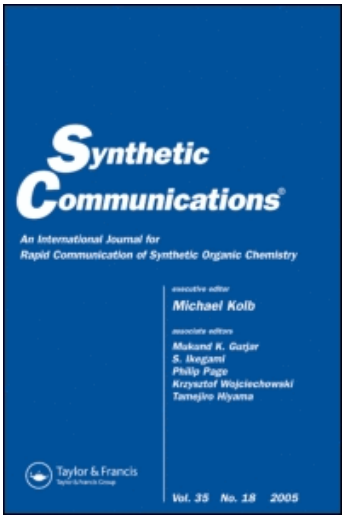

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Efficient and Practical Synthesis of Dissymmetrical Ethers of 4-Nitrocatechol

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Abstract: An efficient and practical synthesis of dissymmetrical ethers of 4-nitrocatechol from 5-nitrosalicyladehyde and 2-hydroxy-5-nitroacetophenone via Baeyer–Villiger oxidation is described. These dissymmetrical ethers are useful in the synthesis of various coccidiostats and other important pharmaceutical intermediates.

Keywords: Baeyer–Villiger oxidation, coccidiostats, 2-hydroxy-5-nitroacetophenone, 4-nitrocatechol, 5-nitrosalicyladehyde

INTRODUCTION

Coccidiostats are 4-hydroxy-6,7-substituted 3-carboalkoxyquinolines (**1**) that are valuable agents in the control of coccidiosis in poultry.[1] Mizzoni et al. report a detailed study on the structural requirements for anticoccidial activity for a series of quinates **1**.[2] Some examples of well-known coccidiostats (Fig. 1) are decoquinate (**1a**), *iso*-decoquinate (**1b**), buquinolate (**1c**), methyl benzoquate (**1d**), and cyproquinidate (**1e**). These quinolines also act as antimalarials[3] and serve as synthons for the synthesis of complex natural products.[4,5]

The synthetic route often used for the preparation of these quinolines, as depicted in Scheme 1, employs the dissymmetrical ethers of 4-nitrocatechol as the starting material.[6,1f] There are also a few other methods of synthesis of these quinolines, but these are not commercially

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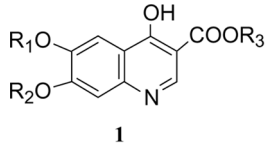
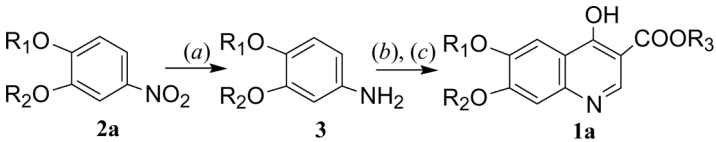


1

1a $R_1 = (CH_2)_9CH_3$, R_2,$R_3 = CH_2CH_3$
1b R_1,$R_3 = CH_2CH_3$, $R_2 = (CH_2)_9CH_3$
1c R_1,$R_2 = CH_2CH(CH_3)CH_3$, $R_3 = CH_2CH_3$
1d $R_1 = (CH_2)_3CH_3$, $R_2 = PhCH_2$, $R_3 = CH_3$
1e R_1,$R_2 = CH_2$-◁ , $R_3 = CH_2CH_3$

Figure 1. 4-Hydroxyquinoline-3-carboxylate.



2a **3** **1a**

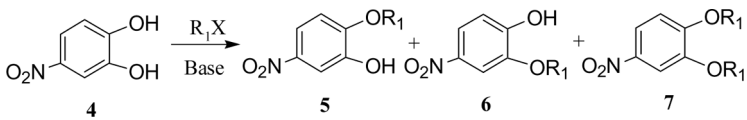
$R_1 = (CH_2)_9CH_3$, R_2, $R_3 = CH_2CH_3$

Scheme 1. Synthesis of decoquinate: (a) 10% Pd/C, H_2, 6 bar, EtOH–EtOAc (3:1), rt, 30 min, 97%, (b) diethylethoxy methylene malonate, 35–40 °C, 4 h, 98%; (c) Dowtherm A, 250–260 °C, 15 min, 57%.

significant.[3,7] The key starting material (viz., the dissymmetrical ethers of 4-nitrocatechol **2**), though structurally not complex, is not easy to access by the regioselective mono-alkylation. Presently, there is no good method for regioselective alkylation of electron-poor catechol. We report an efficient and practical method for the synthesis of dissymmetrical ethers of 4-nitrocatechol via Baeyer–Villiger oxidation.

RESULTS AND DISCUSSION

A variety of methods are known in literature for alkylation of bisphenols in literature,[8] but there are only a few reports on regioselective alkylation of electron-poor bisphenols.[9–11] Initially, we explored the regioselective alkylation of 4-nitrocatechol **4** using NaH (1.0 eq.) and alkyl halide (1.0 eq.) in DMF. This yielded a mixture of three compounds, the monoethers **5** and **6** and the *bis*-ether **7** (Scheme 2).



4 **5** **6** **7**

Scheme 2. Alkylation of 4-nitrocatechol.

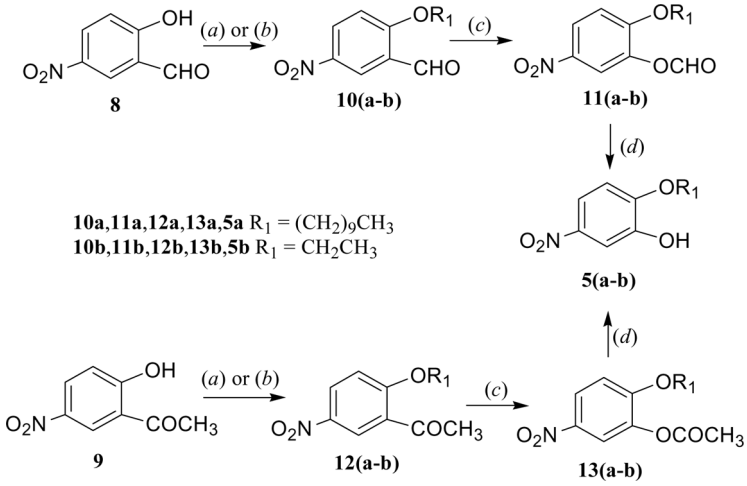
Cao et al.[10] reported the selective methylation of **4** using NaOH/MeI catalyzed by solid–liquid phase-transfer catalyst PEG400. They selectively obtained the monoether, and no *bis*-ethers were isolated. The authors do not mention which monoether was obtained. Several attempts of the same reaction in our hands afforded a mixture of the monoethers **5** and **6** (no bisether **7**), and the conversion was also very poor (viz. 25%). Pfister et al.[11] claim that the 4-acyl catechol could be regioselectively *O*-alkylated at the 1-position with alkylhalide in DMF using Li_2CO_3 at 55 °C. Similarly, when we attempted the reaction of 4-nitrocatechol **4** with decylbromide in dimethylformamide (DMF) under Pfister's condition, neither did we observe any regioselectivity nor did the reaction go to completion even after 48 h.

