Natural Product Synthesis

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# Collective Synthesis of Cladiellins Based on the Gold-Catalyzed Cascade Reaction of 1,7-Diynes**

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***Abstract:*** *The cladiellin family of natural products, which includes molecules with various biological activities, continues to invite new synthetic studies. A gold-catalyzed tandem reaction of 1,7-diynes to construct the 6-5-bicyclic ring systems that are present in a number of natural products was developed. This reaction was applied as the key step to realize the formal and total syntheses of nine members of the cladiellin family in an enantio- and diastereoselective manner. This modular and efficient approach could also be used for the construction of other cladiellins, as well as their analogues, for follow-up studies.*

The cladiellins (compounds **1**–**9**) are a group of structurally complex natural products that have attracted considerable attention from the organic synthesis community.[1] Among them, (−)-sclerophytin A (**1**) is of particular interest because it has been reported to be toxic to mouse lymphocytic leukemia L1210 cells at concentrations as low as 3 nM.[2] Several other cladiellins have also been reported to possess potential antitumor activities, including (+)-vigulariol (**6**), which exhibited in vitro cytotoxicity towards human lung adenocarcinoma A-549 cells, and (−)-pachycladin D (**9**), which showed anti-invasive activity.[3,4] Another cladiellin, (+)-polyanthellin A (**4**), has been reported to be an antimalarial reagent based on its inhibitory activity towards *Plasmodium falciparum*.[5] Despite these reports, the antitumor and antimicrobial activities of the many other compounds belonging to the cladiellin family have not been extensively evaluated. Comparison studies with cladiellins and their unnatural structural analogues through the use of biological assays could provide a detailed understanding of their structure–activity relationships and could effectively highlight the potential of cladiellins as lead compounds for the development of small-molecule probes and drugs.[6] Several members of the cladiellin family have been successfully synthesized by a number of research groups.[7–15] In fact, research into the total synthesis of cladiellins has played an important role in determining their structures.[7,8,9e] The tricyclic compound **10** has been used as a common late-stage intermediate in a number synthetic strategies for accessing various cladiellins, including **1**, **2**, **5**, and **6**.[9f,12a,c,15] Given that compounds **1–9** differ only in terms of their substituents at C6, C7, and C11 (sclerophytin A numbering used throughout), the development of a method for the conversion of **10** into **3**, **4**, **7**, **8**, and **9** would represent a significant addition to the techniques currently available for the synthesis of cladiellins (Figure 1).[12c]

Among the different strategies that have been developed for the construction of enantiopure **10**,[9f,12c,15] the preferential ring-closing olefin metathesis of bicyclic compound **11** is relatively straightforward but only provides the desired product in 40–50% yield under the reported conditions.[15] Operating under the assumption that the yield for this ring-closing olefin metathesis step could be improved, it was envisaged that the 6-5-bicyclic ring system of **11** could be accessed through the gold-catalyzed cascade reaction of 1,7-diynes that we recently developed during our synthesis of compounds belonging to the drimane family of natural products.[16] The precursor for **11**, compound **12**, could be produced from 1,7-diyne **14** in one step via intermediate **13**. Enantiopure 1,7-diyne **14**, which has three contiguous stereogenic centers, could itself be prepared by a Marshall coupling reaction between propargyl mesylate **15** and ethyl glyoxalate (**16**).[17] Herein, we disclose our contribution towards the development of an efficient and modular strategy for the synthesis of cladiellins that complements other approaches in terms of providing a platform for the synthesis of related analogues.

