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Synthetic approaches to [5,6]-benzannulated spiroketal natural products*

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Abstract: Studies toward the synthesis of three biologically active [5,6]-benzannulated spiroketal natural products are described. The first total synthesis of paecilospirone is reported, employing a late-stage, pH-neutral spiroketalization. A formal synthesis of γ-rubromycin is described, where the spiroketal moiety is formed by delicate manipulation of the electronic properties of the spirocyclization precursor. Finally, model work toward the total synthesis of berkelic acid is summarized, introducing a novel Horner–Wadsworth–Emmons/oxa-Michael (HWE/oxa-M) cascade to access the spiroketal precursor.

Keywords: berkelic acid; natural products; paecilospirone; γ-rubromycin; spiroketals.

INTRODUCTION

There is a continual need to develop new drug candidates, not only to find potential treatments for diseases that currently have no cure, but also to combat increasingly common drug-resistant diseases. Nature has traditionally been the most important source of lead compounds for the development of new therapeutic agents owing to the vast biochemical diversity that has resulted from evolutionary selection pressures. The importance of natural products in the development of new drugs is highlighted by the recently published statistic that 53 % of new chemical entities approved for use in the clinic are compounds derived from knowledge gained from natural products [1]. Therefore, the total synthesis of natural products remains an essential branch of organic chemistry.

The spiroketal moiety is a common architectural feature found in many biologically active natural products [2]. However, benzannulated spiroketals isolated from natural products are considerably less prevalent [3]. Herein we provide an overview of our recent work in the area of [5,6]-benzannulated spiroketal natural product synthesis. We summarize our recently completed total syntheses of γ-rubromycin [4] and paecilospirone [5] and our model studies toward berkelic acid [6].

BERKELIC ACID

In the search for new sources of novel, biologically active natural products, chemists are increasingly turning to organisms that live in extreme environments [7]. A number of novel compounds have been isolated from these sources, which often display interesting biological activity and structural motifs.

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These so-called extremophiles have been found in habitats of high and low temperature, high pressure, high salt, and high and low pH. Berkelic acid belongs to the latter category, having been isolated as a secondary metabolite from a *Penicillium* species collected from Berkeley Pit Lake, a flooded former copper mine in Montana, USA, whose waters have a pH of ~2.5 and contain a number of heavy metals in high concentrations [8]. Berkelic acid was found to inhibit caspase-1 (GI_{50} 98 μM) and matrix metalloprotease-3 (GI_{50} 1.87 μM) as well as exhibiting selective activity against the ovarian cancer cell line OVCAR-3 (GI_{50} 91 nM). Berkelic acid was originally assigned by Stierle and co-workers as having the relative stereochemistry **1**, with the configuration of the C-22 quaternary center unknown (Fig. 1). The potent biological activity of the molecule coupled with its remarkable structural architecture and ambiguity of the chemical structure has led to a number of efforts toward its total synthesis. The group of Fürstner determined the chirality at C-22 to be (*S*) and reassigned the stereochemistry of the C-18 and C-19 center by total synthesis of the methyl ester of berkelic acid [9]. The absolute stereochemistry was subsequently determined by total synthesis of the free acid by Snider et al., confirming the structure of berkelic acid as **2** [10]. Further total and formal syntheses have since been reported by the groups of De Brabander [11] and Pettus [12].

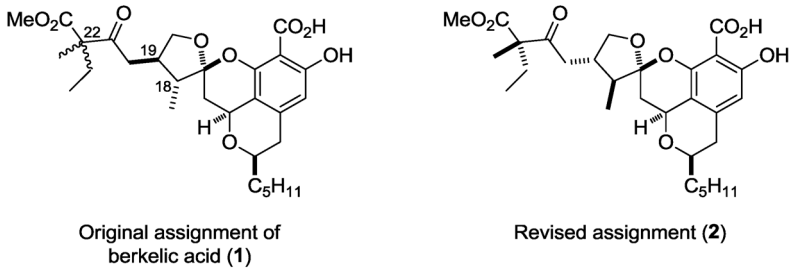
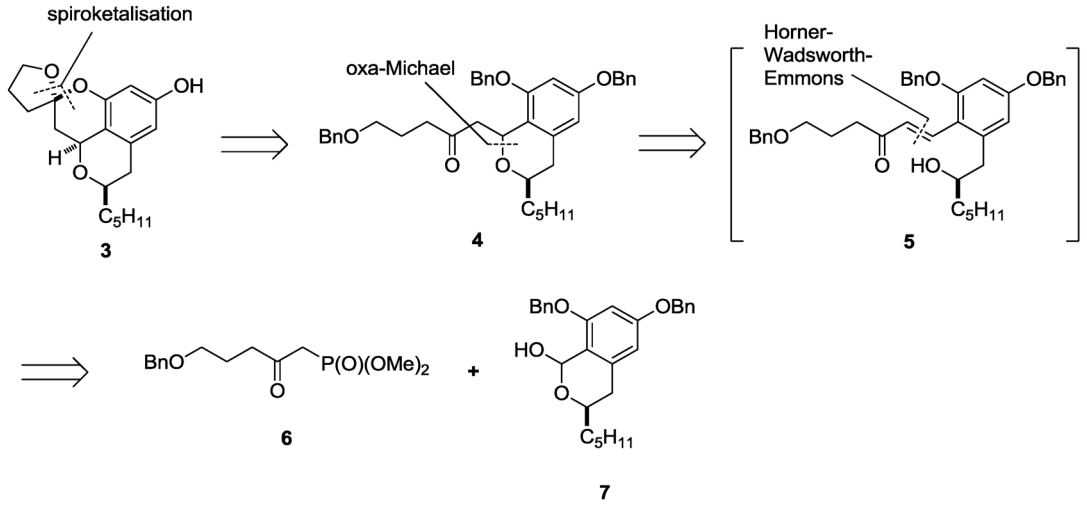


