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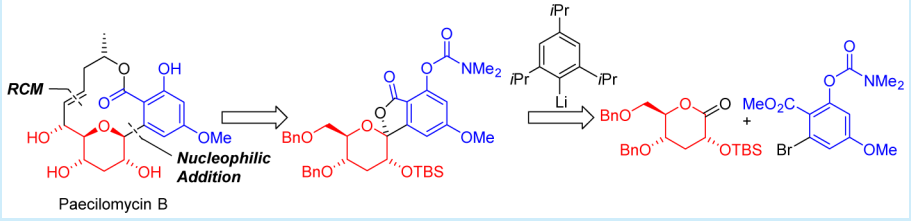
Total Synthesis of Paecilomycin B

Kiyomi Ohba*[,†,‡] and Masaya Nakata[‡]

[†]Medicinal Chemistry Research Laboratories, Mitsubishi Tanabe Pharma Corporation, 1000 Kamoshida-cho, Aoba-ku, Yokohama 227-0033, Japan

[‡]Department of Applied Chemistry, Faculty of Science and Technology, Keio University, 3-14-1 Hiyoshi, Kohoku-ku, Yokohama 223-8522, Japan

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 radicicol[1] 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 Wei[4] 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 antiplasmodial 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 esterification[11] 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 CAN[13] 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 **26**[15] that was prepared from **25** in four steps by the carbamoylation 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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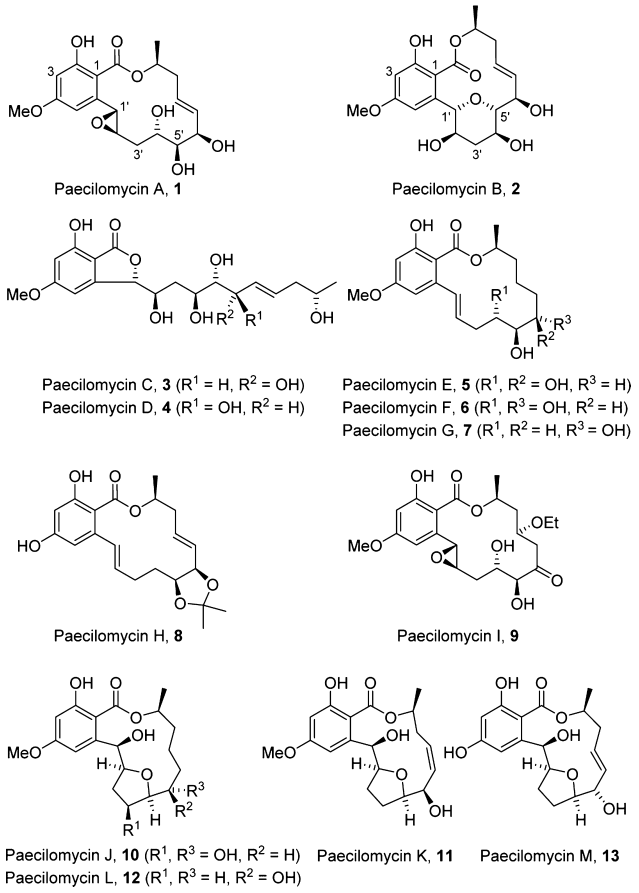
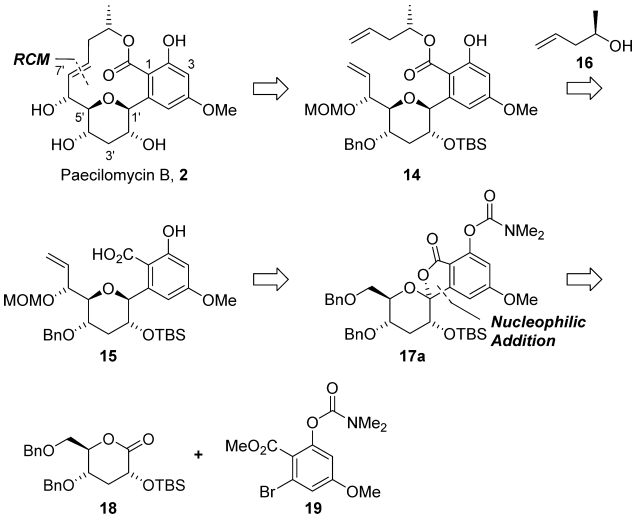


