

Synthesis of Tetrahydropyran/Tetrahydrofuran-Containing Macrolides by Palladium-Catalyzed Alkoxy carbonylative Macrolactonizations**

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Abstract: A novel Pd-catalyzed cascade alkoxy carbonylative macrolactonization to construct tetrahydropyran/tetrahydrofuran-containing bridged macrolactones in one step from alkendiols is described. Products with various ring sizes and substituents were obtained. Challenging macrolactones involving tertiary alcohols were synthesized smoothly as well. Mechanistically, experimental evidence to support a trans-oxypalladation step has been provided. The method was applied to the synthesis of potent anticancer compound 9-demethylneopeltolide.

Macroscopic structural motifs are prevalent in many approved drug molecules, natural products, and other molecules with important function.^[1] Among them, tetrahydropyran (THP) and tetrahydrofuran (THF)-containing macrolides are a diverse group of natural products with a wide range of biological activity.^[2] For example, neopeltolide (**1**),^[3] lyngbyalide B (**2**),^[4] and exiguolide (**3**)^[5] have shown potent anticancer activity (Figure 1). Neopeltolide also exhibits potent antifungal activity against pathogenic yeast *Candida albicans*. Exiguolide specifically inhibits fertilization of sea urchin gametes.

The core structural skeletons of THP/THF-containing natural macrolides can be represented as generic structure **4** (Figure 1). A variety of strategies have been developed to prepare such structural motifs. Currently, most of them are synthesized from seco-acid precursors by various macrolactonizations.^[6] Most of the commonly used macrolactonization methods require multiple steps to prepare the corresponding seco-acids including tedious masking and unmasking of the carboxylic acid and/or alcohol, more than stoichiometric

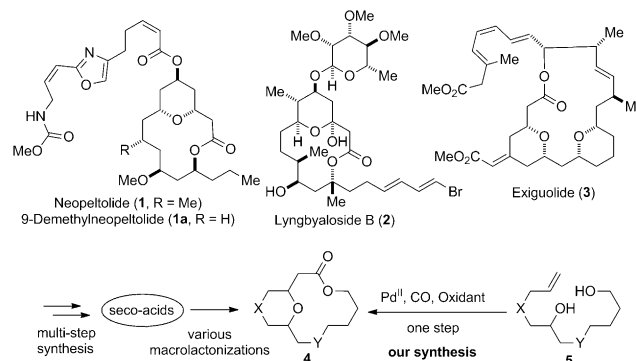


Figure 1. Selected THP-containing macrolides and our synthetic strategy.

metric amount of reagents to activate the carboxylic acid and/or alcohol, and relatively harsh reaction conditions to promote the macrolactonization. While other methods such as ring-closing metathesis,^[7] macrocyclic Prins-type cyclizations,^[8] dual macrolactonization/pyran-hemiketal formation via acylketene intermediate^[9] and transannular oxa-Michael cyclizations^[10] have been used recently to make THP/THF-containing macrolides, highly efficient and catalytic methods are still needed. We envisioned the possibility of synthesizing both the THP/THF ring and the macrolactone ring in one step from relatively simple alkendiols (cf. **5**→**4**, Figure 1) by developing Pd-catalyzed alkoxy carbonylative macrolactonizations. Pd-catalyzed alkoxy carbonylation, the venerable Semmelhack reaction, has been widely used to synthesize THP/THF-containing esters as well as small-sized lactones.^[11] However, to date, Pd-catalyzed alkoxy carbonylative macrolactonization to form products such as **4** has not been reported. Pd-catalyzed carbonylative macrocyclization has been rarely studied as well.^[12] We were hoping to trap the reactive acyl-palladium species derived from a sequence of Wacker-type oxypalladation and CO migratory insertion by a tethered remote alcohol to afford the desired THP/THF-containing bridged macrolactone. The proposed process requires only a catalytic amount of palladium catalyst. Since olefins are relatively inert and compatible in most of the reaction conditions, tedious masking and unmasking practices could be avoided. In addition, no carboxylic acid synthesis and its further activation are required. We were also hoping that the palladium metal center might serve as a template through coordination to bring the remote nucleophilic alcohol and the electrophilic acyl species into proximity and therefore facilitate the macrolactonization by compensating for the entropic disadvantage. Herein, we report a novel Pd-cata-