With a view to find out if bases play any role in regioselectivity, we studied the reaction of **4** with various alkylhalides (viz., decylbromide, methyliodide, and ethyl *p*-toluenesulphonate) using different bases such as Na_2CO_3, K_2CO_3, K_3PO_4, Na_3PO_4, Cs_2CO_3, $Ba(OH)_2$, and Li_2CO_3 in DMF as solvent at 70–80 °C. None of the reactions showed any regioselectivity and afforded only a mixture of **5**, **6**, and **7** . Also, in none of the cases did the reaction go to completion, although the degree of conversion varied depending upon the amount of base used. Also, increasing the equivalence of the alkylating agent or the base did not lead to any selectivity.

Thus we turned our attention to developing a different approach (via Baeyer–Villiger oxidation) for the synthesis of dissymmetrical ethers of **4**, bearing in mind the suitability of the method for large-scale synthesis. A simple retrosynthetic analysis showed that 5-nitrosalicylaldehyde **8** and 2-hydroxy-5-nitroacetophenone **9**, which are commercially available, could be used as starting material. Etherification of **8** and **9** followed by Baeyer–Villiger oxidation of the respective ethers **10** and **12** and saponification of its esters **11** and **13** would lead without any ambiguity to the monoether **5** (Scheme 3). This could subsequently be etherified with an alkylating agent to obtain various dissymmetrical ethers **2**.

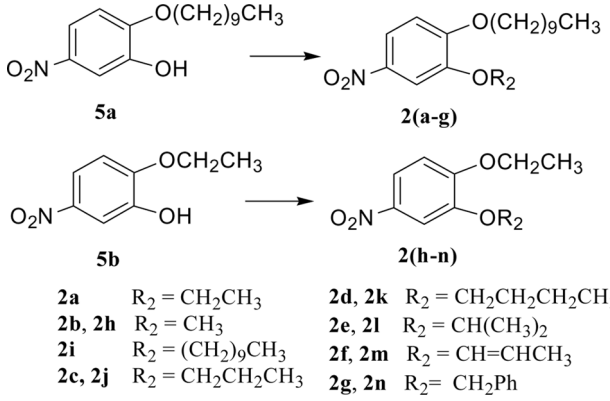
Etherification of the aldehyde **8** and ketone **9** with the alkylating agent (decylbromide or ethyl *p*-toluenesulphonate) using Cs_2CO_3 in DMF afforded the corresponding ethers **10a**,**b** and **12a**,**b**, respectively, in very high yields.

There are many reports in the literature on the Baeyer–Villiger oxidation of the ketones and aldehydes with different peracids to afford the corresponding esters and formats[12] in very good yields, but there are only a few reports on Baeyer–Villiger oxidation of electron-poor aromatic systems using *m*-CPBA,[13a] peracetic acid,[13b,c] and sodium percarbonate,[13d] Baeyer–Villiger oxidation of **10** and **12** could be achieved



Scheme 3. Synthesis of monoethers of 4-nitrocatechol: (a) decylbromide, Cs_2CO_3, DMF, 70–80 °C, (b) Cs_2CO_3, ethyl *p*-toluenesulphonate, DMF, 60–70 °C; (c) $(CF_3CO)_2O$, 30% H_2O_2, CH_2Cl_2, 25–30 °C, 20–30 min; and (d) NaOH, THF, 25–30 °C.

with *m*-CPBA, CH_3CO_3H, CF_3CO_3H, and sodium percarbonate. We found that only CF_3CO_3H could bring about the oxidation at ambient temperature in high yields. In the case of sodium percarbonate, the reaction did not proceed to completion, while *m*-CPBA and CH_3CO_3H needed higher temperatures and longer durations for completion.



Scheme 4. Synthesis of dissymmetrical ethers of 4-nitrocatehol.

Table 1. Synthesis of dissymmetrical ethers of 4-nitrocatechol

S.No.	Substrate	Product	Yield[a] (%)	Mp[Ref.]
1	**5a**	**2a**	80	57–58[1f]
2	**5a**	**2b**	95	49–50[1f]
3	**5a**	**2c**	85	58–61[1f]
4	**5a**	**2d**	86	35–36[1f]
5	**5a**	**2e**	81	45–46[1f]
6	**5a**	**2f**	93	35–37[1f]
7	**5a**	**2g**	84	44–46
8	**5b**	**2h**	94	85–87[14]
9	**5b**	**2i**	95	60–62
10	**5b**	**2j**	89	65–70
11	**5b**	**2k**	88	59–60
12	**5b**	**2l**	81	55–60
13	**5b**	**2m**	82	40–42
14	**5b**	**2n**	91	101–102[6f]

[a]Yields mentioned are isolated yields.

Thus, Baeyer–Villiger oxidation of the respective ethers **10a,b** and **12a,b** using trifluoroacetic anhydride and 30% hydrogen peroxide in CH_2Cl_2 at rt afforded the corresponding formate **11a**,**b** and ester **13a**,**b**, respectively, in good yields. The ^{1}H NMR spectrum of the crude product indicated the presence of minor amounts of the hydrolyzed product (viz. **5**). Thus, crude **11a**,**b** and **13a**,**b**, without further purification, were hydrolyzed using NaOH in THF to afford the monoethers of 4-nitrocatechol **5a**,**b** (Scheme 3) in good yields and purity.

The monoethers **5a** and **5b**, when treated with the base Cs_2CO_3 and its corresponding alkyl halides in DMF, yielded the dissymmetrical ethers of 4-nitrocatechol **2a**–**n** (Scheme 4, Table 1) in high purity and yields, and all these compounds were thoroughly characterized. The dissymmetrical ether **2a** has been converted to the known decoquinate **1a** (Scheme 1) following the literature procedure.[1f]

CONCLUSION

We have developed an efficient and practical method for the synthesis of dissymmetrical ethers of 4-nitrocatechol using the Baeyer–Villiger oxidation strategy. Our approach provides an unambiguous route for the synthesis of monoethers of 4-nitrocatechol at the 1-position. This methodology can be easily exploited for commercial scale.

EXPERIMENTAL

For all the reactions, the commercially available laboratory grade (LR) solvents and LR reagents were used directly without further purification. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance 300-MHz spectrometer with tetramethylsilane (TMS) as reference. Column chromatographic purification was performed using 60- to 120- mesh silica gel. Melting points were taken in a Veego model VMP-PM apparatus and are uncorrected. HRMS data were recorded on QTOF-Micromass-UK instrument. Complete spectral data (^{1}H NMR,^{13}C NMR, IR, mass, and high resolution mass spectroscopy [HRMS]) for all compounds are given here.

2-Decyloxy-5-nitrobenzaldehyde (10a)

A solution of **8** (5 g, 30 mmol), Cs_2CO_3 (10 g, 30 mmol), and iododecane (7.6 mL, 36 mmol) in DMF (25 mL) was stirred at 70–80 °C for about 3 h. The resulting mixture was cooled to 0 °C, water (50 mL) was added and it was acidified with 20% HCl. A yellow solid was precipitated out. The solid was filtered, washed with H_2O (100 mL), and dried.

