Organic Process Research & Development **2000**, *4*, 534–543

High Selectivity in the Oxidation of Mandelic Acid Derivatives and in *O*-Methylation of Protocatechualdehyde: New Processes for Synthesis of Vanillin, *iso*-Vanillin, and Heliotropin

Hans-René Bjørsvik,*,† Lucia Liguori,‡ and Francesco Minisci*,‡

Department of Chemistry, University of Bergen, Allégaten 41, N-5007 Bergen, Norway, and Dipartimento di Chimica del Politecnico di Milano, via Mancinelli 7, I-20131 Milano, Italy

Abstract:

New synthetic procedures for vanillin, *iso*-vanillin, heliotropin, and protocatechualdehyde starting from catechol are described. The utilisation of statistical experimental design and multivariate modelling and the mechanistic interpretation of the acid and base catalysis in the condensation of catechol derivatives with glyoxylic acid and in the regiocontrolled methylation of protocatechualdehyde and of the Cu(II) salt catalysis in the oxidative decarboxylation of mandelic acid derivatives have allowed the development of new highly selective processes.

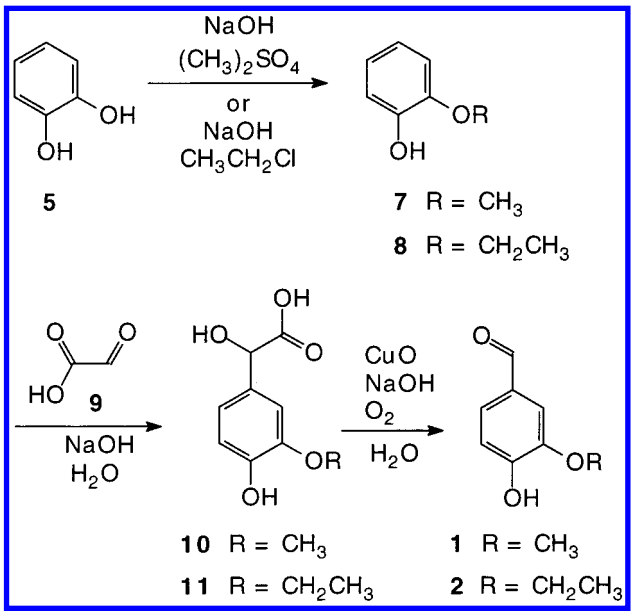
Introduction

Vanillin (3-methoxy-4-hydroxy benzaldehyde) **1**, ethyl-vanillin (3-ethoxy-4-hydroxy benzaldehyde) **2**, *iso*-vanillin (3-hydroxy-4-methoxy benzaldehyde) **3**, and heliotropin (benzo[1,3]dioxol-5-carbaldehyde) **4**, are important products of fine chemical industry. Vanillin **1** is used as intermediate in pharmaceuticals, and it is one of the most important flavouring agents in confectionery, beverage, food, and in perfumery. *iso*-Vanillin **3** is an important building block used in the synthesis of the PDE4 inhibitors,[1,2] Ariflo (SB207499),[2] targeted for treatment of bronchial asthma, and (*R*)-Rolipram[1,3] that is approved as an antidepressant. Since the olfactory profile of *iso*-vanillin **3** varies with the temperature, it is also suitable as a perfumery active ingredient for the cosmetic and perfumery industry.

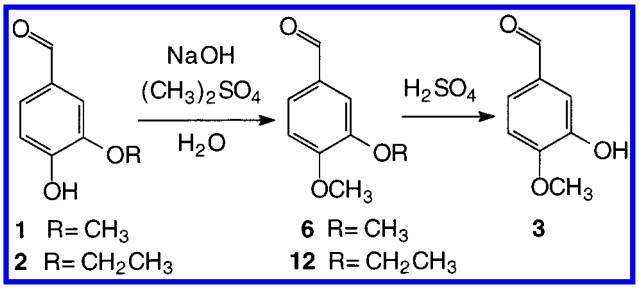
Heliotropin (or piperonal) **4** is also used in perfumery, cherry and vanilla flavors, and as an intermediate for fine chemicals. Vanillin is available from two commercial processes: from catechol **5** (Scheme 1) and by catalytic oxidation of lignosulfonate.[4] Ethyl-vanillin **2** is produced by a process similar to that of Scheme 1.

Two substantial processes (Scheme 2) have been reported for the synthesis of *iso*-vanillin **3**: regiocontrolled demethylation by sulphuric[5] or Lewis acids[6] of veratraldehyde (3,4-dimethoxy benzaldehyde) **6**, obtained by methylation of vanillin **1**. The selectivity of this dealkylation was improved[7] starting from 3-alkoxy-4-hydroxy benzaldehyde, in which the alkoxy group is different from the methoxy and can undergo a faster hydrolysis; the only starting material commercially available on large scale for this purpose is ethylvanillin **2**. Thus, the overall process involves five steps starting from catechol **5**: (i) monomethylation or ethylation of catechol **5**, giving guaiachol **7** and guethol **8**, respectively; (ii) reaction of guaiachol **7** or guethol **8** with glyoxylic acid **9**; (iii) catalytic oxidation of the mandelic acid derivatives, **10** or **11**; (iv) methylation of vanillin **1** or ethylvanillin **2**;

Scheme 1



Scheme 2



* Authors to whom correspondence should be addressed. E-mail: Hans.Bjorsvik@kj.uib.no and Francesco.Minisci@polimi.it.

† University of Bergen.

‡ Politecnico di Milano.

(1) DalPiaz, V.; Giovannoni, M. P.; Castellana, C.; Palacios, J. M.; Beleta, J.; Domenech, T.; Segarra, V. *J. Med. Chem.* **1997**, *40*, 1417.

(2) Torphy, T. J.; Barnette, M. S.; Underwood, D. C.; Griswold, D. E.; Christensen, S. B.; Murdoch, R. D.; Nieman, R. B.; Compton, C. H. *Pulm. Pharmacol. Ther*. **1999**, *12*, 131.

(3) Braun, M.; Opdenbusch, K.; Unger, C. *Synlett* **1995**, 1174.

(4) Bjørsvik, H.-R.; Minisci, F. *Org. Process Res. Dev.* **1999**, *3*, 330.

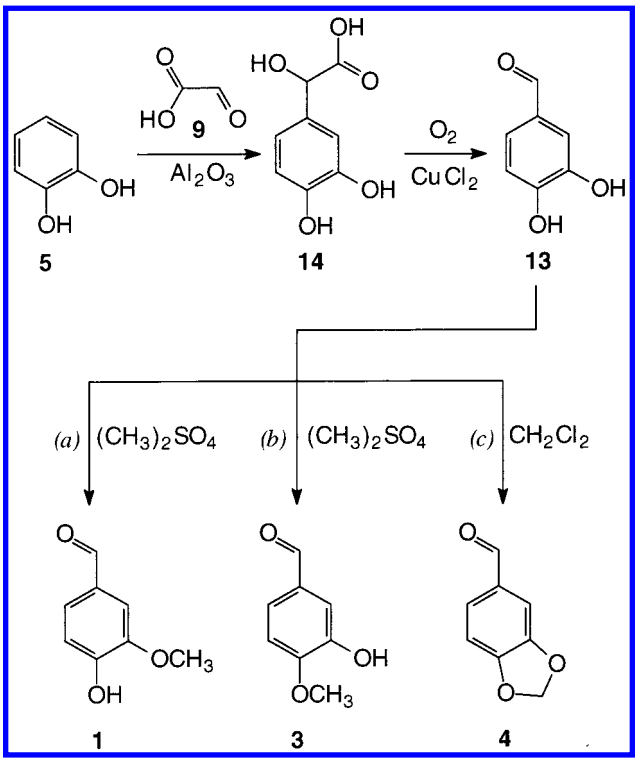
(5) Brossi, A.; Gurien, H.; Rachlin, A. I.; Teitel, S. *J. Org. Chem.* **1967**, *32*, 1269.

