketide origin, in particular small-sized lactones often possess a very broad range of impressive biological activities. An efficient way to demonstrate the concise access to six-membered lactones was emphasized as part of a stereodivergent and protecting-group-free synthesis of all three representatives of the helicascolide family. This strategy features an atom-economical and highly diastereoselective rhodium-catalyzed “head-to-tail” lactonization by an intramolecular addition of ω -allenyl-substituted carboxylic acids to terminal allenes, including the selective construction of a new stereocenter in the newly formed core structures. The excellent selectivities with which the helicascolide precursors were obtained are remarkable, thus resulting in an expeditious and highly efficient natural product synthesis.

Polyketides prevail in a large variety of natural products and have about a five times higher chance of possessing potential biological activity compared to any other class of natural products.^[1,2] Among those, especially natural products holding five- or six-membered lactones in their often very complex substituted scaffolds, exhibit a broad spectrum of biological activity^[3] such as immunosuppressive,^[4a] anticancer,^[4b] antifungal,^[4c] and cytotoxic properties,^[4d] as well as various others (Figure 1).^[4e,f]

Strategic approaches for the synthesis of five- or six-membered lactones, besides the classical lactonization conditions by activation of the corresponding seco-acids,^[5] have been reported in the recent past to proceed in an asymmetric and diastereoselective fashion, including transition metal catalyzed addition reactions,^[6] halo- and selenolactonizations,^[7] lactonizations by ring-closing metathesis,^[8] and others.^[9] However, in many cases these reactions suffer from low selectivities, a lack of atom economy, the requirement of stoichiometric amounts of co-reagents, or the need for a preinstalled stereocenter in the molecule prior to lactonization. Our research group developed a rhodium-catalyzed,^[10] atom-economical, and regioselective addition^[11] of carboxylic acids to allenes^[12] and alkynes,^[13] a method which could be seen as an alternative to metal-catalyzed

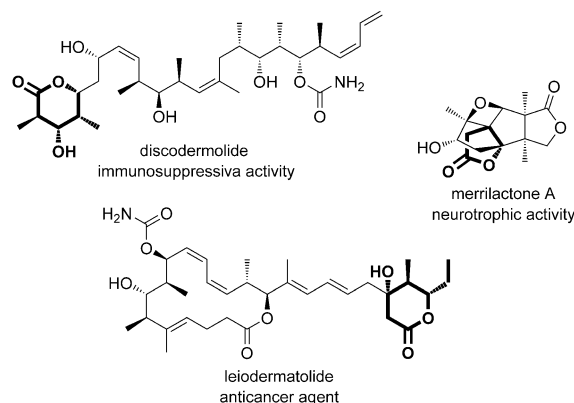


Figure 1. Small selection of structurally diverse bioactive natural products bearing five- and six-membered lactones.

allylic substitution^[14] and oxidation^[15] to generate branched allylic esters.^[16]

In this respect, we recently described a highly atom-economical dimerization strategy as a selective approach towards the C_2 -symmetric macrodiolide clavosolide A.^[12c] Driven by our curiosity as to whether this initial method could be successfully carried over for the selective synthesis of six-membered lactone-based natural products, we targeted helicascolide C (**3**)^[17a] and its two congeners helicascolide A (**1**) and B (**2**; Figure 2),^[17b] which have already garnered attention from organic chemists in the recent past.^[18] Especially **3** showed potent antifungal activity against *Cladosporium cucumerinum*, thus pointing out a possible field in future crop protection.

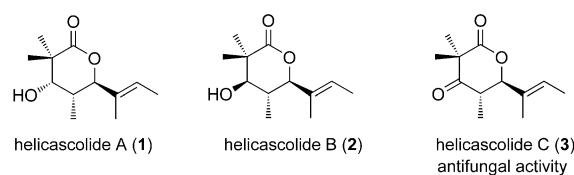
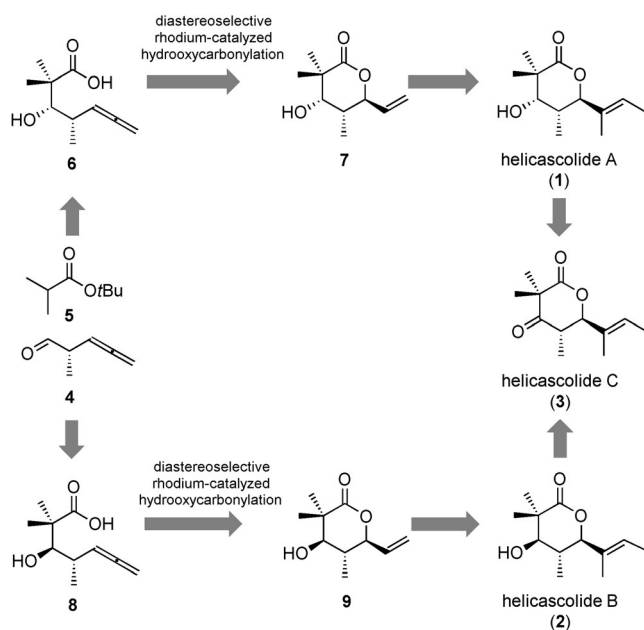