Yield: 9.1 g (99%), mp 39–41 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.88$ (*t*, 3H, $J = 6.0$ Hz, CH_3), 1.28–1.40 (*m*, 12H, $6 \times CH_2$), 1.48–1.60 (*m*, 2H, CH_2), 1.87–1.94 (*m*, 2H, CH_2), 4.22 (*t*, 2H, $J = 6.0$ Hz, OCH_2), 7.10 (*d*, 1H, $J_{3,4} = 9$ Hz, H-3), 8.41 (*dd*, 1H, $J_{3,4} = 9.3$ Hz, $J_{4,6} = 3.0$ Hz, H-4), 8.69 (*d*, 1H, $J_{4,6} = 2.7$ Hz, H-6), 10.48 (*s*, 1H, CHO); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.12 (*q*, CH_3), 22.68 (*t,* CH_2), 25.92 (*t*, CH_2), 28.83, 29.27, 29.51 (3*t*, CH_2), 31.88 (*t*, CH_2), 69.92 (*t*, OCH_2), 112.91 (*d*, C-3), 124.48 (*d*, C-6); 130.65 (*d*, C-4), 141.37, 165.30 (3*s*, C-1, C-2, C-3), 187.65 (*d*, -CHO), IR (KBr, cm^{-1}): 1591 (*m*), 1521 (*s*), 1390 (*w*), 1693 (*s*), 1657 (*w*), 1609 (*s*), 1591 (*m*); mass (*m*/*z*): 308 $[M+H]^+$. HRMS calcd. for $[C_{17}H_{25}NO_4Na]$: 330.1681; found: 330.1681.

2-Ethoxy-5-nitrobenzaldehyde (10b)

A solution of **8** (5 g, 0.0299 mol) and Cs_2CO_3 (10.7 g, 0.0329 mol) in DMF (20 mL) was added slowly ($\sim$20 min) to a mixture of ethyl p-toluenesulphonate (EPTS) (7.9 g, 0.04 mol) in DMF (10 mL) and then heated to 60–70 °C under a nitrogen atmosphere for about 4 h. The resulting mixture was cooled to 0 °C, quenched with water (20 mL), and acidified with 20% HCl. A yellow solid was precipitated. The solid was filtered, washed with water (100 mL), and dried under high vaccum.

Yield: 5.1 g (88%); mp 70–72 °C (lit.[15] = 71–72 °C); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.57$ (*t*, 3H, $J = 6$ Hz, CH_3), 4.33 (*q*, 2H, $J = 9$ Hz OCH_2), 7.13 (*d*, 1H, $J_{3,4} = 9$ Hz, H-3), 8.41 (*dd*, 1H, $J_{3,4} = 9$ Hz, $J_{4,6} = 3$ Hz, H-4), 8.69 (*d*, 1H, $J_{4,6} = 3$ Hz, H-6), 10.48 (*s*, 1H, CHO).

2-Decyloxy-5-nitroacetophenone (12a)

A solution of **9** (3 g, 0.017 mol), Cs_2CO_3 (5.4 g, 0.017 mol), and iododecane (4.2 mL, 0.02 mol) in DMF (15 mL) was stirred at 70–80 °C for about 1 h. The resulting mixture was cooled to 0 °C, water (50 mL) was added, and it was acidified with 20% HCl. The aqueous solution was extracted with CH_2Cl_2 (2×30 mL), and the organic layer was washed with H_2O (100 mL), dried over Na_2SO_4, and concentrated. The crude product (5.4 g) was purified by column chromatography.

Yield: 5 g (94%); mp 35–36.6 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.88$ (*t*, 3H, $J = 6.9$ Hz, CH_3), 1.28–1.55 (*m*, 12H, $6 \times CH_2$), 1.56–1.62 (*m*, 2H, CH_2), 1.86–1.96 (*m*, 2H, CH_2), 2.66 (*s*, 3H, $COCH_3$), 4.19 (*t*, 2H, $J = 6.6$ Hz, OCH_2), 7.07 (*d*, 1H, $J_{3,4} = 9$ Hz, H-3), 8.33 (*dd*, 1H, $J_{3,4} = 9.0$ Hz, $J_{4,6} = 3.0$ Hz, H-4), 8.63 (*d*, 1H, $J_{3,4} = 3$ Hz, H-6), ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 14.11$ (*q*, CH_3), 22.68, 26.08, 28.95, 29.26, 29.28, 29.49, 31.80 (7*t*, $7 \times CH_2$), 31.88 (*q*, $COCH_3$), 69.93 (*t*, OCH_2), 112.53, 126.63 (2*d*, *arom.* CH), 128.42 (*s*, C-1), 141.22, 162.70 (2*s*, C-2, C-3), 197.28 (*s*, CO); IR (KBr, cm^{-1}): 1852 (*w*), 1765 (*m*), 1683 (*s*), 1607 (*s*), 1585 (*s*), 1520 (*s*), 1487 (*s*), 1466 (*s*); mass (*m*/*z*): 322 $[M + H]^+$. HRMS calcd. for $[C_{18}H_{27}NO_4Na]$: 344.1838; found: 344.1837.

2-Ethoxy-5-nitroacetophenone[16] (12b)

A solution of **9** (4 g, 0.022 mol), Cs_2CO_3 (7.9 g, 0.024 mol), and EPTS (5.3 g, 0.026 mol) in DMF (20 mL) was stirred at 70–80 °C under a nitrogen atmosphere for about 5 h. The resulting mixture was cooled to 0 °C, quenched with water (50 mL), and neutralized with 20% dilute HCl. The aqueous solution was extracted with ether (2×50 mL), and the organic layer was washed with water (2×100 mL), dried over Na_2SO_4, and concentrated. The crude product (4 g) was purified by column chromatography using 90:10 (hex.–EtOAc).

Yield: 3.4 g (74%); ^{1}H NMR(300 MHz, $CDCl_3$): $\delta = 1.56$ (*t*, 3H, $J = 6.9$ Hz, CH_3), 2.66 (*s*, 3H, $COCH_3$), 4.28 (*q*, 2H, $J = 6.9$ Hz, OCH_2), 7.06 (*d*, 1H, $J_{3,4} = 9$ Hz, H-3), 8.31–8.35 (*dd*, 1H, $J_{3,4} = 9$ Hz, $J_{4,6} = 3$ Hz, H-4), 8.63 (*d*, 1H, $J_{4,6} = 3$ Hz, H-6).

General Procedure for Baeyer–Villiger Oxidation

Trifluoroacetic anhydride (0.21 mol) was cooled to $-10\,^{\circ}C$ for about 10–20 min, and 30% H_2O_2 (0.05 mol) was added dropwise (maintaining the temperature between 0 and $-10\,^{\circ}C$) and stirred for about 10 min. To this mixture, **10a/10b/12a/12b** (0.016 mol) in CH_2Cl_2 (25 mL) was added slowly and stirred at rt for 10–30 min. After reaction completion, the mixture was cooled to $0\,^{\circ}C$, diluted with CH_2Cl_2 (20 mL), and quenched with water (50 mL). The product was extracted with CH_2Cl_2 (10 mL), and the organic layer was washed with 10% Na_2CO_3 solution (2×50 mL) until the pH was neutral and then washed with water (2×100 mL). The organic layer was dried over Na_2SO_4 and concentrated. This crude product was taken directly to the next stage without further purification.

