η^6-Arene–tricarbonylchromium complexes in the syntheses of *trans*-resveratrol and pinostilbene

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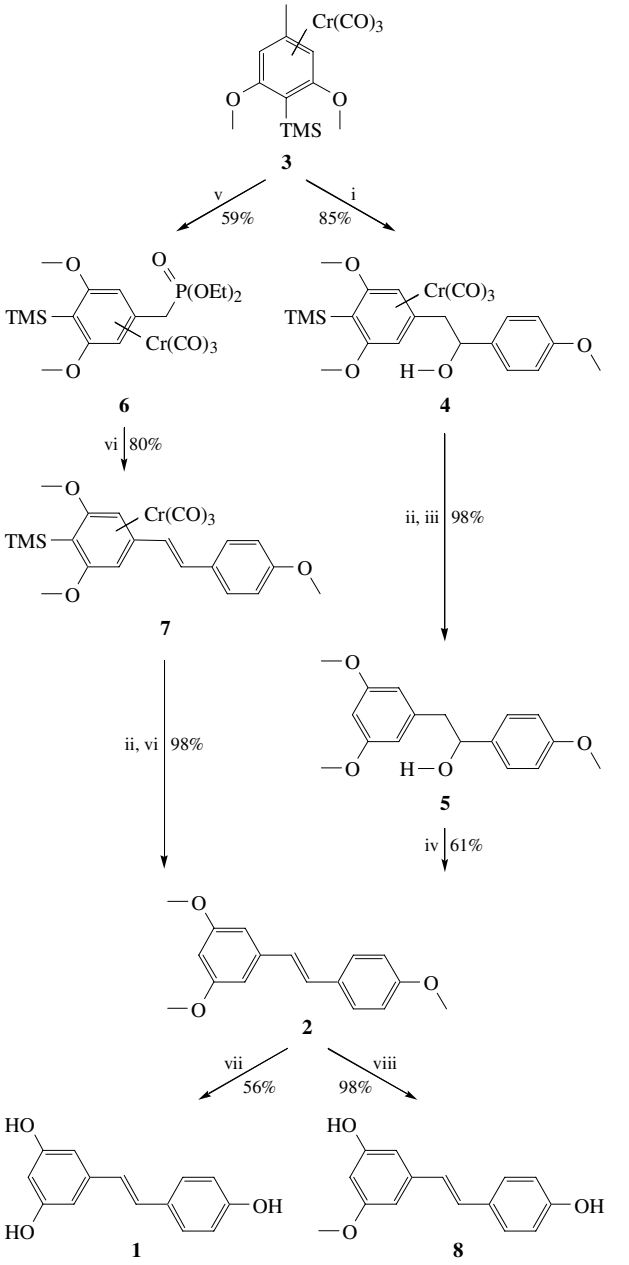
New syntheses of *trans*-resveratrol (*trans*-3,5,4′-trihydroxystilbene) and pinostilbene (*trans*-3,4′-dihydroxy-5-methoxystilbene) *via* nucleophilic demethylation of trimethoxystilbene were performed, whereby *trans*-3,5,4′-trimethoxystilbene was obtained through facilitated benzylic deprotonation of an η^6-benzene-$Cr(CO)_3$ derivative and subsequent coupling with *para*-anisaldehyde in an aldol-type or Wittig–Horner reaction.

During the screening of new substances for anticancer activity, well-known natural product *trans*-resveratrol **1** was identified as a molecule with a very high level of biological activity. For instance, it inhibits the growth and development of cancer cells and preserves contamination of the organism during the development of cancer cells.[1] Furthermore, it was shown that resveratrol has powerful antioxidant and antimutagenic properties.[2] Similar biological activities were also found in pinostilbene and other polyhydroxystilbenes.[3] Stilbenoid compounds also qualify for technical applications such as nonlinear optics, electrophotography and solar energy conversion, owing to their extraordinary optical and optoelectronic characteristics.[4]

A known method for the synthesis of *trans*-resveratrol **1** proceeds through 3,5,4′-trimethoxystilbene **2**, which may be synthesised using a Wittig–Horner reaction from 3,5-dimethoxybenzylbromide and *p*-anisaldehyde *via* the corresponding phosphonate.[5] Another synthesis of **2** uses 3,5-dimethoxy-1-(trimethylsilyloxymethyl)benzene, which is condensed with *p*-anisaldehyde with the help of lithium powder in the presence of naphthalene.[6] Dehydration of the resulting alcohol afforded trimethoxystilbene **2**, which was converted into *trans*-resveratrol **1** by an established methodology. Recently, a Heck reaction has been employed for the synthesis of **1**.[7]

Chromium–arene complexes have frequently proven their value for organic synthesis; they are inexpensive, easy to produce and convenient for synthesis. The chemistry of this class of compounds has been the subject of intense investigations for many years.[8–10] In the course of our research directed towards the synthetic application of η^6-arene-$Cr(CO)_3$ complexes, the preparation of 5-substituted resorcinol derivatives was described.[11–13] We found that the regioselectivity of deprotonation of such complexes may greatly depend on the reaction conditions. For instance, the *ortho*-directing influence of a methoxy substituent can be overcompensated by the use of a sterically hindered base allowing a (contra-thermodynamic) selective functionalization in the 5-position. Furthermore, the benzylic deprotonation/alkylation of 5-methyl-1,3-dimethoxybenzene-$Cr(CO)_3$ derivatives occurs with a surprising ease in excellent yield.[14–15] Oxidative decomplexation of such complexes allows for the liberation of the arene ligands in nearly quantitative yields.[7,12] Scheme 1 is proposed for the synthesis of resveratrol **1** and related stilbenes.

