# Studies on the Alkylation of Phenolate in an Organofluorine Solvent and Its Application to the Synthesis of Myrsinoic Acid A and E

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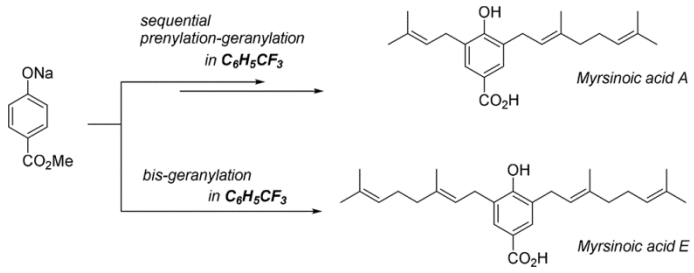
## Abstract

Among the distinct features of organofluorines, solubility properties to molecules often enables unique applications. More importantly, organofluorines can be compatible with chemical reactions in general, even in harsh conditions. In this context, a study on the alkylation of phenolate using an organofluorine solvent were carried out for the preparation of *ortho*-alkyl phenols. Herewith, the study on the alkylation of phenolate in an organofluorine solvent as well as its application to the synthesis of bioactive terpenylated phenolic natural products, myrsinoic acid A and E, will be reported. Our study suggested that organofluorine solvents could be better alternatives to the conventional non-dissociating solvents as organic reaction media to suppress the non-desirable and non-selective side reactions such as in the *ortho*-alkylation of phenolate.

## GRAPHICAL ABSTRACT




**KEYWORDS:** Organofluorine solvent; alkylation of phenolate; terpenylated phenol; myrsinoic acid

## INTRODUCTION

*C*-prenylated phenols are found in diverse natural sources, especially in plant species. Bioactive *C*-prenylated phenols such as benzoic, cinnamic and coumaric acid derivatives as well as prenylated ubiquinones/naphthaquinones, flavonoids and xanthones have attracted considerable scientific attentions due to its unique biological and pharmacological properties which are intimately associated with the presence of phenolic hydroxyl groups[1-4]. Nevertheless, no single synthetic method encompassed the preparation of *C*-prenylated phenols, and some synthesis of prenylated phenols are reported to be challenging[5-6]. Various synthetic methods has been developed so far for the preparation of *ortho*-alkyl phenols: Lewis acid catalyzed *ortho*-alkylation of phenol including the Friedel-Crafts type, Claisen rearrangement, metal-mediated coupling via metal-halogen exchange or directed *ortho*-metalation are popular strategies among them[5-6]. In particular, the *ortho*-alkylation of phenolate is a favored strategy for the preparation of terpenylated phenols especially for the prenylated. Although *ortho*-alkylation of

phenolate is intuitive and tempting, due to the advantages in terms of atom- and step-economy, it is often challenging because of the strong preference of competing *O*-alkylation and non-selective side reactions such as regioisomeric or multiple alkylation depending on the structure. Non-dissociating organic solvents have been utilized to facilitate selective alkylation for the preparation of *ortho*-alkyl phenols[7-9], and in this context, we became interested in using an organofluorine solvent as a novel non-dissociating solvent during our synthetic program for the preparation of bioactive natural products.

Myrsinoic acid A (MAA, **1**), a prenylated phenol, was isolated in 1991 from the leaves of a Brazilian shrub, *Rapanea umbellata* (Figure 1). The structure of MAA has been identified as a terpeno-*p*-hydroxybenzoic acid on the basis of spectroscopic analysis of its methylated derivative[10]. The structure of MAA was later confirmed by an extensive NMR study during a bioassay-guided isolation of anti-inflammatory compounds from the methanolic extract of *Myrsine seguinii*[11]. MAA was also reported to exhibit antibacterial activities[12]. In addition, the anticancer effect of MAA through a novel mechanism of action, *i.e.* the inhibition of heparin-binding epidermal growth factor-like growth factor, attracted attentions[13-14]. Among the structural features of MAA, the carboxylate functionality was found to be of importance for the activity of MAA, and structurally related terpeno-benzoic acids, myrsinoic acid B, C, E (MAE, **2**), and F were also isolated to possess similar activities[15] (Figure 1). All those biological properties of myrsinoic acids made it clear that an efficient and scalable method for the synthesis is urgently in need. In particular, the synthesis of MAA has never been reported yet. Herewith, we

would like to report studies on the alkylation of phenolate in an organofluorine solvent and its application to the synthesis of MAA and MAE via a sequential alkylation strategy.