Formic Acid-2-Decyloxy-5-nitrophenyl Ester (11a)

Yield: 89%; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.88$ (*t*, 3H, $J = 9$ Hz, CH_3), 1.27–1.38 (*m*, 12H, $6 \times CH_2$), 1.38–1.42 (*m*, 2H, CH_2), 1.76–1.86 (*m*, 2H, CH_2), 4.10 (*t*, 2H, $J = 6.0$ Hz, OCH_2), 7.04 (*d*, 1H, $J_{3,4} = 9.0$ Hz, H-3), 8.03 (*d*, 1H, $J_{4,6} = 3$ Hz, H-6), 8.17–8.21 (*dd*, 1H, $J_{3,4} = 9$ Hz, $J_{4,6} = 3$ Hz, H-4), 8.27 (*s*, 1H, OCHO), ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 14.13$ (*q*, CH_3), 22.69, 25.76 (2*t*, CH_2), 28.77, 28.92, 29.22, 29.30, 29.51 (5*t*, CH_2), 31.89 (*t*, CH_2), 69.75 (*t*, OCH_2), 112.17, 118.99, 123.68 (3*d*, C-3, C-4, C-6), 138.28, 140.72 (3*s*, C-1, C-2, C-3), 157.69 (*d*, CHO).

Formic Acid 2-Ethoxy-5-nitrophenyl Ester (11b)

Yield: 97%; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.46$ (*t*, 3H, $J = 6.9$ Hz, CH_3), 4.21 (*q*, 2H, $J = 6.9$ Hz OCH_2), 7.06 (*d*, 1H, $J_{3,4} = 9$ Hz, H-3), 8.03 (*d*, 1H, $J_{4,6} = 2.8$ Hz, H-6), 8.19 (*dd*, 1H, $J_{3,4} = 9$ Hz, $J_{4,6} = 2.8$ Hz, H-4), 8.28 (*s*, 1H, OCHO).

Acetic Acid-2-decyloxy-5-nitrophenyl Ester (13a)

Yield: 96%; mp 59–59.4 °C; ^{1}H NMR(300 MHz, $CDCl_3$): $\delta = 0.88$ (*t*, 3H, $J = 6.9$ Hz, CH_3), 1.28–1.44 (*m*, 14H, $7 \times CH_2$), 1.78–1.83 (*m*, 2H, CH_2), 2.33 (*s*, 3H, $OCOCH_3$), 4.08 (*t*, 2H, $J = 6.3$ Hz, OCH_2), 7.01 (*d*, 1H, $J_{3,4} = 9$ Hz, H-3), 7.97 (*d*, 1H, $J_{4,6} = 3$ Hz, H-6), 8.15 (*dd*, 1H, $J_{3,4} = 9.0$ Hz, $J_{4,6} = 3.0$ Hz, H-4); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 14.12$, 20.40

(2*q*, $2 \times CH_3$), 20.40, 22.68, 25.76, 28.83, 29.23, 29.31, 29.53, 31.89 (8*t*, $8 \times CH_2$), 69.93 (*t*, OCH_2), 111.97, 119.10, 123.25 (3*d*, *arom*. CH), 139.53, 140.73, 156.26 (3*s*, C-1, C-2, C-3), 168.27 (s, CO), IR (KBr, cm^{-1}): 2085 (*w*),1894 (*w*), 1774 (*s*), 1690 (*w*), 1598 (*s*), 1510 (*s*), 1466 (*s*), 1343 (*s*), 1330 (*m*); mass (*m*/*z*): 338 $[M+H]^{++}$. HRMS calcd. for $[C_{18}H_{27}NO_5Na]$: 360.1787; found: 360.1788.

Acetic Acid 2-Ethoxy-5-nitrophenyl Ester (13b)

Yield : 93%, mp: 72.8–73.7 °C; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.45$ (*t*, 3H, $J = 6.9$ Hz, CH_3), 2.34 (*s*, 3H, $OCOCH_3$), 4.16 (*q*, 2H, $J = 6.9$ Hz, OCH_2), 7.00 (*d*, 1H, $J_{3,4} = 9$ Hz, H-3), 7.97 (*d*, 1H, $J_{4,6} = 3$ Hz, H-6), 8.15 (*dd*, 1H, $J_{3,4} = 9$ Hz, $J_{4,6} = 3$ Hz, H-4). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 14.43$, 20.42 (2*q*, $2 \times CH_3$), 65.20 (*t*, OCH_2), 112.01, 119.17, 123.24 (3*d*, arom. CH), 139.53, 140.79, 156.10 (3*s*, C-1, C-2, C-3), 168.27 (s, CO); IR (KBr, cm^{-1}): 1760 (*s*), 1600 (*s*), 1519 (*s*), 1472 (*s*), 1348 (*s*), 1295 (*s*), 1223 (*s*); mass (*m*/*z*): 226 $[M+H]^+$. HRMS calcd. for $[C_{10}H_{11}NO_5Na]$: 248.0535; found: 248.0528.

2-Decyloxy-5-nitrophenol (5a)

NaOH (672 mg, 0.017 mol) was added to a solution of crude **11a** in THF (25 mL) and stirred at rt for about 1 h. After the reaction was complete it was quenched with water (50 mL) and neutralized with 20% HCl. The product was extracted with ether (2×30 mL) and washed with water (2×50 mL). The organic layer was dried over Na_2SO_4, concentrated, and dried.

Yield: 4 g (83%); mp 46–49 °C (lit.[1f] = 46–49 °C), ^1H NMR (300 MHz, $CDCl_3$): $\delta = 0.88$ (*t*, 3H, $J = 6$ Hz, CH_3), 1.28–1.60 (*m*, 14H, $7 \times CH_2$), 1.82–1.91 (*m*, 2H, CH_2), 4.15 (*t*, 2H, $J = 6$ Hz, OCH_2), 5.84 (*s*, 1H, OH), 6.87 (*d*, 1H, $J_{3,4} = 9.0$ Hz, H-3), 7.79–7.84 (*m*, 2H, H-4, H-6).

2-Ethoxy-5-nitrophenol (5b)

NaOH (473 mg, 0.01 mol) was added to a solution of crude **11b** in THF (13 mL) and stirred at rt for about 1 h. After the reaction was complete, it was quenched with water (30 mL) and neutralized with 20% HCl. The aqueous solution was extracted with ether (2×20 mL), and the organic layer was washed with water (2×50 mL), dried over Na_2SO_4, and concentrated.

Yield:2.2 g(98%); mp 113–114 °C (lit.[17] = 113–114 °C), ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.52$ (*t*, 3H, $J = 6$ Hz, CH_3), 4.25 (*q*, 2H, $J = 6.9$ Hz, OCH_2), 5.87 (*s*, 1H, OH), 6.88 (*d*, 1H, $J_{3,4} = 9$ Hz, H-3), 7.80–7.85 (*m*, 2H, H-4, H-6).

