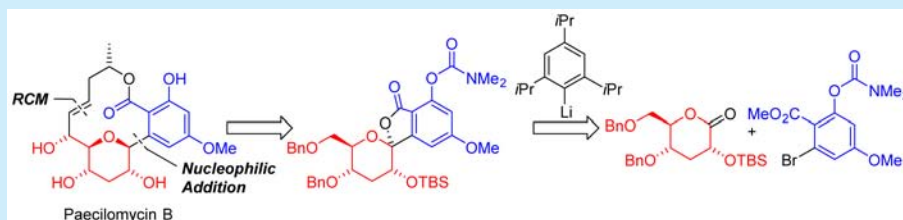


Total Synthesis of Paecilomycin B

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Supporting Information



ABSTRACT: Starting from the glucose-derived δ -lactone and the functionalized aryl bromide, the first total synthesis of naturally occurring paecilomycin B was achieved via functionalized aryl- β -C-glycoside synthesis using 2,4,6-triisopropylphenyllithium under Barbier-type reaction conditions and ring-closing metathesis as the key steps.

Resorcylic acid lactones (RALs)—including the potent HSP90 inhibitor radicicol¹ and hypothemycin,² which inhibits mitogen-activated protein kinases irreversibly—are fungal polyketides characterized by a 14-membered macrocyclic lactone and exhibit various biological activities. In these respects, RALs have attracted much attention, and therefore, many pharmacological and synthetic studies have been reported.³

In 2010, Chen and Wei⁴ reported paecilomycins A–F (1–6) as new RALs; they were first isolated from mycelial solid cultures of *Paecilomyces* sp. SC0924 and showed high to moderate antiparasitic activities (Figure 1). Subsequently, paecilomycins G–I (7–9)⁵ and paecilomycins J–M (10–13)⁶ were isolated. Among them, paecilomycin B (2) is structurally of interest because it contains a tetrahydropyran moiety in its 14-membered lactone ring. Its oxygen bridge between C-1' and C-5' is presumed to be formed by an intramolecular S_N2 reaction between the epoxide and 5'-hydroxy group of paecilomycin A (1).^{4a}

As a result of the novelty of the structures and potent biological activities, paecilomycins have attracted interest as a fascinating target for total synthesis. Although the total syntheses of paecilomycins E (5)^{4b,7} and F (6)^{4b,8} have been successfully described, there is no synthetic report of other paecilomycins. Recently, we reported a novel synthetic method of aryl- β -C-glycosides having an ester, cyano, or carbonyl group on the aromatic ring using 2,4,6-triisopropylphenyllithium (TIPPLi) as a chemoselective halogen–lithium exchange reagent.^{9a} Thus, our finding motivated us to initiate the synthesis of compound 2 that has an aryl- β -C-glycoside scaffold. Herein, we describe the first asymmetric total synthesis of paecilomycin B (2) based on the synthesis of functionalized aryl- β -C-glycosides.

Our retrosynthetic strategy for the synthesis of paecilomycin B (2) is presented in Scheme 1. We planned that the key macrocyclization could be achieved via a ring-closing metathesis (RCM)¹⁰ approach. An intermediate diene 14 would be synthesized from carboxylic acid 15 by Mitsunobu esterification¹¹ using a commercially available chiral alcohol 16. Carboxylic acid 15 could be accessed from spiroketal 17a through the deoxygenation at the anomeric position and the subsequent elongation of the vinyl group. Spiroketal 17a could be obtained as a key step by a nucleophilic coupling reaction between δ -lactone 18 and aryl bromide 19 using TIPPLi under Barbier-type reaction conditions.^{9a} Lactone 18 and bromide 19 could be synthesized from known compounds (*vide infra*).

