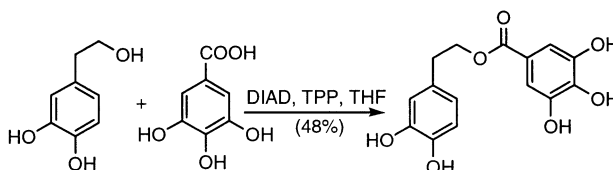# Chemoselective Esterification of Phenolic Acids and Alcohols

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ABSTRACT

The Mitsunobu reaction can distinguish between alcohol and phenol hydroxyls in esterification reactions, providing an expeditious and broadly applicable entry into various phenolics and polyphenolics of biomedical and nutritional relevance.

Phenolic alcohol and phenolic acid ester motifs are widespread within bioactive natural products, with examples being, within primary esters, the NF-κB inhibitors CAPE (**1a**)[1,2] and capsiate (**2**),[3] the honeybee propolis contact allergen prenyl caffeate (**1b**),[4] and the EGCG mimic and HIV-1 reverse transcriptase inhibitor hydroxytyrosol gallate (**3**).[5] These compounds are structurally unsophisticated, but their reported syntheses are not easily amenable to the generation of analogues, due to either a heavy burden of protecting groups or the use of harsh conditions and/or a large excess of one of the reactants.[2−5]

Faced with the problem of building a library of analogues of CAPE and capsiate to unravel their structure−activity relationships, we have investigated in detail the esterification of phenolic acids and phenolic alcohols and report here a practical and rational solution to the problem, endowed with
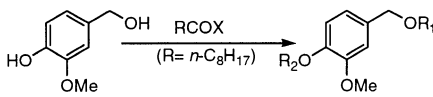
(1) Abbreviations: CAPE, caffeic acid phenylethyl ester; EGCG, epigallocatechin-3-*O*-gallate; PPAA, 1-propylphosphonic acid cyclic anhydride; DEPC, diethyl phosphorocyanidate; DIAD, diisopropyl azodicarboxylate; TPP, triphenylphosphine.

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(3) Sancho, R.; Lucena, C.; Macho, A.; Calzado, M. A.; Blanco Molina, M.; Minassi, A.; Appendino, G.; Muñoz, E. *Eur. J. Immunol.* **2002**, *32*, 1753−1763.

(4) Stüwe, H.-T.; Bruhn, G.; König, W. A.; Hausen, B. M. *Naturwissenshaften* **1989**, *76*, 1989−1990.

(5) Tillekeratne, L. M. V.; Sherette, A.; Grossman, P.; Hupe, L.; Hupe, D.; Hudson, R. A. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2763−2767.

general applicability for the synthesis of primary alkyl (poly)phenolic esters. The esterification of phenolic alcohols and
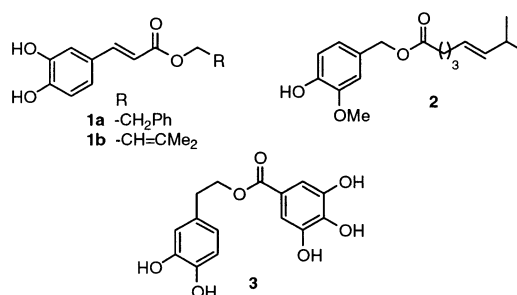
phenolic acids via acyl nucleophilic substitution under nucleophilic catalysis requires protection of phenolic hydroxyls, since acids activated in situ (isoureas and mixed phosphoric anhydrides) or ex situ (chlorides, anhydrides, and mixed anhydrides) show poor discrimination between hydroxyls bound to aliphatic and aromatic carbons. Table 1 vividly demonstrates this, using the synthesis of vanillyl nonanoate (**4**), a capsiate mimic,[2] as an example.

