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Palladium-Catalyzed Medium-Ring Formation for Construction of the Core Structure of *Laurencia* Oxacycles: Synthetic Study of Laurendecumallene B

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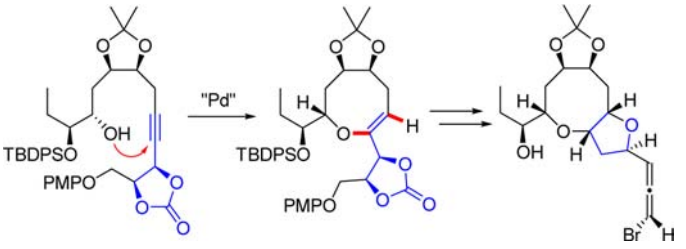
ABSTRACT



Palladium-catalyzed medium-ring formation from a cyclic propargyl carbonate via a ring-opening and -closing cascade proceeded at the central carbon atom of the propargyl unit to provide a tetrahydro-2*H*-oxocine derivative bearing the core structure of laurencia oxacycle. The synthetic application of this reaction to a possible laurendecumallene B precursor is also presented.

The marine genus *Laurencia* specifically produces a significant subset of medium-ring haloethers as secondary metabolites; these typically consist of a C15 carbon skeleton with an enyne or bromoallene side chain.[1] Since the first report of the isolation of (+)-laurencin (**1**) from *Laurencia glandulifera* by Irie et al. in 1965,[2] numerous medium-ring haloethers have been isolated from *Laurencia* red algae. Laurendecumallene B (**2**), a C15 acetogenin isolated from the marine red alga *Laurencia decumbens*, was first reported by Wang et al. in 2007 (Figure 1).[3] Another structurally related laurendecumallene, known as laurendecumallene A (**3**), was also isolated from the same species. To date, the total synthesis of laurendecumallene B has not been reported in the literature. The relative configuration of laurendecumallene B has been partly determined, but the configurations of the axial chirality of bromoallene and the substituent at the C-13 position, and the absolute configuration of the molecule, have not yet been elucidated.

The development of synthetic strategies for the construction of these *Laurencia* oxacycles have been extensively investigated in recent years.[4−6] However, for the syntheses of diverse collections of medium-ring natural products and

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(2) Irie, T.; Suzuki, M.; Masamune, T. *Tetrahedron Lett.* **1965**, *6*, 1091–1099.

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(5) For selected recent syntheses based on ring-closing metathesis, see: (a) Park, J.; Kim, B.; Kim, H.; Kim, S.; Kim, D. *Angew. Chem., Int. Ed.* **2007**, *46*, 4726–4728. (b) Adsool, V. A.; Pansare, S. V. *Org. Biomol. Chem.* **2008**, *6*, 2011–2015. (c) Sasaki, M.; Hashimoto, A.; Tanaka, K.; Kawahata, M.; Yamaguchi, K.; Takeda, K. *Org. Lett.* **2008**, *10*, 1803–1806. (d) Ortega, N.; Martín, V. S.; Martín, T. *J. Org. Chem.* **2010**, *75*, 6660–6672. (e) Kim, M. J.; Sohn, T.; Kim, D.; Paton, R. S. *J. Am. Chem. Soc.* **2012**, *134*, 20178–20188.

(6) For selected recent syntheses without using ring-closing metathesis, see: (a) Kim, H.; Lee, H.; Lee, D.; Kim, S.; Kim, D. *J. Am. Chem. Soc.* **2007**, *129*, 2269–2274. (b) Li, J.; Suh, J. M.; Chin, E. *Org. Lett.* **2010**, *12*, 4712–4715. (c) Snyder, S. A.; Treitler, D. S.; Brucks, A. P.; Sattler, W. *J. Am. Chem. Soc.* **2011**, *133*, 15898–15901. (d) Snyder, S. A.; Brucks, A. P.; Treitler, D. S.; Moga, I. *J. Am. Chem. Soc.* **2012**, *134*, 17714–17721.

