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A Concise Synthesis of the Naphthalene Portion of Purpuromycin

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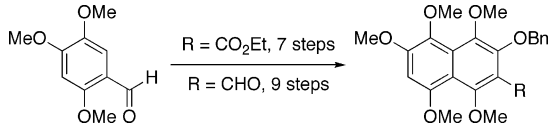
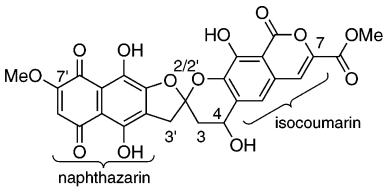


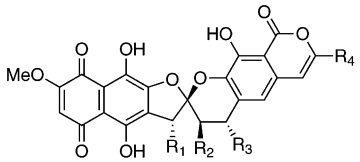
A concise synthesis of naphthalene compounds for incorporation into a synthetic sequence for the rubromycin family of natural products is presented. These highly substituted naphthalenes are generated in seven and nine steps, respectively, from 2,4,5-trimethoxybenzaldehyde. Three ring-forming methods were explored and the controlled oxygenation of different positions was investigated to yield differentially substituted/protected systems. Key steps to the final products include a Stobbe condensation to form the ring system and a novel series of regioselective oxidations to introduce the required oxygen functionality. These naphthalene products incorporate orthogonal protecting groups and are suitable for combination with a variety of coupling partners.

Introduction

Purpuromycin[1,2] (**1**, Figure 1), a member of the rubromycin family of bisbenzannulated spiroketals, is a highly functionalized and oxygenated molecule. This group of natural products, (Figure 1) also includes the rubromycins,[3−8] griseorhodins,[9−27] and heliquinomycin,[28−30] and has attracted considerable attention due to their structural complexity and significant biological profiles. For example, antibacterial[31−36] and antifungal[31−35] properties have been reported leading to clinical use.[36,37] In



Purpuromycin 1



Compound	R_1	R_2	R_3	R_4
γ-Rubromycin	H	H	H	CO_2Me
Heliquinomycinone	OH	OH	H	CO_2Me
Griseorhodin C	OH	OH	OH	CH_3

FIGURE 1. The rubromycin family of bisbenzannulated spiroketals.

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addition, their activities against reverse transcriptase,[38,39] DNA helicase,[40] and human telomerase[39] indicate that this unique structural type has potential as anti-retroviral or anti-cancer agents.

Construction of the naphthazarin[41−44] and isocoumarin[45−48] (Figure 1) portions of this family of molecules has been reported previously by us and others and has recently been reviewed.[49] The formation of the spiroketal subunit has been investigated in several systems.[44,50−57] Further, two members of this class of natural products have succumbed to total synthesis as outlined in the elegant reports of Danishefsky and co-workers[58,59] and, most recently, of Kita and co-workers.[60] Even so, a convergent and broadly applicable synthesis remains elusive and drives further study of these intriguing compounds.

In particular, the naphthazarin subunit is challenging due to its highly substituted and highly oxygenated nature. All approaches have generated this subunit in the reduced naphthalene form and then oxidized to the naphthazarin at an appropriate stage. Surprisingly, general strategies toward highly substituted naphthalenes remain absent. Rather, specific strategies are required depending upon the precise position and constitution of functionality.[61−63] Our goal was to develop a synthetic strategy to the rubromycin naphthalene that is short and efficient. To maximize convergency and analogue production, we wished to generate the entire subunit prior to incorporation into the natural product precursor. Finally, a route that permits production of large quantities of material as well as variants for use in analogue studies is desired.

Herein we report a concise synthesis that produces the desired pattern of seven protected substituents on a naphthalene ring system in 45% yield over seven steps. Further chemistry can transform a residual ester group into the appropriate functionality for any coupling mode desired. Our work has focused primarily on a [3+2] cycloaddition coupling strategy[44,50] (Figure 2). This allows coupling between an isocoumarin bearing a styrene and a naphthalene with a pendant nitro group giving an isoxazoline. Cleavage of the isoxazoline ring reveals a β-hydroxyketone, the functionality needed for the core of purpuromycin. Elucidation to a variety of nitro-derived naphthalenes can easily be accomplished from the aldehyde (**2**, Figure 3) by means of a Henry condensation. Modifications of the Henry protocol can give different functionality at the benzylic position. This synthesis is applicable to all members of this family as they share the same naphthazarin ring system; unveiling the naphthazarin from the naphthalene is straightforward and involves late-stage treatment with a Lewis acid followed by exposure to air.[64,65]

Results and Discussion

Our initial work described a Dötz benzannulation[42] approach to the functionalized naphthalene. This, however, proved

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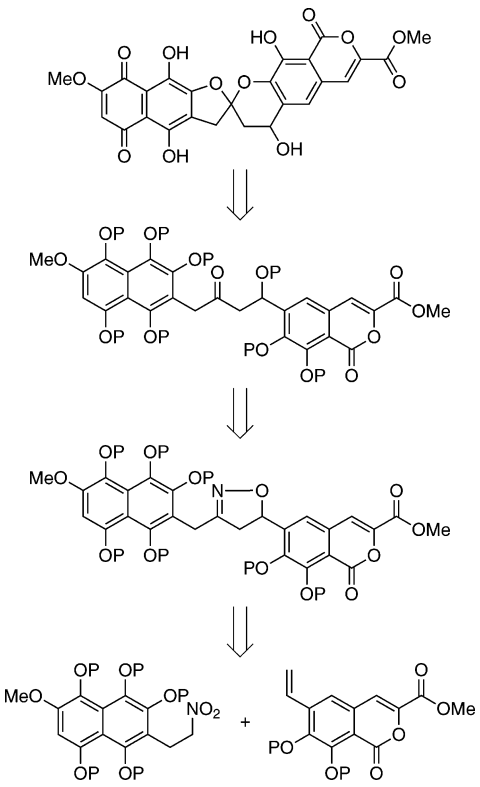


FIGURE 2. Retrosynthesis to a nitroalkane and styrene.