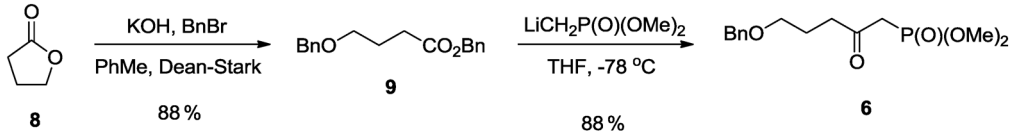
Fig. 1 Original and revised structural assignments of berkelic acid.

We wished to develop a synthesis of berkelic acid using a flexible and convergent approach that would allow future manipulation of its biological activity through analogue synthesis. Our retrosynthetic analysis of the tetracyclic core of berkelic acid **3** is outlined in Scheme 1. We envisaged that isochroman **4** would spontaneously undergo spiroketalization upon global debenzylation under acidic conditions. In turn, isochroman **4** could be accessed from phosphonate **6** and lactol **7** by a Horner–Wadsworth–Emmons/oxa-Michael (HWE/oxa-M) cascade via enone **5**. This approach provides increased flexibility compared to previous routes, with the stereochemistry installed at a late stage and the HWE/oxa-M cascade allowing access to a range of berkelic acid analogues by reacting any 2-benzyloxy benzannulated lactol with a library of β-keto phosphonates in two simple operations.



Scheme 1 Retrosynthesis of tetracyclic model **3**.

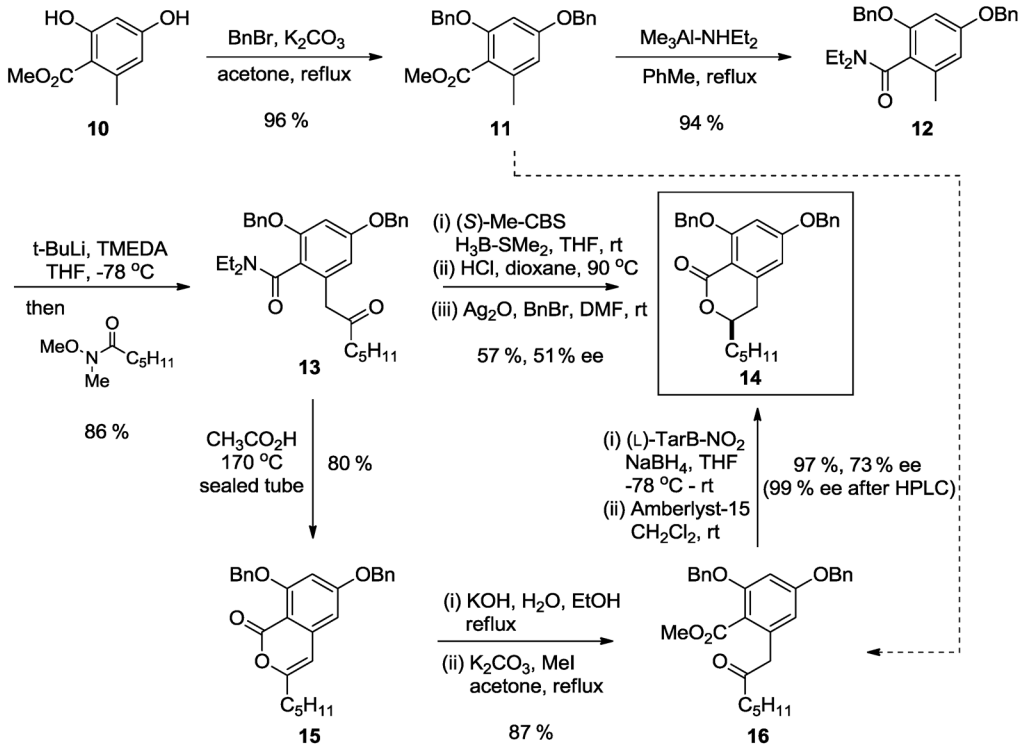
The synthesis of phosphonate **6** was accomplished by ring-opening of γ-butyrolactone (**8**) with potassium hydroxide and in situ trapping of the resulting hydroxy acid with benzyl bromide under Dean–Stark conditions (Scheme 2). Addition of lithium dimethyl methylphosphonate to the resulting benzyl ester afforded coupling partner **6**.



Scheme 2 Synthesis of phosphonate **6**.