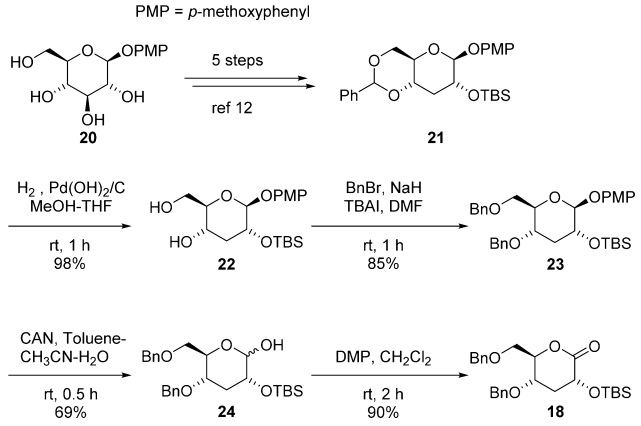
Figure 1. Structures of paecilomycins A–M, **1**–**13**.

Scheme 1. Retrosynthesis of Paecilomycin B, 2

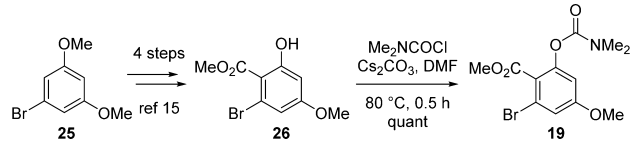


With lactone **18** and aryl bromide **19** in hand, we performed the key nucleophilic addition reaction using TIPPLi under Barbier-type reaction conditions (Scheme 4);[9a] i.e., to a solution of TIPPLi in THF, which was readily prepared from 2,4,6-triisopropylphenyl bromide and *n*-BuLi at −78 °C, a 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 deoxgenation at the anomeric position of the spiroketal **17a** using Et_3SiH and $BF_3{\cdot}Et_2O$ 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, $BF_3{\cdot}Et_2O$, 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 Å was required.[17] Aldehyde **30** was subjected to a Nozaki–Hiyama–Kishi coupling[18] with vinyl iodide to give a coupling product **31a** in 44% yield along with its C6′ epimer **31b** in 45% yield. The stereochemistry of C6′ 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 C6′*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,