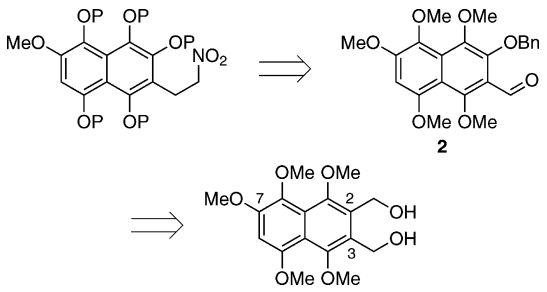


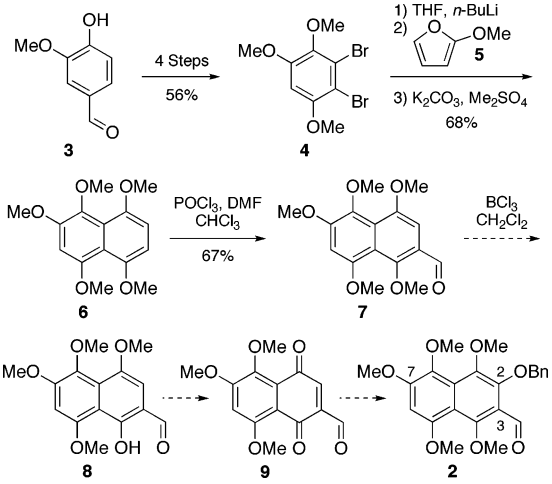
FIGURE 3. Nitroalkane precursors.

capricious and a more reliable route was sought. In our prior work,[44] a cycloaddition and Claisen condensation provided a naphthalene with symmetrically protected benzyl alcohols at the C2 and C3 positions (Figure 3, this numbering system will the used throughout the paper). Differentiation was affected by treatment with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ), which oxidized the more electron rich C3 benzylic alcohol as directed by the C7 methoxy group. Subsequent chemistry at the C2 position terminated with a Dakin oxidation and protection of the resulting phenol as a triethylsilyl ether.

Both of our prior approaches exploited electronic aspects of the naphthalene system to differentiate the C2 and C3 positions. While successful, the necessary oxidative cleavage of the undesired carbon substituent to reveal a C2 hydroxyl was difficult as the material readily oxidized to a naphthaquinone. Also, protection of the spiroketalizing phenol as the triethylsilyl ether[44] did not prove to be as robust as we had hoped.

To circumvent these problems, we began investigating a late-stage formylation of an electron-rich naphthalene system (Scheme 1) wherein the same electronic features are used to direct substitution of the C2 and C3 positions. Starting from vanillin (**3**), 5,6-dibromo-1,2,4-trimethoxybenzene (**4**) can be prepared in 4 steps.[66,67] Benzyne generation followed by reaction with 2-methoxyfuran (**5**) gives pentamethoxynaphthalene species **6** after protection.[68] We now planned to regioselectively install the desired aldehyde functionality at the C3 position using the C7 methoxy ether as a directing group as there is good precedent for reactions of this type.[69,70] Gratifyingly, Vilsmeier formylation gave naphthaldehyde **7**.[41] In spite of strong precedent,[71,72] selective deprotection directed by the aldehyde failed. Instead of naphthol **8**, we saw a mixture of naphthols. As a result, the quinone intermediate **9** needed for the Michael/oxidation sequence to introduce the C2 oxygenation is not accessible via this route.

SCHEME 1. The Attempted Synthesis of Target Aldehyde 2 from Vanillin



Our next approach attempted to generate the entire substitution pattern in the ring-forming reaction to avoid problems during substituent introduction. A report by Sartori and co-workers[73] showed that related oxygen-rich naphthalene systems could be formed via a Friedel−Crafts acylation process. In our hands, acylation of 1,2,4-trimethoxybenzene (**10**, Scheme 2) proceeded well to form β-ketoester **11**. Lewis acid-catalyzed condensation of **11** with oxalyl chloride gave intermediate **12**, which then underwent intramolecular acylation to form the oxygenated naphthalene ring system **13**. In contrast to the closely related dimethoxy analogue,[73] the Lewis acid also promoted cleavage of the methyl ethers. While the desired product **13** did form in approximately 10% yield, the majority of the material was a mixture of quinones **14a** and **14b**, the products of further deprotection.

Although the above route could not produce the desired coupling partner, it directed our thinking toward a similar disconnection. In particular, the use of a facile naphthalene

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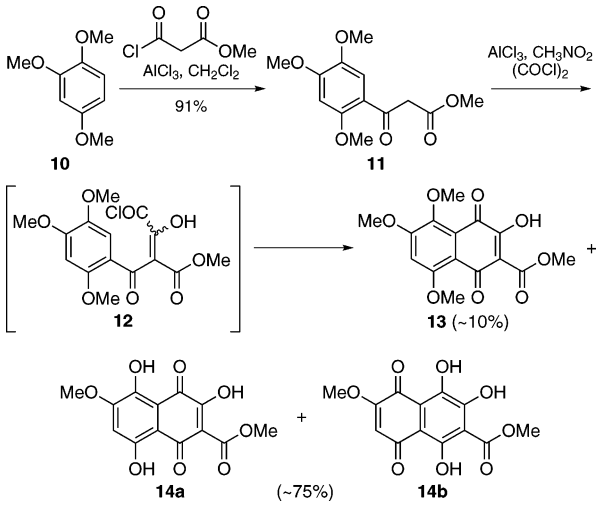
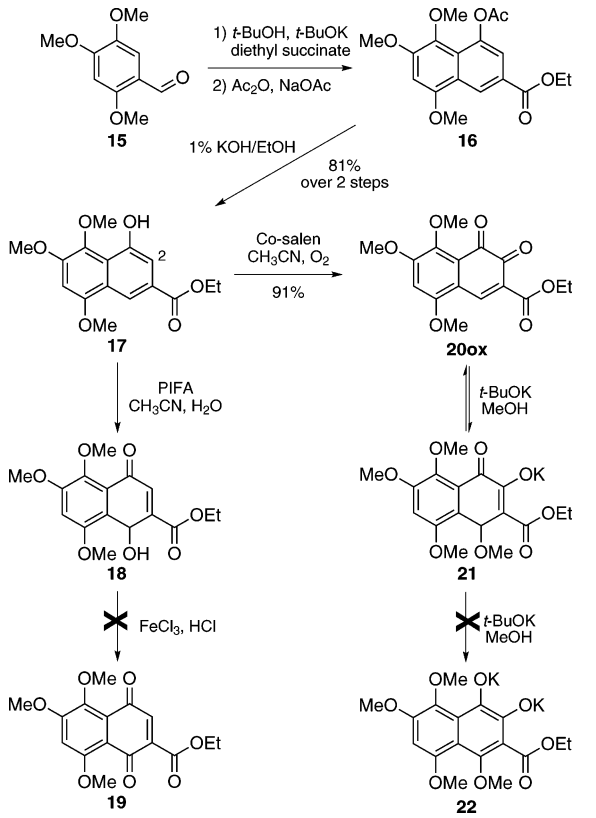
SCHEME 2. Investigation of the Friedel−Crafts Acylation Method