## RESULTS AND DISCUSSION

We envisioned that a straightforward synthesis of MAA and MAE could be achieved via sequential *ortho*-alkylation or bis-alkylation of metal phenolate, respectively (Figure 2). Unlike conventional alkylation of enolates, however, *C*-alkylation of phenolates are often challenging. The preference of phenolate toward *O*-alkylation over *C*-alkylation, which is less likely for the conventional alkylation of enolates, can be understood by the disruption of aromaticity during the *C*-alkylation of phenolates. In spite of that, the composition of the products is known to be determined by the relative nucleophilicity of each atom in relation to the electrophile in a kinetically controlled condition[16], and attempts to achieve an efficient *ortho*-alkylation has been continued. Several pioneers successfully provided conditions by exploring counterion, additives, concentration, temperature, pressure, leaving group, and the structure of substrate or electrophile[7-8]. For the countercation of phenolates, for example, [$Na^+$] is known to favor *C*-alkylation whereas [$K^+$] and [$Li^+$] favor *O*-alkylation and bis-alkylation[7]. Among the factors influencing the alkylation of phenolate, interestingly, the regioselectivity is strongly dependent on the solvent. Considering that the cation is coordinated to the atom with the maximal electron density, the preferential *C*-alkylation over *O*-alkylation is expected in a poorly cation-solvating solvent. In fact, toluene and benzene are representative solvents of choice when it comes to *C*-alkylation of phenolate.[9] Thus, our study commenced with the screening of reaction

conditions for the *ortho*-alkylation of metal phenolate to provide methyl 4-hydroxy-3-(3'-methyl-2'-butenyl)benzoate, especially focused on the potential non-dissociating solvents.

Looking for a better non-dissociating solvent alternative to the reported such as diethyl ether or toluene, we came up with the idea of using organofluorines. Among the distinct features of organofluorines, solubility properties to molecules often enables unique applications: they are found in various applications including anesthetics, pharmaceuticals, agrichemicals, fluoropolymers, refrigerants, oil and water repellents, surfactants, reagents in catalysis, and many more. In addition, organofluorines can be compatible with chemical reactions in general, even in harsh conditions. It is noteworthy that the utilization of organofluorines as reaction media has been scarcely reported.

As shown in Table 1, the examined reactions in diethyl ether, toluene and tetrahydrofuran seemed far less than ideal with commercially available sodium phenolate **3'**.(Entry 1-3) Although there has been several successful reports for the *C*-prenylation of phenolates[6], only a small amount of the desired product **4** was isolated in both diethyl ether and toluene, in spite of the attempt to optimize conditions. (Entry 1-4). It is noteworthy that electron-withdrawing groups in a phenolate substrate is known be detrimental for the *C*-alkylation of phenolate as it lowers electron density[17]. Using tetrahydrofuran as the reaction solvent afforded *O*-prenylated product **5** in a relatively high yield, and which is in consistent with the reported[7] (Entry 5). The preference of *O*-prenylation in tetrahydrofuran might be attributed to the strong basicity of tetrahydrofuran to make stronger coordination with the counter-cation. Thus, we decided to explore the reaction in

organofluorines for the prenylation of phenolate. Commercially available, and less expensive organofluorines, *i.e.* trifluorotoluene, hexafluorobenzene, and trifluoroethanol were selected as non-dissociating organofluorine solvents. To our delight, the reactions in trifluorotoluene afforded the desired product **4** in higher yield than the reactions in diethyl ether or toluene (Entry 6). An elevated reaction temperature of 40 °C was proven to be beneficial (Entry 7), while even higher temperature was not (Entry 8). It was also interesting to find bis-prenylated phenol **6** as a major product at 80 °C. Surprisingly, the reactions in hexafluorobenzene, a perfluoroaromatic compound, produced *O*-prenylated product **5** in high yield (Entry 9, 10). The reaction in trifluorobenzene provided *C*-prenylated product 4 as a major product (Entry 11), while the reaction in perfluoro(methylcyclohexane) also provided *O*-prenylated product **5** as a major product (Entry 12). Interestingly, the reactions in trifluoroethanol, a polar organofluorine, produced bis-prenylated product **6** as a major (Entry 13, 14).