Figure 2. Configuration of all three representatives of the helicascolide family.

Given the six-membered lactone core, we envisioned that an intramolecular stereoselective hydrooxycarbonylation of the ω -allenyl-substituted carboxylic acids **6** and **8** might provide straightforward access to obtain the scaffolds of **7** and **9**, respectively (Scheme 1). At the same time, the structures **7**

[*] A. M. Haydl, D. Berthold, P. A. Spreider, Prof. Dr. B. Breit
Institut für Organische Chemie, Albert-Ludwigs-Universität Freiburg
Albertstrasse 21, 79104 Freiburg im Breisgau (Germany)
E-mail: bernhard.breit@chemie.uni-freiburg.de

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.201600632>.



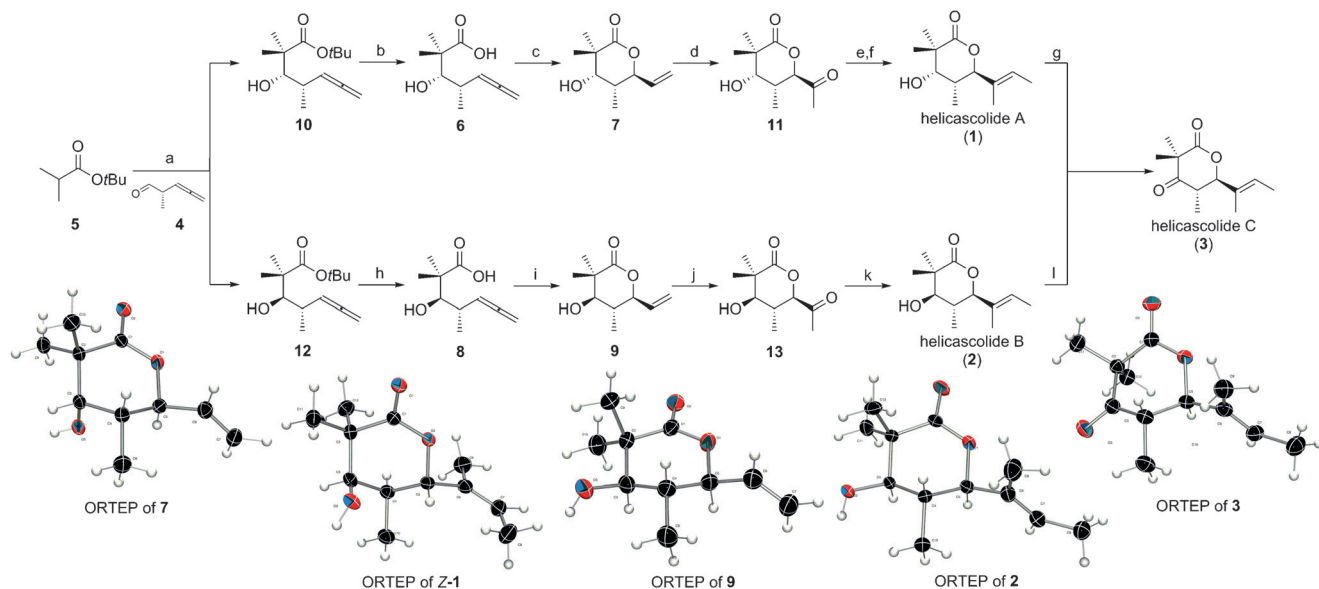
Scheme 1. Retrosynthetic disconnection of the helicascoldes A–C (1–3) by utilizing a stereodivergent diastereoselective C–O bond-forming addition of carboxylic acids to allenes as a key step.