(6) Prager, R. H.; Tan, Y. T. *Tetrahedron Lett.* **1967**, 3661.

(7) Maliverney, C. (Rhone-Polenc Chimie). EP 0 709 361 A1, 1996.

 10.1021/op0000529 CCC: $19.00
Published on Web 10/28/2000

Scheme 3



(v) regiocontrolled dealkylation of compound **6** or **12**. The complete process is shown by Schemes 1 and 2. Another method reported[8] for synthesis of *iso*-vanillin **3** involves the mono *O*-methylation of protocatechualdehyde **13** by using sodiumhydride and methyliodide in dimethyl sulfoxide, but is too expensive from industrial point of view. The synthesis of heliotropin **4** involves the chromic oxidation of piperonyl alcohol, the condensation of 4-bromo benzo[1,3]dioxole[9] by *N*-methylformanilide and ozonolysis,[10] or chromic(VI)salt oxidation of *iso*-safrole. We have designed a new strategy for the synthesis of vanillin **1**, *iso*-vanillin **3**, and heliotropin **4** from catechol-based general Scheme 3.

We succeeded in the development of an efficient synthesis of protocatechualdehyde **13** and the selective mono *O*-methylation by dimethylsulphate to vanillin **1** or *iso*-vanillin **3**, depending on the reaction conditions. However, attempts to obtain heliotropin **4** from protocatechualdehyde **13** according to the route c of Scheme 3 gave only moderate results, and we realized that the best way to heliotropin **4** from catechol was to reverse the oxidation and methylation steps according to Scheme 4.

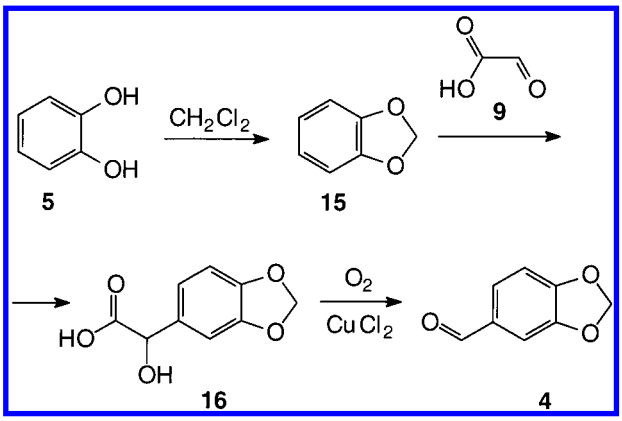
In any case all of the syntheses in Schemes 3 and 4 involve only three steps, starting from catechol.

Methods and Results

Synthesis of Protocatechualdehyde 13. The synthesis of 3,4-dihydroxymandelic acid **14** from catechol **5** and glyoxylic acid **9** (Scheme 3) was previously[11] reported, but

(8) Kessar, S.; Gupta, Y. P.; Mohammad, T.; Goyal, M.; Sawal, K. K. *J. Chem. Soc., Chem. Commun.* **1983**, *7*, 400.
(9) Holum, J. R. *J. Org. Chem.* **1961**, *26*, 4815.
(10) Feugeas C. *Bull. Soc. Chim.* **1964**, 1892.
(11) Umemura, S.; Takamitsu, N.; Enomiya, T.; Shirashi, H.; Nakamura, T. (Ube Industries Ltd.). German Patent DE 28 04 063 B2, 1980.

Scheme 4



our attempts to reproduce the reported procedure led to poor yields (<20%). The synthesis is based on the reaction of catechol with glyoxylic acid in aqueous basic medium (NaOH) and in the presence of Al_2O_3; it is substantially similar to the industrial procedure for the synthesis of vanillin (Scheme 1). We have performed a development of this reaction by using statistical experimental design[12] and multivariate modelling,[13] since, as mentioned above, the availability of protocatechualdehyde **13** is a restricting factor for the success of our new process. An assessment of the existing synthetic procedure gave that the following variables could be considered in an optimisation study: the amount of catechol (f_1), the volume of water (f_2), the reaction time (f_3), the amount of glyoxylic acid (x_1), the amount of aluminium oxide (x_2), the reaction temperature (x_3), and the amount of NaOH (x_4). Initially, the variables indicated as x_1-x_4 were selected as independent variables for the experimental design, whereas the other variables, f_1-f_3 were selected at convenient fixed levels. A full factorial design at two levels with two "center" experiments ($2^4 + 2 \rightarrow 18$ run) was set up. Some introductory experiments were performed to obtain a preliminary overview of the experimental variables' effects on the response parameters: the amount of recovered catechol (r [mmol]), the amount of 3,4-dihydroxy mandelic acid (o [mmol]), the selectivity percent to 3,4-dihydroxy mandelic acid (s [%]), and finally the yield percent of 3,4-dihydroxy mandelic acid calculated from catechol (y [%]). These introductory experiments showed that the isolated product was found to be much more impure when an excess of NaOH was used in the reaction mixture (implies that both catechol and glyoxylic acid appear as Na salts) compared to the experiments performed under less basic conditions. Thus, only the variables x_1-x_3 were explored in a full factorial design ($2^3 + 1 \rightarrow 9$ experiments), and the variable "amount of sodium hydroxide" (x_4) turned out to be the fourth variable used at a fixed experimental level ($x_4 \rightarrow f_4$). The statistical experimental design with the variables x_1-x_3 with their adjacent measured and calculated responses $\eta = [r, o, s, y]$ are given in Table 1. The response s, [%]-selectivity, and the variables x_1-x_3 with their interactions

(12) Box, G. E. P.; Hunter, W. G.; Hunter, J. S. *Statistics for Experimenters, An Introduction to Design, Data Analysis, and Model Building*; Wiley: New York, 1978.
(13) Martens, H.; Næs, T. *Multivariate Calibration*; Wiley: Chichester, 1989.

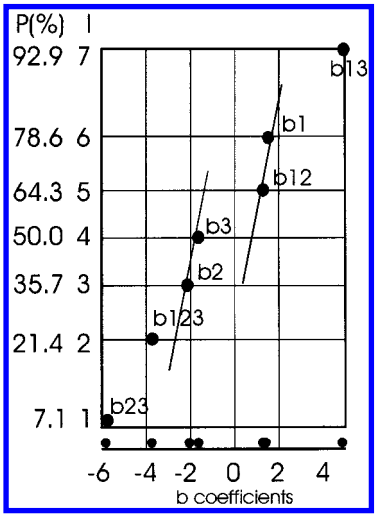


Figure 1. **CND plot of the model for 3,4-dihydroxy mandelic acid.**

Table 1. **Experimental conditions with corresponding measured and calculated responses for the screening and introductory optimization study of the reaction 5 + 9 → 14 (3,4-dihydroxy mandelic acid)**

	experimental variables[a]			responses[b]			
no.	x_1	x_2	x_3	r	o	s	y
1	−1	−1	−1	10.34	24.78	70.66	54.57
2	+1	−1	−1	11.00	18.53	53.81	40.81
3	−1	+1	−1	15.08	20.67	68.15	45.52
4	+1	+1	−1	9.22	25.75	71.15	56.71
5	−1	−1	+1	12.80	20.11	61.67	44.29
6	+1	−1	+1	10.04	27.99	79.13	61.64
7	−1	+1	+1	12.15	16.88	50.75	37.17
8	+1	+1	+1	6.87	22.57	58.56	49.70
9	0	0	0	12.09	19.76	59.30	43.51

[a] In each of the experiments: 45.41 mmol of catechol, 80.37 mmol of NaOH, 55 mL of water, and a reaction time of 24h was used. The other experimental variables were varied: x_1: amount of glyoxylic acid /[mmol] [34.96, 45.41], x_2: amount of aluminiumoxide /[mmol] [22.70, 31.79], x_3: reaction temperature /[°C] [25, 50]. [b] r = mmol recovered catechol, o = mmol of 3,4-dihydroxy mandelic acid, s = percent selectivity to 3,4-dihydroxy mandelic acid, and y = yield percent of 3,4-dihydroxy mandelic acid calculated from catechol.

