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Intramolecular Cationic [5 +2]Cycloaddition Reaction of Penta- substituted Phenols by Using Anodic Oxidation

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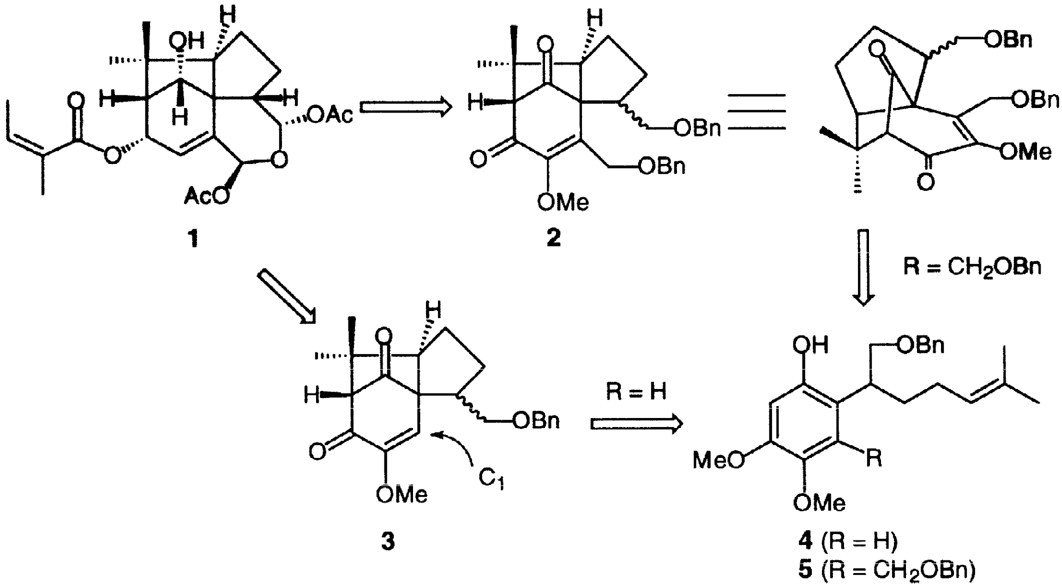
Abstract

In connection with *Acourita* sesquiterpenes, anodic oxidation is useful for construction of the corresponding tricyclo[5.3.1.0^{1,5}]undec-9-en-8,11-diones from penta-substituted phenols.

Keywords: electrochemical reactions; cycloadditions; terpenes and terpenoids; phenols

In 1965, a cationic [5+2]cycloaddition reaction was first reported by Joseph-Nathan *et al.* [1], followed by Büchi *et al.,* who successfully applied this methodology to the total synthesis of neolignans[2, 3], although their yields were not satisfactory. Recently, Grieco *et al.* reported that cationic [5+2]cycloaddition reactions can be dramatically promoted by



Scheme 1

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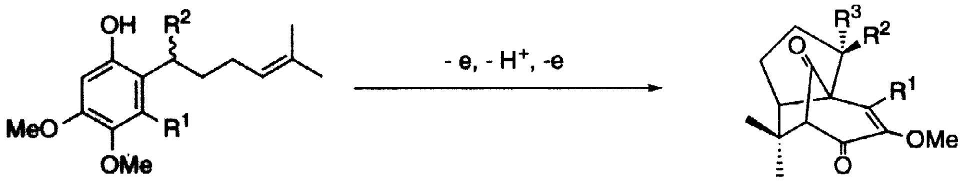
employing trimethylsilyl triflate and lithium perchlorate in ethyl acetate [4]. In their method, an unstable phenoxy cation will be formed by the action of Lewis acid to the quinone monoketal, which was prepared by DDQ oxidation of the corresponding phenol. Independently, we have extensively developed our own synthetic methodology by means of anodic oxidation of phenols to synthesize a variety of natural products including 8,14-cedranoxide [5, 6, 7]. In these experiments, our investigation was focused on the intramolecular cationic [5 + 2]cycloaddition reactions of tri- or tetra-substituted phenols with an alkyl chain bearing an olefinic double bond.

Since Stork's original synthesis of cedrol [8], a number of synthetic studies on simple cedrane-type sesquiterpenes have been carried out. However, such highly functionalized cedranes as found in *Acourtia nana* [9] have not been synthesized. In connection with these sesquiterpenes represented by **1**, whose retrosynthesis is shown in Scheme 1, we describe herein some intramolecular cationic [5 + 2]cycloadditions of penta-substituted phenols with an alkyl chain bearing an olefinic double bond, in addition to a tetra-substituted phenol.

Table 1. Electrochemical synthesis of some tricyclic compounds.