and **9** should bring valuable allylester moieties into reach, and they might then be further elaborated to **1** and **2**, respectively. This disconnection relies on a Wacker oxidation which preserves diastereoelectivity,^[19] followed by an *E*-selective olefination reaction^[20] to efficiently deliver the trisubstituted olefinic backbone. Subsequent oxidation of the hydroxy

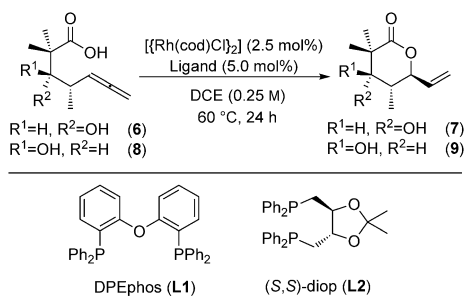
functionality might fuse both **1** and **2** with only little extra synthetic effort to its superior structure analogue **3**. To this end, our synthetic plan to forge the two diastereomeric ω -allenyl-substituted carboxylic acid precursors is predicated on a simple stereodivergent aldol addition reaction as outlined in Scheme 1.

Thus, our synthesis begins from the enolate of the ester **5** by treatment with the known α -chiral homoallenyl aldehyde **4**, which had already been used by the group of Baran^[21] and could be readily prepared by us in an enantiopure way in gram quantities within just a few steps (Scheme 2).^[22] The resulting separable aldol adducts **10** and **12** were obtained in good yield (80%) with an a.d.r. value of 1:1, thus enabling the best possible material supply for both pathways in the targeted stereodivergent synthesis. At this point, cleavage of the *tert*-butyl esters **10** and **12** by treatment with TFA paved the way to the corresponding ω -allenyl-substituted carboxylic acids **6** and **8**, respectively, which were obtained in excellent yields. Both served as the entry point to investigations on the rhodium-catalyzed intramolecular hydrooxycarbonylation of carboxylic acids to allenes.

Following on from prior studies,^[12,13] we carried out initial reactivity assays with **6** in the presence of $[\text{Rh}(\text{cod})\text{Cl}]_2$ (2.5 mol%) and DPEphos (5.0 mol%) in DCE at slightly elevated temperatures (60°C). We were pleased to discover that the reaction of **6**, bearing an unprotected hydroxy functionality in the vicinity of the allenyl moiety, furnished the desired **7**, a precursor to **1**, both in good yield and with an extraordinarily high diastereoselectivity (d.r. > 95:5; Table 1, entry 1). Notably, the newly generated stereocenter was selectively installed without the aid of a chiral ligand, just



Scheme 2. Total syntheses of **1–3**. Reagents and conditions: a) **4**, **5**, LDA, THF, –78°C, then RT, 80% (d.r. 1:1); b) TFA, CH_2Cl_2 at 0°C then room temperature, 96%; c) $[\text{Rh}(\text{cod})\text{Cl}]_2$ (2.5 mol%), DPEphos (5.0 mol%), DCE, 60°C, 24 h, 78% (d.r. > 95:5); d) PdCl_2 (10 mol%), 1,4-benzoquinone, DMF/ H_2O (7:1), RT, 24 h, 92% (d.r. > 95:5); e) EtPPh_3Br , KHMDS, THF at –78°C, then RT, 18 h, 70% (> 5:95 *E*:*Z*); f) PhSH, AIBN, toluene, 85°C, 72 h, 88% (6:1 *E*:*Z*); g) DMP, CH_2Cl_2 at 0°C, then RT, 24 h, 93%; h) TFA, CH_2Cl_2 at 0°C, then RT, 98%; i) $[\text{Rh}(\text{cod})\text{Cl}]_2$ (5.0 mol%), (*S,S*)-diop (10 mol%), DCE, 60°C, 24 h, 54% (d.r. 89:11); j) PdCl_2 (10 mol%), 1,4-benzoquinone, DMF/ H_2O (7:1), RT, 24 h, 78% (d.r. > 95:5); k) EtPPh_3Br , LiHMDS, toluene at –78°C, then RT, 18 h, 71% (13:1 *E*:*Z*); l) DMP, CH_2Cl_2 at 0°C, then RT, 24 h, 93%. AIBN = azobis(isobutyronitril), cod = 1,5-cyclooctadiene, DCE = 1,2-dichloroethane, DMF = *N,N*-dimethylformamide, DMP = Dess–Martin periodinane, KHMDS = potassium bis(trimethylsilyl)amide, LDA = lithium diisopropylamide, TFA = trifluoroacetic acid.

