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Atom-Economical Dimerization Strategy by the Rhodium-Catalyzed Addition of Carboxylic Acids to Allenes: Protecting-Group-Free Synthesis of Clavosolide A and Late-Stage Modification

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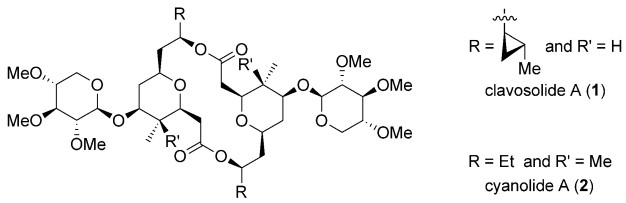
Abstract: *Natural products of polyketide origin with a high level of symmetry, in particular C_2-symmetric diolides as a special macrolactone-based product class, often possess a broad spectrum of biological activity. An efficient route to this important structural motif was developed as part of a concise and highly convergent synthesis of clavosolide A. This strategy features an atom-economic "head-to-tail" dimerization by the stereoselective rhodium-catalyzed addition of carboxylic acids to terminal allenes with the simultaneous construction of two new stereocenters. The excellent efficiency and selectivity with which the C_2-symmetric core structures were obtained are remarkable considering the outcome under classical dimerization conditions. Furthermore, this approach facilitates late-stage modification and provides ready access to potential new lead structures.*

Naturally occurring dimers of polyketide origin have attracted much attention in the last two decades.[1,2] Aside from a high level of symmetry, impressive biological activity can be found in many carbacyclic[1] and oxacyclic[2] dimeric natural products. In particular, oxacyclic dimers, also known as diolides, are considered to be a special macrolactone-based product class and exhibit a broad spectrum of biological activity,[3] such as immunosuppressive,[4a–c] antipsoriatic,[4d] antibiotic,[4e–g] anti-HIV,[4h] and various other properties.[4i,j]

Strategic approaches for the construction of such symmetrical core structures, besides the classical dimerization conditions by anhydride-type activation of the seco acid,[5] have been demonstrated in a number of formal and total syntheses, including a one-pot double Mitsunobu reaction,[6a] double transesterification,[6b] double Sakurai allylation,[6c] double Suzuki cross-coupling,[6d] and alkyne metathesis.[6e] However, general drawbacks of these reactions with regard to atom economy are either the requirement of a stoichiometric amount of a reagent for the activation of the monomers, thus leading to the generation of a stoichiometric amount of waste, or the need for preinstalled stereocenters in the molecule prior to dimerization. Our research group recently developed a rhodium-catalyzed[7] atom-economical and regioselective addition[8] of carboxylic acids to allenes[9] and alkynes,[10] a method which could be seen as an alternative to metal-catalyzed allylic substitution[11] and oxidation[12] to generate branched allylic esters.[13] When we attempted to extend this methodology to the synthesis of lactones and macrolactones (in particular, medium-sized lactones) by an intramolecular addition of carboxylic acids to alkynes, the "head-to-tail" dimerization product was formed exclusively.[10b]

To investigate the synthesis of diolides in combination with the previous findings on the enantioselective addition of carboxylic acids to terminal allenes,[9] we chose the C_2-symmetric target clavosolide A (**1**; Scheme 1).[14] The clavosolide family and its closely related analogue cyanolide A[15]



Scheme 1. The polyketides clavosolide A and cyanolide A as examples of natural products with a C_2-symmetric dimeric scaffold.

have garnered significant attention from organic chemists owing to their high level of molecular complexity; thus, a large number of formal and total syntheses have been described in recent years.[16,17] Herein, we report a novel and highly convergent total synthesis of clavosolide A and various late-stage modifications in the absence of protecting groups and premetalated C-nucleophiles. The desired product was formed in less than half the number of steps required in any previous approaches by a direct atom-economical diastereoselective dimerization strategy for the construction of its 16-membered macrolide skeleton.

