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Two-step, high-yielding total synthesis of antibiotic pyrones†

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A simple two-step dialkylation protocol was developed to synthesize biologically active antibiotics photopyrones, pseudopyronines, and violapyrones from bio-renewable triacetate lactone in excellent yields. These pyrones are functionally modified into another set of pyrone natural products by a single *O*-methylation reaction. The high-yielding gram scale synthesis of four natural products [pseudopyronine A, photopyrone A, pseudopyronine B and photopyrone C] demonstrated the viability for industrial applications.

Introduction

When we delve into nature's chemistry, we see several exciting chemical scaffolds, designed by a sequence of reactions catalysed by enzymes. For instance, polyketides, active metabolites synthesized by fungi, bacteria, plants and animals through various metabolic pathways,[1] display a wide range of biological activities such as antiviral, antibiotic, antibacterial, antifungal, and antineoplastic properties. A plethora of interesting polyketides engineered by polyketide synthases, typically by sequential decarboxylative Claisen condensation reactions, produce α-pyrones, especially 3,6-dialkyl-2*H*-pyran-2-ones, which are inclusive structures of different classes of natural products.[2] Hence, a myriad of attempts are being made to synthesize them either by chemical methods or by generating bio-catalytic pathways owing to their exciting activities (Fig. 1).

Among them, photopyrones have a unique ability to work as cell signalling molecules in bacteria enabling communication among them and thereby mediating a group-coordinated behaviour. This phenomenon, known as quorum sensing,[3] enables them to interact with other species and regulate phenotypic behaviour such as virulence factor secretion, competence, bioluminescence, swarming motility, sporulation, and biofilm formation. Moreover, α-pyrones show an extensive range of biological activities, *e.g.* violapyrones[4] present anti-H1N1, anti-H3N2, anticancer, antiviral, and antibacterial activities; pseudopyronines[5] show antibiotic, algicidal, anti-atherosclerosis, and anti-tubercular activities; fistupyrone[6] has antifungal activity; germicidin[7] shows antibiotic activity and so on (Fig. 1).

Although the metabolic pathway enables the synthesis of a diverse range of 3,6-dialkyl-2*H*-pyran-2-ones, their laboratory synthesis is highly challenging owing to the lack of an operationally simple route to access them. Therefore, a simple one-pot method that generates a vast library of different α-pyrones smoothly is highly desired. Herein, we want to develop a common method to synthesize 3,6-dialkyl-2*H*-pyran-2-ones, as the known target-oriented methods suffer from drawbacks

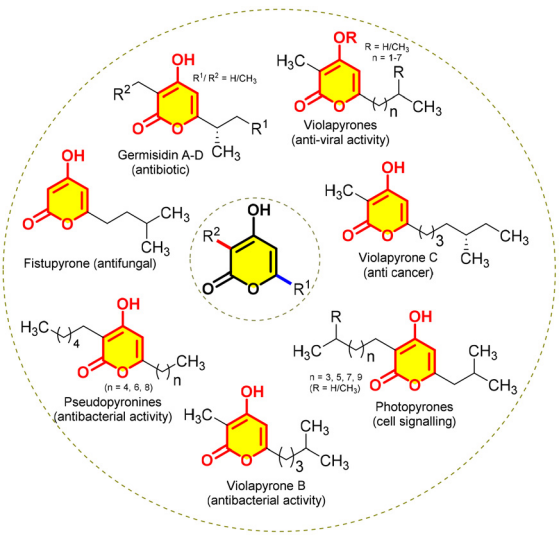

Fig. 1 4-Hydroxy-2*H*-pyran-2-one-containing natural products.