Table 1: Diastereoselective rhodium-catalyzed intramolecular hydroxy carbonylation of the ω -allenyl-substituted carboxylic acids **6** and **8**.^[a]

Entry	Substrate	Product	Ligand	Yield [%] ^[b]	d.r. ^[c]
1	6	7	L1	78	> 95:5
2	8	9	L1	20	90:10
3 ^[d]	8	9	L1	28	90:10
4 ^[d]	8	9	L2	54	89:11

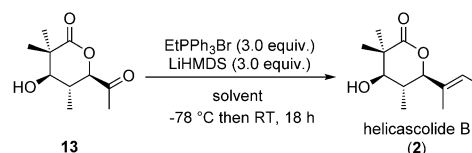
[a] Reaction conditions: allene (0.54 mmol), $[\text{Rh}(\text{cod})\text{Cl}]_2$ (2.5 mol %) and DPEphos (5.0 mol %) in 2.2 mL of DCE at 60 °C, 24 h. [b] Yields are those of diastereomeric mixtures isolated after silica gel chromatography. [c] Diastereoselectivity determined by ^1H -NMR analysis of the crude reaction mixture. [d] The reaction was performed with allene (0.54 mmol), $[\text{Rh}(\text{cod})\text{Cl}]_2$ (5.0 mol %), and ligand (10 mol %) in 2.2 mL of DCE at 60 °C, 24 h. cod = 1,5-cyclooctadiene, DCE = 1,2-dichloroethane.

by substrate control. Additionally, the required relative configuration could be confirmed by single-crystal X-ray analysis, which was in agreement with previous conformation analysis using NOE experiments of **7** (Scheme 2).^[22] To our surprise, when subjecting the helicacolide B precursor **8** to the indicated reaction conditions used earlier for the synthesis of **7**, we were pleased to discover that the reaction worked well and furnished the desired allylester moiety **9** in high diastereoselectivity (d.r. 90:10), albeit in poor yields, irrespective of the amount of catalyst used (entries 2 and 3). To circumvent this detrimental effect of the hydroxy group within the vicinity of the allenyl moiety, a substitution of the ligand was attempted. Finally, high diastereoselectivities along with improvements in terms of the obtained yield of **9** could be achieved when using elevated loadings of a Rh/(S,S)-diop system (entry 4). Furthermore, the structure of **9** could be secured at this point by X-ray crystallographic analysis in addition to NOE experiments (Scheme 2).^[22]

Next on the route to **1** and **2** was the Tsuji–Wacker-type oxidation reaction to install the required ketones in **11** and **13**, as they were necessary for construction of the *E*-selective trisubstituted double bond present in all representatives of this natural product family. To prevent erosion of the stereochemistry of **7** and **9**, by π -allyl-palladium insertion as in the opening sequence of the Tsuji–Trost reaction,^[14] the Wacker-type oxidation conditions developed by Sigman and co-workers^[23a] were used to circumvent this issue. However, the reactions conditions proved to be incompatible with **7** and **9**, thus resulting in poor yields of the obtained products. Gratifyingly **7** and **9**, in contrast, were smoothly oxidized to the corresponding ketones **11** and **13** in presence of PdCl_2 (10 mol %) and benzoquinone to furnish good (78 % for **13**)

to excellent yields (92 % for **11**) with even an enhanced diastereoselectivity after the reaction leading to **13** (d.r. > 95:5).^[23b]

Next, the setup of the trisubstituted *E*-configured double bond, derived from tiglic acid in all previous syntheses,^[18] proved to be a challenging exercise. Initial experiments were conducted by subjecting the phosphonium salt EtPPh_3Br in the presence of LiHMDS to **13**, which granted an acceleration of the stereochemical drift,^[24] thus resulting in a slight excess of the *E*-configured **2** (Table 2, entry 1).

