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Total Synthesis of Polyrhacitides A and B by Use of an Iterative Strategy for the Stereoselective Synthesis of 1,3-Polyol Arrays

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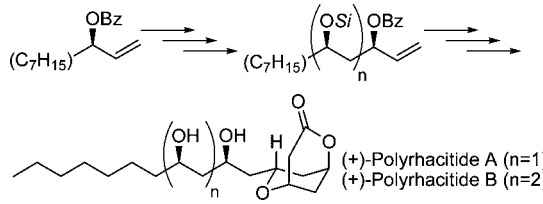
ABSTRACT



The first total syntheses of polyrhacitides A and B, secondary metabolites from Chinese medicinal ants, were accomplished via an iterative approach to the 1,3-polyol motif. For the construction of all stereogenic centers, the catalytic asymmetric Overman esterification was utilized.

Ants produce an astounding array of secondary metabolites,[1] including a number of peptides,[2] alkaloids,[3] and aromatic polyketides[4] that were identified in Australian and African ants. In 2008, Jiang and Kouno reported the isolation of polyrhacitide A (**1**) and polyrhacitide B (**2**) from the Chinese ant species *Polyrhachis lamellidens* Smith (Figure 1).[5] These aliphatic polyketides are comprised of a bicyclic lactone unit that is unusual in ants, although related compounds occurr in plants of various families.[6] The structures of polyrhacitides A and B have been established on the basis of extensive NMR investigations, whereas the absolute configuration was assigned by applying acetonide and Mosher's MTPA ester methods. Biological activity of the polyrhacitides has not been extensively studied presumably due to the limited supply from natural sources (e.g., 19.2 mg of **2** from 2 kg of ants). However, the Chinese medicinal ant *P. lamellidens* has been used traditionally as a folk medicine for the treatment of rheumatoid arthritis and hepatitis in China. This role in folk medicine was substantiated by the recent findings that extracts of *P. lamellidens* exhibit significant analgesic and anti-inflammatory effects.[7] An inherently flexible and enantioselective chemical synthesis entry to polyrhacitides

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would allow further exploration of the largely unexplored pharmacology of these compounds. Herein, we report the first total synthesis of polyrhacitides A and B by an iterative sequence capable of providing meaningful amounts of the polyketide-derived natural products.

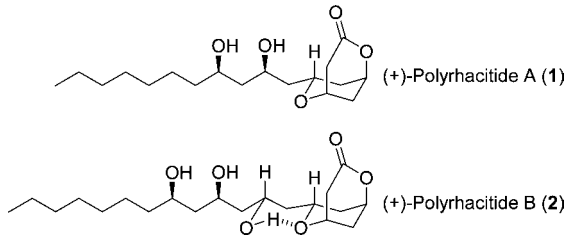
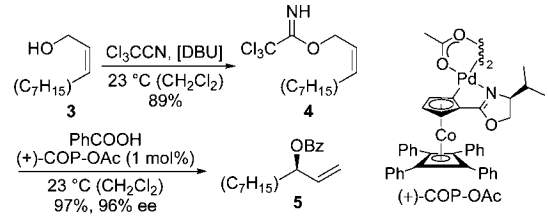


Figure 1. Structures of polyrhacitide A (**1**) and polyrhacitide B (**2**).

The polyrhacitides A and B possess an archetypal polyacetate-derived 1,3-polyol substructure that nature typically evolves with a great diversity through an iterative and flexible approach.[8] Although numerous synthetic methods for the stereoselective assembly of 1,3-diols were developed over the past decades,[9,10] strategies that mimick nature's iterative approach through repetition of a simple sequence have recently attracted renewed interest. In particular, the iterative allylmetalation of aldehydes has found broad use in reagent-controlled sequences that utilize chiral boron[11] or titanium[12] reagents.[13] While an impressive level of stereocontrol is achieved when employing asymmetric allylboration and allyltitanation protocols, the need for stoichiometric amounts of the chiral reagents limits somewhat their use in large-scale applications. To overcome this constraint, several synthetic routes for the synthesis of 1,3-polyol substructures were reported that involve fully catalyst-controlled construction of the stereogenic centers. The central issue concerned with iterative chain elongations of this type is the incorporation of a catalytic asymmetric method that overrides the control through the chirality of the already established 1,3-polyol chain.[14] For example, Ir-catalyzed allylation (Krische et al., 2009),[15] Cr-mediated allylation (Kishi et al., 2008),[16] proline-catalyzed α-aminoxylation (Kumar et al., 2009),[17] and a number of asymmetric epoxidations[18] have been successfully employed as catalyzed key steps. In 2007, we reported an iterative approach to 1,3-polyols utilizing the asymmetric Overman esterification, the Pd(II)-catalyzed reaction of prochiral (*Z*)-allylic trichloroacetimidates with carboxylic acids to branched allylic esters,[19] for the construction of all stereogenic centers.[20] When the palladium(II) catalyst was either enantiomer of COP-OAc,[21] the stereogenic centers were created under predictable and excellent catalyst control.