δ -Lactone 18 was synthesized from the known glycoside 21,¹² which was prepared from *p*-methoxyphenyl β -D-glucopyranoside 20 in five steps (Scheme 2). The benzylidene moiety of 3-deoxy glucoside 21 was removed by hydrogenation to give the corresponding diol 22. The resulting hydroxy groups of 22 were benzylated to afford 23 in an 83% two-step yield. The removal of the *p*-methoxyphenyl group of 23 was achieved using CAN¹³ to afford an anomeric mixture of 24. The generated hydroxy group of 24 was oxidized with Dess–Martin periodinane (DMP)¹⁴ to produce lactone 18 in 62% yield from 23. Moreover, aryl bromide 19 was quantitatively prepared from the known compound 26¹⁵ that was prepared from 25 in four steps by the carbamylation of its hydroxy group (Scheme 3). The *N,N*-dimethylcarbamoyl group was selected because of its inert character under acidic conditions and moderate resistant ability for nucleophilic attack.

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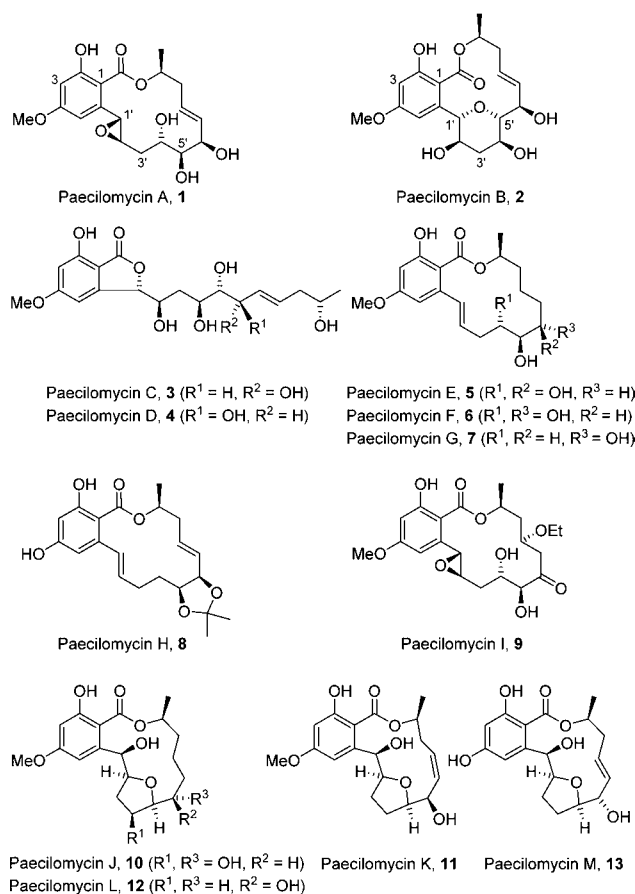
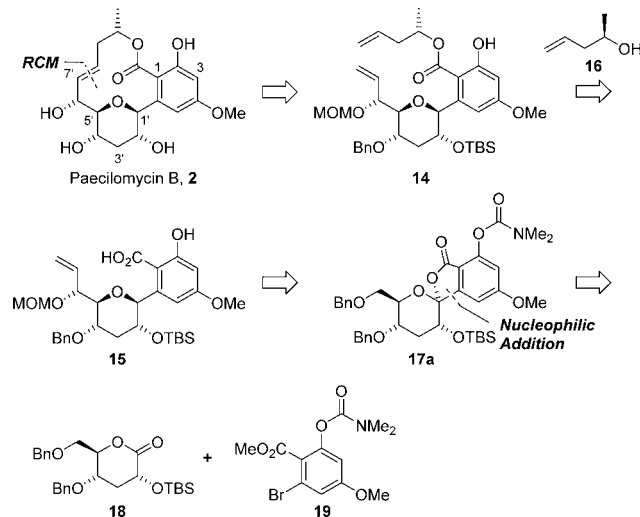


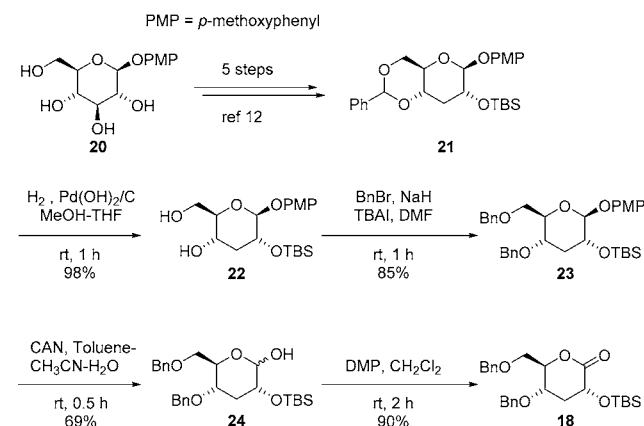
Figure 1. Structures of paecilomycins A–M, 1–13.