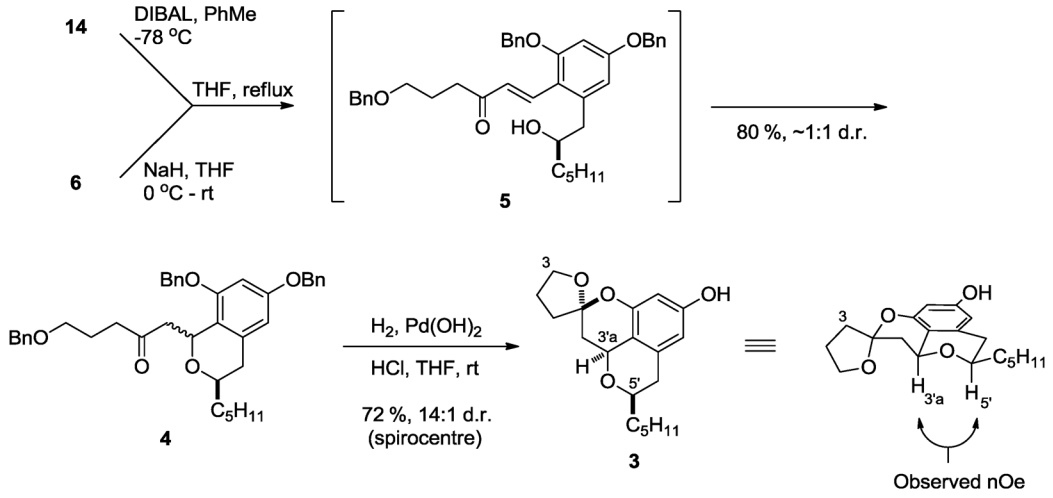
Our initial strategy to lactone **14** required the toluate anion addition of benzyl-protected methyl orsellinate **11** [13] to the Weinreb amide of hexanoic acid to afford ketone **16** (Scheme 3). However, after extensive screening of reagents and conditions we were unable to effect this transformation. Instead, methyl ester **11** was converted to its corresponding diethyl amide **12** with trimethylaluminum-diethylamine complex. Pleasingly, amide **12** proved more amenable to the toluate anion addition chemistry, providing access to ketone **13** in good yield. Lactone **14** could now be accessed via a chiral reduction-cyclization strategy. We found that the highest level of enantiocontrol in the reduction step was provided by (*S*)-methyl-CBS to afford the corresponding hydroxy amide in 51 % ee. Cyclization to the lactone required harsh conditions, resulting in partial deprotection of the *ortho* benzyl ether. Subsequent reprotection with benzyl bromide and silver(I) oxide provided lactone **14** in moderate yield.

In order to increase the level of enantiocontrol in the chiral reduction step, amide **13** was transformed to methyl ester **16** via isocoumarin **15**. Methyl ester **16** rapidly reconverted to isocoumarin **15** upon exposure to acid or base, but with careful handling could be subjected to further manipulation. Reduction with (L)-TarB-NO_2 followed by cyclization of the resulting hydroxyl ester provided lactone **14** with an improved 73 % ee. Lactone **14** could be obtained in >99 % ee by a facile preparatory-scale high-performance liquid chromatography (HPLC) separation.



Scheme 3 Synthesis of lactone **14**.

Lactone **14** was reduced with diisobutylaluminum (DIBAL) to the corresponding lactol, which was added directly to deprotonated phosphonate **6**, triggering the desired HWE/oxa-M cascade to afford isochroman **4** as a 1:1 mixture of diastereoisomers (Scheme 4). This mixture could be equilibrated with HCl in tetrahydrofuran (THF) to provide predominantly the undesired *trans*-isomer. However, when the 1:1 mixture of *cis*- and *trans*-isomers were subjected to the deprotection/cyclization conditions, we were delighted to find that the desired *cis*-configured tetracyclic core **3** was obtained exclusively, as evidenced by a strong nOe interaction between H-3'a and H-5'. The tetracyclic core **3** was obtained as a 14:1 mixture of diastereoisomers around the spiroketal center, with the major isomer being tentatively assigned as the anomerically stabilized compound, owing to the lack of an nOe correlation between H3'a and H-3. The observed equilibration is in agreement with a study of a similar tetracyclic model of berkelic acid, in which a mixture of four possible spiroketals underwent equilibration to a single isomer upon treatment with acid [14].



Scheme 4 HWE/oxa-M cascade and synthesis of model compound **3**.

RUBROMYCIN

The rubromycins are a family of structurally related natural products that contain a highly oxygenated naphthoquinone moiety and an isocoumarin unit. With the exception of α-rubromycin (**21**), these two fragments are connected through an optically active [5,6]-spiroketal ring system. β-Rubromycin and γ-rubromycin have attracted interest as lead compounds for the development of anticancer drugs owing to their potent activity against human telomerase (IC_{50} = 3 μM) [15]. It seems likely that the spiroketal moiety is an essential pharmacophore for the inhibition of telomerase as α-rubromycin (**21**) displays substantially decreased potency (IC_{50} > 200 μM) [14e]. A number of related natural products also contain the aromatic spiroketal motif, such as purpuromycin (**18**) [16], a potential topical agent for vaginal infections and heliquinomycin (**19**) [17], a selective inhibitor of DNA helicase.