Given the C_2-symmetrical dimeric macrodiolide structure (Scheme 2), we envisioned that a "head-to-tail" addition of the ω-allenyl-substituted carboxylic acid **4** might provide straightforward access to scaffold **3** with the selective generation of two of its 22 stereocenters. The proposed rhodium-catalyzed diastereoselective dimerization is a novel combination of two methodologies recently described by our research group.[9a,10b] At the same time, the interim structure **3** should bring a valuable allylester moiety into reach, which could then be further elaborated either by double cross-metathesis[18] with (*Z*)-butene and double stereoselective Simmons–Smith cyclopropanation[19] for the synthesis of the targeted natural product **1** or by other late-stage modifications with only little extra synthetic effort. Our synthetic plan

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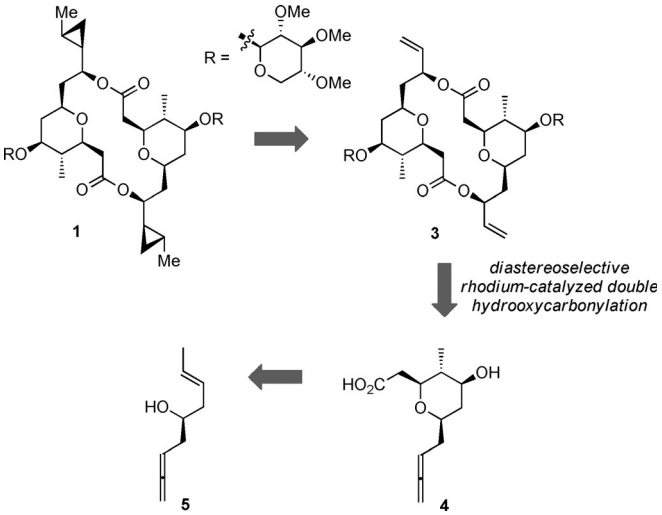
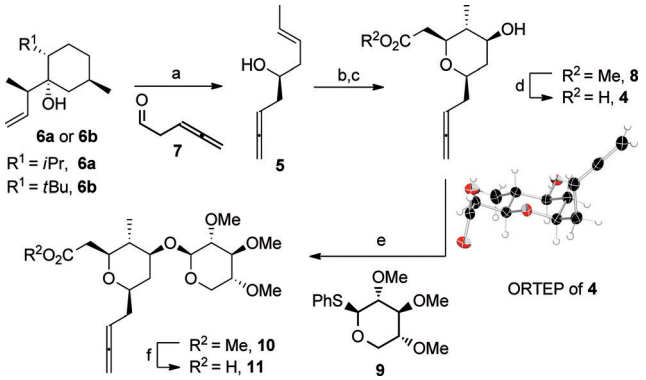


Scheme 2. Retrosynthetic disconnection of clavosolide A on the basis of a diastereoselective C–O bond-forming addition of carboxylic acids to allenes as the key step.



Scheme 3. Synthesis of the tetrasubstituted-pyran precursors. Cited yields are those of the single diastereomers after silica-gel chromatography. Reagents and conditions: a) **6b**, **7**, *p*TsOH·H_2O (10 mol%), CH_2Cl_2, room temperature, 90% (>99% *ee*); b) HC≡CCO_2Me, quinuclidine, TFA, CH_2Cl_2, 0°C then room temperature (d.r. 87:13); c) K_2CO_3, MeOH, room temperature, 71% (2 steps); d) LiOH·H_2O, THF/H_2O/MeOH (2:1:1), room temperature, 96%; e) **9**, MeOTf, MS (4 Å), Et_2O, room temperature, 64% (d.r. 77:23); f) LiOH·H_2O, THF/H_2O/MeOH (2:1:1), room temperature, 94%. MS = molecular sieves, TFA = trifluoroacetic acid, Tf = trifluoromethanesulfonyl, *p*Ts = *p*-toluenesulfonyl.

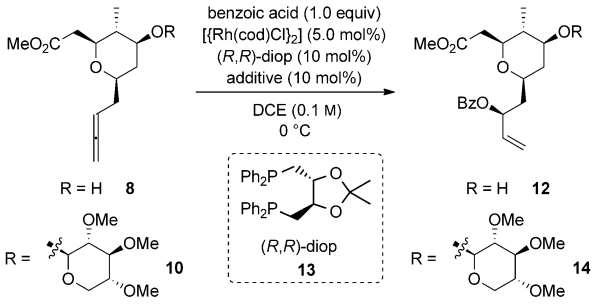
for the synthesis of the key fragment **4**, either glycosylated or devoid of any sugar residue, from chiral homoallylic alcohol **5** involved an elegant cascading oxa-Michael/Prins-type cyclization reaction previously described by Willis and co-workers.[20] In any case, this strategic approach to efficiently deliver symmetrical subunits of polyketide natural products is considered to be of more general interest, since it shows enormous potential for late-stage modification by diverted total synthesis, thus enabling great possibilities for further biological screening.[21]

