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Synthesis of polyhydroxylated ester analogs of the stilbene resveratrol using decarbonylative Heck couplings

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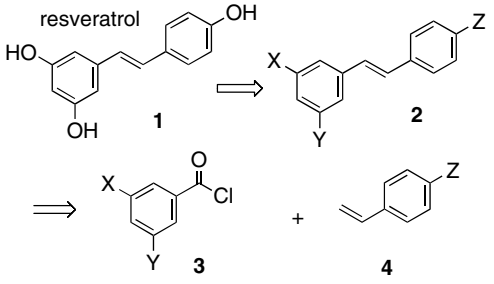
Abstract—Protected 3,5-hydroxy-benzoyl chlorides **3** were coupled with styrenes **4** to give hydroxylated stilbenes, analogs of resveratrol, an important antioxidant disease preventative agent isolated from grape skins and other dietary sources. Levulinate and chloroacetate protecting groups allowed for the selective production of mono- and di-acetate variations under palladium-*N*-heterocyclic carbene (NHC) catalyzed decarbonylative coupling conditions. Fluorinated analogs were also produced using Heck conditions with bromofluorobenzenes. Human HL-60 cell assays showed the 4′-acetoxy variant **11** to have improved activity (ED_{50} 17 μM) relative to resveratrol (24 μM).

We previously reported a short, efficient synthesis of the antioxidant disease preventative stilbene resveratrol **1** using a palladium catalyzed decarbonylative coupling of a benzoyl chloride derived from resorcylic acid **3** (X, Y = OH) and acetoxystyrene **4** (Scheme 1).[1] Interest continues to grow concerning the biological activity and therapeutic potential for this phytoalexin compound isolated from grape skins (50 μg/g) and other sources.[2] Resveratrol has been identified as the causative agent of the 'French Paradox,' and the 'Mediterranean Diet' in that moderate consumption of wine is associated with lower incidence of heart disease and cancer.[3] Recently, resveratrol has also been shown to extend lifetime in yeast and *Caenorhabditis elegans* through activation of sirtuin (SIRT-1, 2) an NAD dependent histone deacetylase that has been shown to directly correlate with cellular longevity.[4] While various biological targets have been implicated and identified, the mechanism of resveratrol's integrated effect on various cellular pathways remains unclear.[5] To facilitate these efforts, we now report the systematic, selective syntheses of acetate and fluoro analogs[6] of resveratrol **2** using decarbonylative Heck couplings[7] with protected resorcylic acid derivatives and styrenes under palladium-*N*-heterocyclic carbene conditions. Resorcylic acid is an ideal, inexpensive starting material as it has the requisite 3,5-substitution pattern and it is easily converted to acid chloride derivatives. Suitable protecting groups on this template can now be employed that allow for efficient cross-couplings with appropriate partners for the selective synthesis of specific resveratrol analogs.



Scheme 1.

4-Acetoxyresveratrol was synthesized in five steps beginning with resorcylic acid **5** (3,5-dihydroxybenzoic acid). Treatment with sodium hydride followed by MOMCl (methoxymethyl chloride) and exposure to sodium hydroxide gave **6** in 91% isolated yield (Scheme 2). Thionyl chloride with added benzotriazole provided acid chloride **7**.[8] Thionyl chloride on its own, without added benzotriazole, was found to be ineffective for this transformation. Decarbonylative Heck coupling with 4-acetoxy styrene **8** was performed using palladium acetate

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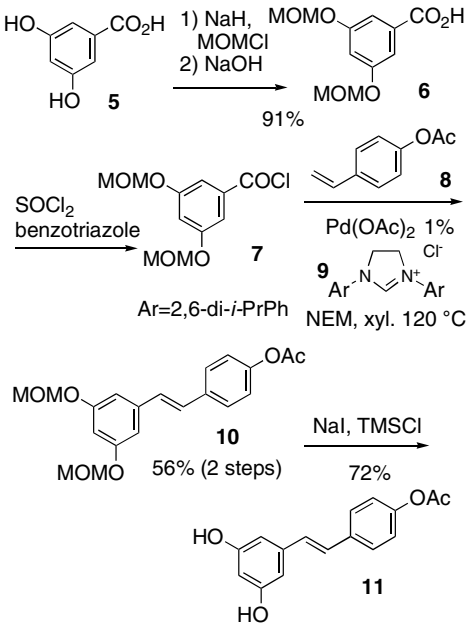


Scheme 2.

