

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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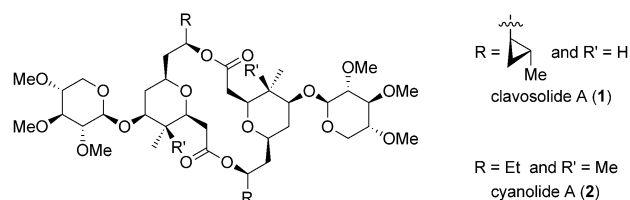
Abstract: Natural products of polyketide origin with a high level of symmetry, in particular C_2 -symmetric diolides as a special macrolactone-based product class, often possess a broad spectrum of biological activity. An efficient route to this important structural motif was developed as part of a concise 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]



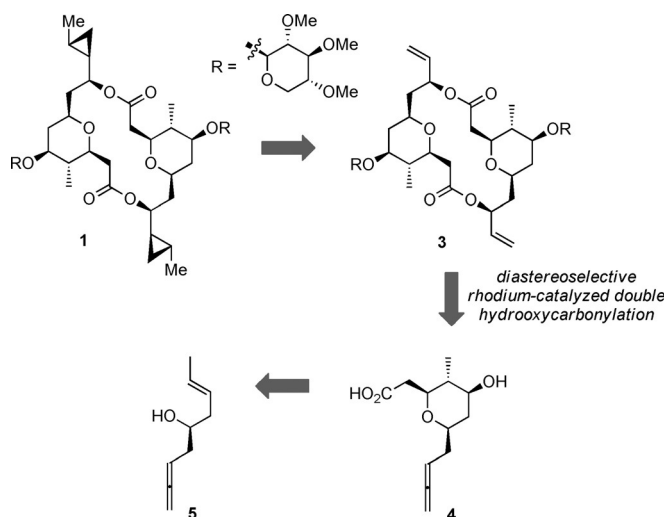
Scheme 1. The polyketides clavosolide A and cyanolide A as examples of natural products with a C_2 -symmetric dimeric scaffold.

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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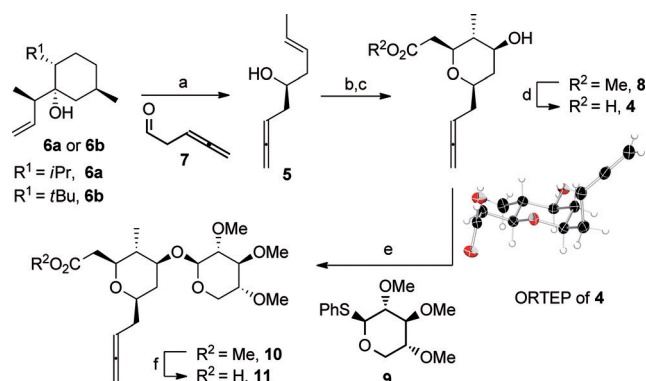
Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/ange.201506618>.



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.

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 homoallyl 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



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·H₂O (10 mol %), CH₂Cl₂, room temperature, 90% (> 99% *ee*); b) HC≡CCO₂Me, quinuclidine, TFA, CH₂Cl₂, 0°C then room temperature (d.r. 87:13); c) K₂CO₃, MeOH, room temperature, 71% (2 steps); d) LiOH·H₂O, THF/H₂O/MeOH (2:1:1), room temperature, 96%; e) **9**, MeOTf, MS (4 Å), Et₂O, room temperature, 64% (d.r. 77:23); f) LiOH·H₂O, THF/H₂O/MeOH (2:1:1), room temperature, 94%. MS = molecular sieves, TFA = trifluoroacetic acid, Tf = trifluoromethanesulfonyl, *p*Ts = *p*-toluenesulfonyl.

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 Cs₂CO₃ (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	<i>t</i>	Yield [%] ^[c]	d.r. ^[d]
1 ^[e]	8 (12)	—	18	97	63:37
2	8 (12)	—	18	50	80:20
3	8 (12)	Cs ₂ CO ₃	18	62	95:5
4	8 (12)	Cs ₂ CO ₃	96	95	95:5
5 ^[f]	8 (12)	Cs ₂ CO ₃	96	79	93:7
6 ^[g]	8 (12)	Cs ₂ CO ₃	96	94	10:90
7	10 (14)	Cs ₂ CO 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 ¹H 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), Cs₂CO₃ (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

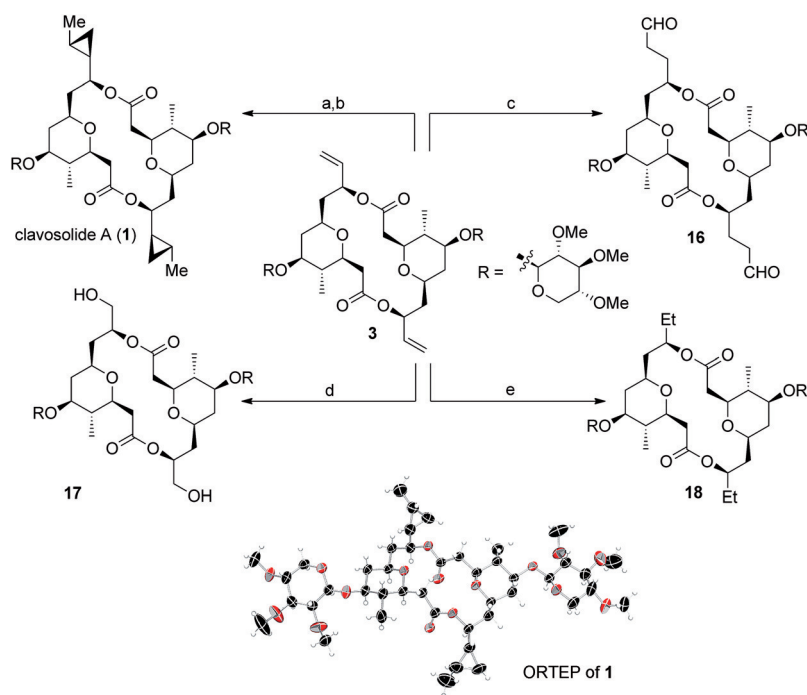
[a] Glycosidation after catalysis: **9**, MeOTf, MS (4 Å), Et₂O, room temperature, 85 % (43 % yield for the β,β-anomer). [b] Yield of the diastereomeric mixture isolated after silica-gel chromatography. [c] The diastereomeric ratio was determined by ¹H NMR spectroscopy of the crude reaction mixture. [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] C₁ 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 premetallated 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 , $0 \rightarrow 15^{\circ}\text{C}$, 63%; c) $[\{\text{Rh}(\text{CO})_2\text{acac}\}]$ (1.5 mol%), 6-DPPon (30 mol%), CO/H_2 (1:1, 20 bar), toluene, 80°C , 81% (9:1 I,I/l,l,b); d) O_3 ; NaBH_4 , $\text{CH}_2\text{Cl}_2/\text{MeOH}$ (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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