SCHEME 3. Unprotected Para Oxidation Attempts

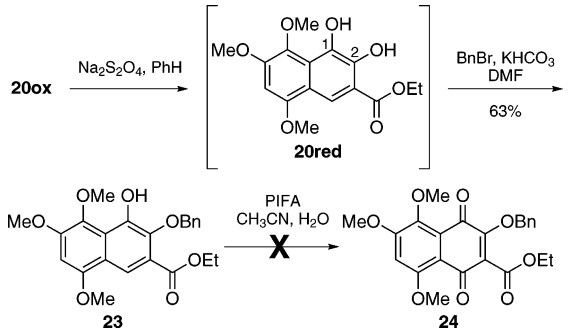


synthesis was a focus. The synthesis of naphthols from aryl aldehydes via a Stobbe condensation/cyclization sequence is such a process and, to our delight, had previously been elucidated by Green and co-workers.[74] A modification of their protocol readily gave us **17** (Scheme 3) in two steps and up to 81% yield from commercially available 2,4,5-trimethoxybenzaldehyde (**15**). Compound **17** bears the needed methoxy substitution, an ester where we desire a carbon chain, and, most importantly, a free C1 naphthol that can be used to direct further oxidation. The use of a Stobbe product, however, would require development of selective oxygenation conditions.

(74) Giles, R. G. F.; Green, I. R.; van Eeden, N. *Eur. J. Org. Chem.* **2004**, 4416−4423.

Initially, direct generation of *p*-quinone (**19**) was attempted as there was precedent for this type of transformation.[75] Installation of the necessary oxygenation pattern (**18**) was successful using phenyliodonium bis(trifluoroacetate) (PIFA).[76] However, further transformation to quinone **19** was unsuccessful. Tautomerization of **18** is likely slow due to the stable double conjugation of the alkene in the right-hand ring with the ketone and ester groups. Apparently, oxidation of the trimethoxy-substituted ring is competitive with this tautomerization, which is needed for oxidation to *p*-quinone **19**. Examination of other oxidants revealed that the cobalt(II) salen complex (Co-salen)[77] elicited selective oxidation to *o*-quinone **20ox** in good yield. In the hope of initiating a Michael addition into the quinone system and trapping the resultant catechol as the dianion, this material was treated with basic methanol. While the methanol adduct **21** did form as observed by ^{1}H NMR spectroscopy, dianion **21** could not be achieved, even under more forceful conditions (reflux).

SCHEME 4. Protected Para Oxidation Attempts



This dilemma was resolved by first reducing *o*-quinone **20ox** to catechol **20red** (Scheme 4) and selectively protecting in situ. While methods exist for the selective protection of catechols adjacent to electron-withdrawing groups,[78] we have seen superior results when using potassium bicarbonate, a weak base with a noncoordinating counterion. This protocol allowed selective benzylation of the more acidic C2 position of **20red** yielding naphthol **23**. Unfortunately, treatment with PIFA did not introduce oxidation at C4; only reversion to *o*-quinone **20ox** occurred (Figure 4).

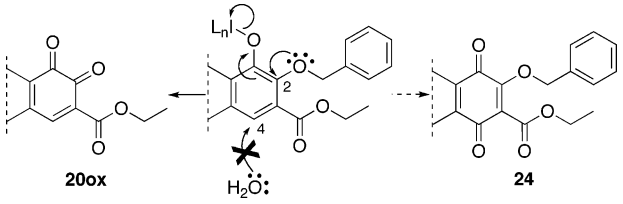


FIGURE 4. Competing oxidation pathways.

At this point, a review of the results was instructive. Oxidation to the *p*-naphthaquinone could not be achieved on any compound bearing an oxygen functionality at the C2 position; intramolecular reaction from the C2 position to form the *o*-naphthaquinone was more rapid than introduction of an external nucleophile at C4 (Figure 4). Nor could *p*-naph-

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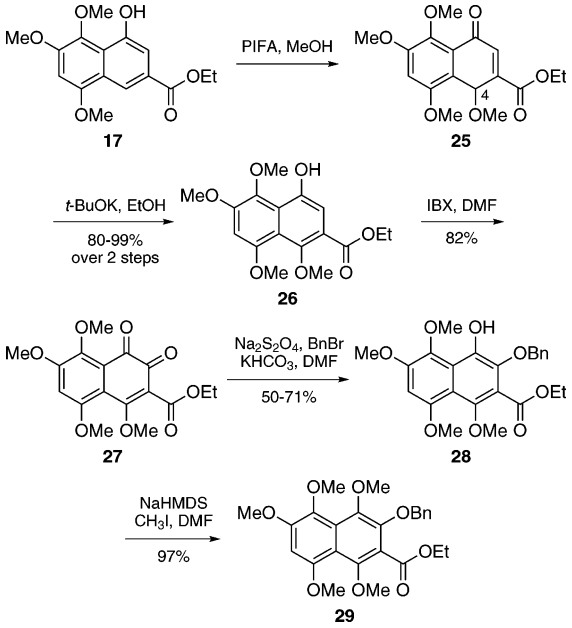
thaquinone formation be affected directly from a compound without C2 oxygenation (that is, naphthol **17**); this oxidation stalled due to the stability of the pseudohydroquinone (**18**, Scheme 3) as illustrated above. To circumvent these issues, we proposed that formation of the methoxy analogue of **18** (**25**, Scheme 5) would permit controlled tautomerization at C4 prior to oxidation. Thus, the PIFA oxidation was reexamined, but with methanol instead of water.