Our synthesis proceeded from the menthone-based Nokami crotyl-transfer reagent[22] **6a** by treatment with the known homoallenyl aldehyde **7**[23] (Scheme 3), which could be readily prepared in multigram quantities in two steps.[24] The resulting chiral homoallylic alcohol **5** was obtained in good yield (86%) but with only 72% *ee*. When we increased the steric bulk of the chiral transfer agent by introducing a *tert*-butyl substituent to create **6b**, we obtained **5** in good yield (90%) with remarkable enantioselectivity (>99% *ee*).[25] A one-pot oxa-Michael/Prins-type cyclization according to the method developed by Willis and co-workers[16a,b] then furnished the tetrasubstituted pyran **8** in satisfying yield as a separable 7:1 mixture of diastereomers. Compound **8** served as the entry point for the preparation of the precursors **4**, **10**, and **11** required for the rhodium-catalyzed C–O bond-forming addition of carboxylic acids to allenes, and was saponified to give the corresponding aglyconic carboxylic acid **4**. At this point, the required absolute and relative configuration could be confirmed by single-crystal X-ray analysis, which was in agreement with previous conformation analysis by NOE experiments on **8**.[24] Next, we moved on for the preparation of the glycosylated carboxylic acid **11**. Classic glycosylation conditions developed by Schmidt and co-workers[26] and used in previous syntheses of clavosolide A and cyanolide A proved to be incompatible with **8**, thus resulting in a complex product mixture. To circumvent this issue, we treated **8** with phenyl thioglycoside **9**[27] in the presence of methyl triflate.[28] The resulting glycosylated ester **10** was obtained as a separable 3:1 mixture of diastereomers in favor of the β anomer. Compound **10** was saponified to give the corresponding glycosylated ω-allenyl-substituted carboxylic acid **11**, which served as one of four substrates for subsequent investigations on the rhodium-catalyzed addition of carboxylic acids to allenes.

Following on from prior studies,[9] we carried out initial reactivity assays with **8** and benzoic acid in the presence of [{Rh(cod)Cl}$_2$] (5.0 mol%) and (*R*,*R*)-diop (10 mol%) in DCE at room temperature (Table 1). We were pleased to discover that the reaction proceeded well with **8** bearing an unprotected hydroxy functionality in terms of yield, albeit with only moderate diastereoselectivity (d.r. 63:37; Table 1, entry 1). The feasibility of benzoic acid as a benchmark acidic nucleophile encouraged us to screen a variety of conditions. To our delight, when the reaction temperature was lowered and Cs_2CO_3 (10 mol%) was added (Table 1, entries 2 and 3), increased diastereoselectivity was observed. However the drop in reactivity led to incomplete conversion and therefore a lower yield (62%). Finally, the reaction time was extended, and complete conversion was observed after 96 h (Table 1, entry 4). To demonstrate the synthetic utility of the method, the reaction was performed on a larger scale furnishing 1.43 g of **12** (79% yield) with good diastereoselectivity (d.r. 93:7; Table 1, entry 5). Under the optimized reaction conditions, even **10** bearing a sugar residue attached to the hydroxy group present in **8** reacted to give **14** in good yield with only slightly diminished diastereoselectivity (Table 1, entry 7).[29]

On the basis of these results, we expanded the strategic approach to investigate the "head-to-tail" dimerization reaction of the ω-allenyl-substituted carboxylic acids **4** and **11** (Table 2). Adapted reaction conditions proved successful for the transformation of aglycone **4** on a small scale (Table 2, entry 1). Thus, diolide **15** was obtained exclusively in good