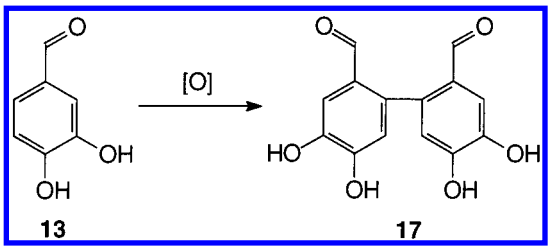
were multivariate-correlated using the multiple linear regression (MLR)[14] method to obtain a regression model as given in eq 1

$$s = 63.68 + 1.428 \times x_1 - 2.082 \times x_2 - 1.708 \times x_3 + 1.275 \times x_1 \times x_2 + 4.890 \times x_1 \times x_3 - 5.790 \times x_2 \times x_3 - 3.688 \times x_1 \times x_2 \times x_3 \quad (1)$$

with R^2 of 0.968. Even though cumulative normal probability plot (CND-plot)[15] is a rough method for assessment of model parameters, it is a suitable method for assessment of such a simple model as eq 1. The CND plot given in Figure 1 shows that the β_{13}, β_{23}, and possibly β_{123} also are the significant parameters of this model and gives information about the main direction of the experimental domain. Due to an aberrant response in Table 1, the inlying values of the CND plot are fitted by two straight lines in parallel, and not by only one straight line. See Box et al.[15]

The obtained model $s = f(x_1, x_2, x_3)$ eq 1 holds out expectations of high selectivity for the reaction **5** + **9** → **14** when one simultaneously (i) increases the quantity of glyoxylic acid **9** to slightly more than 1 equiv of catechol **5**, (ii) adjusts the quantity fraction catechol:aluminiumoxide within the range 2.17−2.28, and (iii) adjusts the temperature to be within the range 50−60 °C. Even though the model shows that it may be beneficial with a low quantity of aluminium oxide, experiments have shown that without aluminium oxide present, the reaction did not proceed at all. Increased quantity of glyoxylic acid implies double alkylation on the aromatic ring, with a consequence of a lower selectivity and higher cost of the process. The model eq 1 is graphically represented as a response surface projection in Figure 2, from which the conditions for an optimising experiment were predicted. The model predicted a selectivity of 100% for 3,4-dihydroxymandelic acid **14**; the selectivity of the optimised experiment was 90.5% with a conversion of 78.4%. The unconverted catechol **5** was easily recovered and recycled by extraction under suitable acidity; the aqueous phase containing the mandelic acid derivative **14**, was directly utilised for the oxidative decarboxylation to obtain protocatechualdehyde **13**.

Scheme 5



Preliminary attempts of oxidation by oxygen and Cu(II) catalysis, which is effective for vanillin (Scheme 1) and heliotropin **4** (Scheme 4), led to poor yields of protocatechualdehyde **13** due to the formation of a large amount of a by-product, which from NMR analysis appears to arise from oxidative dimerisation of protocatechualdehyde **13** to give **17** (Scheme 5).

We have therefore developed a different procedure involving a two-liquid system (water:ethyl acetate) and the use of a 3-fold excess of $CuCl_2$ and HCl under nitrogen. The large excess of the copper salt is used to ensure a complete conversion of the mandelic acid derivative **14**. Under these conditions the oxidation take place with high yields (>95%); the organic phase, containg **13**, is separated, and $CuCl_2$ is regenerated in the aqueous phase by bubbling air and recycled so that the overall process is catalytic in $CuCl_2$ and the actual oxidant is air.

Selective *O*-Methylation of Protocatechualdehyde 13. The *O*-methylation of protocatechualdehyde **13** by dimethylsulphate in basic medium can lead to three different products: vanillin **1**, veratraldehyde **6**, and *iso*-vanillin **3** (Scheme 6).

(14) Montgomery, D. C.; Peck, E. A. *Introduction to Linear Regression Analysis*; Wiley: New York, 1982; Draper, N. A.; Smith, H. *Applied Regression Analysis*, 2nd ed.; Wiley: New York, 1981.

(15) Daniel, C. *Technometrics* **1959**, *1*, 311. Box, G. E. P.; Draper, N. R. *Empirical Model-Building and Response Surfaces*; Wiley: New York, 1987; pp 128−134.

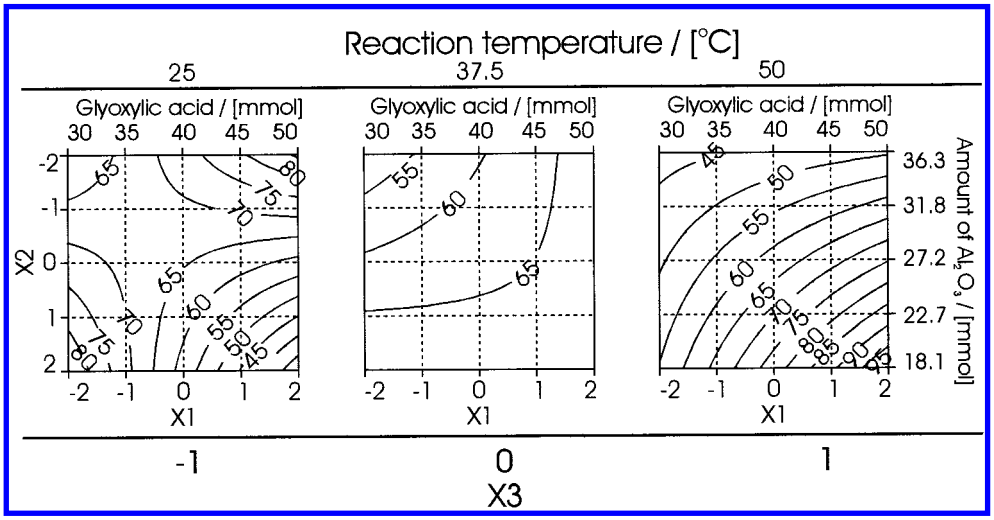
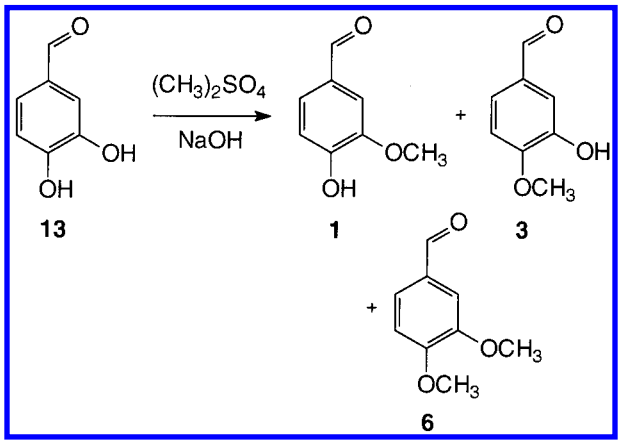


Figure 2. **Contour projections of the response surface where the response is the selectivity to 3,4-dihydroxymandelic acid 12.**

Scheme 6



Clearly the formation of veratraldehyde **6** is related to the conversions; with an excess of dimethylsulphate and NaOH and complete conversion veratraldehyde **6** is the only reaction product. Thus partial conversions are necessary in order to obtain vanillin **1** and *iso*-vanillin **3**. On the basis of the differences in the pK_a values of protocatechualdehyde **13** (p$K_{a(3\text{-OH})} \approx 11.6$, and p$K_{a(4\text{-OH})} \approx 7.5$) we tried to develop direct *O*-methylation procedures to *iso*-vanillin **3** or vanillin **1**. We carried out some *O*-methylation preliminary experiments on protocatechualdehyde **13**, that showed that the product distribution, the quantity of vanillin **1**, *iso*-vanillin **3**, and veratraldehyde **6** varied, depending on several of the experimental variables; the addition time of reagents (x_1), the reaction time (x_2), the amount of NaOH added during the reaction (x_3), the start amount of NaOH (x_4), the reaction temperature (x_5), the amount of dimethyl sulphate (x_6), the volume of methylene chloride (which revealed better than ethyl acetate) (x_7), and the volume of water (x_8). To study these variables' influence on the selectivity and the yield, a fractional factorial design of the type 2^{8-4}, including two experiments in the centre of the experimental domain was used. The experimental levels and design with adjacent measured responses from the experimental runs are reported in Table 2.