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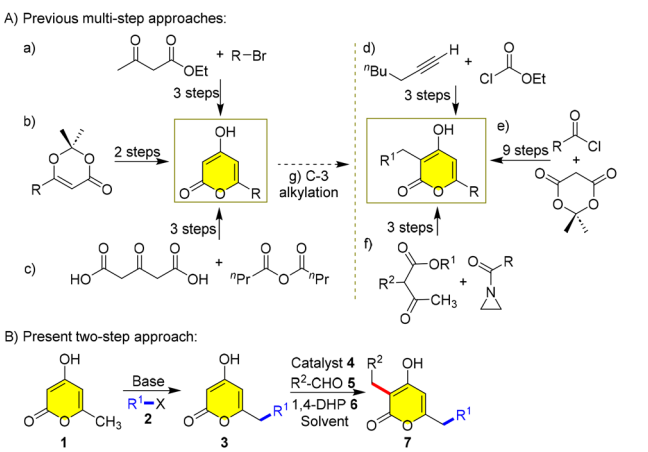
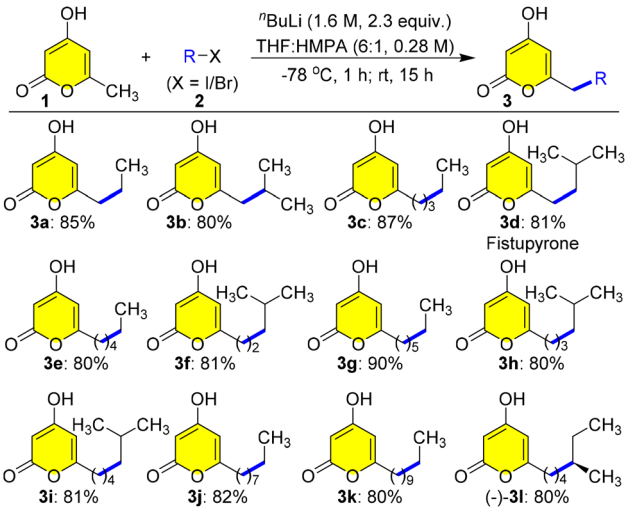
such as a large number of steps, low overall yields, extreme conditions, use of sensitive reagents, non-availability of starting materials and absence of cost-effectiveness (Scheme 1A).[8–14]

Herein, we envision to synthesize 3,6-dialkyl-2*H*-α-pyrones by a protection-free two-step dialkylation, starting from the triacetate lactone **1** (Scheme 1B). In the first step, an electrophilic substitution at the *C*-7 position of **1** with alkyl halide **2** through base-mediated dienolate occurs to generate **3**. And then, Ramachary reductive *C*-alkylation of **3** with aldehyde **5**, 1,4-DHP **6** and amine **4** catalyst affords *C*-3 alkylated products **7**. Although this strategy was used by Kraus *et al.* previously for synthesizing photopyrone A, they have not elaborately screened the conditions, as indicated by their low overall yield[14] and incomplete understanding of substrate scope, and the synthesis of only one derivative has made it worthwhile for us to revisit the screening of both *C*-7 and *C*-3 alkylations to exemplify the importance of this protocol and synthesize for the first time various natural pyrones and analogues **7** (Scheme 1B).



Scheme 1 Previous and present strategies for the synthesis of 3,6-dialkyl-2*H*-pyrones.



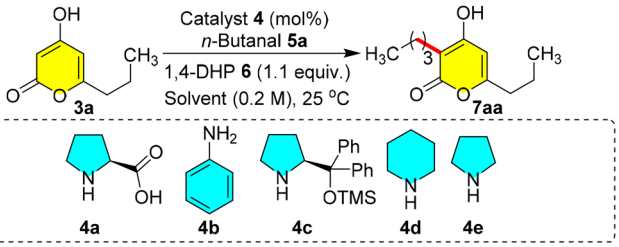
Scheme 2 Synthesis of 7-alkyl-4-hydroxy-2*H*-pyran-2-ones **3** from triacetate lactone **1**. Reaction conditions: the reaction mixture of **1** (5.0 mmol) in THF/HMPA (6 : 1, 17.5 mL) with ⁿBuLi (1.6 M, 2.3 equiv.) at −78 °C was stirred for 1 h before addition of alkyl halide **2a–l** (2.0 equiv.) followed by stirring at rt for 15 h. Yields refer to the column purified products.

