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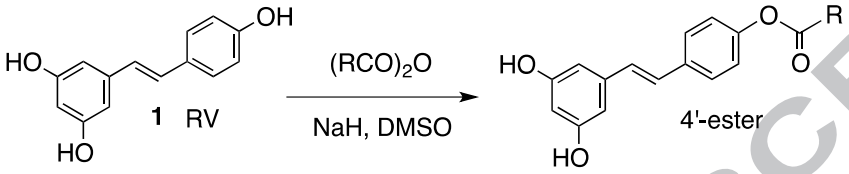

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Selective esterification of the polyphenol resveratrol at the 4'-position

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ABSTRACT

Selective esterification of the polyphenol resveratrol was performed under thermodynamic conditions using NaH and acid anhydrides to directly access 4'-esters. Standard conditions with acetyl chloride and pyridine showed poor selectivity, favoring esterification at the 3-position. The extended 4'-phenolate anion is generated in preference to the 3-phenolate under the new anhydride-sodium hydride-DMSO conditions. Acylation occurs to access the 4'-ester products with modest selectivity and yield with minimal formation of the 3-monoester, 3,5-diester and triester products.

Selective functionalization of natural products allows for modifications that can lead to improvements in biological activity, stability, availability, solubility, and metabolism.[1] Many natural products have potent in vitro activity, as seen in cell-based assays, and yet suffer from poor bioavailability in whole organisms being rapidly cleared with low cell permeability and transport. Poor pharmacodynamics are often due to low solubility, and oxidation or glycosylation leading to rapid clearance.[2] Covalent attachment of suitable functionality can be used to address these drawbacks by modulating the polarity of the compound to improve transport and blocking sights of oxidation and glycosylation to lower clearance. Selective modification can also allow for unmasking of active functionality in a pro-drug manner once target proximity is achieved.[3] Added functionality holds potential to minimize off target interactions by lowering affinity with unwanted receptors. Plant polyphenols possess numerous beneficial activities as demonstrated with in vitro assays, yet they show poor bioavailability characteristics with rapid clearance.[4] Resveratrol (RV), 3,5,4'-trihydroxystilbene **1**, a phytoalexin polyphenol present in various plants (Figure 1),[5] has a short ½-life (30 min) due to rapid glycosylation and sulfate formation.[6] Yet, reports show that this compound holds promise with potent activity as an activator of the protein deacetylase SIRT1 that controls gene silencing, cell cycle regulation, and longevity.[7] Resveratrol is also an inhibitor of quinone reductase II[8] and apurinic endonuclease I (APE/Ref-I),[9] a DNA repairase.

Previously, we reported the synthesis of RV esters, including **2** and **3**, and diesters using a palladium-*N*-heterocyclic carbene catalysis decarbonylative Heck approach with protected benzoyl chlorides and 4-acetoxystyrenes in four steps.[10] We now report the development of a selective acylation approach to 4'-RV esters through direct treatment of RV **1** with anhydrides via thermodynamic deprotonation.

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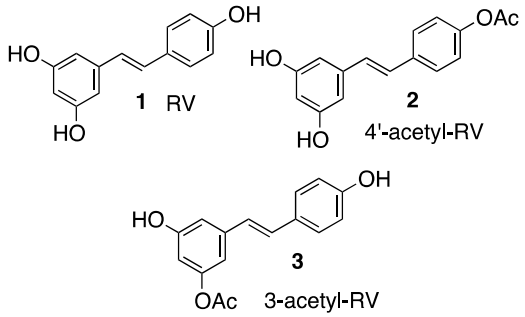
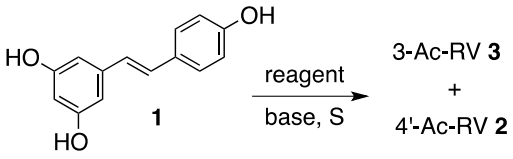


