First Synthesis of 5-Cyanosalicylates by Formal [3+3] Cyclocondensations of 1,3-Bis(silyloxy)-1,3-butadienes

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Abstract: A variety of functionalized benzonitriles were regioselectively prepared by formal [3+3] cyclocondensation of 1,3-bis(silyloxy)-1,3-butadienes with 3-ethoxy- and 3-silyloxy-2-cyano-2-en-1-ones.

Key words: arenes, benzonitriles, cyclizations, regioselectivity, silyl enol ethers

Functionalized benzonitriles represent important building blocks for fine chemical synthesis. In addition, they are important substructures of various dyes, pharmaceuticals, agrochemicals, herbicides, and pesticides.[1] The present paper is focussed on the synthesis of functionalized 5-cyanosalicylates, which can be regarded as functionalized 4-cyanophenols. This substructure is present in a great variety of pharmacologically active compounds; in fact, a Beilstein database search reveals more than 900 4-cyanophenols which show a broad spectrum of pharmacological activities. 5-Cyanosalicylates and 2-acyl-4-cyanophenols are the specific derivatives studied in the present report. Their pharmacological properties include, for example, antiallergic activity,[2] inhibition of HIV-1,[3] anti-dopaminergic activity,[4] vasorelaxing activity,[5] inhibition of LTD4-induced contraction of lung membranes,[6] leukotriene D4 inhibitory activity,[7] antibacterial activity,[8] binding to CHO cell membranes,[9] antagonistic activity against βTC3 cells,[10] inhibition of recombinant human aldehyde reductase,[11] or inhibition of catechol *O*-methyltransferase.[12]

Simple benzonitriles are prepared on industrial scales by ammoxidation of toluenes. In addition, 'classical' reactions of copper(I) cyanide with aryl halides or aryl diazonium salts using, for example, the Rosenmund-von-Braun or the Sandmeyer reaction, are often used. In recent years, various catalytic variants have been developed.[13,14] Substituted 5-cyanosalicylates represent highly functionalized arenes containing a nitrile, ester and hydroxy group. Due to their polyfunctional nature, they represent versatile synthetic building blocks. 5-Cyanosalicylates have been previously prepared by transformation of oximes into nitriles,[15] by cyanation of aryl halides,[16] by palladium(0)-catalyzed reaction of aryl halides with zinc or potassium cyanide,[17] and by Grignard reaction of 4-hydroxy-3,5-diiodobenzonitrile with carbon dioxide.[18]

Despite their great synthetic utility, catalytic cyanations can suffer from several drawbacks, such as low turnover numbers. In addition, reactions of *ortho*-substituted aryl halides are often problematic or not possible at all or require the use of toxic thallium reagents.[19] It is important to note that the synthesis of the required starting materials – functionalized or highly substituted aryl halides or triflates – can be a difficult and tedious task due to the low *ortho*/*para* regioselectivity of electrophilic substitutions, harsh reaction conditions, and several other drawbacks.

An interesting alternative approach to the synthesis of benzonitriles is based on the application of a 'building-block strategy'. Examples include the base-mediated cyclocondensation of ethoxymethylene-malononitrile with β-keto esters,[20] the cyclization of diethyl acetone-1,3-dicarboxylate with 3-oxopentanedioic acid diethyl ester,[21] and the reaction of malodinitrile with methyl 2-acetyl-3-methoxyacrylate.[22] Another building-block approach to the synthesis of benzonitriles relies on [4+2] cycloaddition reactions of cyano-substituted dienes or dienophiles.[23] This includes, for example, the [4+2] cycloaddition of 3-cyano-2,4-bis(silyloxy)penta-1,3-diene with methyl propynoate.[24] Recently, we have reported[25] the synthesis of functionalized 5-cyanosalicylates by formal [3+3] cyclocondensations[26,27] of 1,3-bis(silyloxy)-1,3-butadienes[28] with cyano-substituted 3-ethoxy- and 3-silyloxy-2-en-1-ones. These reactions provide a convenient and regioselective approach to a variety of 5-cyanosalicylates which are not readily available by other methods. Herein, we report a comprehensive study on the preparative scope of this approach.

2-Cyano-3-ethoxy-2-en-1-ones **2a**–**e** were prepared, following a known procedure,[29] by reaction of ketonitriles **1a**–**e** with ethyl orthoformate and acetic anhydride (Table 1). 1,3-Bis(silyloxy)-1,3-butadienes **3a**–**k** were prepared from the corresponding β-keto esters in two steps.[16] The titanium tetrachloride mediated cyclization of **2a** with **3a** afforded the 5-cyanosalicylate **4a** (Scheme 1). The cyclization proceeded with excellent regioselectivity. The formation of product **4a** might be explained by titanium tetrachloride mediated conjugate addition of the terminal carbon atom of **3a** to **2a**, to give intermediate **A**,

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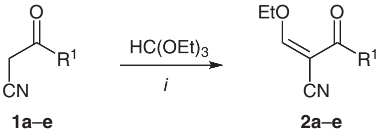
cyclization via the central carbon of **3a** to give intermediate **B** (S_N' reaction), and subsequent aromatization. The formal [3+3] cyclization of 2-cyano-3-ethoxy-2-en-1-ones **2a**–**e** with 1,3-bis(silyloxy)-1,3-butadienes **3a**–**k** afforded the 5-cyanosalicylates **4a**–**ac** in 33–64% yields (Table 2). The substituent R^1, located next to the carbonyl group of **2a**–**e**, has some influence on the yields. Better yields were generally obtained for the products **4h**–**ac** derived from **2b**–**e**, containing an aryl group, compared to products **4a**–**g**, derived from **2a**, which contains a methyl group. The best yields were observed for the products derived from chloro- or bromo-substituted enones **2c** and **2d**. This might be explained by the fact that the electron-withdrawing halogen atoms increase the reactivity of the enone. The substitution pattern of the diene had no significant influence on the yield.

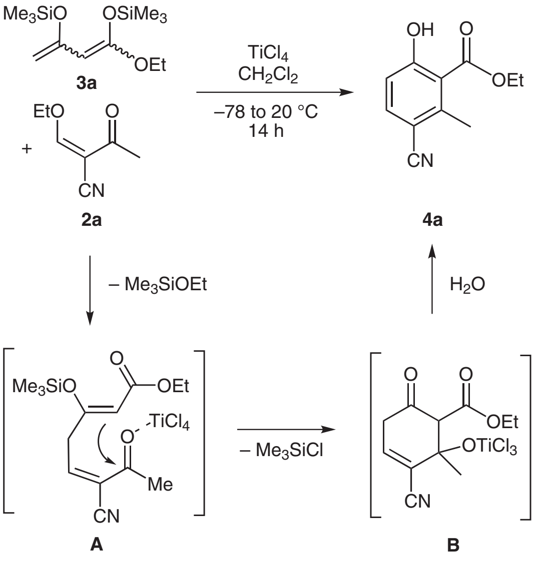
Table 1 Synthesis of **2a**–**e**



2	R^1	Yield (%)[a]
a	Me	100
b	Ph	88
c	4-ClC_6H_4	98
d	4-BrC_6H_4	96
e	4-$(MeO)C_6H_4$	95

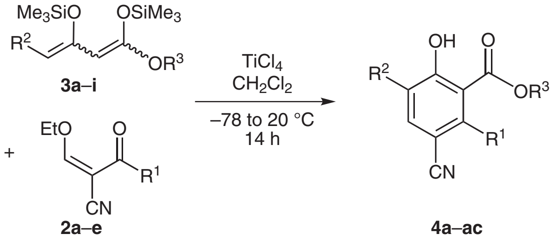
[a] Reaction conditions: **1a**–**e** (1.0 equiv), $HC(OEt)_3$ (3.0 equiv), Ac_2O, reflux, 2 h.

[a] Yield of isolated products.



