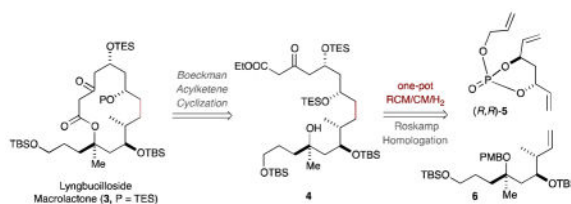# Synthetic Studies to Lyngbouilloside: A Phosphate Tether-Mediated Synthesis of the Macrolactone Core

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Abstract

A concise synthetic pathway to the originally assigned structure of lyngbouilloside macrolactone (**3**) is reported. The core macrocycle **3** was synthesized via a phosphate tether-mediated, one-pot, sequential RCM/CM/chemoselective hydrogenation reaction, Roskamp homologation, and a high yielding Boeckman acylketene cyclization.

Keywords

Phosphate Tether; (−)-Lyngbouilloside; Total Synthesis; Metathesis

Lyngbouilloside (**1**)[1] and lyngbyaloside B (**2**)[2] are two similar cytotoxic macrolactones isolated in 2002 from two different marine cyanobacteria of the genus *Lyngbya bouillonii* (*Oscillatoriaceae*) (Figure 1). Initial biological screening demonstrated that **1** and **2** were modestly cytotoxic against neuroblastoma and KB cells with IC$_{50}$ values of 17 μM and 4.3 μM, respectively.[3] Spectroscopic analysis and chemical derivatization revealed the structure of **1** as a glycosylated 14-membered macrolide (**1**, Figure 1), containing a six-membered cyclic hemiketal, an (*E,E*)-octadienyl side chain, as well as an L-rhamnose-derived pyranoside.

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Lyngbouilloside has attracted significant attention from the synthetic community due to its stereochemical ambiguities, along with its biological activity and natural scarcity.[4, 5,6] In 2008, Cossy and coworkers, reported the first stereoselective synthesis of the carbon backbone of **1** using a pivotal cross-metathesis (CM) between the C1–C8 and C9–C13 fragments.[4a] In 2009, Ley and coworkers reported a synthesis of the lyngbouilloside macrolactone core using a late-stage ring-closing metathesis (RCM)/hydrogenation sequence for macrocyclization, and also brought to light stereochemical issues regarding this natural product.[4b] In 2012, Cossy and coworkers confirmed the stereochemical issues in their first total synthesis of the lyngbouilloside aglycon using a pivotal acylketene macrolactonization of a tertiary methyl carbinol (C13 in **1**) to circumvent fundamental issues associated with macrolactonizations of sterically encumbered alcohols.[5] In addition, Cossy proposed a revised structure of lyngbouilloside with stereochemical reassignment of the C11 stereogenic center having an epimeric C11 stereogenic center and thus a *syn* C10/C11 relationship.[5]

In 2014, Fuwa and coworkers[7] completed an elegant total synthesis of (−)-lyngbyaloside B, employing innovative use of an Abiko–Masamune *anti*-aldol and a vinylogous Mukaiyama to install the requisite stereochemistry in the starting building blocks. In this work, synthetic, spectroscopic and molecular modeling studies provided unequivocal stereochemical reassignment of (−)-lyngbyaloside B having epimeric stereogenic centers at C10/C11 and C13 as shown for the reassigned lyngbyaloside B (**2b**) (Figure 1) when compared with the original assigned structure of lyngbyaloside B (**2a**). Moreover, the authors tested the titled compound and several derivatives and found good inhibition potencies against the proliferation of HL-60 cells. The authors also surmise that the structures of (−)-lyngbouilloside and the natural congeners of (−)-lyngbyaloside B be reconsidered accordingly. In this regard, confirmation of the complete stereostructure of **1** is still unknown, warranting continued effort for its total synthesis. Recently, we have engaged in the synthesis of biologically active natural products using phosphate tether-mediated approaches,[8,9] and have developed a one-pot, sequential RCM/CM/chemoselective hydrogenation protocol mediated by a phosphate tether for the synthesis of advanced polyol and polyketide synthons.[8c] Herein, we report application of a one-pot, sequential RCM/CM/ chemoselective hydrogenation for the concise synthesis of the originally assigned macrolactone core of (−)-lyngbouilloside, with easy adaptability to C10/C11 and C13 diastereomeric analogs.

