Regioselective synthesis of 6-substituted 2-hydroxybenzaldehyde: efficient synthesis of the immunomodulator tucaresol and related analogues

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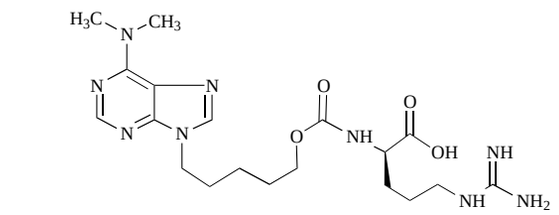
Two new improved procedures have been developed for the preparation of the immunostimulant tucaresol 1 [4-(2-formyl-3-hydroxyphenoxymethyl)benzoic acid]. These approaches, which start from resorcinol or 2,6-dimethoxybenzaldehyde, are practical and therefore amenable to scale-up. In the case of the second approach, the multi-step synthesis reported in the literature has been reduced to three steps. Furthermore, unlike the reported method, our synthesis is versatile for the preparation of tucaresol analogues. The method is general and applicable for the preparation of 6-substituted 2-hydroxybenzaldehydes.

Schiff-base formation between T-cells and antigen presenting cells has been described as essential to the enhancement of the immune response.[1] Recently, it was reported that a substituted benzaldehyde, tucaresol **1**, can mimic this physiological signal to T-cells by Schiff-base formation with cell surface amino groups.[2] The resultant induction of cytokines such as interleukin-2 and interferon-γ was shown to translate into a therapeutic effect in various viral and tumor models. Subsequently, tucaresol was selected for clinical evaluation in AIDS and cancer patients.



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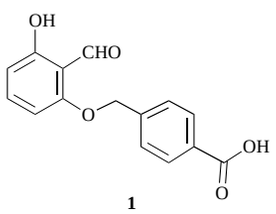

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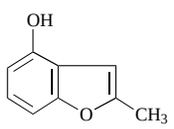

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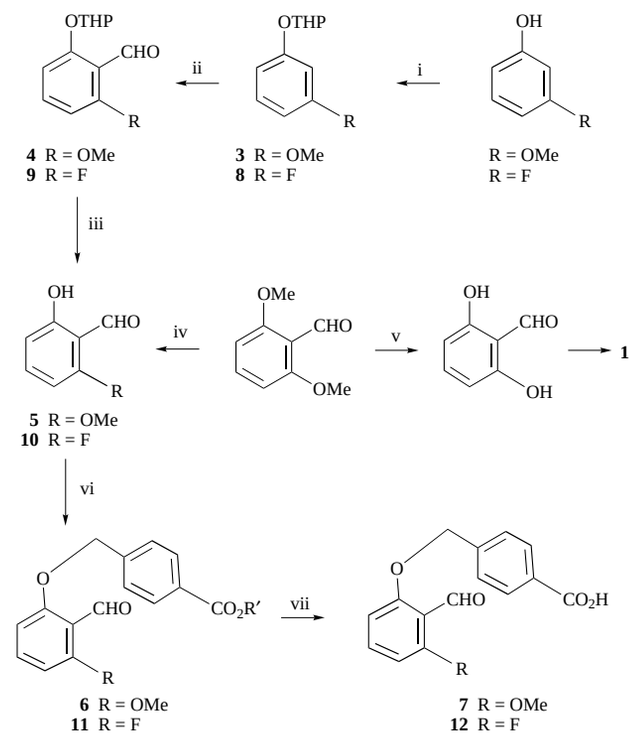
As part of our immunomodulator research program, we identified a small molecule non-toxic T-cell (CTL) stimulant;[3] 6-*N*,*N*-dimethylaminopurin-9-ylpentyloxycarbonyl-D-arginine (BCH-1393). Thus, tucaresol **1** was required for comparative studies. The preparation described in the literature involves a multi-step synthesis with low overall yield. The key reported step is the ozonolysis of 4-hydroxy-2-methylbenzofuran **2** at 65 °C with stirring and exclusion of moisture. This is awkward for large-scale synthesis. Furthermore, compound **2** is not a versatile intermediate for the preparation of analogues of tucaresol, because of the limited number of derivatives that can be synthesized from the benzofuran ring. We therefore developed two short routes for the preparation of 2,6-disubstituted benzaldehydes and in particular 2-hydroxy-6-alkoxybenzaldehyde.

Results and discussion

Two distinct approaches were considered for the preparation of tucaresol: the first route is a regioselective introduction of the formyl group directed by the 2,6-disubstituted ether. The second approach requires selective deprotection of the methyl function of the commercially available 2,6-dimethoxybenzaldehyde, without affecting the formyl moiety.