Scheme 1. Retrosynthesis of Paecilomycin B, 2

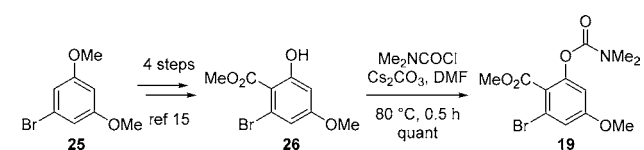


With lactone 18 and aryl bromide 19 in hand, we performed the key nucleophilic addition reaction using TIPPLi under Barbier-type reaction conditions (Scheme 4);^{9a} i.e., to a solution of TIPPLi in THF, which was readily prepared from 2,4,6-triisopropylphenyl bromide and *n*-BuLi at -78 °C, a solution of a 1:1 mixture of 18 and 19 was added over a period of 10 min at -78 °C. After stirring for 10 min, the reaction was quenched with methanol to give the spiroketal 17a in an excellent yield of 89% (basic quenching conditions). In contrast, usual acidic quenching conditions by adding saturated

Scheme 2. Synthesis of δ -Lactone 18



Scheme 3. Synthesis of Aryl Bromide 19



aqueous NH_4Cl afforded 17a as the major coupling product along with lactol 17c as the minor product in various molar ratios of 3–20:1 (17a/17c) in good yields (see Supporting Information). It is presumed that 17a was generated from 17c by spontaneous lactonization. The *C*- β configurations of 17a and 17c were confirmed by NOE measurement between H-2 and the aromatic proton (Figure 2).^{9b} Thus, the coupling reaction smoothly proceeded without any self-condensation despite the presence of the ester and carbamoyl groups on the aromatic group, which are sensitive to nucleophiles.

The direct deoxygenation at the anomeric position of the spiroketal 17a using Et_3SiH and $\text{BF}_3 \cdot \text{Et}_2\text{O}$ failed to produce the desired deoxygenated product but yielded only the desilylated product 17b. Therefore, the spiroketal 17a was previously converted into methyl glycoside 27.^{9a} The treatment of 17a with methanol/methanesulfonic acid afforded 27 in 67% yield, accompanied by 20% recovery of 17b. The deoxygenation of 27 in the presence of Et_3SiH , $\text{BF}_3 \cdot \text{Et}_2\text{O}$, and TFA proceeded smoothly in a stereoselective manner^{9a,16} to afford the aryl- β -*C*-glycoside 28. The *C*- β configuration of 28 was confirmed by NOE measurement between H-1 and H-3/H-5 (Figure 3). The selective acetolysis of its primary benzyl ether and subsequent deacetylation gave alcohol 29 in 89% yield. Dess–Martin oxidation of the primary hydroxy group of 29 afforded the corresponding aldehyde 30. Because the Dess–Martin oxidation followed by an aqueous workup yielded a mixture of 30 and its hydrate, dehydration treatment with MS 4 \AA was required.¹⁷ Aldehyde 30 was subjected to a Nozaki–Hiyama–Kishi coupling¹⁸ with vinyl iodide to give a coupling product 31a in 44% yield along with its $\text{C}6'$ epimer 31b in 45% yield. The stereochemistry of $\text{C}6'$ of 31a was confirmed by the two-step conversion into benzylidene acetal 36 which has a more rigid conformation than 31a (Scheme 5). The coupling constant ($J_{5',6'} = 9.3$ Hz) and NOE measurement of 36 supported $\text{C}6'R$ configuration. Unfortunately, the Grignard reaction of 30 using vinyl magnesium bromide resulted in a low yield, and a catalytic asymmetric approach^{18d,e} did not succeed to induce high stereoselectivity (data not shown). Therefore,

