Tetrahedron 65 (2009) 4917–4922

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Regioselective alkylation of hydroxysalicylaldehydes

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ARTICLE INFO

Article history:
Received 16 February 2009
Received in revised form 30 March 2009
Accepted 30 March 2009
Available online 10 April 2009

ABSTRACT

Schiff-base ligands are often used as backbone ligands for mono- and dinuclear complexes that serve as catalysts during aerobic oxidation reactions. However, their water solubility is low and limits their applicability as catalysts to transform highly water-soluble biomolecules, such as carbohydrates or amino alcohols. A new method to regioselectively incorporate water solubility-promoting polyethylene glycol side chains into a frequently used aldehyde building block of Schiff-base ligands has been developed.

1. Introduction

Many complexes based on salen-type ligands derived from commercially available salicylaldehydes and diamines have been reported.[1–4] The synthesis of these ligands is based on a facile condensation reaction of two aldehyde moieties with an aromatic or aliphatic diamine.[5–15] The use of dinuclear metal complexes with Schiff-base backbone ligands as catalysts includes stereoselective organic transformations, hydroxylation of alkenes, aldol reactions, alkene epoxidations, Baeyer–Villiger oxidations, and Diels–Alder reactions.[16–22] The metal complexes are tailored with groups that promote, e.g., π–π stacking, hydrogen donor or acceptor abilities, or emission of fluorescence signals, depending on their potential use as catalysts, sensors, or screens for bioactivity upon interaction with carbohydrates, proteins, DNA or viruses.[23]

Using Schiff-base complexes to oxidize alcohol or phenol groups of biomolecules, such as in carbohydrates or lignin, appears favorable due to their demonstrated oxidation ability and the ease of preparation. However, increased water solubility of the complexes is required for the transformation of biomolecules in homogeneous catalysis. The synthetic efforts to alter salen-type ligands accordingly usually focus on derivatization of the aldehyde building block to avoid alteration of the geometry around the metal ion core in the resulting ligand.

While peralkylation of phenols with water solubility-promoting site chains has been frequently described since the pioneering work of Cram and Peterson on crown ethers,[24–28] this method is not applicable here. The peralkylation of salicylaldehydes as building blocks for salen complexes limits the number of coordination sites available for metal ions and consequently decreases their stability. A reliable method for the *regioselective alkylation* of hydroxysalicylaldehydes with polar, water solubility-promoting side chains is therefore needed.[29]

Toward that end, we choose commercially available 4-hydroxysalicylaldehyde (**1**) as starting material for a regioselective derivatization of the 4-hydroxy group with polar side chains. Moreover, the *regioselective alkylation* of *n*-hydroxysalicylaldehydes is still not well understood and consequently still cumbersome. To overcome this obstacle, we report our experimental results supported by theoretical calculations.

2. Results and discussion

The incorporation of *water solubility* promoting polyethylene glycol (PEG) side chains into **1** using literature procedures developed for the monoalkylation of *n*-hydroxysalicylaldehydes resulted in disappointing overall yields (<5%) as concluded from ^{1}H and ^{13}C NMR spectroscopic data.[22,30] The attempted derivatization was conducted as a Williamson ether synthesis of **1** using poly(ethylene glycol) chlorides **2a–c**, then poly(ethylene glycol) monomethyl ethers **3a–c**[22] and last tetrahydro-2*H*-pyranyl poly(ethylene glycol) monomethyl ethers **4a–c** in DMF, acetone, dichloromethane, or acetonitrile at 60–100 °C over a period of 24–72 h as described by others (Fig. 1).[22,30]

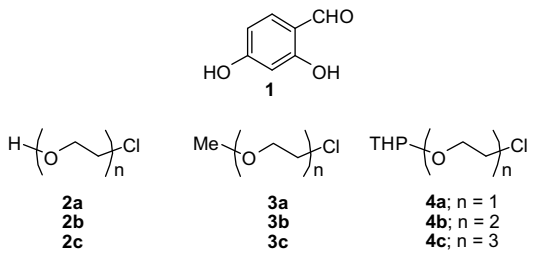

Figure 1. 4-Hydroxysalicylaldehyde **1**, polyethylene glycol chlorides **2a–c**, polyethylene glycol monomethyl ethers **3a–c**, and polyethylene glycol tetrahydro-2*H*-pyrans **4a–c**.