Table 2: Reaction conditions for the stereoselective Wittig reaction of **13** (see Scheme 2).^[a]

Entry	Solvent	c [M]	Yield [%] ^[b]	<i>E/Z</i> ^[c]
1	THF	0.1	42	2.5:1
2	toluene	0.1	64	9:1
3	toluene	0.05	71	13:1

[a] Reaction conditions: A mixture of phosphonium salt (3.0 equiv) and LiHMDS (3.0 equiv) was subjected to **13** (0.20 mmol) diluted in the indicated solvent. [b] Yields are those of isomeric *E/Z* mixtures isolated after silica gel chromatography. [c] *E/Z* selectivity determined by ^1H NMR spectroscopy of the crude reaction mixture. LiHMDS = lithium bis(trimethylsilyl)amide, THF = tetrahydrofuran.

Replacement of the solvent and lowering of the concentration (entries 2 and 3) paved the way to obtaining **2** in good yield (71 %), along with an excellent *E* selectivity (13:1 *E/Z*) as confirmed by single-crystal X-ray analysis for the first time (Scheme 2).^[22] Attempts to carry over these reaction conditions for the synthesis of **1** resulted did not succeed despite an intense screening of different olefination conditions. The difficulty resulted from the decomposition of **11** into a complex product mixture. Therefore one extra synthetic step was needed for the selective transformation of **11** under lithium-salt-free conditions in good yield (70 %) and with an excellent *Z* selectivity (> 5:95 *E/Z*) to (*Z*)-helicacolide A [(*Z*)-**1**], thus confirming its structure by X-ray analysis. Next, after isomerization of its *Z*-substituted olefinic backbone by a mild, radical-mediated equilibration,^[25] **1** was obtained in excellent yield (88 %) with a good overall selectivity (6:1 *E/Z*). At this point, the lower selectivity underscores the small drawback of our synthetic approach, given the necessity of the correct installation of the double bond at the very end of the synthesis. To this end, **3** was obtained in excellent yield, by a convergent oxidation with DMP,^[18] by starting from either **1** or **2**. The synthetic **3** exhibited spectral properties identical in all respects to those reported for the natural product.^[17a] Furthermore its structural configuration was secured by X-ray crystallographic analysis.^[22]

Overall, we have accomplished a highly atom-economical diastereoselective rhodium-catalyzed direct lactonization strategy involving the construction of a new stereocenter in

just one step. This methodology was readily employed in a stereodivergent, robust, and concise total synthesis of all three representatives of the helicascolde family in five, six, and seven steps (for **1**, **2**, and **3**, respectively) in the absence of protecting groups, premetalated C-nucleophiles, or chiral auxiliaries. It illustrates the ease of lactone synthesis and reveals the concept of transition metal catalyzed C–O bond-forming cyclizations in small-molecule synthesis. Further studies regarding the elaboration of this strategic approach to access small-, medium-, and large-membered lactones in an enantioselective fashion, as well as its application in target-orientated synthesis are ongoing in our laboratory.

Acknowledgements

This work was supported by the DFG, the International Research Training Group “Catalysts and Catalytic Reactions for Organic Synthesis” (IRTG 1038). We thank Solvias, Umicore, BASF, and Wacker for generous gifts of chemicals. Dr. Manfred Keller is acknowledged for highly qualified X-ray structure analysis.

Keywords: allenes · allylic compounds · natural products · rhodium · total synthesis

How to cite: *Angew. Chem. Int. Ed.* **2016**, *55*, 5765–5769
Angew. Chem. **2016**, *128*, 5859–5863