Scheme 4. Synthesis of Paecilomycin B, 2

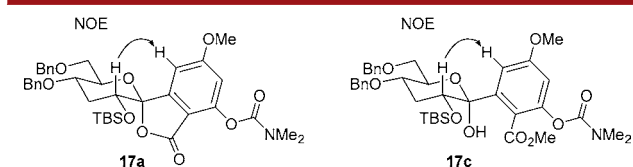
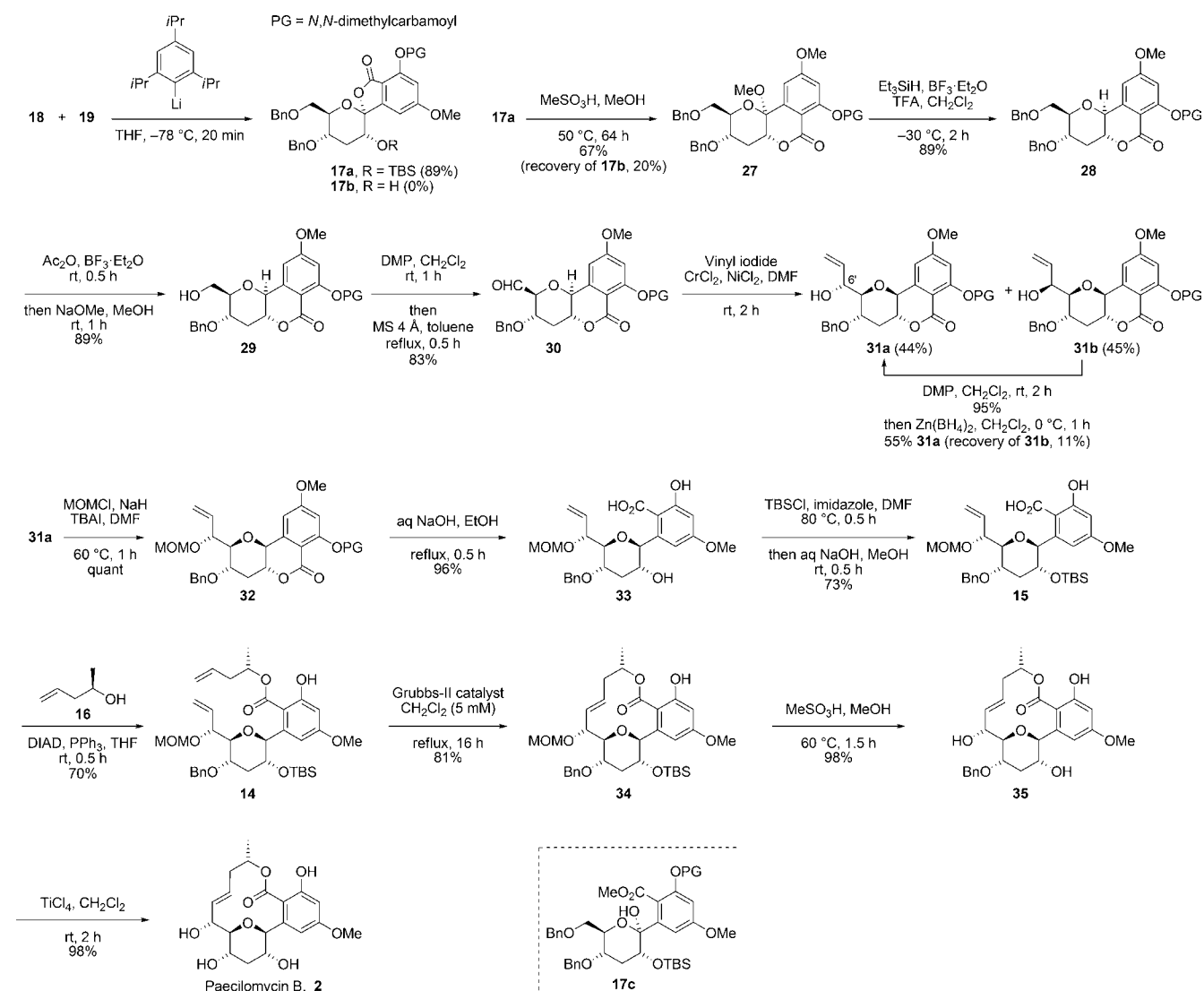


Figure 2. Determination of the configurations of 17a and 17c.