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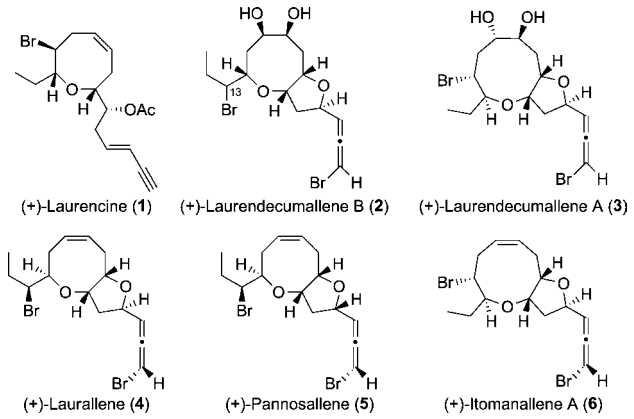


Figure 1. Structures of naturally occurring haloethers from *Laurencia* species.

their derivatives, the development of efficient approaches for the construction of medium-ring ethers, not only those based on ring-closing metathesis,[5] remains important.[6] Because of the interesting activities of eight-membered *Laurencia* oxacycles,[7] attempts were made in this study to complete the first total synthesis of laurendecumallene B.

Despite the presence of several stereogenic centers, the configuration of the axial chirality of the bromoallene moiety in *Laurencia* oxacycles can be predicted from their strong optical rotation values, which are in good agreement with Lowe's rule.[8] Based on the positive value of the optical rotation of laurendecumallene B ($[\alpha]^{18}_{D}$ = +60.6 in $CHCl_3$), its axial chirality was assumed to be (*S*). The target structures were therefore identified as compounds **2a**–**d** (Figure 2). The decision was taken to develop a synthetic route to compounds **2a/b** based on the absolute configuration of the core structures of the related bromoallenes from *Laurencia* species, such as (+)-laurallene (**4**), (+)-pannosallene (**5**), and (+)-itomanallene A (**6**) (Figure 1). If necessary, the other possible isomers **2c**/**d** could be formed as their antipodes (*ent*-**2c**/**d**) from the common intermediate for the synthesis of **2a**/**b** at a later stage of the synthesis.

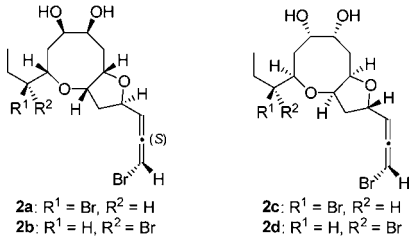
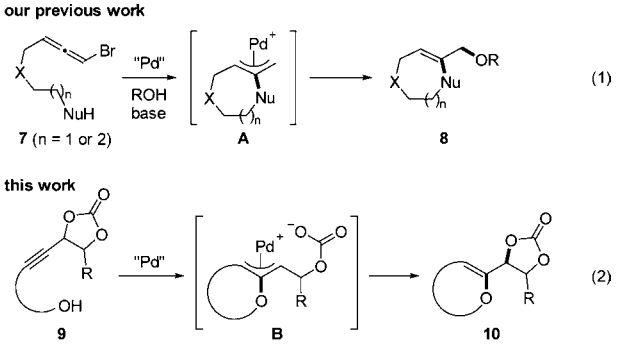


Figure 2. Possible structures of laurendecumallene B.

In 2003, the author's group reported that bromoallenes such as **7**, which are synthetic equivalents of propargylic compounds, were extremely useful for the synthesis of medium-sized rings **8** (Scheme 1, eq 1).[9] We have also shown that cyclization through ring opening and closing is a convenient strategy for the construction of bicyclic structures.[10] In 2001, Yoshida, Ihara, and co-workers developed a methodology for the synthesis of cyclic carbonates, based on a Pd-catalyzed cascade reaction involving a CO_2 elimination–fixation process.[11] In the current work, we tried to apply these chemistries to the synthesis of *Laurencia* oxacycles (eq 2), in which a cyclic propargyl carbonate **9** possessing a strategically positioned hydroxy functionality could undergo Pd-mediated medium-ring formation through ring-opening and -closing reactions via an η^3-allylpalladium complex **B**. These compounds could then be trapped by the pendant carbonate, providing medium-sized ethers **10**.