Scheme 1 Possible mechanism for formation of **4a**

Table 2 Synthesis of **4a**–**ac**



2	3	4	R^1	R^2	R^3	Yield (%)[a]
a	**a**	**a**	Me	H	Me	34
a	**b**	**b**	Me	H	Et	33
a	**c**	**c**	Me	Me	Me	35
a	**d**	**d**	Me	Et	Et	34
a	**e**	**e**	Me	*n*-Bu	Me	35
a	**f**	**f**	Me	*n*-Hex	Me	42
a	**g**	**g**	Me	*n*-Hept	Me	34
b	**b**	**h**	Ph	H	Et	45
b	**c**	**i**	Ph	Me	Me	43
b	**d**	**j**	Ph	Et	Et	42
b	**e**	**k**	Ph	*n*-Bu	Me	41
b	**g**	**l**	Ph	*n*-Hept	Me	42
b	**h**	**m**	Ph	*n*-Oct	Me	40
b	**k**	**n**	Ph	4-ClC_6H_4	Me	44
c	**c**	**o**	4-ClC_6H_4	Me	Me	61
c	**d**	**p**	4-ClC_6H_4	Et	Et	62
c	**f**	**q**	4-ClC_6H_4	*n*-Hex	Me	64
c	**h**	**r**	4-ClC_6H_4	*n*-Oct	Me	59
c	**j**	**s**	4-ClC_6H_4	*i*-Pent	Me	62
d	**c**	**t**	4-BrC_6H_4	Me	Me	58
d	**d**	**u**	4-BrC_6H_4	Et	Et	60
d	**f**	**v**	4-BrC_6H_4	*n*-Hex	Me	55
d	**h**	**w**	4-BrC_6H_4	*n*-Oct	Me	55
d	**i**	**x**	4-BrC_6H_4	*n*-Non	Me	57
e	**b**	**y**	4-$(MeO)C_6H_4$	H	Et	50
e	**c**	**z**	4-$(MeO)C_6H_4$	Me	Me	51
e	**d**	**aa**	4-$(MeO)C_6H_4$	Et	Et	49
e	**f**	**ab**	4-$(MeO)C_6H_4$	*n*-Hex	Me	52
e	**h**	**ac**	4-$(MeO)C_6H_4$	*n*-Oct	Me	50

[a] Yield of isolated products.

An optimization study was carried out for the synthesis of **4e** (Table 3). The best yields were obtained when the reaction was carried out in a highly concentrated solution, however, the stoichiometry (**2a**–**3e**–$TiCl_4$ = 1:1.1:1.1), the temperature (slow warming from –78 to 20 °C), and the reaction time also played important roles. The use of TMSOTf, $BF_3 \cdot OEt_2$, and $SnCl_4$ resulted in the formation of complex mixtures. The moderate yields might be explained by $TiCl_4$-mediated oxidative dimerization of the diene; this type of reaction has been previously reported.[30] In addition, some hydrolysis of the enone was observed.

Table 3 Optimization of the Synthesis of **4e**

Entry	**2a**:**3e**:$TiCl_4$	Concn of **2a** (mol/L)[a]	Temp (°C)	Time (h)	**4e** (%)[b]
1	1:1.1:1.1	0.5	–78→20	14	35
2	1:1:2	0.5	–78→20	14	20
3	1:2:1	0.5	–78→20	14	15
4	1:2:2	0.5	–78→20	14	29
5	1:1.1:1.1	0.2	–78→20	14	10
6	1:1.1:1.1	0.1	0→20	14	trace
7	1:1.1:1.1	0.5	0→20	14	0
8	1:1.1:1.1	0.5	–78→20	5	15

[a] All experiments were carried out on a 1.0 mmol scale.
[b] Isolated yields.

The configuration of all products was established by spectroscopic methods (2D NMR). The structures of benzonitriles **4b**–**d**,**i**,**o**,**t** were independently confirmed by X-ray crystal structure analyses – one of which is exemplarily depicted in Figure 1.[31]

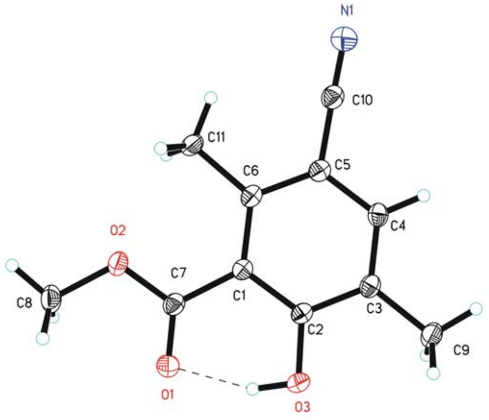
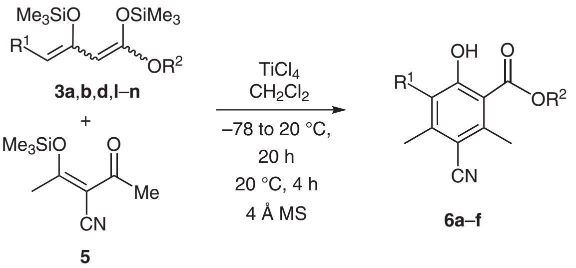


Figure 1 Ortep plot of **4c** (hydrogen at O3 found in the difference map and refined freely)

3-Cyano-4-(trimethylsilyloxy)pent-3-en-2-one (**5**) was prepared by silylation of known[32] 3-cyano-acetylacetone. The $TiCl_4$-mediated [3+3] cyclocondensation of **5** with **3a**,**b**,**d**,**l**–**n** afforded the 5-cyanosalicylates **6a**–**f** in moderate yields (except for **6d**) (Table 4). The best yields were again obtained when the reactions were carried out in a highly concentrated solution. The low yield of **6d** can be explained by $TiCl_4$-mediated cleavage of the *tert*-butyl ester.

Table 4 Synthesis of **6a**–**f**



3	**6**	R^1	R^2	**6** (%)[a]
a	**a**	H	Me	34
b	**b**	H	Et	41
l	**c**	H	*i*-Bu	40
m	**d**	H	*t*-Bu	8
n	**e**	Et	Me	44
d	**f**	Et	Et	58

[a] Yields of isolated products.

In conclusion, we have reported a convenient and regioselective synthesis of functionalized benzonitriles by what are, to the best of our knowledge, the first formal [3+3] cyclizations of 1,3-bis(silyloxy)-1,3-butadienes with cyano-substituted enones. The products are not readily available by other methods. The reactions are easy to perform and the starting materials are readily available. We are currently studying the preparative scope of the methodology and applications to the synthesis of pharmacologically active products.

All solvents were dried by standard methods and all reactions were carried out under an Argon atmosphere. For ^1H and ^{13}C NMR spectra, the deuterated solvents indicated were used. Mass spectrometric data (MS) were obtained by electron ionization (EI, 70 eV), chemical ionization (CI, *i*-Bu) or electrospray ionization (ESI). For preparative scale chromatography, silica gel 60 (0.063–0.200 mm, 70–230 mesh) was used.

2-Cyano-3-ethoxy-2-en-1-ones 2a–e; General Procedure

To a flask containing Ac_2O (2.5 mL/10.0 mmol of **1**), was added ketonitrile **1a**–**e** (1.0 equiv) and $CH(OEt)_3$ (3.0 equiv). The mixture was stirred under reflux for 2 h, then Ac_2O was removed in vacuo and the solid residue was purified by crystallization from EtOH to give **2a**–**e**.

2-(Ethoxymethylene)-3-oxobutane-nitrile (2a)

Starting with **1a** (2.00 g, 24.4 mmol) and $CH(OEt)_3$ (12.17 mL, 73.1 mmol), **2a** was isolated after recrystallization from EtOH.

Yield: 3.387 g (100%); brown crystals; mp 70–71 °C.

IR (KBr): 2958 (w), 2922 (m), 2852 (w), 2253 (w), 2226 (w), 1693 (m), 1671 (m), 1612 (s), 1612 (s), 1590 (m), 1469 (w), 1445 (w), 1394 (w), 1383 (w), 1309 (m), 1294 (m), 1232 (s), 1153 (m), 1094 (m), 1075 (m), 999 (m), 957 (m), 908 (m), 877 (m), 784 (w), 728 (m), 648 (w), 638 (m), 624 (m), 608 (m), 537 (w) cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.44 (t, ^3J = 7.2 Hz, 3 H, $OCH_2\mathit{CH}_3$), 2.38 (s, 3 H, CH_3), 4.36 (q, ^3J = 7.2 Hz, 2 H, $O\mathit{CH}_2CH_3$), 8.0 (s, 1 H, CH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.3, 28.2 (CH_3), 74.1 (OCH_2), 94.4 (*C*CN), 114.4 (CN), 171.8 (CH), 191.8 (CO).