1-Decyloxy-2-ethoxy-4-nitrobenzene (2a)

A solution of **5a** (200 mg, 0.67 mmol), and Cs_2CO_3 (221 mg, 0.67 mmol), and EPTS (148 mg, 0.74 mmol) in DMF (2.5 mL) was stirred at 70–80 °C under a nitrogen atmosphere for about 1.5 h. The resulting mixture was cooled to 0 °C, water (20 mL) was added, and it was neutralized with 20% HCl. The aqueous solution was extracted with ether (2×10 mL) and the organic layer was washed with water (2×50 mL), dried over Na_2SO_4 and concentrated.

Yield: 0.44 g (80%); mp 57–58 °C (lit.[1f] = 57.5–58.5 °C); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.88$ (*t*, 3H, $J = 6.9$ Hz, CH_3), 1.27–1.46 (*m*, 14H, $7 \times CH_2$), 1.49 (*t*, 3H, $J = 6.9$ Hz, CH_2), 1.82–1.91 (*m*, 2H, CH_2), 4.07–4.19 (*m*, 4H, $2 \times OCH_2$), 6.86 (*d*, 1H, $J_{5,6} = 9.0$ Hz, H-6), 7.72 (*d*, 1H, $J_{3,5} = 3$ Hz, H-3), 7.87 (*dd*, 1H, $J_{5,6} = 9$ Hz, $J_{3,5} = 3$ Hz, H-5).

1-Decyloxy-2-methoxy-4-nitrobenzene (2b)

A solution of **5a** (500 mg, 1.69 mmol), Cs_2CO_3 (606 mg, 1.85 mmol), and methyl iodide (0.1 mL, 2.03 mmol) in DMF (2.5 mL) was stirred at rt under a nitrogen atmosphere for about 1 h. The resulting mixture was cooled to 0 °C, water (20 mL) was added, and it was neutralized with 20% HCl. The aqueous solution was extracted with ether (2×10 mL), and the organic layer was washed with water (2×50 mL), dried over Na_2SO_4, and concentrated.

Yield: 502 mg (95%); mp 48–50 °C (lit.[1f] = 49–50 °C); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.88$ (*t*, 3H, $J = 6.9$ Hz, CH_3), 1.27–1.48 (*m*, 14H, $7 \times CH_2$), 1.83–1.93 (*m*, 2H, CH_2), 3.95 (*s*, 3H, OCH_3), 4.10 (*t*, 2H, $J = 6$ Hz, OCH_2), 6.90 (*d*, 1H, $J_{5,6} = 9.0$ Hz, H-6), 7.75 (*d*, 1H, $J_{3,5} = 3$ Hz, H-3), 7.90 (*dd*, 1H, $J_{5,6} = 9$ Hz, $J_{3,5} = 3$ Hz, H-5).

1-Decyloxy-2-propyloxy-4-nitrobenzene (2c)

A solution of **5a** (2 g, 6.77 mmol), Cs_2CO_3 (2.4 g, 7.48 mmol), and *n*-propylbromide (0.74 mL, 8.1 mmol) in DMF (20 mL) was stirred at 70–80 °C under a nitrogen atmosphere for about 4 h. The resulting mixture was cooled to 0 °C, water (50 mL) was added, and it was neutralized with

20% HCl. The aqueous solution was extracted with ether (2×100 mL), and the organic layer was washed with water (2×100 mL), dried over Na_2SO_4, and concentrated.

Yield: 1.95 g (85%); mp 58–61 °C (lit.[1f] = 59–61 °C); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.88$ (*t*, 3H, $J = 6$ Hz, CH_3), 1.07 (*t*, 3H, $J = 6$ Hz, CH_3), 1.27–1.55 (*m*, 14H, $7 \times CH_2$), 1.82–1.92 (*m*, 4H, $2 \times CH_2$), 4.01–4.11 (*m*, 4H, $2 \times OCH_2$), 6.87 (*d*, 1H, $J_{5,6} = 9.0$ Hz, H-6), 7.73 (*d*, 1H, $J_{3,5} = 2.4$ Hz, H-3), 7.87 (*dd*, 1H, $J_{5,6} = 9$ Hz, $J_{3,5} = 2.7$ Hz, H-5).

1-Decyloxy-2-butyloxy-4-nitrobenzene (2d)

A solution of **5a** (2 g, 6.77 mmol), Cs_2CO_3 (2.4 g, 7.48 mmol), and *n*-butylbromide (0.88 mL, 8.13 mmol) in DMF (20 mL) was stirred at 70–80 °C under a nitrogen atmosphere for about 4 h. The resulting mixture was cooled to 0 °C, water (50 mL), was added and it was neutralized with 20% HCl. The aqueous solution was extracted with ether (2×100 mL), and the organic layer was washed with water (2×100 mL), dried over Na_2SO_4, and concentrated.

Yield: 2.0 g (86%); mp 35–36 °C (lit.[1f] = 35–37 °C), ^{1}H NMR(300 MHz, $CDCl_3$): $\delta = 0.88$ (*t*, 3H, $J = 6$ Hz, CH_3), 1.0 (*t*, 3H, $J = 7.5$ Hz, CH_3), 1.27–1.38 (*m*, 12H, $6 \times CH_2$), 1.43–1.56 (*m*, 4H, $2 \times CH_2$), 1.80–1.91 (*m*, 4H, $2 \times CH_2$), 4.05–4.11 (*m*, 4H, $2 \times OCH_2$),6.89 (*d*, 1H, $J_{5,6} = 9$ Hz, H-6), 7.73 (*d*, 1H, $J_{3,5} = 2.6$ Hz, H-3), 7.86–7.89 (*dd*, 1H, $J_{5,6} = 8.7$ Hz, $J_{3,5} = 2.7$ Hz, H-5).

1-Decyloxy-2-isopropyloxy-4-nitrobenzene (2e)

A solution of **5a** (500 mg, 1.69 mmol), Cs_2CO_3(660 mg, 1.94 mmol), and isopropyl bromide (0.5 mL, 0.0042 mol) in DMF (2.5 mL) was stirred at 70–80 °C under a nitrogen atmosphere for about 9 h. The resulting mixture was cooled to 0 °C, water (50 mL) was added, and it was neutralized with 20% HCl. The aqueous solution was extracted with ether (2×20 mL), and the organic layer was washed with water (2×50 mL), dried over Na_2SO_4, and concentrated.

Yield: 0.46 g (81%); mp 45–46 °C (lit.[1f] = 45.5–47.5 °C); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.88$ (*t*, 3H, $J = 6.9$ Hz, CH_3) 1.27–1.35 (*m*, 12H, $6 \times CH_2$), 1.38 (*s*, 3H, CH_3), 1.40 (*s*, 3H, CH_3), 1.45–1.47 (*m*, 2H, CH_2), 1.81–1.90 (*m*, 2H, CH_2), 4.08 (*t*, 2H, $J = 9$ Hz, OCH_2), 4.53–4.61 (*m*, 1H, OCH), 6.87 (*d*, 1H, $J_{5,6} = 9.0$ Hz, H-6), 7.77 (*d*, 1H, $J_{3,5} = 3$ Hz, H-3), 7.87 (*dd*, 1H, $J_{5,6} = 9$ Hz, $J_{3,5} = 3$ Hz, H-5).

