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A new efficient resveratrol synthesis

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Abstract—The (*E*)-3,4′,5-trihydroxystilbene (resveratrol) was synthesised via Heck reaction in few steps and with an overall 70% yield.

1. Introduction

In the last few years great interest has arisen concerning resveratrol **1** because of its biological properties: heart protecting activity,[1] platelet antiaggregating capability,[2] herpes simplex viruses inhibition,[3] etc.

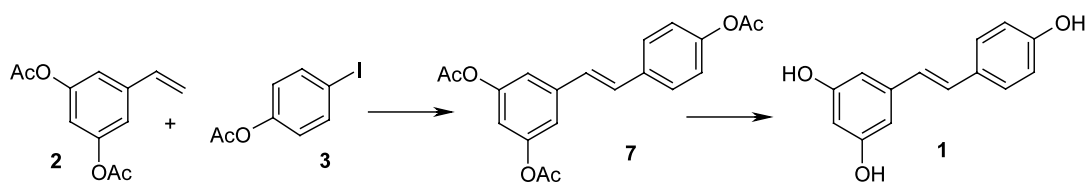
Resveratrol is present only in small amounts in *Vitis vinifera*,[4] and its quantity depends on the stress situation of the plant, as it occurs for all the other phytoalexins. For these reasons it cannot be obtained in large quantities by extractive procedures.

Therefore, many syntheses of **1** have been carried out, generally by using a Wittig reaction to form the ethylenic bridge. In 1985 Moreno-Manas et al.[5] achieved a synthesis of **1** by reacting *p*-hydroxy-benzaldehyde, previously protected as 4-trimethylsilyloxy derivative, with the phosphonium ylid prepared from orcinol. The authors, by this way, obtained only the (*E*)-3,4′,5-trihydroxy-stilbene, but the yield (10%) was very poor. In 1997 Orsini et al.[6] carried out a new synthesis by a Wittig reaction between the 3,5-bis-(*tert*-butyldimethylsilyloxy)benzaldehyde and the phosphonium ylid obtained from (4-methoxybenzyl)-triphenyl-phosphonium chloride; the product of this reaction was a *Z*/*E* mixture, (ratio 2.3:1), of 3,4′,5-trihydroxy-stilbenes. In the same year Alonso et al.[7] synthesised **1** by a lithiation/condensation reaction between 4-methoxy-benzaldehyde and the silyl derivative of 3,5-dimethoxy-benzyl alcohol; the subsequent dehydration of the obtained product, gave only the *E* isomer, however, with low yield (21%). In 1999 Wang et al.[8] reported another synthesis in which 3,5-dimethoxy-benzaldehyde reacted with the triethylphosphate, prepared from 4-methoxy-benzyl bromide, to give, after deprotection and purification, a 45% yield of resveratrol **1**.

Here we report a new efficient synthesis of **1** in which the key step to form the ethylenic bridge between the aromatic rings is a Heck reaction, affording only the natural *E* isomer of resveratrol, as expected by the reported data of original Heck paper.[9]

2. Results and discussion

The synthetic strategy we used, is reported in Scheme 1 and consists of the coupling, through the Heck reaction, of a suitable styrene derivative **2** with the *p*-iodo derivative **3**.



Scheme 1. Refs. 15 and 18.

Keywords: resveratrol; Heck reaction.

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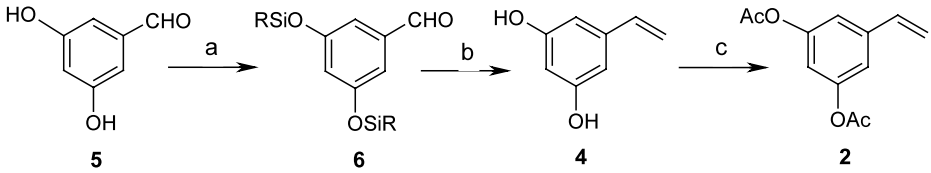

Scheme 2. (a) *N*,*N*,*N*-Diisopropyl-ethylamine, *tert*-butyldimethylsilyl-chloride, anhydrous DMF; (b) $Ph_3P{=}CH_2$, anhydrous DMSO (see text); (c) Ac_2O/Py. Ref. 18.

We chose to utilise the acetyl derivative **3**[10] because it is well known that the Heck reaction gives better yield if phenolic functions are protected.[9]

The 3,5-diacetoxy-stirene, **2**,[11] (Scheme 2) was obtained by acetylation of the 3,5-dihydroxy-stirene **4**[12] which was achieved by Wittig reaction between 3,5-dihydroxy-benzaldehyde, **5**, previously protected as di-*tert*-butyldimethylsilyl-ether **6**[13] and a methylen-triphenyl-phosphorane solution, prepared by suspending NaH in anhydrous DMSO as reported by Greenwald et al.[14]

The Heck reaction was carried out using 1 mol% of $Pd(OAc)_2$, based upon the aryl halide, as catalyst, PPh_3 as ligand (P/Pd 3.5 mol), Et_3N as base and acetonitrile as solvent.[15] The reaction was carried out for about 17 h and the fully acetylated resveratrol **7**[16] was obtained (70% yield) besides small amounts of partially deacetylated ones. Subsequently, compound **7** was deacetylated to obtain resveratrol **1**.[17]