GC–MS (EI, 70 eV): *m/z* (%) = 139 (50) [M$^+$], 124 (8), 111 (21), 96 (100), 83 (81), 68 (93), 52 (10).

HRMS (EI): *m/z* [M$^+$] calcd for $C_7H_9O_2N$: 139.06278; found: 139.063030.

2-Benzoyl-3-ethoxyacrylonitrile (2b)

Starting with **1b** (2.00 g, 13.8 mmol) and $CH(OEt)_3$ (6.9 mL, 41.3 mmol), **2b** was isolated after recrystallization from EtOH.

Yield: 2.43 g (88%); brown solid; mp 70–71 °C.

IR (KBr): 3060 (w), 2985 (w), 2937 (w), 2219 (w), 1645 (m), 1598 (s), 1577 (s), 1492 (w), 1472 (w), 1446 (m), 1393 (m), 1376 (m), 1352 (m), 1301 (m), 1288 (m), 1231 (s), 1180 (m), 1153 (m), 1104 (m), 1004 (m), 922 (m), 909 (m), 870 (w), 796 (w), 716 (m), 698 (m), 670 (m), 611 (w), 555 (w) cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.41 (t, ^3J = 7.2 Hz, 3 H, $OCH_2\mathit{CH}_3$), 4.34 (q, ^3J = 7.2 Hz, 2 H, $O\mathit{CH}_2CH_3$), 7.40–7.52 (m, 3 H, CH_{Ar}), 7.77–7.82 (m, 2 H, CH_{Ar}), 8.03 (s, 1 H, CH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.4 (CH_3), 74.3 (OCH_2), 94.1 (*C*CN), 114.7 (CN), 128.5 ($2 \times CH_{Ar}$), 128.7 ($2 \times CH_{Ar}$), 133.1 (CH_{Ar}), 136.9 (C_{Ar}), 174.4 (CH), 187.9 (CO).

GC–MS (EI, 70 eV): *m/z* (%) = 201 (13) [M$^+$], 200 (14), 183 (2), 172 (19), 158 (2), 145 (3), 116 (3), 105 (100), 89 (5), 77 (43), 51 (13), 29 (7).

HRMS (EI): *m/z* [M$^+$] calcd for $C_{12}H_{11}O_2N$: 201.07843; found: 201.078326.

2-(4-Chlorobenzoyl)-3-ethoxyacrylonitrile (2c)

Starting with **1c** (2.00 g, 11.1 mmol) and $CH(OEt)_3$ (5.56 mL, 33.4 mmol), **2c** was isolated after recrystallization from EtOH.

Yield: 2.57 g (98%); pink crystals; mp 95–97 °C.

IR (KBr): 3026 (w), 2982 (w), 2937 (w), 2227 (m), 1921 (w), 1642 (m), 1594 (m), 1487 (m), 1394 (m), 1373 (w), 1354 (m), 1308 (m), 1258 (s), 1180 (m), 1157 (m), 1106 (m), 1090 (m), 1005 (m), 965 (w), 955 (m), 914 (m), 867 (m), 836 (m), 785 (m), 753 (s), 730 (m), 694 (m), 628 (w), 585 (m), 563 (m) cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.42 (t, ^3J = 7.2 Hz, 3 H, $OCH_2\mathit{CH}_3$), 4.36 (q, ^3J = 7.2 Hz, 2 H, $O\mathit{CH}_2CH_3$), 7.37–7.41 (m, 2 H, CH_{Ar}), 7.75–7.79 (m, 2 H, CH_{Ar}), 8.05 (s, 1 H, CH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.4 (CH_3), 73.6 (OCH_2), 92.7 (*C*CN), 113.6 (CN), 128.0 ($2 \times CH_{Ar}$), 129.2 ($2 \times CH_{Ar}$), 134.1, 138.5 (C_{Ar}), 173.8 (CH), 185.4 (CO).

GC–MS (EI, 70 eV): *m/z* (%) = 235 (13) [^{35}Cl; M$^+$], 234 (8) [^{37}Cl; M$^+$], 206 (14), 172 (8), 139 (100), 123 (3), 111 (31), 75 (17), 50 (5), 29 (8).

HRMS (EI): *m/z* [M$^+$] calcd for $C_{12}H_{10}O_2NCl$: 235.03946; found: 235.039090.

2-(4-Bromobenzoyl)-3-ethoxyacrylonitrile (2d)

Starting with **1d** (2.00 g, 8.9 mmol) and $CH(OEt)_3$ (4.46 mL, 26.8 mmol), **2d** was isolated after crystallization from EtOH.

Yield: 2.40 g (96%); pink crystals; mp 99–102 °C.

IR (KBr): 3073 (w), 3042 (w), 2920 (w), 2852 (w), 2221 (m), 1921 (w), 1621 (m), 1586 (m), 1537 (m), 1504 (m), 1483 (m), 1384 (m), 1317 (m), 1245 (m), 1184 (m), 1166 (m), 1116 (m), 1071 (m), 1021 (m), 1010 (m), 980 (m), 906 (m), 827 (s), 749 (s), 689 (m), 626 (m), 604 (m), 576 (m), 559 (m), 533 (m) cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.42 (t, ^3J = 7.1 Hz, 3 H, $OCH_2\mathit{CH}_3$), 4.36 (q, ^3J = 7.4 Hz, 2 H, $O\mathit{CH}_2CH_3$), 7.53–7.58 (m, 2 H, CH_{Ar}), 7.67–7.72 (m, 2 H, CH_{Ar}), 8.05 (s, 1 H, CH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.2 (CH_3), 74.4 (OCH_2), 93.5 (*C*CN), 114.4 (CN), 128.1 (C_{Ar}), 130.2 ($2 \times CH_{Ar}$), 131.9 ($2 \times CH_{Ar}$), 135.5 (C_{Ar}), 174.7 (CH), 186.5 (CO).

GC–MS (EI, 70 eV): *m/z* (%) = 281 (16) [^{81}Br; M$^+$], 279 (16) [^{79}Br; M$^+$], 278 (11), 252 (15), 238 (4), 225 (6), 200 (10), 185 (97), 183 (100), 172 (12), 157 (29), 155 (29), 143 (8), 115 (5), 96 (4), 76 (21), 68 (6), 50 (12), 29 (12).

HRMS (EI): *m/z* [M$^+$] calcd for $C_{12}H_{10}O_2NBr$: 278.98894; found: 278.988999.

3-Ethoxy-2-(4-methoxybenzoyl)acrylonitrile (2e)

Starting with **1e** (2.00 g, 11.4 mmol) and $CH(OEt)_3$ (5.70 mL, 34.3 mmol), **2e** was isolated after recrystallization from EtOH.

Yield: 2.50 g (95%); reddish-brown solid; mp 45–50 °C.

IR (KBr): 3066 (w), 2929 (w), 2844 (w), 2215 (m), 1911 (w), 1738 (w), 1682 (w), 1631 (m), 1597 (m), 1574 (m), 1556 (m), 1504 (m), 1462 (m), 1450 (m), 1423 (m), 1377 (m), 1308 (m), 1255 (s), 1167 (s), 1125 (m), 1022 (s), 974 (m), 960 (m), 838 (s), 812 (m), 800 (m), 751 (m), 700 (m), 632 (m), 605 (m), 541 (m), 531 (m) cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.41 (t, ^3J = 7.1 Hz, 3 H, $OCH_2\mathit{CH}_3$), 3.80 (s, 3 H, OCH_3), 4.33 (q, ^3J = 7.0 Hz, 2 H, $O\mathit{CH}_2CH_3$), 6.87–6.90 (m, 2 H, CH_{Ar}), 7.86–7.89 (m, 2 H, CH_{Ar}), 8.02 (s, 1 H, CH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.3 (CH_3), 55.6 (OCH_3), 74.0 (OCH_2), 93.6 (*C*CN), 113.8 ($2 \times CH_{Ar}$), 115.1 (CN), 131.3 ($2 \times CH_{Ar}$), 161.2, 163.7 (C_{Ar}), 174.0 (CH), 185.8 (CO).

