# Diastereo-differentiating Coupling of Phenoxy Radical Moiety Controlled by 2,4-Pentanediol Tether.
# Preparation of Optically Active Pummerer's Ketone Analogs

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*Abstract:* The highly diastereo-differentiating coupling of the phenoxy radical could be achieved by a 2,4-pentanediol tethered reaction to give a single diastereomer of Pummerer's ketone analog. By the removal of the chiral auxiliary, the optically active phenoxy radical dimer was obtained in good yield. © 1998 Elsevier Science Ltd. All rights reserved.

Dimerization is an important process in biosynthesis to convert a small and simple molecule to a large and complex one.[1] Many phenolic natural products are produced through the dimerization of the radical coupling reaction of phenolic precursors. Since the stereocontrol of the radical reaction is still less known field,[2] asymmetric synthesis of such a compound through a biogenetic process is a challenging issue in organic synthesis. Usnic acid, a yellow pigment widely found in the lichen family, is a dimer of methylphloracetophenone and its chirality is produced during the dimerization process.[3] Although many attempts to mimic this dimerization by chemical oxidation, represented by conversion of *p*-cresol to Pummerer's ketone, have been studied,[4-6] most of them afford many isomers with polymeric products, and no stereodifferentiating reaction to produce the optically active dimer has been reported. In this communication, we would like to report that a chiral 2,4-pentanediol (PD) tether between two units of the *p*-cresol moiety could sufficiently control the radical coupling under complete diastereo-differentiation in giving a single diastereomer of Pummerer's ketone analog.



(–)-usnic acid                    (+)-usnic acid



Pummerer's ketone
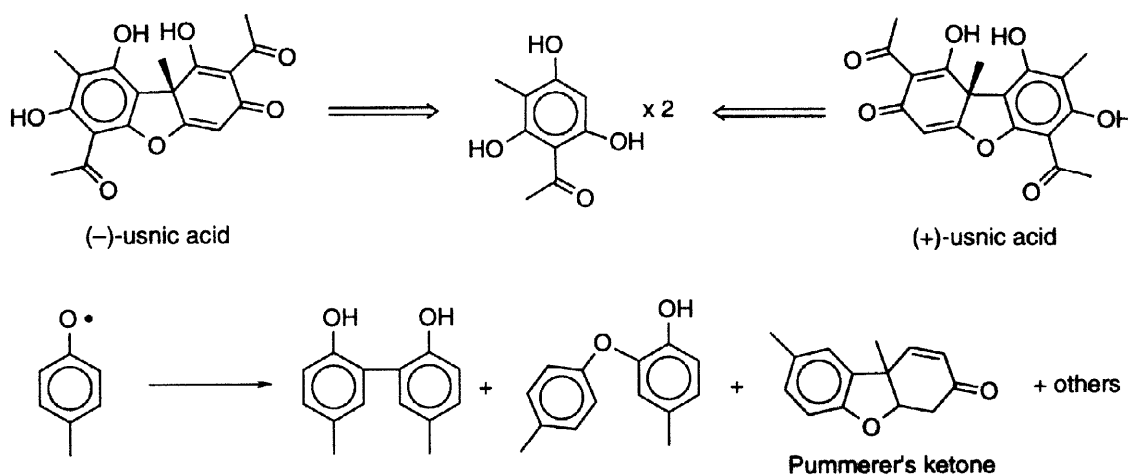
The PD tethered reaction, a prochiral substrate and a reagent are tied by a PD tether before the reaction, is a widely applicable stereocontrol method, and various reactions though ionic and concerted processes resulted in

over a 99% diastereomeric excess (de) of the products.[7] The present study of the stereodifferentiating intramolecular phenoxy radical coupling is shown in Scheme 1. The Mitsunobu reaction of (2R,4R)-PD and 1[8] (2 equivalents) with tributylphosphine and diethyl azodicarboxylate afforded a mono ether in 85.5% yield. In the reaction mixture, its diastereomer was not detected after careful analyses. Introduction of the second molecule of 1 to the mono ether was successful with 1 (1.2 equivalents) under the same reaction conditions to afford 2 as the sole diastereomer in 68.8% yield. Thus, both chiral centers on PD were completely inverted, and enantio- and diastereomerically pure (2S,4S)-2 was obtained. The one step preparation of 2 from PD was also possible with 6 equivalents of 1 resulting in a 70% yield of 2. The treatment of 2 with sodium ethanethiolate in DMF at reflux temperature afforded 3 in 97.8% yield.
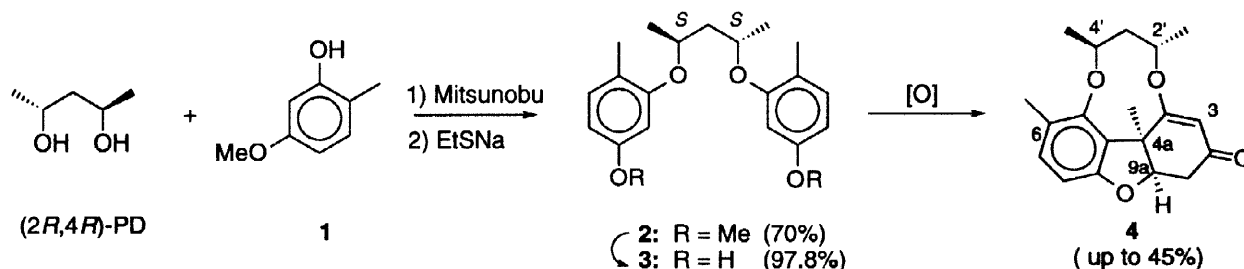