Our first approach was to use the ability of certain 1,3-substituents on aromatic systems to direct metallation at a position *ortho* to these groups using organolithium reagents. This phenomenon is of synthetic interest since electrophilic attack on aryllithium intermediates represents a useful method for the functionalization of aromatic compounds.[4] Accordingly, factors which control regioselectivity and efficiency of lithiation of aromatic substrates have been the subject of many studies in recent years.[4] Numerous functional groups are known to promote *ortho*-lithiation.[5] However, with many of these groups, problems are encountered with lack of discrimination between non-equivalent *ortho* positions or between the ring positions and other acidic sites within the substrate.[6]

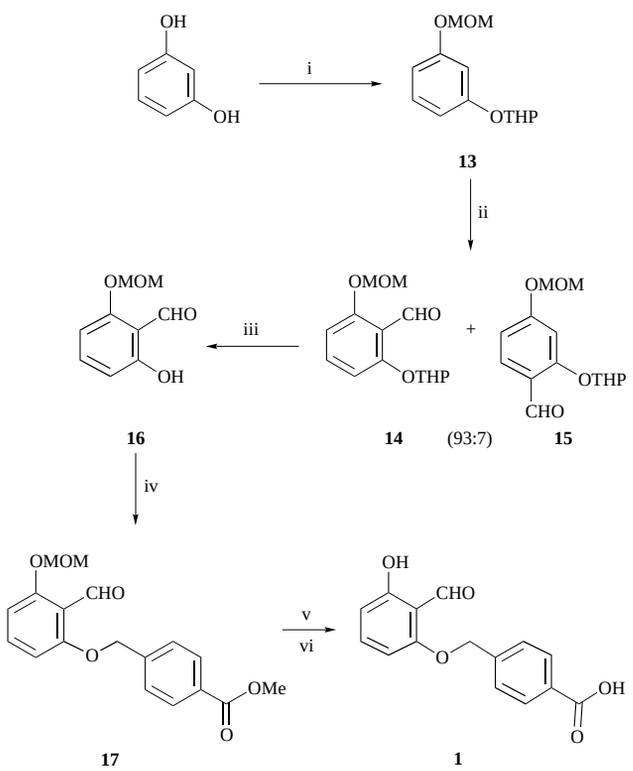


Scheme 1 *Reagents and conditions:* i, 3,4-dihydro-2*H*-pyran, PPTS; ii, BuLi, Et_2O, DMF; iii, H^+; iv, LiCl, DMF, D; v, $AlBr_3$–benzene; vi, Cs_2CO_3, 4-bromomethyl benzoate; vii, NaOH

As a model compound, we selected *O*-THP protected 3-methoxyphenol **3** (Scheme 1). An early investigation[6] revealed that *ortho*-lithiation of 1,3-di-OMe or 1,3-di-OTHP benzene gave selective metallation at the common *ortho* site.[6] Encouraged by these results, we investigated the reaction between BuLi and the protected phenol **3** in the presence of DMF as electrophile and ether solvent. We found that lithiation of **3** occurred with high regioselectivity between the two *ortho* directing groups to give **4** in high yield (95%). Scheme 1 summarizes these results. The OTHP group from the aldehyde **4** was deprotected with catalytic PTSA to afford the phenol **5**. This latter intermediate was successfully benzylated using methyl or *tert*-butyl 4-bromomethylbenzoate,[7] and caesium carbonate in DMF. This procedure offered a more practical work-up to that reported in the literature (alkyl halide, Bu^{t}OK, DMSO[2] or alkyl halide, K_2CO_3).

In order to complete the synthesis of tucaresol, selective demethylation of compound **6** was necessary. Previous work has demonstrated that alkyl aryl ethers are cleaved under neutral conditions using lithium halide in aprotic solvents.[8] The reaction is facilitated by the presence of electron-withdrawing substituents in the *ortho*-positions.[9] We therefore investigated the reaction between the aldehyde **5** or **6** with lithium chloride or bromide in boiling DMF under the standard conditions.[9] However, decomposition of starting material took place.

In an effort to replace the methoxy group, we examined the *ortho*-directing ability of the OTHP substituent relative to other *ortho*-directing substituents in the metallation with BuLi. An attractive alternative was the methoxymethyl group (MOM) since it is known to efficiently direct *ortho*-metallation.[10] To our knowledge, formylation of 1,3-di-*O*-substituted phenols bearing two different acid sensitive, strong *ortho*-directing groups has not been reported. The results are described in Scheme 2. Thus, resorcinol was selectively monoprotected as the methoxymethyl ether by reaction with chloromethyl ether in acetone in the presence of caesium carbonate.[11] The resulting aryl ether was treated with tetrahydropyran to afford quantitatively the bis protected phenol **13**. Lithiation of this compound was conducted in a similar manner as described above. Again, a significant degree of regioselective control of metallation between the protected hydroxy groups was obtained (the ratio of aldehydes **14**:**15** is 93:7). The product yield remained high.