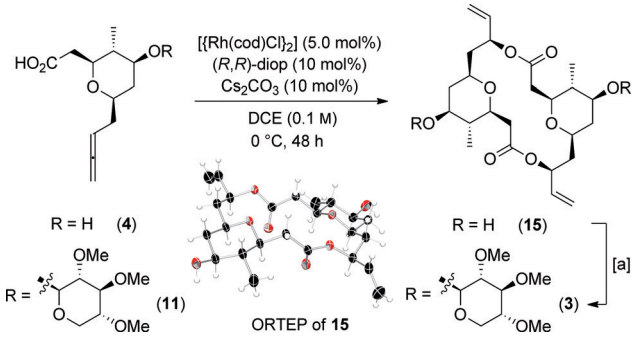
Table 1: Diastereoselective rhodium-catalyzed addition of benzoic acid to the terminal allenes **8** and **10**.[a]



Entry	Substrate[b]	Additive	*t*	Yield [%][c]	d.r.[d]
1[e]	**8** (**12**)	–	18	97	63:37
2	**8** (**12**)	–	18	50	80:20
3	**8** (**12**)	Cs_2CO_3	18	62	95:5
4	**8** (**12**)	Cs_2CO_3	96	95	95:5
5[f]	**8** (**12**)	Cs_2CO_3	96	79	93:7
6[g]	**8** (**12**)	Cs_2CO_3	96	94	10:90
7	**10** (**14**)	Cs_2CO_3	96	63	89:11

[a] General reaction conditions: allene (0.6 mmol), benzoic acid (0.5 mmol), DCE (5.0 mL), 0 °C. [b] The corresponding product is indicated in parenthesis. [c] Yield of the isolated product. [d] The diastereomeric ratio was determined by ^{1}H NMR spectroscopy of the crude reaction mixture. The relative configuration was determined by conversion into **3** (see the Supporting Information for further details). [e] The reaction was performed at room temperature. [f] Reaction conditions: allene (6.0 mmol), benzoic acid (5.0 mmol), Cs_2CO_3 (10 mol%), [{Rh(cod)Cl}$_2$] (5.0 mol%), (*R*,*R*)-diop (10 mol%), DCE (50 mL), 0 °C, 96 h. [g] The reaction was performed with (*S*,*S*)-diop (10 mol%). Bz = benzoyl, cod = 1,5-cyclooctadiene, DCE = 1,2-dichloroethane.

Table 2: Diastereoselective rhodium-catalyzed "head-to-tail" dimerization of the Ω-allenyl-substituted carboxylic acids **4** and **11**.



Entry	Substrate	Product	Yield [%][b]	d.r.[c]
1[d]	**4**	**15**	82	>95:5
2[e]	**4**	**15**	75	>95:5
3[f]	**4**	**15**	80	18:82
4[g]	**11**	**3**	72	92:8

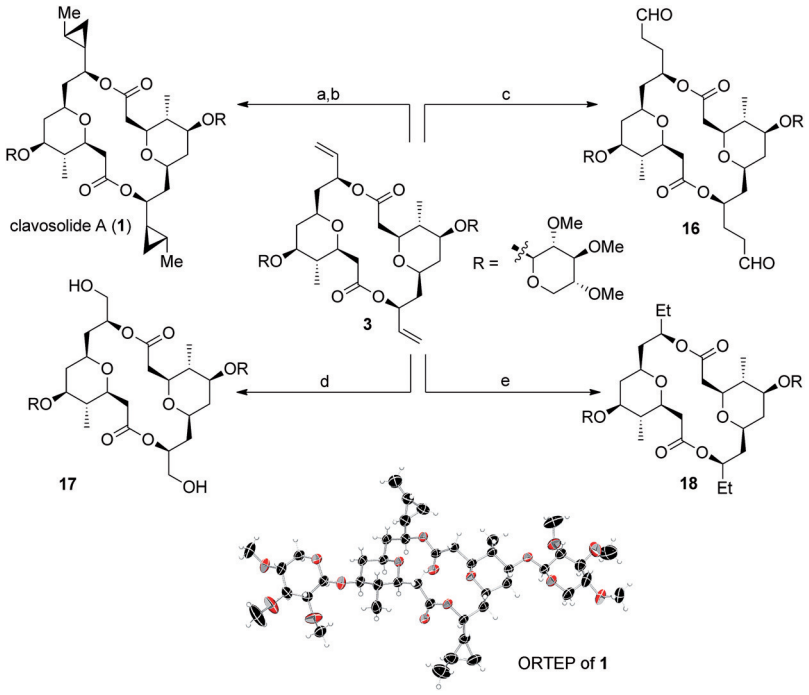
[a] Glycosidation after catalysis: **9**, MeOTf, MS (4 Å), Et_2O, room temperature, 85% (43% yield for the β,β-anomer). [b] Yield of the diastereomeric mixture isolated after silica-gel chromatography. [c] The diastereomeric ratio was determined by ^{1}H NMR spectroscopy of the crude reaction mixture. [d] The reaction was performed with 0.5 mmol of the allene. [e] The reaction was performed with 6.6 mmol of the allene. [f] The reaction was performed with (*S*,*S*)-diop (10 mol%). [g] The reaction was performed with 0.37 mmol of the allene.