GC–MS (EI, 70 eV): *m/z* (%) = 231 (23) [M$^+$], 216 (2), 202 (6), 188 (4), 174 (3), 160 (2), 136 (9), 135 (100), 107 (6), 92 (11), 77 (13), 64 (5), 50 (2).

HRMS (EI): *m/z* [M$^+$] calcd for $C_{13}H_{13}O_3N$: 231.08899; found: 231.089338.

Cyanosalicylates 4a–ac; General Procedure

To a stirred solution of **2a**–**e** in CH_2Cl_2 (2.0 mL/1.0 mmol of **2**), was added **3a**–**k** (1.1 mmol) and, subsequently, $TiCl_4$ (1.1 mmol) at –78 °C under an argon atmosphere. The temperature of the reaction mixture was allowed to rise to 20 °C during 14 h with stirring. To the solution was added HCl (10%, 20 mL) and the organic and the aqueous layer were separated. The latter was extracted with CH_2Cl_2 (3 × 20 mL) and the combined organic layers were dried (Na_2SO_4), filtered and the filtrate was concentrated in vacuo. The residue was purified by column chromatography (silica gel; heptanes–EtOAc) to give **4a**–**ac**.

Methyl 3-Cyano-6-hydroxy-2-methylbenzoate (4a)

Starting with **2a** (0.209 g, 1.5 mmol) and **3a** (0.430 g, 1.7 mmol), **4a** was isolated after chromatography (silica gel; heptanes–EtOAc).

Yield: 0.097 g (34%); yellow solid; mp 84–85 °C.

IR (KBr): 2957 (w), 2927 (w), 2854 (w), 2252 (w), 2222 (w), 1737 (w), 1669 (m), 1590 (m), 1469 (m), 1442 (m), 1385 (w), 1352 (m), 1323 (m), 1303 (m), 1224 (m), 1172 (w), 1135 (w), 1057 (w), 1019 (w), 940 (w), 910 (m), 835 (w), 811 (w), 773 (w), 731 (s), 649 (w), 606 (w), 562 (w) cm^{-1}.

^{1}H NMR (250 MHz, CDCl$_3$): δ = 2.71 (s, 3 H, CH$_3$), 3.95 (s, 3 H, OCH$_3$), 6.85 (d, ^3J = 8.9 Hz, 1 H, CH$_{Ar}$), 7.54 (d, ^3J = 8.9 Hz, 1 H, CH$_{Ar}$), 11.69 (s, 1 H, OH).

^{13}C NMR (75 MHz, CDCl$_3$): δ = 21.9 (CH$_3$), 52.9 (OCH$_3$), 105.9 (*C*CN), 113.4 (*C*COOCH$_3$), 117.0 (CH$_{Ar}$), 118.4 (CN), 137.8 (CH$_{Ar}$), 146.5 (C$_{Ar}$), 165.7 (COH), 171.1 (CO).

GC–MS (EI, 70 eV): *m*/*z* (%) = 191 (76) [M$^+$], 160 (68), 159 (100), 131 (55), 130 (48), 103 (21), 77 (21), 76 (15), 63 (4), 51 (11).

HRMS (EI): *m*/*z* [M$^+$] calcd for $C_{10}H_9O_3N$: 191.05769; found: 191.057322.

Ethyl 3-Cyano-6-hydroxy-2-methylbenzoate (4b)
Starting with **2a** (0.209 g, 1.5 mmol) and **3b** (0.446 g, 1.7 mmol), **4b** was isolated after chromatography (silica gel; heptanes–EtOAc).

Yield: 0.101 g (33%); white solid; mp 86–87 °C.

IR (KBr): 3072 (w), 2991 (w), 2923 (w), 2851 (w), 2777 (w), 2692 (w), 2589 (w), 2224 (w), 1660 (s), 1588 (m), 1570 (w), 1476 (m), 1450 (w), 1398 (m), 1375 (s), 1348 (m), 1318(m), 1302 (m), 1231 (s), 1182 (w), 1146 (m), 1108 (w), 1057 (w), 1021 (m), 996 (w), 909 (w), 856 (m), 831 (m), 723 (w), 632 (w), 609 (w), 558 (w) cm^{-1}.

^{1}H NMR (250 MHz, CDCl$_3$): δ = 1.39 (t, ^3J = 7.0 Hz, 3 H, OCH$_2$C*H*$_3$), 2.72 (s, 3 H, CH$_3$), 4.42 (q, ^3J = 7.3 Hz, 2 H, OC*H*$_2$CH$_3$), 6.84 (d, ^3J = 8.8 Hz, 1 H, CH), 7.53 (d, ^3J = 8.9 Hz, 1 H, CH), 11.78 (s, 1 H, OH).

^{13}C NMR (75 MHz, CDCl$_3$): δ = 13.1 (CH$_3$), 20.8 (OCH$_2$*C*H$_3$), 61.7 (OCH$_2$), 104.8 (*C*CN), 112.6 (*C*COOCH$_2$CH$_3$), 116.0 (CH), 117.4 (CN), 136.7 (CH), 145.5 (*C*CH$_3$), 164.8 (*C*OH), 169.62 (CO).

GC–MS (70 eV): *m*/*z* (%) = 205 (26) [M$^+$], 159 (100), 130 (22), 103 (8), 77 (12), 51 (6).

HRMS (EI): *m*/*z* [M$^+$] calcd for $C_{11}H_{11}O_3N$: 205.07334; found: 205.073572.

Methyl 3-Cyano-6-hydroxy-2,5-dimethylbenzoate (4c)
Starting with **2a** (0.208 g, 1.5 mmol) and **3c** (0.457 g, 1.7 mmol), **4c** was isolated after chromatography (silica gel; heptanes–EtOAc).

Yield: 0.107 g (35%); white solid; mp 134–136 °C.

IR (KBr): 2990 (w), 2956 (w), 2926 (w), 2851 (w), 2217 (m), 1667 (s), 1605 (m), 1592 (m), 1580 (m), 1444 (s), 1413 (m), 1377 (m), 1334 (s), 1264 (s), 1199 (s), 1166 (s), 1077 (m), 1019 (m), 979 (m), 910 (m), 889 (m), 803 (s), 770 (m), 688 (m), 659 (m).

^{1}H NMR (250 MHz, CDCl$_3$): δ = 2.15 (s, 3 H, CH$_3$), 2.66 (s, 3 H, CH$_3$), 3.93 (s, 3 H, OCH$_3$), 7.40 (s, 1 H, CH$_{Ar}$), 11.99 (s, 1 H, OH).

^{13}C NMR (75 MHz, CDCl$_3$): δ = 15.6, 21.6 (CH$_3$), 52.6 (OCH$_3$), 104.9 (*C*CN), 112.7 (*C*COOCH$_3$), 118.7 (CN), 126.5 (C$_{Ar}$), 138.2 (CH$_{Ar}$), 143.7 (C$_{Ar}$), 164.5 (COH), 171.6 (CO).

GC–MS (EI, 70 eV): *m*/*z* (%) = 205 (37) [M$^+$], 174 (25), 173 (100), 145 (90), 144 (20), 116 (19), 91 (11), 90 (14), 89 (19).

HRMS (EI): *m*/*z* [M$^+$] calcd for $C_{11}H_{11}O_3N$: 205.07334; found: 205.073468.

Ethyl 3-Cyano-5-ethyl-6-hydroxy-2-methylbenzoate (4d)
Starting with **2a** (0.209 g, 1.5 mmol) and **3d** (0.498 g, 1.7 mmol), **4d** was isolated after chromatography (silica gel; heptanes–EtOAc).

Yield: 0.119 g (34%); white solid; mp 72–73 °C.