Retrosynthetic analysis reveals a late-stage installation of the C16–C17 *E*-olefin and L-rhamnose-derived pyranoside. The macrolactone core **3** can be constructed by Boeckman acylketene cyclization[10] of *β*-keto ester **4**, formed via a pivotal one-pot, sequential RCM/CM/chemoselective hydrogenative coupling of the phosphate triene (*R,R*)-**5** with the advanced C8–C16 fragment **6**, followed by Roskamp homologation and deprotection of the C13 tertiary carbinol. Triene (*R,R*)-**5** is readily prepared in 2-steps via sequential tripodal coupling of the C_2-symmetric *anti*-diene diol (*R,R*)-**7** and allyl alcohol with $POCl_3$ or in one step utilizing phosphoramidite chemistry.[9a] Fragment **6** is obtainable by Brown *anti*-crotylation and Sharpless asymmetric epoxidation of commercially inexpensive geraniol (**8**) in a scalable 9-step route (Scheme 1).

Initial synthetic studies focused on the construction of the C8–C16 fragment **6** from Sharpless asymmetric epoxidation[11] of geraniol (**8**) using (–)-DET, TBHP, Ti(O^{i}Pr)$_4$, followed by regioselective epoxide opening mediated by Red-Al,[12] and subsequent protection of the 1,3-diol moiety to afford the PMP acetal **9** as a 1:1 ratio of diastereomers in excellent yield (Scheme 2). Ozonolysis of compound **9**, followed by *in situ* reductive workup, afforded alcohol **10** in 87% overall yield. Silylation of the primary alcohol **10** with TBSCl generated the corresponding silyl ether and subsequent regioselective opening of the PMP-acetal with DIBAL-H produced primary alcohol **9** in 89% yield. Parikh-Doering oxidation[13] of the resulting alcohol **11**, followed by reagent-controlled enantioselective Brown *anti*-crotylation, [14] furnished desired homoallylic alcohol **12** in good yield. Silylation of homoallyl alcohol **12** afforded the required C8–C16 fragment **6** in 95% yield.

Construction of subunit **13** was achieved from triene (*R*,*R*)-**5** via a one-pot, sequential RCM/CM/chemoselective hydrogenation with the C8–C16 fragment **6** as the CM partner (Scheme 3). Following the previously reported optimized conditions for RCM/CM/"H$_2$",[8c] triene (*R*,*R*)-**5** was first subjected to RCM reaction with the second generation Hoveyda–Grubbs catalyst (HG-II)[15] (6 mol %) in CH$_2$Cl$_2$ (0.007 M), and upon completion, the CM partner **6** in DCE (0.1 M) was added. The reaction was continued at 90 °C with simultaneous evaporation of low boiling solvent from the previous reaction to reach optimal concentration (~ 0.1 M) for cross-metathesis (Scheme 3). Subsequent chemo-selective diimide reduction, by simple addition of *o*-NBSH[16] and Et$_3$N into the reaction mixture, provided the bicyclic phosphate phosphate **13** in 65% overall yield, representing an 87% average yield/reaction in the one-pot, sequential protocol. Next, a Pd-catalyzed, reductive allylic transposition was carried out to regioselectively open the phosphate tether with hydride [Pd(OAc)$_2$/Bu$_3$PHBF$_4$, HCOOH, Et$_3$N, then methylation with TMSCHN$_2$ in MeOH] affording monocyclic phosphate ester in excellent overall yield (82%) and regioselectivity. Complete removal of the phosphate tether in the presence of LiAlH$_4$ provided diol **14** as a single diastereomer in good yield (76%).

