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SPECIAL FEATURE: BRIEF COMMUNICATION

Construction of a 6/5/9-membered tricyclic structure of cladiellins via radical-polar crossover reaction

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Abstract

A three-component coupling reaction of structurally simple **6**–**8** was successfully applied for expeditious synthesis of the 6/5/9-membered tricyclic structure **3** of cladieunicellin D (**1**) and klysimplexin U (**2**). Upon treatment with the Et_3B/O_2 reagent system, α-alkoxyacyl telluride **6**, six-membered enone **7**, and (*Z*)-4-hexenal (**8**) were linked in one pot to provide the densely functionalized **5** via sequential decarbonylative radical generation, radical addition, boron enolate formation, and intermolecular aldol reaction. Subsequent Lewis acid-promoted reductive etherification and SiO_2-induced C10-epimerization gave rise to the *cis*-fused five-membered ether of **4**. Finally, cyclization of the nine-membered ring was achieved by the ring-closing metathesis reaction, giving rise to **3**. Compound **3** possesses the six stereocenters of **1** and **2**, and would thus serve as an advanced intermediate for their total syntheses.

More than 100 cladiellin diterpenoids (a.k.a. eunicellins) have been isolated from marine invertebrates in diverse locations, and many of them exhibit potent biological activities [1, 2]. As exemplified by the structures of cladieunicellin D (**1**) [3] and klysimplexin U (**2**) [4] (Scheme 1), these natural products all possess a characteristic 6/5/9-membered ring skeleton, but differ in their oxidation and unsaturation levels. The intricately fused and highly oxidized structures of cladiellins have inspired chemists to develop new synthetic methods for their efficient assembly. Extensive synthetic studies and various total syntheses have been disclosed to date [5–11].

Three-component coupling is an extremely useful method for increasing the structural and functional complexity of the molecule in a single step [12]. Radical-based three-component reactions are particularly advantageous for constructing highly oxygenated carboskeletons of terpenoids, because radical reactions enable chemoselective formation of ring-connecting hindered carbon–carbon (C–C) bonds without affecting the preexisting oxygen functionalities of the fragments [13–19]. In this context, we recently developed Et_3B/O_2-mediated radical-polar crossover reactions of α-alkoxyacyl tellurides, comprising a sequential radical addition and an aldol reaction [20, 21]. As part of our continuing interest in exploring this powerful method, we decided to devise a new efficient strategy for assembling cladiellin diterpenes. Accordingly, the cladiellin skeleton **3** was selected as an initial synthetic target. Compound **3** was designed to have the six tertiary stereogenic carbons (C1, 2, 4, 9, 10, and 14) that correspond to those of **1** and **2**, and to possess the C3-OH, C5-olefin, and C11-ketone that would function as handles for completing the total syntheses. Herein we report the expeditious construction of this complex molecule **3** using the radical-polar crossover reaction as the pivotal transformation.

The three-component coupling reaction allowed for a simple synthetic strategy (Scheme 1). The 6/5/9-tricycle **3** was retrosynthetically dissected into α-alkoxyacyl telluride **6** as a radical precursor, (–)-cryptone (**7**) as a radical acceptor, and (*Z*)-4-hexenal (**8**) as an electrophile. Coupling of these three fragments **6**–**8** would connect the C1–C2 and C9–C10 bonds with stereoselective installation of the three stereocenters (C1, 9, and 10). Since the entire carbon

Dedication: Dedicated with respect and admiration to Professor SJ Danishefsky for his many outstanding contributions to natural product synthesis.

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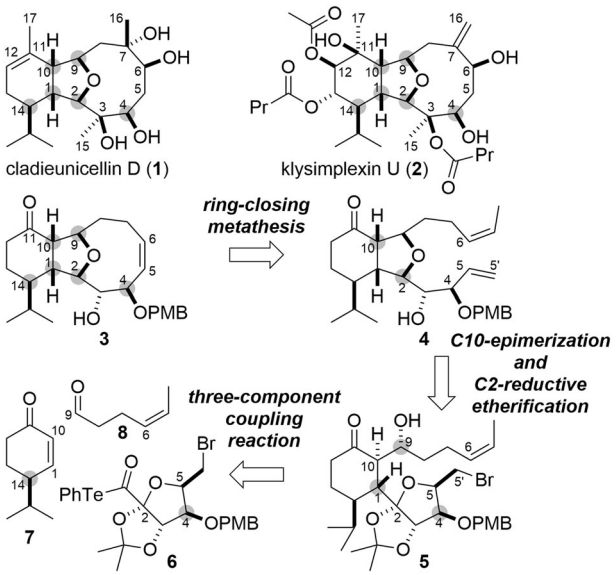