Results and discussion

Hence, our investigation of the three-component Ramachary reductive *C*-alkylation commenced,[15] after synthesizing a library of *C*-7 alkylated products **3** from the commercially available triacetate lactone **1** with various aliphatic alkyl iodides or bromides **2** as starting materials using modified Hsung's protocol in very good to excellent yields (Scheme 2).[16] First, *C*-7 alkylation was performed by addition of ⁿBuLi at −78 °C to **1** in THF and HMPA (6 : 1) followed by addition of ethyl iodide **2a**, and stirring at 25 °C for 15 h gave the desired selective *C*-7 alkylated pyrone **3a** in a very good yield of 85% (Scheme 2). Further we tested the feasibility of this protection-free selective alkylation protocol by choosing different aliphatic alkyl halides **2b** to (−)-**2l** having linear and branched chains to generate a library of pyrones **3b** to (−)-**3l** in very good yields owing to the exciting finding of these structures in bioactive natural product synthesis (Scheme 2). Astonishingly, fistupyrone **3d**, isolated from Streptomyces sp. TP-A0569,[6] was synthesized from **1** and isobutyl iodide **2d** in a single step. It is an antifungal agent that inhibits spore germination in the infection of Chinese cabbage by *Alternaria brassicicola*, the cause of leaf spot disease in cabbage,[6] highlighting the importance of this regioselective *C*-7 alkylation protocol.

We commenced the optimization of *C*-3 alkylation through reductive coupling using pyrone **3a** and *n*-butanal **5a** as coupling partners. When **3a** (0.2 mmol) was reacted with **5a** and diethyl 1,4-dihydropyridine dicarboxylate (1,4-DHP) **6** in the presence of proline **4a** (10 mol%) in EtOH (0.2 M) at 25 °C, an enthralling yield of 86% of **7aa** was observed in 12 h (entry 1, Table 1). Furthermore, when we carried out the same reaction in a polar aprotic solvent such as DMSO (0.2 M), the reaction did not endure well, even after stirring for 24 h, producing only 46% yield of **7aa** (entry 2, Table 1), but with chloroform and acetonitrile, there is a sharp increase in the yield to 93% and 95%, respectively, within 1.0 h (entries 3 and 4, Table 1). The reaction in THF also produced a high yield of 91% in 2.0 h (entry 5, Table 1). Similarly, when DCE and DCM were tried, 86% and 97% yields of **7aa** were obtained, respectively, within 1.0 h (entries 6 and 7, Table 1). Based on these reactions, we concluded that polar aprotic solvents such as DCM/acetonitrile/chloroform are the most suitable solvents for **7aa** without any side reactions. Changing the equivalence of **5a** from 1.2 to 1.3 improved the yield slightly to 98% (entry 8, Table 1). And then a decrease in the equivalence of **5a** from 1.2 to 1.0 showed a decrease in the yield from 97% to 84% (entry 9), and similarly decreasing the catalyst loading from 10 mol% to 5 mol% also showed a slight reduction in the yield to 93%

Table 1 Reaction optimization[a]



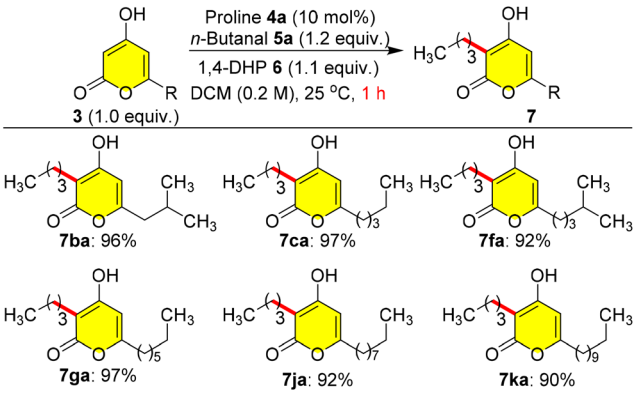
Entry	3a (equiv.)	5a (equiv.)	4 (10 mol%)	Solvent (0.2 M)	*t* (h)	7aa yield (%)
1	1	1.2	**4a**	EtOH	12	86
2	1	1.2	**4a**	DMSO	24	46
3	1	1.2	**4a**	$CHCl_3$	1	93
4	1	1.2	**4a**	CH_3CN	1	95
5	1	1.2	**4a**	THF	2	91
6	1	1.2	**4a**	DCE	1	86
7	**1**	**1.2**	**4a**	**DCM**	**1**	**97**
8	1	1.3	**4a**	DCM	1	98
9	1	1.0	**4a**	DCM	1	84
10[b]	1	1.2	**4a**	DCM	1	93
11	1	1.2	**4b**	DCM	1	87
12	1	1.2	**4c**	DCM	6	60
13	1	1.2	**4d**/AcOH (1 : 1)	DCM	1	88
14	1	1.2	**4e**/AcOH (1 : 1)	DCM	1	48

[a] Reactions were carried out in solvent (1.0 mL, 0.2 M) with 1.2 equiv. of **5a** (0.24 mmol) and 1.1 equiv. of **6** (0.22 mmol) relative to **3a** (0.2 mmol) in the presence of 10 mol% of **4**, and yields refer to the column-purified products. [b] 5 mol% of catalyst **4a** was used.