The unprecedented structural architecture and varied biological activity of this family of natural products have attracted considerable attention from the synthetic community [18]. However, despite these substantial efforts, only two successful total syntheses of the rubromycin family had been achieved when we started our investigations in this area. Danishefsky and co-workers completed their synthesis of heliquinomycin (**19**) in 2001 [19], which was followed six years later by the total synthesis of γ-rubromycin (**17**) by Kita et al. [20].

The low success rate for the total synthesis of the rubromycin family can be mainly attributed to difficulties assembling the spiroketal core under acidic conditions. Despite this seemingly straightforward approach, difficulties in spiroketalization have been reported by the groups of Danishefsky [19], Kozlowski [21], and Reissig [18,22] in their work toward purpuromycin (**18**) and heliquinomycin (**19**). Through the attempted spiroketalization of a number of model compounds, Kozlowski [21] and Reissig [18,22] proposed that the presence of electron-withdrawing groups on the isocoumarin moiety decreases the nucleophilicity of the phenolic OH group owing to inductive and mesomeric effects (see inset, Fig. 2), reducing the efficiency of the critical spiroketalization step.

Previous work within our group has led to a mild and efficient spiroketalization protocol for the synthesis of a number of bisbenzannulated spiroketal compounds [23]. We proposed that this methodology could be extended to the synthesis of γ-rubromycin by the spiroketalization of an appropriate isocoumarin ring precursor that possesses the correct electronics to allow the formation of the spiroketal. This led us to disconnect the molecule to ketone **23** (Scheme 5), whereby the mesomeric effect of the isocoumarin is eliminated (see inset, Fig. 2). We hoped that subjecting **23** to acid conditions would pro-

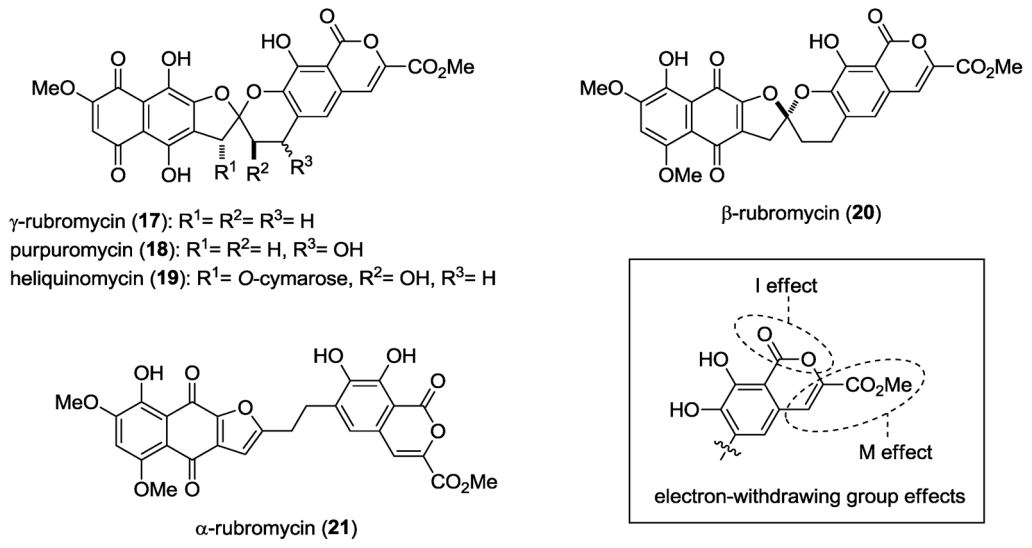
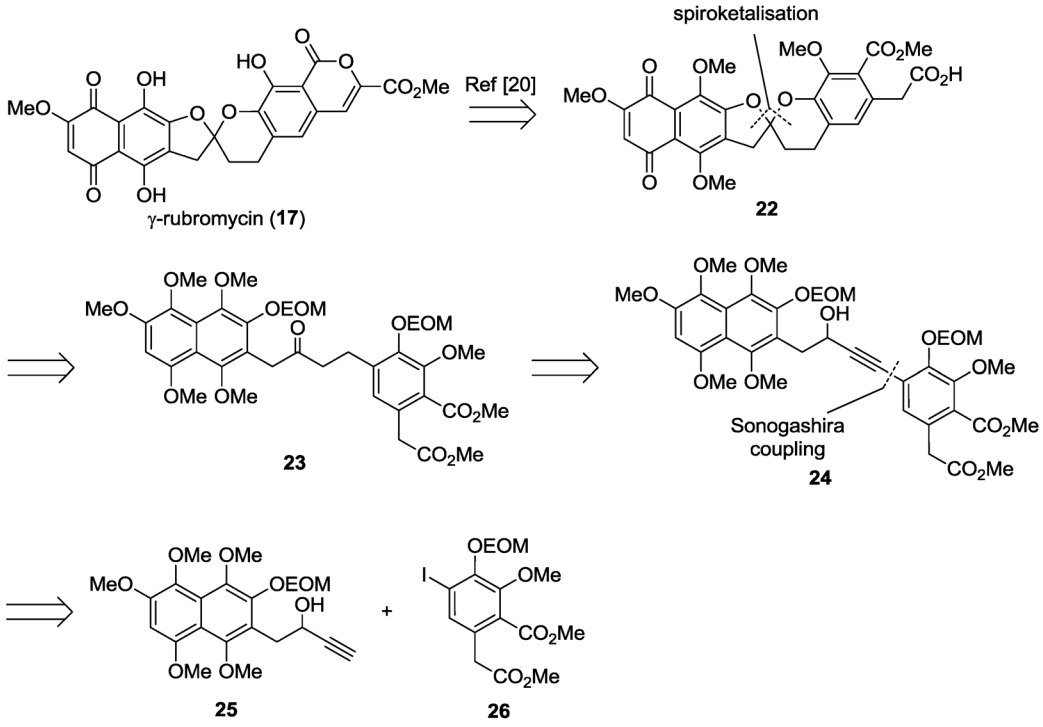