The estimated models [$y_1 = f(x_1-x_8)$ and $y_3 = h(x_1-x_8)$] which relate the observed responses (y_1 = mol % yield of vanillin **1** and y_3 = mol % yield of *iso*-vanillin **3**) to the experimental variables are two linear models to which cross-product terms have been added. However, due to the resolution (resolution = IV) of the experimental design that has been used, all of cross-terms in the two models have a certain confounding pattern with the other cross-terms. The regression coefficients were estimated by application of the partial least-squares regression (PLSR)[13] method, and their significances were determined by using CND plots and

Table 2. **Experimental design with adjacent measured responses, the quantities of vanillin 1, veratraldehyde, *iso*-vanillin 3, and protocatechualdehyde**

	experimental variables[a]								responses[b]			
no.	x_1	x_2	x_3	x_4	x_5	x_6	x_7	x_8	y_1	y_2	y_3	y_4
1	−1	−1	−1	−1	−1	−1	−1	−1	6.46	2.09	19.06	63.73
2	+1	−1	−1	−1	+1	−1	+1	+1	6.15	1.60	31.23	59.75
3	−1	+1	−1	−1	+1	+1	−1	+1	1.49	0.94	34.43	34.88
4	+1	+1	−1	−1	−1	+1	+1	−1	3.02	0.63	14.35	77.23
5	−1	−1	+1	−1	+1	+1	+1	−1	6.86	5.92	21.57	56.70
6	+1	−1	+1	−1	−1	+1	−1	+1	4.70	4.70	13.85	42.35
7	−1	+1	+1	−1	−1	−1	+1	+1	4.01	2.76	11.93	74.67
8	+1	+1	+1	−1	+1	−1	−1	−1	6.74	8.38	26.74	49.95
9	−1	−1	−1	+1	−1	+1	+1	+1	4.28	2.09	14.52	68.61
10	+1	−1	−1	+1	+1	+1	−1	−1	6.85	4.07	38.01	40.81
11	−1	+1	−1	+1	+1	−1	+1	−1	6.35	3.48	32.13	51.39
12	+1	+1	−1	+1	−1	−1	−1	+1	5.58	3.25	26.47	63.89
13	−1	−1	+1	+1	+1	−1	−1	+1	8.10	10.01	23.42	51.31
14	+1	−1	+1	+1	−1	−1	+1	−1	2.12	2.71	10.80	65.34
15	−1	+1	+1	+1	−1	+1	−1	−1	7.95	10.01	19.06	56.57
16	+1	+1	+1	+1	+1	+1	+1	+1	8.32	10.37	25.84	47.04
17	0	0	0	0	0	0	0	0	5.92	4.31	29.78	46.88
18	0	0	0	0	0	0	0	0	6.20	4.78	27.88	52.16

[a] Generators for the experimental design: $x_5 = x_1x_2x_3$; $x_6 = x_2x_3x_4$; $x_7 = x_1x_3x_4$; $x_8 = x_1x_2x_4$. The present experimental design makes it possible to estimate the effects of the single variables and the values for the following confounded two-factor interactions: $\beta_{12} + \beta_{35} + \beta_{48} + \beta_{67}$, $\beta_{13} + \beta_{25} + \beta_{47} + \beta_{68}$, $\beta_{23} + \beta_{15} + \beta_{46} + \beta_{78}$, $\beta_{14} + \beta_{28} + \beta_{37} + \beta_{56}$, $\beta_{24} + \beta_{18} + \beta_{36} + \beta_{57}$, $\beta_{34} + \beta_{17} + \beta_{26} + \beta_{58}$, $\beta_{16} + \beta_{27} + \beta_{38} + \beta_{45}$. Experimental variables [−1, +1] /unit x_1: addition time [45, 75]/min., x_2: reaction time [45, 75]/min., x_3: amount of NaOH added during the reaction [0.70, 0.85]/g, x_4: start amount of NaOH [0.18, 0.23]/g, x_5: reaction temperature [35, 55]/°C, x_6: amount of dimethyl sulphate [2.3, 2.7]/g, x_7: volum of methylene chloride [14, 20]/mL, x_8: volum of water [14, 20]/mL. [b] Confounding patterns for the present design are: y_1: yield mol % of vanillin **1**, y_2: yield mol % veratraldehyde **6**, y_3: yield mol % of iso-vanillin **3**, y_4 unconverted mol % protocathecuic aldehyde **13**.

Table 3. **Estimated model parameter values for eq 2 and eq 3**

model parameters for y_3[a] (*iso*-vanillin)					model parameters for the y_1[b] (vanillin)				
	coef./value	std. err.	*P*	conf. int. ±		coef./value	std. err.	*P*	conf. int. ±
α_0	23.018	0.64	3.34×10^{-9}	1.514	β_0	5.582	0.249	5.09×10^{-7}	0.608
α_1	0.700	0.66	0.324	1.56	β_1	−0.138	0.256	0.611	0.627
α_2	1.150	0.66	0.125	1.56	β_2	−0.138	0.256	0.611	0.627
α_3	−3.562	0.66	1.01×10^{-3}	1.56	β_3	0.537	0.256	0.081	0.627
α_4	1.062	0.66	0.151	1.56	β_4	0.638	0.256	0.047	0.627
α_5	6.437	0.66	2.52×10^{-5}	1.56	β_5	0.788	0.256	0.022	0.627
α_7	−2.425	0.66	0.008	1.56	β_{12}	0.612	0.256	0.054	0.627
α_{12}	−1.212	0.66	0.109	1.56	β_{13}	−0.513	0.256	0.092	0.627
α_{24}	0.950	0.66	0.193	1.56	β_{15}	0.787	0.256	0.022	0.627
α_{45}	−0.387	0.66	0.575	1.56	β_{24}	0.987	0.256	0.008	0.627
					β_{45}	0.413	0.256	0.158	0.627

[a] Statistical products for the model y_3 describing the formation of *iso*-vanillin (PLS components = 4, $N = 17$, confidence level = 95%) $R^2 = 0.956$, $Q^2 = 0.734$, RMSEP = 2.64. [b] Statistical products for the model y_1 describing the formation of vanillin (PLS components = 4, N = 17, Confidence level = 95%): $R^2 = 0.905$, $Q^2 = 0.523$, RMSEP = 1.0247.

statistical analysis.[14] The final model- and statistical parameters are given in Table 3.

Model for *iso*-Vanillin 3. The experimental variables, x_1, x_2, x_3, x_4, x_5, and x_7 were the variables that were determined to have influence on the formation of *iso*-vanillin **3**. Three two-factor interaction terms were also determined to have influence in the model; x_1x_2, x_2x_4, and x_4x_5. The final multivariate predictive model for *iso*-vanillin **3** is shown in eq 2, numerical values are given in Table 3. The statistical products, (root mean squares-error of prediction) RMSEP = 2.64, $R^2 = 0.956$, and $Q^2 = 0.734$ indicate a quite good explanatory power of the model. The model eq 2 was estimated using the PLS method.[13]

$$y_3 = \alpha_0 + \alpha_1x_1 + \alpha_2x_2 + \alpha_3x_3 + \alpha_4x_4 + \alpha_5x_5 + \alpha_7x_7 + \alpha_{12}x_1x_2 + \alpha_{24}x_2x_4 + \alpha_{45}x_4x_5 \quad (2)$$

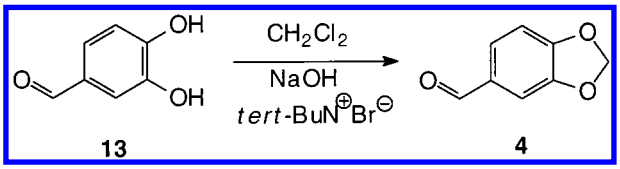
The model in eq 2 was used to produce the response surface given in Figure 3. By using such a response surface, a selectivity of 94.6% was obtained for the *para O*-methylation of 3,4-dihydroxybenzaldehyde. The conversion is kept low (42.5%) to limit formation of veratraldehyde **2**.