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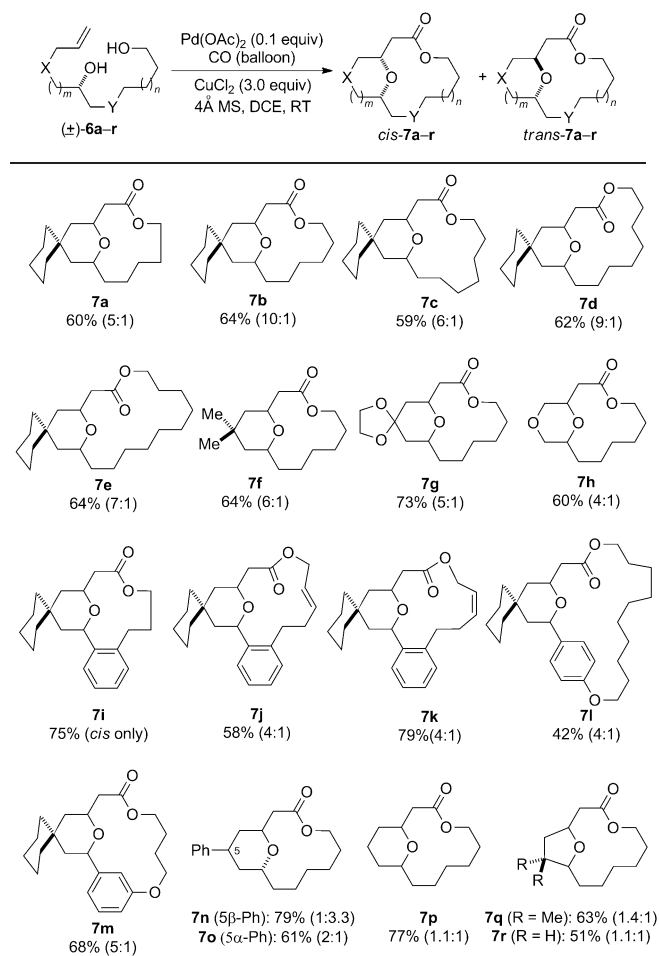
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lyzed cascade alkoxycarbonylative macrolactonization to synthesize various THP/THF-containing bridged macrolactones including 9-demethylneopeltolide (**1a**).

Our exploration started with the commonly used Semmelhack reaction conditions and the Lambert carbonylation conditions.^[13] After investigating several reaction parameters, we found that various THP/THF-containing macrolactones could be obtained using Pd(OAc)₂ (0.1 equiv) as catalyst and CuCl₂ (3.0 equiv) as oxidant under carbon monoxide atmosphere (balloon) in 1,2-dichloroethane (DCE, 0.002 M) at room temperature with slow addition of the starting alkediols (Table 1). As the macrolactone ring changes from 13- to 18-

Table 1: Substrate scope.^[a]

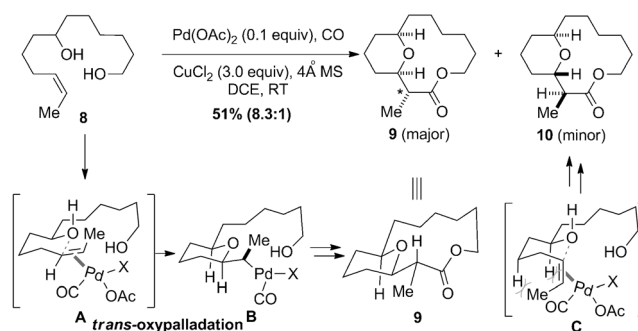


[a] Yields of isolated products are given with *cis/trans* ratio in parenthesis.

membered ring (**7a–h**), there is no significant change in the reaction yield and *cis*-2,6-disubstituted THP-containing macrolactones were produced as the predominant products. The reaction condition is compatible with ketal group (**7g**). Both internal *cis* and *trans* double bonds are tolerated as well (**7j,k**). Notably, *para*- and *meta*-cyclophanes were synthesized in **7l** and **7m**, respectively. A 23-membered macrolactone ring was formed in the case of **7l**, which represents the largest ring size we have explored so far. The structure of *cis*-**7m** was

unambiguously assigned by X-ray crystallography.^[14] Epimeric substrates **6n** and **6o** underwent the cascade reaction and gave products **7n** and **7o** in 79% and 61% yield, respectively. While *cis*-THP product is slightly favored in the case of **7o** (d.r. 2:1), *trans*-THP product dominates in the case of **7n** (d.r. 1:3.3). Product **7p** was obtained in 77% yield, surprisingly, with almost no diastereoselectivity. THF-containing macrolactones were formed in good yield as well (**7q,r**) but with poor diastereoselectivity. The reaction tolerates sterically hindered alcohol next to an all-carbon quaternary center (**7q**).