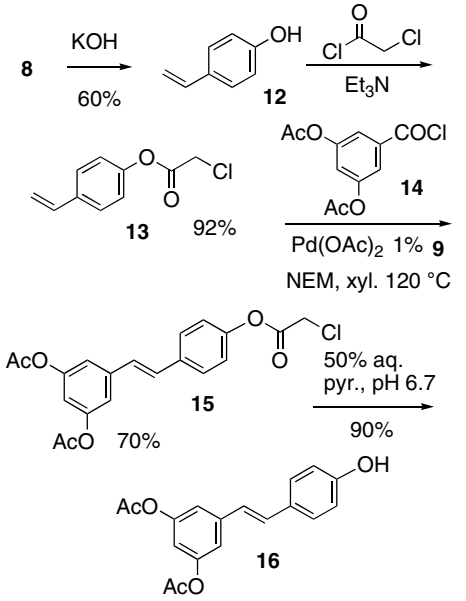
(1 mol %) and *N*,*N*-bis-2,6-diisopropylphenyl-4,5-dihydro chloride **9** (H_2IPr) as an *N*-heterocyclic carbene (NHC) ligand[9] with NEM (*N*-ethylmorpholine) as base in xylenes at 120 °C following the previous route.[1] The di-MOM stilbene **10** was isolated in 56% yield for the two steps, from **6**. The MOM groups were removed using TMSI, generated from TMSCl and sodium iodide, to give 4′-acetoxy-resveratrol **11**.

The 3,5-diacetoxy analog was generated from the unstable intermediate, 4-vinylphenol **12**,[10] which was accessed from acetoxy **8** (Scheme 3). To differentiate between the 3,5 and 4′-hydroxyls in this case, the chloroacetate protecting group[11] was found to be superior to the previously employed MOM ether. Chloroacetate **13** was formed in high yield using chloroacetyl chloride. 3,5-Diacetoxybenzoate, reported previously for the synthesis of resveratrol,[1] was reacted under palladium–NHC **9** conditions to give stilbene **15** (70%). Efficient removal of the chloroacetate, in the presence the 3,5-diacetates, was performed using 50% aqueous pyridine (pH 6.7) to give 3,5-acetoxy resveratrol **16** in 90% isolated yield.

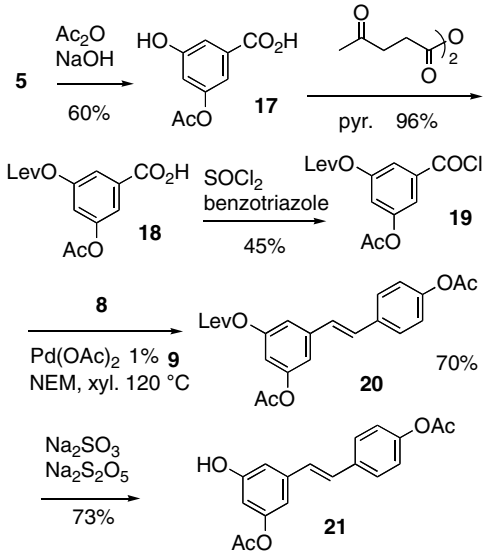
To begin the synthesis of 3-acetoxy resveratrol, resorcylic acid was mono-acetylated in 60% yield using acetic anhydride (1 equiv) and sodium hydroxide (3 equiv) to give **17** (Scheme 4).[12] Protection of the 5-hydroxyl was found to be most efficient using the seldom employed levulinate (Lev, 4-oxopentanoate) group.[13] This group was found to be stable to various reaction conditions, including acid chloride formation and the palladium coupling step, and is readily removed using sodium sulfite via the hydroxysulfite adduct. Mono-acetate **17** was treated with levulinic anhydride in the presence of pyridine to give **18** in 96% isolated yield. Formation of the acid chloride **19** was then performed using thionyl chloride again with added benzotriazole. Coupling under palladium–**9** conditions, as before, generated levulinic ester **20** (70%). The Lev group was then removed by sodium sulfite and thiosulfate to access the desired 3,4′-diacetoxy resveratrol analog **21**.

The levulinate strategy also proved to be most effective for the synthesis of the 3-acetoxy analog (Scheme 5). 4-Hydroxystyrene was treated with levulinic anhydride to give the Lev-protected **22**. Coupling with **19** under the decarbonylative Heck conditions gave the protected stilbene **23** in 72% yield. Removal of the two Lev groups gave 3-acetoxy resveratrol.

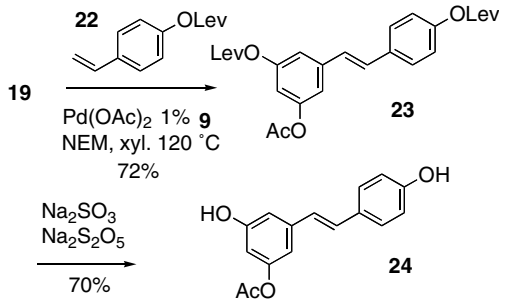
Fluoro analogs were also produced using the decarbonylative coupling reaction (Scheme 6). Resveratrol has been found to have a limited cellular lifetime.[4b,14]



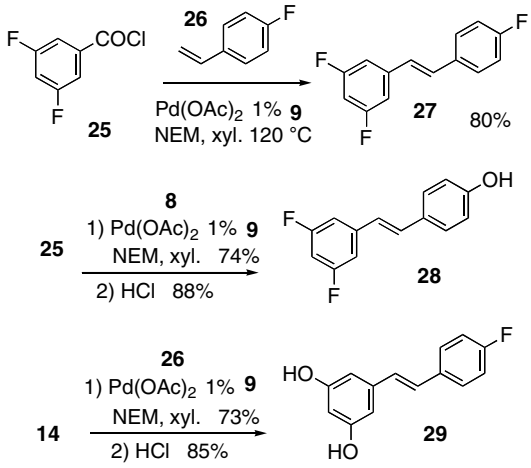
Scheme 3.