The optimized reaction condition in hands, a sequential protocol of prenylation and geranylation was successfully utilized for the synthesis of MAA (Scheme 1). The prenylated phenol **4**, prepared from sodium phenolate **3'** as above, was metallated with sodium hydride, and then reacted with geranyl bromide in trifluorotoluene to afford the desired methyl ester **9** in high yield. The yield of *C*-alkylation reaction of phenolate increases as the length of electrophilic isoprene units increases in organic solvents[7-9], and which seems to be in consistent with the alkylation in an organofluorine solvent. The methyl ester **9** was shortly hydrolyzed to complete the synthesis of MAA. Next, the synthesis of MAE could also be achieved with a slight modification of our protocol.

Sodium phenolate **3'** was reacted with a slight excess amount of geranyl bromide for the bis-geranylation, and which successfully provided the methyl ester **10** along with a small amount of *O*-geranylated byproduct. The methyl ester **10** was hydrolyzed to complete the synthesis of MAE. The synthesized MAA and MAE were identical to the reported, based on the comparison of spectral data (See, Supplementary Information.).

## CONCLUSION

In conclusion, a study on the alkylation of phenolate using an organofluorine solvent were carried out. *C*-Alkylation reaction of sodium phenolate in trifluorotoluene was found to be superior to the reaction in conventional non-dissociating solvents including diethyl ether and toluene. This study demonstrated organofluorine solvents can provide non-dissociating environment to facilitate the *C*-alkylation of phenolate while suppressing the non-desirable *O*-alkylation. In addition, the developed protocol using trifluorotoluene was also successfully applied to the synthesis of bioactive terpenylated phenolic natural products, MAA and MAE, via sequential alkylation and bis-alkylation respectively. Considering that MAA and MAE are promising bioactive natural products as well as potential precursors for the preparation of other myrsinoic acids, our protocol would expedite further studies related in the biological properties of myrsinoic acids and their derivatives. We also believe our protocol would provide an intuitive and efficient synthetic route for the preparation of other terpenylated phenols which display a wide range of significant biological activities.

## EXPERIMENTAL

**Typical Procedure For The Mono-*C*-Alkylation**

**Preparation Of Methyl 4-Hydroxy-3-(3'-Methylbut-2'-En-1'-Yl)Benzoate (4)**

Sodium phenolate **3'** (174 mg, 1 mmol) was suspended in trifluorotoluene (4 mL), and 1-bromo-3-methyl-2-butene (179 mg, 1.2 mmol) was added dropwise to the suspension. The suspension was stirred for a 24 h at a given temperature (40 °C). The resulting reaction was then quenched with aqueous $NH_4Cl$ solution, and extracted with EtOAc. The organic layer was dried over anhydrous $MgSO_4$, and volatiles were removed under the reduced pressure. The residue was purified by $SiO_2$ chromatography. Yield 51% (112 mg); Rf 0.3 (EtOAc : *n*-hexane = 1 : 5); White wax; $^1$H-NMR (500 MHz, $CDCl_3$) δ 7.82 (2H, m), 6.82 (1H, d, *J* = 8.9 Hz), 5.63 (1H, bs), 5.31 (1H, t, *J* = 7.3 Hz), 3.88 (3H, s), 3.39 (2H, d, *J* = 7.2 Hz), 1.79 (6H, s); $^{13}$C-NMR (125 MHz, $CDCl_3$) δ 167.7, 158.9, 134.8, 131.8, 129.6, 127.3, 122.1, 121.2, 115.4, 52.0, 29.2, 25.8, 17.9; IR (ATR-IR) $\nu_{max}$ 3254, 1676, 1596 cm$^{-1}$; HRMS (EI) *m/z* $[M]^+$ calc. for $C_{13}H_{16}O_3$ 220.1099, found 220.1100.