- [1] For selected reviews of polyketides in natural products, see: a) D. O'Hagan, *The Polyketide Metabolites*, Ellis Horwood, Chichester, **1991**; b) A. M. Rimando, S. R. Baerson, *Polyketides: Biosynthesis, Biological Activity, and Genetic Engineering*, American Chemical Society, Washington, **2007**; c) J. Staunton, K. J. Weissman, *Nat. Prod. Rep.* **2001**, *18*, 380–416.
- [2] J. Rohr, *Angew. Chem. Int. Ed.* **2000**, *39*, 2847–2849; *Angew. Chem.* **2000**, *112*, 2967–2969.
- [3] T. Janecki, *Natural Lactones and Lactams: Synthesis Occurrence and Biological Activity*, Wiley-VCH, Weinheim, **2013**.
- [4] a) R. E. Longley, D. Caddigan, D. Harmond, M. Gunasekara, S. P. Gunasekara, *Transplantation* **1991**, *52*, 650–661; b) I. Pateron, K. K.-H. Ng, S. Williams, D. C. Millican, S. M. Dalby, *Angew. Chem. Int. Ed.* **2014**, *53*, 2692–2695; *Angew. Chem.* **2014**, *126*, 2730–2733; c) H. Ohkuma, N. Naruse, Y. Nishiyama, T. Tsuno, Y. Hoshino, Y. Sawada, M. Konishi, T. Oki, *J. Antibiot.* **1992**, *45*, 1239–1249; d) K. Gerth, D. Schummer, G. Höfle, H. Irschik, H. Reichenbach, *J. Antibiot.* **1995**, *48*, 973–976; e) J.-M. Huang, R. Yokoyama, C.-S. Yang, Y. Fukuyama, *Tetrahedron Lett.* **2000**, *41*, 6111–6114; f) J. Egger, P. Bretscher, S. Freigang, M. Kopf, E. M. Carreira, *J. Am. Chem. Soc.* **2014**, *136*, 17382–17385.
- [5] A. Parenty, X. Moreau, J.-M. Campagne, *Chem. Rev.* **2006**, *106*, 911–939.
- [6] a) Z. Huo, N. T. Patil, T. Jin, N. K. Pahadi, Y. Yamamoto, *Adv. Synth. Catal.* **2007**, *349*, 680–684; b) X. Chaminade, L. Coulombel, S. Olivero, E. Dunach, *Eur. J. Org. Chem.* **2006**, 3554–3557; c) L. A. Adrio, L. S. Quek, J. G. Taylor, K. K. Hii, *Tetrahedron* **2009**, *65*, 10334–10338; d) C.-G. Yang, N. W. Reich, Z. Shi, C. He, *Org. Lett.* **2005**, *7*, 4553–4556; e) G. Hamilton, E. J. Kang, M. Mba, F. D. Toste, *Science* **2007**, *317*, 496–499; f) J. L. Arbour, H. Rzepa, S. J. Contreras-Garcia, L. A. Adrio, E. M. Barreiro, K. K. Hii, *Chem. Eur. J.* **2012**, *18*, 11317–11324; g) W. Lim, J. Kim, Y. H. Rhee, *J. Am. Chem. Soc.* **2014**, *136*, 13618–13621; h) T. Liang, W. Zhang, M. J. Krische, *J. Am. Chem. Soc.* **2015**, *137*, 16024–16027; i) M. Nagamoto, T. Nishimura, *Chem. Commun.* **2015**, *51*, 13466–13469; j) V. Boucard, G. Broustal, J. M. Campagne, *Eur. J. Org. Chem.* **2007**, 225–236; k) X.-Z. Shu, S. C. Nguyen, Y. He, F. Oba, Q. Zhang, C. Canlas, G. A. Somorjai, A. P. Alivisatos, F. D. Toste, *J. Am. Chem. Soc.* **2015**, *137*, 7083–7086; l) M. A. Bigi, S. A. Reed, M. C. White, *J. Am. Chem. Soc.* **2012**, *134*, 9721–9726; m) P. E. Gorminsky, M. C. White, *J. Am. Chem. Soc.* **2011**, *133*, 12584–12589; n) L. Wang, P. E. Floreancig, *Org. Lett.* **2004**, *6*, 4207–4210; o) M. Bischof, J. Pietruszka, *Synlett* **2011**, 2689–2692.
- [7] a) M. S. Oderinde, H. N. Hunter, S. W. Bremner, M. G. Organ, *Eur. J. Org. Chem.* **2012**, 175–182; b) S. E. Denmark, M. T. Burk, *Proc. Natl. Acad. Sci. USA* **2010**, *107*, 20655–20660; c) C. Aprile, M. Gruttadauria, M. E. Amato, F. D'Anna, P. L. Meo, S. Riela, R. Noto, *Tetrahedron* **2003**, *59*, 2241–2251; d) S. Ranganathan, K. M. Muraleedharan, N. K. Vaish, N. Jayaraman, *Tetrahedron* **2004**, *60*, 5273–5308; e) W. Niu, Y.-Y. Yeung, *Org. Lett.* **2015**, *17*, 1660–1663; f) S. E. Denmark, W. R. Collins, *Org. Lett.* **2007**, *9*, 3801–3804.