Model for Vanillin 1. The experimental variables x_1, x_2, x_3, x_4, and x_5 were found to have significant influence in the model. In this model some more two-factor interactions were determined to have influence; x_1x_2, x_1x_3, x_1x_5, x_2x_4, and x_4x_5. The final multivariate predictive model for vanillin **1** is shown in Equation 3. Also for this model, the statistical products, RMSEP = 1.025, $R^2 = 0.905$, and $Q^2 = 0.523$ indicate a fairly good explanatory power of the model. The estimation of the model eq 3 was also here carried out using the PLS method.[13]

$$y_1 = \beta_0 + \beta_1x_1 + \beta_2x_2 + \beta_3x_3 + \beta_4x_4 + \beta_5x_5 + \beta_{12}x_1x_2 + \beta_{13}x_1x_3 + \beta_{15}x_1x_5 + \beta_{24}x_2x_4 + \beta_{45}x_4x_5 \quad (3)$$

As for *iso*-vanillin, the derived model for vanillin in eq 3 was used to produce a response surface as given in Figure 4. By using such a response surface, a selectivity of 86.8%

Scheme 7



of vanillin with 44.6% conversion of protocatechualdehyde **13** was obtained.

For both of the two procedures, for vanillin **1** and for *iso*-vanillin **3**, the reaction was carried out in a two-phase system (water:ethyl acetate), and the unreacted protocatechualdehyde **13** is easily recovered and recycled by taking advantage of the higher acidity of protocatechualdehyde **13** compared to that of vanillin **1** and *iso*-vanillin **3**.

Synthesis of Heliotropin 4. (A) The reaction of protocatechualdehyde **13** with CH_2Cl_2 to obtain heliotropin **4**, Scheme 7 was known.[16−18] On the basis of the reported[16] synthetic procedure an experimental study concerning the ring-closure step using statistical experimental design[12] with subsequently multivariate modelling[13] was performed.

From this study we have derived a mathematical model, which describes the yield of heliotropin **4** under the influence of the experimental variables: the amount of NaOH, reaction temperature, reaction time, and amount of phase-transfer catalyst (*tert*-$Bu_4N^+Br^-$). Optimised experiments based on this model have led to selectivity in the range 61−64%, which are not sufficient for an industrial development. On the other hand attempts to reproduce the results reported in the literature[16] gave much lower yields (<20%).

(B) The process according to Scheme 4 appeared more convenient for the synthesis of heliotropin **4**. In this case the basic medium is not suitable for the condensation of glyoxylic acid with benzo[1,3]dioxol **15**, as in the reaction with catechol for obtaining protocatechualdehyde **13** (Scheme 3). We have developed an acid catalysis, which has allowed

(16) Kirby, J. A. (Eli Lilly & Co.). U.S. Patent 4,082,774, 1978.
(17) Maggioni, P. (Brichima SpA). U.S. Patent 4,183,861, 1980.
(18) Gensler W. J.; Samour, C. M. *J. Org. Chem.* **1953**, *18*, 13; Tampta, M.; Aoyopi, Y. *Chem. Pharm. Bull.* **1968**, *16*, 523; Bonthrone W.; Cornorth, J. W. *J. Chem. Soc. (C)* **1969**, 1202.

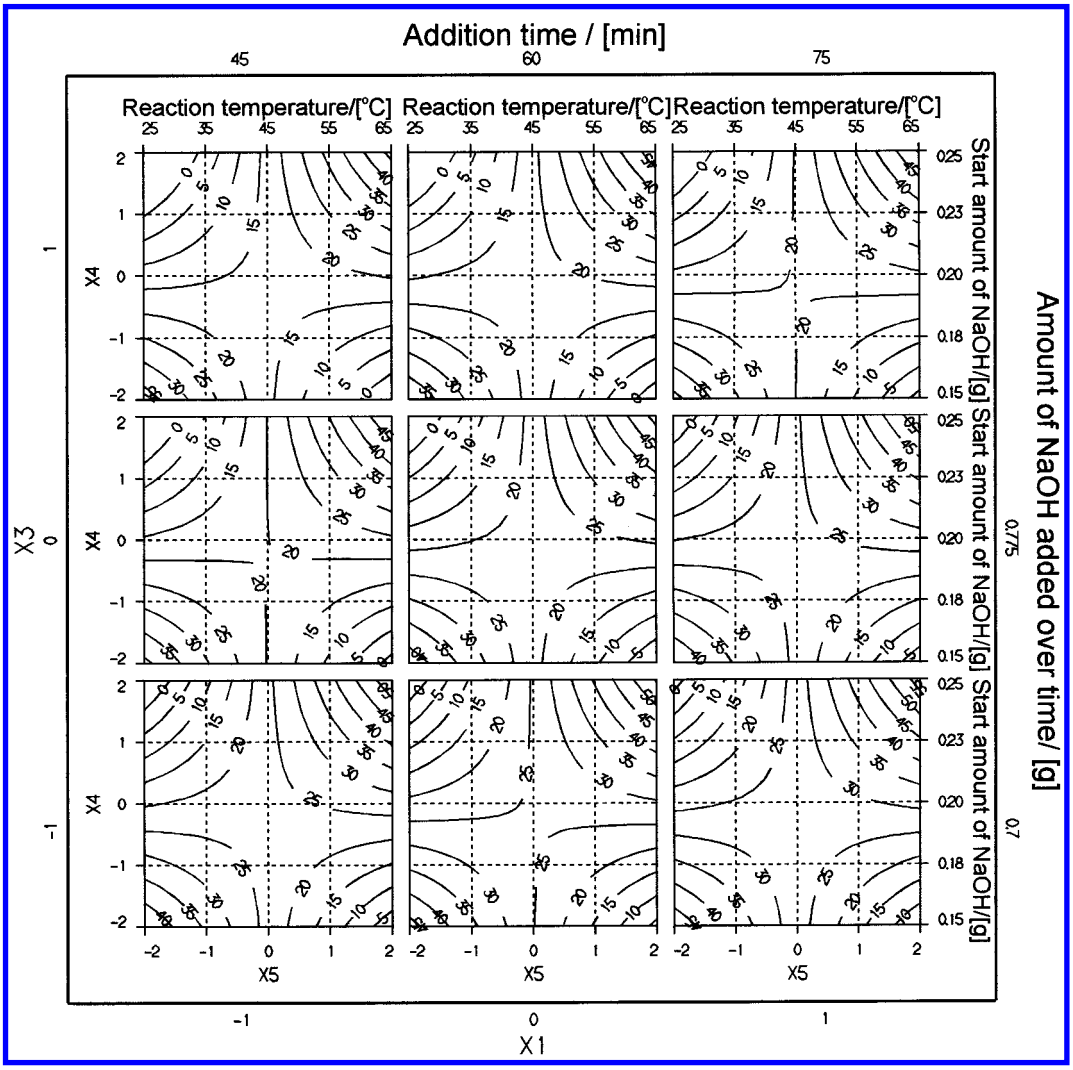


Figure 3. **Contour projections of the response surface where the response is the selectivity to *iso*-vanillin 3.**

the synthesis of 3,4-dioxymethylene mandelic acid in high yields (in the range 86−90%). The oxidative decarboxylation was carried out in a two-phase system (water:toluene) by oxygen and $CuCl_2$ catalysis with quantitative yield of heliotropin **4**. The oxidative decarboxylation was carried out also with high yields by $Na_2S_2O_8$ and catalysis by Ag(I) salt.