Two variants for the construction of the stilbene were suggested. The first method utilises the facile benzylic deprotonation of tricarbonyl-[η^6-1,3-dimethoxy-5-methyl-2-trimethylsilylbenzene]-chromium(0) **3** and the subsequent (aldol-type) addition of the resulting intermediate with *p*-anisaldehyde. This reaction was conducted in a nitrogen atmosphere by adding BuLi at –40 °C to a solution of complex **3** in dry THF. After stirring for 45 min at the same temperature, the yellow solution was allowed to slowly warm to –10 °C. A colour change to deep red indicated the formation of the benzylic deprotonated intermediate. After cooling to –40 °C, anisaldehyde was added, and the solution was allowed to warm to 0 °C for 1.5 h. After



Scheme 1 *Reagents and conditions*: i, BuLi, THF, –40 °C, *p*-anisaldehyde, –40 °C → 0 °C, 1.5 h; ii, Bu_4NF, THF, one drop of H_2O, 2 h; iii, *hv*, AcOH/Et_2O (1:10), 2 days; iv, *p*-TsOH, PhH, 80 °C, 13 h; v, BuLi, THF, –40 °C, 15 min, Cl–P(O)(OEt)$_2$, –30 °C → 0 °C, 1.5 h; vi, BuLi, THF, –30 °C, *p*-anisaldehyde, –30 °C → 0 °C, 1.5 h; vii, MeMgI, 100 °C, 0.5 h; viii, LiSEt, DMF, 160 °C, 2 h.

workup, product **4**† was obtained as a yellow oil in 85% yield. Desilylation with tetrabutylammonium fluoride and oxidative decomplexation afforded alcohol **5**, which was converted into stilbene **2**.[6]

In the second set of experiments, we prepared stilbene **7** from phosphonate **6** by means of a Wittig–Horner olefination. While some related reactions have been described in arene chromium chemistry,[16] it has never been reported that the required phosphonates (such as **6**) can be directly prepared from the benzylic deprotonated intermediates by reaction with diethylchlorophosphate. Interestingly, phosphonate **6**‡ could be synthesised through the deprotonation of complex **3** with *n*-BuLi in dry THF at –40 °C in a nitrogen atmosphere and the subsequent addition of diethylchlorphosphate to the deep red solution of the deprotonated intermediate at –30 to 0 °C. The Wittig–Horner reaction between phosphonate **6** and *p*-anisaldehyde was then achieved through the deprotonation of **6** with *n*-BuLi followed by the addition of the reaction partner at a low temperature (–30 °C) and warming up to 0 °C. The complexed stilbene **7**§ was obtained as red needles in 80% yield.

The synthesis of key complex **3** from 1,3-dimethoxybenzene has been conducted in three steps in 61% overall yield.[13] While the first method described for the conversion of **3** into stilbene **2** (*via* **4** and **5**) proceeded in four steps with 51% yield, the same overall transformation was achieved (*via* **6** and **7**) in 46% overall yield using the Wittig–Horner reaction as a key step. In the latter case, both the desilylation and decomplexation steps proceeded cleanly with almost quantitative yields.

As a final step for the synthesis of resveratrol **1**, the triple demethylation of trimethoxystilbene **2** had to be performed. The described methods for this transformation (using BBr_3, MeMgI or $LiPPh_2$ as a reagent) afforded the product in 30–60% yield. As a consequence of our positive experience employing lithium thioethylate (LiSEt) for the double demethylation of 1,2-dimethoxybenzene derivatives,[17] we treated **2** (a DMF solution of **2**) with an excess of LiSEt at 160 °C for 2 h. We were surprised and delighted to find that monomethoxystilbene **8** was formed under these conditions in 98% yield. Actually, compound **8** is a well-known natural product called pinostilbene,[1,18] which is found in the bark of *Pinus sibericahas* and exhibits interesting biological properties as an inhibitor of cyclooxygenase (COX-1). It has never been synthesised before. Thus, the selective conversion of **2** to **8** with LiSEt opens an efficient synthetic access to pinostilbene and its derivatives.[19]

When the reaction time of the treatment of **8** with LiSEt was extended to 12 h, resveratrol **1** was formed in 30% yield. Note that all reaction products were fully characterised by ^{1}H, ^{13}C NMR and IR spectroscopy and mass spectrometry.