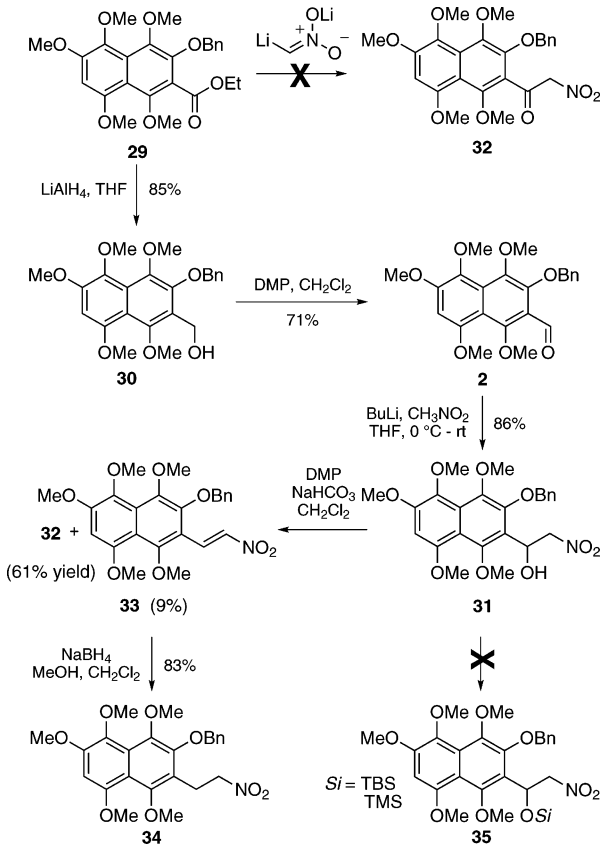
SCHEME 5. Construction of Ester 29



As anticipated, this oxidation installed a methyl ether in the C4 position to yield **25** (Scheme 5). Over oxidation is typical in such systems, but did not occur here due to the resistance of pseudohydroquinones to tautomerization as discussed above. Screening of tautomerization conditions revealed that *t*-BuOK in ethanol provides naphthol **26** in good yield. *o*-Iodoxybenzoic acid (IBX),[79,80] an oxidant that regioselectively forms *o*-quinones via an intramolecular transfer, was examined. Even though IBX is reported to fail when electron-withdrawing groups are present, we believed that the four electron-donating alkoxy groups would offset the ester. Indeed, *o*-quinone **27** was formed in high yield. With all needed oxygen functionality in place, selective benzylation, again mediated by potassium bicarbonate, was applied to furnish **28** in moderate yields. Finally, methylation provided fully protected naphthalene **29** in 45% yield over seven steps.

With subunit **29** available on scale, we turned toward introducing the desired nitro group (Figure 3) to enable a [3+2] cycloaddition (Figure 2). Direct attack on the ester with the dianion of nitromethane (**29**, Scheme 6) as demonstrated by Seebach and co-workers[81] was first examined. Ester **29** was fairly unreactive under these conditions, presumably due to steric bulk (bis-ortho substitution) around the electrophilic center. Barring this route, a Henry reaction was investigated to generate the necessary nitro derivative. Direct formation of aldehyde **2** could not be achieved with DIBAL. Thus, reduction to the benzylic alcohol **30** and subsequent Dess−Martin periodinane (DMP)[82] oxidation was undertaken. Treatment of **2** under Henry conditions provided β-hydroxynitro **31**. Notably, a large excess of the lithium salt of $MeNO_2$ was required. These conditions limited elimination to **33** and subsequent conjugate addition of a second molecule of $MeNO_2$. Since the hydroxyl group of **31** was incompatible with the planned [3+2] cycloaddition (Figure 2), protection as a silyl ether (**35**) was investigated. While we have seen success on other substrates, elimination or decomposition was the only product due to the steric hindrance of the position and the high acidity of the proton adjacent to the nitro group. Oxidation of **31** to β-ketonitro **32** was successful, but even with mild conditions (DMP) a small amount (9%) of **33** was produced. The formation of nitroalkene **33** could be optimized as we have shown previously.[44] As such, byproduct **33** was also transformed into a coupling partner (**34**) by conjugate reduction with $NaBH_4$.

SCHEME 6. Synthesis of Aldehyde 2 and Completion of Nitro Coupling Partners



Conclusions

We have shown that the naphthalene portion of purpuromycin can be efficiently synthesized with orthogonal protection. Construction of **29** bearing an ester group at the C3 chain attachment point was affected in seven steps and a 45% yield permitting facile access to gram quantities of material. Aldehyde **2** was synthesized in two additional steps (overall yield of 27% for nine steps). Compared to our prior approaches to similar structures,[42,44] this approach is much shorter and provides the oxygenation pattern without resorting to an oxidative C−C bond cleavage. This route also offers improvement over alternative

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syntheses where aldehyde **2** was synthesized in 9% yield over 12 steps.[43] The high efficiency of this route permits ready entry into the intermediates needed in our work as well as that of others.[43,52,54−56] For example, 2 g of aldehyde **2** could be produced from 10 g of 2,4,5-trimethoxybenzaldehyde in less than two weeks. The synthetic schemes herein are amenable to many other naphthalene oxygenation patterns. From aldehyde **2**, suitable nitro analogues were synthesized. These are easily coupled to an isocoumarin portion with a pendant styrenyl moiety via [3+2] cycloaddition chemistry.[44,50] The advanced intermediates generated will be used to further explore spiroketalization modes for purpuromycin and other members of this natural product family.