Scheme 2 *Reagents and conditions:* i, chloromethyl methyl ether; 3,4-dihydro-2*H*-pyran, PPTS; ii, BuLi, Et_2O, DMF; iii, LiCl–DMF (75 °C) or cat. PTSA or 5% HCl adsorbed on SiO_2; iv, Cs_2CO_3, 4-bromomethyl (or *tert*-butyl) benzoate; v, H^+; vi, NaOH

The next step was investigation of selective hydrolysis conditions for the removal of the THP moiety in the presence of the MOM protecting group. Under neutral conditions, a mild and efficient procedure was developed to give the phenol **16** using an excess of LiCl in DMF at 75 ° (Scheme 2). This method is general and has been applicable to a variety of aliphatic and aromatic compounds bearing THP ethers in the presence of the MOM group.[12] Selective deprotection in acidic medium was also successful. The best conditions employed aqueous HCl acid adsorbed on silica gel or catalytic amount of PTSA in dichloromethane to afford compound **16** (Scheme 2). The latter was converted in two steps to tucaresol **1** by the same procedure described above.

Our approach to the synthesis of tucaresol **1** demonstrates that the *ortho* directing abilities of OTHP and OMOM groups in a 1,3-disubstituted benzene permit high regiocontrol of metallation. Both groups are convenient for protecting phenols but are acid labile. The ability to control the removal of the THP substituent in the presence of the MOM group make this procedure attractive for the synthesis of differentially functionalized resorcinol and particularly 6-substituted 2-hydroxybenzene derivatives. Our method also constituted an alternative to other electrophilic substitutions[4a] especially if *ortho* substitution is desired.

As an extension of this approach, the preparation of analogues of **1** was undertaken. These compounds cannot be obtained by the original synthesis. Fluorotucaresol **12** was chosen as a synthetic target since the introduction of fluorine into biologically active molecules often induces new pharmacological properties.[13] Previous studies[14] reported that lithiation of 3-fluoroanisole occurred in the doubly activated 2 position at −78 °C. At this temperature, benzyne formation is minimized.[14] In contrast to these results, Kirk[16] showed that fluorine competes significantly with the methoxy group as an *ortho* director. For example, the lithiation of 3-dimethyl-*tert*-butylsilyl ethers of fluorophenols proceeded exclusively *ortho* to fluorine and not in the doubly activated 2-position. Therefore, we examined the metallation of 3-fluorophenol *O*-protected by THP **8**. Scheme 1 summarizes our results. Treatment of compound **8** in THF at −78 °C in the presence of DMF gave exclusively the formyl product **9** in high yield. In contrast to the previous observation of Kirk, our results demonstrate that the steric bulk of the THP group does not predominate and coordination by oxygen is important. The synthesis of fluorotucaresol **12** was completed in a similar manner as described for tucaresol **1** (Scheme 1).

Our second approach was based on the use of commercially available benzaldehyde derivatives protected at the 2- and/or 6-positions. We first examined the demethylation of 2,6-dimethoxybenzaldehyde. As noted above, attempts to remove the methyl group of **5** and **6** using lithium halides in boiling DMF were unsuccessful. It was decided to shorten the reaction time from 12 to 6 h in order to minimize product decomposition. Thus, treatment of 2,6-dimethoxybenzaldehyde with lithium chloride in DMF at reflux for 6 h removed only one methyl group to give the phenol **5**. Upon application of further heat, this compound started to decompose. Efforts were then directed to other dealkylating reagents. Boron trichloride is known to demethylate methoxy groups that are *ortho* to a carbonyl moiety.[16] This dealkylation occurred if a six-membered ring is formed due to the complexation of the boron atom and the two oxygens of the carbonyl and the methoxy group.[16] The stronger the complex, the easier the demethylation. Unfortunately, this dual complex is not possible when the carbonyl function is *ortho* to both methoxy groups and only monodemethyl-

ation was observed in the case of 2,6-dimethoxybenzaldehyde.[16] Aluminium halides have proven successful as ether cleavage reagents.[17,18] Therefore, treatment of a solution of 2,6-dimethoxybenzaldehyde or the aldehyde **5** in benzene with aluminium chloride or bromide at ambient temperature for a few hours afforded 2,6-dihydroxybenzaldehyde.[19,20] The latter was selectively mono benzylated with methyl 4-bromomethylbenzoate then hydrolysed, as described before, to give tucaresol **1**. The major advantage of this procedure lies in the facile synthesis of compound **1** in three steps starting from commercially available material. A similar approach starting from the commercially available aldehyde **5** was also successful. Protection of the 2-hydroxy function as acetate then demethylation of the ether followed by alkylation and alkaline hydrolysis gave tucaresol **1** in good yield.

