Shortest Enantioselective Total Syntheses of (+)-Isolaurepinnacin and (+)-Neoisoprelaurefucin

Victoria Sinka,* Daniel A. Cruz,* Víctor S. Martín, and Juan I. Padrón*

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ABSTRACT: The shortest enantioselective total syntheses of (+)-isolaurepinnacin and (+)-neoisoprelaurefucin have been accomplished. These syntheses were based on a common parallel synthetic strategy using Prins−Peterson cyclization in their core construction. In only one step, a seven-membered ring oxacycle with the correct cis-stereochemistry ring closure and the Δ^4 position of the endocyclic double bond in (+)-isolaurepinnacin was obtained. This unsaturation was also necessary to accede to the bromodioxabicycle on (+)-neoisoprelaurefucin.
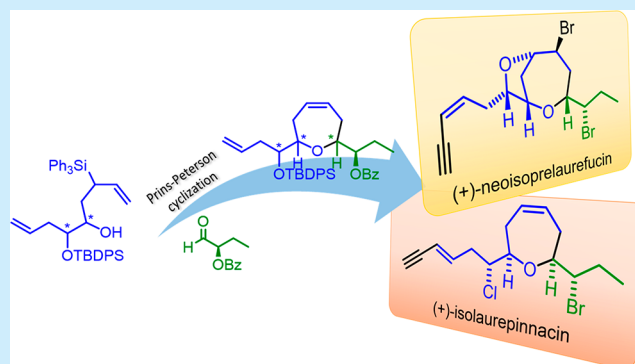
(+)-Isolaurepinnacin and (+)-neoisoprelaurefucin are marine natural products, containing a seven-membered cyclic ether unit, isolated from red seaweeds of the genus *Laurencia*, the first from *Laurencia pinnata* Yamada[1] and the second from *Laurencia nipponica* Yamada.[2] These macroalgae produce a large number of unique metabolites, such us lauroxanes, a family of nonterpenoid C_{15}-metabolites that exhibit a wide range of biological properties ranging from antitumor to antiepileptic activity (Figure 1).[3−6]
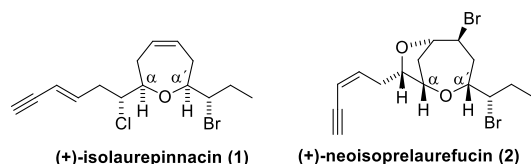

Figure 1. Structures of (+)-isolaurepinnacin (**1**) and (+)-neo-isoprelaurefucin (**2**).

Among the members of the lauroxane family, (+)-isolaur-epinnacin (**1**) and (+)-neoisoprelaurefucin (**2**) are representative examples of compounds containing an oxepane ring. Both of them share a central seven-membered oxacycle with α,α'-cis-disubstitution furnished with two lateral chains, including halogen atoms and a terminal enyne moiety.

The main difference lies in the configuration of the enyne E on (+)-isolaurepinnacin (**1**) and Z on (+)-neoisoprelaurefucin (**2**), in addition to the fused five-membered oxacycle leading to a bromodioxabicycle on (+)-neoisoprelaurefucin (**2**). The literature only shows one total synthesis performed by Overman et al. in 1993 and a formal approach by Suzuki et

al. in 2001 for (+)-isolaurepinnacin (**1**),[7−9] whereas (+)-neo-isoprelaurefucin (**2**) has had only one total synthesis, accomplished by Kim et al. in 2003 (Figure 2).[10]

Our research group has developed synthetic methodologies that were successfully applied in the preparation of several medium size oxacycles.[11−14] Moreover, we reported a straightforward method to gain access to cis-disubstituted Δ^4-unsaturated oxepanes in one step that was supported by the excellent previous work of other authors.[15] Thus, we resolved to apply our experience to the total synthesis of (+)-iso-laurepinnacin (**1**) and (+)-neoisoprelaurefucin (**2**) using a common parallel synthetic strategy (Scheme 1).