Experimental Section

1,4,5,6,8-Pentamethoxynaphthalene-2-carbaldehyde (7).[41] To a solution of $POCl_3$ (0.50 mL, 5.4 mmol) and DMF (0.42 mL, 5.4 mmol) in $CHCl_3$ (9 mL) was added **6**[68] (0.27 g, 0.97 mmol) in $CHCl_3$. After heating at reflux for 12 h, additional $POCl_3$ (0.50 mL, 5.4 mmol) and DMF (0.42 mL, 5.4 mmol) in $CHCl_3$ (9 mL) were added. Heating at reflux was continued for 6 h after which the mixture was poured into ice water, extracted with CH_2Cl_2, dried (Na_2SO_4), and concentrated. Chromatography[83] (50% EtOAc/hexanes, SiO_2) afforded a yellow solid in 67% yield (0.20 g, 0.65 mmol): ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.48 (s, 1H), 7.13 (s, 1H), 6.78 (s, 1H), 4.03 (s, 3H), 4.01 (s, 3H), 3.97 (s, 3H), 3.90 (s, 3H), 3.80 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 189.6, 158.1, 154.8, 153.8, 152.7, 138.8, 127.6, 124.0, 116.6, 101.6, 98.1, 65.6, 62.1, 57.1, 57.0, 56.7; IR (film) 2999, 2934, 2845, 1668, 1594, 1459 cm^{-1}; HRMS (CI) calcd for $C_{16}H_{18}O_6$ (M^+) 306.1103, found 306.1107.

Methyl 3-(2,4,5-Trimethoxyphenyl)-3-oxopropanoate (11). 10 (0.50 mL, 3.3 mmol) was added to a solution of $AlCl_3$ (0.65 g, 4.9 mmol) in CH_2Cl_2 (15 mL) and the solution was stirred for 5 min. Methyl malonyl chloride (0.43 mL, 4.0 mmol) was added dropwise and the resulting mixture was stirred at room temperature for 6 h. The reaction mixture was cooled to 0 °C and quenched with saturated $NaHCO_3$, acidified to a pH of 6, extracted with EtOAc, dried (Na_2SO_4), and concentrated. Trituration with 10% PhH/hexanes afforded an off-white solid in 91% yield (0.81 g, 3.0 mmol): mp 107−108 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 (s, 1H), 6.41 (s, 1H), 3.87 (s, 3H), 3.85 (s, 3H), 3.81 (s, 3H), 3.78 (s, 3H), 3.63 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 190.4, 168.8, 155.5, 154.6, 143.0, 117.1, 112.1, 95.8, 55.94, 55.90, 55.6, 51.7, 50.2; IR (film) 3003, 2953, 2910, 2841, 1737, 1656, 1606 cm^{-1}; HRMS (CI) calcd for $C_{13}H_{16}O_6$ (M^+) 268.0947, found 268.0935.

4-Hydroxy-5,6,8-trimethoxynaphthalene-2-carboxylic Acid Ethyl Ester (17).[74] To a solution of 2,4,5-trimethoxybenzaldehyde (**15**) (5.52 g, 28.1 mmol) in *t*-BuOH (105 mL) was added diethyl succinate (12.3 mL, 73.9 mmol) and *t*-BuOK (6.3 g, 56 mmol). After being stirred at rt for 2 h, the mixture was poured into water, acidified (pH 1) with 1 N HCl, and extracted with EtOAc. The combined organic layers were washed with aq Na_2CO_3, dried (Na_2SO_4), and concentrated. The resultant material was dissolved in Ac_2O (100 mL) and NaOAc (5.0 g, 61 mmol) was added. The mixture was heated to reflux where it was stirred for 4 h. After cooling, the mixture was poured into a slurry of ice water and neutralized (pH 7) by the addition of KOH. The mixture was extracted with EtOAc, dried with Na_2SO_4, and concentrated giving **16**. **16** was dissolved in 1% KOH/EtOH (200 mL), heated to reflux, and stirred for 10 min. The mixture was cooled, poured into a slurry of ice water, and acidified (pH 1) with 1 N HCl. The resulting precipitate was filtered and dried to afford an off-white solid in 81% yield (7.0 g, 23 mmol): mp 150−152 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.68 (s, 1H), 8.42 (d, J = 1.7 Hz, 1H), 7.44 (d, J = 1.6 Hz, 1H), 6.64 (s, 1H), 4.40 (q, J = 7.1 Hz, 2H), 4.02 (s, 3H), 4.012 (s, 3H), 4.006 (s, 3H), 1.42 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.7, 154.2, 153.2 (2), 149.2, 126.6, 121.8, 120.5, 116.5, 110.4, 95.4, 62.2, 60.9, 57.0, 55.9, 14.4; IR (film) 3277, 2988, 2949, 2841, 1702, 1613, 1451 cm^{-1}; HRMS (CI) calcd for $C_{16}H_{19}O_6$ (MH^+) 307.1182, found 307.1168.

Ethyl 3,4-Dihydro-5,6,8-trimethoxy-3,4-dioxonaphthalene-2-carboxylate (20ox). To a solution of **17** (0.500 g, 1.63 mmol) in CH_3CN (160 mL) was added Co-salen[77] (0.200 g, 0.615 mmol). O_2 was bubbled through the mixture for 5 min after which it was stirred for 12 h. The mixture was concentrated and recrystallized from hot MeOH to afford a red solid in 91% yield (0.476 g, 1.49 mmol): mp 189−192 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.70 (s, 1H), 6.67 (s, 1H), 4.35 (q, J = 7.1 Hz, 2H), 3.98 (s, 3H), 3.97 (s, 3H), 3.87 (s, 3H), 1.37 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 179.2, 177.8, 164.2, 160.1, 156.6, 148.5, 145.7, 125.7, 123.9, 113.1, 101.6, 61.7, 61.6, 56.8, 56.7, 14.5; IR (film) 2926, 2856, 1729, 1695, 1656 cm^{-1}; HRMS (CI) calcd for $C_{16}H_{16}O_7Na$ (MNa^+) 343.0794, found 343.0804.

