Facile Synthesis of (−)-Ascochlorin Using Palladium-catalyzed Three Component Coupling Reaction

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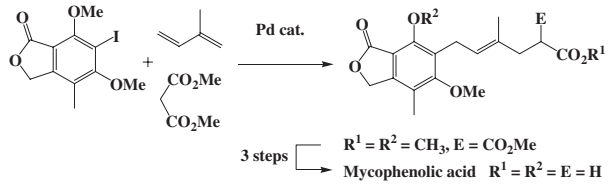
(−)-Ascochlorin was synthesized using palladium-catalyzed three component coupling reaction. Reaction of the aryl iodide **3**, isoprene, and sodium *p*-toluenesulfinate in the presence of $Pd_2(dba)_3CHCl_3$ catalyst and $NaHCO_3$ gave the 4-aryl-2-methyl-2-butenylsulfone **5** selectively in 68% yield. The allylic sulfone **5** was converted into the useful intermediate **2** in 5 steps, which was subjected to Julia olefination with the aldehyde **4** and deprotection gave (−)-ascochlorin.

In the course of studies on development of transition metal-catalyzed reactions toward organic synthesis, we have synthesized mycophenolic acid by a palladium-catalyzed three component coupling reaction, in which the requisite carbon framework was prepared in one pot (Scheme 1).[1]

The method is applicable to other biologically active phenols having functionalized isoprenoid chains such as (−)-ascochlorin (**1**) and a related compound, ascofuranone. These natural prenyl phenols exhibit important biological activities as antiviral, antibiotic, and antitumor activities.[2] The relationship of these activities and the unique structures as multi-substituted aromatic ring connecting with functionalized isoprenoid chains prompts chemists to synthesize the ascochlorin family (Figure 1).

Several synthetic methods are known for these functionalized prenyl phenols, however, the syntheses require many steps.[3] To extend the palladium-catalyzed three component coupling reaction to the synthesis of various prenyl phenols we have studied the reaction with sodium *p*-toluenesulfinate as a nucleophile to synthesize 4-sulfonylprenyl phenols, from which (−)-ascochlorin and related compounds can be synthesized by furnishing the requisite carbon frameworks of the biologically active prenyl



Scheme 1. Synthesis of mycophenolic acid.

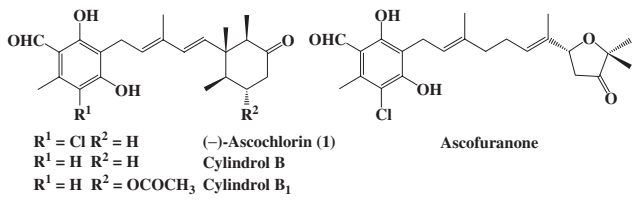
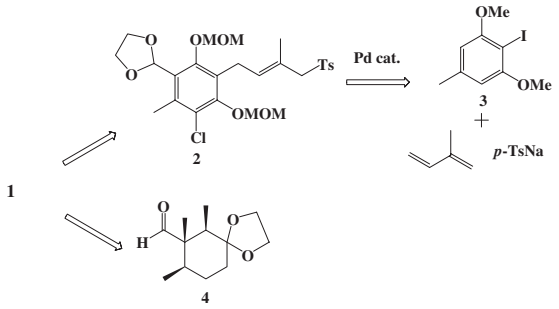


Figure 1. Ascochlorin family of sesquiterpenyl phenol.



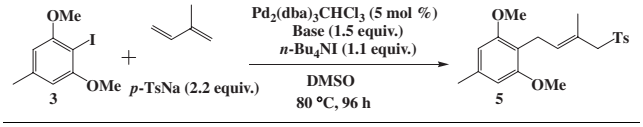
Scheme 2. Retrosynthetic analysis of (−)-ascochlorin (**1**).

phenols on the basis of organo-sulfone chemistry.[4] In this paper, we have realized a facile synthesis of (−)-ascochlorin by means of the palladium-catalyzed three component coupling reaction.