In previous work, we demonstrated the ability of iron(III) salts to catalyze the Prins cyclization, which is now a prolific synthetic tool to obtain medium size oxacycles. Among the various types of oxacycles that can be accessed, synthesis of Δ^4-2,7-disubstituted oxepenes in a single step is one of the most striking applications to date. The Prins−Peterson cyclization (PPC) is highly efficient and stereoselective and only requires a substoichiometric amount of $FeBr_3$.[15]

Encouraged by these results, we decided to test the capabilities of PPC as the key and main step in the synthesis of two marine natural products: (+)-isolaurepinnacin (**1**) and (+)-neoisoprelaurefucin (**2**).
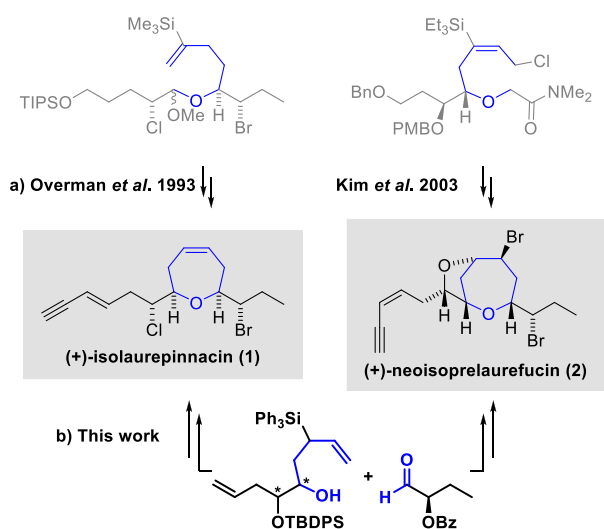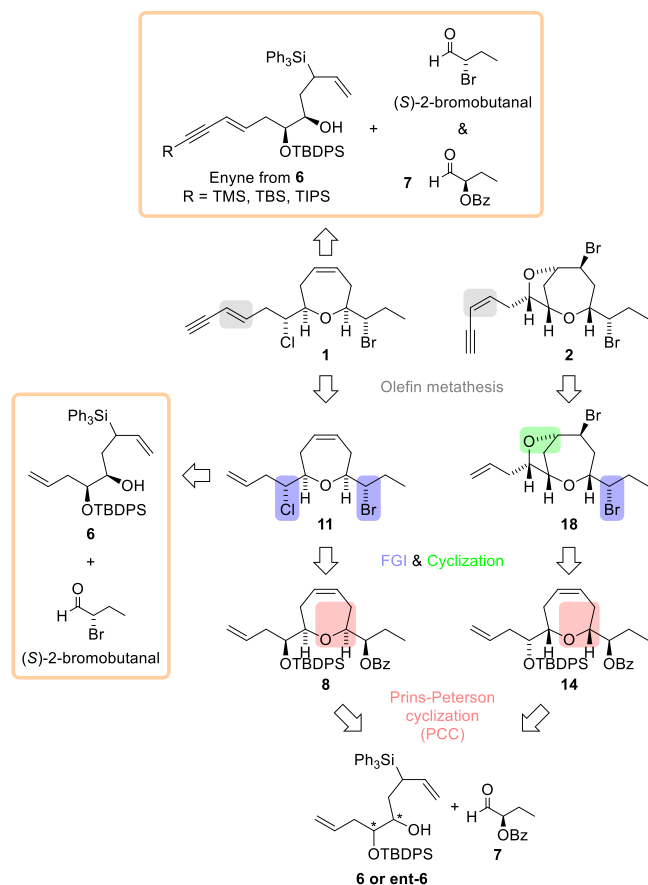
Figure 2. (+)-Isolaurepinnacin and (+)-neoisoprelaurefucin total syntheses. (a) Previous approaches. (b) Our proposal.

Scheme 1. Retrosynthetic Analysis to Access (+)-Isolaurepinnacin (1) and (+)-Neoisoprelaurefucin (2) from the Bis-homoallylic Silyl Alcohol 6 or ent-6

We envisioned the preparation of these natural products through this methodology as a great opportunity to achieve more efficient total syntheses by reducing the number of steps. A retrosynthetic analysis for both compounds was designed to use a parallel but common synthetic strategy. This maintained our goal of forging two routes with the highest level of similarity.