2-Allyloxy-1-decyloxy-4-nitrobenzene (2f)

A solution of **5a** (500 mg, 1.69 mmol), Cs_2CO_3 (683 mg, 2.0 mmol), and allylbromide (0.4 mL, 4.6 mol) in DMF (2.5 mL) was stirred at 60–70 °C under a nitrogen atmosphere for about 5 h. The resulting mixture was cooled to 0 °C, water (50 mL) was added, and it was neutralized with 20% HCl. The aqueous solution was extracted with ether (2×20 mL), and the organic layer was washed with water (2×50 mL), dried over Na_2SO_4, and concentrated.

Yield: 0.53 g (93%); mp 36–37 °C (lit.[11f] = 36–38 °C), ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.88$ (*t*, 3H, $J = 6$ Hz, CH_3), 1.27–1.42 (*m*, 12H, $6 \times CH_2$), 1.43–1.54 (*m*, 2H, CH_2), 1.83–1.92 (*m*,2H, CH_2), 4.10 (*t*, 2H, $J = 6$ Hz, OCH_2), 4.67 (*dt*, 2H, $J = 5.2$ Hz, OCH_2), 5.34 (*dq*, 1H, $J = 1.5$, 9.0 Hz, H-A), 5.47 (*dq*, 1H, $J = 1.5$, 18 Hz, H-B), 6.01–6.14 (*m*, 1H, H-C), 6.91 (*d*, 1H, $J_{5,6} = 9$ Hz, H-6), 7.75 (*d*, 1H, $J_{3,5} = 3$ Hz, H-3), 7.89 (*dd*, 1H, $J_{5,6} = 9$ Hz, $J_{3,5} = 3$ Hz, H-5).

2-Benzyloxy-1-decyloxy-4-nitrobenzene (2g)

A solution of **5a** (500 mg, 1.69 mmol), Cs_2CO_3 (606 mg, 1.86 mmol), and benzyl chloride (0.2 mL, 0.0202 mole) in DMF (2.5 mL) was stirred at 60–70 °C under N_2 atm for about 1 h. The reaction mixture was cooled to 0 °C, water (50 mL) was added, and it was neutralized with 20% HCl and worked up as usual.

Yield: 0.55 g (84%); mp 39–42 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.88$ (*t*, 3H, $J = 6$ Hz, CH_3), 1.27–1.42 (*m*, 12H, $6 \times CH_2$), 1.44–1.55 (*m*, 2H, CH_2), 1.83–1.92 (*m*, 2H, CH_2), 4.11 (*t*, 2H, $J = 6$ Hz, OCH_2), 5.19 (*s*, 2H, $PhCH_2$), 6.92 (*d*, 1H, $J_{5,6} = 9$ Hz, H-6), 7.33–7.48 (*m*, 5H, *arom*. CH), 7.81 (*d*, 1H, $J_{3,5} = 3$ Hz, H-3), 7.90 (*dd*, 1H, $J_{5,6} = 9$ Hz, $J_{3,5} = 3$ Hz, H-5); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 14.13$ (*q*, CH_3), 22.70, 25.95 (2*t*, CH_2), 28.92, 29.33, 29.53, 29.58 (4*t*, CH_2), 31.90 (*t*, CH_2), 69.45 (*t*, OCH_2), 71.18 (*t*, $PhCH_2$), 109.25, 111.13, 118.30, 127.27, 128.18, 128.63 (6*d*, *arom*. CH), 136.06, 141.02, 147.98, 155.00 (4*s*, *arom*. C); IR (KBr, cm^{-1}): 2940(s), 2917 (*s*), 2851 (*s*), 1590 (*m*), 1516 (*s*), 1504 (*s*), 1388 (*w*), 1352 (*s*); mass (*m*/*z*): 385 $[M + H]^+$; HRMS: calcd. for $[C_{23}H_{31}NO_4Na]$: 408.2151; found: 408.2157.

1-Ethoxy-2-methoxy-4-nitrobenzene (2h)

A solution of **5b** (0.2 g, 1.09 mmol), Cs_2CO_3 (0.355 g, 0.01 mol), and methyl iodide (0.3 mL, 4.81 mmol) in DMF (1 mL) was stirred at rt under a nitrogen atmosphere for about 3 h. The resulting mixture was cooled to

0 °C, quenched with water (50 mL), and neutralized with 20% HCl. The aqueous solution was extracted with ether (2 × 20 mL), and the organic layer was washed with water (2 × 50 mL), dried over Na_2SO_4, and concentrated.

Yield: 0.2 g (94%), mp 85–87 °C (lit.[14] = 85–88 °C); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.52$ (*t*, 3H, $J = 9$ Hz, CH_3), 3.96 (*s*, 3H, OCH_3), 4.22 (*q*, 2H, $J = 9$ Hz, OCH_2), 6.91 (*d*, 1H, $J_{5,6} = 9$ Hz, H-6), 7.75 (*d*, 1H, $J_{3,5} = 3$ Hz, H-3), 7.90 (*dd*, 1H, $J_{5,6} = 9$ Hz, $J_{3,5} = 3$ Hz, H-5).

2-Decyloxy-1-ethoxy-4-nitrobenzene (2i)

A solution of **5b** (0.3 g, 1.63 mmol), Cs_2CO_3 (587 mg, 1.86 mmol), and decylbromide (0.4 mL, 1.95 mmol) in DMF (3 mL) was stirred at 60–70 °C under N_2 atm for about 30 min. The resulting mixture was cooled to 0 °C, quenched with H_2O (50 mL), and neutralized with 20% HCl, then worked up as usual. The crude was crystallized with methanol (5 mL) and dried. Yield: 502 mg (95%); mp 60–62 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.88$ (*t*, 3H, $J = 6$ Hz, CH_3) 1.28 (*m*, 12H, $6 \times CH_2$), 1.48–1.54 (*m*, 5H, $J = 6$ Hz, CH_3, CH_2), 1.84–1.89 (*m*, 2H, CH_2), 4.07 (*t*, 2H, $J = 6$ Hz, Hz, OCH_2), 4.19 (*q*, 2H, $J = 6$ Hz, OCH_2), 6.90 (*d*, 1H, $J_{5,6} = 9$ Hz, H-6), 7.74 (*d*, 1H, $J_{3,5} = 3$ Hz, H-3), 7.89 (*dd*, 1H, $J_{5,6} = 9$ Hz, $J_{3,5} = 3$ Hz, H-5); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 14.33$, 14.55 (2*q*, $2 \times CH_3$), 22.69 (*t*, CH_2), 25.90 (*t*, CH_2), 28.88 (*t*, CH_2), 29.33, 29.54 (4*t*, $2 \times 2CH_2$),), 64.97 (*t*, OCH_2) 64.53 (*t*, OCH_2), 107.95, 110.96, 117.65 (3*d*, $3 \times$ *arom.* CH), IR (KBr, cm^{-1}): 2853 (*m*), 2274 (*m*), 1584 (*m*), 1513 (*s*), 1344 (*s*), 1279 (*s*), 1232 (*s*); mass (*m*/*z*): 323 $[M + H]^+$. HRMS calcd. for $[C_{18}H_{30}NO_4]$: 324.2175; found: 324.2182.