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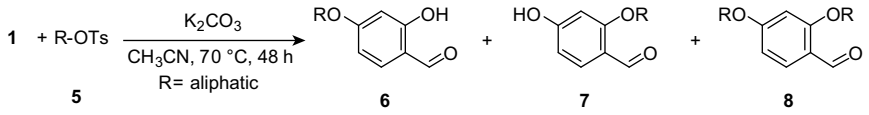
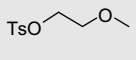
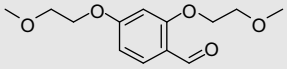
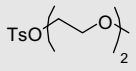
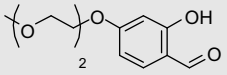
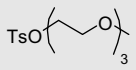
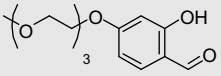
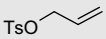
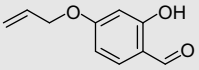
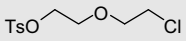
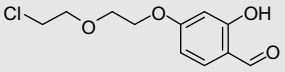
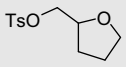
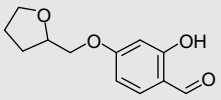
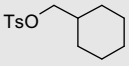
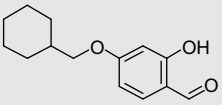
doi:10.1016/j.tet.2009.03.104



Scheme 1. Regioselective alkylation of **1**.

Table 1
Distribution of mono-alkylated alkoxysalicylaldehydes **6** and **7** and di-alkylated product **8** after tosylation of **1** with **5**

Entry	Tosylate	**5**	Ratio **6**/**7**/**8** (yield in %)[a]	Alkylated aldehyde	**6** or **8**	Yield[b] of **6** (%)
1		**a**	1:<0.1[c]:4.4 (75)		**8a**	25
2		**b**	>99.9:<0.1[c]:<0.1[c] (46)		**6b**	37
3		**c**	>99.9:<0.1[c]:<0.1[c] (62)		**6c**	55
4		**d**	>99.9:<0.1[c]:<0.1[c] (71)		**6d**	48
5		**e**	>99.9:<0.1[c]:<0.1[c] (74)		**6e**	50
6		**f**	>99.9:<0.1[c]:<0.1[c] (32)		**6f**	—[d]
7		**g**	—[d]		**6g**	17

[a] The total yield of the alkylation is given in percent and based on the conversion of **5** as determined by HPLC analysis.
[b] The isolated yield is determined after column chromatography on silica gel.
[c] Below detection limit.
[d] Not isolated or determined.

Increasing the catalytic amount of potassium iodide to a stoichiometric quantity, which usually enhances the reactivity of the halide,[31] did not promote alkylation of **1**. Changing the base from potassium carbonate to sodium/potassium bicarbonate[32] or sodium/potassium hydroxide[33,21] leads to recovery of starting material when polar aliphatic instead of benzyl halides are employed. The use of sodium hydride to deprotonate **1** and subsequent addition of the alkylhalide promotes undesired peralkylation as well.[24–28] Considerable amounts of di-substituted product (up to 50%) were also observed during the alkylation of **1** with **2** or **4** in DMF in the presence of potassium carbonate and potassium iodide above 100 °C, even when stoichiometric amounts of the chlorides were used. A similar observation was reported by Mendelson et al. for the regioselective 4-benzylation of **1** with benzyl bromide in acetone.[32] Mono-alkylated products derived from **1** were not observed at all when an excess of **2** or **4** was used, as concluded from ^{1}H and ^{13}C NMR spectra.

In subsequent attempts, benzyl halides were used as model compounds for the alkylation of **1**. These studies revealed that the use of a slight molar excess of **1** over the halide (1.35:1) results in the formation of mono-alkylated **1** as the predominant product in acetonitrile. The product can be easily separated from the excess of starting material and traces of di-substituted product (if any) by column chromatography over silica gel. The separation of an almost equimolar mixture of mono- and di-substituted **1**, which results after use of stoichiometric amounts or excess of halide, was found to be very tedious.

Keeping all of these results in mind, we achieved *regioselective* 4-alkoxylation of **1** with water solubility-promoting *aliphatic* polyethylene glycol chains in a one-step reaction after activation of polyethylene glycol monomethyl ethers by tosylation and fine-tuning of the reaction conditions.[34] The tosylates **5a**–**g** (Table 1) were prepared from commercially available aliphatic alcohols and tosyl chloride as described.[35] The compounds were purified when necessary by distillation or column chromatography over silica gel using ethyl acetate–cyclohexane mixtures as eluent. The identity of the tosylates was confirmed by ^{1}H and ^{13}C NMR spectroscopy prior to use (Supplementary data).[36–42]

2.1. Regioselective monoalkylation of hydroxysalicylaldehydes with aliphatic tosylates

The tosylates **5a**–**g** were treated with excess of **1** in the presence of potassium carbonate at 60–70 °C in dry acetonitrile for 48 h (Scheme 1). Purification of the crude reaction products by column chromatography over silica gel using ethyl acetate–cyclohexane mixtures as eluent removed the remaining excess of **1** and unreacted tosylate.