Phenolic acids have been esterified with excellent chemoselectivity in the presence of strong protic acids (Fischer esterification), but the harsh reaction conditions and the excess of alcohol required to drive the reaction to a

X	conditions	R_1=COR R_2=COR	R_1=COR R_2=H, (**4**)	R_1=H R_2=COR
Cl	pyridine	22%	29%	7%
OCOR	pyridine	17%	25%	9%
OPiv	TEA, DMAP	36%	10%	
OH	DCC, DMAP	4%	11%	20%
OH	DEPC,TEA	9%	42%	18%
OH	PPAA, TEA	13%	14%	19%
Cl	Yb(OTf)$_3$, THF		19%	
OH	DIAD,TPP,THF		67%	

[a] Reactions were carried out at room temperature on a 2 mmol scale, with equimolecular amounts of reagents and condensing agents (DCC, DEPC, PPAA, DIAD−TPP) and catalytic (10%) amounts of promoters (DMAP, Yb(OTf)$_3$), when indicated. Reactions were worked up after 24 h, except for the Yb(OTf)$_3$-promoted esterification, which was worked up after 96 h due to a slower conversion. [b] Isolated yield after column chromatography (silica gel, petroleum ether−EtOAc gradient).

satisfactory degree of conversion make this strategy of limited applicability.[6] A certain degree of chemoselectivity in the esterification of phenolic alcohols was also reported for Lewis acid-catalyzed acylations,[7] a type of reaction that takes place under more benign conditions than Fischer esterification. Indeed, at least with the test reaction of Table 1, excellent chemoselectivity was observed in the ytterbium triflate-promoted esterification.[8] However, the yield was modest, and the long reaction time requested for the reaction (96 h) made it unsuitable for more hydroxylated and sensitive substrates. Apart from protection, no other general strategy seems possible for the esterification of phenolic acids using acyl activation.[9]

Switching from carbonyl- to hydroxyl activation would be a mechanistically rational alternative to the "protection racket",[10] since phenolic carbons are not substrates for S_N2-type reactions. Thus, the cesium salts of phenolic acids[11] have been reported to react with alkyl halides in a highly chemoselective way,[4] but the modest yield, also with an excess of halides, leaves margin for further research and improvement. In particular, the scope and versatility of the alkyl activation strategy would be substantially improved if

alcohols, a type of compounds more easily available than halides, could be directly used in the reaction. In this way, the reaction could be extended to multifunctional substrates such as phenolic alcohols, providing an expeditious entry into several classes of polyphenolics of biomedical and nutritional interest.

We reasoned that in the esterification of acids and alcohols promoted by the Mitsunobu redox couple, phenolic hydroxyls present on either substrate should essentially behave as "inert spectators", even though the reaction has been largely employed for the synthesis of phenolic ethers.[12] Thus, the S_N2-type mechanism of the reaction rules out aromatic carbons as electrophilic substrates, while the generation of the nucleophilic species by deprotonation with a stabilized azaenolate, a relatively weak base,[13] secures that carboxylates rather than phenates are formed, provided that stoichiometric amounts of reagents are employed.[14] This turned out to be the case, and the excellent results observed in the Mitsnunobu esterification of vanillic alcohol with nonanoic acid (Table 1) could be extended to the preparation of esters of phenolic acids related to CAPE (Table 2) and of esters of phenolic alcohols related to capsiates (Table 3).
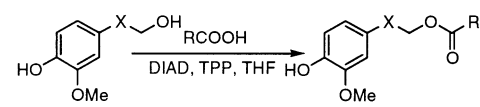
R_1	R_2	R_3	X	yield
H	OH	PhCH$_2$−	(E) −CH=CH−	54%
OMe	OMe	PhCH$_2$−	(E) −CH=CH−	59%
H	OH	(Me)$_2$C=CH−	(E) −CH=CH−	42%
H	OH	CH$_3$−(CH$_2$)$_6$−	(E) −CH=CH−	59%
H	OMe	PhCH$_2$−	−CH$_2$−CH$_2$−	81%
H	OMe	PhCH$_2$−	−CH$_2$−	78%
H	OMe	PhCH$_2$−		58%
H	H	PhCH$_2$−		64%
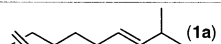
The application to the synthesis of caffeates is worthy of mention, since the esterification of caffeic acid is notoriously troublesome[15] and has led to alternative protocols based on

(6) As an example, treatment of caffeic acid with 15 molar equiv of β-phenethyl alcohol under the conditions of Fischer esterification (*p*-toluenesulfonic acid, refluxing overnight in benzene with a Dean−Stark trap) has been reported to afford CAPE in 35% yield (Burke, T. R., Jr.; Fesen, M. R.; Mazumder, A.; Wang, J.; Carothers, A. M.; Grunberger, D.; Driscoll, J.; Kohn, K.; Pommier, Y. *J. Med. Chem.* **1995**, *38*, 4171−4178).