In summary, we have developed two simple, practical, and general procedures for the preparation of 2-hydroxy-6-alkoxy substituted benzaldehyde. The success of our first strategy relies on the highly regioselective *ortho* 2-lithiation of both OTHP and OMOM groups in 1,3-disubstituted benzenes. Selective hydrolysis conditions for the removal of the THP in the presence of the MOM protecting group make this procedure attractive for use in the functionalization of polysubstituted aromatic compounds. Of particular interest, the second approach involved the selective alkylation of 2,6-dihydroxybenzaldehyde which was readily available by treating 2,6-dimethoxybenzaldehyde or 2-hydroxy-6-methoxybenzaldehyde with aluminium halides. Both synthetic routes have been employed to supply gram quantities of tucaresol and offer the advantage of practical and general routes for the preparation of analogues. Biological data of analogues and structure–activity relationships will be reported in due course.

Experimental

Melting points were taken on a Fisher-Johns melting apparatus and are uncorrected. TLC was performed on Merck silica gel GOF_{254} plates with solvent systems; (A) 5% EtOAc–hexanes; (B) 15% EtOAc–hexanes; 25% EtOAc–hexanes; (D) 50% EtOAc–hexanes; (E) EtOAc; (F) 25% MeOH–EtOAc. ^{1}H, ^{13}C and ^{19}F NMR spectra were obtained on a Bruker DRX-400 or a Varian VXR-300 spectrometer. *J* Values are given in Hz. Mass spectra were recorded on a Kratos MS-50 TA instrument. All reagents were obtained from Aldrich Chemical Co. (Milwaukee WI), except for 2-methoxy-6-hydroxybenzaldehyde which originated from Lancaster (Windham).

Protection of the phenolic group with tetrahydropyran (THP)

General procedure. To a solution of monoprotected phenol (40 mmol) and pyridinium toluene-*p*-sulfonate (PPTS, 16 mmol) in dry dichloromethane (40 ml) was added 3,4-dihydro-2*H*-pyran (44 mmol) under argon. The reaction mixture was stirred at room temperature overnight after which it was evaporated under reduced pressure. The residue was then partitioned between 5% aqueous sodium hydrogen carbonate (60 ml) and ethyl acetate (70 ml). The organic layer was separated, dried (Na_2SO_4), filtered and evaporated. The remaining oil was purified by silica gel column chromatography to give the product.

1-Methoxy-3-tetrahydropyran-2-yloxybenzene 3.[22] Starting with 3-methoxyphenol (5 g, 40.32 mmol), we obtained **3** (5.10 g, 61%) as a colourless oil (this compound is volatile under reduced pressure and some product was lost during evaporation of solvents); TLC R_f 0.50 (B); δ_H(300 MHz; $CDCl_3$) 7.28–7.15 (1H, m, ArH), 7.20–6.52 (3H, m, ArH), 5.50–5.40 (1H, m, CH-O), 3.94–3.82 (1H, m, 6-H), 3.78 (3H, s, O-CH_3), 3.68–3.55 (1H, m, 6-H) and 2.10–1.52 (6H, m, 3 × CH_2).

1-Fluoro-3-tetrahydropyran-2-yloxybenzene 8. Starting with 3-fluorophenol (4 ml, 44.20 mmol) we obtained **8** (0.62 g, 72%) as a low-melting solid, mp 48–50 °C; TLC R_f 0.57 (A); δ_H(300 MHz; $CDCl_3$) 7.27–7.15 (1H, m, ArH), 6.88–6.75 (2H, m, ArH), 6.70–6.60 (1H, m, ArH), 5.42–5.35 (1H, m, CH-O), 3.94–3.82 (1H, m, 6-H), 3.68–3.55 (1H, m, 6-H) and 2.10–1.50 (6H, m, 3 × CH_2).

1-Methoxymethoxy-3-tetrahydropyran-2-yloxybenzene 13.[23] A solution of resorcinol (3.30 g, 30.00 mmol) in acetone (30 ml) was treated with caesium carbonate (8.88 g, 27.24 mmol) at 0 °C under argon. To the resulting white suspension was added dropwise chloromethyl methyl ether (2.07 ml, 27.24 mmol) and the mixture was maintained at 0 °C for 1.5 h. Insoluble material was filtered off and the filtrate was evaporated under reduced pressure. The crude material was purified by silica gel column chromatography using an EtOAc–hexanes gradient. Appropriate fractions were combined to give the following. 3-Methoxymethoxyphenol[23] (2.1 g, 50%) as a colourless oil, bp 105 °C, 1.7 mmHg, TLC R_f 0.50 (D); δ_H(300 MHz; $CDCl_3$) 7.22–7.08 (1H, m, ArH), 6.70–6.48 (3H, m, ArH), 5.85 (1H, s, OH), 5.16 (2H, s, CH_2-O) and 3.55 (3H, s, O-CH_3).