Scheme 1. Synthesis of Allylic Ester **5**



We reasoned that our iterative approach to polyketide-type structures would lend itself to the rapid assembly of

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(16) Zhang, Z.; Aubry, S.; Kishi, Y. *Org. Lett.* **2008**, *10*, 3077.

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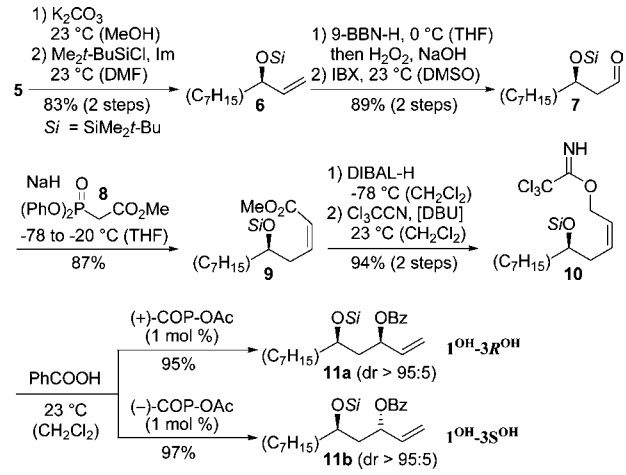
(18) (a) Tosaki, S.-y.; Horiuchi, Y.; Nemoto, T.; Ohshima, T.; Shibasaki, M. *Chem.—Eur. J.* **2004**, *10*, 1527. (b) Gerber-Lemaire, S.; Vogel, P. *Eur. J. Org. Chem.* **2003**, 2959. (c) Burova, S. A.; McDonald, F. E. *J. Am. Chem. Soc.* **2002**, *124*, 8188. (d) Ma, P.; Martin, S.; Masamune, S.; Sharpless, K. B.; Viti, S. M. *J. Org. Chem.* **1982**, *47*, 1378.

polyrhacitides A and B. Accordingly, the first stereogenic center was introduced by reaction of trichloroacetimidate **4** with benzoic acid in the presence of palladacyclic (+)-COP-OAc (1 mol %). The reaction provided (*R*)-allylic ester **5** in 97% yield and 96% ee (Scheme 1).

We then found that the iterative cycle initially developed in 2007 performs worse in terms of entirely reproducible overall yields when switching from triethylsilyl to *tert*-butyldimethylsilyl protecting groups.[22] Although the use of triethylsilyl ethers could have worked well in the envisaged synthesis, we chose to make use of the alternate approach depicted in Scheme 2. The major drawback of the novel iterative approach to 1,3-polyol substructures remains the relatively large number of synthetic steps required for each iteration (eight steps). The sequence begins with the removal of the benzoate group and subsequent silylation to form *tert*-butyldimethylsilyl ether **6**. Hydroboration[23] with 9-BBN-H followed by oxidative workup and IBX-oxidation[24] of the alcohol product provides aldehyde **7** in good yield. Olefination with diphenylphosphonate **8** under Ando conditions[25] yields formation of *Z*-olefin **9** in 87% yield after separation of the minor *E*-isomer (6%) by silica gel chromatography. The ester is reduced with DIBAL-H, and then the *Z*-configured allylic alcohol was converted into trichloroacetimidate **10**. The imidate was subsequently reacted with benzoic acid in the presence of (+)-COP-OAc (1 mol %) to create the next stereogenic center. Under catalyst control, protected *syn*-1,3-diol **11a** was produced in excellent diastereoselectivity. Notably, the *anti*-diastereoisomer **11b** is obtained exclusively when conducting the sequence with (−)-COP-OAc. In summary, the chain extension cycle consists of well-established and simple-to-perform transformations and proceeds in high overall yields (57% for **5**→**11a**, $1^{OH}-3R^{OH}$; 59% for **5**→**11b**, $1^{OH}-3S^{OH}$). We feel the use of the sequence outlined in Scheme 2 is particularly attractive for synthetic tasks that require a short development time since it minimizes the risk of failure (e.g., unexpected loss of material in the course of the synthesis) and the need for optimization (e.g., readjustment of experimental details depending on the exact type of substrate).