As depicted in Scheme 1, the first disconnection was the lateral E or Z enyne chain. Next, we focused on introducing halogen atoms in the case of (+)-isolaurepinnacin ($11 \rightarrow 8$) and on inversion of the hydroxyl group and further bromo-etherification to arrive at (+)-neoisoprelaurefucin ($18 \rightarrow 14$). Finally, the Prins–Peterson cyclization as the key reaction of our retrosynthetic proposal should lead to the functionalized oxepene rings. It has the correct stereochemistry and would start from the unsaturated silyl alcohols **6** and ent-**6**.[15]

Equally, more direct PPC disconnections were attempted for the total synthesis of (+)-isolaurepinnacin. The first was the construction of the Prins cyclization precursor with the enyne chain, leaving the generation of the oxepene ring for the last steps of the synthesis. In this case, none of the cyclization conditions tested with aldehyde **7** or (S)-2-bromobutanal gave rise to the desired oxepene (Scheme 1). The second focused on obtaining the intermediate oxepene **11** from the cyclization of the alcohol precursor **6** and (S)-2-bromobutanal. However, cyclization with this aldehyde proved unsuccessful. In general, the aldehyde with a α-bromo-((S)-2-bromobutanal) was unreactive in all the PPC reactions tested (Scheme 1).

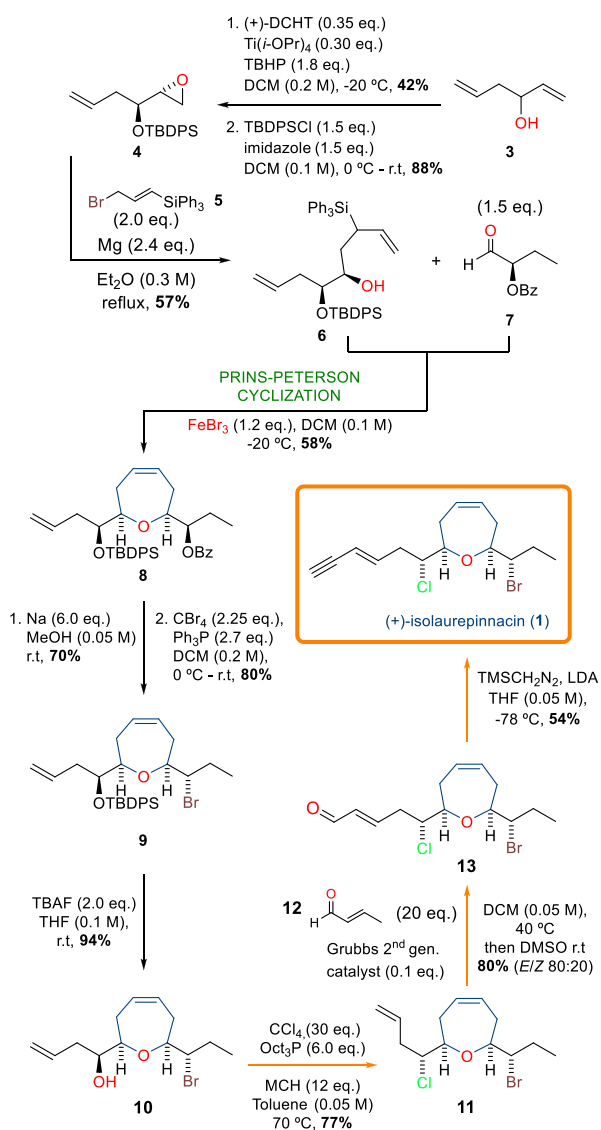The synthesis of (+)-isolaurepinnacin started with the enantioselective epoxidation of the 1,5-hexadien-3-ol (**3**) developed by Sharpless et al. (Scheme 2).[16] Then we protected the resulting epoxy alcohol with TBDPSCl to obtain the desired epoxide **4** in an excellent yield. Next, the epoxide was opened by nucleophilic attack using the silane **5**, following Corriu et al., which afforded us the unsaturated silyl alcohol **6** in 57% yield.[17,18] We decided to use this method because of the better ratio between the (desired) α attack versus γ attack in opening the epoxide. In comparison, the analogous strategy developed by Schaumann et al. provided a worse outcome in this reaction (see Supporting Information).[19,20]

