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A Short and Efficient Total Synthesis of (±)-Ascofuranone

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Ascofuranone is a potent inhibitor of trypanosome alternative oxidase. A short and efficient total synthesis of (±)-ascofuranone was accomplished in only seven steps starting with geranyl acetate. The synthetic concept and methodology described in detail here provide a short and simple synthesis for ascofuranone and its derivatives.

Ascofuranone (**1**), one of many natural phenolic compounds[1] in the fungus *Ascochyta viciae*, was first isolated in 1972 (Figure 1).[2] It has received considerable attention because of its biological activity as an antitumor protective,[3] hypolipidemic,[4] and differentiation-inducing agent.[5] In addition, Kita et al. recently found that ascofuranone is potentially a strong inhibitor of trypanosome alternative oxidase (TAO).[6] TAO is a terminal oxidase in the unique respiratory system of African trypanosomes. These protozoan parasites cause African trypanosomiasis in human and animals, and are transmitted by tsetse flies. Since TAO is specific to the African trypanosomes and does not exist in mammalian hosts, it is a potent target for chemotherapy of trypanosomiasis by ascofuranones. This necessitates the development of a shorter and simpler synthesis of ascofuranone than our previous synthesis.

To date, several synthetic methods have been reported for ascofuranone. However, these methods are somewhat complicated and involve multiple steps.[7] We have previously reported a 12-step synthesis for (±)-ascofuranone and related compounds.[8] For convergent synthesis of (±)-ascofuranone, it is rational to split the compound into the aromatic ring and prenyl side chains. Consequently, to achieve total synthesis of ascofuranone, the aromatic moiety needs to be connected to the prenyl side chain, with or without phenolic protection. In our previous synthesis, for the aromatic moiety we employed a resorcinol derivative with an ester group, and hydroxy groups protected by 2-(trimethylsilyl)ethoxymethyl (SEM).[8b] Protection–deprotection of the phenolic hydroxys and transformation of the ester group into the formyl group hampered the synthetic efficiency. In this study, we have reduced the protection and deprotection protocols in our synthetic strategy in view of improving the synthetic efficiency. Herein, we report the details of a short and simple total synthesis of (±)-ascofuranone.

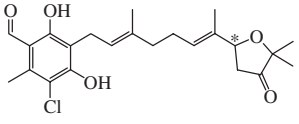
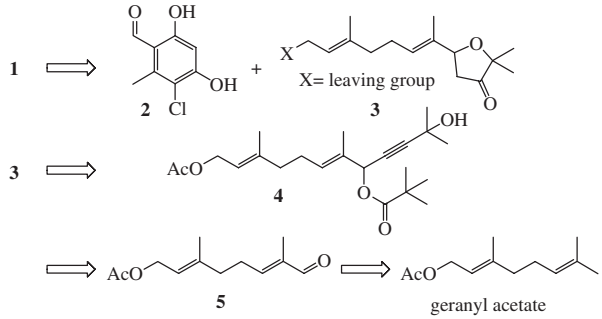
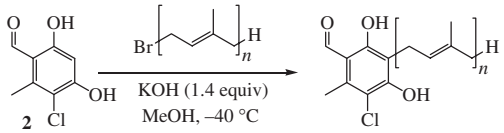


Figure 1. Structure of (±)-ascofuranone (**1**).



Scheme 1. Retrosynthetic analysis of (±)-ascofuranone (**1**).

Table 1. Direct coupling of phenol derivatives **2** with allyl bromides[a]

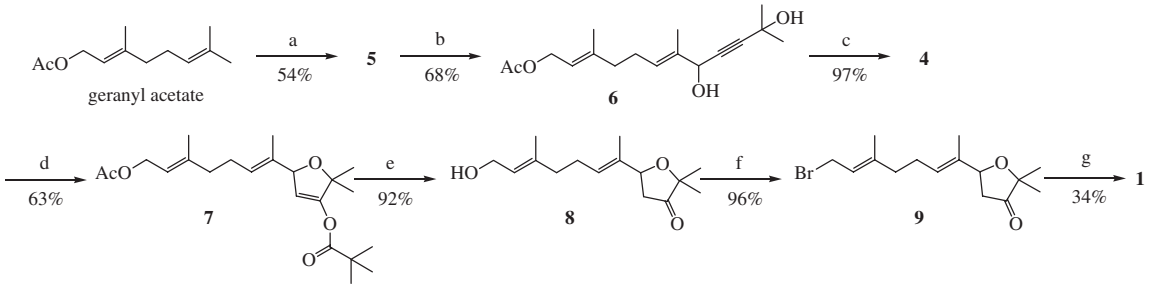


Entry	*n*	Additives	Yield/%[b]
1	2	—	28
2	2	$CaCl_2$ (0.7 equiv)	44
3[c]	1	—	25
4	1	$CaCl_2$ (0.7 equiv)	35

[a]Reaction conditions: 2 (0.54 mmol), allyl bromide (0.64 mmol), KOH (0.76 mmol), $CaCl_2$ (0.38 mmol), and MeOH (1.0 mL). [b]Isolated yields. [c]10% KOH(aq), 0 °C (Ref. 7b).