yield (82%) with extraordinarily high diastereoselectivity (d.r. > 95:5) in the absence of protecting groups. On a gram scale, the homodimerization reaction also furnished **15** in good yield (75%) with excellent diastereoselectivity (d.r. > 95:5; Table 2, entry 2). Gratifyingly, after this step, purification was possible by a single recrystallization of the crude product without the aid of column chromatography and provided single crystals for determination of the relative and absolute configuration by X-ray crystallographic analysis (Table 2). Subsequent treatment of **15** after catalysis under previous described glycosidation conditions led to a mixture of anomers in 85% yield in favor of the β,β-anomeric diolide **3** (d.r. 50:33:17). We further extended the scope of the reaction to the more complex ω-allenyl-substituted carboxylic acid **11** and were pleased to find good reactivity in terms of diolide formation: Compound **3** was obtained both in good yield (72%) and with satisfactory diastereoselectivity (d.r. 92:8; Table 2, entry 4).

For the further synthesis of clavosolide A (**1**), very little was known about the proposed conversion of the intermediate structure **3** by cross-metathesis with either propene or (*Z*)-butene to give the corresponding double homologated olefin, although it seemed to be straightforward (Scheme 4).[30,31] Instead, approaches involving more than one step, such as C–C bond-cleaving ozonolysis or Lemieux–Johnson oxidation followed by an olefination reaction, prevail in the literature.[32] Gratifyingly, double cross-metathesis under solvent-free conditions in (*Z*)-butene with the Grubbs II catalyst furnished a 5:1 mixture of the desired *E*,*E* product in good yield. Subjection of the latter to Simmons–Smith cyclopropanation conditions,[33] as reported for previous syntheses,[16a,b] finally led to clavosolide A (**1**) in only eight steps from **6b**. The synthetic clavosolide A exhibited spectral properties identical in all respects to those reported for the natural product.[14] Furthermore, its relative and absolute configuration could be confirmed by single-crystal X-ray analysis.

To emphasize the flexibility made possible in late-stage synthesis by our chosen approach, we subjected **3** to assorted transformations to generate structural derivatives of clavosolide A (Scheme 4). Double hydroformylation of the terminal double bonds with our self-assembled ligand 6-diphenylphosphanylpyridone (6-DPPon) furnished **16** in high yield and with high regioselectivity.[34] C_1 cleavage by ozonolysis gave **17** in 78% yield.[35] Furthermore, the double bond could readily be defunctionalized to give the cyanolide A analogue substructure **18**.[36]

In summary, we have developed a highly atom-economical diastereoselective rhodium-catalyzed direct homodimerization strategy involving the construction of two new stereocenters in just one step. This methodology proved to be highly functional-group-tolerant and resulted in a concise total synthesis of clavosolide A in only eight steps in the absence of protecting groups and premetalated C-nucleophiles. Our synthetic results provide an intriguing glimpse of how such an approach can be used for the synthesis of complex polyketide natural products and opens up new routes to a selection of structural analogues for potential biological investigations. Further studies towards the generalization of



Scheme 4. Transformation of the core structure **3** into clavosolide A and late-stage structure modification to give other potentially active derivatives. Reagents and conditions: a) Grubbs II catalyst (30 mol%) neat in (*Z*)-2-butene, −78°C then 40°C, 89% (83:17 *E*,*E*/*Z*,*E*); b) ICH_2Cl, Et_2Zn, CH_2Cl_2, 0→15°C, 63%; c) [{$Rh(CO)_2$acac}] (1.5 mol%), 6-DPPon (30 mol%), CO/H_2 (1:1, 20 bar), toluene, 80°C, 81% (9:1 l,l/l,b); d) O_3; $NaBH_4$, CH_2Cl_2/MeOH (2:1), −78°C then room temperature, 78%; e) Pd/C (10 mol%), H_2 (1 atm), MeOH, room temperature, 99%. acac = acetylacetonate.

this strategic approach for the synthesis of other related natural product classes as well as its application in target-oriented synthesis are being pursued in our laboratory.