Scheme 1 Structure of cladieunicellin D (**1**) and klysimplexin U (**2**), and synthetic plan for cladiellin skeleton **3**

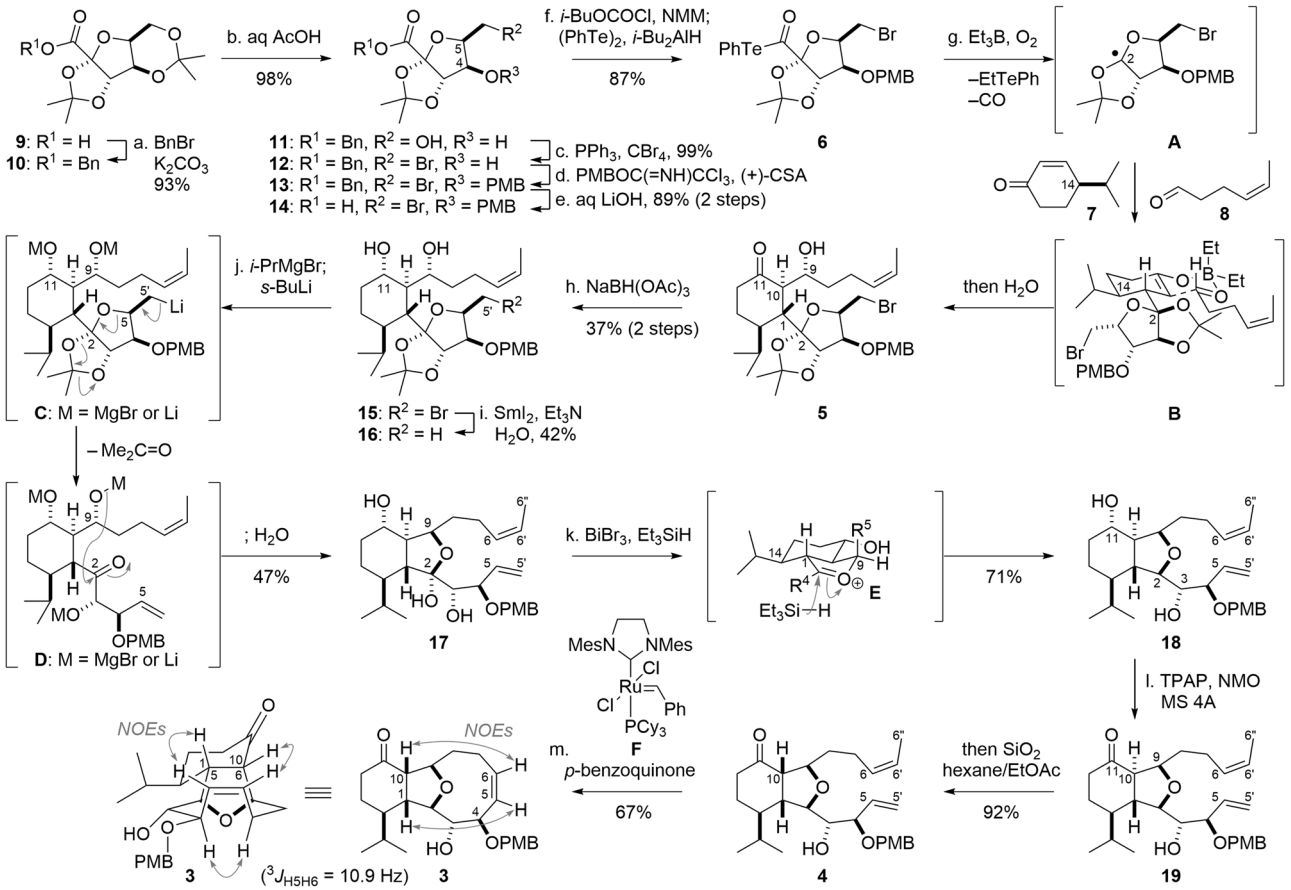
framework would be assembled in this single reaction, the remaining processes from **5** to **3** would not involve further carbon-chain extension. The C5'-bromo ether and C2-acetal structures of **5** would be utilized to construct the C5-olefin and C2-ether, respectively. After C10-epimerization, the C5- and C6-double bonds of **4** would participate in a ring-closing metathesis reaction to cyclize the nine-membered ring of the target **3**.