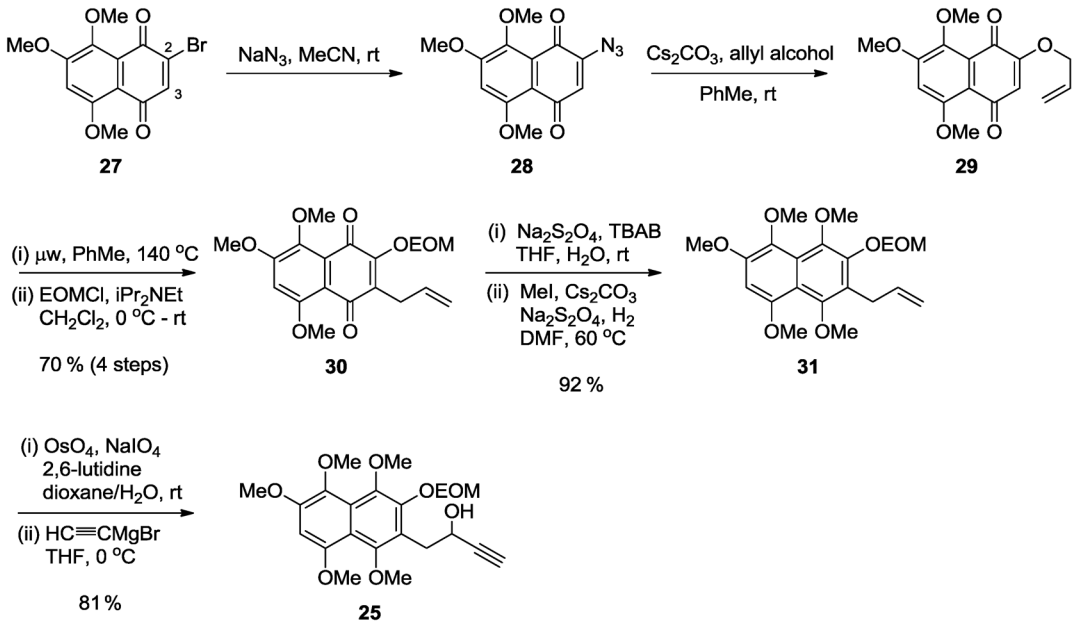
Fig. 2 Selected examples of the rubromycin family. Inset: inductive (I) and mesomeric (M) electron-withdrawing effects of the isocoumarin moiety.



Scheme 5 Retrosynthesis of γ-rubromycin.

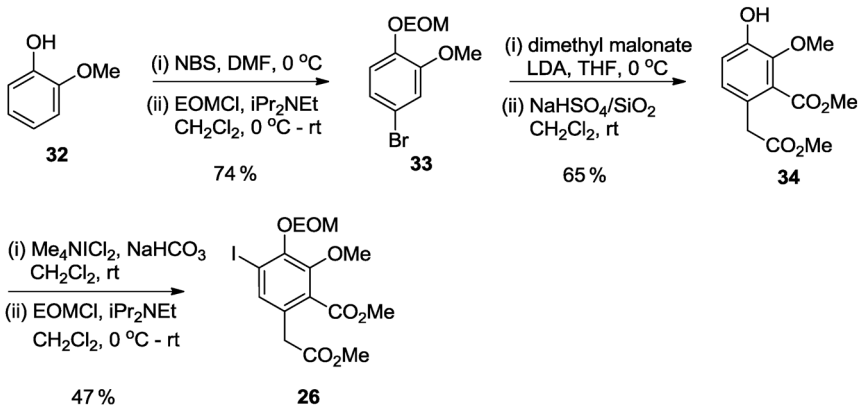
vide access to spiroketal **22**, an intermediate in Kita's total synthesis of γ-rubromycin [20]. Ketone **23** could be accessed from propargylic alcohol **24**, which in turn could arise from a Sonogashira coupling of acetylene **25** with iodide **26**.

