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Sébastien Combes [a] & Jean-Pierre Finet [a]
[a] Laboratoire Chimie, Biologie et Radicaux Libres, UMR - CNRS 6517 Faculté des Sciences Saint-Jérome, 13397, Marseille, Cedex 20, France
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A SIMPLE SYNTHESIS OF THE NATURAL 2,5-DIALKYLRESORCINOL FREE RADICAL SCAVENGER ANTIOXIDANT: RESORSTATIN

Sébastien Combes and Jean-Pierre Finet*

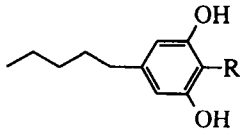
Laboratoire Chimie, Biologie et Radicaux Libres, UMR - CNRS 6517
Faculté des Sciences Saint-Jérôme, 13397 Marseille Cedex 20 - France

Abstract: 3,5-Dimethoxybenzoic acid **3** has been transformed into olivetol dimethyl ether **6** in three steps in 79% yield. Directed *ortho*-metallation-alkylation of **6**, followed by boron tribromide demethylation resulted in a simple and inexpensive synthesis of resorstatin, in 70% overall yield from **3**.

Autooxidation of organic compounds induces a deterioration of the physical properties of long chain hydrocarbons and of polymers.[1] Rancidification of fats and oils is also an important problem in the food industry.[2] The involvement of Reactive Oxygen Species is now well recognised in a variety of diseases.[3,4] A wide range of compounds, belonging to different types of chemical structural families, can act as efficient antioxidants to prevent the effects of autooxidation.[3] Phenols are among the most numerous and most active chain-breaking antioxidants inhibiting the chain propagation of peroxyl radicals. One such compound, which has been recently isolated from *Pseudomonas* sp. DC165, is

*To whom correspondence should be addressed.

Resorstatin **1**.[5] Resorstatin is a low toxic substance, with a weak antibacterial activity, which showed an inhibitory effect on lipid peroxidation of the same activity as the well-known synthetic phenolic antioxidant, BHT (2,6-di-*tert*-butyl-4-hydroxytoluene): resorstatin has an IC_{50} = 2.06 μM against an IC_{50} = 2.44 μM for BHT. Resorstatin belongs to the family of the 5-substituted resorcinols, which present a variety of biological activities, such as fungicidal, bactericidal as well as they behave as DNA-cleaving agents.[6-8]



1 R = $(CH_2)_5CH_3$
2 R = H

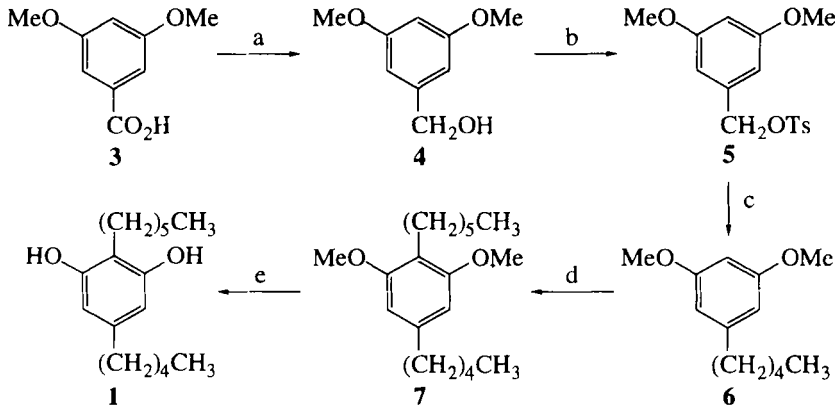
In this paper, we report a short and high-yielding synthesis of this compound. Directed *ortho*-metallation-alkylation[9] of a conveniently protected 5-substituted resorcinol derivatives such as olivetol **2** appeared as an attractive approach, as the synthesis of these precursors is relatively well documented, if not always straightforward. Two major general approaches towards 5-substituted resorcinol have been developed. One is the Michael-type cyclisation of a linear substrate bearing all the required substituents. The methods of this type suffer from poor yields when bulky substituents are present.[10] The other group of methods, involving the elaboration of the side chain of a 5-substituted resorcinol precursor offers a more flexible approach to various structural types.[11] We decided to investigate the elaboration of the relatively inexpensive 3,5-dimethoxybenzoic acid into olivetol dimethyl ether, followed by alkylation of the C-2 carbon atom to prepare resorstatin **1**.