(entry 10, Table 1). We further screened various catalysts such as primary and secondary amines. In the case of aniline **4b**, the reaction was well tolerated with 87% yield, and with DPPOTMS **4c**, we could notice a sharp plummet in the yield to 60% in 6 h (entries 11 and 12, Table 1). The use of piperidine **4d** and pyrrolidine **4e** along with co-catalyst acetic acid could not give any betterment compared to **4a** (entries 13 and 14, Table 1). Therefore, 10 mol% of proline **4a** was the most suitable catalyst for the promotion of olefination compared to other amines **4b–4e** whose reactivity was high, resulting in self-aldol reactions of aldehydes rather than the olefination. With the suitable catalytic conditions for selective *C*-3 reductive alkylation, we endeavoured to address the scope of this one-pot method for various other derivatives.

As a model study, first we investigated the role of alkyl chain lengths at the *C*-6 position of **3** in the reductive coupling using *n*-butanal **5a** as a coupling partner in *C*-3 alkylation. Initially, a **4a**-catalysed reaction of **3b** with **5a** was performed using **6** as a reducing source at 25 °C in DCM (0.2 M), which give **7ba** in excellent yield (96%) within 1.0 h (Scheme 3). When we tried the catalytic **5a** reaction with other pyrones containing various *C*-6 alkyl groups such as **3c**, **3f**, **3g**, **3j** and **3k**, the reaction gave extremely good yields (90–97%) of natural pyrone analogues **7ca**, **7fa**, **7ga**, **7ja** and **7ka** at 25 °C within 1.0 h without any steric factors of *C*-6 alkyl groups (Scheme 3).

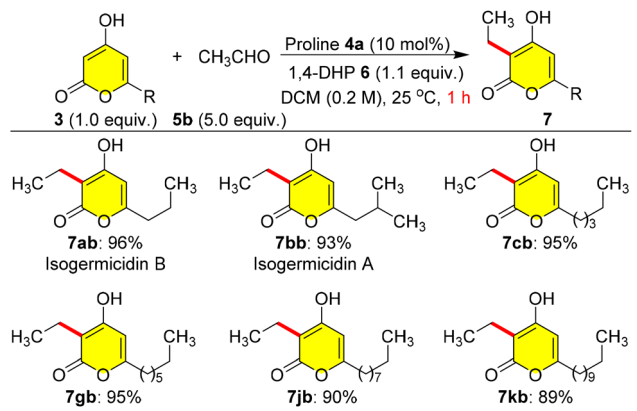
Furthermore, the sensitivity of the reaction was tested using volatile acetaldehyde **5b** as a coupling partner with various *C*-6



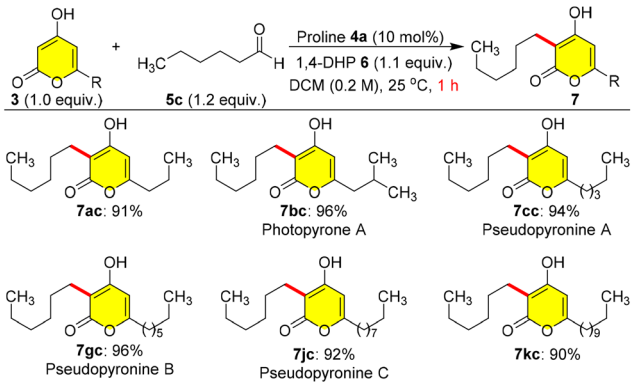
Scheme 3 Synthesis of photopyrone analogues.

alkylated pyrones **3a–k**; here we used 5.0 equiv. of **5b** due to the volatile nature, and the reaction endured well with yields of **7ab–7kb** ranging from 89 to 96% within 1.0 h at 25 °C (Scheme 4). Inadvertently, we ended up synthesizing isogermicidin A (**7bb**) and isogermicidin B (**7ab**), two natural products isolated from the fermentation broth of marine derived *Streptomyces* sp. MDW-06,[7] as a first total synthesis highlighting the efficiency of this coupling protocol.