Our synthesis of the acetylene fragment commenced from known bromoquinone **27** (Scheme 6) [24]. Interestingly, allyloxylation of **27** resulted in a mixture of regioisomers, where substitution had occurred at both C-2 and C-3. We found that by changing the leaving group, the regiochemistry of the reaction could be controlled to favor either isomer. Allyloxylation of the corresponding iodide resulted in the exclusive formation of the C-3 substituted allyl ether, whereas azidoquinone **28** provided the desired C-2 substituted product **29** with excellent stereocontrol. A microwave-assisted Claisen rearrangement of **29** afforded the corresponding naphthol product in good yield, which was smoothly protected as its ethoxymethyl (EOM) ether **30**. Reductive dimethylation of **30** required the careful use of a reductive environment (hydrogen atmosphere and sodium dithionite) with cesium carbonate as a base to obtain good conversion to naphthalene **31**. Oxidative cleavage of the terminal olefin followed by addition of ethynyl magnesium bromide to the resulting aldehyde provided acetylene **25**.



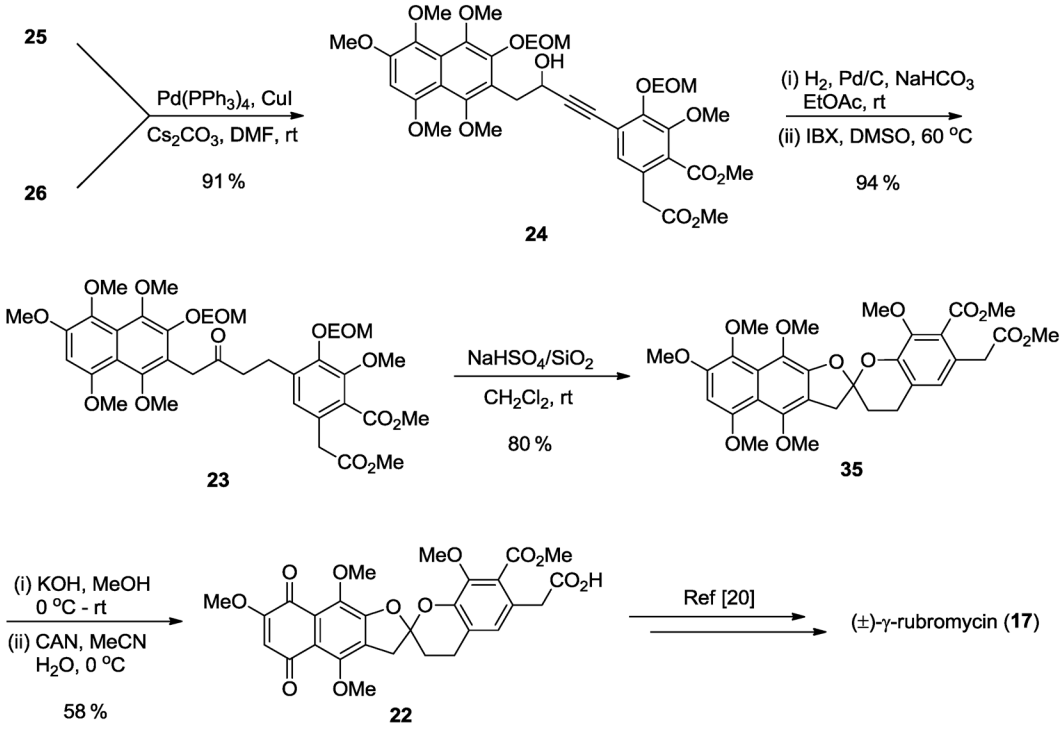
Scheme 6 Synthesis of acetylene **25**.

The synthesis of iodide fragment **26** commenced by *para*-selective bromination of commercially available guaiacol (**32**) with *N*-bromosuccinimide (NBS), followed by protection of the phenol as its EOM ether **33** (Scheme 7). Addition of deprotonated dimethyl malonate to bromophenol **33** and subsequent deprotection of the EOM ether afforded diester **34**. Iodination was performed by treatment of **34** with tetramethylammonium dichloroiodate. Reprotection of the free phenol with EOMCl provided key coupling partner **26**.



Scheme 7 Synthesis of iodide **26**.

Sonogashira reaction of **25** and **26** afforded propargylic alchohol **24** (Scheme 8). We found that the use of a non-amine base (cesium carbonate) and degassed solvents were required to minimize the formation of homocoupled product. Reduction of the triple bond by hydrogenation over 10 % Pd/C buffered with sodium bicarbonate, followed by oxidation of the secondary alcohol with *o*-iodosoxybenzoic acid (IBX) provided ketone **23**. The key spiroketalization step was then attempted using the mild procedure previously developed by our group [23]. Pleasingly, treatment of **23** with silica-supported sodium hydrogen sulfate in dichloromethane afforded spiroketal **35** in 80 % yield. Finally, selective saponification of the aliphatic ester and adjustment of the naphthalene moiety oxidation state



Scheme 8 Completion of formal synthesis.

afforded **22**, completing a formal synthesis of γ-rubromycin. Following the publication of this work, the Pettus group have since described a total synthesis of γ-rubromycin utilizing a late-stage [3 + 2] cycloaddition between a naphthoquinone and an exocyclic enol ether [25].