Our modular and scalable synthesis of chiral 1,7-diyne **14** is shown in Scheme 1. The diastereoselective α-alkylation of amide **18**, which was prepared from commercially available hex-5-ynoic acid (**17**), afforded the tertiary stereogenic center at C14 of the cladiellins.[18] The superiority of pseudoephenamine as an auxiliary in asymmetric alkylation reactions involving isopropyl iodide as the electrophile allowed **19** to be prepared on a multigram scale.[19] Successive hydrolysis and amide coupling reactions yielded a Weinreb amide, which was subsequently allowed to react with an acetylenyl Grignard reagent to give ketone **21**. The asymmetric reduction of ketone **21** with (*S*)-alpine-borane[20] followed by mesylation of the resulting alcohol afforded mesylate **15** as a single diastereomer in 56% yield. Marshall coupling of **15** and aldehyde **16** under optimized conditions afforded a separable

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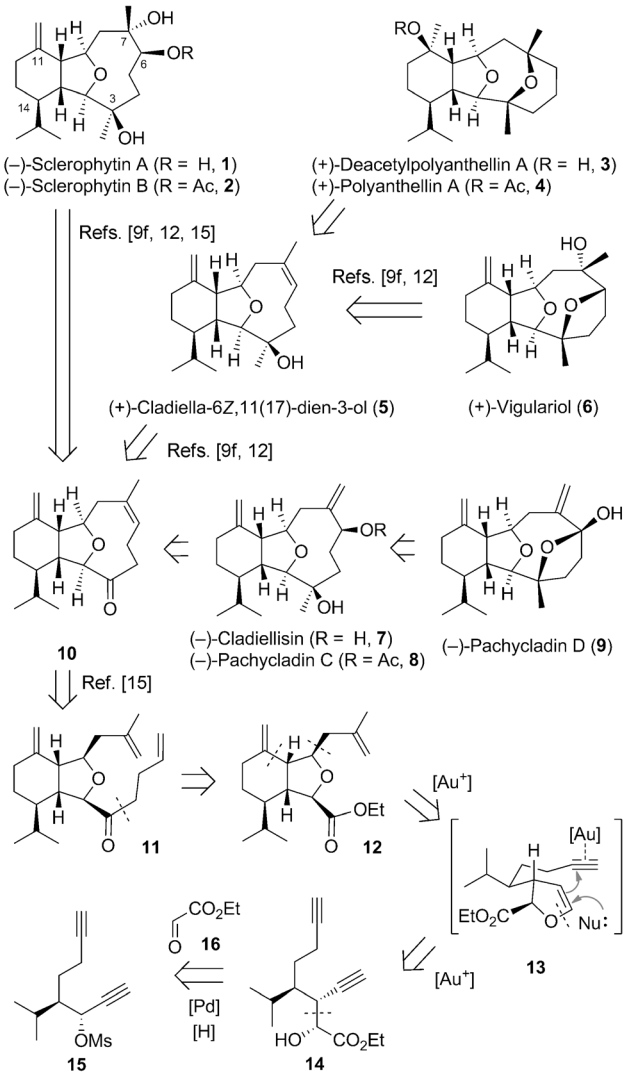
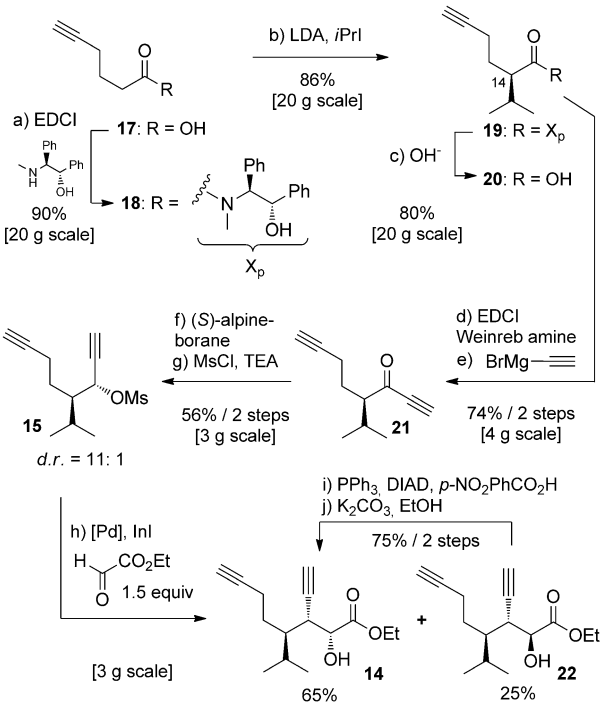



*Figure 1.* Retrosynthetic analysis of cladiellins via key intermediate **10**: a strategy enabled by the gold-catalyzed cascade reaction of 1,7-diyne **14**.