Reduction of 3,5-dimethoxybenzoic acid **3** by $LiAlH_4$ afforded the 3,4-dimethoxy benzyl alcohol **4** quantitatively. Reaction of **4** with *p*-toluenesulfonyl chloride in the presence of an amine led to intractable mixtures or to *N*-benzylpyridinium salt

quantitative yield. The critical step appeared to be the *ortho*-alkylation of **6**, which at first seemed trivial in view of the results described with related systems.[13-15] However, in their studies on the C-2 alkylation of 5-alkylresorcinol dimethyl ether derivatives, Achenbach *et al.* reported that only the 5-methyl compound was efficiently alkylated on the C-2 atom.[13] When the C-5 chain contained two or more carbon atoms, the yields of the alkylation reactions dropped dramatically. As the reaction of the C-2 lithiated species (generated by action of *n*-butyllithium on **6**) with *N*,*N*-dimethylformamide afforded high yields of the corresponding benzaldehydes, the problem seemed restricted to the alkylation reaction step of the sequence. However, in our hands, the results of Achenbach were not reproducible. Indeed, whatever the conditions of the metalation step, including the presence or absence of tetramethylethylenediamine, (TMEDA), in a variety of combinations of solvent and reaction temperatures, no trace of alkylation products could be detected. In fact, trapping with D_2O of the reaction mixture, resulting from the action of *n*-BuLi on **6**, indicated that metallation was not occurring. But when the reaction of **6** with *tert*-butyllithium was monitored by ^1H NMR study of the product of trapping with D_2O, it appeared that the metallation was now complete in a few minutes. Alkylation of the lithium salt of **6** with *n*-hexyl bromide failed or gave poor yields of **7**, when the reaction was performed at -10 °C or 0 °C. At room temperature, less than 15 % of **7** were estimated to be present by ^1H NMR. Moreover, a second new product was observed in 15-25% yields by NMR. This was eventually identified as the oxidation product, 2,6-dimethoxy-4-pentylphenol. When the reaction mixture was stirred under heating at 50 °C after the addition of the alkylating agent, the expected product **7** was now observed in 50-55% yields by NMR, together with less than 10% of the oxidation product. Eventually, the yield of **7** raised to 95% when, after addition of hexyl bromide, the reaction was heated under reflux. Removal of the methyl protecting groups was easily realised

when pyridine was used as a base. However, the tosylate **5** was cleanly obtained by reaction of the lithium salt of the benzyl alcohol derivative **4** with *p*-toluenesulfonyl chloride. Attempted direct displacement of the tosyloxy group by reaction of **5** with the appropriate alkyllithium (*n*-BuLi) resulted in an equimolecular mixture of unreacted **5** and 1-(3',5'-dimethoxyphenyl)pentan-1-ol.

Scheme 1. Sequence of reactions for the synthesis of resorstatin **1**



a) $LiAlH_4$, THF, reflux, 97%; **b)** *i*: MeLi, THF, -10 °C *ii*: *p*-toluenesulfonyl chloride, -10 °C, 90%; **c)** Bu_2CuLi, THF, -10 °C, 91%; **d)** *i*: *tert*-BuLi, THF *ii*: *n*-$C_6H_{13}Br$, THF, reflux, 2h, 90%; **e)** BBr_3, CH_2Cl_2, 25 °C, 2h, 98%

The formation of this latter product can be explained by a Swern-type oxidation of the easily formed α-tosyloxybenzyllithium derivative to 3,5-dimethoxybenzaldehyde, which reacts instantly with the excess of butyllithium to lead to the pentan-1-ol derivative. Indeed, when the tosylate **5** was treated with two equivalents of *n*-BuLi, a near quantitative yield of the pentan-1-ol derivative was obtained. Not unexpectedly, reaction of **5** with *n*-butylmagnesium bromide in the presence of a catalytic amount of copper (I) iodide resulted in the formation of the dimeric 1,2-diarylethane derivative.[12] Eventually, **5** was converted into the required olivetol derivative **6** by reaction with lithium di-*n*-butyl cuprate in a near

by treatment of **7** with BBr_3 in methylene dichloride at room temperature and led to resorstatin **1** in 98% yield.