PAECILOSPIRONE

Isolated in 2000 from the marine fungus *Paecilomyces* Sp. by Namikoshi and co-workers, paecilospirone (**36**) contains a novel spiro[chroman-2,1'(3'*H*)-isobenzofuran] core (Fig. 3) [26]. It was identified as a potential antimitotic agent (20 % inhibition at 50 μM) using an assay screening for microtubule assembly inhibitors. Despite the isolation of paecilospirone more than a decade ago, no total synthesis of this natural product has yet been reported [27].

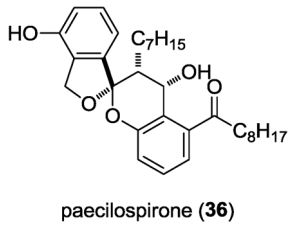
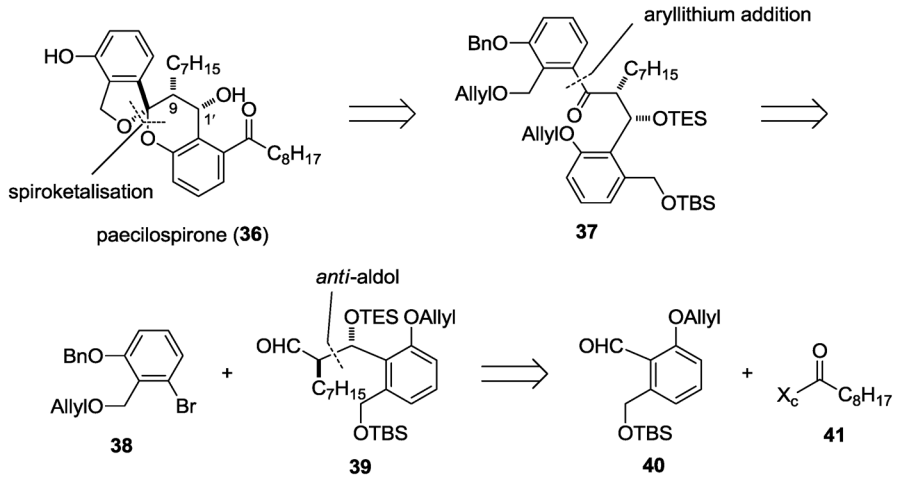


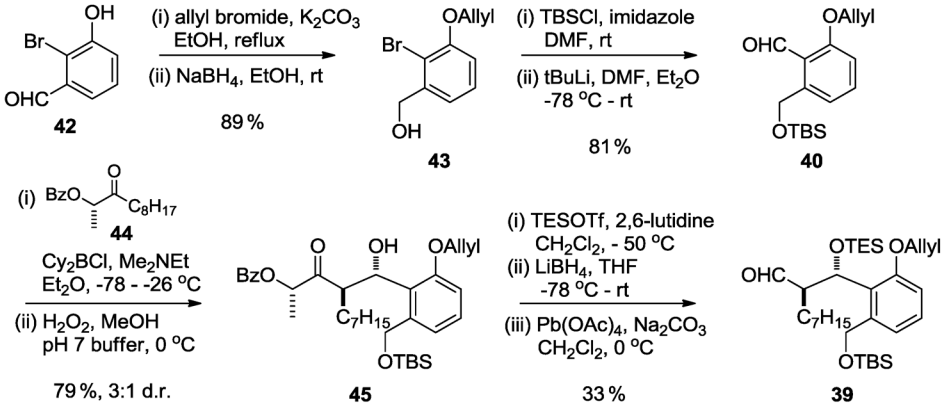
Fig. 3 Structure of paecilospirone.

Our retrosynthetic strategy to paecilospirone (**36**) was based on a late-stage formation of the spiroketal moiety by deprotection of an appropriate precursor such as **37** (Scheme 9). However, initial studies showed that the hydroxyl group β to the spiroketal center underwent facile elimination under acidic conditions. This observation can be explained by the antiperiplanar relationship between the hydroxyl group and the H-9 proton. Based on these observations, judicious choice of protecting group was required so that the key deprotection/spiroketalization could be carried out under neutral conditions. We proposed that bis-allyl ether **37** would undergo Pd^0-catalyzed deprotection and in situ spiroketalization. In turn, **37** could be accessed from an aryllithium addition of bromide **38** to aldehyde **39**. Disconnection of **39** through an *anti*-selective aldol addition leads to aldehyde **40** and an appropriate chiral auxiliary **41**.