Discussion

The good yields and the simple and convenient procedure for the synthesis of protocatechualdehyde **13** by statistical experimental design and multivariate modelling for the synthesis of 3,4-dihydroxy mandelic acid **14** and the development of a highly selective catalytic process for its oxidation suggested that protocatechualdehyde **13** could be an interesting intermediate for the synthesis of vanillin **1**, *iso*-vanillin **3**, and heliotropin **4**. A critical point for the oxidation of 3,4-dihydroxy mandelic acid **14** was the presence of oxygen, which leads to large amounts of the by-product **17**, Scheme 5. We explain this behaviour by the mechanism of the Scheme 8.

The hydrogen abstraction by the peroxyl radical **B** is faster for the hydroxyl group in position 3, which is less acidic ($pK_{a(3\text{-}OH)} \approx 11.6$) than the hydroxyl group in position 4 ($pK_{a(4\text{-}OH)} \approx 7.5$) because of the influence of the carbonyl group in the *para* position. To overcome this inconvenience we have developed an oxidation process in two steps and a two-phase system (water:ethyl acetate). The first step was carried out under nitrogen atmosphere by an excess of $CuCl_2$ and HCl so that route *b* of Scheme 8 was avoided and only route *a* took place. The oxidation occurs in the aqueous phase, and the organic solvent continuously extracts the formed aldehyde; the aqueous phase is separated, and CuCl is oxidised by bubbling air and recycled. In this way the process is always catalytic in $CuCl_2$, and the selectivity is very high (>95%) with complete conversion.

For the synthesis of vanillin **1** and *iso*-vanillin **3** from protocatechualdehyde **13** the critical point was the regio-controlled *O*-methylation. We have taken advantage of the different acidity of the two hydroxyl groups, as mentioned before. In the presence of an excess of NaOH both the hydroxyl groups are salified, but the phenoxide ion in position 3 is more nucleophilic, and it is preferentially attacked by dimethylsulphate leading to vanillin **1**, due to the conjugation of the phenoxide ion in position 4 with the carbonyl group (Scheme 9).

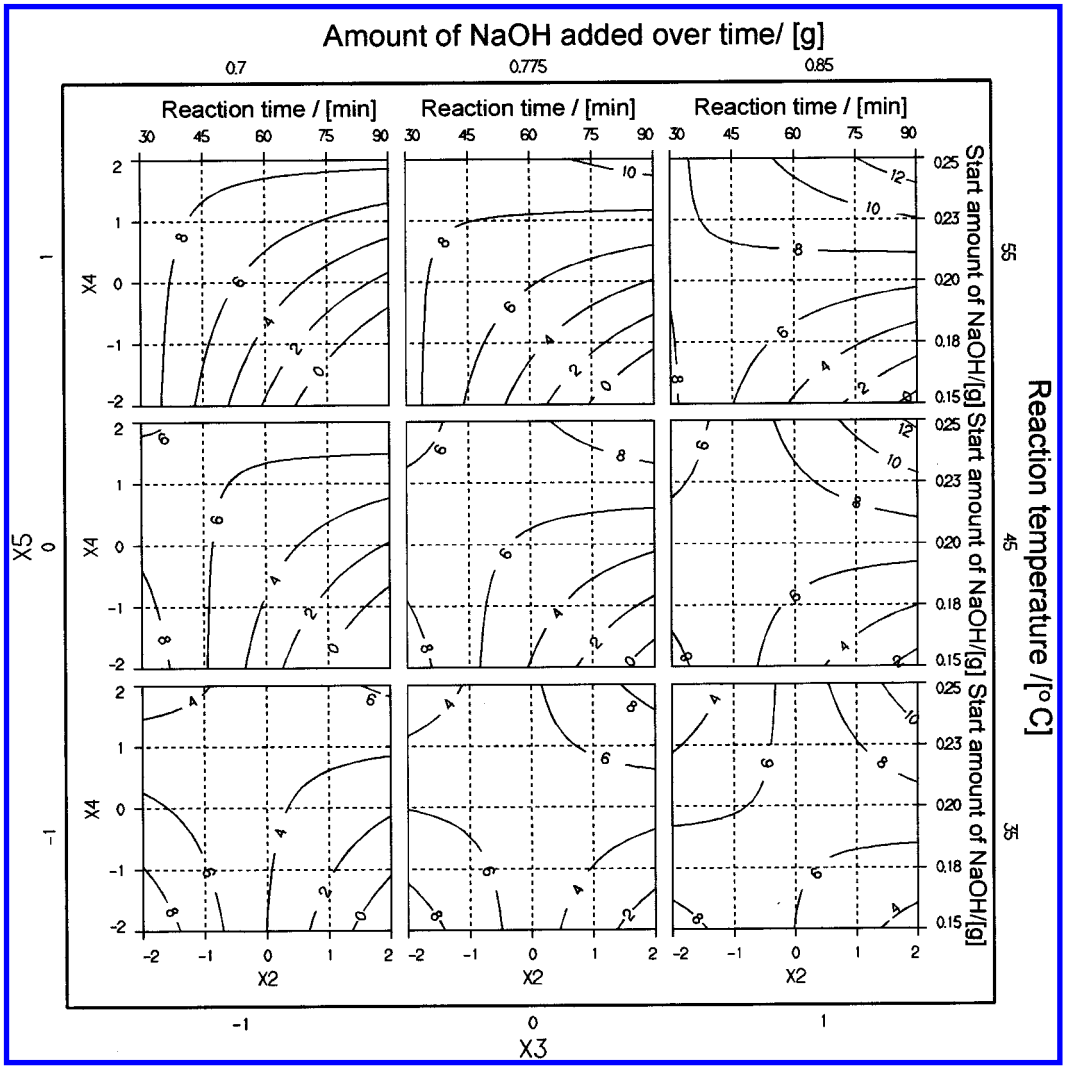


Figure 4. **Contour projections of the response surface where the response is the selectivity to vanillin 1.**

For the same reason when we use one mole or less of NaOH per mole of protocatechualdehyde **13**, the hydroxylgroup in position 4 is more acidic, is preferentially salified, and is attacked by dimethylsulphate leading to *iso*-vanillin **3** (Scheme 10).

In both cases partial conversion (40−50%) is necessary to avoid dimethylation leading to veratraldehyde **6**, but the separation and the recycle of unreacted protocatechualdehyde **13** is quite simple and inexpensive; protocatechualdehyde **13** remains in the water phase while the reaction products (**1**, **3**, **6**) are soluble in dichloromethane. The starting aldehyde **13** can then be recovered by acidifying the water phase and extracting with ethyl acetate. The recovered substrate **13** is practically pure enough to be reused, but an eventually further purification can be performed by using the different acidity of the compounds. Attempts to utilise Scheme 3 for the synthesis of heliotropin **4** led to 64% maximum selectivity, probably because of the instability of protocatechualdehyde **13** under basic experimental conditions. Thus, Scheme 4 appeared to be more convenient in this case. Contrary to the behaviour of guaiachol **7** (Scheme 1) or catechol **5** (Scheme 3), the condensation of benzo[1,3]-dioxole **15** with glyoxylic acid **9** cannot be catalysed by a basic mechanism; we have further developed catalysis by sulphuric acid which leads under high selectivity to the mandelic acid derivative **16** (Scheme 11).