The analysis of crude reaction mixtures by analytical HPLC, combined with the analysis of the isolated compounds by ^{1}H and ^{13}C NMR spectroscopy and ESI mass spectrometry revealed the formation of 4-alkoxysalicylaldehydes **6b**–**f** as major reaction products in moderate yields; the formation of 2-alkoxysalicylaldehydes **7** was not observed in any case. Surprisingly, the di-substituted product **8a** is the major product for the transformation of **1** with tosylate **5a** (see

below). Alkylation of **1** with **5e** that contains both a chloride and a tosylate confirmed the increased reactivity of the tosylate over the halide as leaving group in aprotic polar solvents; the obtained reaction product **6e** contains the chloride.

The allocation of structures to the reaction products was based on the combination of several observations: firstly, the amounts of protons in the ^{1}H NMR spectra of the isolated compounds **6b–f** indicate the formation of mono-alkylated products only and do not support the presence of di-alkylated **8**; this assignment was confirmed by ESI mass spectrometry of the corresponding isolated compounds. Secondly, the composition of the crude reaction mixtures was obtained by quantitative analysis using analytical HPLC on RP 18; the analysis furthermore revealed the selectivity for the formation of **6** versus **7** or **8** and the total yield of the alkylation based on the amount of remaining tosylate **5** (Table 1; Supplementary data). Thirdly, the structure assignment for the products was further supported by ^{13}C NMR spectroscopy. The ^{13}C NMR spectra of the reaction products **7** or **8** with an alkylated 2-hydroxyl group show a shift of the signal of the carbonyl carbon from 196 ppm (in **1**) to 188 ppm (in **7** or **8**) indicating alkylation of **1** in close proximity to the aldehyde group (see Supplementary data). The ^{13}C NMR spectra of the 4-alkylated reaction products **6** show signals for the carbonyl carbon at 196 ppm (see Supplementary data).

To estimate the amount of de-alkylation of the reaction products during the prolonged reaction time (48 h), **6g** was treated with an excess of potassium carbonate in dry acetonitrile. Formation of **1** was not observed and only starting material, i.e., **6g**, was recovered as shown by HPLC analysis of the crude reaction mixture (see Supplementary data). The amount of de-alkylation due to prolonged reaction times is therefore negligible. Attempts to derive mono-alkylated products with the developed reactions from 3-hydroxysalicylaldehyde (**9**) failed. Instead, peralkylated products **10d** and **10e** were isolated after reactions of **9** with tosylates **5d** or **5e** as major products (Fig. 2). The alkylation of 5-hydroxysalicylaldehyde **11** with **5e** yielded an equimolar mixture of 2- and 5-alkylated products **11A** and **11B** in very poor yield (<1%, see Supplementary data) and was not further investigated.

IR spectra reveal the absence of any hydroxyl group and intramolecular hydrogen bond after exposing **1** to excess potassium carbonate in dry acetonitrile, which supports the formation of dianion **12** as first step in the reaction prior to alkylation with tosylate **5** (Fig. 3).

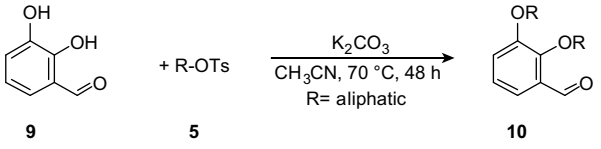


Figure 2. Alkylation of 3-hydroxysalicylaldehyde.

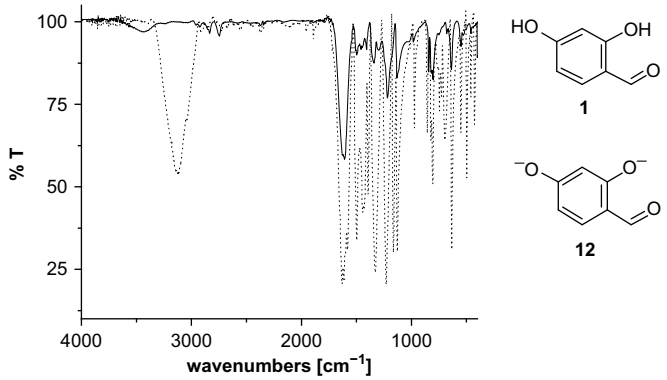


Figure 3. IR spectra of **12** (solid line) and **1** (dotted line).