(7) Chandra, K. L.; Saravanan, P.; Singh, R. K.; Singh, V. K. *Tetrahedron* **2002**, *58*, 1369−1374.

(8) Damen, E. W. P.; Braamer, L.; Scheeren, H. *Tetrahedron Lett.* **1998**, *39*, 6081−6082. See also: Holton, R. A.; Zhang, Z.; Clarke, P. A.; Nadizadeh, H.; Procter, D. J. *Tetrahedron Lett.* **1998**, *39*, 2883−2886.
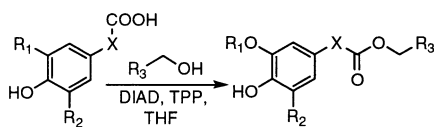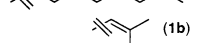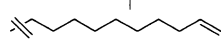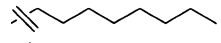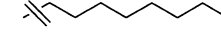
(9) Deprotection of polyphenolic esters is often not a trivial operation. See, for instance: Kim, D. S. H. L.; Kim, J. Y. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2541−2543.

(10) Gani, D. *Nature* **2001**, *414*, 703−705.

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(12) (a) Hughes, D. L. *Org. Prep. Proced. Int.* **1996**, *28*, 127−164. (b) Hughes, D. L. *Org. React.* **1992**, *42*, 335−656. (c) Castro, B. R. *Org. React.* **1983**, *29*, 1−162. (d) Mitsunobu, O. *Synthesis* **1981**, 1−28.

(13) Hughes, D. L.; Reamer, R. A.; Bergan, J. J.; Grabowski, E. *J. Am. Chem. Soc.* **1988**, *110*, 6487−6491.

(14) The mechanism of the Mitsunobu reaction is still controversial. Over the years, a proposal involving formation of the "consensus" alkoxyphosphonium intermediate (**C**) by alcoholate displacement of an acyloxyphoshponium ion (**B**) rather than by direct reaction of an alcohol with the protonated Mitsunobu betaine (**A**) has gained support (Hughes, D. L.; Reamer, R. A. *J. Org. Chem.* **1996**, *61*, 2967−2971). This mechanism is capable of rationalizing the retention of configuration observed in the Mitsunobu lactonization of hindered secondary hydroxy acids, where alcoholate attack at the carbonyl rather than the phosphor atom of intermediate **B** apparently takes place (Ahn, C.; Correia, R.; DeShong, P. *J. Org. Chem.* **2002**, *67*, 1751−1753). However, the chemoselectivity observed in the Mitsunobu esterification of phenolic alcohols is better explained by a mechanism that does not involve deprotonated alcohols, since phenol etherification should compete with alkyl ester formation if

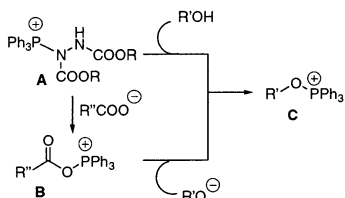**Table 3.** Mitsunobu Esterification of Phenolic Alcohols

R	X	yield
(1a)	-	51%
(1b)	-	59%
	-	62%
	-CH₂-	73%
	(E)-CH=CH-	67%

Scheme 1. Mitsunobu Esterification of Polyphenolic Acids with the Polyphenolic Alcohol **5**[a]

[a] Conditions: DIAD, TPP, THF, rt.

the Wittig reaction of 3,4-dihydroxybenzaldehyde and alkoxycarbonyl phosphoranes under sonochemical activation.[16]

As a final point, we would like to remark that the Mitsunobu reaction can also be applied to the chemoselective esterification of polyphenolic acids *with* polyphenolic alcohols, as demonstrated by the condensation of hydroxytyrosol (**5**), a major antioxidant of olive oil,[17] with gallic acid and with caffeic acid (Scheme 1). Compound **3** had previously been prepared in five steps and 5% overall yield.[5] Remarkably, under Mitsunobu conditions, it could be prepared in one step only (48% yield) and without resorting to any protecting group.