Figure 1. Stilbene polyphenol RV **1** and acetates **2** and **3**

Plant polyphenols typically possess at least three aryl hydroxyls appended on two benzenes, as with the flavones and isoflavones, quercetin, genistein, which readily undergo oxidation to the para-quinone, glycosylation, uronylation, or sulfation generating polar metabolites.[11] RV **1** lacking a 1,4-diol needed for para-quinone formation undergoes glycolsylation and sulfation primarily through the 4'-hydroxyl.[6] The multi-drug resistance transport proteins, MRP2 and BCRP, also contribute to the low bioavailability of RV.[12] The synthesis of various 3, 5, and 4'-ester analogs and fluoro variants of RV **1** have been reported together with anticancer activity and longevity promotion assays.[10] 4'-Acetyl RV **2** (4AR, Figure 1) was modestly more active (ED_{50} 17 μM) compared to RV (22 μM) with HL-60 cells[10b] and was found to be more effective with melanoma cells.[10a] 4'-Acetyl RV **2** was resistant to decomposition, remaining stable as a pure white solid over extended time, compared to RV which rapidly yellows. Longevity studies with yeast using 4'-acetyl RV **2** also showed improved stability and activity compared to RV **1** by extending lifespan at a reduced dose.[13] Direct access, now in one step from RV **1,** to improved analogs offers the potential for new therapeutic applications with enhanced stability and bioavailability.[2] Selective esterification also holds potential for improving related polyphenols that show similar poor availability.[14] Enzymatic based approaches to direct RV acylation require vinyl acetate and are limited in scope with low yields and poor selectivity.[15]

Initial efforts for direct RV **1** esterification focused on the use of standard conditions with acetyl chloride and pyridine in methylene chloride (Table 1).[16] In all cases with various equivalents, solvent, and temperature changes, the undesired triacetate was found to be the dominant product. Use of less reactive acetic anhydride with NaOH in water,[17] the mono-RV esters could be obtained with the 3-acetate **3** dominant 1.2:1.0 over the desired 4'-acetate **2**. Unreacted RV was also obtained in these cases. Potassium carbonate as base in ethanol showed similar selectivity for **3**. A significant improvement was finally achieved using acetic anhydride in excess (1.5 equiv) at rt to provide selective 4'-mono-acetate formation with **2** dominant 4.6 to 1.0 over **3**. Excess sodium hydride in THF[18] at elevated temperature led to further improvement to 5 to 1 for the 4'-acetate **2**, however, the problem of unreacted starting material remained.

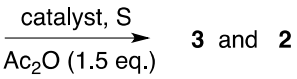
Table 1. Acylation of RV **1** with AcCl or Ac_2O.



reagt	equiv.	base	solvent	T (°C)	**3:2**
AcCl	3	pyr.	CH_2Cl_2	rt	tri-Ac-1
Ac_2O	1	"	acet.	rt	"
"	1	NaOH	H_2O	0 °C	1.2:1.0
"	1	K_2CO_3	EtOH	rt	1.3:1.0
"	1.5	K_2CO_3	acet.	rt	1.0:4.6
"	1.5	NaH	THF	50 °C	**1.0:5.0**

Mild Lewis acid catalyzed conditions were also explored for selective RV esterification (Table 2). Use of iron(III) chloride (1 mol%) with acetic anhydride (1.5 equiv.)[19] gave a mixture of products with slight selectivity for 4'-acetyl-RV **2**. Unreacted RV **1** remained and the reaction did not proceed further after 45 min. Catalytic nickel(II) chloride[20] proceeded at a slower rate with higher selectivity for **2**, 3 to 1 over **3**, yet RV **1** remained as the major product. Other catalysts attempted, $TiCl_3 \cdot 4H_2O$,[21] $ErCl_3$,[22] TiO_2,[23] and $InCl_3$ in acetonitrile[24] as solvent, all showed moderate selectivity for 3-acetyl RV **3** over **2**. $TiCl_3 \cdot 4H_2O$ was best, requiring 48 hr to give **3** 2.4 to 1 over **2**. TiO_2 conditions rapidly gave products, **3** again being slightly favored, with RV **1** remaining largely unreacted.

Table 2. Catalytic Lewis Acid Acylation of RV **1**.



catalyst	solvent	time	**3:2:1**
$FeCl_3$ 1mol%	THF	45 min	1.0:1.4:3.3
$NiCl_2$ 10mol%	"	24 hr	1.0:3.1:5.1
$TiCl_3 \cdot 4H_2O$	MeCN	48 hr	2.4:1.0:1.6
$ErCl_3$	"	"	1.3:1.0:1.3
TiO_2	"	45 min	1.6:1.0:27
$InCl_3$	"	48 hr	2.7:1.0:1.2

The analysis of the product distribution in these cases was made straightforward due to our experience with the synthesis of individual RV esters and diesters reported previously.[10b] Analysis of the ^{1}H NMR (500 MHz) 6 to 8 ppm shift range of the crude material allowed for product identification and quantification due to well resolved C4 proton signals for the esters and the starting material RV (Figure 2). TLC readily distinguished RV **1** from mono-, di-, the tri-ester formation and ^{1}H NMR allowed for reliable monoester differentiation due to a C4 proton shift difference of 0.2 ppm between **3** and **2**. The example shown corresponds to the conditions of acetic anhydride and potassium carbonate in ethanol (Table 1.)