The requisite α-alkoxyacyl telluride **6** was readily prepared from commercially available diprogulic acid (**9**) in six steps (Scheme 2). After converting carboxylic acid **9** to benzyl ester **10** using K_2CO_3 and benzyl bromide, the less-hindered acetonide of **10** was chemoselectively removed to provide diol **11**. The primary alcohol of **11** was regioselectively brominated by employing PPh_3 and CBr_4, and the remaining secondary alcohol was protected as the PMB-ether by the action of PMBOC(=NH)CCl_3 and (+)-CSA [22]. The benzyl ester of **13** was in turn hydrolyzed by an aqueous LiOH solution to generate the carboxylic acid of **14**. Then, α-alkoxyacyl telluride **4** was derivatized from **14** via a one-pot procedure: formation of the activated ester with *i*-BuOCOCl and *N*-methylmorpholine, and subsequent replacement of the *i*-$BuOCO_2$ group with the TePh group using *i*-Bu_2AlH and $(PhTe)_2$ [23].

The key radical-polar crossover coupling reaction significantly increased the complexity of the molecule under mild conditions. When **6**, **7** (3 equiv.), and **8** (10 equiv.) were treated with Et_3B (5 equiv.) [24] in hexane (0.2 M) under air at room temperature, the three-component product **5** was indeed produced by linking the two sterically encumbered C1–C2 and C9–C10 bonds, and introducing the correct C1- and C9-stereocenters of the target **3**. As the C11-ketone turned out to be prone to a retro-aldol reaction, the yield was calculated to be 37% yield (two steps) after stereoselective reduction of **5** to 1,3-syn-diol **15** with $NaBH(OAc)_3$ [25]. In the coupling reaction, an ethyl radical generated from Et_3B and O_2 promotes homolysis of the C–Te bond of **6** to form an acyl radical. The acyl radical expels carbon monoxide to produce C2-acetal radical **A** [26]. Nucleophilic radical **A** chemoselectively adds to an electron-deficient double bond of **7** in the presence of the electron-rich disubstituted olefin of **8**. Moreover, **A** stereoselectively establishes the C1-position of the two-component adduct by approaching from the opposite face of the bulky C14-isopropyl group of **7**. This radical intermediate is then captured by Et_3B to form boron enolate, which reacts with aldehyde **8** through the chair-like six-membered transition state **B** to install the C9- and C10-stereocenters of ketone **5** [27]. It should be noted that the potentially reactive primary bromides of the intermediates survived treatment with nucleophilic *i*-$Bu_2AlTePh$ (**14** → **6**) and radical-generating Et_3B/O_2 (**6** → **5**), indicating the mildness of the present procedure using α-alkoxyacyl telluride.

Having realized the chemo- and stereoselective three-component coupling reaction, the bromo ether structure of **15** was utilized to unmask the C2-ketone and C5-olefin. Such a ring-opening reaction, however, required us to screen the reductants and conditions. While Zn failed to react with bromide **15**, the $SmI_2/H_2O/Et_3N$ mixture in THF [28] reduced the bromide, but did not promote the elimination of the C2-oxygen functionality, thereby furnishing debrominated **16** after aqueous work-up. In contrast to these results, sequential addition of *i*-PrMgBr and *s*-BuLi to **15** in THF from -78 °C to 0 °C resulted in reductive cleavage of the bromo ether to produce **17**. This reaction would involve the following cascade processes: deprotonation of the C9- and C11-alcohols with *i*-PrMgBr, bromine-lithium exchange induced by *s*-BuLi (**15** → **C**), E1cB elimination of the C2-oxygen functionality, C2-ketone generation through the ejection of acetone (**C** → **D**), and C2-hemiacetal formation by nucleophilic addition of the C9-alkoxide to the C2-ketone, followed by protonation (**D** → **17**).