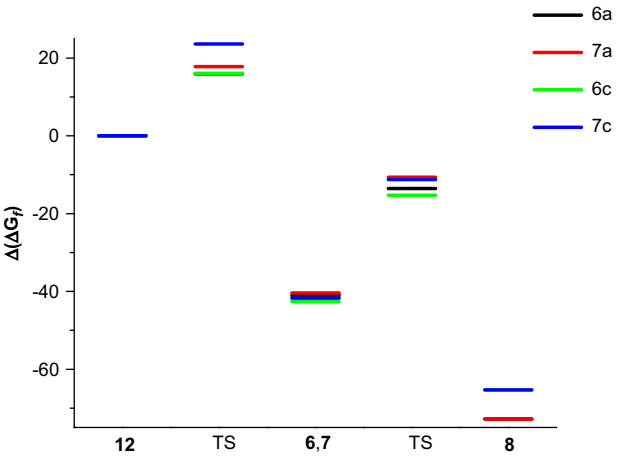
As both phenol oxygen atoms in **1** allow conjugation with the carbonyl oxygen after deprotonation, alkylation of the dianion **12** should be *equally likely* at both phenolate oxygen atoms. The observed regioselective alkylation of **1** with tosylates **5b–g** is therefore remarkable and requires further investigation. In this regard, we examined the alkylation of **1** with the tosylates **5a** and **5c** by computational methods. The bimolecular nucleophilic substitution S_N2 is among the most widely used organic reactions, and has been frequently studied both experimentally and with a computational approach using density functional theory.[40,41,43–45]

2.2. Putative causes for regioselectivity—a theoretical investigation

All computations were performed using the Gaussian 03 suite.[46] The geometry of all structures was optimized using Becke's three-parameter functional coupled with the correlation function of Lee et al. (B3LYP) and the basis set 6-31G(d).[47,48] This level of theory was proven to be applicable for the investigation of nucleophilic substitutions including the transition states of S_N2 reactions.[43,44]

The Gibbs free energies ΔG^{298} for the reaction of **12** with **5a** and **5c** as representative examples of all other alkyl tosylates were calculated using the B3LYP/6-31G(d) level of theory. Vibrational frequencies were computed at the same level of theory in order to define optimized geometries as minima or as saddle points with one unique imaginary frequency; its vibrational stretching corresponds to the forming and breaking of bonds in the transition state. Activation energies $\Delta(\Delta G^{\#})$ and overall changes in free reaction energies $\Delta(\Delta G_f)$ were predicted from solvation free energies

Table 2
Relative free energies $\Delta(\Delta G_f^{298})$ (in kcal/mol) and relative activation energies $\Delta(\Delta G_f^{\#,298})$ (in kcal/mol) of the TS of the mono- and di-alkylation of dianion **12** with alkyl tosylates **5a** and **5c** at the B3LYP/6-31+G(d) level of theory in acetonitrile at 298.15 K, 1 atm[a]



Starting material		Product	$\Delta(\Delta G_f^{298})$	$\Delta(\Delta G^{\#,298})$
12	**5a**	**6a**	−41.0	15.9
12	**5a**	**7a**	−40.4	17.8
12	**5a**	**8a**	−72.8	
12	**5c**	**6c**	−42.6	16.1
12	**5c**	**7c**	−41.7	23.6
12	**5c**	**8c**	−65.3	
6a	**5a**	**8a**	−31.7	27.5
7a	**5a**	**8a**	−32.4	29.8
6c	**5c**	**8c**	−22.8	27.3
7c	**5c**	**8c**	−23.6	30.5

[a] Solvation free energies in acetonitrile are computed at the CPCM/B3LYP/6-31+G(d) level of theory.

computed as single point calculations of the geometry-optimized structures at the CPCM/B3LYP/6-31+G(d) level of theory in acetonitrile.

Initially, the changes in free energies for the alkylation of **12** with **5** yielding **6**, **7**, and **8** were calculated (Table 2). Both the mono- and di-alkylation reactions are spontaneous. The differences in the reaction free energies for the formation of 2- or 4-mono-alkylated products **6a** and **7a**, and **6c** and **7c**, respectively, are 0.6–0.9 kcal/mol and therefore insignificant.