IR (KBr): 2975 (w), 2933 (w), 2221 (w), 1658 (m), 1610 (w), 1577 (w), 1559 (w), 1541 (w), 1507 (w), 1437 (m), 1398 (w), 1376 (m), 1352 (w), 1325 (m), 1293 (w), 1265 (w), 1244 (m), 1188 (s), 1086 (w), 1019 (w), 909 (m), 874 (w), 811 (w), 733 (s), 686 (w), 667 (w), 649 (w) cm^{-1}.

^{1}H NMR (250 MHz, CDCl$_3$): δ = 1.14 (t, ^3J = 8.1 Hz, 3 H, CH$_3$), 1.38 (t, ^3J = 6.9 Hz, 3 H, OCH$_2$C*H*$_3$), 3.43 (q, ^3J = 8.1 Hz, 2 H, CH$_2$), 2.68 (s, 3 H, CH$_3$), 4.41 (q, ^3J = 6.3 Hz, 2 H, OC*H*$_2$CH$_3$), 7.40 (s, 1 H, CH$_{Ar}$), 12.10 (s, 1 H, OH).

^{13}C NMR (75 MHz, CDCl$_3$): δ = 12.1, 13.2, 20.5 (CH$_3$), 21.6 (CH$_2$), 61.6 (OCH$_2$), 104.0 (*C*CN), 111.9 (*C*COOCH$_2$CH$_3$), 118.0 (CN), 130.9 (C$_{Ar}$), 135.4 (CH$_{Ar}$), 142.7 (C$_{Ar}$), 163.1 (COH), 170.3 (CO).

GC–MS (EI, 70 eV): *m*/*z* (%) = 233 (28) [M$^+$], 187 (60), 172 (9), 159 (100), 144 (7), 130 (7), 116 (8), 103 (7), 89 (9), 77 (8), 51 (3), 29 (5).

HRMS (EI): *m*/*z* [M$^+$] calcd for $C_{13}H_{15}O_3N$: 233.10464; found: 233.104263.

Methyl 3-Butyl-5-cyano-2-hydroxy-6-methylbenzoate (4e)
Starting with **2a** (0.209 g, 1.5 mmol) and **3e** (0.522 g, 1.7 mmol), **4e** was isolated after chromatography (silica gel; heptanes–EtOAc).

Yield: 0.130 g (35%); slightly yellowish oil.

IR (KBr): 2957 (m), 2931 (m), 2862 (w), 2222 (m), 1717 (w), 1666 (s), 1609 (w), 1577 (w), 1559 (w), 1541 (w), 1507 (w), 1456 (m), 1438 (m), 1384 (w), 1354 (m), 1338 (m), 1299 (m), 1262 (w), 1234 (w), 1203 (m), 1171 (m), 1105 (w), 1077 (w), 988 (w), 911 (w), 812 (m), 772 (w), 733 (m), 695 (w), 649 (w) cm^{-1}.

^{1}H NMR (250 MHz, CDCl$_3$): δ = 0.86 [t, ^3J = 7.3 Hz, 3 H, (CH$_2$)$_3$C*H*$_3$], 1.24–1.33 (m, 2 H, CH$_2$), 1.45–1.52 (m, 2 H, CH$_2$), 2.54 (t, ^3J = 7.3 Hz, 2 H, CH$_2$), 2.65 (s, 3 H, CH$_3$), 3.93 (s, 3 H, OCH$_3$), 7.38 (s, 1 H, CH$_{Ar}$), 11.98 (s, 1 H, OH).

^{13}C NMR (75 MHz, CDCl$_3$): δ = 13.1, 20.6 (CH$_3$), 21.6, 28.3, 30.2 (CH$_2$), 52.0 (OCH$_3$), 104.1 (*C*CN), 112.0 (*C*COOCH$_3$), 118.0 (CN), 129.9 (C$_{Ar}$), 136.3 (CH$_{Ar}$), 143.0 (C$_{Ar}$), 163.2 (*C*OH), 170.9 (CO).

GC–MS (EI, 70 eV): *m*/*z* (%) = 247 (32) [M$^+$], 215 (29), 198 (16), 186 (19), 173 (100), 159 (3), 145 (36), 130 (5), 116 (11), 103 (6), 89 (19), 77 (6), 63 (4), 51 (3), 39 (5), 29 (3).

HRMS (EI): *m*/*z* [M$^+$] calcd for $C_{14}H_{17}O_3N$: 247.12029; found: 247.119876.

Methyl 3-Cyano-5-hexyl-6-hydroxy-2-methylbenzoate (4f)
Starting with **2a** (0.208 g, 1.5 mmol) and **3f** (0.568 g, 1.7 mmol), **4f** was isolated after chromatography (silica gel; heptanes–EtOAc).

Yield: 0.173 g (42%); yellowish oil.

IR (KBr): 2955 (m), 2927 (m), 2856 (w), 2221 (w), 1665 (m), 1608 (w), 1579 (w), 1438 (m), 1334 (m), 1245 (w), 1201 (m), 1170 (m), 1077 (w), 989 (w), 908 (m), 812 (w), 731 (s), 649 (w) cm^{-1}.

^{1}H NMR (250 MHz, CDCl$_3$): δ = 0.67 [t, ^3J = 7.4 Hz, 3 H, (CH$_2$)$_5$C*H*$_3$], 1.06–1.13 (m, 6 H, 3 × CH$_2$), 1.31–1.42 (m, 2 H, CH$_2$), 2.39 (t, ^3J = 7.5 Hz, 2 H, CH$_2$), 2.52 (s, 3 H, CH$_3$), 3.79 (s, 3 H, OCH$_3$), 7.25 (s, 1 H, CH$_{Ar}$), 11.83 (s, 1 H, OH).

^{13}C NMR (75 MHz, CDCl$_3$): δ = 13.9, 21.6 (CH$_3$), 22.6, 28.7, 29.0, 29.4, 31.6 (CH$_2$), 52.8 (OCH$_3$), 104.9 (*C*CN), 112.7 (*C*COOCH$_3$), 118.7 (CN), 130.7 (C$_{Ar}$), 137.2 (CH$_{Ar}$), 143.5 (C$_{Ar}$), 164.0 (COH), 171.6 (CO).

GC–MS (EI, 70 eV): *m*/*z* (%) = 275 (37) [M$^+$], 244 (12), 243 (29), 226 (13), 215 (15), 214 (33), 200 (13), 187 (13), 186 (22), 174 (20), 173 (100), 145 (36), 144 (15), 116 (11), 89 (19) cm^{-1}.

HRMS (EI): *m*/*z* [M$^+$] calcd for $C_{16}H_{21}NO_3$: 275.15160; found: 275.151528.

Methyl 3-Cyano-5-heptyl-6-hydroxy-2-methylbenzoate (4g)
Starting with **2a** (0.209 g, 1.5 mmol) and **3g** (0.420 g, 1.7 mmol), **4g** was isolated after chromatography (silica gel; heptane–EtOAc).

Yield: 0.148 g (34%); yellow oil.

IR (KBr): 2955 (m), 2926 (m), 2855 (m), 2222 (w), 1665 (m), 1609 (w), 1579 (w), 1438 (m), 1384 (w), 1354 (m), 1335 (m), 1262 (w), 1238 (w), 1202 (m), 1171 (m), 1122 (w), 1077 (w), 988 (w), 908 (m), 812 (w), 772 (w), 732 (m), 696 (w), 649 (w) cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.81 [t, ^3J = 6.7 Hz, 3 H, $(CH_2)_6CH_3$], 1.21–1.25 (m, 8 H, 4 × CH_2), 1.48–1.55 (m, 2 H, CH_2), 2.54 (t, ^3J = 7.4 Hz, 2 H, CH_2), 2.67 (s, 3 H, CH_3), 3.94 (s, 3 H, OCH_3), 7.39 (s, 1 H, CH_{Ar}), 11.98 (s, 1 H, OH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1, 21.6 (CH_3), 22.7, 28.9, 29.1, 29.3, 29.5, 31.8 (CH_2), 52.9 (OCH_3), 104.9 (*C*CN), 112.8 (*C*$COOCH_3$), 118.8 (CN), 130.7 (C_{Ar}), 137.1 (CH_{Ar}), 143.6 (C_{Ar}), 164.0 (COH), 171.7 (CO).