1-Ethoxy-4-nitro-2-propyloxybenzene (2j)

A solution of **5b** (0.3 g, 1.63 mmol), Cs_2CO_3 (587 mg, 1.86 mmol), and *n*-propyl bromide (0.18 mL, 1.95 mmol) in DMF (3 mL) was stirred at 60–70 °C under N_2 atm for about 3 h. The resulting mixture was cooled to 0 °C, quenched with H_2O (50 mL), and neutralized with 20% HCl, then worked up as usual.

Yield:0.32 g (89%); mp 65–67 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.07$ (*t*, 3H, $J = 7.5$ Hz, CH_3), 1.50 (*t*, 3H, $J = 7.2$ Hz, CH_3), 1.91 (*sexet*, 2H, $J = 7.2$ Hz, CH_2), 4.04 (*t*, 2H, $J = 6$ Hz, OCH_2), 4.20 (*q*, 2H, $J = 6$ Hz, OCH_2), 6.90 (*d*, 1H, $J_{5,6} = 9$ Hz, H-6), 7.73 (*d*, 1H, $J_{3,5} = 3$ Hz, H-3), 7.89 (*dd*, 1H, $J_{5,6} = 9$ Hz, $J_{3,5} = 3$ Hz, H-5); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 10.39$ (*q*, CH_3), 14.55 (*q*, CH_3), 22.30 (*t*, CH_2), 64.98, 70.92 (2*t*, $2 \times CH_2$), 108.01, 111.00, 117.68 (3*d*, $3 \times$ *arom.*

om. CH), 141.22, 148.54, 154.42 (3*s*, 3 × *arom*. C), IR (KBr, cm^{-1}): 2939 (*m*), 2879 (*m*), 1586 (*m*), 1500 (*s*), 1347 (*s*), 1289 (*s*), 1231 (*s*), 1140 (*w*); mass (*m*/*z*): 225 $[M + H]^+$. HRMS calcd. for $[C_{11}H_{16}NO_4]$: 226.1079; found: 226.1073.

2-Butoxy-1-ethoxy-4-nitrobenzene (2k)

A solution of **5b** (0.3 g, 1.63 mmol), Cs_2CO_3 (587 mg, 1.86 mmol), and *n*-butylbromide (0.2 mL, 1.96 mmol) in DMF (3 mL) was stirred at 70–80 °C under N_2 atm for about 0.5 h. The resulting mixture was cooled to 0 °C, quenched with H_2O (50 mL), and neutralized with 20% HCl, then worked up as usual.

Yield: 0.35 g (88%); mp 59–60 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.00$ (*t*, 3H, $J = 7.5$ Hz, CH_3), 1.46–1.56 (*m*, 5H, CH_3, CH_2), 1.86 (*m*, 2H, CH_2), 4.08 (*t*, 2H, $J = 6$ Hz, OCH_2), 4.19 (*q*, 2H, $J = 6$ Hz, OCH_2), 6.90 (*d*, 1H, $J_{5,6} = 9$ Hz, H-6), 7.74 (*d*, 1H, $J_{3,5} = 3$ Hz, H-3), 7.88 (*dd*, 1H, $J_{5,6} = 9$ Hz, $J_{3,5} = 3$ Hz, H-5), ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 13.85$, 14.55 (2*q*, 2 × CH_3), 19.18, 30.95 (2*t*, 2 × CH_2), 64.98, 69.23 (2*t*, 2 × OCH_3), 107.98, 110.99, 117.66 (3*d*, 3 × *arom*. CH), 141.23, 148.58, 154.42 (3*s*, 3 × *arom.* C); IR (KBr, cm^{-1}): 2935 (*m*), 2874 (*m*), 1587 (*m*), 1522 (*s*), 1504 (*s*), 1476 (*w*), 1396 (*w*), 1341 (*s*), 1282 (*s*); mass (*m*/*z*): 239 $[M + H]^+$. HRMS calcd. for $[C_{12}H_{18}NO_4]$: 240.1236; found: 240.1237.

1-Ethoxy-2-isopropoxy-4-nitrobenzene (2l)

A solution of **5b** (0.5 g, 2.7 mmol), Cs_2CO_3 (890 mg, 2.7 mmol), and isopropylbromide (0.3 mL, 3.2 mmol) in DMF (2.5 mL) was stirred at 70–80 °C under N_2 atm for about 5 h. The resulting mixture was cooled to 0 °C, quenched with H_2O (50 mL), and neutralized with 20% HCl, then worked up as usual.

Yield: 0.5 g (81%); mp 55–57 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.39$, 1.41 (2*s*, 6H, 2 × CH_3), 1.49 (*t*, 3H, $J = 9$ Hz, CH_3), 4.16 (*q*, 2H, $J = 9$ Hz, OCH_2), 4.59 (*septet*, 1H, $J = 6$ Hz, OCH), 6.89 (*d*, 1H, $J_{5,6} = 9$ Hz, H-6), 7.76 (*d*, 1H, $J_{3,5} = 3$ Hz, H-3), 7.88 (*dd*, 1H, $J_{5,6} = 9$ Hz, $J_{3,5} = 3$ Hz, H-5); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 14.55$ (*q*, CH_3), 21.92 (*q*, CH_3), 64.96 (*t*, OCH_2), 72.52 (*d*, OCH), 111.12, 111.44, 118.06 (3*d*, 3 × *arom*. C-H), 141.10, 147.30, 155.50 (3*s*, 3 × *arom.* om. C), IR (KBr, cm^{-1}): 2896 (*m*), 2636 (*w*), 1852 (*w*), 1583 (*m*), 1504 (*s*), 1474 (*m*), 1340 (*s*), 1260 (*s*), 1229 (*s*), 1109 (*m*); mass (*m*/*z*): 225 $[M + H]^+$. HRMS calcd. for $[C_{11}H_{16}NO_4]$: 226.1079; found: 226.1081.