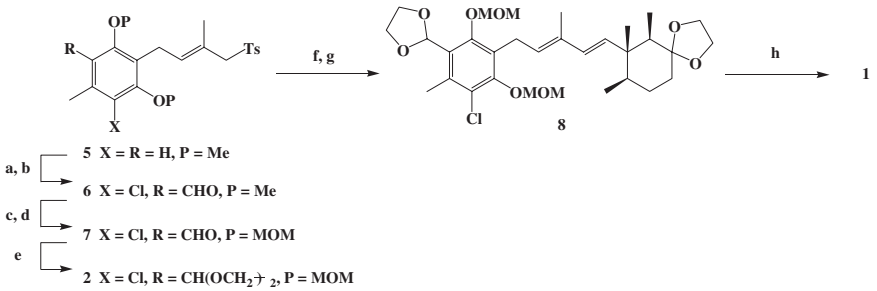
Our retrosynthetic approach is shown in Scheme 2. (−)-Ascochlorin is synthesized by Julia olefination[4b] of the allylic sulfone segment **2** and the aldehyde segment **4**. The allylic sulfone **2** is accessible from three components, aryl halide **3**, isoprene, and sulfinate by the palladium-catalyzed reaction.

Actually the key intermediate **5** was prepared form the aryl halide **3**, which was prepared from 5-methyl resorcinol in two steps (NIS in CH_3CN at 0 °C, 91%, then, MeI in DMF at r.t. quant.). Reaction of aryl halide **3**, isoprene, and sodium *p*-toluenesulfinate was carried out under various conditions. Excess isoprene was necessary because of its volatility. The reaction proceeded without phosphines or phosphites, which are normally used as ligand of the catalysts to prevent precipitating the metal. Reaction without adding base did not proceed smoothly, and addition of bases is necessary for the reaction. The reactions at 80 °C with various bases are summarized in Table 1. The choice of base was important for the three component coupling, thus, Et_3N, NaOAc, and K_2CO_3 did not give satisfactory results, but $NaHCO_3$ was found to be suitable, and the best result was obtained (Entry 4).

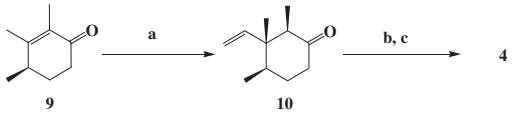
Table 1. Palladium-catalyzed reaction of aryl halide **3**, isoprene and sodium *p*-toluenesulfinate[5]



Entry	Base	Yield (%)
1	Et_3N	49
2	NaOAc	34
3	K_2CO_3	29
4	$NaHCO_3$	68



Scheme 3. Reagents and conditions; a) NCS, MeCN, reflux, quant.; b) $CHCl_2OCH_3$, $TiCl_4$, CH_2Cl_2, 0 °C to r.t., 65%; c) BBr_3, CH_2Cl_2, −78 to 0 °C, 73%; d) MOMCl, DIPEA, r.t., quant.; e) ethylene glycol, PPTS cat., benzene, 75%; f) **4**, LHMDS, Ac_2O, THF, −78 °C to r.t., 88%; g) Na/Hg (10%), Na_2HPO_4, MeOH, 57%; h) 1 M HCl, THF, 81%.



Scheme 4. Reagents and conditions; a) vinylmagnesium bromide, CuI, THF, −25 °C, 63%; b) ethylene glycol, PTSA cat., toluene, 91%; c) O_3, Me_2S, MeOH, −78 °C to r.t., 85%.

Conversion of the allylic sulfone **5** to ascochlorin (**1**) was shown in Scheme 3. Chlorination of **5** with NCS followed by formylation of the aromatic ring with dichloromethyl methyl ether using $TiCl_4$ gave the aromatic aldehyde **6**. After the protecting group of the phenol **6** was changed from methyl to the methoxy methyl ether **7** and the acetal protection of the aldehyde with ethylene glycol, the allylic sulfone segment **2** was subjected to Julia olefination with the aldehyde segment **4**[6] to afford the diene **8**. Finally, simultaneous deprotection of acetal and MOM ether of **8** with 1 M HCl gave (−)-ascochlorin (**1**) (Scheme 3).

In summary, we have developed a novel method to synthesize (−)-ascochlorin (**1**) by means of the palladium-catalyzed three component coupling reaction with the aryl halide, isoprene and sodium *p*-toluenesulfinate, which provides a useful methodology, especially for biologically active phenols substituted with functionalized prenyl groups. Synthesis of the other phenol isoprenoid such as ascofuranone or related compounds for structure–activity relationship study is in progress.