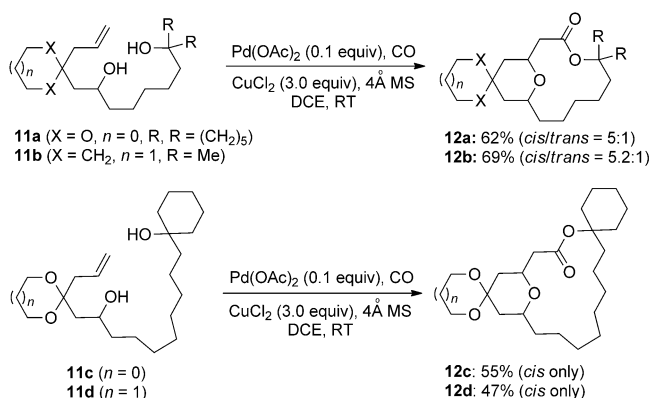
Since the new stereocenter is formed in the oxypalladation step, we wondered about the details of this step in our case. *trans*-Oxypalladation has been proposed for the Semmelhack reaction.^[11,15] Recently, elegant studies from several groups^[16] including those of Stoltz, Hayashi, Wolfe, and Henry have shown that, in the Wacker-type reaction, both *cis*- and *trans*-oxypalladation pathways are feasible. Similar phenomena have been observed in the related aminopalladation reactions.^[17] Thus, substrate **8** with a *cis*-double bond was prepared and subjected to the carbonylative macrolactonization conditions. Products **9** and **10** were obtained in 51% yield with 8.3:1 diastereoselectivity favoring *cis* product **9** (Scheme 1). The relative configuration of **9** was assigned



Scheme 1. A mechanistic study of the oxypalladation step.

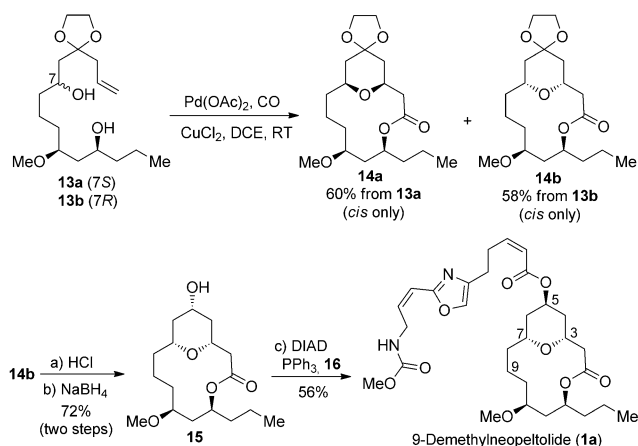
based on NOE studies. The stereochemical outcome at the α -carbon (asterisked) of **9** supports a *trans*-oxypalladation process via a chair-like transition state (**8**→**A**→**B**→**9**). The minor product was tentatively assigned as **10** based on transition state **C**, which is less favored than **A** due to strong steric repulsions. Since CuCl₂ was used as oxidant, at this stage, we cannot exclude the formation of acyl chlorides for the macrolactonization.^[13,18]

We then wondered whether the Pd-catalyzed alkoxycarbonylative macrolactonization would provide challenging tertiary macrolactones, which are common structural feature of many natural products such as lyngbyaloside B (**2**). Macrolactonization involving the OH group of a tertiary alcohol presents a great synthetic challenge and has not been well studied.^[9,19] We evaluated tertiary alcohol substrates **11a–d** (Scheme 2). All of them underwent the cascade cyclization smoothly and gave the desired tertiary macrolactones in good yield and diastereoselectivity.



Scheme 2. Alkoxy carbonylative macrolactonization of tertiary alcohols.

We then tested the effectiveness of the Pd-catalyzed alkoxy carbonylative macrolactonization for synthesizing 9-demethylneopeltolide,^[20] a simplified neopeltolide^[8a,b,21] analog but with similar inhibitory activity against P388 murine leukemia cells ($IC_{50} = 0.813$ nM). In order to evaluate the Pd-catalyzed alkoxy carbonylative macrolactonization in different stereo-settings and generate stereoisomers of 9-demethylneopeltolide, we prepared epimers **13a** and **13b** (see Supporting Information for their synthesis). Both **13a** and **13b** underwent the desired cyclization and products **14a** and **14b** were produced, respectively, in good yield and excellent *cis*-selectivity (Scheme 3). Compound **14b** was then con-



Scheme 3. Alkoxy carbonylative macrolactonization of **13a** and **13b** and synthesis of 9-demethylneopeltolide (**1a**). Reagents and conditions: a) HCl (0.5 N), MeOH; then HCl (1 N), THF, RT; b) NaBH₄ (3.9 equiv), MeOH, 0°C, 74% from **14b**; c) PPh₃ (3.8 equiv), DIAD (3.8 equiv), **16** (4.0 equiv), benzene, RT, 56%; DIAD = diisopropyl azodicarboxylate.

verted to 9-demethylneopeltolide (**1a**) uneventfully through a sequence of ketal removal, reduction and Mitsunobu reaction with the known acid **16** (see Supporting Information for its structure).^[22]

In summary, we have developed an efficient Pd-catalyzed cascade alkoxy carbonylative macrolactonization to construct

THP/THF-containing macrolactones with different ring sizes and substituents. Challenging macrolactones involving tertiary alcohols were synthesized efficiently as well. Mechanistically, experiments have been conducted to support a Wacker-type *trans*-oxypalladation step. The application of this method was demonstrated in the synthesis of 9-demethylneopeltolide.

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