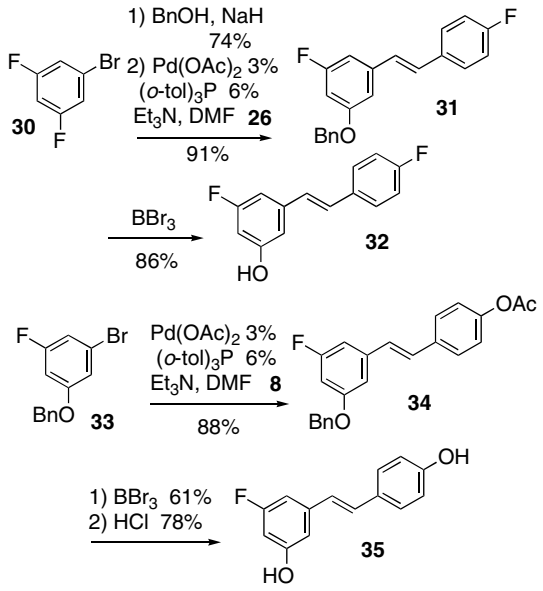
Scheme 4.



Scheme 5.



Scheme 6.



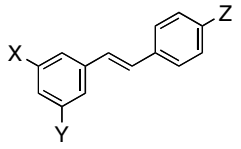
Scheme 7.

Fluoride is isosteric with hydroxyl and the stability of the substituted C–F bond can lead to improved activity and resistance to metabolism.[15] 3,5-Difluorobenzoyl chloride **25** reacted with 4-fluorostyrene to give **27** in 80% yield. Coupling of **25** with 4-acetoxystyrene **8** occurred in 74% yield and the difluoro analog **28** was generated in 88% isolated yield. 3,5-Diacetoxybenzoic acid **14** was also coupled using 4-fluorostyrene **26** to generate 4′-fluoro resveratrol **29** in good overall yield.

To complete the synthesis of the fluoro analog series, it was found that use of bromobenzene substrates under standard Heck coupling conditions known to produce stilbenes[16] was superior to the previous decarbonylative conditions (Scheme 7). 1-Bromo-3,5-difluorobenzene was reacted with benzyl alcohol under sodium hydride conditions to give the benzyloxy substituted product.[17] Heck coupling with 4-fluorostyrene and catalytic palladium acetate with tri-*o*-toluylphosphine gave benzyloxy stilbene **31**. Boron tribromide mediated removal of the benzyl ether generated the 3,4′-difluoro analog **32**. Treatment of the benzyloxy adduct **33**, formed from **30**, with **8** gave stilbene **34** which was converted to the 3-fluoro analog **35** following protecting group removal.

The analogs were tested with human leukemia HL-60 cells to determine anti-cancer potential related to resveratrol (Table 1). The cells were cultured over various times (24, 48, and 72 h) exposed to compounds (5–100 μM) and ED_{50} values were determined using an established protocol.[18,5d] Triacetoxy **2** and 3-acetoxy **24** were found to be comparable to resveratrol (23 μM), while the 3,5- and 3,4′-diacetoxy analogs were less potent. Only the 4′-acetoxy variant **11** showed somewhat improved anti-cancer activity at 17 μM. In general, the fluoro analogs were found to be toxic to this and other cell lines, limiting their potential for future investigations.

Table 1. ED_{50} of resveratrol analogs with HL-60 cells



Compound	X	Y	Z	ED_{50}
1	–OH	–OH	–OH	23
2	–OAc	–OAc	–OAc	27
11	–OH	–OH	–OAc	17
16	–OAc	–OAc	–OH	33
21	–OH	–OAc	–OAc	30
24	–OH	–OAc	–OH	24

A new approach to the synthesis of resveratrol analogs has been developed using efficient decarbonylative cross couplings with substituted acid chlorides and styrenes. Chloro acetate and levulinate protecting groups have been shown to be suitable for this transformation, facilitating selective routes to mono and di-acetoxy analogs. Heck coupling conditions were found to be more effective for 3-fluoro and 3,4′-difluoro resveratrol synthesis. The 4′-acetoxy variant **11** was found to be more potent than resveratrol using an HL-60 cell assay. Further investigations of the biological activities of these compounds, together with the synthesis of a range of 4′-analogs, can now be pursued using this approach.

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Supplementary data

Experimental and ^{1}H NMR data for all compounds are included. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.05.065.

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