Ethyl 3-(Benzyloxy)-4-hydroxy-5,6,8-trimethoxynaphthalene-2-carboxylate (23). To a solution of **20ox** (0.20 g, 0.62 mmol) in PhH (20 mL) in a separatory funnel was added $Na_2S_2O_4$ (2 g) in H_2O (20 mL). After 3 min of shaking, the layers were separated and the organic layer was dried and concentrated to afford the catechol **20red**, which was used immediately. This catechol was dissolved in DMF (6 mL), then treated with BnBr (0.12 mL, 1.0 mmol), $KHCO_3$ (0.10 g, 1.0 mmol), and $Na_2S_2O_4$ (0.050 g, 0.29 mmol). After 12 h of stirring, the mixture was quenched with saturated NH_4Cl, extracted with EtOAc, dried (Na_2SO_4), and concentrated. Chromatography (10−20% EtOAc/hexanes, SiO_2) afforded a yellow oil in 63% yield (0.16 g, 0.39 mmol): ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.74 (s, 1H), 8.14 (s, 1H), 7.60 (d, J = 7.3 Hz, 2H), 7.38 (t, J = 7.3 Hz, 2H), 7.31 (t, J = 7.3 Hz, 1H), 6.56 (s, 1H), 5.22 (s, 2H), 4.36 (q, J = 7.3 Hz, 2H), 4.012 (s, 3H), 4.010 (s, 3H), 3.98 (s, 3H), 1.34 (t, J = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.5, 153.9, 149.1, 145.9, 140.9, 138.0, 135.7, 128.3, 128.2, 127.7, 124.2, 120.9, 118.1, 116.4, 94.3, 74.9, 62.2, 61.0, 57.0, 55.8, 14.3; IR (film) 3296, 2980, 2941, 2849, 1718, 1613, 1459 cm^{-1}; HRMS (ES) calcd for $C_{23}H_{24}O_7Na$ (MNa^+) 435.1420, found 435.1409.

Ethyl 1,4-Dihydro-1,5,6,8-tetramethoxy-4-oxonaphthalene-2-carboxylate (25). To a solution of **17** (0.015 g, 0.049 mmol) in MeOH (1.5 mL) was added PIFA (0.023 g, 0.053 mmol) at room temperature. After 5 min of stirring, the reaction was quenched with saturated $NaHCO_3$, extracted with EtOAc, dried (Na_2SO_4), and concentrated to afford a yellow oil that was carried on directly to the next reaction without purification: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.06 (s, 1H), 6.79 (s, 1H), 5.74 (s, 1H), 4.35 (q, J = 7.1 Hz, 2H), 3.94 (s, 3H), 3.93 (s, 3H), 3.84 (s, 3H), 3.24 (s, 3H), 1.37 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 185.5, 165.6, 154.6, 154.3, 143.1, 141.9, 136.3, 126.2, 119.4, 101.9, 65.7, 61.8, 61.5, 56.4, 56.3, 55.1, 14.1; IR (film) 2984, 2937, 2845, 1722, 1671, 1590 cm^{-1}; HRMS (CI) calcd for $C_{17}H_{20}O_7$ (M^+) 336.1209, found 336.1217.

Ethyl 4-Hydroxy-1,5,6,8-tetramethoxynaphthalene-2-carboxylate (26). To a solution of **25** from above in EtOH (2 mL) was added *t*-BuOK (0.030 g, 0.27 mmol). After 5 min of stirring, the reaction was quenched with saturated NH_4Cl, extracted with EtOAc, dried (Na_2SO_4), and concentrated to afford a yellow oil in 99% yield (0.016 g, 0.048 mmol): ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.78, (s, 1H), 7.13 (s, 1H), 6.70 (s, 1H), 4.38 (q, J = 7.1 Hz, 2H), 4.01 (s, 3H), 3.980 (s, 3H), 3.979 (s, 3H), 3.84 (s, 3H), 1.40 (t, J = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.4, 155.3, 150.2, 149.0, 148.9, 136.6, 122.1, 121.0, 117.1, 110.9, 97.6, 63.6, 62.3, 60.9, 57.1, 56.7, 14.3; IR (film) 3308, 2980, 2937, 2845, 1725, 1610 cm^{-1}; HRMS (ES) calcd for $C_{17}H_{20}O_7Na$ (MNa^+) 359.1107, found 359.1117.

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Ethyl 3,4-Dihydro-1,5,6,8-tetramethoxy-3,4-dioxonaphthalene-2-carboxylate (27). To a solution of **26** (1.14 g, 3.39 mmol) in DMF (35 mL) was added IBX[79] (1.0 g, 3.6 mmol). After 12 h of stirring, the mixture was filtered through Celite, diluted with EtOAc, washed with NH_4Cl, dried (Na_2SO_4), and concentrated. Chromatography (50% EtOAc/hexanes, SiO_2) afforded a red solid in 82% yield (0.971 g, 2.77 mmol): mp 120−122 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.72 (s, 1H), 4.34 (q, J = 7.2 Hz, 2H), 3.99 (s, 3H), 3.94 (s, 3H), 3.91 (s, 3H), 3.84 (s, 3H), 1.34 (t, J = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 179.5, 178.3, 170.2, 164.6, 158.1, 156.0, 147.4, 124.5, 116.0, 110.6, 103.9, 61.6, 61.4, 60.7, 57.4, 56.2, 14.1; IR (film) 2984, 2945, 2845, 1725, 1594 cm^{-1}; HRMS (ES) calcd for $C_{17}H_{18}O_8Na$ (MNa^+) 373.0899, found 373.0908.