In conclusion, our synthesis of resorstatin shows that *ortho*-alkylation of resorcinol dimethyl ether can be efficiently performed under carefully controlled conditions and this method should be easily extended to the synthesis of various 2,5-disubstituted resorcinol derivatives of biological interest.[6,7]

Experimental

Melting points were taken on a Büchi capillary apparatus and are uncorrected. ^{1}H-NMR spectra were obtained at 200 MHz and ^{13}C-NMR spectra at 50.36 MHz on a Bruker AC 200 spectrometer. Chemical shifts (δ) are reported in ppm for solutions of the compounds in $CDCl_3$ with internal Me_4Si. In the NMR description of the attributions of compounds **1** and **7**, the carbon atoms of the chain attached to the aromatic C-5 carbon are numbered from 7 to 11, and the carbon atoms of the chain attached to the aromatic C-2 carbon are numbered from 12 to 17. Ether refers to diethyl ether. The organic extracts were always dried over magnesium sulfate.

3,5-Dimethoxybenzyl alcohol 4: A solution of 3,5-dimethoxybenzoic acid **3** (10 g) in anhydrous THF (100 cm^3) was added to a stirred suspension of lithium aluminium hydride (2.5 g) in anhydrous THF (40 cm^3). The mixture was heated under reflux for 1 h, cooled in an ice bath and dilute sulfuric acid (100 cm^3 of a 5% aqueous solution) was added. The aqueous layer was saturated with NaCl and extracted with ether (3 x 20 cm^3). The combined organic extracts were washed with aqueous sodium bicarbonate, brine, and dried. The solvent was distilled and the crude product recrystallised from CCl_4 to afford 3,5-dimethoxybenzyl alcohol **4** as white needles (8.89 g, 97%); mp 48 °C, (lit.[11d] 48-49 °C).

3,5-Dimethoxybenzyl *p*-toluenesulfonate 5: Methyllithium (7 cm^3 of a 1.6 M solution in ether) was slowly added to a solution of 3,5-dimethoxybenzyl alcohol **4** (1.68 g, 10 mmol) in anhydrous THF (30 cm^3) under argon at -10 °C. After stirring at -10 °C for 0.5 h, a solution of *p*-toluenesulfonyl chloride (2.29 g, 12 mmol) in anhydrous THF (20 cm^3) was added. The mixture was stirred for 1 h and then hydrolysed with brine (50 cm^3). The aqueous phase was extracted with dichloromethane and the combined organic solutions were dried. After distillation of the solvent under reduced pressure, ether (10 cm^3) was added to the residue. The 3,5-dimethoxybenzyl tosylate **5** started to crystallise at room temperature. The mixture was kept overnight at - 15 °C and filtered to afford **5** as colorless plates (2.90 g, 90%), mp 64 °C; δ_H 2.42 (3H, s, 4'-Me), 3.72 (6H, s, MeO), 4.96 (2H, s, C<u>H</u>$_2$O), 6.34-6.37 (3H, m, 2-, 4- and 6-H), 7.30 (2H, d, J_{AB} 8.4, 3'- and 5'-H) and 7.77 (2H, d, J_{AB} 8.4, 2'- and 6'-H); δ_C 21.6 (4'-Me), 55.4 (2MeO), 71.9 (C<u>H</u>2O), 101.0 (C-4), 106.2 (C-2 and C-6), 128.0 (C-3' and C-5'), 129.9 (C-2' and C-6'), 133.3 (C-4'), 135.4 (C-1'), 144.9 (C-1) and 160.9 (C-3 and C-5) (Found: C, 59.48; H, 5.64. $C_{16}H_{18}O_5S$ requires: C, 59.61; H, 5.63%).