With diol **14** in hand, silylation of both alcohols with TESOTf (2,6-lutidine, CH$_2$Cl$_2$) generated the differentially protected subunit **15** in quantitative yield (Scheme 4). Oxidative cleavage of the terminal olefin in **15** using a modified Johnson-Lemieux protocol developed by Jin[17] and coworkers (OsO$_4$, NaIO$_4$, 2,6-lutidine), yielded the corresponding aldehyde which was immediately subjected to a two-carbon Roskamp homologation[18] with ethyl diazoacetate in the presence of SnCl$_4$•5H$_2$O to furnish *β*-keto ester **16** in 76% overall yield over the final two steps. Deprotection of the PMB ether by oxidative cleavage using DDQ produced the Boeckman cyclization precursor **4** in excellent yield. Pyrolysis of *β*-keto ester **4** in toluene under dilute conditions (0.0007 M) using a Dean-Stark condenser with azeotropic removal of EtOH afforded macrolactone **3** in excellent yield (90%) using Boeckman cyclization conditions previously reported by several in the context of complex macrolactonization.[5,10]

The mechanism of the high yielding Boeckman cyclization of β-keto ester **4** is worth noting and presumably proceeds as outlined in Scheme 5.[19] Thus, initial formation of acylketene **C** proceeds under thermal conditions from **4**, with subsequent addition of an accessible

hydroxyl group leading to enol-**D** and final tautomerization affording the β-keto macrolactone **3**. Overall, this high yielding cyclization enables macrocyclization from the hindered C13 carbinol and circumvents the aforementioned issues noted by Cossy in their synthesis of lyngbouilloside aglycon.[5]

In conclusion, we report a concise route to the originally assigned structure of lyngbouilloside macrolactone core **3** that is easily adaptable[20] to potential C10/C11 and C13 variants proposed by the revised structure of lyngbouilloside **1** reported by Cossy and coworkers,[5] as well as implied in the work of Fuwa in 2014 on the unambiguous determination of the closely related structure of lyngbyaloside B (**2b**).[7] Highlights of the synthesis include a phosphate tether-mediated, one-pot, sequential RCM/CM/ chemoselective hydrogenation reaction, Roskamp homologation, and a high yielding Boeckman acylketene cyclization. Overall, the synthesis is highly modular and will enable analog synthesis. Efforts aimed at completing the total synthesis as well as simplified analogs are in process and will be reported in due course.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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19. For recent mechanistic insight on the Boeckman macrocyclization, see Hoye reference 10f.