- [8] a) D. K. Mohapatra, G. Umamaheshwar, M. M. Rao, D. Uma-devi, J. S. Yadav, *RSC Adv.* **2014**, *4*, 8335–8340; b) K. C. Nicolaou, R. M. Rodríguez, H. J. Mitchell, F. L. van Delft, *Angew. Chem. Int. Ed.* **1998**, *37*, 1874–1876; *Angew. Chem.* **1998**, *110*, 1975–1977.
- [9] a) H. Ren, P. Wang, L. Wang, Y. Tang, *Org. Lett.* **2015**, *17*, 4886–4889; b) A. Bunesco, Q. Wang, J. Zhu, *Chem. Eur. J.* **2014**, *20*, 14633–14638; c) T. G. Elford, D. G. Hall, *J. Am. Chem. Soc.* **2010**, *132*, 1488–1489; d) J. O. Guevara-Pulido, J. M. Andrés, R. Pedrosa, *J. Org. Chem.* **2014**, *79*, 8638–8644; e) P. S. Tiseni, R. Peters, *Chem. Eur. J.* **2010**, *16*, 2503–2517; f) J.-L. Hsu, J.-M. Fang, *J. Org. Chem.* **2001**, *66*, 8573–8584.
- [10] a) M. L. Cooke, K. Xu, B. Breit, *Angew. Chem. Int. Ed.* **2012**, *51*, 10876–10879; *Angew. Chem.* **2012**, *124*, 11034–11037; b) K. Xu, N. Thieme, B. Breit, *Angew. Chem. Int. Ed.* **2014**, *53*, 2162–2165; *Angew. Chem.* **2014**, *126*, 2194–2197; c) K. Xu, N. Thieme, B. Breit, *Angew. Chem. Int. Ed.* **2014**, *53*, 7268–7271; *Angew. Chem.* **2014**, *126*, 7396–7399; d) C. Li, B. Breit, *J. Am. Chem. Soc.* **2014**, *136*, 862–865; e) C. Li, M. Kähny, B. Breit, *Angew. Chem. Int. Ed.* **2014**, *53*, 13780–13784; *Angew. Chem.* **2014**, *126*, 14000–14004; f) A. B. Pritzius, B. Breit, *Angew. Chem. Int. Ed.* **2015**, *54*, 3121–3125; *Angew. Chem.* **2015**, *127*, 3164–3168; g) A. M. Haydl, K. Xu, B. Breit, *Angew. Chem. Int. Ed.* **2015**, *54*, 7149–7153; *Angew. Chem.* **2015**, *127*, 7255–7259; h) A. B. Pritzius, B. Breit, *Angew. Chem. Int. Ed.* **2015**, *54*, 15818–15822; *Angew. Chem.* **2015**, *127*, 16044–16048; i) T. Beck, B. Breit, *Org. Lett.* **2016**, *18*, 124–127.
- [11] a) R. Zimmer, C. Dinesh, E. Nandan, A. F. Khan, *Chem. Rev.* **2000**, *100*, 3067–3125; b) I. S. Kim, M. J. Krische, *Org. Lett.* **2008**, *10*, 513–515; c) T. Kawamoto, S. Hirabayashi, X. Guo, T. Nishimura, T. Hayashi, *Chem. Commun.* **2009**, 3528–3530; d) J. Moran, A. Preetz, R. A. Mesch, M. J. Krische, *Nat. Chem.* **2011**, *3*, 287–290; e) B. M. Trost, W. Brieden, K. H. Baringhaus, *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 1335–1336; *Angew. Chem.* **1992**, *104*, 1392–1394; f) L. M. Lutete, I. Kadota, Y. Yamamoto, *J. Am. Chem. Soc.* **2004**, *126*, 1622–1623.
- [12] a) P. Koschker, A. Lumbroso, B. Breit, *J. Am. Chem. Soc.* **2011**, *133*, 20746–20749; b) C. Schotes, D. Ostrovskyi, J. Senger, K. Schmidtkunz, M. Jung, B. Breit, *Chem. Eur. J.* **2014**, *20*, 2164–2168; c) A. Haydl, B. Breit, *Angew. Chem. Int. Ed.* **2015**, *54*, 15530–15534; *Angew. Chem.* **2015**, *127*, 15750–15754.
- [13] a) A. Lumbroso, P. Koschker, N. R. Vautravers, B. Breit, *J. Am. Chem. Soc.* **2011**, *133*, 2386–2389; b) A. Lumbroso, N. Abermil, B. Breit, *Chem. Sci.* **2012**, *3*, 789–793; c) P. Koschker, M. Kähny, B. Breit, *J. Am. Chem. Soc.* **2015**, *137*, 3131–3137.
- [14] a) B. M. Trost, *Chem. Rev.* **1996**, *96*, 395–422; b) B. M. Trost, M. L. Crawley, *Chem. Rev.* **2003**, *103*, 2921–2943; c) Z. Lu, S.