At this point in the synthesis, we introduced the PPC to achieve the pivotal reaction of the route. Here, a stoichiometric amount of FeBr$_3$ and low temperature were essential to enable cyclization with the freshly prepared aldehyde **7** (see Supporting Information). In this case, we obtained the desired Δ^4-2,7-disubstituted oxepene ring **8** with a 58% yield. A bulky substituent, the TBDPS group, is present at the α-position relative to the hydroxyl group of unsaturated silyl alcohols. This bulky substituent drives the PPC toward the exclusive formation of the cis-oxepene.[15]

Once oxepene **8** was ready, the next step was substitution of the benzoate group by a bromine atom, with suitable stereochemistry of the final natural product **1**. We completed this modification in good yield after basic hydrolysis of the ester and the subsequent Appel reaction to obtain **9**.[21] For this basic hydrolysis of the benzoate group, it was necessary to perform several trials with different bases. The best conditions were with Na/MeOH at room temperature (see Supporting Information). Cleavage of the silyl protecting group of oxepene **9** was facilitated using TBAF, with a yield of 94%.

When the alcohol **10** was prepared, we again took advantage of the Appel reaction by replacing the hydroxyl group with a chlorine atom in good yield (**11**). Next, an olefin metathesis reaction catalyzed by the second-generation Grubbs catalyst led us to the conjugated aldehyde **13** in 80% yield, with an E/Z ratio of 80:20, which was favorable for the desired compound E.[22,23] Finally, the Colvin rearrangement afforded (+)-iso-laurepinnacin (**1**) in 54% yield,[24−26] completing the total synthesis in 10 steps with an overall yield of 5%.

Scheme 2. Total Synthesis for (+)-Isolaurepinnacin (1)

Scheme 3. Total Synthesis for (+)-Neoisoprelaurefucin (2)
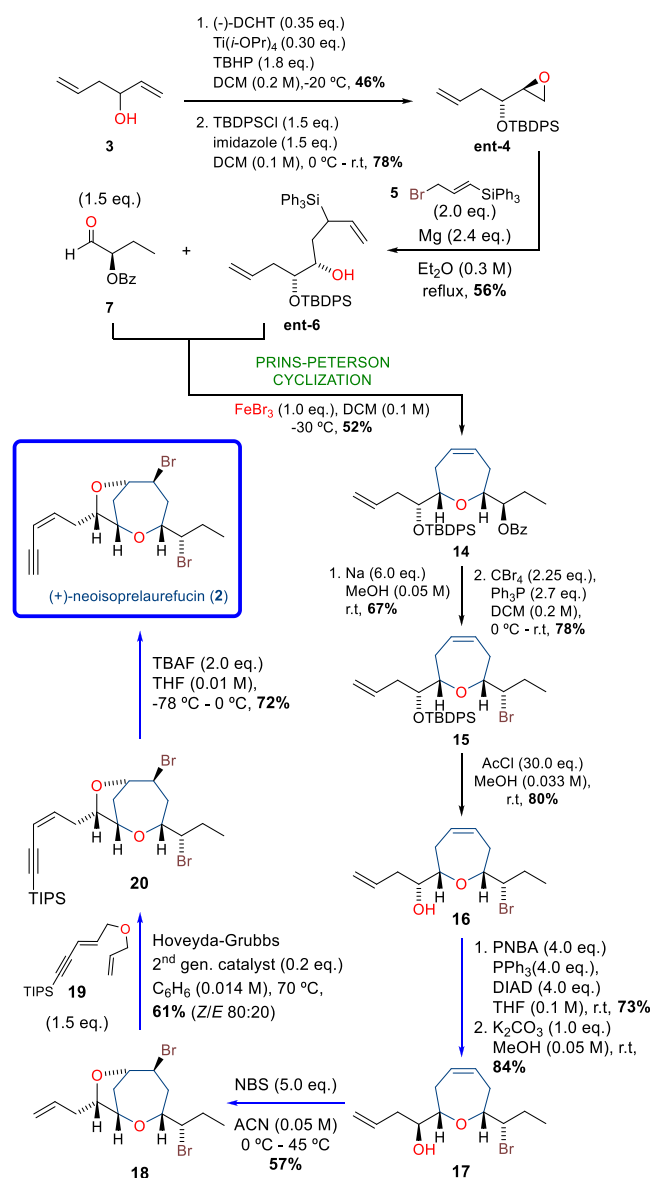
Next, the synthesis of (+)-neoisoprelaurefucin was designed to use the maximum number of common steps of (+)-isolaurepinnacin (Scheme 3). Therefore, alcohol **3** was epoxidized with the protocol by Sharpless et al. but using (−)-DCHT, followed by protection with TBDPSCl to obtain the epoxide *ent*-**4**. The opening of *ent*-**4** with silane **5** provided the silyl alcohol *ent*-**6** in 56% yield, and the subsequent PPC reaction led us to the oxepene **14** in 52% yield. Now, deprotection of the benzoate group and Appel reaction were conducted to install the bromine atom with suitable stereochemistry in oxepene **15**. The conditions previously used for the cleavage of the TBDPS group were unsuccessful for oxepene **15**, as it led to an undesired elimination reaction. Therefore, we switched to a milder method to avoid the generation of TBAF byproducts using the AcCl/MeOH system to obtain alcohol **16** in 80% yield.[27] From this step onward, this route went its own way due to structural differences between the natural products (Scheme 3).