Scheme 1. Cyclization of Propargylic/Allenic Compounds



The retrosynthetic analysis of the possible stereoisomers **2a**/**b** is shown in Scheme 2. It was envisaged that **2a**/**b** could be derived from **12** by deoxygenation at the C-5 position, followed by the introduction of a bromoallene side chain and a Br-atom at the C-13 position. The fused tetrahydrofuran **12** could be constructed from the cyclic carbonate **13** via a sequence of hydroboration–oxidation and cyclization by intramolecular S_N2 displacement reactions, which would use the resulting hydroxy group as a leaving group. The eight-membered ring in **13** could in turn be constructed via the Pd-catalyzed cyclization of the cyclic propargyl carbonate **14**, which could be synthesized via a

(7) Watanabe, K.; Umeda, K.; Miyakado, M. *Agric. Biol. Chem.* **1989**, *53*, 2513–2515.

(8) (a) Lowe, G. *Chem. Commun.* **1965**, 411–413. The absolute configurations of the bromoallene moiety can be sometimes predicted by their optical rotation values, even if the molecules have several chiral centers. For example, see: (b) Ohno, H.; Ando, K.; Hamaguchi, H.; Takeoka, Y.; Tanaka, T. *J. Am. Chem. Soc.* **2002**, *124*, 15255–15266.

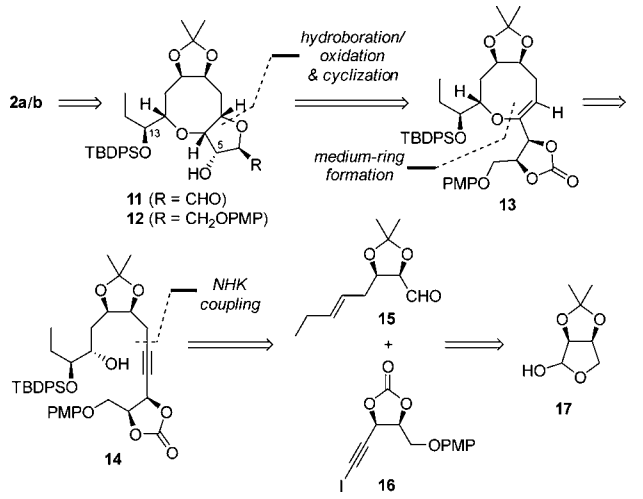
(9) (a) Ohno, H.; Hamaguchi, H.; Ohata, M.; Tanaka, T. *Angew. Chem., Int. Ed.* **2003**, *42*, 1749–1753. (b) Ohno, H.; Hamaguchi, H.; Ohata, M.; Kosaka, S.; Tanaka, T. *J. Am. Chem. Soc.* **2004**, *126*, 8744–8754.

(10) Okano, A.; Oishi, S.; Tanaka, T.; Fujii, N.; Ohno, H. *J. Org. Chem.* **2010**, *75*, 3396–3400.

(11) (a) Yoshida, M.; Ihara, M. *Angew. Chem., Int. Ed.* **2001**, *40*, 616–619. (b) Yoshida, M.; Fujita, M.; Ishii, T.; Ihara, M. *J. Am. Chem. Soc.* **2003**, *125*, 4874–4881.

(12) (a) Okude, Y.; Hirano, S.; Hiyama, T.; Nozaki, H. *J. Am. Chem. Soc.* **1977**, *99*, 3179–3181. (b) Jin, H.; Uenishi, J.; Christ, W. J.; Kishi, Y. *J. Am. Chem. Soc.* **1986**, *108*, 5644–5646. (c) Takai, K.; Tagashira, M.; Kuroda, T.; Oshima, K.; Utimoto, K.; Nozaki, H. *J. Am. Chem. Soc.* **1986**, *108*, 6048–6050.

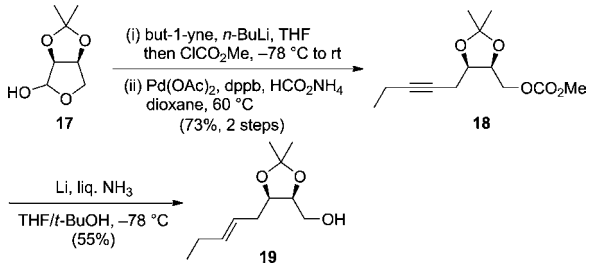
Scheme 2. Retrosynthetic Analysis of Possible Isomers **2a**/**b**



Nozaki–Hiyama–Kishi (NHK) coupling reaction[12] between aldehyde **15** and alkyne **16**, and several subsequent functional group manipulations. It was envisaged that the known L-arabinose-derived hemiacetal **17**[13] could be used as a common intermediate for the syntheses of **15** and **16**.