GC–MS (EI, 70 eV): *m/z* (%) = 289 (38) [M$^+$], 257 (29), 240 (12), 214 (33), 200 (11), 186 (21), 173 (100), 159 (9), 145 (34), 130 (5), 116 (12), 103 (6), 89 (19), 77 (6), 55 (4), 41 (11).

HRMS (EI): *m/z* [M$^+$] calcd for $C_{17}H_{23}O_3N$: 289.17507; found: 289.17512.

Ethyl 6-Cyano-3-hydroxybiphenyl-2-carboxylate (4h)

Starting with **2b** (0.302 g, 1.5 mmol) and **3b** (0.446 g, 1.7 mmol), **4h** was isolated after chromatography (silica gel; heptanes–EtOAc).

Yield: 0.180 g (45%); yellow solid; mp 122–124 °C.

IR (KBr): 3061 (w), 2984 (w), 2939 (w), 2227 (w), 1730 (w), 1668 (m), 1584 (m), 1548 (w), 1462 (m), 1444 (m), 1400 (w), 1376 (m), 1324 (m), 1222 (s), 1140 (w), 1097 (w), 1075 (w), 1013 (w), 910 (w), 836 (w), 759 (m), 731 (m), 716 (m), 699 (m), 645 (w), 598 (w), 550 (w) cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.64 (t, ^3J = 8.3 Hz, 3 H, OCH_2CH_3), 3.89 (q, ^3J = 7.0 Hz, 2 H, OCH_2CH_3), 7.01 (d, ^3J = 8.2 Hz, 1 H, CH_{Ar}), 7.14–7.19 (m, 2 H, CH_{Ph}), 7.34–7.37 (m, 3 H, CH_{Ph}), 7.64 (d, ^3J = 8.6 Hz, 1 H, CH_{Ar}), 11.47 (s, 1 H, OH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.8 (CH_3), 61.9 (OCH_2), 105.7 (*C*CN), 113.5 (*C*COOEt), 117.7 (CN), 118.1 (CH_{Ar}), 128.0 (3 × CH_{Ph}), 128.3 (2 × CH_{Ph}), 137.4 (CH_{Ar}), 138.9, 149.6 (C_{Ar}), 164.7 (COH), 169.9 (CO).

GC–MS (EI, 70 eV): *m/z* (%) = 267 (34) [M$^+$], 221 (100), 193 (41), 164 (21), 139 (11), 114 (3), 88 (2), 63 (3).

HRMS (EI): *m/z* [M$^+$] calcd for $C_{16}H_{13}O_3N$: 267.08899; found: 267.088732.

Methyl 6-Cyano-3-hydroxy-4-methylbiphenyl-2-carboxylate (4i)

Starting with **2b** (0.302 g, 1.5 mmol) and **3c** (0.457 g, 1.65 mmol), the product was isolated after chromatography (silica gel; heptanes–EtOAc).

Yield: 0.172 g (43%); light-yellowish solid; mp 105–107 °C.

IR (KBr): 3071 (w), 3027 (w), 2954 (w), 2924 (w), 2217 (w), 1722 (m), 1673 (m), 1594 (w), 1566 (w), 1461 (m), 1434 (s), 1377 (m), 1322 (s), 1259 (m), 1241 (m), 1162 (m), 1076 (m), 1022 (m), 983 (m), 848 (m), 809 (s), 757 (s), 702 (s), 677 (m), 552 (m) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.24 (s, 3 H, CH_3), 3.37 (s, 3 H, OCH_3), 7.12–7.17 (m, 2 H, CH_{Ph}), 7.30–7.35 (m, 3 H, CH_{Ph}), 7.51 (s, 1 H, CH_{Ar}), 11.53 (s, 1 H, OH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.7 (CH_3), 52.2 (OCH_3), 104.9 (*C*CN), 112.6 (*C*$COOCH_3$), 118.2 (CN), 127.6 (C_{Ar}), 127.9 (2 × CH_{Ph}), 128.1 (3 × CH_{Ph}), 137.9 (CH_{Ar}), 138.9, 147.2 (C_{Ar}), 163.1 (COH), 170.6 (CO).

GC–MS (EI, 70 eV): *m/z* (%) = 267 (32) [M$^+$], 236 (19), 235 (100), 234 (15), 207 (12), 206 (16), 179 (10), 178 (14), 151 (10), 76 (7).

HRMS (EI): *m/z* [M$^+$] calcd for $C_{16}H_{13}O_3N$: 267.08899; found: 267.088902.

Ethyl 6-Cyano-4-ethyl-3-hydroxybiphenyl-2-carboxylate (4j)

Starting with **2b** (0.302 g, 1.5 mmol) and **3d** (0.498 g, 1.7 mmol), **4j** was isolated after chromatography (silica gel; heptanes–EtOAc).

Yield: 0.186 g (42%); yellow crystalline solid; mp 47–48 °C.

IR (KBr): 3061 (w), 2972 (w), 2937 (w), 2877 (w), 2252 (w), 2226 (w), 1663 (s), 1601 (w), 1567 (w), 1445 (m), 1424 (m), 1401 (m), 1376 (m), 1329 (m), 1306 (m), 1269 (w), 1242 (m), 1196 (s), 1147 (m), 1113 (w), 1096 (w), 1067 (w), 1021 (w), 909 (m), 841 (w), 819 (m), 762 (m), 732 (s), 701 (m), 649 (w), 549 (w) cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.58 (t, ^3J = 7.4 Hz, 3 H, CH_2CH_3), 1.15 (t, ^3J = 7.4 Hz, 3 H, OCH_2CH_3), 2.61 (q, ^3J = 7.2 Hz, 2 H, CH_2CH_3), 3.83 (q, ^3J = 6.9 Hz, 2 H, OCH_2CH_3), 7.08–7.11 (m, 2 H, CH_{Ph}), 7.25–7.29 (m, 3 H, CH_{Ph}), 7.46 (s, 1 H, CH_{Ar}), 11.65 (s, 1 H, OH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.8, 13.1 (CH_3), 22.7 (CH_2), 61.6 (OCH_2), 105.1 (*C*CN), 112.8 (*C*COOEt), 118.2 (CN), 127.9 (2 × CH_{Ph}), 128.0 (CH_{Ph}), 128.2 (2 × CH_{Ph}), 133.4 (C_{Ar}), 136.1 (CH_{Ar}), 139.2, 146.9 (C_{Ar}), 162.9 (COH), 170.2 (CO).

GC–MS (EI, 70 eV): *m/z* (%) = 295 (48) [M$^+$], 249 (59), 231 (100), 220 (12), 203 (21), 190 (9), 177 (14), 165 (12), 151 (13), 139 (4), 102 (2), 77 (3), 51 (2).

HRMS (EI): *m/z* [M$^+$] calcd for $C_{18}H_{17}O_3N$: 295.12029; found: 295.120225.

Methyl 4-Butyl-6-cyano-3-hydroxybiphenyl-2-carboxylate (4k)

Starting with **2b** (0.302 g, 1.5 mmol) and **3e** (0.522 g, 1.7 mmol), **4k** was isolated after chromatography (silica gel; heptanes–EtOAc).

Yield: 0.190 g (41%); slightly yellow viscous oil.

IR (KBr): 2954 (w), 2920 (w), 2223 (w), 1742 (w), 1663 (m), 1593 (w), 1565 (w), 1494 (w), 1435 (s), 1333 (m), 1314 (m), 1261 (m), 1205 (s), 1170 (m), 1074 (w), 1029 (w), 985 (w), 856 (w), 815 (m), 759 (s), 699 (s), 658 (m), 549 (m) cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.86 [t, ^3J = 7.5 Hz, 3 H, $(CH_2)_3CH_3$], 1.26–1.35 (m, 2 H, CH_2), 1.46–1.55 (m, 2 H, CH_2), 2.59 (t, ^3J = 7.9 Hz, 2 H, CH_2), 3.33 (s, 3 H, OCH_3), 7.08–7.13 (m, 2 H, CH_{Ph}), 7.27–7.31 (m, 3 H, CH_{Ph}), 8.46 (s, 1 H, CH_{Ar}), 11.45 (s, 1 H, OH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.9 (CH_3), 22.5, 29.2, 31.2 (CH_2), 52.2 (OCH_3), 105.2 (*C*CN), 112.7 (*C*$COOCH_3$), 118.1 (CN), 127.9 (2 × CH_{Ph}), 128.1 (3 × CH_{Ph}), 132.1 (C_{Ar}), 137.0 (CH_{Ar}), 139.1, 146.6 (C_{Ar}), 163.0 (COH), 170.9 (CO).