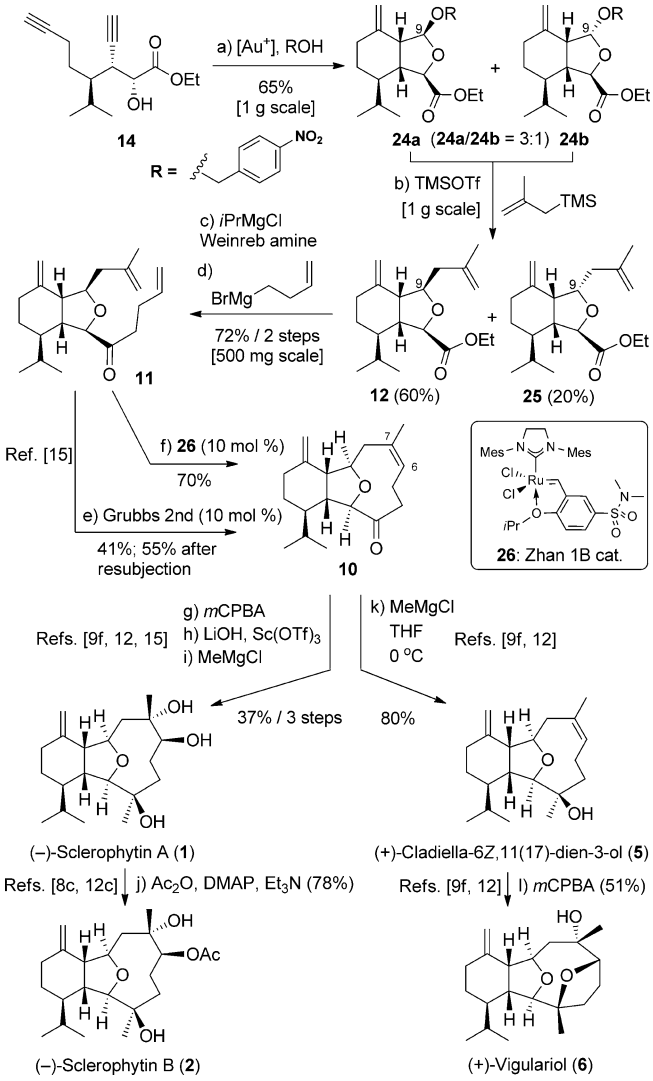



***Scheme 1.*** Scalable enantioselective synthesis of 1,7-diyne **14**. Yields of isolated products (%) are indicated. Reagents and conditions: a) EDCI (1.1 equiv), HOBt (1.1 equiv), (−)-(1*S*,2*S*)-pseudoephenamine (1.1 equiv), DIPEA (3.0 equiv), DMF, RT. b) LiCl (6.0 equiv), LDA (4.0 equiv), isopropyl iodide (6.0 equiv), THF. c) $nBu_4NOH$ (5.0 equiv), *tert*-butyl alcohol/water = 1:1, reflux. d) EDCI (3.0 equiv), HOBt (3.0 equiv), DIPEA (6.0 equiv), *N*,*O*-dimethylhydroxylamine hydrochloride (3.0 equiv), DMF. e) ethynylmagnesium chloride (2.0 equiv), THF. f) (*S*)-alpine borane (2.0 equiv). g) MsCl (2.0 equiv), $Et_3N$ (4.0 equiv), $CH_2Cl_2$. h) 5% $[Pd(dppf)Cl_2]\cdot CH_2Cl_2$, InI (1.1 equiv), **16** (2.0 equiv), THF/HMPA = 3:1. i) $PPh_3$ (2.5 equiv), DIAD (3.0 equiv), *p*-$NO_2PhCO_2H$ (2.5 equiv), THF. j) $K_2CO_3$ (2.0 equiv), EtOH. EDCI = 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide, HOBt = 1-hydroxybenzotriazole, LDA = lithium diisopropylamide, DIPEA = diisopropylethylamine, Ms = methanesulfonyl, TEA = triethylamine, dppf = 1,1′-bis(diphenylphosphanyl)ferrocene, HMPA = (hexamethylphosphoramide, DIAD = diisopropyl azodicarboxylate.

