Naturally Occurring Prenylated Phthalides: First Total Synthesis of Salfredin B_{11}

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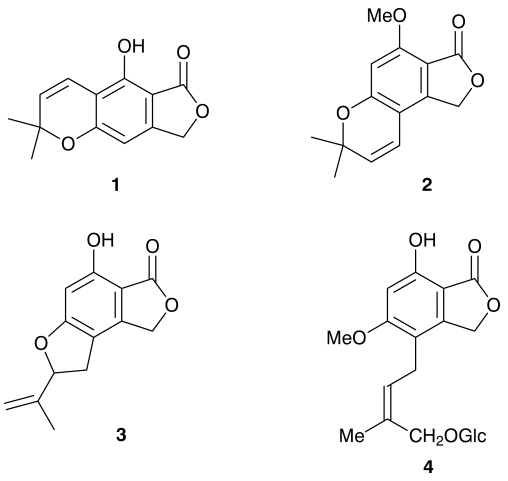
Convenient syntheses of salfredin B_{11} (**1**) and dihydrophthalidochromene (**14b**), from hydroxyphthalides (**7** and **10**), are described.

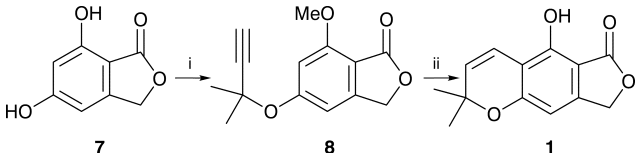
A few prenylated phthalides and their derivatives have been reported from natural sources. Salfredin B_{11} (**1**), for example, has been isolated[1] from the fermentation broth of *Crucibulum sp*. RF-3817, and phthalidochromene[2] (**2**) and platypterophthalide[2] (**3**) from the roots of *Helichrysum platypterum*. Another prenylated phthalide arenophthalide A (**4**), has been reported from the roots of *H. arenarium*.[3] These prenylated phthalides are valuable as they possess significant biological activities. Thus salfredin B_{11} (**1**) has aldose reductase inhibitor activity,[1,5] while arenophthalide A (**4**) has antibacterial properties.[3]



The syntheses of salfredin B_{11} (**1**) and phthalidochromene (**2**) have not been reported so far in the literature. In view of the impressive biological activities exhibited by prenylated phthalides, in general, and salfredin B_{11} (**1**) and phthalidochromene (**2**), in particular, it was decided to develop convenient methods for their syntheses.

The present approach developed for the synthesis of salfredin B_{11} (**1**), is depicted in Scheme 1. The dihydroxyphthalide **7** was monoprop-2-ynylated using 3-chloro-3-methylbut-1-yne in DMF solution in the presence of K_2CO_3, KI and CuI at 60 °C to give the prop-2-ynyl ether **8**. The ether **8**, on heating in *N*,*N*-dimethylaniline solution at 210 °C, provided salfredin B_{11} (**1**), in 62% yield. The yield of **1** was improved to 82% when the reaction was carried out under microwave irradiation (MWI) for 3 min. The IR and NMR spectral properties exhibited by compound **1** are identical with those of natural salfredin B_{11}.

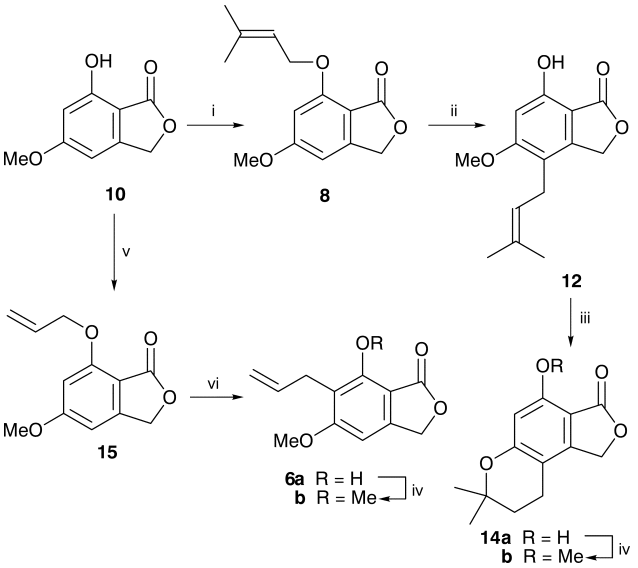
The approach developed for the synthesis of dihydrophthalidochromene (**14b**) is shown in Scheme 2. 7-Hydroxy-5-methoxyphthalide[7] (**10**), on prenylation using 4-bromo-2-methylbut-2-ene, in DMF solution, gave the prenyl ether **11** in 92% yield. The prenyl ether **11** on heating in *N*,*N*-dimethylaniline at 210 °C for 22 h, gave the 4-prenylphthalide (**12**) in 61% yield, which on reaction with pyridine hydrochloride at 180 °C for 1 h provided the dihydropyranophthalide (**14a**) in 53% yield. Methylation of **14a**, using methyl iodide, furnished the dihydrophthalidochromene **14b** in 85% yield.