After these studies, we attempted to use *n*-hexanal **5c** as an appropriate coupling partner with **3** for the synthesis of pseudopyronine and photopyrone natural products (Scheme 5). Therefore, we carried out a coupling reaction between **3a** and **5c** under the optimized conditions to synthesize the photopyrone A analogue **7ac** in 91% yield within 1.0 h. Interestingly, when **3b** was reductively coupled with **5c**, we could obtain photopyrone A **7bc** in 96% yield at 25 °C in 1.0 h. In a similar manner, we synthesized pseudopyronine A **7cc** by coupling **3c** with **5c** in 94% yield, pseudopyronine B **7gc** using **3g** and **5c** in 96% yield, pseudopyronine C **7jc** by coupling **3j** and **5c** in 92% yield, and the pseudopyronine C analogue **7kc** by coupling **3k** and **5c** in 90% yield (Scheme 5). Photopyrone A **7bc** is a cell signalling molecule isolated from *Photorhabdus luminescens*, and pseudopyronines A–C were first isolated from



Scheme 4 Synthesis of isogermicidin A, isogermicidin B and analogues.

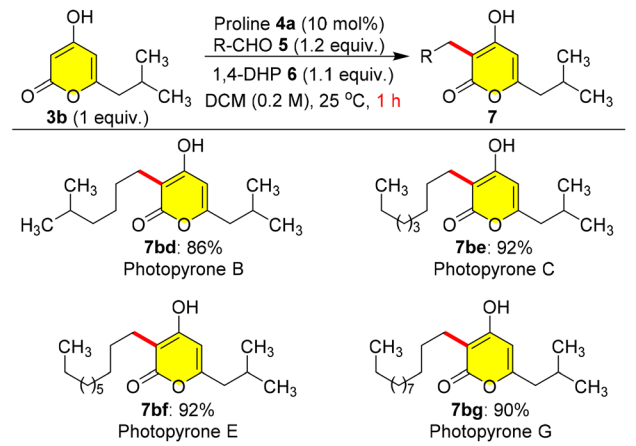


Scheme 5 Total synthesis of pseudopyronines and photopyrones.

Pseudomonas fluorescens and they showed interesting biological activities.[3,5]

As there were no earlier reports on methods for the total synthesis of photopyrones, herein we endeavoured to synthesize cell signalling natural products in high yields (Scheme 6). Hence, we employed pyrone **3b** as a coupling partner, and treated it with different branched and long chain aliphatic aldehydes such as **5d**, **5e**, **5f**, and **5g** which furnished the corresponding natural products photopyrone B **7bd**, photopyrone C **7be**, photopyrone E **7bf**, and photopyrone G **7bg** in excellent yields ranging from 86% to 92% within 1.0 h at 25 °C (Scheme 6).

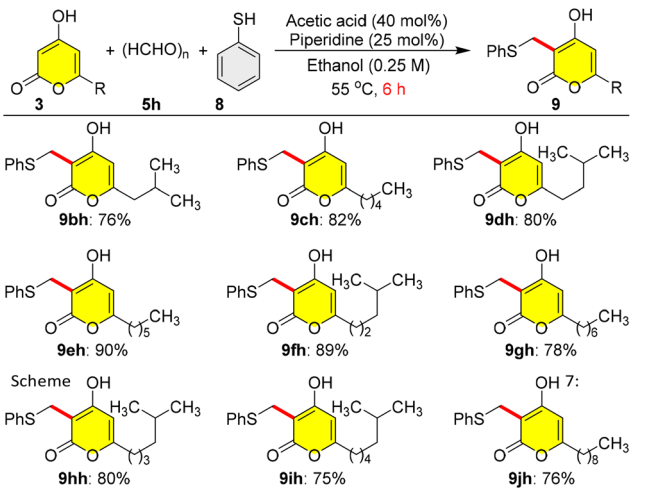
After the successful synthesis of photopyrones and pseudopyronines, we planned to synthesize violapyrones, a similar class of natural products having exciting pharmacological activities. Violapyrones are 4-hydroxy-2*H*-α-pyrones having a methyl group at *C*-3 and alkyl chains at *C*-6. At this juncture, we encountered an obstacle in our design, as our direct **4a**-catalysed reductive *C*-3 alkylation of the pyrones **3** failed when employing formaldehyde **5h** as a coupling partner and 1,4-DHP **6** as a hydrogen source, due to many side reactions. In order to address this drawback, we employed another three-component organocatalytic reaction,[17] where thiophenol **8** was