1-(3',5'-Dimethoxyphenyl)pentan-1-ol: *n*-Butyllithium (1.25 cm^3 of a 2.5 M solution in hexane) was added to a solution of 3,5-dimethoxybenzyl *p*-toluenesulfonate **5** (0.5 g, 1.55 mmol) in anhydrous THF (2 cm^3) under argon at -20 °C. The mixture was stirred for 10 minutes and then hydrolysed with a 10% NH_4Cl aqueous solution. The aqueous layer was extracted with ether, and the combined organic extracts were dried. The solvent was distilled and the residue was purified by flash column chromatography on silica gel (pentane-ether) to give the title compound (0.3 g, 86%) as a oil; δ_H 0.85 (3H, t, *J* 6.8, 5-H), 1.21-1.35 (4H, m, 3- and 4-H), 1.64-1.74 (2H, m, 2-H), 1.92 (1H, s, OH), 3.77 (6H, s, MeO), 4.57(1H, t, *J* 6.6, 1-H), 6.34 (1H, t, *J* 2.3, 4'-H) and 6.48 (2H, d, *J* 2.3, 2'- and 6'-H); δ_C 14.0

(C-5), 22.6 (C-4), 28.0 (C-3), 38.7 (C-2), 55.3 (2 MeO), 74.7 (C-1), 99.3 (C-4'), 103.8 (C-2' and C-6'), 147.7 (C-1') and 160.8 (C-3' and C-5') (Found: C, 69.51; H, 8.91. $C_{13}H_{20}O_3$ requires: C, 69.60; H, 8.99%).

5-Pentyl-1,3-dimethoxybenzene or Olivetol dimethyl ether 6: *n*-Butyllithium (5.6 cm^3 of a 1.6 M solution in hexane, 9 mmol) was added to a suspension of copper (I) iodide (0.86 g, 4.5 mmol) in anhydrous THF (10 cm^3) at -10 °C under argon. After stirring for 10 minutes at -10 °C, a solution of 3,5-dimethoxybenzyl tosylate **5** (0.966 g, 3 mmol) in anhydrous THF (10 cm^3) was added dropwise, and the reaction mixture was stirred for 10 minutes. The mixture was then hydrolysed with a saturated NH_4Cl aqueous solution. The aqueous layer was extracted with ether (3x20 cm^3), and the combined organic extracts were washed with brine (3x20 cm^3) and dried. The solvent was distilled and the crude product was fractionnally distilled to give the title compound **6** (0.567 g, 91%), bp 68 °C (0.01mm) [lit.[11e] 114 °C (2mm)]; δ_H 0.87 (3H, t, *J* 6.7, 11-H), 1.21-1.37 (4H, m, 9- and 10-H), 1.51-1.66 (2H, m, 8-H), 2.53 (2H, t, *J* 7.6, 7-H), 3.76 (6H, s, MeO), 6.28 (1H, t, *J* 2.2, 2-H) and 6.33 (2H, d, *J* 2.2, 4- and 6-H); δ_C 14.0 (C-11), 22.6 (C-10), 31.0 (C-8), 31.5 (C-9), 36.2 (C-7), 54.8 (2 MeO), 97.4 (C-2), 106.3 (C-4 and C-6), 145.1 (C-5) and 160.7 (C-1 and C-3) (Found: C, 74.79; H, 9.63. $C_{13}H_{20}O_2$ requires: C, 74.95; H, 9.68%).