**Typical Procedure For The Di-*C*-Alkylation**

**Preparation Of Methyl 3,5-Bis((E)-3,7-Dimethylocta-2,6-Dien-1-Yl)-4-Hydroxybenzoate (10)**

Sodium phenolate **3'** (174 mg, 1 mmol) was suspended in trifluorotoluene (4 mL), and geranyl bromide (0.476 ml, 2.4 mmol) was added dropwise to the suspension. The suspension was stirred for a 24 h at rt, and the reaction was then quenched with aqueous $NH_4Cl$ solution. The mixture was extracted with EtOAc. The organic layer was dried over anhydrous $MgSO_4$, and volatiles were removed under the reduced pressure. The residue was purified by HPLC. Yield 45% (191 mg); Rf 0.7 ($CH_2Cl_2$); Colorless oil; $^1$H-

NMR (500 MHz, $CDCl_3$) δ 7.70 (2H, s), 5.85 (1H, s), 5.31 (2H, m), 5.08 (2H, m), 3.86 (3H, s), 3.38 (4H, d, J=7.2), 2.09 (8H, m), 1.76 (3H, s), 1.68 (3H, s), 1.60 (3H, s); $^{13}$C-NMR (125 MHz, $CDCl_3$) δ 166.9, 162.7, 141.8, 131.9, 131.6, 123.7, 122.5, 118.9, 114.3, 65.1, 51.8, 39.5, 26.3, 25.7, 17.7, 16.7; IR (ATR-IR) $\nu_{max}$ 3408, 2921, 2858, 2347,1562, 1413 $cm^{-1}$; HRMS (EI) *m/z* $[M]^+$ calc. for $C_{28}H_{40}O_3$ 424.2977, found 424.2981.


## ACKNOWLEDGEMENT

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## SUPPORTING INFORMATION

Full experimental detail including $^1$H and $^{13}$C NMR spectra for this article can be found via “Supplementary Content” section of this article’s webpage.

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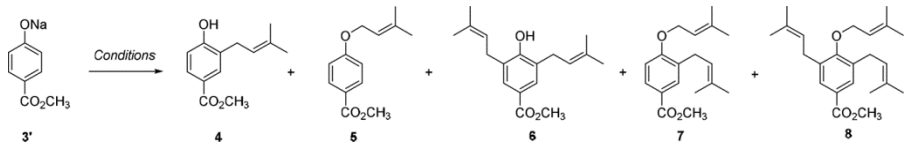
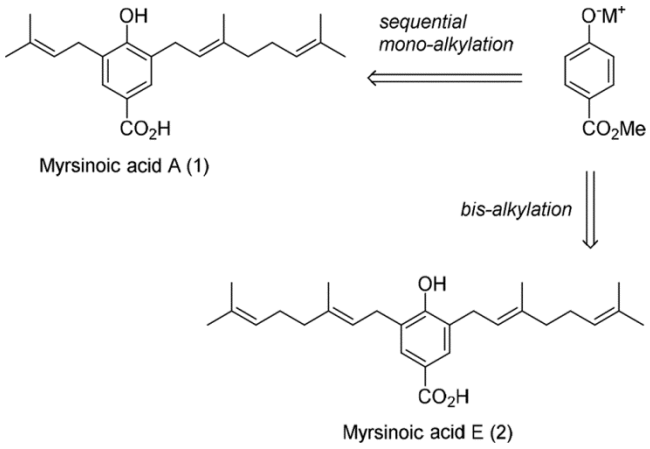
**Table 1.** Comparison of alkylation in various organofluorine solvents[a]