The first specific step in the synthesis of (+)-neo-isoprelaurefucin (**2**) was inversion of the hydroxyl group in oxepene **16**. In this case, the Mitsunobu reaction and

subsequent hydrolysis of the resulting *p*-NO$_2$ benzoate provided the new alcohol **17** in 61% yield (two steps).[28]

At this point, we also considered the possibility of a more direct and convergent approach to access oxepene **17** via a Mitsunobu reaction on the hydroxyl group of precursor **6**. This approach would allow us to save one reaction step and shorten the total synthesis; however, the inversion of the configuration in the secondary alcohol did not work. This attempt failed probably due to the high steric hindrance caused by the presence of the TPS and OTBDPS groups (see Supporting Information).

Next, we used *N*-bromosuccinimide to promote stereo-specific cyclization from the hydroxyl group over the bromonium ion to obtain the bromodioxabicycle **18** with a yield of 57%. At this stage, we introduced the alkyne group into the side chain. This required the method developed by Lee et al.,[29] wherein the allyl enyne ether **19** is essential to afford the dioxabicycle **20** containing the *Z* isomer as the major product (*E*/*Z* = 20:80). Finally, the TIPS group was deprotected at a low temperature to avoid the formation of possible byproducts,

providing the (+)-neoisoprelaurefucin (**2**) in 72% yield. Thus, this total synthesis was achieved in 12 steps and 1.3% overall yield (Scheme 3).

In conclusion, we have achieved enantioselective total syntheses for the two marine natural products (+)-isolaurepinnacin (**1**) and (+)-neoisoprelaurefucin (**2**). The design of the synthetic routes depends on a parallel approach to maximize the number of common steps, while taking the Prins−Peterson cyclization methodology as the pivotal synthetic step. This approach allows us to obtain the (+)-isolaurepinnacin in 10 reaction steps with an overall yield of 5% and the (+)-neoisoprelaurefucin in 12 steps with an overall yield of 1.3%. Thus, we report the shortest convergent total syntheses to date for both compounds.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.2c01769.

> Experimental procedures and characterization data for new compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

Victoria Sinka − *Instituto de Productos Naturales y Agrobiología (IPNA), CSIC, 38206 La Laguna, Tenerife, Spain*; Email: vsinka@ipna.csic.es

Daniel A. Cruz − *Instituto de Productos Naturales y Agrobiología (IPNA), CSIC, 38206 La Laguna, Tenerife, Spain*; Email: danielcruz@ipna.csic.es

Juan I. Padrón − *Instituto de Productos Naturales y Agrobiología (IPNA), CSIC, 38206 La Laguna, Tenerife, Spain*; ⊙ orcid.org/0000-0002-0745-2259; Email: jipadron@ipna.csic.es

Author

Víctor S. Martín − *Organic Chemistry Department Avda, Universidad de La Laguna, Instituto Universitario de Bio-Orgánica Antonio González (IUBO), 38206 La Laguna, Tenerife, Spain*; ⊙ orcid.org/0000-0003-0300-9636

Complete contact information is available at:
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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

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