20. Cossy and coworkers have tentatively reassigned the structure of **1** as having a *syn* C10/C11 stereorelationship (C11 epimer of **1**). This C11 epimer of **1,** as well as all variants, could be accessed by simple use of either enantiomeric *syn-* or *anti-*crotylation methods in the synthesis of **12** en route to **6**. Accordingly, use of the enantiomeric Sharpless epoxidation would derive the C13 epimer in compounds **9**–**12** and **6**.
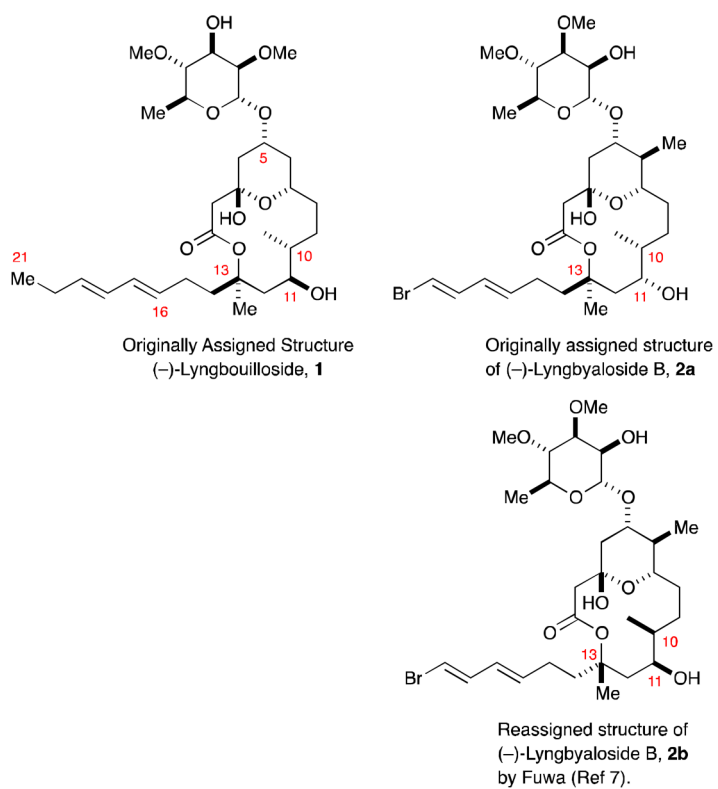
Figure 1.
Original proposed structure of (−)-lyngbouilloside (**1**) and (−)-lyngbyaloside B (**2a**) and the reassigned structure of lyngbyaloside B (**2b**) by Fuwa.
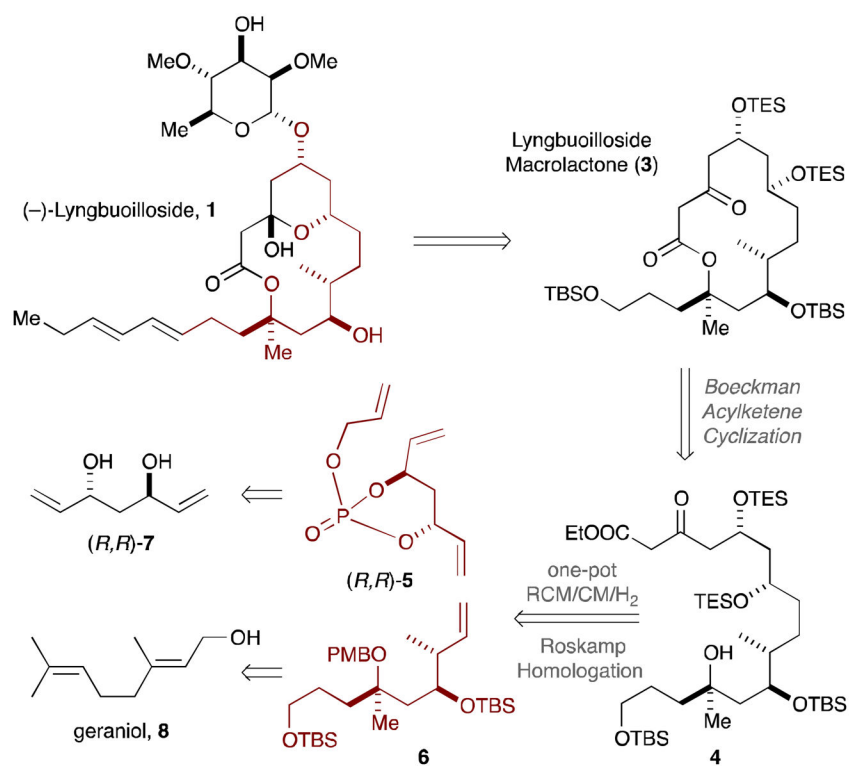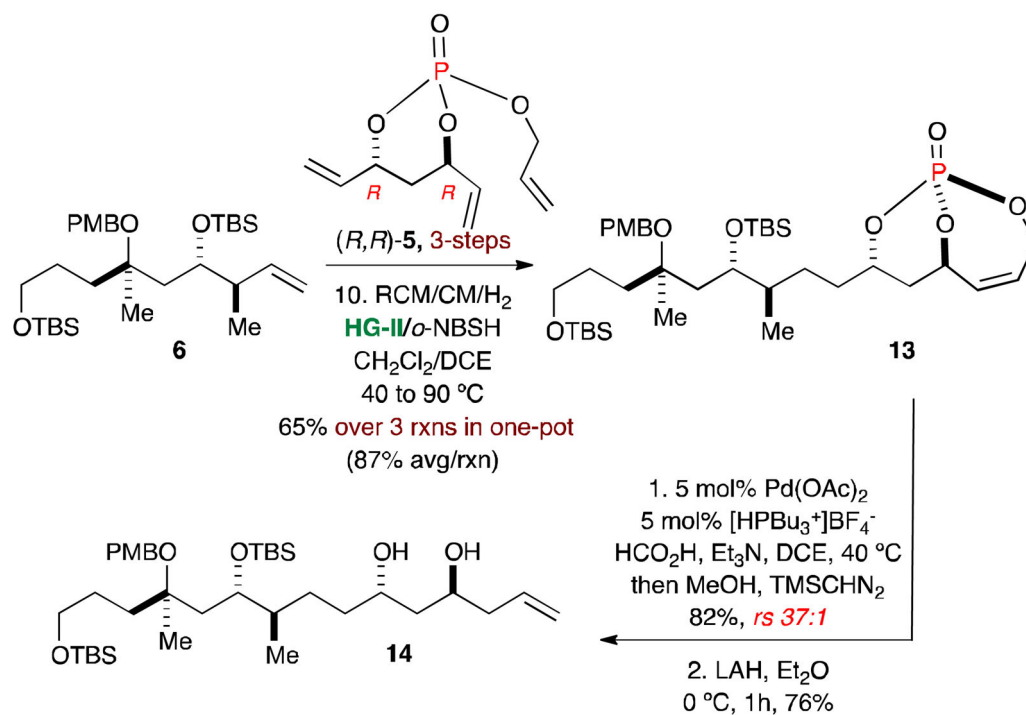