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[1] G. Lian, B. Yu, *Chem. Biodiversity* **2010**, *7*, 2660–2691.
[2] E. J. Kang, E. Lee, *Chem. Rev.* **2005**, *105*, 4348–4378.
[3] a) E. M. Driggers, S. P. Hale, J. Lee, N. K. Terrett, *Nat. Rev. Drug Discovery* **2008**, *7*, 608–624; b) E. Marsault, M. L. Peterson, *J. Med. Chem.* **2011**, *54*, 1961–2004; c) B. Proska, *Ceska Slov. Farm.* **2000**, *49*, 221–228.
[4] a) E. J. Corey, K. C. Nicolaou, T. Toru, *J. Am. Chem. Soc.* **1975**, *97*, 2287–2288; b) K. F. Burri, R. A. Cardone, W. Y. Chen, P. Rosen, *J. Am. Chem. Soc.* **1978**, *100*, 7069–7071; c) A. Zajícová, M. Múcková, M. Krulová, Z. Rychnavská, V. Holán, *Int. Immunopharmacol.* **2001**, *1*, 1939–1945; d) R. Barth, J. Mulzer, *Angew. Chem. Int. Ed.* **2007**, *46*, 5791–5794; *Angew. Chem.* **2007**, *119*, 5893–5896; e) K. C. Nicolaou, A. L. Nold, R. R. Milburn, C. S. Schindler, K. P. Cole, J. Yamaguchi, *J. Am. Chem. Soc.* **2007**, *129*, 1760–1768; f) P. A. Evans, M.-H. Huang, M. J. Lawler, S. Maroto, *Nat. Chem.* **2012**, *4*, 680–684; g) H. C. Kwon, C. A. Kauffman, P. R. Jensen, W. Fenical, *J. Am. Chem. Soc.* **2006**, *128*, 1622–1632; h) A. Fürstner, M. Albert, J. Mlynarski, M. Matheu, E. DeClerq, *J. Am. Chem. Soc.* **2003**, *125*, 13132–13142; i) E. J. Kang, E. J. Cho, Y. E. Lee, M. K. Ji, D. M. Shin, Y. K. Chung, E. Lee, *J. Am. Chem. Soc.* **2004**, *126*, 2680–2681; j) I. Paterson, J. D. Smith, R. A. Ward, J. G. Cumming, *J. Am. Chem. Soc.* **1994**, *116*, 2615–2616.
[5] a) J. Inanaga, K. Hirata, H. Saeki, T. Katsuki, M. Yamaguchi, *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989–1993; b) H. Tone, T. Nishi, Y. Oikawa, M. Hikota, O. Yonemitsu, *Tetrahedron Lett.* **1987**, *28*, 4569; c) M. Hikota, H. Tone, K. Horita, O. Yonemitsu, *Tetrahedron* **1990**, *46*, 4613; d) M. Hikota, Y. Sakurai, K. Horita, O. Yonemitsu, *Tetrahedron Lett.* **1990**, *31*, 6367.
[6] a) B. M. Trost, A. Quintard, *Angew. Chem. Int. Ed.* **2012**, *51*, 6704–6708; *Angew. Chem.* **2012**, *124*, 6808–6812; b) T. Nishimaru, M. Kondo, K. Takeshita, K. Takahashi, J. Ishihara, S. Hatakeyama, *Angew. Chem. Int. Ed.* **2014**, *53*, 8459–8462; *Angew. Chem.* **2014**, *126*, 8599–8602; c) M. R. Gesinski, S. D. Rychnovski, *J. Am. Chem. Soc.* **2011**, *133*, 9727–9729; d) A. W. H. Speed, T. J. Mann, R. V. O'Brien, R. R. Schrock, A. H. Hoveyda, *J. Am. Chem. Soc.* **2014**, *136*, 16136–16139; e) K. J. Ralston, H. C. Ramstadius, R. C. Brewster, H. S. Niblock, A. N. Hulme, *Angew. Chem. Int. Ed.* **2015**, *54*, 7086–7090; *Angew. Chem.* **2015**, *127*, 7192–7196.
[7] 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.
[8] a) R. Zimmer, C. Dinesh, E. Nandanan, 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, *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.
[9] 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.