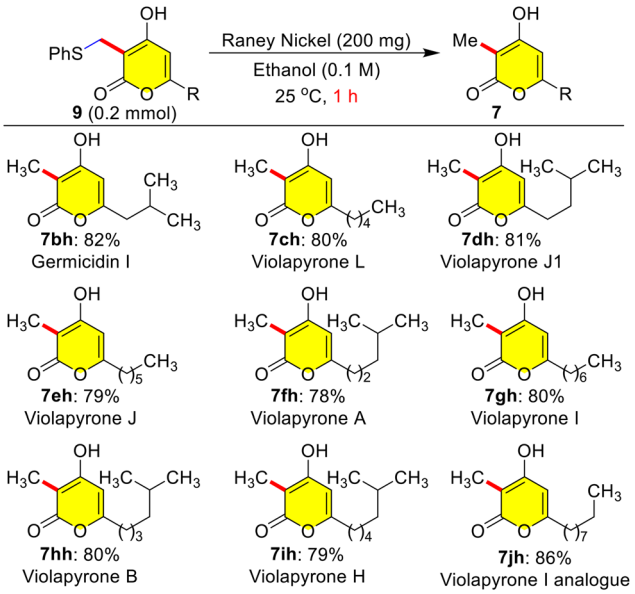
Scheme 6 Total synthesis of photopyrones B-G.

used to mask the *in situ* formed olefin from the reaction of pyrone **3** with paraformaldehyde **5h** under piperidine/acetic acid-catalysis in ethanol at 55 °C for 6 h, which gave phenyl sulfide masked violapyrones **9** in very good yields (Scheme 7). Interestingly, the three-component reaction of pyrone **3b** with paraformaldehyde **5h** and thiophenol **8** under the catalysis of proline **4a** (10 mol%) or piperidine/acetic acid in DCM (0.25 M) at 25 °C for 6 h furnished the expected phenyl sulfide masked germicidin-I **9bh** in only <7% yield; but the same piperidine/acetic acid-catalysed reaction at 55 °C in a sealed tube for 6 h furnished **9bh** in moderate (31%) yield (results not shown in Scheme 7). In a further development, the three-component organocatalytic reaction of pyrone **3b** with paraformaldehyde **5h** and thiophenol **8** under the catalysis of piperidine/acetic acid in ethanol at 55 °C for 6 h furnished the phenyl sulfide masked germicidin-I **9bh** in 76% yield (Scheme 7). A protic polar (EtOH) solvent at 55 °C induced the three-component reaction rate in a better manner than an aprotic polar (DCM) solvent at 25 °C. In a similar manner, a series of different *C*-6 alkylated pyrones **3** having varied linear and branched alkyl chains were employed in the three-component organocatalytic reaction to synthesize the phenyl sulfide masked violapyrones **9ch** to **9jh** in very good yields within 6 h as shown in Scheme 7.

Masked violapyrones **9bh–9jh** were converted into natural violapyrones **7bh–7jh** by single transformation as first total synthesis. When we treated phenyl sulfide masked **9bh** (0.2 mmol) with freshly prepared RANEY®-nickel (200 mg) in ethanol at 25 °C for 1.0 h, the germicidin I **7bh** was furnished in 82% yield (Scheme 8).[7] In a similar manner, treatment of other masked violapyrones **9ch–9jh** with RANEY®-nickel at 25 °C for 1.0 h furnished the following medicinally important



Scheme 7 Synthesis of methyl-masked violapyrones **9** *via* three-component *C*-3 alkylation of pyrones **3** with paraformaldehyde **5h** and thiophenol **8**. Reaction conditions: reactions were carried out by dissolving **3** (0.5 mmol) in ethanol (1.0 mL) and adding this solution to a mixture of 1.0 equiv. of **5h** (0.5 mmol), 3.0 equiv. of **8** (1.5 mmol), 40 mol% of acetic acid, and 25 mol% of piperidine in ethanol (1.0 mL) at 55 °C and stirring for 6 h. Yields refer to the column-purified products.