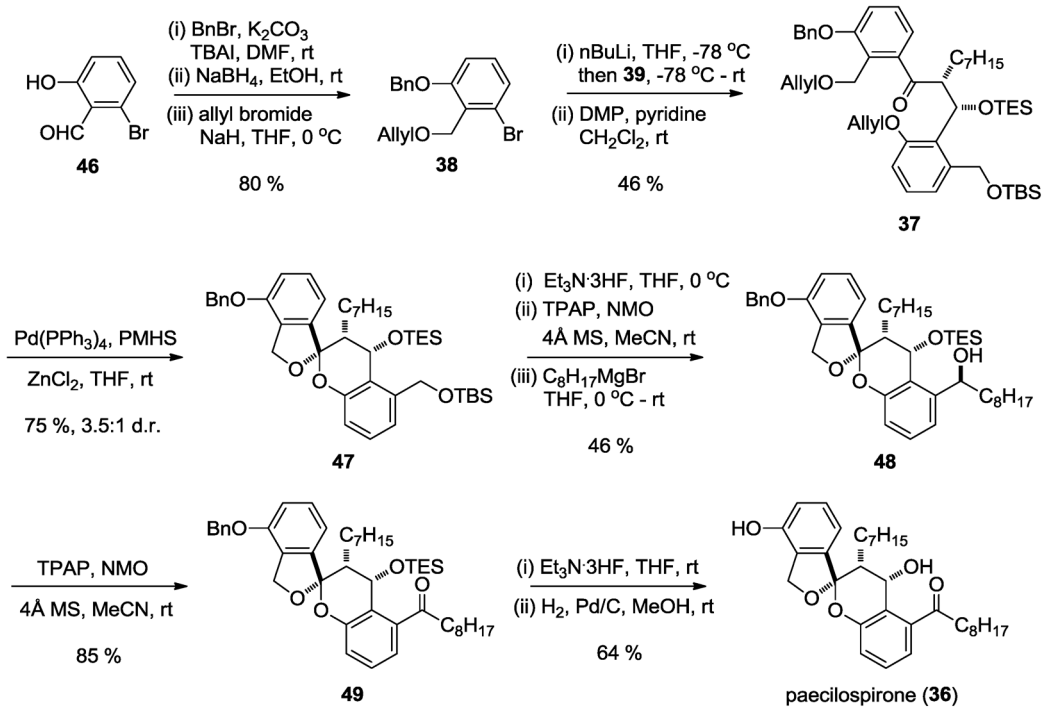
Scheme 9 Retrosynthesis of paecilospirone.

Our approach to aldehyde **39** commenced with the allyl protection of known phenol **42** [28], followed by reduction of the aldehyde with sodium borohydride (Scheme 10). The resulting alcohol **43** was protected as its *tert*-butyldimethylsilyl (TBS) ether, which was subjected to a lithium-halogen exchange/formylation procedure to afford aldol precursor **40**. The *anti*-aldol reaction was found to proceed in the highest yields by the use of the lactate-derived CH(OBz)Me auxiliary. Accordingly, the addition of aldehyde **40** to the boron enolate of ketone **44** provided aldol product **45** in good yield, as an inseparable 3:1 mixture of diastereoisomers. Protection of the secondary alcohol with triethylsilyl trifluoromethanesulfonate (TESOTf) allowed separation of the diastereoisomers by chromatography. The absolute stereochemistry of **45** was unambiguously determined by X-ray crystallography of a derivative [29]. Reduction of the benzoate ester with $LiBH_4$ followed by oxidative cleavage of the resulting glycol provided aldehyde **39** as the single (4*R*,5*S*) isomer.



Scheme 10 Synthesis of aldehyde **39**.

Known benzaldehyde **46** [30], readily synthesized from salicylaldehyde, was converted into bromide **38** in three steps (Scheme 11). Benzyl protection of the phenol, followed by reduction of the aldehyde and allylation of the resulting alcohol provided **38** in good yield. Lithium-halogen exchange of bromide **38** by treatment with *n*BuLi and subsequent addition to aldehyde **39** afforded the corresponding alcohol in moderate yield. Attempts to improve the yield of the coupling by the use of *t*BuLi were unsuccessful, resulting in the partial cleavage of the phenolic allyl ether. Oxidation of the resulting alcohol with DMP provided ketone **37**. The stage was then set for the key pH-neutral spiroketalization step. Pleasingly, treatment of **37** with Pd^0 and PMHS-$ZnCl_2$ resulted in smooth deallylation/spiroketalization to afford **47** in good yield as an inseparable 3.5:1 mixture of diastereoisomers, with no dehydration products observed. The major diastereoisomer was determined to be the anomerically stabilized isomer by analysis of nOe interactions. The required C_8 alkyl chain was introduced by selective deprotection of the primary TBS ether, followed by oxidation of the resulting alcohol with tetrapropylammonium perruthenate (TPAP) and Grignard addition of octyl magnesium bromide to afford alcohol **48**. At this point, the two anomeric diastereoisomers were readily separable by chromatography. The major isomer was then converted to paecilospirone (**36**) by oxidation of the benzylic alcohol and stepwise deprotection of the benzyl and triethylsilyl (TES) ethers. This route represents the first reported total synthesis of paecilospirone (**36**), and one that is scalable and highly amenable to the production of analogues for future biological investigations.



Scheme 11 Synthesis of bromide **38** and completion of total synthesis.

CONCLUSIONS

The strategies employed toward the synthesis of three spiroketal natural products, γ-rubromycin, paecilospirone, and berkelic acid, have been described. The spiroketal moiety was introduced at a late stage in the synthesis of all three compounds, by deprotection of a ketone containing two appropriately protected OH groups. Three varied strategies were employed for the preparation of each of the three spiroketal precursors, namely, use of a Sonogashira coupling, aryllithium addition, and an HWE/oxa-M cascade for the syntheses of γ-rubromycin, paecilospirone, and berkelic acid, respectively.

ACKNOWLEDGMENTS

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