[10] 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.
[11] 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 Haitsma, 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.
[12] 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.
[13] A. Lumbroso, M. L. Cooke, B. Breit, *Angew. Chem. Int. Ed.* **2013**, *52*, 1890 – 1932; *Angew. Chem.* **2013**, *125*, 1942 – 1986.
[14] a) R. M. Rao, D. J. Faulkner, *J. Nat. Prod.* **2002**, *65*, 386 – 388; b) K. L. Erickson, K. R. Gustafson, L. K. Pannell, J. A. Beutler, M. R. Boyd, *J. Nat. Prod.* **2002**, *65*, 1303 – 1306.
[15] A. R. Pereira, C. F. McCue, W. H. Gerwick, *J. Nat. Prod.* **2010**, *73*, 217 – 220.
[16] For prior syntheses of the clavosolide family, see: a) C. S. Barry, J. D. Elsworth, P. T. Seden, N. Bushby, J. R. Harding, R. W. Alder, C. L. Willis, *Org. Lett.* **2006**, *8*, 3319 – 3322; b) P. T. Seden, J. P. H. Charmant, C. L. Willis, *Org. Lett.* **2008**, *10*, 1637 – 1640; c) J. B. Son, S. N. Kim, N. Y. Kim, D. H. Lee, *Org. Lett.* **2006**, *8*, 661 – 664; d) V. Simov, A. B. Smith III, *Org. Lett.* **2006**, *8*, 3315 – 3318; e) T. K. Chakraborty, V. R. Reddy, P. K. Gajula, *Tetrahedron* **2008**, *64*, 5162 – 5167; f) J. D. Carrick, M. P. Jennings, *Org. Lett.* **2009**, *11*, 769 – 772; g) G. Peh, P. E. Floreancig, *Org. Lett.* **2012**, *14*, 5614 – 5617.
[17] For prior syntheses of cyanolide A, see: a) H. Kim, J. Hong, *Org. Lett.* **2010**, *12*, 2880 – 2883; b) A. K. Hajare, V. Ravikumar, S. Khaleel, D. Bhuniya, D. S. Reddy, *J. Org. Chem.* **2011**, *76*, 963 – 966; c) Z. Yang, X. Xie, P. Jing, G. Zhao, J. Zheng, C. Zhao, X. She, *Org. Biomol. Chem.* **2011**, *9*, 984 – 986; d) S. Pabbaraja, K. Satyanarayana, B. Ganganna, J. S. Yadav, *J. Org. Chem.* **2011**, *76*, 1922 – 1925; e) G. C. Tay, M. R. Gesinski, S. D. Rychnovsky, *Org. Lett.* **2013**, *15*, 4536 – 4539; f) R. J. Sharpe, M. P. Jennings, *J. Org. Chem.* **2011**, *76*, 8027 – 8032; g) A. R. Waldeck, M. J. Krische, *Angew. Chem. Int. Ed.* **2013**, *52*, 4470 – 4473; *Angew. Chem.* **2013**, *125*, 4566 – 4569; and Ref. [6c].
[18] a) K. C. Nicolaou, P. G. Bulger, D. Sarlah, *Angew. Chem. Int. Ed.* **2005**, *44*, 4490 – 4527; *Angew. Chem.* **2005**, *117*, 4564 – 4601; b) A. Fürstner, *Angew. Chem. Int. Ed.* **2000**, *39*, 3012 – 3043; *Angew. Chem.* **2000**, *112*, 3140 – 3172; c) T. M. Trnka, R. H. Grubbs, *Acc. Chem. Res.* **2001**, *34*, 18 – 29.
[19] a) H. Lebel, J.-F. Marcoux, C. Molinaro, A. B. Charette, *Chem. Rev.* **2003**, *103*, 977 – 1050; b) H. M. L. Davies, R. E. J. Beckwith, *Chem. Rev.* **2003**, *103*, 2861 – 2904.
[20] C. S. Barry, N. Bushby, J. R. Harding, C. L. Willis, *Org. Lett.* **2005**, *7*, 2683 – 2686.