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5 Preparation of **5** as a typical procedure for the palladium-catalyzed three component coupling reactions in Table 1: A mixture of 3,5-dimethoxy-4-iodotoluene (**3**) (55.6 mg, 0.200 mmol), sodium *p*-toluenesulfinate (78.4 mg, 0.440 mmol), sodium hydrogen carbonate (26.2 mg, 0.312 mmol), tetra-*n*-butylammonium iodide (77.6 mg, 0.210 mmol), $Pd_2(dba)_3CHCl_3$ (10.4 mg, 5 mol %), isoprene (0.4 mL) in DMSO (0.606 mL) was stirred at 80 °C for 96 h in Pyrex tube. The mixture was quenched with NH_4Cl aq. The organic layer was extracted with dichloromethane, washed with brine, dried over $MgSO_4$ and filtered. The filtrate was concentrated in vacuo. The residue was chromatogaraphed on silica gel (10% ethyl acetate in hexane) to give the product **6** as a yellow oil (50.7 mg, 68%): ^{1}H NMR (400 MHz $CDCl_3$) δ 1.90 (s, 3H, CH_3), 2.31 (s, 3H, CH_3), 2.33 (s, 3H, CH_3), 3.20 (d, $J = 7.6$ Hz, 2H, $BnCH_2$), 3.61 (s, 2H, CH_2), 3.72 (s, 6H, OCH_3), 4.94 (t, $J = 7.5$ Hz, 1H, $CHCH_2$), 6.31 (s, 2H, aromatic H), 7.02 (d, $J = 8.1$ Hz, 2H, aromatic H), 7.52 (d, $J = 8.2$ Hz, 2H, aromatic H); ^{13}C NMR (100 MHz $CDCl_3$) δ 16.6, 21.5, 22.0, 22.3, 55.5, 66.3, 104.3, 113.1, 122.5, 128.4, 130.0, 134.5, 134.8, 136.9, 143.6, 157.6; IR (film) 2937, 2836, 1589, 1463, 1413, 1313, 1164, 1118, 1087 cm^{-1}; HRMS (FAB) calcd for $C_{21}H_{27}O_4S$ $[M + H]^+$ 375.1552, found 375.1636.

6 The segment **4** (97%ee) was prepared according to the procedure reported[3c] from (4*R*)-(−)-2,3,4-trimethyl-2-cyclohexenone[3b] (Scheme 4).

7 (−)-Ascochlorin (**1**): mp 172–174 °C (lit:[2b] 172–173 °C); $[\alpha]_D^{25}$ − 30.7 (*c* 0.69, MeOH) (lit:[2b] $[\alpha]_D^{25}$ − 31 (*c* 0.99, MeOH)); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.69 (s, 3H, CH_3), 0.80–0.84 (m, 6H), 1.60–1.67 (m, 1H), 1.89–1.96 (m, 2H), 1.92 (s, 3H, CH_3), 2.33–2.46 (m, 3H), 2.60 (s, 3H, CH_3), 3.53 (d, $J = 7.6$ Hz, 2H, $BnCH_2$), 5.38 (d, $J = 16.1$ Hz, 1H), 5.52 (t, $J = 7.6$ Hz, 1H, $CHCH_2$), 5.90 (d, $J = 16.1$ Hz, 1H), 6.39 (s, 1H, OH), 10.14 (s, 1H, CHO), 12.70 (s, 1H, OH); ^{13}C NMR (100 MHz $CDCl_3$) δ 8.99, 10.4, 12.7, 14.6, 16.4, 22.3, 31.2, 40.9, 41.6, 48.5, 53.6, 113.1, 113.6, 113.7, 127.4, 133.1, 134.0, 135.6, 137.7, 156.0, 162.1, 193.1, 212.6; IR (film) 3268, 2960, 2925, 2871, 1708, 1614, 1454, 1423, 1375, 1328, 1282, 1249, 1172, 1110, 1012, 970, 906, 798, 713, 590 cm^{-1}; HRMS (FAB) calcd for $C_{23}H_{30}ClO_4$ $[M + H]^+$ 405.1754, found 405.1817.

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