2-Allyloxy-1-ethoxy-4-nitrobenzene (2m)

A solution of **5b** (0.5 g, 2.7 mmol), Cs_2CO_3 (889 mg, 2.7 mmol), and allylbromide (0.27 mL, 3.2 mmol) in DMF (2.5 mL) was stirred at 70–80 °C under N_2 atm for about 1 h. The resulting mixture was cooled to 0 °C, quenched with H_2O (50 mL), and neutralized with 20% HCl, then worked up as usual. The crude solid (580 mg) was purified by column chromatography. Yield: 0.5 g (82%); mp 40–42 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.51$ (*t*, 3H, $J = 6.9$ Hz, CH_3), 4.20 (*q*, 2H, $J = 6.9$ Hz OCH_2), 4.68 (*dt*, 2H, $J = 1.5$, 6.0 Hz, OCH_2), 5.35 (*dq*, 1H, $J = 1.5$, 9.0 Hz, H-A), 5.47 (*dq*, 1H, $J = 1.5$, 18 Hz, H-B), 6.02–6.16 (*m*, 1H, H-C), 6.90 (*d*, 1H, $J_{5,6} = 9$ Hz, H-6), 7.75 (*d*, 1H, $J_{3,5} = 2.6$ Hz, H-3), 7.91 (*dd*, 1H, $J_{5,6} = 8.8$ Hz, $J_{3,5} = 2.6$ Hz, H-5); ^{13}C NMR(75 MHz, $CDCl_3$): $\delta = 14.54$ (*q*, CH_3), 64.99 (*t*, OCH_2), 70.05 (*t*, OCH_2), 108.54 (*d*, C-3), 110.95 (*d*, C-6), 118.02 (*d*, C-5), 118.58 ($t = CH_2$), 132.22 (*d*, CH), 141.08, 147.83, 154.44 (3*s*, *arom*. C), IR (KBr, cm^{-1}): 2932 (*m*), 2937 (*w*), 1586 (*w*), 1514 (*s*), 1345 (*s*), 1277 (*s*), 1232 (*s*), 1137 (*w*), 1093 (*m*). mass (*m*/*z*): 223 $[M + H]^+$. HRMS calcd. for $[C_{11}H_{13}NO_4Na]$: 246.0742; found: 246.0745.

2-Benzyloxy-1-ethoxy-4-nitrobenzene (2n)

A solution of **5b** (0.2 g, 1.09 mmol), Cs_2CO_3 (355 mg, 1.09 mmol), and benzylchloride (0.15 mL, 1.3 mmol) in DMF (1 mL) was stirred at 60–70 °C under a nitrogen atmosphere for about 2 h. The resulting mixture was cooled to 0 °C, quenched with water (30 mL), and neutralized with 20% HCl. The aqueous solution was extracted with ether (2×30 mL), and the organic layer was washed with water (2×40 mL), dried over Na_2SO_4, concentrated, and dried. Yield: 0.27 g (91%); mp 101-102 °C (lit.[6f] = 101–102 °C); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.53$ (*t*, 3H, $J = 7.2$ Hz, CH_3), 4.21 (*q*, 2H, $J = 7.2$ Hz OCH_2), 5.20 (*s*, 2H, OCH_2Ph), 6.92 (*d*, 1H, $J_{5,6} = 9$ Hz, H-6), 7.31–7.48 (*m*, 5H, *arom*. CH), 7.80 (*d*, 1H, $J_{3,5} = 3$ Hz, H-3), 7.90 (*dd*, 1H, $J_{3,5} = 9$ Hz, $J_{5,6} = 3$ Hz, H-5).

4-Decyloxy-3-ethoxy-phenylamine[1f] (3)

To a solution of **2a** (50 g, 0.156 mol) dissolved in ethyl acetate (300 mL) and ethanol (100 mL) 10% Pd/C was added and kept under 6 bar of hydrogen for 30 min. The solution was filtered over Celite® and washed with ethyl acetate (50 mL). The filtrate was concentrated and dried. Yield: 44.2 g (97%), ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.88$ (*t*, 3H, $J = 6.9$ Hz, CH_3), 1.27 (*s*, 12H, $6 \times CH_2$), 1.39–1.44 (*m*, 5H, $J = 6.9$ Hz,

CH_3, CH_2), 1.70–1.80 (*m*, 2H, $J = 7.5$ Hz, CH_2), 3.39 (*s*, 2H, NH_2), 3.90 (*t*, 2H, $J = 6.9$ Hz, OCH_2), 4.02 (*q*, 2H, $J = 6.9$ Hz, OCH_2), 6.20 (*dd*, 1H, $J_{5,6} = 9.0$ Hz, $J_{6,2} = 3.0$ Hz, H-6), 6.30 (*d*, 1H, $J_{2,6} = 3.0$ Hz, H-2), 6.74 (*d*, 1H, $J_{5,6} = 9.0$ Hz, H-5).

6-Decyloxy-7-ethoxy-4-hydroxy-quinoline-3-carboxylic Acid Ethyl Ester (1a)

Synthesis of Intermediate 2-[(4-Decyloxy-3-ethoxy-phenylamino)-methlylene]-malonic acid diethyl ester

Diethylethoxy methylenemalonate (6.3 g, 0.029 mol) to **3** (8.6 g, 0.029 mol) was added, and stirred at 35–40 °C for about 4 h. Reaction was monitored by thin-layer chromatography (TLC). After reaction completion, the reaction mixture was concentrated to remove ethanol.

Yield: 13.2 g (98%); mp 38– 40 °C (lit.[11] = 38–40 °C); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.88$ (*t*, 3H, $J = 6.0$ Hz, CH_3), 1.22–1.40 (*m*, 20H, $10 \times CH_2$), 1.43–1.48 (*m*, 5H, CH_2, CH_3), 1.76–1.86 (*m*, 2H, CH_2), 3.98 (*t*, 2H, $J = 6.0$ Hz, OCH_2), 4.09 (*q*, 2H, $J = 6.0$ Hz, OCH_2), 4.21–4.34 (*m*, 4H, $2 \times OCH_2$), 6.66–6.69 (*m*, 2H, H-5, H-2), 6.88 (*d*, 1H, $J_{5,6} = 9.0$ Hz, H-6), 8.41 (*d*, 1H, $J = 15.0$ Hz, = CH), 10.99 (*d*, 1H, $J = 12.0$ Hz, NH).

Synthesis of 1a from 2-[(4-Decyloxy-3-ethoxy-phenylamino)methylene]-malonic acid diethyl ester

A solution of 2-[(4-decyloxy-3-ethoxy-phenylamino)-methlylene]-malonic acid diethyl ester (5 g) in Dowtherm A (20 mL) was heated to 260–270 °C for about 15 min. The reaction mixture was cooled and diluted with hexane (300 mL). A white solid was precipitated. The solid was filtered and washed with hexane, then dried at high vacuum.

Yield: 2.6 g (57%); mp 246–248 °C (lit.[11] = 244–246 °C); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.88$ (*t*, 3H, $J = 6.9$ Hz, CH_3), 1.27–1.36 (*m*, 11H, CH_3, $4 \times CH_2$), 1.45–1.57 (*m,* 9H, CH_3, $3 \times CH_2$), 1.87–1.97 (*m*, 2H, CH_2), 4.15 (*t*, 2H, $J = 6.9$ Hz, OCH_2), 4.26 (*q*, 2H, $J = 6.9$ Hz, OCH_2), 4.48 (*q*, 2H, $J = 6.9$ Hz, OCH_2), 7.33, 7.50 (2*s*, 2H,H-5, H-8), 8.95 (*s*, 1H, H-2), 12.14 (*s*, 1H, OH).

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