The activation energies for the formation of the transition states TS**6** and TS**7** from the reaction of **12** with **5a** or **5c** favor the substitution at 4- over a substitution at 2-position (Table 2). While both reactions show comparable activation energies for the substitution at 4-position of **12**, the required activation energy for the formation of TS**7a** and TS**7c** leading to substitution at 2-position is by 1.9 kcal/mol and 7.5 kcal/mol, respectively, higher. The computational results are thus in line with the experimental observations.

The relative free energies of the mono-substituted products indicate furthermore a competition between **6**, **7**, and **12** for the alkylation reagent. The alkylation of **6** at the 2-position is predicted to require 2.3–3.2 kcal/mol more activation energy than an alkylation of **7** at the 4-position. Thus, once formed, 4-alkylated mono-substituted product **6** is easier to trap at that level than **7**. The activation energy for the second transition state is about 11.6–12 kcal/mol larger than for the first, while the di-substituted products **8** are thermodynamically the most stable overall reaction products (Fig. 4). Product **8a** is more stable by 7.5 kcal/mol than **8c**, which is ascribed to a decreased flexibility in a shorter side chain.

Overall, the calculations are in line with the experimental results and provide further insides into the alkylation of **1**. The formation of 4-substituted alkylation products **6b**–**f** upon reaction of **12** with **5b**–**f** correlates to the trapping of kinetically controlled reaction products. The developed reaction conditions do not lead to the thermodynamically most stable di-substituted products **8b**–**f**. Steric hindrance by bulky tosylates appears to hamper an attack of the 2-oxo phenolate of **12** on tosylates **5b**–**f**, and therefore 2- and di-substituted products are not observed. However, the small size of tosylate **5a** allows the formation of the thermodynamically most stable product **8a** and results in an energy gain based on decreased flexibility of the side chains compared to a reaction with **5c** (7.5 kcal/mol).

In summary, our method allows regioselective 4-alkoxylation of the least expensive hydroxysalicyl-aldehyde **1**, facilitates separation and isolation of the 4-alkylated product from the crude reaction mixture, avoids formation of di-alkylated aldehydes (which was recognized as a major drawback of common reaction procedures by others[32]) with bulky tosylates and provides comparable or slightly higher yields to described procedures[22,49,50,51] by using acetonitrile and a weak base that avoids handling of sodium hydride in dry solvents.[52] We furthermore provide insight in the reaction pathway by theoretical investigations and reveal the trapping of mono-substituted reaction products as intermediates under kinetically controlled reaction conditions.

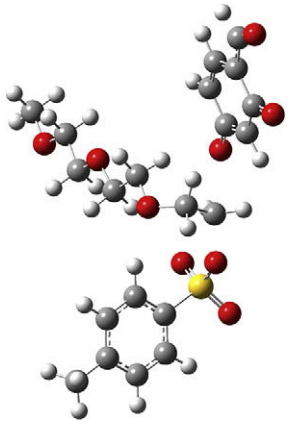


Figure 4. TS for the alkylation of **12** with **5c** yielding **6c**; carbon atoms are colored in gray, hydrogen atoms in white, oxygen atoms in red, sulfur atoms in yellow.

3. Experimental

3.1. Instrumentation

^{1}H and ^{13}C NMR spectra were recorded on a Bruker AV400 or AC250 spectrometer (400.2 or 250 MHz for ^{1}H, and 100.6 or 62.9 MHz for ^{13}C). Chemical shifts (δ) in ^{1}H NMR are expressed in parts per million and coupling constants (J) in hertz. Signal multiplicities are denoted as s (singlet), d (doublet), t (triplet), and m (multiplet). Deuterated chloroform was used as solvent, and chemical shift values are reported relative to the residual signals of this solvent (δ=7.24 for ^{1}H and δ=77.0 for ^{13}C). IR spectra were of the samples were recorded as thin films on KBr or KBr pellets; ν in cm^{-1}. Elemental analysis was performed by Atlantic Microlab Inc., Atlanta, GA. HRMS data were measured in the Laboratory for Biological Mass Spectrometry, Texas A & M University, College Station, TX. Semi-preparative and analytical HPLC were performed on a Shimadzu HPLC system on RP18 (Luna 3 μm, 50×3 mm or 100×10 mm, respectively) and UV–vis detection of the eluting compounds at 230 nm.