**Scheme 1.**

The biradical of 3 was generated by several oxidation methods.[6] When 3 was treated with an aqueous basic solution of $K_3[Fe(CN)_6]$, 4 was obtained accompanied by polymeric byproducts. The yield of 4 was varied in the range of 10–37% depending on the reaction conditions, such as concentration, pH of the solution, and addition method, but the other regioisomers or diastereomer of 4 were not detected in all cases. The best result was obtained using the following procedure: To a mixture of $K_3[Fe(CN)_6]$ (4.1 equivalents) in 0.4 M $Na_2CO_3$ aqueous solution (500 ml) and ether (100 ml), a solution of 3 (110.5 mg) in ether (200 ml) was slowly added over 12.5 h at room temperature. Extraction and silica gel chromatography of the mixture gave a colorless solid of 4 (41.0 mg, 37.1%). Electrochemical oxidation of 3 with a platinum anode in a methanol solution of NaOH and $LiClO_4$ also afforded 4 up to a 45% yield. Again, no regioisomer or diastereomer of 4 was detected during the oxidation, although some decomposition of 3 giving polymeric products was observed. The oxidation of 3 with $AgCO_3$-Celite, $Mn(acac)_3$, di-t-butylperoxyoxalate, or $Ce(NH_4)_2(NO_3)_6$ did not give 4, but only produced polymeric products.

The stereochemistry of 4 was determined as (4aR,9aR) from the nOe signals between 4a-methyl and 4'-H, and those between 4a-methyl and 9a-H.[9]
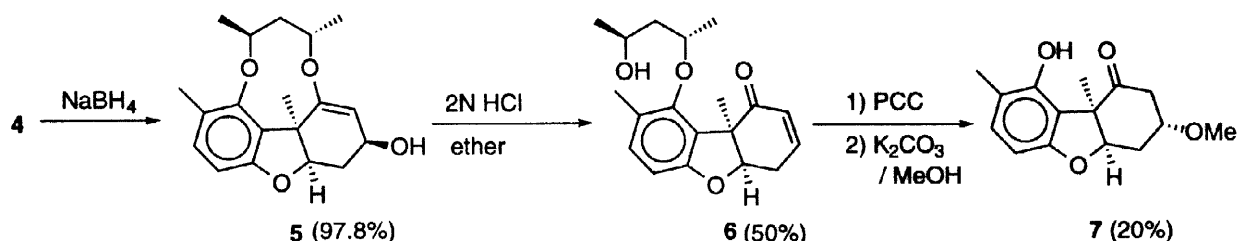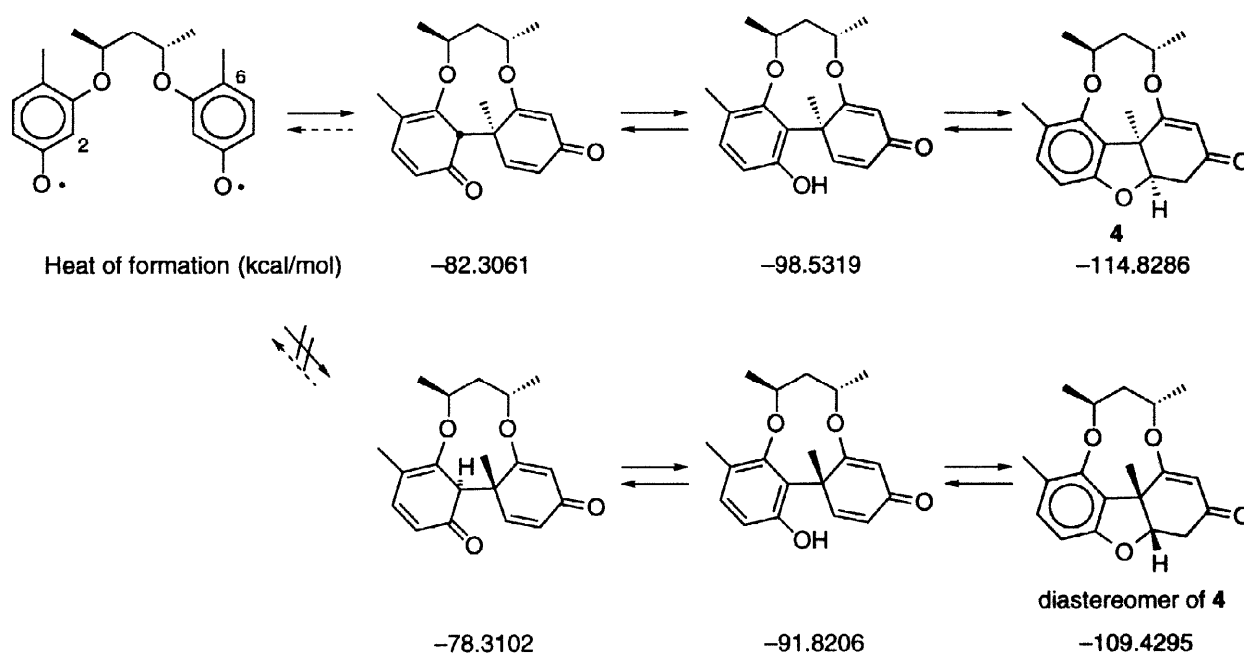