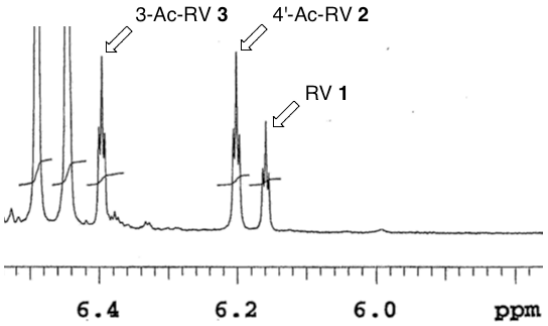
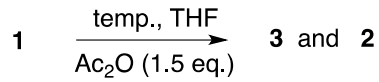


Figure 2. ^{1}H NMR analysis of RV **1** acetylation showing key C4 proton shifts at 6.18 ppm for RV **1**, 6.20 ppm for 4'-Ac-RV **2** and 6.40 for 3-Ac-RV **3**.

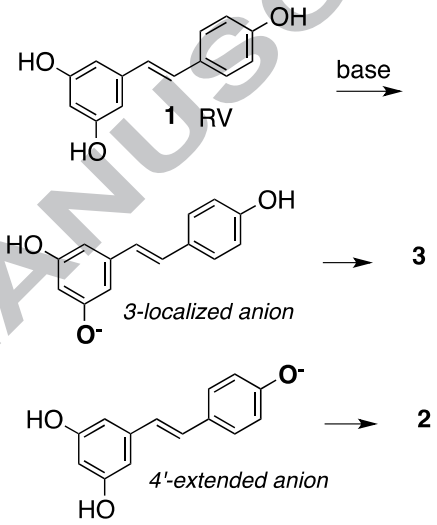
The moderately selective result for 4'-acylation giving **2** over **3** using the conditions reported by Rappoport with NaH in THF[18] was further explored over a wide temperature range (Table 3). NaH (1 equiv.) used at -78 °C with RV **1** (30 min) followed by addition of Ac_2O gave **2** with slight 2 to 1 selectivity over **3**. After 3.5 hr with gradual warming to rt, unreacted RV remained dominant. With *n*-butyllithium as base under comparable conditions[25] the selectivity for **2** increased and it was now found to be the major product. Prolonged reaction times and use of excess base or anhydride gave more 3-ester **3** and 3,5-diester products in these cases. Using 2 equiv. of NaH at 0 °C, the product **2** was further enhanced. Further increases in the temperature, from 25 °C to 65 °C, increased reactions rates, improved selectivity for **2**, and lowered the amount of unreacted RV **1**.

Selective RV **1** acylation using acetic anhydride at this point appeared to be governed primarily by the nature of the solvent and to a lesser extent by the base and reaction temperature. Use of protic solvents, ethanol and water, provided the 3-acetate **3** in slight preference 1.3 to 1 over the 4'-product **2** (Table 1). Switching to acetone and THF showed a dramatic shift in selectivity to the desired 4'-RV acetate **2**, 5 to 1. The pK_a values for RV have been measured showing the 4'-hydroxyl to be most acidic at 8.9 (H_2O), followed by the 3-hydroxyl at 10.[26] The 4'-phenolate is an extended anion that benefits from delocalization through the stilbene alkene (Scheme 1) and can be considered the thermodynamic site of deprotonation leading to **2** following acylation. The 3-phenolate is cross conjugated to the alkene and is not fully delocalized. Due to the presence of the two hydroxyls, at C3 and C5, this site of deprotonation is statistically more probable and can be considered a kinetic pathway giving **3**. In addition, with protic solvents reversible deprotonation is facilitated generating more 3-phenolate leading to more 3-acetyl RV **3** formation. In aprotic solvents, equilibration of deprotonation is less favored promoting the 4'-phenolate to give 4-acetyl RV **2** as the major product. Faster acylation at the 4'-position also leads to lower amounts of diester formation. When the 3-acetate **3** is favored in protic solvents, higher amounts of 3,5-diester was observed. A proximity effect for a second deprotonation shows that the 3-acetate **3** reacts faster than the 4'-acetate **2** when excess anhydride and base are present. Having an ester at the 3-position thus lowers the pK_a of the 5-hydroxyl, while the 4'-ester, being more remote, has less of an effect on diester formation.

Table 3. Temperature variations.