mixture of diynes **14** and **22** in 90% overall yield with a moderate level of stereoselectivity (d.r. = 2.5:1; Table S1, see the Supporting Information for details). Pleasingly, the undesired diastereomer **22** could be readily converted into **14** in two steps through the inversion of one stereogenic center.

With abundant 1,7-diyne **14** in hand, we proceeded to investigate the feasibility of our key cascade transformation for the construction of the 6-5-bicyclic skeleton. Subjecting **14** to the gold-catalyzed cascade reaction in the presence of excess methylallyl trimethylsilane, however, led only to the *O*-TMS protection product **23**,[21] and decomposition was observed when phenol was added to scavenge the TMS group.[22] By contrast, the use of *p*-nitrobenzylic alcohol as a nucleophile allowed the desired 6-5-bicyclic skeleton to be formed successfully, albeit as a pair of diastereomers **24a** and **24b**. Following a period of optimization (Table S2 in the Supporting Information), **14** could be converted into **24a** (98% *ee*) and **24b** in 65% yield with 3:1 diastereoselectivity on a gram scale (Scheme 2). Given that both **24a** and **24b** could be used in the next step, the mixture of **24a** and **24b** was treated with excess (methylallyl)trimethylsilane and TMSOTf[23] to give **12** and its C9 diastereomer **25** in yields of 60 and 20%, respectively. Ester **12** was then converted into **11** through sequential Weinreb amide formation and Grignard reactions. Morken and co-workers. reported the ring-closing metathesis of **11** to afford **10** in 55% yield after resubjection of the recovered starting material and side product to the reaction conditions,[15] and this result was successfully reproduced in our hands. Pleasingly, however, the use of the Zhan 1B catalyst **26** led to a significant increase in the efficiency of the desired transformation, presumably because of the enhanced stability of the catalyst.[24] This modification afforded the key intermediate **10** in 70% yield in a single operation. The analytical data for **10** were identical to those reported[9f,12a,c,15] and confirmed that we had produced the material required to explore the synthesis of compounds **1**–**9**. Our initial efforts focused on the synthesis of compounds