**Scheme 2.**

Removal of the PD tether from 4 affords an optically active Pummerer's ketone analog. Cleavage of the ethers at the 2'- and 4'-positions of 4 with $BBr_3$ resulted only in decomposition. Hydrolysis of the enol ether part at the 4-position by an acid or base catalyst needs severe conditions, and no clear product was obtained. To weaken the enol ether bond for hydrolysis, 4 was converted to 5 with $NaBH_4$ (in methanol, 98% yield). The

hydrolysis of **5** under mild acidic conditions resulted in **6** in 50% yield and removal of the PD part by the conventional method afforded an optically active Pummerer's ketone analog **7** in 20% yield.[10]

The formation mechanism of **4** and its diastereomer could be represented as shown in Scheme 3. That is, the intramolecular coupling of the biradical of **3** proceeded from the *si*-face at the 2-position of one phenoxy radical, and from the *re*-face at the 6-position of the other one. After enolization (aromatization) of the couple, the resulting phenolic hydroxyl group was added to the other ring at the β-position of the enone to construct the *cis*-fused furan ring. The heat of formation for each intermediate and **4** was estimated by calculation using the MOPAC-PM3 method (see Scheme 3, upper). The corresponding diastereomers (Scheme 3, lower) were less stable in all three compounds. The major structural difference throughout the process is conformations of 5'-methyl: **4** and its intermediates are *pseudo*-equatorial, whereas their diastereomers are *pseudo*-axial.



Heat of formation (kcal/mol)       −82.3061                −98.5319                −114.8286

                                      −78.3102                −91.8206                −109.4295

**Scheme 3.**

In conclusion, we have demonstrated that the stereocontroller using the PD tether was also effective for controlling the radical coupling, and optically active Pummerer's ketone analogue was obtained under complete diastereo-differentiation. Although the coupling yield is not high using the ordinary oxidation conditions so far examined, this method is attractive enough to synthesize optically active usnic acid and the other dimer type natural products through a biogenetic pathway.

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9.  The assignment of 4'-H was as follows: 5'-methyl and 1'-methyl was assigned by nOe signals between 5'-methyl and 6-methyl, and those between 1'-methyl and 3-H. From spin decoupling experiments of 1'-methyl and 5'-methyl, 2'-H and 4'-H were assigned.

10. Data for **7**: $[\alpha]_D^{20}$ = –48.2 (c 0.3, methanol). $^1$H NMR (CDCl$_3$, 400 MHz) δ 7.99 (s, 1H, –OH), 6.86 (d, J = 8.3 Hz, 1H), 6.37 (d, J = 8.3 Hz, 1H), 4.82 (dd, J = 8.1, 5.6 Hz, 1H), 3.83 (m, 1H), 3.37 (s, 3H), 2.70–2.60 (m, 2H), 2.42 (m, 1H), 2.09 (s, 3H), 2.05 (m, 1H), 1.58 (s, 3H).