The purification of polar and highly air-sensitive compounds such as **3** and **6** was greatly simplified by gel permeation chromatography.[18] Thus, the strong affinity of Sephadex LH-20 for polyphenolics made possible an easy removal of the Mitsunobu byproducts (triphenylphosphine oxide and hydrazodicarboxylates) by simple step gradient

elution.[19] This procedure was ineffective for the purification of the more lipophilic esters reported in Tables 2 and 3, which were purified by conventional gravity column chromatography on silica gel.

Despite the growing popularity of the Mitsunobu reaction to carry out nucleophilic substitutions directly on alcohols,[12] its potential for the chemoselective esterification of phenolic alcohols and phenolic acids had surprisingly gone unnoticed.[20] Due to the mild conditions and the possibility of capitalizing on Sephadex chromatography for a quick recovery of the products from the reaction mixture, the Mitsunobu reaction is especially suitable for the synthesis of multifunctional and air-sensitive polyphenolics, a class of compounds of great biomedical and nutritional relevance.[21,22]

deprotonation is not limited to the acid. Similar considerations apply to the chemoselective Mitsunobu esterification of 2,3-dihydroxyesters, where esterification has been observed to occur chemoselectively to the least acidic, and therefore more nucleophilic in the nonionized form, β-hydroxyl (Ko, S. Y. *J. Org. Chem.* **2002**, *67*, 2689−2691).
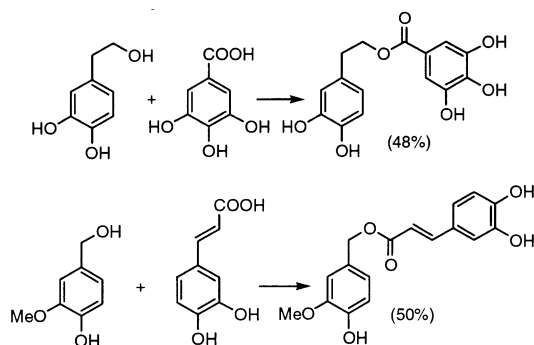

(15) For instance, octyl caffeate, a powerful cytotoxic analogue of CAPE, was recently reported in 7% yield from the reaction of the sodium caffeate and *n*-octyl bromide (Etzenhouser, B.; Hansch, C.; Kapur, S.; Selassie, C. D. *Bioorg. Med. Chem.* **2001**, *9*, 199−209). This yield is over 1 order of magnitude lower than that obtained with the Mitsunobu protocol (Table 2).

(16) Bankova, V. S. *J. Nat. Prod.* **1990**, *53*, 821−824.

(17) Visioli, F.; Galli, C. *Crit. Rev. Food Sci. Technol.* **2002**, *43*, 209−221.

(18) Cardellina, J. H., II. *J. Nat. Prod.* **1983**, *46*, 196−199.

(19) Synthesis of **3** as a representative protocol. To a cooled (0 °C) solution of freshly prepared (Baraldi, P. G.; Simoni, D.; Manfredini, S.; Menziani, E. *Liebigs Ann. Chem.* **1983**, 684−686) hydroxytyrosol (260 mg, 1.64 mmol) and gallic acid (286 mg, 1.64 mmol, 1 molar equiv) in dry THF (3.5 mL) were added TPP (459 mg, 1.64 mmol, 1 molar equiv) and DIAD (342 µL, 1.64 mmol). After stirring at room temperature for 48 h, the reaction was worked up by removal of the solvent, and the residue was partitioned between EtOAc and saturated NaHCO₃ (ca. 50 mL each). The organic phase was washed with brine, dried (Na₂SO₄), and evaporated. The residue was purified by chromatography on Sephadex LH-20 (35 mL after EtOAc swelling), using EtOAc to remove the Mitsunobu byproducts, and 5:5 EtOAc−MeOH to recover **3** (240 mg, 48%), obtained as a yellowish powder (HPLC purity: 94%).

(20) The Mitsunobu reaction has, however, been employed to differentiate hydroxyls having different acidities. See ref 14.

(21) Haslam, E. *Shikimic Acid. Metabolism and Metabolites*; Wiley & Sons: Chichester, UK, 1993.

(22) For leading studies in polyphenolics synthesis, see: Kozikowski, A. P.; Tückmantel, W.; Hu, Y. *J. Org. Chem.* **2001**, *66*, 1287−1296 and previous articles in this series.