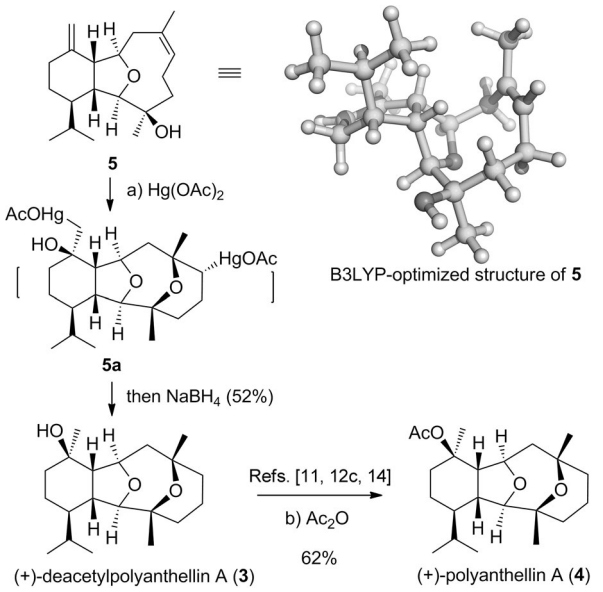
  




***Scheme 2.*** Synthesis of (−)-sclerophytin A (**1**), (−)-sclerophytin B (**2**), (+)-cladiella-6*Z*,11(17)-dien-3-ol (**5**), and (+)-vigulariol (**6**). Yields of isolated products (%) are indicated. Reagent and conditions: a) [(IPr)AuCl] (5 mol%), $AgSbF_6$ (5 mol%), *p*-$NO_2PhCH_2OH$ (1.5 equiv). b) TMSOTf (1.6 equiv), methylallyl-trimethylsilane (3.2 equiv), $CH_3CN$. c) *N*,*O*-Dimethylhydroxylamine hydrochloride (3.0 equiv), isopropylmagnesium chloride (6.0 equiv), THF. d) 3-Butenyl magnesium bromide (2.0 equiv), THF. e) Grubbs 2nd generation catalyst (10 mol%), PhH, reflux. f) Zhan 1B catalyst (10 mol%), toluene, reflux. g) *m*CPBA (1.4 equiv), $CHCl_3$, −12 °C. h) LiOH (18.0 equiv), dioxane, $H_2O$; then $KHSO_4$ (18.0 equiv), $Sc(OTf)_3$ (1.5 equiv), $CH_3CN$, $H_2O$, RT. i) MeMgCl (120.0 equiv), THF, 52 °C, 24 h. j) $Ac_2O$ (3.0 equiv), $Et_3N$ (7.5 equiv), DMAP (1.0 equiv), $CH_2Cl_2$, 0 °C. k) MeMgCl (20.0 equiv), THF, 0 °C. l) *m*CPBA (2.0 equiv), $CH_2Cl_2$, 0 °C. TMS = trimethylsilyl, Tf = trifluoromethanesulfonyl, *m*CPBA = *m*-chloroperbenzoic acid, DMAP = 4-dimethylaminopyridine.

**1**, **2**, **5**, and **6** by using the published procedures.[8c,9f,12,15] The spectroscopic data ($^1H$ and $^{13}C$ NMR spectra, HRMS analyses, and optical rotation) of the synthesized samples of **1**, **2**, **5**, and **6** were in good agreement with those reported for the corresponding natural materials.[9f,12,13,15]

Given that (+)-polyanthellin A (**4**) can be prepared by the acetylation of (+)-deacetylpolyanthellin A (**3**),[11,12c,14] we




***Scheme 3.*** Synthesis of (+)-deacetylpolyanthellin A (**3**) and (+)-polyanthellin (**4**). Yields of isolated products (%) are indicated. Reagents and conditions: a) $Hg(OAc)_2$ (2.0 equiv), THF, RT, 2 h; then $H_2O$, $Hg(OAc)_2$ (2.0 equiv), 2 h; then $Et_3B$ (10.0 equiv), $NaBH_4$ (10.0 equiv), −20 °C to RT, overnight. b) $Ac_2O$ (5.0 equiv), $Et_3N$ (5.0 equiv), DMAP (5.0 equiv), $CH_2Cl_2$, RT, 24 h.

aimed to prepare **3** from **5** by installing additional cyclic ether and tertiary alcohol moieties (Scheme 3). A regio- and stereoselective double oxymercuration followed by a reduction, the combination of which is an efficient one-pot protocol that has successfully been used for the synthesis of **3** from the other two advanced intermediates,[11,14] accomplished this task in moderate yield. Thus, the total synthesis of the natural product (+)-polyanthellin A (**4**) was achieved in 62% yield by the reaction of **3** with acetic anhydride in the presence of $Et_3N$ and DMAP.[11,12c,14]