Resorstatin dimethyl ether 7: *Tert*-butyllithium (2.6 cm^3 of a 1.4 M solution in pentane) was slowly added to a cooled (-10 °C) solution of **6** (0.624 g, 3 mmol) in anhydrous THF (5 cm^3) under argon. After stirring for 1 h, the temperature was allowed to reach room temperature. A solution of freshly distilled (over P_2O_5) *n*-hexyl bromide (0.620 g, 3.75 mmol) in anhydrous THF (5 cm^3) was then added. After the addition, the mixture was stirred for 2 h under reflux. After cooling, it

was poured into a saturated NH_4Cl aqueous solution (10 cm^3). The aqueous layer was extracted with ether (3x5 cm^3), and the combined organic extracts were washed three times with brine and dried. The solvent was distilled under reduced pressure and fractionnal distillation of the residue afforded resorstatin dimethyl ether **7** (0.79 g, 90%), bp 110 °C (0.01 mm); δ_H 0.86 (3H, t, *J* 6.6, 17-H), 0.88 (3H, t, *J* 6.7, 11-H), 1.2-1.5 (10H, m, 9-, 10-, 14-, 15- and 16-H), 1.5-1.7 (4H, m, 8- and 13-H), 2.5-2.7 (4H, m, 7- and 12-H), 3.77 (6H, s, MeO) and 6.34 (2H, s, 4- and 6-H); δ_C 13.8 (C-11), 13.9 (C-17), 22.4 (C-10), 22.5 (C-16), 22.6 (C-12), 29.2 (C-13), 29.4 (C-14), 31.1 (C-8), 31.5 (C-9), 31.6 (C-15), 36.4 (C-7), 55.4 (2 MeO), 103.8 (C-4 and C-6), 116.8 (C-2), 141.5 (C-5) and 158.1 (C-1 and C-3) (Found: C, 78.03; H, 11.01. $C_{19}H_{32}O_2$ requires: C, 78.02; H, 11.04%).

2,6-Dimethoxy-4-*n*-pentylphenol: When the previous reaction was stirred at room temperature for 24 hours after the addition of hexyl bromide, 15 to 25% of the title compound was obtained as an oil; δ_H 0.88 (3H, t, *J* 6.6, 11-H), 1.23-1.33 (4H, m, 9- and 10-H), 1.53-1.61 (2H, m, 8-H), 2.51 (2H, t, *J* 7.7, 7-H), 3.86 (6H, s, MeO), 5.34 (1H, s, OH) and 6.38 (2H, s, 3- and 5-H); δ_C 13.8 (C-11), 22.3 (C-10), 29.5 (C-8), 31.3 (C-9), 35.9 (C-7), 56.0 (2 MeO), 104.7 (C-3 and C-5), 132.4 (C-4), 133.8 (C-1) and 146.6 (C-2 and C-6) (Found: C, 69.57; H, 8.96. $C_{13}H_{20}O_3$ requires: C, 69.60; H, 8.99%).

Resorstatin 1: Boron tribromide (3.3 cm^3 of a 1 M solution in anhydrous dichloromethane) was added dropwise to a cooled (0 °C) solution of resorstatin dimethyl ether **7** (0.292 g, 1 mmol) in anhydrous dichloromethane (10 cm^3) under argon. The reaction mixture was then stirred for 2 h at 25 °C. Water (5 cm^3) was added, followed by addition of brine (20 cm^3). The organic phase was washed with brine (3x10 cm^3), dried and concentrated under reduced pressure. The

residue was recrystallised from hexane to afford resorstatin **1** (0.258 g, 98%) as white microcrystals, mp 92 °C, [lit.[5] 88-91 °C]; λ_{max} (ethanol)/nm (ε) 202 (76656), 268 (1776) and 276 (1679); ν_{max} (KBr)/cm^{-1} 3405, 3265, 2925, 2855, 1635, 1585, 1465, 1440, 1330, 1265, 1165, 1110, 1010 and 835; δ_H 0.86 (3H, t, *J* 6.7, 17-H), 0.88 (3H, t, *J* 6.7, 11-H), 1.26-1.40 (10H, m, 9-, 10-, 14-, 15- and 16-H), 1.41-1.62 (4H, m, 8- and 13-H), 2.43 (2H, t, *J* 7.9, 7-H), 2.56 (2H, t, *J* 7.9, 12-H) and 6.22 (2H, s, 4- and 6-H); δ_C 14.1 (C-11), 14.2 (C-17), 22.6 (C-10), 22.7 (C-16), 23.2 (C-12), 29.3 (C-13), 29.6 (C-14), 30.9 (C-8), 31.6 (C-9), 31.9 (C-15), 35.5 (C-7), 108.1 (C-4 and C-6), 112.6 (C-2), 142.3 (C-5) and 154.4 (C-1 and C-3) (Found: C, 77.09; H, 10.55. $C_{17}H_{28}O_2$ requires: C, 77.22; H, 10.67%).