| Entry | Solvent | Temp. | Time | Yield[b] | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | **4** | **5** | **6** | **7** | **8** | **3**[c] |
| 1 | Diethyl ether | rt | 24h | 36 | 26 | <1 | 6 | 5 | 27 |
| 2 | Toluene | rt | 24h | 34 | 19 | <1 | 4 | 8 | 35 |
| 3 | Toluene | 40 $^{o}$C | 24h | 37 | 16 | <1 | 5 | 3 | 39 |
| 4 | Toluene | 80 $^{o}$C | 24h | 34 | 18 | <1 | 2 | 3 | 43 |
| 5 | Tetrahydrofuran | rt | 24h | <1 | 61 | <1 | 4 | <1 | 35 |
| 6 | Trifluorotoluene | rt | 24h | 43 | 18 | <1 | 7 | 4 | 28 |
| 7 | Trifluorotoluene | 40 $^{o}$C | 24h | 51 | 18 | <1 | 4 | 5 | 22 |
| 8[d] | Trifluorotoluene | 80 $^{o}$C | 24h | <1 | 3 | 39 | 2 | <1 | 56 |
| 9 | Hexafluorobenzene | rt | 24h | <1 | 70 | <1 | 4 | <1 | 26 |
| 10 | Hexafluorobenzene | 40 $^{o}$C | 24h | 3 | 63 | <1 | 7 | 1 | 26 |
| 11 | Trifluorobenzene | 40 $^{o}$C | 24h | 29 | 9 | 11 | 3 | 8 | 40 |
| 12 | Perfluoro(methylcyclohexane) | 40 $^{o}$C | 24h | 6 | 41 | 2 | 4 | 4 | 43 |
| 13 | Trifluoroethanol | rt | 24h | 2 | 1 | 22 | 3 | 3 | 69 |
| 14 | Trifluoroethanol | 40 $^{o}$C | 24h | <1 | 5 | 33 | 4 | 6 | 51 |

[a]Refer to the Experimental Section. Briefly, sodium salt of methyl 4-hydroxybenzoate (1 eq.) and 1-bromo-3-methyl-2-butene (1.2 eq.) were subjected to the given reaction condition unless noted otherwise; [b]Determined by isolated yields or HPLC analysis; [c]Methyl 4-hydroxybenzoate; [d]2.4 eq. of 1-bromo-3-methyl-2-butene was used.

**Scheme 1**. Synthetic strategy for the synthesis of myrsinoic acid A and E



**Scheme 2.** Synthesis of myrsinoic acid A and E

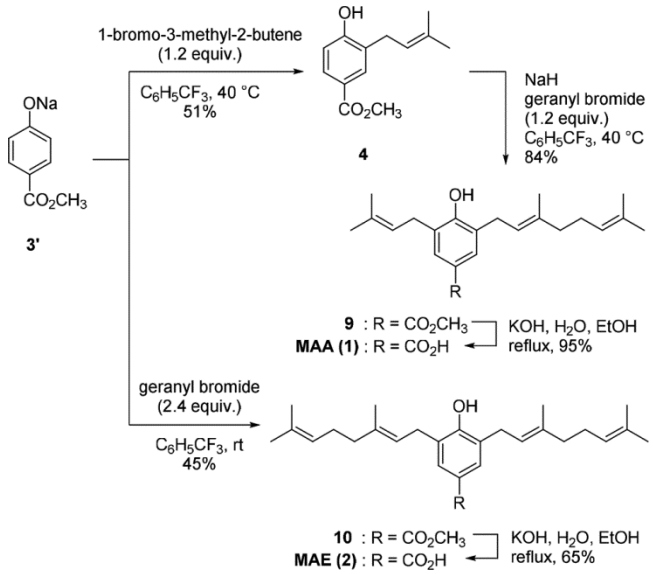
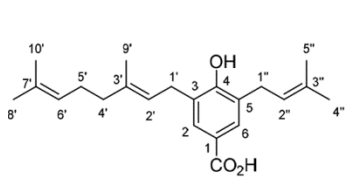
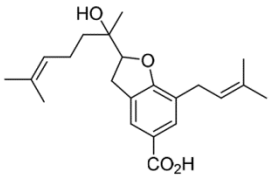


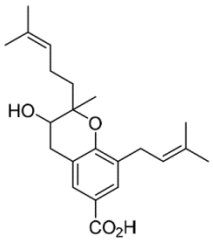
**Figure 1**. The structures of natural myrsinoic acids



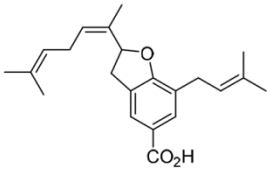

Myrsinoic acid A (**1**)



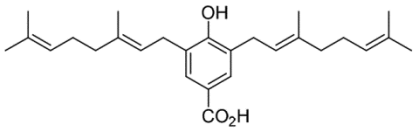

Myrsinoic acid B




Myrsinoic acid C




Myrsinoic acid F




Myrsinoic acid E (**2**)