[21] a) R. M. Wilson, S. J. Danishefsky, *Angew. Chem. Int. Ed.* **2010**, *49*, 6032 – 6056; *Angew. Chem.* **2010**, *122*, 6168 – 6193; b) A. M. Szpilman, E. M. Carreira, *Angew. Chem. Int. Ed.* **2010**, *49*, 9592 – 9628; *Angew. Chem.* **2010**, *122*, 9786 – 9823; c) A. Fürstner, *Isr. J. Chem.* **2011**, *51*, 329 – 345; d) J.-Y. Wach, K. Gademann, *Synlett* **2012**, 163 – 170.
[22] J. Nokami, K. Nomiyama, S. Matsuda, N. Imai, K. Kataoka, *Angew. Chem. Int. Ed.* **2003**, *42*, 1273 – 1276; *Angew. Chem.* **2003**, *115*, 1311 – 1314.
[23] W. G. Dauben, V. P. Rocco, G. Shapiro, *J. Org. Chem.* **1985**, *50*, 3155 – 3160.
[24] For further details, see the Supporting Information.
[25] The modified Nokami crotyl-transfer reagent **6b** is a new reagent and was prepared in three steps from commercially available (*R*)-pulegone. For further details, see the Supporting Information.
[26] a) R. R. Schmidt, J. Michel, *Angew. Chem. Int. Ed. Engl.Angew. Chem. Int. Ed.* **1980**, *19*, 731 – 732; *Angew. Chem.* **1980**, *92*, 763 – 764; b) R. R. Schmidt, *Adv. Carbohydr. Chem. Biochem.* **1994**, *50*, 21 – 123.
[27] R. Lopez, A. Fernandez-Mayoralas, *J. Org. Chem.* **1994**, *59*, 737 – 745, and Ref. [17g].
[28] H. Lönn, *J. Carbohydr. Chem.* **1987**, *6*, 301 – 306, and Ref. [17g].
[29] For further details concerning the transformation of **12** and **14** into **3** to confirm their relative configuration, see the Supporting Information.
[30] For studies concerning C_1 homologation through cross-metathesis with propene or (*Z*)-butene analogues, see: a) S. Imhof, S. Randl, S. Blechert, *Chem. Commun.* **2001**, 1692 – 1693; b) C. J. Morten, T. F. Jamison, *J. Am. Chem. Soc.* **2009**, *131*, 6678 – 6679.
[31] Cross-metathesis with higher olefins is more common and usually gives better *E*/*Z* product ratios; see: a) T. Seiser, F. Kamena, N. Cramer, *Angew. Chem. Int. Ed.* **2008**, *47*, 6483 – 6485; *Angew. Chem.* **2008**, *120*, 6583 – 6585; b) S. A. Snyder, A. P. Brucks, D. S. Treitler, I. Moga, *J. Am. Chem. Soc.* **2012**, *134*, 17714 – 17721; and Ref. [9b].
[32] a) B. M. Trost, J. L. Gunzer, O. Dirat, Y. H. Rhee, *J. Am. Chem. Soc.* **2002**, *124*, 10396 – 10415; b) D. P. Curran, T. Furukawa, *Org. Lett.* **2002**, *4*, 2233 – 2235.
[33] The diastereoselectivity of this reaction could not be determined easily, but is known to be high in transformations with related structures; see Refs. [16a,b].
[34] a) B. Breit, *Angew. Chem. Int. Ed.* **2005**, *44*, 6816 – 6825; *Angew. Chem.* **2005**, *117*, 6976 – 6986; b) B. Breit, W. Seiche, *J. Am. Chem. Soc.* **2003**, *125*, 6608 – 6609.
[35] J. U. Rhee, M. J. Krische, *J. Am. Chem. Soc.* **2006**, *128*, 10674 – 10675.
[36] P. Wipf, S. R. Spencer, *J. Am. Chem. Soc.* **2005**, *127*, 225 – 235.

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