Our rationalized synthesis of (±)-ascofuranone primarily involves preparation of the prenyl side chain precursor bearing a furanone ring, and coupling of this with the aromatic moiety. The retrosynthetic analysis is depicted in Scheme 1. Direct coupling of the aromatic **2**, without phenolic protection, and prenyl side chain **3** affords **1**. In this step, the phenolate presumably reacts via an S_N2 reaction with prenyl side chain **3**, which has good leaving groups such as halides and sulfonates.[7b,9] Prenyl side chain precursor **3** is accessible from pivaloyl ester **4** via Ag(I)-catalyzed rearrangement and cyclization[10] followed by displacement of a leaving group. Pivaloyl ester **4** is easily obtained from commercially available geranyl acetate by allylic oxidation and carbon chain extension reaction.

First, we investigated the effect of a calcium reagent ($CaCl_2$/KOH) on the direct coupling of pentasubstituted benzene **2** with allyl bromides in methanol (Table 1). With addition of $CaCl_2$ the reaction yields of hexasubstituted benzenes were improved, and only the desired products were



Scheme 2. Total synthesis of (±)-ascofuranone (**1**). Reagents and conditions: a) SeO_2, EtOH, reflux; b) 2-methyl-3-butyn-2-ol (0.9 equiv), *n*-BuLi (2.0 equiv), THF, −50 °C; c) *t*-BuCOCl (2.2 equiv), DMAP, pyridine, $CHCl_3$, 0 °C; d) $AgBF_4$ (8 mol %), toluene, 80 °C; e) NaOMe, MeOH, rt; f) CBr_4 (2.5 equiv), $(n\text{-}C_8H_{17})_3P$, Et_2O, 0 °C; g) **2** (0.8 equiv), $CaCl_2$, KOH, MeOH, 0 °C.

synthesized without other by-products in both cases (Entries 2 and 4).[11] In the reaction of phenolate with allyl bromide, $CaCl_2$ acts as a Lewis acid to coordinate both molecules enough to react.

Thus, the synthesis of ascofuranone is described in Scheme 2. Geranyl acetate was treated with SeO_2 in EtOH under reflux to afford aldehyde **5**[12] with the desired *E* geometry in 54% yield. Aldehyde selective addition of a lithium salt of 2-methyl-3-butyn-2-ol was accomplished at −50 °C to give **6** in 68% yield. This was then further transformed into pivaloyl ester **4** in 97% yield. Treatment of ester **4** with a catalytic amount (8 mol %) of $AgBF_4$ in toluene afforded compound **7** (63% yield) via pivaloyloxy migration and cyclization. Simultaneous deprotection of the acetyl and pivaloyl groups of **7** with sodium methoxide gave allyl alcohol **8** in 92% yield. Treatment of allyl alcohol **8** with carbon tetrabromide and trioctylphosphine at −78 °C afforded the prenylated bromide **9** in 96% yield. Coupling of prenylated bromide **9** with 5-chloroorsellinaldehyde **2**[7b] using $CaCl_2$ as a Lewis acid and KOH in MeOH at 0 °C gave (±)-ascofuranone in 34% yield. The final product exhibited physical and spectroscopic data in agreement with the literature.[7c] Thus, the total synthesis of (±)-ascofuranone was accomplished in seven steps (6.7% overall yield) from geranyl acetate.[13]

In conclusion, we have achieved a more facile and efficient synthesis of ascofuranone using only seven steps, starting from commercially available geranyl acetate. This methodology could be practically applied to the preparation of various ascofuranone derivatives. Further rationalization of the synthetic process and investigation of the biological activities of these derivatives will be reported in due course.

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11 By-products such as corresponding chromenes[8a] and *O*-allylated ethers were not isolated, and phenol **2** (29–47%) was recovered. However, in the case of 2′,4′-dihydroxyacetophenone, ^{1}H NMR analysis of crude products indicated that both *C*- and *O*-allylated products were formed.

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13 Supporting Information is available electronically on the CSJ-Journal Web site, http://www.csj.jp/journals/chem-lett/index.html.