Ethyl 3-(Benzyloxy)-4-hydroxy-1,5,6,8-tetramethoxynaphthalene-2-carboxylate (28). To a solution of **27** (3.8 g, 10.8 mmol) in PhH (100 mL) in a separatory funnel was added $Na_2S_2O_4$ (10 g) in H_2O (100 mL). After 3 min of shaking, the layers were separated. The organic layer was dried and concentrated to afford the catechol, which was used immediately. This catechol was dissolved in DMF (100 mL) and treated with BnBr (2.7 mL, 22.7 mmol) and $KHCO_3$ (2.2 g, 22.0 mmol). After 12 h of stirring, the reaction was quenched with saturated NH_4Cl, extracted with EtOAc, dried (Na_2SO_4), and concentrated. Chromatography (30% EtOAc/hexanes, SiO_2) afforded a yellow oil in 71% yield (3.4 g, 7.7 mmol): ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.99 (s, 1H), 7.51 (d, J = 7.8 Hz, 2H), 7.36 (t, J = 7.5 Hz, 2H), 7.30 (t, J = 7.6 Hz, 1H), 6.61 (s, 1H), 5.22 (s, 2H), 4.34 (q, J = 7.1 Hz, 2H), 4.02 (s, 3H), 3.99 (s, 3H), 3.97 (s, 3H), 3.81 (s, 3H), 1.29 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.2, 154.2, 148.2, 145.7, 141.5, 138.3, 137.9, 136.4, 128.2, 128.0, 127.7, 122.7, 120.8, 113.5, 95.9, 74.9, 64.0, 62.3, 61.3, 56.8, 56.6, 14.2; IR (film) 3273, 2980, 2937, 2845, 1729, 1613 cm^{-1}; HRMS (ES) calcd for $C_{24}H_{26}O_8Na$ (MNa^+) 465.1525, found 465.1545.

Ethyl 3-(Benzyloxy)-1,4,5,6,8-pentamethoxynaphthalene-2-carboxylate (29). A solution of **28** (1.2 g, 2.7 mmol) in DMF (30 mL) at 0 °C was treated with 2 M NaHMDS (4.2 mL, 4.8 mmol) and MeI (1.0 mL, 16 mmol) and then warmed to room temperature. After 12 h of stirring, the reaction was quenched with 1 M HCl, extracted with EtOAc, dried (Na_2SO_4), and concentrated. Chromatography (20% EtOAc/hexanes, SiO_2) afforded a yellow oil in 97% yield (1.2 g, 0.26 mmol): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49 (d, J = 7.5 Hz, 2H), 7.38 (t, J = 7.5 Hz, 2H), 7.31 (t, J = 7.1 Hz, 1H), 6.67 (s, 1H), 5.23 (s, 2H), 4.34 (q, J = 7.1 Hz, 2H), 4.00 (s, 3H), 3.97 (s, 3H), 3.89 (s, 3H), 3.84 (s, 6H), 1.30 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.2, 153.7, 150.9, 150.2, 146.5, 143.6, 137.7, 136.7, 128.3, 128.0, 127.8, 127.3, 121.7, 114.1, 96.4, 75.8, 63.8, 62.1, 61.9, 61.4, 56.82, 56.75, 14.1; IR (film) 2934, 2845, 1729, 1602, 1455 cm^{-1}; HRMS (ES) calcd for $C_{25}H_{28}O_8Na$ (MNa^+) 479.1682, found 479.1701.

(2-(Benzyloxy)-1,4,5,7,8-pentamethoxynaphthalen-3-yl)methanol (30). A solution of **29** (0.10 g, 0.22 mmol) in THF (3 mL) was treated with $LiAlH_4$ (0.084 g, 2.2 mmol) at 0 °C and then warmed to room temperature. After 6 h of stirring, the reaction was quenched with a saturated solution of NaKtartrate, extracted with EtOAc, dried (Na_2SO_4), and concentrated. Chromatography (50% EtOAc/hexanes, SiO_2) afforded a clear, colorless oil in 85% yield (0.077 g, 0.19 mmol): ^{1}H NMR (500 MHz, C_6D_6) δ 7.44 (d, J = 8.1 Hz, 2H), 7.17 (m, 3H), 6.45 (s, 1H), 5.23 (s, 2H), 5.01 (s, 2H), 3.98 (s, 3H), 3.88 (s, 3H), 3.73 (s, 3H), 3.57 (s, 3H), 3.46 (s, 3H), 2.42 (s, 1H); ^{13}C NMR (125 MHz, C_6D_6) δ 154.0, 152.6, 151.1, 150.0, 144.4, 138.4, 129.1, 128.8, 128.7, 128.6, 127.6, 126.2, 115.8, 98.7, 76.0, 63.2, 61.9, 61.8, 56.98, 56.95, 56.3; IR (film) 3486, 2934, 2841, 1602, 1455 cm^{-1}; HRMS (ES) calcd for $C_{23}H_{26}O_7Na$ (MNa^+) 437.1576, found 437.1608.

3-(Benzyloxy)-1,4,5,6,8-pentamethoxynaphthalene-2-carbaldehyde (2).[43] A solution of **30** (0.031 g, 0.075 mmol) in CH_2Cl_2 (1 mL) at 0 °C was treated with DMP[82] (0.039 g, 0.092 mmol) and then the mixture was stirred for 0.5 h. The mixture was filtered and concentrated. Chromatography (20%−50% EtOAc/hexanes, SiO_2) afforded a yellow solid in 71% yield (0.022 g, 0.053 mmol): mp 121−122 °C; ^{1}H NMR (500 MHz, C_6D_6) δ 10.74 (s, 1H), 7.63 (d, J = 7.4 Hz, 2H), 7.21 (t, J = 7.5 Hz, 2H), 7.13 (t, J = 7.4 Hz, 1H), 6.29 (s, 1H), 5.23 (s, 2H), 3.91 (s, 3H), 3.87 (s, 3H), 3.71 (s, 3H), 3.47 (s, 3H), 3.39 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 188.7, 158.8, 155.4, 153.3, 149.5, 144.8, 138.2, 137.8, 130.3, 128.9, 128.6, 128.5, 121.8, 114.9, 97.7, 76.3, 64.3, 61.9, 61.7, 56.5, 56.3; IR (film) 3092, 3038, 2934, 2845, 1687, 1598 cm^{-1}; HRMS (ES) calcd for $C_{23}H_{24}O_7Na$ (MNa^+) 435.1420, found 435.1417. A crystal structure was obtained for this compound confirming the aromatic substitution pattern (see the Supporting Information).