In conclusion, we found a new strategy for the synthesis of substituted stilbenes such as *trans*-resveratrol exploiting the specific reactivity of 3,5-dimethoxybenzene-$Cr(CO)_3$ complexes. Moreover, the surprisingly selective conversion of trimethoxystilbene **2** into pinostilbene deserves attention as it opens possibilities for the preparation of novel resveratrol analogues with potentially interesting properties. The described route could also be extended for the preparation of other plant hydroxystilbenes, for instance, piceatannol (3,5,4′,5′-tetrahydroxystilbene) and tunalbene (3,3′-dihydroxy-5-methoxystilbene).[19]

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† *Tricarbonyl-[2-(η⁶-3,5-dimethoxy-4-trimethylsilylphenyl)-1-(4′-methoxyphenyl)ethanol]-chromium(0)* **4**: mp 120 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.34 (s, 9H, MeSi), 2.04 (d, 1H, OH, *J* 3 Hz), 2.85 (dd, 1H, CH_2, *J* 14 Hz, *J* 5 Hz), 2.93 (dd, 1H, CH_2, *J* 14 Hz, *J* 8 Hz), 3.61, 3.64 (s, 6H, OMe), 3.82 (s, 3H, OMe), 4.58, 4.65 (s, 2H, 2-C, 6-C), 4.93 (m, 1H, C*H*OH), 6.91 (d, 2H, 2′-C, 6′-C, *J* 9 Hz), 7.29 (d, 3′-C, 5′-C, *J* 2 Hz, *J* 9 Hz). ^{13}C NMR (67.7 MHz, $CDCl_3$) δ: 1.5 (q, MeSi), 26.9 (d, C*H*OH), 45.4 (t, CH_2), 55.4, 55.29, 55.27 (q, OMe), 73.2, 74.6 (d, 2-C, 6-C), 108.3 (s), 114.0 (d, 3′-C, 5′-C), 127.2 (d, 2′-C, 6′-C), 135.3 (s), 148.1 (s), 159.5 (s), 234.5 [s, $Cr(CO)_3$]. IR (KBr, ν/cm^{-1}): 3586 (OH), 2954, 1950, 1865 [C=O, $Cr(CO)_3$]. MS (EI, 70 eV), *m*/*z* (%): 496 (8) $[M]^+$, 412 (100).

‡ *Tricarbonyl-[1-(η⁶-3,5-dimethoxy-4-trimethylsilylphenyl)-methyldiethylphosphonate]-chromium(0)* **6**: mp 130 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.32 (s, 9H, MeSi), 1.34 (t, 6H, Me, *J* 7 Hz), 2.96 (d, 2H, CH_2, $^2J_{PH}$, *J* 20.5 Hz), 3.69 (s, 6H, OMe), 4.13 (m, 4H, OCH_2), 4.74 (s, 2H, 2-C, 6-C). ^{13}C NMR (67.7 MHz, $CDCl_3$) δ: 1.5 (q, MeSi), 16.4, 16.5 (q, Me), 32.7, 34.9 (t, OCH_2), 62.5 (t, CH_2P), 72.27, 72.31 (d, 2-C, 6-C), 79.3 (s, 1-C), 102.3 (s, 4-C), 148.0 (s, 3-C, 5′-C), 234.2 [s, $Cr(CO)_3$]. MS (EI, 70 eV), *m*/*z* (%): 496 (2) $[M]^+$, 412 (100), 285 (68). IR (KBr, ν/cm^{-1}): 2903, 1951, 1866 [C=O, $Cr(CO)_3$], 1230.

§ *Tricarbonyl-[1-(η⁶-3,5-dimethoxy-4-trimethylsilylphenyl)-2-(4′-methoxyphenyl)ethene]-chromium(0)* **7**: mp 202 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.45 (s, 9H, Me-TMS), 3.76 (s, 6H, OMe), 3.83 (s, 3H, OMe), 4.93 (s, 2H, 2-C, 6-C), 6.72 (d, 1H, olefin, *J* 17 Hz), 6.91 (d, 2H, 2′-C, 6′-C, *J* 9 Hz), 6.98 (d, 1H, olefin, *J* 17 Hz), 7.44 (d, 2H, 3′-C, 5′-C, *J* 9 Hz). ^{13}C NMR (67.7 MHz, $CDCl_3$) δ: 1.5 (q, Me-TMS), 55.2, 55.3, 55.4 (q, OMe), 68.9 (d, 2-C, 6-C), 79.4 (s), 106.5 (s), 114.4 (d, 3′-C, 5′-C), 123.9 (d, olefin), 128.3 (d, 2′-C, 6′-C), 128.4 (s), 131.8 (d, olefine), 148.3 (s), 160.2 (s), 234.0 [s, $Cr(CO)_3$]. IR (KBr, ν/cm^{-1}): 2978, 2956, 1935, 1843 [C=O, $Cr(CO)_3$], 1605. MS (EI, 70 eV), *m*/*z* (%): 478 (1) $[M]^+$, 394 (8) $[M - 3CO]^+$, 342 (92) $[M - 3CO - Cr]^+$, 267 (100).