- Ma, *Angew. Chem. Int. Ed.* **2008**, *47*, 258–297; *Angew. Chem.* **2008**, *120*, 264–303; d) D. C. Vrieze, G. S. Hoge, P. Z. Hoerter, J. T. Van Haitma, B. M. Samas, *Org. Lett.* **2009**, *11*, 3140–3142; e) T. Hayashi, A. Okada, T. Suzuka, M. Kawatsura, *Org. Lett.* **2003**, *5*, 1713–1715; f) P. A. Evans, D. K. Leahy, *J. Am. Chem. Soc.* **2002**, *124*, 7882–7883.
- [15] a) G. Liu, Y. Wu, *Top. Curr. Chem.* **2010**, *292*, 195–209; b) M. S. Chen, M. C. White, *J. Am. Chem. Soc.* **2004**, *126*, 1346–1347; c) G. Liu, S. S. Stahl, *J. Am. Chem. Soc.* **2007**, *129*, 6328–6335; d) G. Yin, Y. Wu, G. Liu, *J. Am. Chem. Soc.* **2010**, *132*, 11978–11987.
- [16] A. Lumbroso, M. L. Cooke, B. Breit, *Angew. Chem. Int. Ed.* **2013**, *52*, 1890–1932; *Angew. Chem.* **2013**, *125*, 1942–1986.
- [17] a) K. Tarman, G. J. Palm, A. Porzel, K. Merzweiler, N. Arnold, L. A. Wessjohann, M. Unterseher, U. Lindequist, *Phytochem. Lett.* **2012**, *5*, 83–86; b) G. K. Poch, G. J. Gloer, *J. Nat. Prod.* **1989**, *52*, 257–260.
- [18] a) J. S. Yadav, A. B. Reddy, K. S. Shankar, *Synthesis* **2013**, 1034–1038; b) P. R. Krishna, V. S. Mallula, P. V. A. Kumar, *Tetrahedron Lett.* **2012**, *53*, 4997–4999.
- [19] J. Tsuji, *Synthesis* **1984**, 369–384.
- [20] a) E. Vedejs, M. J. Peterson, *Topics in Stereochemistry*, Wiley, New York, **1994**; b) B. E. Maryanoff, A. B. Reitz, *Chem. Rev.* **1989**, *89*, 863–927; c) P. R. Blakemore, W. J. Cole, P. J. Kocienski, A. Morley, *Synlett* **1998**, 26–28.
- [21] a) L. Jørgensen, S. J. McKerrall, C. A. Kuttruff, F. Ungeheuer, J. Felding, P. S. Baran, *Science* **2013**, *341*, 878–882; b) S. J. McKerrall, L. Jørgensen, C. A. Kuttruff, F. Ungeheuer, P. S. Baran, *J. Am. Chem. Soc.* **2014**, *136*, 5799–5810.
- [22] For further details, see the Supporting Information. CCDC 1448405 (**7**), 1448406 (**9**), 1448407 [(**Z**)-**1**], 1448408 (**2**), and 1448409 (**3**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.
- [23] a) B. W. Michel, A. M. Camelio, C. N. Cornell, M. S. Sigman, *J. Am. Chem. Soc.* **2009**, *131*, 6076–6077; b) D. G. Miller, D. D. M. Wayner, *J. Org. Chem.* **1990**, *55*, 2924–2927.
- [24] A. B. Reitz, S. O. Nortey, A. D. Jordan, Jr., M. S. Mutter, B. E. Maryanoff, *J. Org. Chem.* **1986**, *51*, 3302–3308.
- [25] G. Campiani, L.-Q. Sun, A. P. Kozikowski, P. Aagaard, M. McKinney, *J. Org. Chem.* **1993**, *58*, 7660–7669.

Received: January 20, 2016

Published online: April 4, 2016