Scheme 1 *Reagents and conditions*: i, 3-chloro-3-methylbut-1-yne, K_2CO_3, KI, CuI, DMF, 60 °C, 4 h; ii, $PhNMe_2$, 210 °C, 6 h or MWI, 3 min

The synthesis of 6-allyl-5,7-dimethoxyphthalide (**6b**) has also been achieved as shown in Scheme 2. When the allyloxy phthalide **15**, obtained in 92% yield by allylation of **10**, was heated at 210 °C, in *N*,*N*-dimethylaniline solution for 4 h, 6-allyl-7-hydroxy-5-methoxyphthalide (**6a**) was obtained in 82% yield. The methylation of **6a** to obtain **6b** was achieved using methyl iodide. 6-Allyl-5,7-dimethoxyphthalide (**6b**), an intermediate used for the synthesis of hericenone A analogues (**5b**), has been synthesized earlier[6] using a multistep reaction sequence. In the present work its synthesis has been achieved in three steps from the phthalide **10** (Scheme 2).

In conclusion, the present paper describes convenient methods for the syntheses of salfredin B_{11} (**1**), dihydrophthalidochromene (**14b**) and 6-allyl-5,7-dimethoxyphthalide (**6b**), which is a useful intermediate for hericenone **A** analogues.



Scheme 2 *Reagents and conditions:* i, 4-bromo-2-methylbut-2-ene, K_2CO_3, DMF, room temp. 6 h; ii, $PhNMe_2$, 210 °C, 22 h or MWI, 11 min; iii, Py–HCl, 180 °C, 1 h; iv, MeI, K_2CO_3, DMF, room temp., 1 h; v, 3-bromopropene, K_2CO_3, DMF, room temp., 6 h; vi, $PhNMe_2$, 210 °C, 6 h

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Techniques used: IR, ^{1}H NMR, elemental analyses, TLC and column chromatography

References: 10

Figures: 3

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References cited in this synopsis

1 K. Matosumoto, K. Nagashima, T. Kamigauchi, Y. Kawamura, Y. Yasuda, K. Ishii, N. Uotani, T. Sato, H. Nakai, Y. Terui, J. Kikuchi, Y. Ikenisi, T. Yoshida, T. Kato and H. Itazaki, *J. Antibiot*., 1995, **48**, 439.
2 J. Jakupovic, A. Schuster, H. Sun, F. Bohlmann and D. S. Bhakuni, *Phytochemistry*, 1987, **26**, 580.
3 J. Vrkoc, M. Budesinsky, L. Dolejs and S. Vasickova, *Phytochemistry*, 1975, **14**, 1845.
5 (*a*) M. Nishikawa, Y. Turumi, H. Murai, K. Yoshida, M. Okamoto, S. Takase, H. Tanaka, H. Hirota, M. Hashimoto and M. Kohsaka, *J. Antibiot*., 1991, **44**, 130; (*b*) K. Ozasa, T. Oneda, M. Hirasawa, K. Suzuki, K. Tanaka, S. Kadota and M. Iwanami, *J. Antibiot*., 1991, **44**, 768.
6 A. V. Rama and R. G. Reddy, *Tetrahedron Lett*., 1992, **31**, 373.
7 R. S. Mali, P. G. Jagtap and S. G. Tilve, *Synth. Commun*., 1990, **20**, 2841.