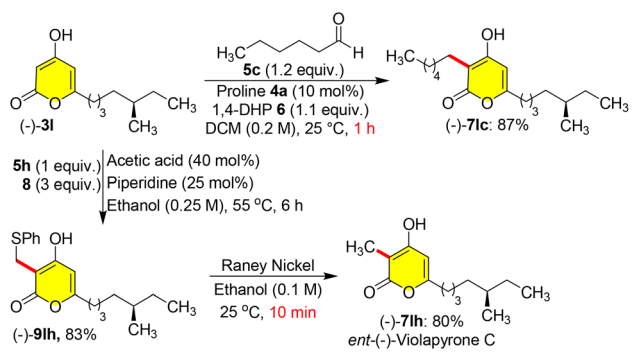


Scheme 8 Total synthesis of violapyrones A–L.

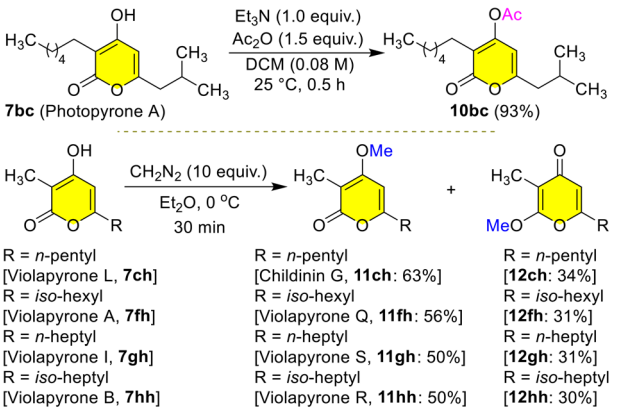
violapyrones (VLPs): VLP-A **7fh** in 78%, VLP-B **7hh** in 80%, VLP-I **7gh** in 80%, VLP-J **7eh** in 79%, VLP-J1 **7dh** in 81%, VLP-H **7ih** in 79%, and VLP-L **7ch** in 80% yields (Scheme 8).[4] With this impetus, we further showed interest to synthesize chiral *ent*-(−)-violapyrone C and its analogue. Natural (+)-violapyrone C was isolated from the mass culture of an actinomycete, *Streptomyces* sp. 112CH148,[18] and is known to possess cytotoxicity against a panel of six human tumor cell lines and has an inhibitory effect on the HIF (hypoxia-inducible factor) pathway, which is related to tumor progression, invasion, and metastasis.[19] Therefore, we ventured on a route to synthesize *ent*-(−)-violapyrone C starting from (*S*)-(−)-citronellal, a commercially available starting material, which was transformed into the chiral pyrone (−)-**3l** in 8 steps with 25% overall yield (Scheme S1, see the ESI†). Chiral pyrone (−)-**3l** was then employed in a catalytic reductive *C*-3 alkylation with *n*-hexanal **5c** and 1,4-DHP **6** to synthesize the violapyrone derivative (−)-**7lc** in 87% yield (Scheme 9). Similarly, sulphur masked three-component methylation of (−)-**3l** was performed to obtain (−)-**9lh**, followed by its desulfurization with freshly prepared RANEY®-nickel, which furnished the opposite enantiomer (−)-violapyrone C (−)-**7lh** in 80% yield (Scheme 9).