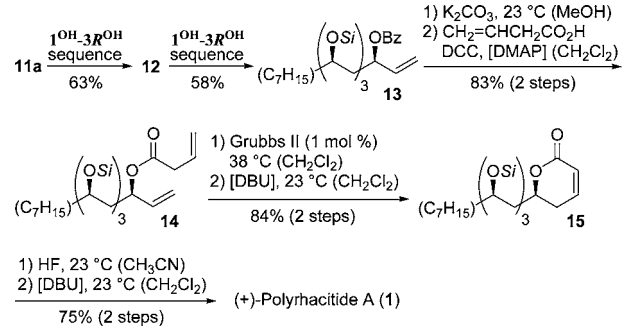
With **11a** in hand, the stage was set for the introduction of the remaining stereogenic centers of polyrhacitides A and B through multiple use of the $1^{OH}-3R^{OH}$ sequence. As shown in Scheme 3 for the synthesis of polyrhacitide A, two further cycles of iteration led to diastereomerically pure tetraol precursor **13**. To complete the synthesis of polyrhacitide A, we now needed to construct the bicyclic lactone core. To this end, removal of the benzoate protecting group and

Scheme 2. Synthesis of (*R*,*R*)-Diol **11a** (via the $1^{OH}-3R^{OH}$ Sequence)



subsequent esterification of the alcohol with vinylacetic acid under Steglich conditions[26] delivered ester **14** in 83% yield. Ring-closing metathesis[27] and base-catalyzed double-bond isomerization[28] led to the formation of α,β-unsaturated δ-lactone **15** in 84% yield.[29] Global silyl deprotection was accomplished with HF resulting in a 1:1 mixture of the corresponding α,β-unsaturated δ-lactone and the bicyclic lactone **1**. The crude mixture was treated with DBU under conditions developed previously by Waldmann[11b] to complete the conversion into (+)-polyrhacitide A (**1**), $[\alpha]^{20}_{D} = +8.2$ (*c* 0.3, MeOH), which was obtained in a respectable 9% yield over all the steps starting from **3**.[30]

Scheme 3. Synthesis of Polyrhacitide A (See Scheme [2] for the $1^{OH}-3R^{OH}$ Sequence)



The conversion of intermediate **13** to (+)-polyrhacitide B (**2**) is outlined in Scheme 4. Using the $1^{OH}-3R^{OH}$ sequence,

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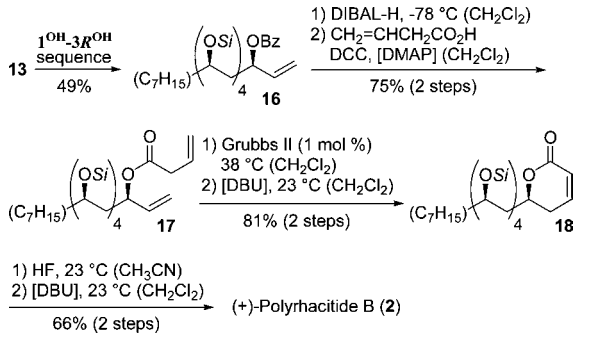
Scheme 4. Synthesis of Polyrhacitide B (See Scheme [2] for the $1^{OH}-3R^{OH}$ Sequence)



benzoate **16** was secured in 49% overall yield. An endgame related to the one employed for polyrhacitide A then provided (+)-polyrhacitide B (**2**), $[\alpha]^{20}_{D} = +9.0$ (*c* 1.0, MeOH), in 40% yield from **16**. The spectroscopic data of the synthetic samples were in excellent agreement with those reported in the literature.[5]

In summary, the first total syntheses of polyrhacitides A and B were accomplished using a practical and fully catalyst-controlled iterative approach. Due to the complete control over the stereochemical course, this synthetic strategy that is based on the asymmetric Overman esterification shows significant stereochemical flexibility and provides substantial amounts of the target compounds for investigations into the biological activity of the polyrhacitides and their derivatives.

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Supporting Information Available: Experimental procedures for all compounds and copies of ^{1}H and ^{13}C NMR. This material is available free of charge via the Internet at http://pubs.acs.org.

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(30) Synthetic polyrhacitide A showed ^{1}H NMR and ^{13}C NMR spectra and mass spectral data that compared favorably to those of the natural isolate [ref 5]. The intramolecular hydrogen bond reported for the natural material was not unequivocally identified in synthetic polyrhacitide A. However, spectroscopic data of the acetonide of synthetic **1** were in perfect agreement with those reported on the acetonide derived from natural **1** (see Supporting Information; ref 5).