To access (−)-cladiellinsin (**7**), (−)-pachycladin C (**8**), and (−)-pachycladin D (**9**), we first converted **10** into hemiketal **27** by following known procedures (Scheme 4).[9f,15] Selective protection of the hemiketal hydroxy group in **27** afforded tertiary alcohol **28**, which underwent regioselective dehydration followed by deprotection to furnish hemiketal **29** in 72% yield over three steps.[25,26] The addition of methylmagnesium chloride at an elevated temperature afforded **7** in 93% yield as a single diastereoisomer. Finally, **7** was converted into **8** and **9** by acetylation and oxidation of the secondary alcohol, respectively. The analytical data for **7**, **8**, and **9** corresponded well with those reported from the isolated natural materials.[4]

In summary, we have developed a concise and general strategy to access a number of cladiellins through the gold-catalyzed cascade reaction of 1,7-diynes. The modularity of our approach will enable the efficient preparation of a variety of natural product analogues. The biological activities of our synthesized cladiellins, especially their cytotoxicities against various cancer cells, are under evaluation.

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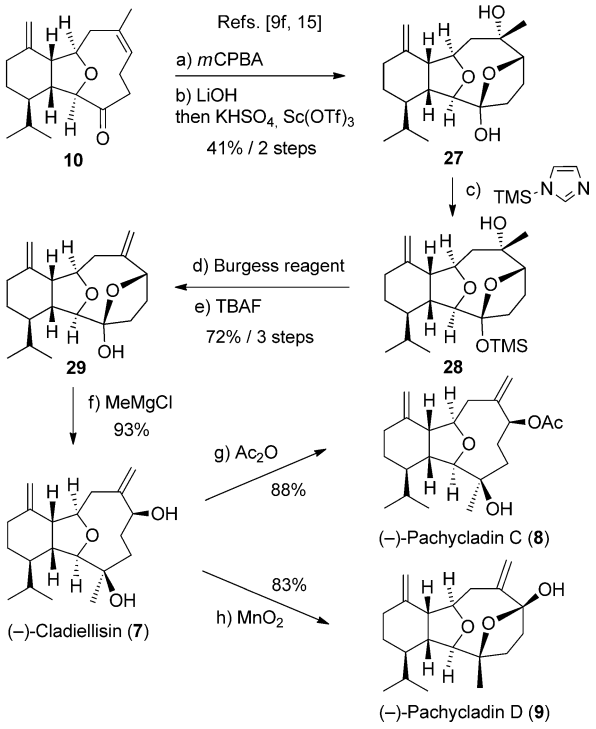


***Scheme 4.*** Total synthesis of (−)-cladiellinsin (**7**), (−)-pachycladin C (**8**) and (−)-pachycladin D (**9**). Yields of isolated products (%) are indicated. Reagents and conditions: a) *m*CPBA (1.4 equiv), $CHCl_3$, −12 °C. b) LiOH (18.0 equiv), dioxane, $H_2O$; then $KHSO_4$ (18.0 equiv), $Sc(OTf)_3$ (1.5 equiv), $CH_3CN$, $H_2O$, RT. c) *N*-(Trimethylsilyl)imidazole (10.0 equiv), $CH_2Cl_2$. d) Burgess reagent (4.0 equiv), toluene, 70 °C. e) TBAF (8.0 equiv), THF. f) MeMgCl (90.0 equiv), toluene, 100 °C. g) $Ac_2O$ (3.0 equiv), $Et_3N$ (6.0 equiv), DMAP (2.0 equiv). h) $MnO_2$ (60.0 equiv). TBAF = tetra-*n*-butylammonium fluoride.

**Keywords:** cascade reaction · cyclization · gold · natural products · total synthesis

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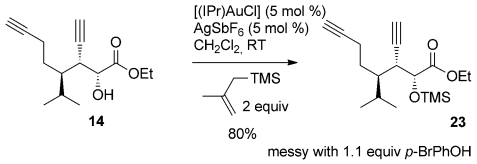


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