Thin layer chromatography (TLC) was done using silica gel TLC plates from SORBENT Technologies, 200 μm, 4×8 cm, aluminum backed, with fluorescence indicator F_{254} with detection by charring with anthrone sulfate, and/or by UV light when applicable. Column chromatography was carried out using silica gel 60 from Silicycle® (40–63 μm, 230–240 mesh) as stationary phase. All melting points were recorded on a Mel-Temp melting point apparatus; the values are uncorrected. All chemicals were reagent grade or better and were used as received from commercial suppliers.

All electronic structure calculations in gas phase and solution were performed with the Gaussian 03 program at the Alabama Supercomputer Center.[46] Low energy conformers of the reactants **1** and **3** (or **5**), and of the products **6** were calculated with density functional theory at the B3LYP/6-31G(d) theory level throughout.[48,47] All stationary points were examined with vibrational analyses and confirmed as minima. The transition states were initially optimized at the B3LYP/3-21G level, and the obtained structures re-optimized at the B3LYP/6-31G(d) level of theory as low energy conformers. All transition states were characterized by a single imaginary frequency (ν_{imag}). The solvation free energies are computed as single point calculations at the CPCM/B3LYP/6-31+G(d) level of theory in acetonitrile at 298.15 K and 1 atm.[53] The free energy of the reaction in acetonitrile was computed using Eq. 1; $\varepsilon(CH_3CN)$=36.64.

$$\Delta G(CH_3CN) = \Delta G(gas) + \Delta G(solvation) \quad (1)$$

3.2. 4-(2-Methoxyethoxy)-salicylaldehyde (6a)

A mixture of 2,4-dihydroxybenzaldehyde (3.04 g, 22 mmol), toluene-4-sulfonic acid 2-methoxy-ethyl ester (4 g, 17.6 mmol), and potassium carbonate (3 g, 22 mmol) in 150 mL acetonitrile was stirred for 48 h at 60 °C. The reaction mixture was then cooled to ambient temperature, filtered, and the solvent evaporated to obtain a crude yellow oil. The crude product was purified by column chromatography over silica gel using CH_2Cl_2/MeOH (98:2) to obtain

a crystalline colorless solid (750 mg, 21%). R_f 0.87, SiO_2, CH_2Cl_2/MeOH (98:2); mp 63–64 °C. Found: C 61.27, H 6.16%; $C_{10}H_{12}O_4$ requires C 61.22, H 6.16%. δ_H (400.2 MHz, $CDCl_3$) 11.50 (s, 1H, O*H*), 9.74 (s, 1H, C*H*O), 7.46 (d, 8.6, 1H, Ar*H*), 6.61 (dd, 8.7, 2.4, 1H, Ar*H*), 6.47 (d, 2.3, 1H, Ar*H*), 4.19 (t, 4.9, 2H, ArOCH_2–), 3.79 (t, 4.9, 2H, –CH_2–O–), 3.48 (s, 3H, –OCH_3); δ_C (100.6 MHz, $CDCl_3$) 194.5, 166.0, 164.4, 135.3, 115.3, 108.9, 101.2, 71.9, 70.6, 67.8, 59.3; ν_{max} (thin film) 2929, 2890w (CH), 1627s (C=O), 1225m, 1173s (C–O–C) cm^{-1}; HRMS ($^+$TOF MS) *m*/*z* found: 197.0811; calcd for $C_{10}H_{12}O_4+H^+$ (M+H^+) 197.0814.

3.3. 2,4-Bis(2-methoxyethoxy)benzaldehyde (8a)

Colorless oil; δ_H (400.2 MHz, $CDCl_3$) 10.31 (s, 1H, C*H*O), 7.78 (d, 8.6, 1H, Ar*H*), 6.54 (dd, 8.6, 1.5, 1H, Ar*H*), 6.49 (d, 2.0, 1H, Ar*H*), 4.16 (m, 4H, ArOCH_2–), 3.75 (m, 4H, –CH_2–O–CH_3), 3.43 (s, 6H, –CH_3); δ_C (100.6 MHz, $CDCl_3$) 188.3, 162.9, 130.3, 119.4, 106.4, 99.7, 70.7, 70.6, 68.1, 67.6, 59.3, 59.2; HRMS ($^+$TOF MS) *m*/*z* found 255.1224; calcd for $C_{13}H_{18}O_5+H^+$ (M+H^+) 255.1232.