Finally, the oxygen-bridged five- and nine-membered ring structure of **3** was constructed using the C2-hemiacetal and C5-olefin as chemical handles. First, reductive etherification of **17** was realized by applying a catalytic amount of $BiBr_3$ and stoichiometric Et_3SiH [29], leading to the five-membered ether of **18** as the sole C2-stereoisomer. Thus, as the bulky C9-substituent and C14-isopropyl groups blocked the top side of the molecule, Et_3SiH attached on oxocarbenium ion **E** from the bottom side, introducing the requisite C2-trisubstituted stereocenter of **18**. The secondary C11-OH of **18** was then regioselectively oxidized to the C11-ketone of **19** in the presence of the secondary C3-OH by employing TPAP reagent [30]. This C11-oxidation



Scheme 2 Construction of the cladiellin skeleton. Reagents and conditions: (a) BnBr, K_2CO_3, DMF, r.t., 93%; (b) 50% aq AcOH, 50 °C, 98%; (c) PPh_3, CBr_4, pyridine, THF, 50 °C, 99%; (d) PMBOC(=NH)CCl_3, (+)-CSA (5 mol%), CH_2Cl_2, r.t.; (e) 1 M aq LiOH, THF, r.t., 89% (2 steps); (f) *i*-BuOCOCl, NMM, THF; $(PhTe)_2$, *i*-Bu_2AlH, 87%; (g) Et_3B (5 equiv.), air, **7** (3 equiv.), **8** (10 equiv.), hexane, r.t.; (h) $NaBH(OAc)_3$, benzene, r.t., 37% (2 steps); (i) SmI_2, Et_3N, H_2O, THF, r.t., 42%; (j) *i*-PrMgBr, THF, −78 °C; *s*-BuLi, −78 to 0 °C, 47% from **15**; (k) $BiBr_3$ (25 mol%), Et_3SiH, MeCN, 0 °C, 71%; (l) TPAP (20 mol%), NMO, MS 4 A, r.t., 92%; (m) **F** (20 mol%), *p*-benzoquinone, toluene, 130 °C, 67%. Bn, benzyl; r.t., room temperature; PMB, *p*-methoxybenzyl; CSA, 10-camphorsulfonic acid; NMM, *N*-methylmorpholine; TPAP, tetrapropylammonium perruthenate; NMO, *N*-methylmorpholine *N*-oxide; MS, molecular sieve; Mes, mesityl; Cy, cyclohexyl

enabled us to epimerize the C10-stereochemistry that was established at the radical coupling reaction. Interestingly, upon purification **19** on silica gel, the 6/5-*trans*-fused ring system of **19** was readily converted to the thermodynamically more stable 6/5-*cis*-fused tetrahydrofuran of **4** [31]. In this reaction, the potential E1cB elimination of the C9-oxygen functionality was impeded, presumably due to the orthogonal relationship between the $\sigma^*_{(C9–O)}$ orbital and the $\pi_{(C10–C11)}$ orbital of the C11-enol intermediate. The thus-obtained diene **4** was treated with 20 mol% of a second-generation Grubbs catalyst (**F**) at 130 °C in toluene using 1,4-benzoquinone as the additive to prevent unwanted olefin isomerization [32]. The nine-membered ether ring successfully formed, delivering cladiellin skeleton **3** with the 6/5/9-membered ring system. The (*Z*)-geometry of C5-olefin and the 6/5-*cis*-fused structure of the tricyclic compound **3** was confirmed by the coupling constant ($^3J_{H5H6}$ = 10.9 Hz) and NOE measurement.

In summary, we synthesized cladiellin skeleton **3** in 12 steps from diprogulic acid (**9**). The three-component coupling reaction of **6**–**8** effectively connected the sterically hindered C1–C2 and C9–C10 bonds with introduction of the C1-, C9-, and C10-stereocenters. The present radical-polar crossover coupling reaction allowed access to a densely functionalized structure that is difficult to obtain by conventional polar or radical reactions, thereby simplifying the overall route to **3**. The *i*-PrMgBr/*s*-BuLi-promoted ring-opening of bromo ether **15** revealed the C2-hemiacetal and the C5-olefin. At the last stage of the synthesis, $BiBr_3$-catalyzed reductive etherification of hemiacetal **17**, SiO_2-promoted C10-epimerization of ketone **19**, and a ring-closing metathesis reaction of diene **4** were performed as key transformations to produce the targeted **3**. Because of its multiple reactive functional groups applicable for further derivatization, **3** can serve as an advanced intermediate for the total syntheses of various cladiellin diterpenoids, including **1** and **2**.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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