3-Methoxymethoxyphenol was THP-protected according to the procedure described above, starting with the monoprotected phenol **3** (1.5 g, 9.73 mmol) to give **13** (2.19 g, 95%) as a colourless oil, bp 103 °C, 2 mmHg TLC R_f 0.44; δ_H(300 MHz; $CDCl_3$) 7.28–7.13 (1H, m, ArH), 6.80–6.66 (3H, m, ArH), 5.50–5.40 (1H, m, CH-O), 5.15 (2H, s, CH_2-O), 3.94–3.82 (1H, m, 6-H), 3.68–3.55 (1H, m, 6-H), 3.50 (3H, s, O-CH_3) and 2.10–1.52 (6H, m, 3 × CH_2) (Found: C, 62.11; H, 6.54. $C_8H_{10}O_3$ requires C, 62.33; H, 6.54%).

Lithiation of 1,3-di-*O*-substituted phenols

General procedure. A solution of diprotected phenol (2.02 mmol) in dry ether (10 ml) at 0 °C was treated dropwise with butyllithium (1.6 M solution in hexanes; 2.42 mmol). Stirring was continued at room temperature for 2 h under a flow of argon. To this pale yellow solution was added dry DMF (6.05 mmol) after which the mixture was stirred for 2 h. The reaction was quenched with brine and extracted with diethyl ether (3 25 ml). The combined extracts were dried (Na_2SO_4), filtered and evaporated. The residue was purified by silica gel column chromatography using an EtOAc–hexanes gradient.

6-Methoxy-2-tetrahydropyran-2-yloxybenzaldehyde 4. Starting with phenol **3** (0.42 g, 2.02 mmol) we obtained the aldehyde **4** (0.36 g, 76%) as a white solid, mp 72–74 °C; TLC R_f 0.34; δ_H(300 MHz; $CDCl_3$) 10.58 (1H, s, CHO), 7.44 (1H, t, *J* 8.3, ArH), 6.80 (1H, d, *J* 8.2, ArH), 6.58 (1H, d, *J* 8.2, ArH), 5.70–5.50 (1H, m, CH-O), 3.89 (3H, s, OCH_3), 3.87–3.82 (1H, m, 6-H), 3.79–3.60 (1H, m, 6-H) and 2.01–1.86 (6H, m, 3 × CH_2); *m*/*z* (FAB, thioglycerol) 152 (MH^+ − THP, MH^+ − 85) (Found: M − THP, 152.0463. $C_8H_8O_3$ requires *M*, 152.0473).

6-Fluoro-2-tetrahydropyran-2-yloxybenzaldehyde 9. In this case the reaction temperature was maintained below −70 °C. Starting with phenol **8** (1.54 g, 7.82 mmol) we obtained the aldehyde **9** (1.65 g, 95%). This compound is volatile under high pressure and some product can be lost during the evaporation; TLC R_f 0.36; δ_H(300 MHz; $CDCl_3$) 10.46 (1H, s, CHO), 7.50–7.45 (1H, m, ArH), 7.00–6.50 (2H, m, ArH), 5.80–5.50 (1H, m, CH-O), 3.96–3.90 (1H, m, 6-H), 3.76–3.60 (1H, m, 6-H) and 2.01–1.52 (6H, m, 3 × CH_2).

6-Methoxymethoxy-2-tetrahydropyran-2-yloxybenzaldehyde 14 and 2-methoxymethoxy-4-tetrahydropyran-2-yloxybenzaldehyde 15. Starting with **13** (0.7 g, 2.94 mmol) we obtained **14** as the major product (0.48 g, 62%); TLC R_f 0.22; δ_H(300 MHz; $CDCl_3$) 10.48 (1H, s, CHO), 7.44 (1H, t, *J* 8.3, ArH), 6.88 (1H, d, *J* 8.3, ArH), 6.79 (1H, d, *J* 8.3, ArH), 5.50–5.40 (1H, m, CH-O), 5.15 (2H, s, CH_2-O), 3.94–3.82 (1H, m, 6-H), 3.68–3.55 (1H, m, 6-H), 3.50 (3H, s, OCH_3) and 2.10–1.50 6H, m, 3 × CH_2). A minor product **15** was also isolated (0.03 g, 4%); TLC R_f 0.26; δ_H(300 MHz; $CDCl_3$) 10.40 (1H, s, CHO), 7.80 (1H, d, *J* 8.3, ArH), 6.80 (1H, s, ArH), 6.70 (1H, d, *J* 8.4, ArH), 5.55–5.45 (1H, m, CH-O), 5.17–5.09 (2H, m, CH_2-O), 3.92–3.82 (1H, m, 6-H), 3.69–3.60 (1H, m, 6-H), 3.50 (3H, s, O-CH_3) and 2.05–1.50 (6H, m, 3 × CH_2).