3.4. 4-[2-(2-Methoxyethoxy)-ethoxy]-salicylaldehyde (6b)

A mixture of 1.41 g (10 mmol) 2,4-dihydroxybenzaldehyde, 1.81 g (7.1 mmol) 2-(2-methoxyethoxy)ethyl-4-methylbenzenesulfonate, and 1.41 g (10 mmol) potassium carbonate was stirred in 150 mL acetonitrile at 70 °C for 48 h. The reaction mixture was then cooled to room temperature and filtered over a silica gel with CH_2Cl_2. A crude brown oil (1.8 g) was obtained that was purified by column chromatography over silica gel with cyclohexane–ethyl acetate (1:1) yielding 0.6 g (2.50 mmol, 37%) of a colorless oil. δ_H (400.2 MHz, $CDCl_3$) 11.46 (s, 1H, O*H*), 9.71 (s, 1H, C*H*O), 7.42 (d, 8.6, 1H, Ar*H*), 6.56 (dd, 8.7, 2.4, 1H, Ar*H*), 6.43 (d, 2.3, 1H, Ar*H*), 4.19 (t, 4.9, 2H, ArOCH_2–), 3.87 (t, 4.9, 2H, –CH_2CH_2O–), 3.72 (m, 2H, –CH_2–), 3.58 (m, 2H, –CH_2–), 3.39 (s, 3H, –CH_3); δ_C (100.6 MHz, $CDCl_3$) 194.6, 166.2, 164.6, 135.4, 115.4, 108.9, 101.5, 72.1, 71.0, 69.5, 68.0, 59.3; ν_{max} (thin film) 3247br (OH), 3063w, 2868s, 1646s (C=O), 1109s (C–O) cm^{-1}; HRMS ($^+$TOF MS) *m*/*z* found: 247.1160; calcd for $C_{12}H_{16}LiO_5$ (M+Li^+) 247.1158.

3.5. 4-[2-(2-(Methoxyethoxy)-ethoxy)-ethoxy]-salicylaldehyde (6c)

Compound **6c** was synthesized and characterized previously.[54]

3.6. 4-Allyloxysalicylaldehyde (6d)

A mixture of 1.5 g (10.6 mmol) 2,4-dihydroxybenzaldehyde, 1.5 g (7.1 mmol) allyl tosylate, and 1.2 g (10.8 mmol) potassium carbonate was stirred in 150 mL acetonitrile at 60 °C for 12 h. The reaction mixture was then cooled to ambient temperature, filtered, and the solvent evaporated to obtain a brown solid. The residue was dissolved in 10 mL of distilled water and extracted using chloroform (2×50 mL). The combined organic layers were dried over anhydrous sodium sulfate and evaporated to obtain 1.10 g of a crude product that was purified by column chromatography over silica gel with cyclohexane/ethyl acetate (9:1) as eluent yielding 0.61 g (3.42 mmol, 48%) of a colorless oil. Found: C 67.13, H 5.65%; $C_{10}H_{10}O_3$ requires C 67.41, H 5.66%. δ_H (400.2 MHz, $CDCl_3$) 11.44 (s, 1H, ArO*H*), 9.68 (s, 1H, ArC*H*O), 7.40 (d, 8.6, 1H, Ar*H*), 6.53 (dd, 8.6, 2.3, 1H, Ar*H*), 6.41 (d, 2.3, 1H, Ar*H*), 6.00 (m, 1H, –C*H*=CH_2), 5.40 (ddd, 17.2, 3.0, 1.6, 1H, –CH=CH_2), 5.31 (ddd, 10.5, 2.7, 1.4, 1H, –CH=CH_2), 4.56 (dt, 5.3, 1.5, 2H, –CH_2–); δ_C (100.6 MHz, $CDCl_3$) 194.4, 165.7, 164.4, 135.2, 131.9, 118.5, 115.2, 108.8, 101.4, 69.1; ν_{max} (thin film) 3259w (OH), 3084w (arom. C–H), 2840, 2748w (CHO), 1628s (C=O), 1577m (C=C), 1222s (C–O–C) cm^{-1}; HRMS ($^+$TOF MS) *m*/*z*, found: 179.0709; calcd for $C_{10}H_{10}O_3+H^+$ (M+H^+) 179.0708.