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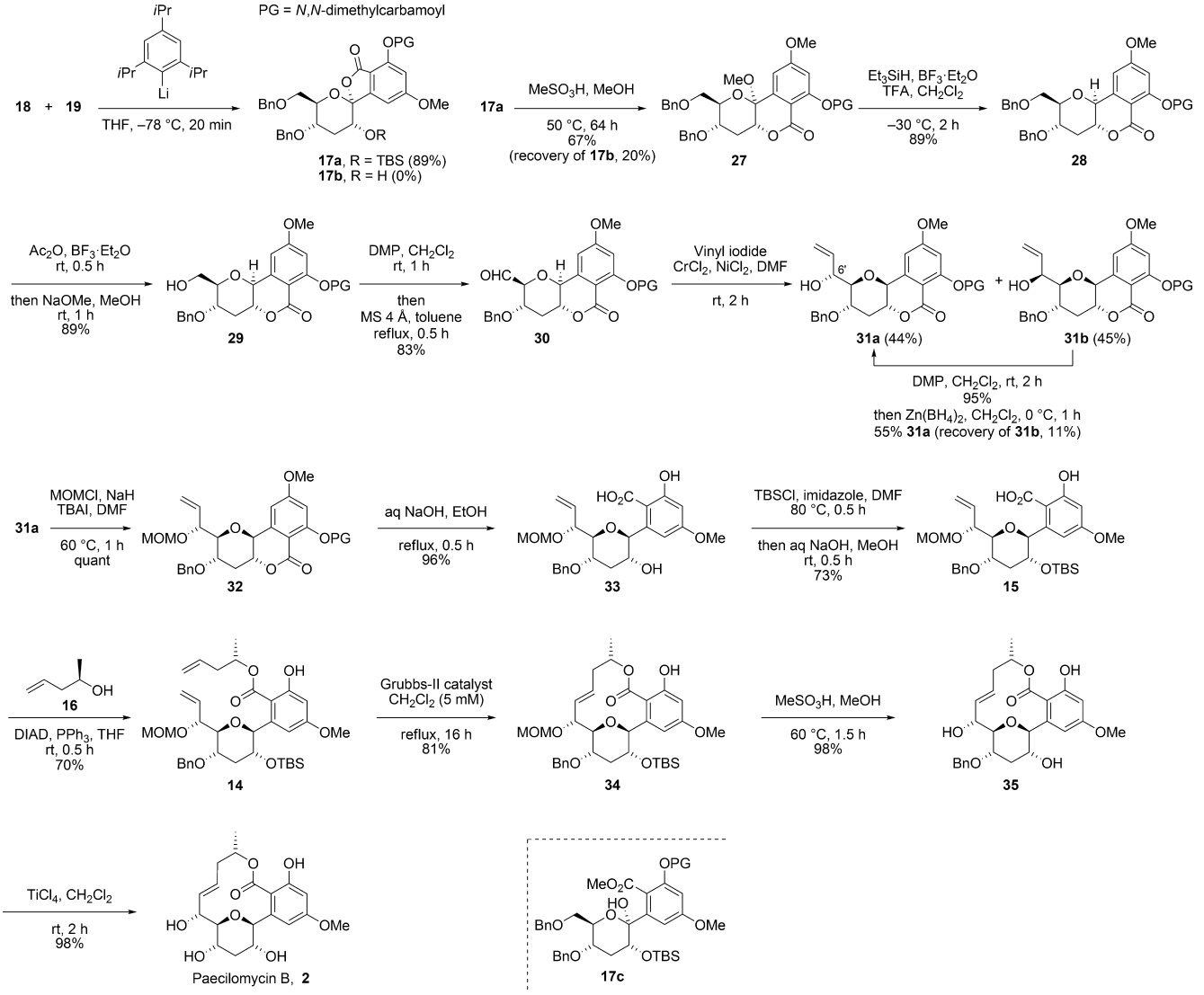
Scheme 4. Synthesis of Paecilomycin B, 2



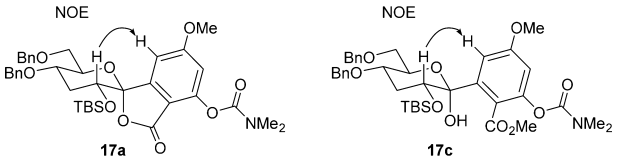


Figure 2. Determination of the configurations of **17a** and **17c**.

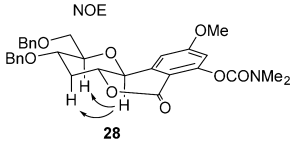
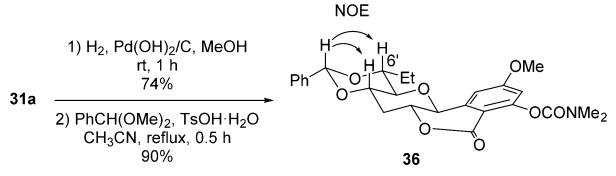


Figure 3. Determination of the configuration of **28**.

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



the epimer **31b** was converted into **31a** by oxidation and subsequent stereoselective reduction. The usage of $Zn(BH_4)_2$[19] as a reducing reagent in CH_2Cl_2 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 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

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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.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: ohba.kiyomi@mf.mt-pharma.co.jp.

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**).

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