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References

1. Babich, H.; Reisbaum, A. G.; Zuckerbraun, H. L. *Toxicol. Lett*. **2000**, *114*, 143.
2. Zbikowska, H. M.; Olas, B.; Wachowicz, B.; Krajewski, T. *Platelets* **1999**, *10*, 247.
3. Docherty, J. J.; Fu, M. M. H.; Stiffler, B. S.; Limperos, R. J.; Pokabla, C. M.; et al. *Antiviral Res*. **1999**, *43*, 145.
4. Ourtoule, J. C.; Bourhis, M.; Vercauteren, J. *Tetrahedron Lett*. **1996**, *37*, 4697.
5. Moreno-Manas, M.; Pleixats, R. *An. Quim., Ser. C* **1985**, *81*, 157–161.
6. Orsini, F.; Pelizzoni, F.; Bellini, B.; Miglierini, G. *Carbohydr. Res*. **1997**, *301*, 95–109.
7. Alonso, E.; Ramon, D. J.; Yus, M. *J. Org. Chem*. **1997**, *62*, 417–421.
8. Wang, M.; Jin, Y.; Ho, C. T. *J. Agric. Food Chem*. **1999**, *47*, 3974–3977.
9. Ziegler, C. B., Jr.; Heck, R. F. *J. Org. Chem*. **1978**, *43* (15), 2941–2946.
10. *p*-Acetoxy-iodobenzene **3**: ^1H NMR ($CDCl_3$) δ (Hz): 7.66 (2H, d, $J=8.7$, H-3 and H-5); 6.84 (2H, d, $J=8.7$, H-2 and H-6); 2.27 (3H, s, CH_3-CO).
11. 3,5-Diacetoxy-stirene **2**: ^1H NMR ($CDCl_3$) δ (Hz): 7.04 (2H, H-4 and H-8) 6.84 (1H, d, $J=2.0$, H-6); 6.66 (1H, dd, $J_{trans}=17.7$, $J_{cis}=11.0$, H-2); 5.75 (1H, d, $J_{trans}=17.7$, H-1a); 5.33 (1H, d, $J_{cis}=11.0$, H-1b); 2.30 (6H, s, $2CH_3$-CO).
12. 3,5-Dihydroxy-stirene **4**: ^1H NMR ($CDCl_3$) δ (Hz): 6.56 (1H, dd, $J_{trans}=17.7$, $J_{cis}=10.8$); 6.46 (2H, H-4 and H-8); 6.25 (1H, pt, H-6); 5.67 (1H, d, $J_{trans}=17.7$, H–1a); 5.23 (1H, d, $J_{cis}=10.8$, H-1b).
13. 3,5-Bis-(*tert*-butyldimethyl)silyloxy-benzaldehyde **6**: ^1H NMR ($CDCl_3$) δ 9.86 (1H, s, H-1); 6.98 and 6.92 (1H, dd, H-3 and H-7); 6.63 (1H, t, H-5); 0.99 (18 H, s, 2 *tert*-Bu-Si); 0.23 (12H, s, 4 CH_3-Si).
14. Greenwald, R.; Chaykovsky, M.; Corey, E. J. *J. Org. Chem*. **1963**, *28*, 1128–1129.
15. **Experimental procedure**. Compounds **2** (90 mg) and **3** (85 mg) were dissolved in acetonitrile (2 ml); Et_3N (1 ml), $Pd(OAc)_2$ (0.7 mg) and PPh_3 (5.4 mg) were added. The mixture was stirred under an Ar stream and heated at 85°C for 17 h. Small additional portions of **3**, solvent and base were added during the reaction time and product formation was checked by thin-layer chromatography on silica gel (hexane–diethyl ether, 6:4) to follow the disappearance of **2**. The mixture was frozen, acidified by diluting with about 20 ml 1N HCl and twice extracted by diethyl ether. The organic layer, washed by brine, dried and evaporated under reduced pressure gave crude **7** which was purified on silica-gel in hexane–diethyl ether, 4:6, by carrying it at the top of the column adsorbed on silica-gel. The successive removing of acetyl groups was obtained by adding a catalytic amount of sodium methoxide in anhydrous THF–MeOH and stirring under Ar stream. This procedure afforded the resveratrol **1** (yield 99%) which was purified on silica-gel by eluting with diethyl ether–hexane, 8:2.
16. 3,4′,5-Triacetoxy-stilbene **7**: ^1H NMR (CD_3COCD_3) δ (Hz): 7.64 (2H, d, $J=8.4$, H2′ and H6′), 7.30 (1H, d, $J_{trans}=16.5$, H-β), 7.25 (2H, bs, H-2 and H-6), 7.21 (1H, d, $J_{trans}=16.5$, H-α), 7.14 (2H, d, $J=8.4$, H-3′ and H-5′), 6.88 (1H, t, $J=2.1$, H-4), 2.26 (6H, s, $2CH_3$-CO), 2.24 (3H, s, CH_3-CO).
17. Resveratrol **1**: ^1H NMR (CD_3COCD_3) δ (Hz): 7.39 (2H, d, $J=8.1$, H-2′ and H-6′), 6.98 (1H, d, $J_{trans}=16.2$, H-β), 6.87 (1H, d, $J_{trans}=16.2$, H-α), 6.82 (2H, d, $J=8.1$, H-3′ and H-5′), 6.52 (2H, H-2 and H-6), 6.24 (1H, t, $J=2.1$, H-4). ^{13}C NMR (CD_3COCD_3) ppm: 159.3 (C_3, C_5), 158.1.($C_{4'}$), 140.6 (C_1), 129.8 ($C_{1'}$), 128.9 (Cβ), 128.5 ($C_{2'}$, $C_{6'}$), 126.6 (Cα), 116.2 ($C_{3'}$, $C_{5'}$), 105.5 (C_2, C_6), 102.5 (C_4).
18. All isolated compounds afforded satisfactory elemental analysis.