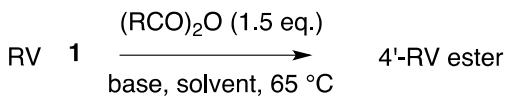
base	equiv.	T (°C)	time (hr)	**3**:**2**:**1**
NaH	1.0	-78-rt	3.5	1.0:2.9:3.9
n-BuLi	1.1	"	1.1	1.0:4.4:3.6
NaH	2.0	0	4	1.0:4.0:2.9
"	1.0	25	2.5	1.0:4.3:2.3
"	1.0	50	2	1.0:5.0:3.2
"	1.1	65	2	1.0:5.0:1.9

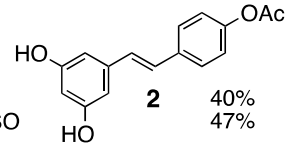
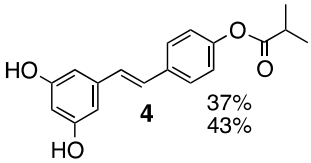
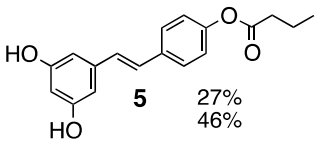
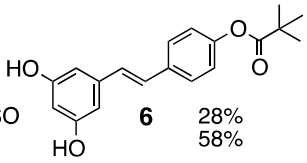
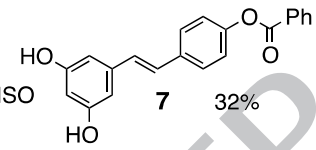


Scheme 1. 3- versus 4'-deprotonation.

Building on the observed 4'-selectivity, developed using THF as solvent, the process was optimized with other anhydrides to provide access to a range of RV ester products (Table 4). Modest isolated yields were obtained for these products using a slight excess of anhydride (1.5 equiv.) in THF or DMSO. Following standard work-up and chromatography 4'-RV acetate **2** (R=Me) was obtained in 40% yield using NaH in THF as developed in previous experiments. The 65 °C reaction temperature proved critical to minimize remaining starting material RV **1**. Use of triethylamine in DMSO showed an improved isolated yield of 47% for product **2**. Less reactive isobutyryl anhydride (R=*i*-Pr) in THF with NaH base gave the 4'-ester **4** in 37% yield. Use of DMSO further improved the yield to 43%. These conditions also provided a useful yield of the *n*-butyryl ester **5** in 46% following chromatography. The slower reacting pivalic anhydride was employed in DMSO with NaH to give the pivaloyl ester product **6** in reasonable 58% yield. Again, use of THF or switching the base to K_2CO_3 gave reduced yields. The corresponding benzoate RV ester **7** was also investigated. Benzoyl chloride with K_2CO_3 gave the best results with a lower 32% yield in this case.

Table 4. Selective 4'-Esterification of RV **1**



R	Base/S	prdt, %yield
Me	NaH, THF Et_3N, DMSO	 **2** 40% 47%
i-Pr	NaH, THF NaH, DMSO	 **4** 37% 43%
n-Pr	NaH, THF NaH, DMSO	 **5** 27% 46%
t-Bu	K_2CO_3, DMSO NaH, DMSO	 **6** 28% 58%
Ph[a]	K_2CO_3, DMSO	 **7** 32%

[a]PhCOCl was used as acylating agent.

The selective mono esterification of the polyphenol RV has been developed using anhydrides in DMSO as solvent to access a variety of 4'-esters. Modest isolated yields of pure products are obtained with 5 to 1 selectivity over the 3-ester and unreacted RV. The process appears to be consistent with a thermodynamic deprotonation and acylation pathway through the 4'-phenolate anion. Use of protic solvents switched the selectivity giving preference for the 3-ester product through reversible formation of the phenolate intermediate. Other types of acyl functionality, including carbonates and carbamates, can now be installed in similar fashion using this one-step approach to directly access new RV variations. The method should also extend to other polyphenols for selective monoacylation and related transformations.

Acknowledgments

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Supplementary Material

Experimental procedures, characterization, including NMR spectra. Supplementary data associated with this article can be found, in the online version, at ScienceDirect.

Selective esterification of the polyphenol resveratrol at the 4'-position

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Highlights

• The polyphenol resveratrol was selectively acylated at the 4'-position using simple reagents.
• Various 4'-esters of resveratrol are now available in moderate yields.
• Selective esterification is due primarlity to the stability of the fully delocalized phenolate ion intermediate.
• Optimal conditions include use of sodium hydride or triethylamine in DMSO.

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