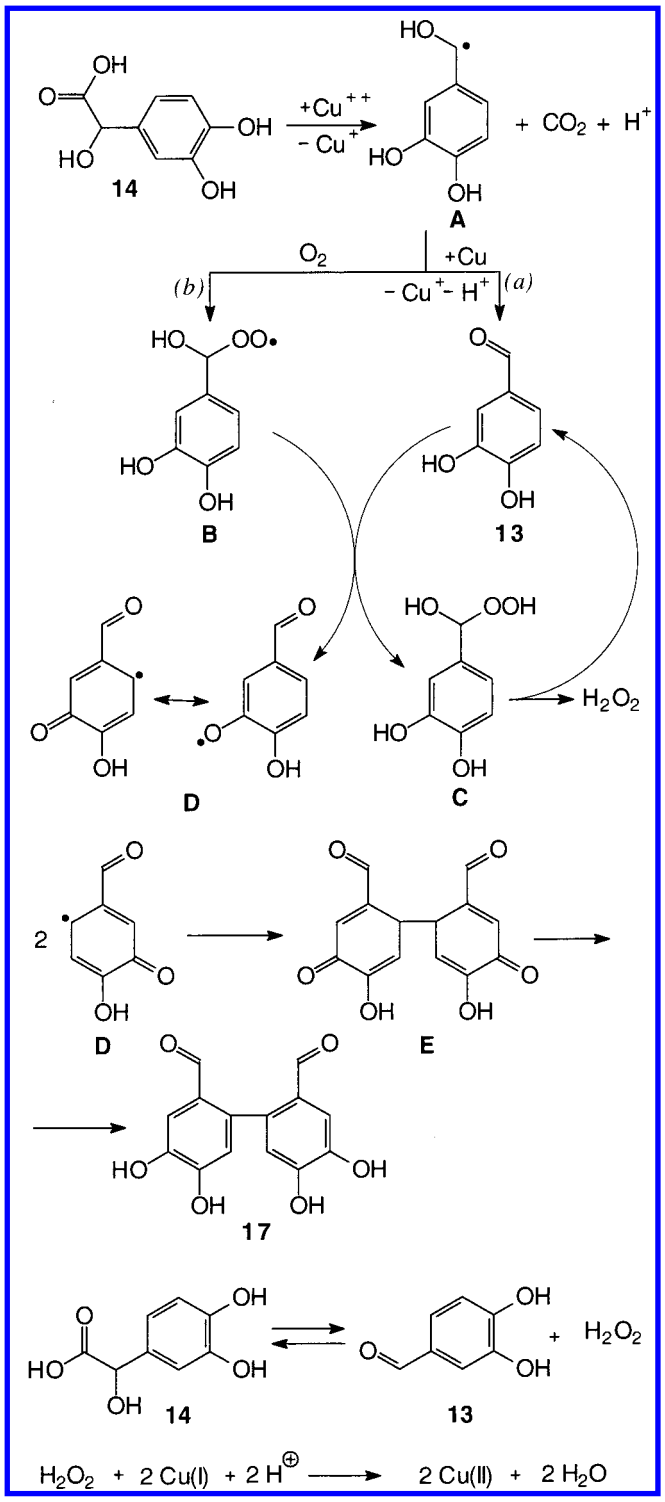
The basic catalysis on the contrary involves the nucleophilic addition of phenoxide ion to the carbonyl group (Scheme 12).

The oxidative decarboxylation of the mandelic acid derivative **16** to heliotropin **4** can be carried out in high yield with catalytic amount of Cu(II) salt in the presence of oxygen because the absence of hydroxyl groups prevents the oxidative dimerisation of heliotropin **4** by a process similar to that described in Scheme 8. The oxidative decarboxylation was carried out also by Ag(I)-catalysed $Na_2S_2O_8$ oxidation. The mechanism is shown in Scheme 13.

Conclusions

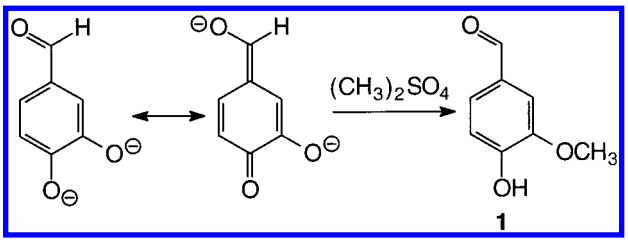
A new strategy of industrial interest for the synthesis of protocatechualdehyde **13**, vanillin **1**, *iso*-vanillin **3**, and heliotropin **4** was designed and optimised. The condensation of catechol or benzo[1,3]dioxole with glyoxylic acid, the oxidative decarboxylation of the mandelic acid derivatives, and the regiocontrolled *O*-methylation of protocatechualdehyde **13** were the key points in all of these syntheses and

Scheme 8

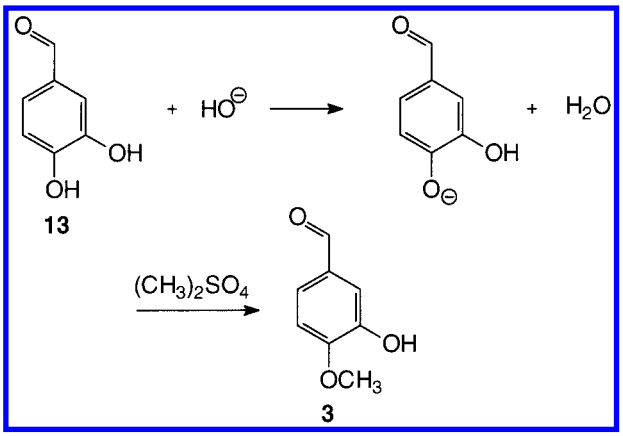


they were developed by a combination of statistical experimental design, multivariate modelling, and reaction mechanisms. A flexible procedure that allows to perform the *O*-methylation of the hydroxy groups either in position 3 or 4 of protocatechualdehyde **13** to obtain respectively vanillin **1** and *iso*-vanillin **3** was developed; it was based on the different acidity of the two hydroxyl groups. For the synthesis of heliotropin **4** it appeared more convenient to start from benzo[1,3]dioxole **15** than from protocatechualdehyde **13**.

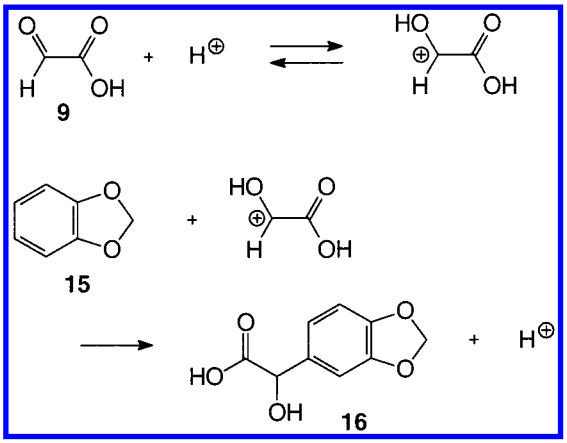
Scheme 9



Scheme 10



Scheme 11



Experimental Section

General Methods. Mass spectra were performed on a GLC−MS Finnigan TSQ 70 instrument, using a Varian 3700 gas chromatograph equipped with SBP-1 fused silica column (*L* 30 m × 0.2 mm i.d., 0.2 μm film thickness) and He as carrier gas.

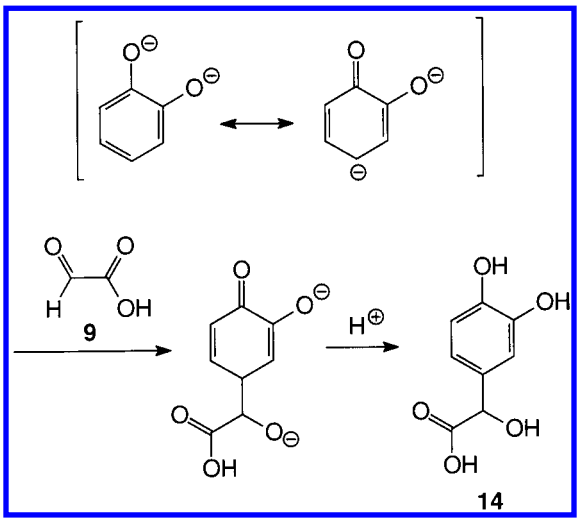
GLC analyses were performed on a capillary gas chromatograph equipped with SBP-5 fused silica column (*L* 25 m × 0.25 mm i.d., 1 μm film thickness) at a hydrogen flow rate of 8 cm^3 min^{-1}, PTV injector, and flame ionisation detector.