GC–MS (EI, 70 eV): *m/z* (%) = 309 (40) [M$^+$], 277 (27), 259 (18), 244 (10), 236 (17), 235 (100), 234 (35), 221 (8), 206 (10), 178 (11), 177 (15), 151 (18).

HRMS (EI): *m/z* [M$^+$] calcd for $C_{19}H_{19}O_3N$: 309.13594; found: 309.135859.

Methyl 6-Cyano-4-heptyl-3-hydroxybiphenyl-2-carboxylate (4l)

Starting with **2b** (0.302 g, 1.5 mmol) and **3g** (0.591 g, 1.7 mmol), **4l** was isolated after chromatography (silica gel; heptanes–EtOAc).

Yield: 0.221 g (42%); light yellowish oil.

IR (neat): 2952 (w), 2924 (m), 2854 (w), 2223 (w), 1745 (w), 1664 (m), 1599 (w), 1566 (w), 1439 (m), 1335 (m), 1234 (m), 1204 (s), 1146 (m), 1074 (w), 990 (w), 897 (w), 815 (m), 760 (s), 724 (w), 699 (s), 549 (w) cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.82 [t, ^3J = 7.6 Hz, 3 H, $(CH_2)_6CH_3$], 1.26–1.35 (m, 8 H, 4 × CH_2), 1.51–1.61 (m, 2 H, CH_2), 2.62 (t, ^3J = 7.6 Hz, 2 H, CH_2), 3.37 (s, 3 H, OCH_3), 7.12–7.17 (m, 2 H, CH_{Ph}), 7.30–7.36 (m, 3 H, CH_{Ph}), 7.49 (s, 1 H, CH_{Ar}), 11.49 (s, 1 H, OH).

^{13}C NMR (75 MHz, CDCl$_3$): δ = 14.0 (CH$_3$), 22.6, 28.9, 29.1, 29.4, 29.5, 31.8 (CH$_2$), 52.2 (OCH$_3$), 104.9 (*C*CN), 112.7 (*C*COOCH$_3$), 118.1 (CN), 127.9 (2 × CH$_{Ph}$), 128.1 (3 × CH$_{Ph}$), 132.1 (C$_{Ar}$), 137.1 (CH$_{Ar}$), 139.1, 147.0 (C$_{Ar}$), 162.9 (COH), 170.8 (CO).

GC–MS (EI, 70 eV): *m/z* (%) = 351 (39) [M$^+$], 320 (9), 319 (32), 236 (23), 235 (100), 234 (45), 231 (9), 219 (13), 206 (10), 178 (10), 177 (13), 151 (15), 41 (7).

HRMS (EI): *m/z* [M$^+$] calcd for C$_{22}$H$_{25}$O$_3$N: 351.18290; found: 351.183058.

Methyl 6-Cyano-3-hydroxy-4-octylbiphenyl-2-carboxylate (4m)

Starting with **2b** (0.302 g, 1.5 mmol) and **3h** (0.614 g, 1.7 mmol), **4m** was isolated after chromatography (silica gel; heptanes–EtOAc).

Yield: 0.219 g (40%); yellowish oil.

IR (neat): 2952 (w), 2923 (m), 2853 (m), 2224 (w), 1749 (w), 1665 (m), 1600 (w), 1567 (w), 1436 (m), 1335 (m), 1234 (m), 1205 (s), 1146 (m), 1074 (w), 999 (w), 907 (w), 816 (m), 760 (s), 727 (w), 700 (s), 549 (w) cm^{-1}.

^{1}H NMR (250 MHz, CDCl$_3$): δ = 0.83 [t, ^3J = 7.5 Hz, 3 H, (CH$_2$)$_7$C*H*$_3$], 1.06–1.08 (m, 10 H, 5 × CH$_2$), 1.52–1.62 (m, 2 H, CH$_2$), 2.50 (t, ^3J = 7.3 Hz, 2 H, CH$_2$), 3.46 (s, 3 H, OCH$_3$), 7.13–7.18 (m, 2 H, CH$_{Ph}$), 7.31–7.37 (m, 3 H, CH$_{Ph}$), 7.50 (s, 1 H, CH$_{Ar}$), 11.50 (s, 1 H, OH).

^{13}C NMR (75 MHz, CDCl$_3$): δ = 14.0 (CH$_3$), 22.6, 28.8, 29.2, 29.3, 29.4, 29.5, 31.8 (CH$_2$), 52.2 (OCH$_3$), 105.0 (*C*CN), 112.7 (*C*COOCH$_3$), 118.1 (CN), 127.9 (2 × CH$_{Ph}$), 128.1 (3 × CH$_{Ph}$), 132.1 (C$_{Ar}$), 137.0 (CH$_{Ar}$), 139.0, 147.0 (C$_{Ar}$), 162.9 (COH), 170.9 (CO).

GC–MS (EI, 70 eV): *m/z* (%) = 365 (21) [M$^+$], 333 (29), 236 (26), 235 (100), 234 (47), 231 (13), 222 (11), 221 (10), 219 (24), 218 (12), 207 (15), 206 (18), 190 (11), 179 (11), 178 (17), 177 (18), 152 (12), 151 (25), 129 (20), 116 (39), 101 (12), 98 (10), 97 (11), 85 (11), 81 (9), 71 (20), 69 (32), 57 (42), 55 (34).

HRMS (EI): *m/z* [M$^+$] calcd for C$_{23}$H$_{27}$O$_3$N: 365.19885; found: 365.198427.

Methyl 6-Cyano-3-hydroxy-4-(4-chlorophenyl)biphenyl-2-carboxylate (4n)

Starting with **2b** (0.302 g, 1.5 mmol) and **3k** (0.612 g, 1.7 mmol), **4n** was isolated after chromatography (silica gel; heptanes–EtOAc).

Yield: 0.240 g (44%); yellow solid; mp 149–151 °C.

IR (KBr): 3086 (w), 3061 (w), 3027 (w), 2954 (w), 2929 (w), 2852 (w), 2252 (w), 2226 (w), 1737 (w), 1667 (m), 1593 (w), 1553 (w), 1493 (w), 1437 (m), 1393 (m), 1330 (m), 1249 (w), 1208 (m), 1182 (m), 1094 (m), 1081 (w), 1031 (w), 1015 (w), 987 (w), 909 (m), 834 (m), 764 (m), 732 (s), 704 (m), 661 (w), 650 (w), 544 (w) cm^{-1}.

^{1}H NMR (250 MHz, CDCl$_3$): δ = 3.40 (s, 3 H, OCH$_3$), 7.17–7.23 (m, 2 H, CH$_{Ph}$), 7.28–7.47 (m, 7 H, CH$_{ClPh,Ph}$), 7.67 (s, 1 H, CH$_{Ar}$), 11.73 (s, 1 H, OH).

^{13}C NMR (75 MHz, CDCl$_3$): δ = 53.6 (OCH$_3$), 106.9 (*C*CN), 114.9 (*C*COOCH$_3$), 118.6 (CN), 128.9 (2 × CH$_{Ph}$), 129.0 (2 × CH$_{Ph}$), 129.3 (CH$_{Ph}$), 129.6 (2 × CH$_{ClPh}$), 130.7 (C$_{Ar}$), 131.5 (2 × CH$_{ClPh}$), 134.4, 135.3 (C$_{Ar}$), 138.7 (CH$_{Ar}$), 139.4, 149.5 (C$_{Ar}$), 162.7 (COH), 171.7 (CO).

MS (ESI+): *m/z* [M + H]$^+$ calcd for C$_{21}$H$_{15}$ClNO$_3$: 364.0735; found: 364.07353.

MS (ESI+): *m/z* [M + Na]$^+$ calcd for C$_{21}$H$_{14}$ClNNaO$_3$: 386.05544; found: 386.05531.