Scheme 1.
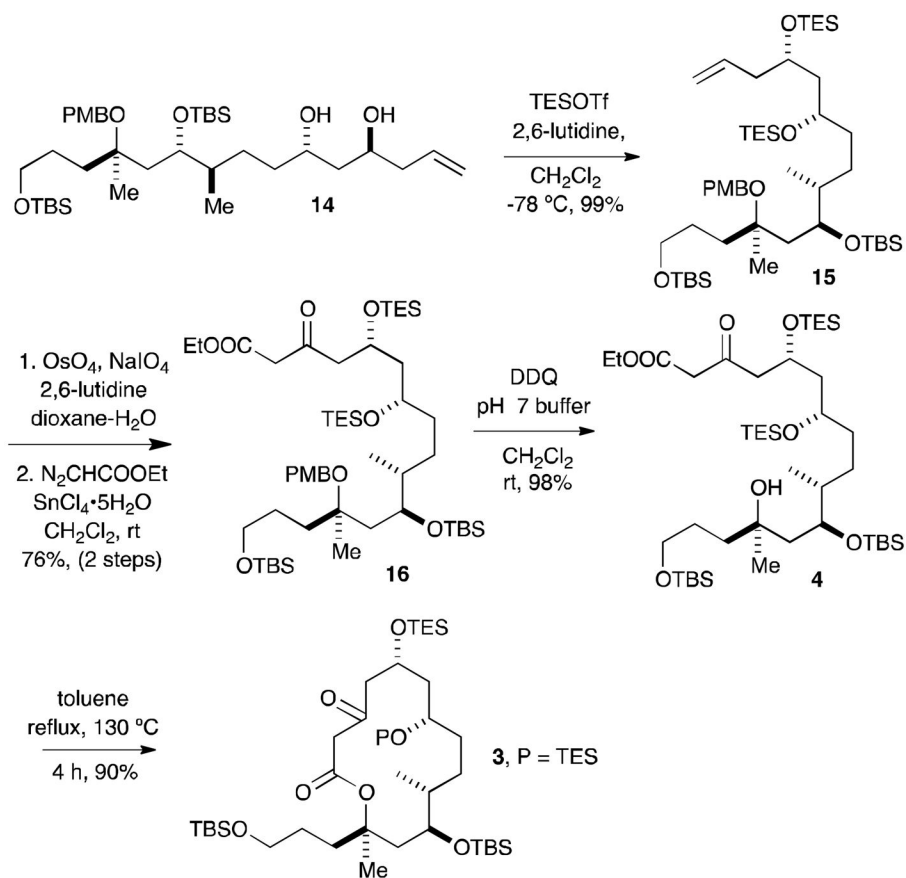Retrosynthetic analysis of (−)-lyngbouilloside.
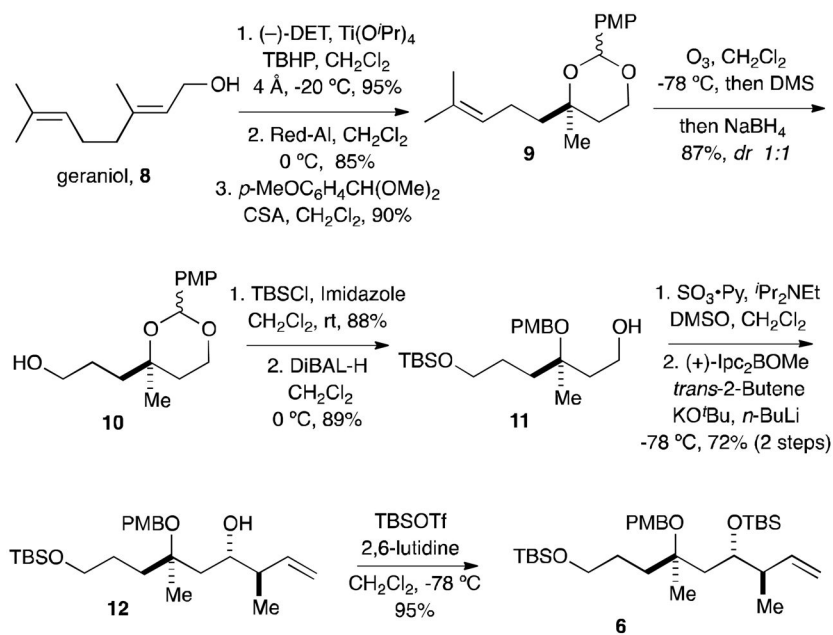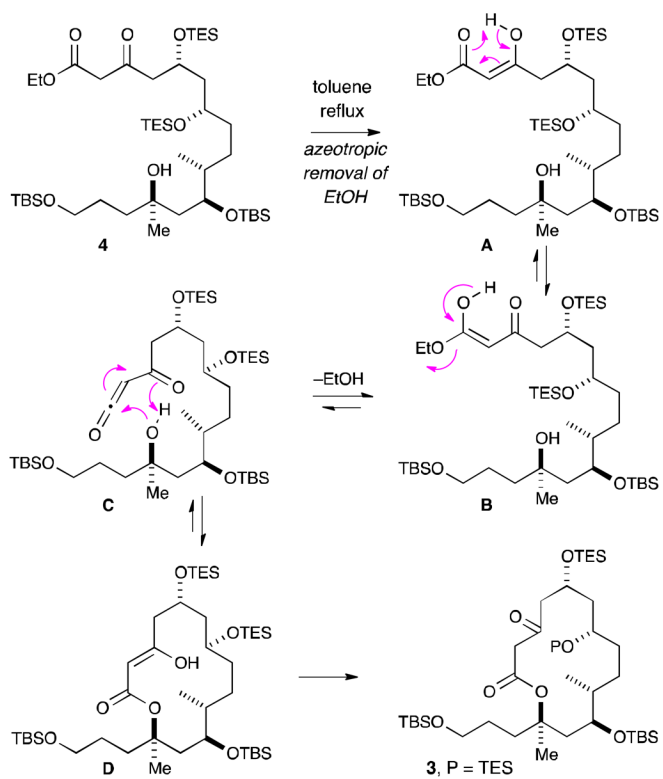
Scheme 2.
Synthesis of C8–C16 fragment.

Scheme 3.
Key one-pot RCM/CM/regioselective hydrogenation.

Scheme 4.
Synthesis of macrolactone **3**.

Scheme 5.
Plausible mechanism of Boeckman cyclization.