We started our synthesis by preparing **19**, the precursor of aldehyde **15** (Scheme 3). The addition of lithium acetylide (prepared from but-1-yne) to the known hemiacetal **17** was quenched with $ClCO_2Me$ to furnish the corresponding methyl carbonate, which was subsequently treated with $Pd(OAc)_2$/dppb/ammonium formate to give the deoxygenated product **18**.[14] Subsequent Birch reduction of the alkyne moiety occurred, with concomitant carbonate cleavage, to afford **19**.

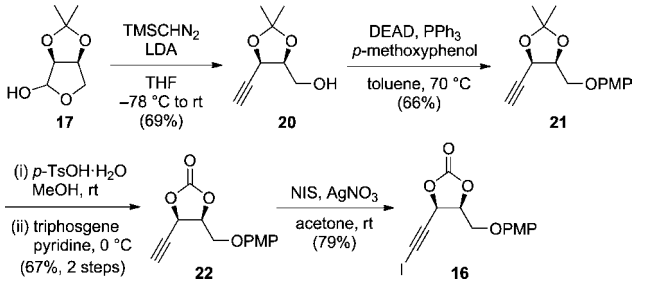
Scheme 3. Synthesis of Alkene **19** (Precursor of **15**)[a]



[a] dppb = 1,4-bis(diphenylphosphino)butane.

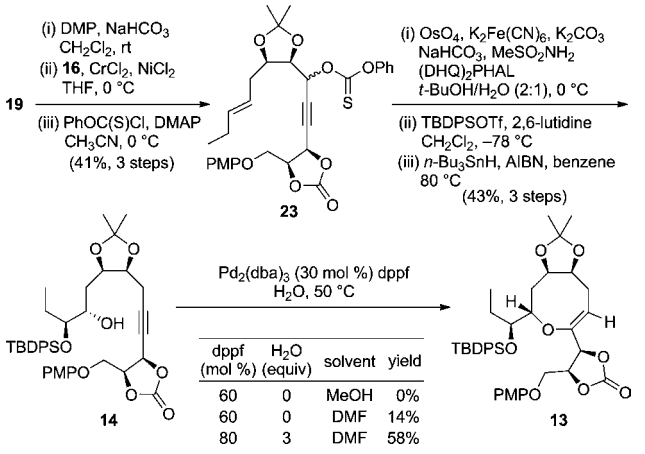
We then proceeded toward the synthesis of alkyne **16** (Scheme 4). Using the method reported by Myers,[15] **17** was converted to alkyne **20** in 69% yield by treatment with lithiated TMS-diazomethane. The hydroxy group was then protected as the corresponding *p*-methoxyphenyl ether, using Mitsunobu conditions, to give **21** in 66% yield.[16] The conversion of the acetonide to the corresponding carbonate group was conducted by exposure of **21** to $TsOH \cdot H_2O$ in MeOH, followed by treatment with triphosgene in the presence of pyridine to give cyclic carbonate **22** in 67% yield. The iodoalkyne **16** was obtained by iodination of the terminal alkyne in **22** using NIS/$AgNO_3$ in 79% yield.[17]

Scheme 4. Synthesis of Alkyne **16**



The synthesis and cyclization of carbonate **14** is illustrated in Scheme 5. Dess–Martin oxidation of the primary alcohol **19** and subsequent Nozaki–Hiyama–Kishi coupling[12] with alkyne **16** gave a propargyl alcohol, which was transformed into thiocarbonate **23**. This material was then immediately subjected to a Sharpless asymmetric dihydroxylation, followed by sequential selective monosilylation and deoxygenation reactions because the thiocarbonates of this series are relatively labile. We then

Scheme 5. Synthesis and Pd-Catalyzed Cyclization of **14**[a]



[a] DMP = Dess-Martin periodinane; $(DHQ)_2PHAL$ = hydroquinine 1,4-phthalazinediyl diether.