Cleavage of the tetrahydropyran (THP) group

General procedure. *Method A: deprotection under neutral conditions.*—The protected phenol (2.12 mmol) was dissolved in DMF (15 ml) and LiCl (6.35 mmol) was added to the solution. The clear solution was stirred for 6 h at 75 °C after which it was filtered to remove insoluble material and then evaporated under reduced pressure. The residue was purified by silica gel column chromatography using a EtOAc–hexanes gradient.

Method B: deprotection under acidic conditions.—(1) The protected phenol (2.12 mmol) was dissolved in THF (25 ml) containing aq. HCl (1 M, 5 ml). The reaction mixture was stirred at room temperature for 5 h, dried (Na_2SO_4), filtered and evaporated to dryness. This gave the phenolic derivative in high yield. This compound was used in the next step without further purification.

(2) The protected phenol (6.24 mmol) was dissolved in dichloromethane (60 ml) and toluene-*p*-sulfonic acid (PTSA, 2.5 mmol) was added to the solution. After being stirred for 3 h at room temperature the yellow mixture was extracted with 5% aq. sodium hydrogen carbonate (2 × 10 ml), dried (Na_2SO_4), filtered and evaporated to give the expected phenol derivative in high yield. This compound was used in the next step without further purification.

2-Hydroxy-6-methoxybenzaldehyde 5.[18] Method A or B-1. Starting with aldehyde **4** (0.5 g, 2.12 mmol) we obtained **5** (0.31 g, 98%) as a white solid, mp 73–75 °C; TLC R_f 0.22; δ_H(300 MHz; $CDCl_3$) 11.98 (1H, s, OH), 10.97 (1H, s, CHO), 7.44 (1H, t, *J* 8.3, ArH), 6.54 (1H, d, *J* 8.0, ArH), 6.40 (1H, d, *J* 8.1, ArH) and 3.89 (3H, s, OCH_3).

2-Fluoro-6-hydroxybenzaldehyde 10.[24] Method B-2. Starting with aldehyde **9** (1.4 g, 6.24 mmol) we obtained **10** (0.86 g, 98%) as a white solid. This compound is volatile under high pressure and some of this material can be lost during the evaporation; TLC R_f 0.65; δ_H(300 MHz; $CDCl_3$) 11.30 (1H, br s, OH), 10.18 (1H, s, CHO), 7.43 (1H, m, ArH) and 6.67 (2H, m, ArH).

Cleavage of the tetrahydropyran (THP) group in the presence of the MOM group

2-Hydroxy-6-methoxymethoxybenzaldehyde 16.[2] A solution of the aldehyde **14** (0.15 g, 0.56 mmol) in methylene dichloride, was added to a stirred mixture of 10% aq. HCl adsorbed on silica (*ca*. 2 g). The reaction mixture was stirred at ambient temperature for 8 h, after which solid sodium hydrogen carbonate was added to it; stirring was continued for 5 min after which the mixture was filtered. The solid material was washed with dichloromethane, and the combined filtrate and washings were evaporated. This gave **16** (0.1 g, 97%) as a viscous oil which solidified with time, mp 48–50 °C;[2] TLC R_f 0.34; δ_H(300 MHz; $CDCl_3$) 11.92 (1H, s, OH), 10.39 (1H, s, CHO), 7.42 (1H, t, *J* 8.2, ArH), 6.66 (2H, d, *J* 8.4, ArH), 5.20 (2H, s, CH_2-O) and 3.50 (3H, s, OCH_3). The material was used in the next step without further purification.

Compound **16** was also prepared by selective deprotection of the THP group using PTSA as described in method B-2 above. In this case starting with **14** (0.3 g, 1.13 mmol) and PTSA (0.071 g, 0.28 mmol) in dichloromethane (30 ml) we obtained **16** (0.2 g, 97%). The material was used in the next step without further purification.

General procedure for benzylation of 2-substituted 6-hydroxybenzaldehyde 5

The phenol derivative (2.12 mmol) was dissolved in anhydrous DMF (15 ml) and caesium carbonate (2.54 mmol) was added to the solution under nitrogen. To this solution, methyl or *tert*-butyl 4-bromomethylbenzoate (2.14 mmol) was added after which the reaction mixture was stirred at room temperature overnight. Insoluble material was removed by filtration and the filtrate evaporated under reduced pressure. The residue was dissolved in dichloromethane (60 ml) and the solution washed with brine and 5% aqueous sodium hydrogen carbonate (30 ml), dried and evaporated. The crude product was purified by silica gel column chromatography using an EtOAc–hexanes gradient.