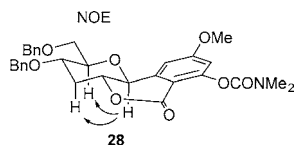
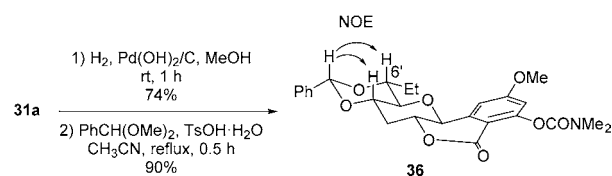


Figure 3. Determination of the configuration of 28.

the epimer **31b** was converted into **31a** by oxidation and subsequent stereoselective reduction. The usage of Zn(BH₄)₂¹⁹ as a reducing reagent in CH₂Cl₂ under high dilution conditions afforded the desired alcohol **31a** in 55% yield with the recovery of **31b** in 11% yield. Furthermore, Luche reduction gave only the undesired **31b**, and the Corey–Bakshi–Shibata reduction did not afford **31a**. The allyl alcohol of **31a** was protected as its

Scheme 5. Two-Step Conversion to 36 for the Determination of the C6' Configuration of 31a



MOM ether, and the resulting **32** was hydrolyzed with aqueous NaOH, which was accompanied by the removal of a *N,N*-dimethylcarbamoyl group to afford carboxylic acid **33** in 96% yield from **31a**. The subsequent treatment of diol **33** with excess TBSCl/imidazole yielded a persilylated compound, which was hydrolyzed with aqueous NaOH to produce monosilylated product **15** in 73% yield. The precursor **14** for RCM was obtained by Mitsunobu esterification between benzoic acid **15** and chiral alcohol **16** in 70% yield. The macrocyclization by RCM as the second key step using the Grubbs-II catalyst successfully produced (*E*)-olefin **34** in 81% yield as the sole cyclization product. The deprotection of **34** with methanesulfonic acid gave benzyl ether **35**, and the

subsequent exposure of **35** to TiCl_4 furnished paecilomycin B (**2**) in 96% yield from **34**, whose analytical data, including MS, ^1H , and ^{13}C NMR, were identical to the reported data.^{4,20}

In summary, we have achieved the first total synthesis of paecilomycin B (**2**) based on a functionalized aryl- β -C-glycoside synthetic method using TIPPLi, which started from *p*-methoxyphenyl β -D-glucopyranoside **20** and 1-bromo-3,5-dimethoxybenzene (**25**). The macrocyclization step was achieved via RCM in good yield and stereoselectivity. Thus, our aryl- β -C-glycoside synthetic method^{9a} is applicable to natural product synthesis because of its good functional group tolerance.

■ ASSOCIATED CONTENT

■ Supporting Information

Experimental procedures and spectral data for all new compounds. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b00983.

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Notes

The authors declare no competing financial interest.

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- (9) (a) Ohba, K.; Koga, Y.; Nomura, S.; Nakata, M. *Tetrahedron Lett.* **2015**, *56*, 1007. (b) In contrast to our previous observations^{9a} of C- α stereoselectivity in nucleophilic coupling reactions between perbenzylated or persilylated δ -gluconolactone and methyl 2-halobenzoate forming C- α spiroketals, C- β configurations of **17a** and **17c** were detected. We presumed that this C- β stereoselectivity was derived from the low reactivity of a methyl ester group on the electron-rich aromatic

ring toward generated alkoxide so that spontaneous lactonization at low temperature might be disturbed, while prompt isomerization of the coupling product to the stable C- β configuration and the following lactonization might occur under reaction or quenching conditions.

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- (20) The specific rotation value of our synthetic paecilomycin B (**2**) is $[\alpha]_D^{25} +85.5$ (c 0.32, MeOH) (lit.^{4a} $[\alpha]_D^{24} +40.4$ (c 0.27, MeOH)). Judging from literature data of ^1H and ^{13}C NMR, the difference might be on the basis of the small amount of contaminated impurity in natural paecilomycin B (**2**).

■ NOTE ADDED AFTER ASAP PUBLICATION

References 7c and d have been added to the version that posted on May 4, 2015. The revised version posted on May 5, 2015.