Entry	Phenol	Products*	Yield (%)
1	**4**: $R^1 = H$ $R^2 = CH_2OBn$	3α: $R^1 = H$ $R^2 = H$, $R^3 = CH_2OBn$	52
		3β: $R^1 = H$ $R^2 = CH_2OBn$, $R^3 = H$	18
2	**5**: $R^1 = CH_2OBn$ $R^2 = CH_2OBn$	**2β**: $R^1 = CH_2OBn$ $R^2 = CH_2OBn$, $R^3 = H$	34
3	**6**: $R^1 = CH_3$ $R^2 = H$	**9** : $R^1 = CH_3$ $R^2 = R^3 = H$	46
4	**7**: $R^1 = CH_3$ $R^2 = CH_2OBn$	**10**: $R^1 = CH_3$ $R^2 = CH_2OBn$, $R^3 = H$	40
5	**8**: $R^1 = CH_2OBn$ $R^2 = H$	**11**: $R^1 = CH_2OBn$ $R^2 = R^3 = H$	33

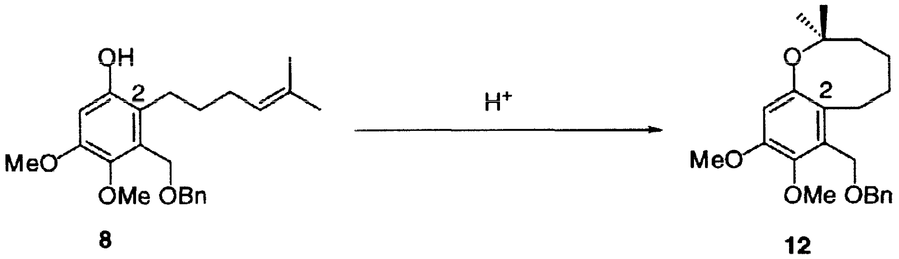
* The spectral data for the new compounds cited herein are in accord with the structure assigned.

According to essentially the same procedure as described in the synthesis of 8,14-cedranoxide [6], the corresponding tetra- and penta-substituted phenols (**4** - **8**) were prepared from commercially available 5-bromovanillin in high yields. These several phenols were subjected to anodic oxidation (*ca.* 7 - 9 mA; *ca.* 2F/mol) in acetic anhydride containing

$^nBuN_4BF_4$ as a supporting electrolyte[1] to afford the corresponding tricyclo[5.3.1.0^{1,5}] undec-9-en-8,11-diones, as shown in Table 1. In the case of the tetra-substituted phenol (**4**), it was converted into a mixture of two stereoisomers (**3α** and **3β**) in 70 % yield (relative ratio: **3α / 3β** = 3/1) (entry 1). As shown in Scheme 1, both of stereoisomers can be converted into the target sesquiterpene (**1**), although one carbon atom must be introduced, as indicated by an arrow (see **3** in Scheme 1).

On anodic oxidation of penta-substituted phenols (**5** - **8**), as shown above, intramolecular cationic [5+2]cycloaddition reactions took place to afford the corresponding desired tricyclo[5.3.1.0^{1,5}] undec-9-en-8,11-dinones (**2β**, **9** - **11**). The structure of the promising synthetic intermediate (**2β**) was unambiguously confirmed by its spectral data: **2β** as an oil: $C_{30}H_{34}O_5$ [m/z 474.2413 (M$^+$)]; IR (film) 1750,1670, 1600 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.04 (3H, s), 1.08 (3H, s), 1.17-1.39 (2H, complex), 1.63-1.86 (2H, complex), 3.18 (1H, s), 3.82 (3H, s), 3.96 (1H, dd, J = 7.6, 9.2 Hz), 4.05 (1H, dd, J = 6.0, 9.2 Hz), 4.49 (1H, d, J = 10.8 Hz), 4.50 (2H, s), 4.51 (1H, s), 4.60 (1H, d, J = 10.8 Hz), 7.29 - 7.38 (10H, complex); ^{13}C NMR ($CDCl_3$) δ 24.8, 24.9, 28.4, 31.5, 36.4, 42.2, 60.7, 64.3, 66.6, 70.0, 72.8, 73.1, 78.8, 127.3, 127.4, 127.7, 128.3, 128.4, 131.6, 132.2, 137.9, 138.7, 150.0, 152.5, 193.3, 204.0.

The stereochemistry of **2** at the C_2-position was determined to be in β–configuration based on NOE experiments together with the anisotropic effect of the CO group at the C_2-position. The α-isomer was not detected in any amount (entry 2) because of steric repulsion between the R^1 and R^2 groups in the cyclic transition state. The tricyclic compound (**10**) was also proved to have the same stereochemistry as that of **2** at the C_2-position, as judged from its NMR spectral data (entry 4). As compared with **4**, in the case of penta-substituted phenols, each yield is relatively low. The corresponding 8-membered cyclic ethers were produced before oxidation because of a proximity effect of the R^1 group (CH_2OBn) on the alkyl chain at the C_2-position, as shown in Scheme 2.



Scheme 2

According to the two different procedures developed by Büchi and Grieco [2, 3, 4], we were able to obtain the desired α-isomer (**3**) from the tetra-substituted phenol (**4**) (Büchi's method: 39%; Grieco's method: 49%). As compared with our method, in the case of the penta-substituted phenol (**5**), the yield of **2β** was relatively low (Büchi's method: 11%; Grieco's method: 22%).

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[1] The anodic oxidation of phenols was carried out at room temperature under an argon atmosphere using a 200ml glassy carbon beaker [GC-20, Tokai Carbon Co. Ltd.] and a platinum wire tip as an anode and a cathode, respectively.

In conclusion, our synthetic methodology using electrolysis is also quite effective for promoting an intramolecular cationic [5 + 2]cycloaddition reaction of penta-substituted phenols, as previously reported in the case of tetra-substituted phenols. [6] Our synthetic studies on *Acourita* sesquiterpenes represented by **1** are in progress using the two synthetic tri-cyclic compounds (**2β** and **3**).

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