Methyl 4-(2-formyl-3-methoxyphenoxymethyl)benzoate 6. Starting with the phenol **5** (0.32 g, 2.12 mmol) we obtained **6** (0.56 g, 89%) as a white solid, mp 122–123 °C; TLC R_f 0.39; δ_H(300 MHz; $CDCl_3$) 10.58 (1H, s, CHO), 8.03 (2H, d, *J* 8.2, ArH), 7.52 (2H, d, *J* 8.0, ArH), 7.44 (1H, m, ArH), 6.60 (1H, d, *J* 8.3, ArH), 6.55 (1H, d, *J* 8.3, ArH), 5.20 (2H, s, CH_2-O), 3.90 (3H, s, OCH_3) and 3.88 (3H, s, OCH_3); *m*/*z* (FAB, thioglycerol) 301 (MH^+) (Found: MH^+, 301.1092. $C_{17}H_{17}O_5$ requires *M*, 301.1076).

Methyl 4-(2-formyl-3-fluorophenoxymethyl)benzoate 11. Starting with the phenol **10** (0.87 g, 6.24 mmol) we obtained **11** (1.61 g, 90%) as a white solid, mp 111–113 °C; TLC R_f 0.35 (D); δ_H[(300 MHz; $CDCl_3$)] 10.48 (1H, s, CHO), 8.16 (2H, d, *J* 8.3, ArH), 7.6 (2H, d, *J* 8.2, ArH), 7.55–7.50 (1H, m, ArH), 6.82–6.77 (2H, m, ArH), 5.29 (2H, s, CH_2-O) and 3.98 (3H, s, OCH_3); *m*/*z* (FAB, thioglycerol) 289 (MH^+) (Found: MH^+, 289.0869. $C_{16}H_{14}FO_4$ requires *M*, 289.0876).

Methyl 4-(2-formyl-3-methoxymethoxyphenoxymethyl)benzoate 17. Starting with the phenol **16** (0.24 g, 1.31 mmol) we obtained **17** (0.37 g, 86%) as a white solid mp 90–92 °C; TLC R_f 0.40 (D); δ_H(300 MHz; $CDCl_3$) 10.58 (1H, s, CHO), 8.10 (2H, d, *J* 8.2, ArH), 7.55 (2H, d, *J* 8.1, ArH), 7.43 (1H, t, 8.3, ArH), 6.82 (1H, d, *J* 8.3, ArH), 6.60 (1H, d, *J* 8.3, ArH), 5.30 (2H, s, CH_2-O), 5.22 (2H, s, CH_2-O), 3.98 (3H, s, OCH_3) and 3.55 (3H, s, OCH_3); *m*/*z* (FAB, thioglycerol) 331 (MH^+) (Found: MH^+, 331.1168. $C_{18}H_{19}O_6$ requires *M*, 331.1181).

Hydrolysis of 4-(3-substituted 2-formylphenoxymethyl)benzoic esters

General procedure. To a suspension of the ester (1.86 mmol) in ethanol (95%; 20 ml) was added aq. NaOH (1 M, 20 ml). The reaction mixture was stirred at room temperature for 2 h after which the pale yellow solution was cooled at 0 °C and acidified with concentrated hydrochloric acid. A white solid was precipitated from the reaction mixture after 2 h at room temperature. This was filtered off, washed with water (1 ml) and dried to give the corresponding acid.

4-(2-Formyl-3-methoxyphenoxymethyl)benzoic acid 7. Starting with ester **6** (0.56 g, 1.86 mmol) we obtained the acid **7** (0.48 g, 90%) as a white solid, mp 203–205 °C; TLC R_f 0.40 (F); δ_H[300 MHz; $(CD_3)_2SO$] 10.62 (1H, s, CHO), 8.15 (2H, d, *J* 8.2, ArH) 7.60 (2H, d, *J* 8.2, ArH), 7.46 (1H, t, *J* 8.4, ArH), 6.64 (d, 2H, d, *J* 8.2, ArH), 5.26 (2H, s, CH_2-O) and 3.92 (3H, s, OCH_3); δ_C(300 MHz; CD_3OD) 170.13, 160.95, 159.60, 144.85, 132.13, 131.73, 131.43, 128.51, 128.08, 107.81, 106.54, 103.14, 71.51 and 56.93; *m*/*z* (FAB, thioglycerol) 287 (MH^+) (Found: MH^+, 287.0913. $C_{16}H_{15}O_5$ requires *M*, 287.0919).