HPLC analyses were performed on a HPLC instrument equipped with a RP-18 (5 μm packing material, *L* 250 mm, 4 mm i.d.) and UV detector (λ = 281 nm).

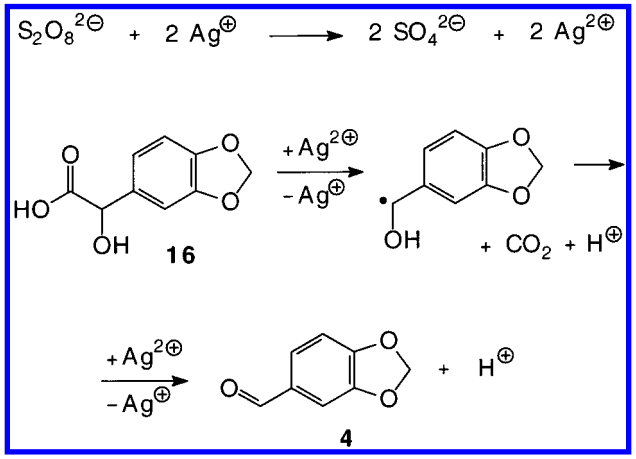
^{1}H NMR spectra were recorded on a NMR spectrometer operating at 400 MHz. Chemical shifts are referenced to internal TMS.

Starting materials and reagents were purchased commercially and used without further purification. All of the

Scheme 12



Scheme 13



reaction products were known and were analysed by GC and GC−MS and by comparison with authentic samples.

3,4-Dihydroxy Mandelic Acid 1 (Optimised Procedure). Catechol (5.00 g, 45.41 mmol) was dissolved in aqueous NaOH (3.21 g, 80.3 mmol in 55.0 mL of water) followed by addition of Al_2O_3 (2.04 g, 20 mmol). After 5 min glyoxylic acid (7.10 g of 50% aqueous solution, 48.0 mmol) was added to the reaction mixture, and the mixture was heated at 60 °C for 24 h under vigorous stirring. The reaction mixture was then allowed to precipitate for 10 min. and filtered to remove Al_2O_3. The obtained filter cake was washed with 1 M NaOH (20 mL). The basic washing water was combined with the water solution, and this was acidified to pH 3−4 with 6.0 mL of 37% HCl and extracted with ethyl acetate to recover the unreacted catechol (1.2 g). The aqueous solution was further acidified to pH 1 by 2 mL of concentrated HCl and extracted with ethyl acetate to isolate the mandelic acid derivative (5.1 g, 28.08 mmol). Conversion 77.5%, selectivity 90.5%.

Protocatechualdehyde 13. 3,4-Dihydroxy mandelic acid (2 g, 10.86 mmol) was dissolved in 140 mL of ethyl acetate, and 11.11 g of $CuCl_2 \cdot 2H_2O$ was dissolved in 30 mL of water. The two-phase system was vigorously stirred and heated at 60 °C for 5 h under nitrogen atmosphere. The organic phase was separated, and the solvent was removed. The HPLC analysis revealed a complete conversion of the mandelic acid derivative and the yield of protocatechualdehyde of 96%. The copper salt aqueous solution/suspension was recycled by oxidising Cu(I) to Cu(II) by air after the removal of the organic phase; the results were substantially unchanged.

Vanillin 1. Protocatechualdehyde **13** (7.2 mmol) and NaOH (18 mmol) were dissolved in 25 mL of water; 20 mL of CH_2Cl_2 was added, and 5 mmol dimethyl sulphate was added dropwise under vigorous stirring during 1 h at a temperature of 55−60 °C. The reaction was run for a further 4 h at the same temperature. The two phases were separated, and the water phase was further extracted with 2 × 25 mL of CH_2Cl_2. The organic layers were combined and dried with sodium sulphate, and the solvent was removed under vacuum to give the desired product. The aqueous phase was acidified by 35% HCl to pH 1−2 and extracted by ethyl acetate (2 × 50 mL) to recover the unreacted protocatechualdehyde **13**. HPLC analyses revealed a recovery of 55.4% of unreacted protocatechualehyde **13** (conversion 44.6%) with a selectivity of 77.5% of vanillin, 8% of *iso*-vanillin, and 3.4% of veratraldehyde.

***iso*-Vanillin 3.** (A) Protocatechualdehyde **13** (7.2 mmol) and NaOH (2.1 mmol) were mixed in 3.5 mL of water and 3.3 mL of CH_2Cl_2; 6 mmol of dimethyl sulphate and 3.7 mmol of NaOH in 1.5 mL of water were simultaneously added dropwise with stirring over a period of 45 min. After the complete addition of the reagents, the reaction mixture was stirred for a further 50 min at a temperature of 55−60 °C. The reaction mixture was allowed to cool to room temperature, the two phases were separated, and the water phase was further extracted with 2 × 25 mL of CH_2Cl_2. The organic layers were combined and dried with sodium sulphate, and the solvent was removed under vacuum to give the desired product. The aqueous phase was acidified by 35% HCl to pH 1−2 and extracted by ethyl acetate (2 × 50 mL) to recover the unreacted protocatechualdehyde **13**. HPLC analyses revealed a conversion of 18.3% with a selectivity of 93.5% of *iso*-vanillin, 5.8% of vanillin, and 0.5% of veratraldehyde.

(B) The reaction was carried out as in (A) at 55 °C by using 21.7 mmol of protocatechualdehyde and 4.5 mmol of NaOH and by simultaneously adding dropwise 21.4 mmol of dimethyl sulphate and 17.5 mmol of NaOH. The conversion was 70.8%, and the selectivity 93.2% in *iso*-vanillin, 4.0% of vanillin, and 2.8% of veratraldehyde.

3,4-Dioxymethylene Mandelic Acid 16. Benzo[1,3]-dioxole **15** (8.20 mmol) was added dropwise over a period of 30 min to a mixture of 8.41 mmol of glyoxylic acid, 14.59 mmol of sulphuric acid, and 11.34 mmol of water at 0−5 °C. The reaction was run for 20 h at 0 °C and then diluted with 20 mL of water. The 3,4-dioxymethylene mandelic acid precipitated and was then filtered off. HPLC analysis revealed a yield of 86% with selectivity >95%.

Heliotropin 4. (A) 3,4-Dioxymethylene mandelic acid (5 mmol), $Na_2S_2O_8$ (6 mmol), and $AgNO_3$ (0.05 mmol) in 30 mL of water and 30 mL of CH_2Cl_2 were refluxed for 5 h. The CH_2Cl_2 phase was removed and analysed by HPLC; a yield of 96% of heliotropin was obtained.

(B) 3,4-Dioxymethylene mandelic acid (5 mmol), $CuCl_2$ (0.5 mmol), and 4.05 g of 37% HCl in 30 mL of water and 30 mL of toluene was heated at 80 °C and bubbling O_2 for 22 h. The organic phase was separated and analysed by HPLC; a yield of 98% of heliotropin was obtained. The aqueous solution is ready to be used for further oxidation.

(C) Protocatechualdehyde (13.1 g, 0.1 mol), NaOH (12 g), and tetrabutylammonium bromide (3.2 g) in 100 mL of water and 100 mL of CH_2Cl_2 were heated for 4 h at 80 °C in an autoclave. The aqueous phase was then separated and analysed by HPLC. The aqueous solution was acidified and extracted by ethyl acetate to recover the unreacted protocatechualdehyde. The conversion was 58.6% and selectivity in heliotropin 64%.

Acknowledgment

Borregaard Synthesis (Norway) is gratefully acknowledged for financial support to this project.

Received for review May 15, 2000.

OP0000529