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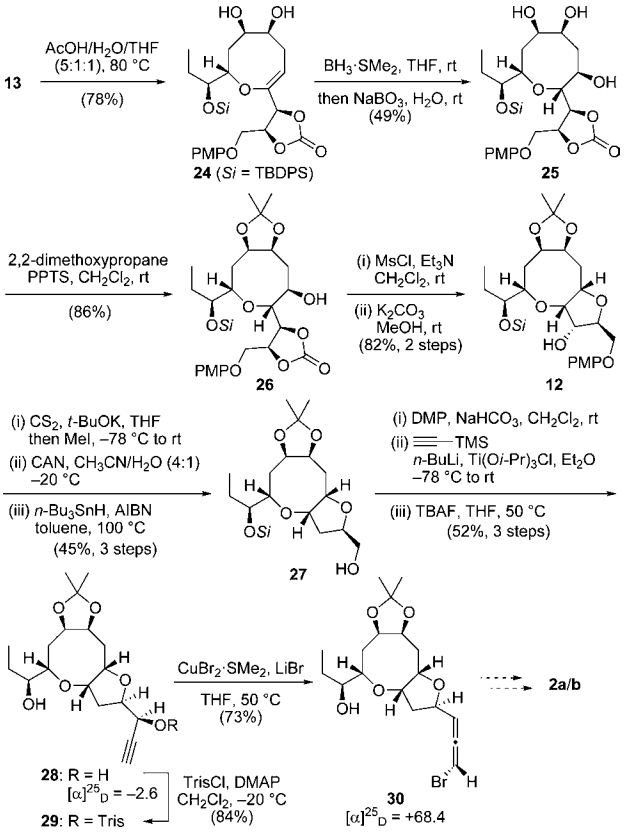
investigated the cyclization of **14** using Pd(0). Treatment of **14** with $Pd_2(dba)_3 \cdot CHCl_3$ and dppf in MeOH at 50 °C only afforded the solvolysis product. However, the reaction in DMF produced the desired oxocine derivative **13**, albeit in 14% yield. The best result was obtained using 30 mol % of $Pd_2(dba)_3$ and 80 mol % of dppf in the presence of 3 equiv of H_2O in DMF (58% yield) (for details, see Supporting Information).

The investigation proceeded toward the construction of the tetrahydrofuran ring (Scheme 6). Unfortunately, initial attempts to introduce the required hydroxy group into acetonide **13** via a hydroboration–oxidation sequence proved unsuccessful. In contrast, application of hydroboration–oxidation to the deprotected enol ether **24** proceeded smoothly with high levels of regio- and stereoselectivity to give triol **25** as a single diastereomer. Reinstallation of the acetonide group, followed by sequential mesylation and methanolysis of the cyclic carbonate, promoted the facile formation of the tetrahydrofuran ring to give **12** bearing the requisite bicyclic core structure. Xanthate formation was followed by CAN-mediated deprotection[18] and Barton–McCombie deoxygenation[19] to give the primary alcohol **27**. The construction of the bromoallene moiety was accomplished using the well-established strategy developed by Overman and Kim.[20] Dess–Martin oxidation of **27** gave the corresponding aldehyde, which was treated with ethynyltitanium triisopropoxide and then desilylated to give the propargyl alcohol **28** as the sole stereoisomer.[20,21] The trysilate **29** was converted to bromoallene **30** via the established *anti* S_N2' substitution using the bromocuprate reagent.[22] The optical rotation value of the bromoallene **30** ($[\alpha]^{25}_D$ = +68.4) supports the (*S*)-axial chirality. Exposure of **30** to the dppe-mediated bromination conditions[23] followed by cleavage of the acetonide with AcOH led to detection of the bromination product, which corresponded well with natural laurendecumallene B (**2**) by ^{1}H NMR and optical rotation values (see Supporting Information). However, further investigations are necessary to achieve the total synthesis elucidating the C-13 stereochemistry.

Scheme 6. Construction of THF Ring and Bromoallene Moiety[a]



[a] Tris = 2,4,6-triisopropylbenzenesulfonyl.

In conclusion, we demonstrated that Pd-catalyzed medium-ring formation is useful for construction of the core structure of *Laurencia* oxacycles. Further studies to achieve the total synthesis of laurendecumallene B, including optimization of bromination conditions and the appropriate protecting group for the vicinal diol moiety, are now underway.

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Supporting Information Available. Our attempts toward total synthesis, detailed results of the Pd-catalyzed cyclization, experimental procedures, and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

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