4-(2-Formyl-3-fluorophenoxymethyl)benzoic acid 12. Starting with the ester **11** (0.62 g, 2.17 mmol) we obtained the acid **12** (0.54 g, 91%) as a white solid, mp 198–200 °C; TLC R_f 0.30 (E); δ_H(300 MHz; $CDCl_3$) 10.55 (1H, s, CHO), 8.16 (2H, d, *J* 8.3, ArH), 7.59 (2H, d, 8.2, ArH), 7.51–7.45 (1H, m, ArH), 6.82–6.77 (2H, m, ArH) and 5.28 (2H, s, CH_2-O); δ_C[300 MHz; $(CD_3)_2SO$] 167.30, 163.75, 160.91, 160.31, 141.35, 137.01, 136.84, 130,49, 129.90, 129.70, 127.40, 113.70, 109.04, 108.77 and 69.93; δ_F[400 MHz; $(CD_3)_2SO$, $CFCl_3$ as a reference] δ −115 (dd, *J* 8.5); *m*/*z* (FAB, thioglycerol) 275 (MH^+) (Found: MH^+, 275.0734. $C_{15}H_{12}FO_4$ requires *M*, 275.0720).

4-(2-Formyl-3-hydroxyphenoxymethyl)benzoic acid, tucaresol 1:[2] deprotection of the MOM group

Hydrochloric acid (3 M, 45 ml) was added dropwise to a solution of the aldehyde **17** (1 g, 303 mmol) in ethanol (45 ml). The reaction mixture was stirred at 60 °C for 1.5 h after which the precipitated solid was filtered off. This was washed with cold water (5 ml), dried and recrystallised from ethanol–water (2:1) to give the corresponding phenol derivative (0.82 g, 94%), mp 123–125 °C; TLC R_f 0.50 (D); δ_H(300 MHz; $CDCl_3$) 11.95

(1H, s, OH), 10.40 (1H, s, CHO), 8.10 (2H, d, *J* 8.1, ArH), 7.55 (2H, d, *J* 8.1, ArH), 7.40 (1H, t, *J* 8.2, ArH), 6.60 (1H, d, *J* 8.4, ArH), 6.40 (1H, d, *J* 6.4, ArH), 5.18 (2H, s, CH_2-O) and 3.99 (3H, s, OCH_3); *m*/*z* (FAB, thioglycerol) 287 (MH^+) (Found: MH^+, 287.0925. $C_{16}H_{15}O_5$ requires *M*, 287.0920). The ester (0.65 g, 2.27 mmol) was hydrolysed according to the procedure described above to give **1** (0.55 g, 89%) as a white solid, mp 240–242 °C; TLC R_f 0.40 (F); δ_H[300 MHz; $(CD_3)_2SO$] 11.75 (1H, br s, OH), 10.35 (1H, s, CHO), 7.94 (2H, d, *J* 8.03, ArH), 7.53 (2H, d, *J* 8.12, ArH), 7.48 (1H, t, *J* 8.34, ArH), 6.68 (1H, d, *J* 8.40, ArH), 6.52 (1H, d, *J* 8.40, ArH) and 5.28 (2H, s, CH_2-O); δ_C[300 MHz; $(CD_3)_2SO$] 167.24, 162.65, 162.38, 161.15, 141.53, 138.92, 130.42, 129.67, 127.40, 110.83, 109.50,103.56 and 69.44 (Found: C, 65.99; H, 4.29. $C_{15}H_{12}O_5$ requires C, 66.17; H, 4.44%).

Preparation of 2,6-dihydroxybenzaldehyde[20]

To a solution 2,6-dimethoxybenzaldehyde (0.456 g, 2.28 mmol) or 2-hydroxy-6-methoxybenzaldehyde (0.424 g, 2.28 mmol) in benzene (25 ml) was added aluminium bromide (1.8 g, 6.84 mmol or 1.21 g, 4.56 mmol, respectively) at room temperature. The complex which formed was precipitated as a red gum. After the mixture had been stirred for 3 h, crushed ice, 3 M hydrochloric acid (15 ml), and ether (30 ml) were added to it. The aqueous layer was separated and extracted with ether (2 × 30 ml). The ether extracts were combined and extracted with 1 M aq. NaOH (5 ml). The alkaline solution was cooled in ice–water and concentrated hydrochloric acid (2 ml) was added to it. The crude yellow product was purified by column chromatography (silica gel, EtOAc–hexanes 1:1) to yield a pale yellow solid (0.18 g, 58%), mp 157–158 °C;[20,21] TLC R_f 0.50 (D); δ_H[300 MHz; $(CD_3)_2SO$] 10.24 (1H, s, CHO), 7.37 (1H, t, *J* 8.0, ArH) and 6.36 (2H, d, *J* 8.1, ArH); *m*/*z* (EI) 138 (MH^+) (Found: MH^+, 138.0317. $C_7H_6O_3$ requires *M*, 138.0318).

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