3.7. 4-[2-(2-Chloroethoxy)ethoxy]-salicylaldehyde (6e)

A mixture of 0.6 g (4.4 mmol) 2,4-dihydroxybenzaldehyde, 1 g (3.6 mmol) 2-(2-chloroethoxy)ethyl 4-methylbenzenesulfonate, and 0.72 g (5.2 mmol) potassium carbonate was stirred in 100 mL acetonitrile at 70 °C for 48 h. The reaction mixture was then cooled to room temperature, filtered over Celite and evaporated. A crude brown oil was obtained that was purified by column chromatography over silica gel using cyclohexane–ethyl acetate (7:3) as eluent to yield 0.44 g (1.8 mmol, 50%) of a colorless oil. Found: C 54.19, H 5.41%; $C_{11}H_{13}ClO_4$ requires: C 54.00, H 5.36%. ν_{max} (thin film) 3088br (OH), 2942s (C–H), 1651s (C=O), 1121s (C–O) cm^{-1}; δ_H (400.2 MHz, $CDCl_3$) 11.44 (s, 1H, O*H*), 9.69 (s, 1H, C*H*O), 7.41 (d, 8.6, 1H, Ar*H*), 6.54 (dd, 8.7, 2.4, 1H, Ar*H*), 6.40 (d, 2.4, 1H, Ar*H*), 4.16 (t, 4.8, 2H, ArOCH_2–), 3.87 (t, 4.7, 2H, –CH_2Cl), 3.80 (m, 2H, –CH_2–), 3.63 (m, 2H, –CH_2–); δ_C (100.6 MHz, $CDCl_3$) 194.6, 166.0, 164.6, 135.5, 115.5, 108.9, 101.5, 71.8, 69.5, 68.5, 68.0, 42.9; HRMS ($^+$TOF MS) *m*/*z*, found 251.0665; calcd for $C_{11}H_{13}ClLiO_4$ (M+Li^+) 251.0662.

3.8. 4-Cyclohexylmethoxysalicylaldehyde (6g)

A mixture of 2.1 g (14.5 mmol) 2,4-dihydroxybenzaldehyde **1**, 2 g (7.5 mmol) cyclohexylmethyl *p*-tosylate **5g**, and 2 g (14.5 mmol) potassium carbonate was stirred in 150 mL acetonitrile at 60 °C for 48 h. The reaction mixture was then allowed to cool to ambient temperature, and filtered; the solvent was evaporated to obtain a dark brown oil. The residue was dissolved in 15 mL of 1 M $HCl_{(aq)}$ and extracted with dichloromethane (2×50 mL). The combined organic layers were washed with 5% $NaHCO_3$ and water, and dried over anhydrous sodium sulfate. The crude product (1.78 g) was purified by column chromatography over silica gel with petroleum ether–diethyl ether (9:1) yielding 0.3 g (1.3 mmol, 17%) of a colorless solid; mp 55–57 °C. Found: C 71.77, H 7.60%; $C_{14}H_{18}O_3$ requires C 71.77, H 7.74%. δ_H (250.1 MHz, $CDCl_3$) 11.46 (s, 1H, ArO*H*), 9.67 (s, 1H, ArC*H*O), 7.39 (d, 8.7, 1H, Ar*H*), 6.50 (dd, 8.7, 2.4, 1H, Ar*H*), 6.38 (d, 2.4, 1H, Ar*H*), 3.77 (d, 6.0, 2H, –OCH_2–), 1.72 (m, 6H, –C_6H_{11}), 1.14 (m, 5H, –C_6H_{11}); δ_C (62.9 MHz, $CDCl_3$) 194.3, 166.6, 164.5, 135.2, 115.0, 108.8, 101.1, 73.9, 37.4, 29.7, 26.4, 25.7; ν_{max} (thin film) 3136w (arom. CH), 2922, 2852s (aliph. CH), 1636s (C=O), 1222s (C–O–C) cm^{-1}; HRMS ($^-$TOF MS) *m*/*z*, found: 233.1186; calcd for $C_{14}H_{17}O_3$ (M−H^+)$^-$ 233.1178.

Acknowledgements

This work was stimulated by an interesting discussion with Akin Akdag. The authors gratefully acknowledge support from Auburn University and the National Science Foundation (CAREER award CHE-0746635 to S.S.); thanks is given to Orlando Acevedo for advice during initial stages of the DFT calculations; the work was made possible in part by a grant of high performance computing resources and technical support from the Alabama Supercomputer Authority.

Supplementary data

The Supplementary data includes all traces of all HPLC analyses, the experimental details and spectra of all tosylates, ^1H and ^{13}C NMR, HRMS, and IR data of all new compounds and the complete citation for the Gaussian 03 package. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2009.03.104.

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