With further applications in mind, we transformed the natural products 7 into another set of natural products **10–12** by simple acetylation/methylation (Scheme 10). The reaction of photopyrone A **7bc** with Ac_2O in DCM at 25 °C for 0.5 h gave the protected photopyrone A **10bc** in 93% yield. Interestingly, the reaction of violapyrone L **7ch** with ethereal diazomethane at 0 °C for 30 min gave the α-pyrone childinin G[20] **11ch** in 63% yield as a major product and γ-pyrone **12ch** in 34% yield as a minor product. Childinins are natural products isolated from the fruiting bodies of *Daldinia childiae*. Similarly, treatment of violapyrones VLP-A **7fh**, VLP-I **7gh** and VLP-B **7hh** with ethereal diazomethane at 0 °C for 30 min gave the α-pyrones VLP-Q **11fh** in 56%, VLP-S **11gh** in 50%, and VLP-R **11hh** in 50% yields as major products and γ-pyrones **12fh** in 31%, **12gh** in 31%, and **12hh** in 30% yields as minor products, respectively (Scheme 10). These α- and γ-pyrones **11**/**12** are well separated and differences in their carbonyl peaks in ^{13}C NMR clearly evidence the structural differences between them (see the ESI† for more information). A simple *O*-methylation of 7 unveiled the synthesis of two distinct classes of natural products α- and γ-pyrones **11**/**12** highlighting the potential of the present protocol (Scheme 10).

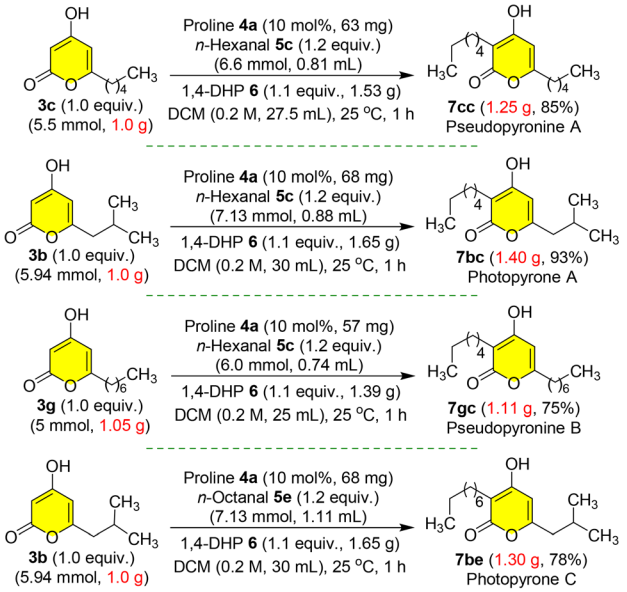
Furthermore, to demonstrate the robustness of our protection-free total synthesis,[21] we performed the gram scale synthesis of four natural products pseudopyronine A **7cc**, photopyrone A **7bc**, pseudopyronine B **7gc** and photopyrone C **7be** with very good overall yields from the corresponding starting materials pyrones **3b**, **3c** or **3g** and *n*-hexanal **5c** or *n*-octanal **5e** (Scheme 11). In these organocatalytic reductive *C*-3 alkylation steps, it was feasible to obtain the final natural products **7cc**, **7bc**, **7gc** and **7be** as fine off-white solids by simple filtration after washing the reaction mixture with hexanes to get rid of the side products without column purification (Fig. S2, see the ESI†).



Scheme 9 Total synthesis of (−)-violapyrone C and its analogue.



Scheme 10 Total synthesis of childinin G and violapyrones Q–S.



Scheme 11 Gram-scale synthesis of pyrones.

Conclusions

In summary, a two-step, *C*-dialkylation strategy was developed for the construction of a library of natural products of pseudopyronines, photopyrones, violapyrones and their analogues in a highly selective manner with excellent yields. A single *O*-methylation reaction was revealed for the synthesis of 4-methoxy-2*H*-α-pyrones and 2-methoxy-4*H*-γ-pyrones covering a colossal niche of natural products, showing extraordinary biological properties. The gram scale synthesis of four natural products demonstrated the method's viability for industrial applications. A study of systematic screening of structure activity relationships (SAR) of the synthesized molecules to reveal their biological properties is under progress.

Data availability

General information, experimental procedures, and characterization data of all new compounds, correlation data of synthetic compounds with natural products and NMR spectra are provided in the ESI.† Data for the crystal structures reported in this paper have been deposited at the Cambridge Crystallographic Data Center (CCDC) under the deposition numbers CCDC 2292620 (**7bb**), CCDC 2292621 (**7bc**), and CCDC 2292622 (**7jb**).

Author contributions

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

Conflicts of interest

There are no conflicts to declare.

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