References

1. Scott, G., *Bull. Chem. Soc. Jpn.*, **1988**, *61*, 165.
2. Löliger, J., The use of antioxidants in foods, in *Free Radicals and Food Additives*, Aruoma, O.I. and Halliwell, B. eds., Taylor and Francis, London, **1991**, pp. 121-150.
3. Halliwell, B.; Aeschbach, R.; Löliger, J. and Aruoma, O.I., *Fd. Chem. Toxic.*, **1995**, *33*, 601.
4. Duchstein, H.-J. and Gurka, H.-J., *Arch. Pharm. (Weinheim)*, **1992**, *325*, 129.
5. Kato, S.; Shindo, K.; Kawai, H.; Matsuoka, M. and Mochizuki, J., *J. Antibiotics*, **1993**, *46*, 1024.
6. Mitscher, L.A.; Park, Y.H.; Al-Shamma, A.; Hudson, P.B. and Haas, T., *Phytochemistry*, **1981**, *20*, 781.
7. Alonso, E.; Ramón, D.J. and Yus, M., *J. Org. Chem.*, **1997**, *62*, 417.
8. Lytollis, W.; Scannell, R.T.; An, H.; Murty, V.S.; Reddy, K.S.; Barr, J.R. and Hecht, S.M., *J. Am. Chem. Soc.*, **1995**, *117*, 12683.

9. a) Narasimhan, N.S. and Mali, R.S., *Synthesis*, **1983**, 957; b) Snieckus, V., *Chem. Rev.*, **1990**, *90*, 879; c) Slocum, D.W. and Jennings, C.A., *J. Org. Chem.*, **1976**, *41*, 3653; d) Crowther, G.P.; Sundberg, R.J.; Sarpeshkar, A.M., *J. Org. Chem.*, **1984**, *49*, 4657.

10. a) Anker, R.M. and Cook, A.H., *J. Chem. Soc.*, **1945**, 311; b) Marmor, R.S., *J. Org. Chem.*, **1972**, *37*, 2901; c) Focella, A.; Teitel, S. and Brossi, A., *J. Org. Chem.*, **1977**, *42*, 3456.

11. a) Cannon, J.R.; Cheong, P.R.; Fallick, C.J.; Hamilton, B.H.; McDonald, I.A. and Vinciquerra, G., *Aust. J. Chem.*, **1973**, *26*, 799; b) Krishnamurty, H.G. and Prasad, J.S. *Tetrahedron Lett.*, **1975**, 2511; c) Adams, R.; Chen, K.H. and Loewe, S., *J. Am. Chem. Soc.*, **1945**, 67, 1534; d) Adams, R.; Harfenist, M. and Loewe, S., *J. Am. Chem. Soc.*, **1949**, *71*, 1624; e) Suter, C.M. and Weston, A.W., *J. Am. Chem. Soc.*, **1939**, *61*, 232.

12. Bullpitt, M. and Kitching, W., *Synth. Commun.*, **1977**, *7*, 316.

13. Achenbach, H.; Kohl, W. and Kunze, B., *Chem. Ber.*, **1979**, *112*, 1841.

14. Kotnis, A.S., *Tetrahedron Lett.*, **1991**, *32*, 3441.

15. Stealey, M.A.; Shone, R.L. and Miyano, M., *Synth. Commun.*, **1990**, *20*, 1869.

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