1-(2-(Benzyloxy)-1,4,5,7,8-pentamethoxynaphthalen-3-yl)-2-nitroethanol (31). To a solution of $MeNO_2$ (0.50 mL) in THF (5 mL) was slowly added 1.6 M *n*-BuLi (0.86 mL, 1.4 mmol) at 0 °C. After 15 min of stirring, a solution of **2** (0.057 g, 0.14 mmol) in THF (5 mL) was added and the mixture was warmed to room temperature. After 12 h of stirring, the mixture was diluted with NH_4Cl until slightly acidic (pH ∼6), extracted with EtOAc, dried (Na_2SO_4), and concentrated. Chromatography (20% EtOAc/hexanes, SiO_2) afforded a clear oil in 86% yield (0.056 g, 0.12 mmol): ^{1}H NMR (500 MHz, C_6D_6) δ 7.43 (d, J = 7.4 Hz, 2H), 7.18 (t, J = 7.3 Hz, 2H), 7.10 (t, J = 7.5 Hz, 1H), 6.38 (s, 1H), 6.19 (dd, J = 3.1, 9.9 Hz, 1H), 5.24 (d, J = 10.8 Hz, 1H), 5.15 (d, J = 10.6 Hz, 1H), 4.98 (dd, J = 10.2, 12.1 Hz, 1H), 4.05 (dd, J = 3.1, 12.3 Hz, 1H), 3.94 (s, 3H), 3.82 (s, 3H), 3.57 (s, 3H), 3.52 (s, 3H), 3.42 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 153.8, 152.3, 151.6, 148.8, 144.4, 138.0, 137.5, 129.3, 129.1, 128.8, 128.6, 122.5, 115.0, 98.3, 80.8, 76.0, 66.5, 63.3, 61.8 (2), 56.8, 56.6; IR (film) 3475, 2934, 2845, 1602, 1455 cm^{-1}; HRMS (ES) calcd for $C_{24}H_{27}NO_9Na$ (MNa^+) 496.1584, found 496.1592.

1-(2-(Benzyloxy)-1,4,5,7,8-pentamethoxynaphthalen-3-yl)-2-nitroethanone (32). A solution of **31** (0.225 g, 0.475 mmol) in CH_2Cl_2 (10 mL) was treated with $NaHCO_3$ (0.84 g, 1.0 mmol) followed by DMP[82] (0.202 g, 0.476 mmol). After 2 h of stirring, the mixture was concentrated and subjected to chromatography (20% EtOAc/hexanes, SiO_2) affording a yellow oil in 61% yield (0.137 g, 0.291 mmol): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 (d, J = 7.1 Hz, 2H), 7.37 (t, J = 7.2 Hz, 2H), 7.34 (t, J = 7.2 Hz, 1H), 6.71 (s, 1H), 5.46 (s, 2H), 5.24 (s, 2H), 4.03 (s, 3H), 4.00 (s, 3H), 3.90 (s, 3H), 3.86 (s, 3H), 3.80 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 189.0, 154.0, 152.0, 151.4, 145.5, 143.9, 141.8, 136.6, 133.3, 129.0, 128.6, 128.4, 122.9, 113.6, 96.2, 84.4, 76.1, 64.6, 62.0 (2), 56.7, 56.5; IR (film) 2937, 2845, 1725, 1602, 1559, 1455 cm^{-1}; HRMS (ES) calcd for $C_{24}H_{25}NO_9Na$ (MNa^+) 494.1427, found 494.1439.

3-Benzyloxy-1,4,5,6,8-pentamethoxy-2-(2-nitrovinyl)naphthalene (33). Isolated as an orange-red solid in 9% yield (0.019 g, 0.042 mmol) from the above reaction: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.42 (d, J = 13.7 Hz, 1H), 8.11 (d, J = 13.7 Hz, 1H), 7.45−7.47 (m, 2H), 7.33−7.39 (m, 3H), 6.68 (s, 1H), 5.19 (s, 2H), 4.03 (s, 3H), 4.02 (s, 3H), 3.92 (s, 3H), 3.87 (s, 3H), 3.77 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.0, 154.7, 152.7, 148.6, 144.2, 139.8, 136.8, 136.6, 130.8, 129.1, 128.8, 128.7, 128.6, 115.7, 114.1, 96.2, 75.9, 63.2, 62.2, 62.1, 56.9, 56.7; IR (film) 2934, 2845, 1594, 1559, 1509, 1455, 1366, 1320 cm^{-1}; HRMS (ES) calcd for $C_{24}H_{26}NO_8$ (MH^+) 456.1658, found 456.1665.

3-Benzyloxy-1,4,5,6,8-pentamethoxy-2-(2-nitroethyl)naphthalene (34). To a solution of **33** (0.010 g, 0.022 mmol) dissolved in CH_2Cl_2 (1 mL) and MeOH (1 mL) was added $NaBH_4$ (0.0073 g, 0.193 mmol) in one portion. After 0.5 h of stirring, the mixture was poured into 1 N HCl (10 mL) and partitioned with CH_2Cl_2 (10 mL). The organic layer was dried (Na_2SO_4) and concentrated. Chromatography (4% Et_2O/CH_2Cl_2, SiO_2) afforded a light yellow oil in 83% yield (0.0083 g, 0.018 mmol): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45−7.46 (m, 2H), 7.33−7.40 (m, 3H), 6.67 (s, 1H), 4.42 (m, 2H), 4.01 (s, 3H), 3.98 (s, 3H), 3.88 (s, 3H), 3.87 (s, 3H), 3.74 (s, 3H), 3.38 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.1,

151.7, 150.4, 148.9, 143.8, 137.6, 136.9, 128.8, 128.7, 128.5, 126.5, 119.8, 114.4, 96.4, 75.4, 74.4, 62.7, 62.1, 61.0, 57.1, 56.9, 23.4; IR (film) 2934, 2841, 1606, 1548, 1455,1359, 1339 cm^{-1}; HRMS (ES) calcd for $C_{24}H_{27}NO_8Na$ (MNa^+) 480.1634, found 480.1636.

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Note Added after ASAP Publication. In the text and in the title of Scheme 1, compound **3** was referred to as isovanillin instead of vanillin in the version published ASAP February 8, 2008; the corrected version was published ASAP February 12, 2008.

Supporting Information Available: Characterization data including ^1H and ^{13}C NMR spectra and X-ray crystal structure data for compound **2**. This material is available free of charge via the Internet at http://pubs.acs.org.

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