Methyl 4′-Chloro-6-cyano-3-hydroxy-4-methylbiphenyl-2-carboxylate (4o)

Starting with **2c** (0.353 g, 1.5 mmol) and **3c** (0.457 g, 1.7 mmol), **4o** was isolated after chromatography (silica gel; heptanes–EtOAc).

Yield: 0.275 g (61%); white solid; mp 167–169 °C.

IR (KBr): 3034 (w), 2958 (w), 2848 (w), 2227 (w), 1932 (w), 1837 (w), 1667 (m), 1597 (m), 1557 (w), 1500 (w), 1435 (m), 1353 (m), 1332 (s), 1268 (m), 1203 (m), 1169 (m), 1147 (m), 1042 (w), 1017 (m), 981 (m), 902 (w), 868 (w), 809 (s), 771 (m), 659 (w), 613 (m), 548 (m) cm^{-1}.

^{1}H NMR (250 MHz, CDCl$_3$): δ = 2.24 (s, 3 H, CH$_3$), 3.42 (s, 3 H, OCH$_3$), 7.06–7.10 (m, 2 H, CH$_{ClPh}$), 7.31–7.35 (m, 2 H, CH$_{ClPh}$), 7.51 (s, 1 H, CH$_{Ar}$), 11.61 (s, 1 H, OH).

^{13}C NMR (75 MHz, CDCl$_3$): δ = 14.7 (CH$_3$), 51.4 (OCH$_3$), 103.9 (*C*CN), 111.3 (*C*COOCH$_3$), 116.8 (CN), 127.2 (C$_{Ar}$), 127.9 (2 × CH$_{ClPh}$), 128.5 (2 × CH$_{ClPh}$), 133.2, 136.3 (C$_{Ar}$), 136.6 (CH$_{Ar}$), 144.7 (C$_{Ar}$), 162.4 (COH), 169.4 (CO).

GC–MS (EI, 70 eV): *m/z* (%) = 303 (11) [^{37}Cl; M$^+$], 301 (31) [^{35}Cl; M$^+$], 271 (21), 270 (13), 269 (61), 235 (17), 234 (100), 178 (9), 177 (14), 151 (11).

HRMS (EI): *m/z* [M$^+$] calcd for C$_{16}$H$_{12}$O$_3$ClN: 301.5002; found: 301.050144.

Ethyl 4′-Chloro-6-cyano-4-ethyl-3-hydroxybiphenyl-2-carboxylate (4p)

Starting with **2c** (0.353 g, 1.5 mmol) and **3d** (0.499 g, 1.7 mmol), **4p** was isolated after chromatography (silica gel; heptanes–EtOAc).

Yield: 0.306 g (62%); light-yellow solid; mp 165–167 °C.

IR (KBr): 2978 (w), 2876 (w), 2227 (w), 1910 (w), 1654 (m), 1568 (w), 1498 (m), 1444 (m), 1420 (m), 1374 (m), 1326 (s), 1274 (w), 1223 (m), 1194 (s), 1142 (m), 1111 (w), 1006 (m), 948 (w), 906 (w), 808 (s), 775 (m), 665 (w), 605 (m), 547 (m) cm^{-1}.

^{1}H NMR (250 MHz, CDCl$_3$): δ = 0.71 (t, ^3J = 6.7 Hz, 3 H, CH$_2$C*H*$_3$), 1.19 (t, ^3J = 7.4 Hz, 3 H, OCH$_2$C*H*$_3$), 2.65 (q, ^3J = 7.4 Hz, 2 H, C*H*$_2$CH$_3$), 3.92 (q, ^3J = 7.4 Hz, 2 H, OC*H*$_2$CH$_3$), 7.07–7.11 (m, 2 H, CH$_{ClPh}$), 7.31–7.34 (m, 2 H, CH$_{ClPh}$), 7.50 (s, 1 H, CH$_{Ar}$), 11.77 (s, 1 H, OH).

^{13}C NMR (75 MHz, CDCl$_3$): δ = 12.9, 13.1 (CH$_3$), 22.7, 62.0 (CH$_2$), 104.9 (*C*CN), 112.5 (*C*COOEt), 117.9 (CN), 128.2 (2 × CH$_{ClPh}$), 129.6 (2 × CH$_{ClPh}$), 133.8, 134.2 (C$_{Ar}$), 136.1 (CH$_{Ar}$), 137.7, 145.7 (C$_{Ar}$), 163.0 (COH), 170.0 (CO).

GC–MS (EI, 70 eV): *m/z* (%) = 331 (9) [^{37}Cl; M$^+$], 329 (26) [^{35}Cl; M$^+$], 285 (12), 283 (35), 249 (18), 248 (100), 177 (11).

HRMS (EI): *m/z* [M$^+$] calcd for C$_{18}$H$_{16}$O$_3$ClN: 329.08183; found: 329.081140.

Methyl 4′-Chloro-6-cyano-4-hexyl-3-hydroxybiphenyl-2-carboxylate (4q)

Starting with **2c** (0.353 g, 1.5 mmol) and **3f** (0.568 g, 1.7 mmol), **4q** was isolated after chromatography (silica gel; heptanes–EtOAc).

Yield: 0.357 g (64%); white solid; mp 45–46 °C.

IR (KBr): 2955 (w), 2929 (w), 2857 (w), 2225 (w), 1668 (m), 1601 (w), 1575 (w), 1496 (w), 1439 (m), 1397 (w), 1345 (m), 1207 (m), 1171 (w), 1148 (w), 1091 (w), 908 (m), 825 (w), 732 (s), 649 (w) cm^{-1}.

^{1}H NMR (300 MHz, CDCl$_3$): δ = 0.82 [t, ^3J = 7.5 Hz, 3 H, (CH$_2$)$_5$C*H*$_3$], 1.18–1.32 (m, 6 H, 3 × CH$_2$), 1.50–1.57 (m, 2 H, CH$_2$), 2.62 (t, ^3J = 7.6 Hz, 2 H, CH$_2$), 3.42 (s, 3 H, OCH$_3$), 7.07–7.10 (m, 2 H, 2 × CH$_{Ph}$), 7.31–7.35 (m, 2 H, 2 × CH$_{Ph}$), 7.49 (s, 1 H, CH$_{Ar}$), 11.59 (s, 1 H, OH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.1 (CH_3), 21.6, 27.8, 28.1, 28.6, 30.7 (CH_2), 51.5 (OCH_3), 103.9 (*C*CN), 111.5 (*C*$COOCH_3$), 116.9 (CN), 127.3 (2 × CH_{Ph}), 128.6 (2 × CH_{Ph}), 131.7, 133.3 (C_{Ar}), 136.0 (CH_{Ar}), 136.4, 144.5 (C_{Ar}), 162.0 (COH), 169.5 (CO).

GC–MS (EI, 70 eV): *m*/*z* (%) = 371 (23) [M^+], 304 (39), 268 (18), 235 (18), 234 (100), 177 (16).

HRMS (EI): *m*/*z* [M^+] calcd for $C_{21}H_{22}O_3NCl$: 371.12827; found: 371.127801.

Methyl 4′-Chloro-6-cyano-3-hydroxy-4-octylbiphenyl-2-carboxylate (4r)

Starting with **2c** (0.353 g, 1.5 mmol) and **3h** (0.614 g, 1.7 mmol), **4r** was isolated after chromatography (silica gel; heptanes–EtOAc).

Yield: 0.354 g (59%); pale-yellow solid; mp 68–71 °C.

IR (KBr): 2953 (w), 2925 (m), 2854 (w), 2224 (w), 1666 (m), 1600 (w), 1576 (w), 1496 (w), 1438 (m), 1397 (m), 1342 (m), 1341 (m), 1259 (w), 1206 (m), 1172 (m), 1091 (m), 1016 (w), 990 (w), 906 (m), 816 (w), 730 (s), 649 (w) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.81 [t, $^3J = 7.4$ Hz, 3 H, $(CH_2)_7CH_3$], 1.17–1.34 (m, 10 H, 5 × CH_2), 1.49–1.58 (m, 2 H, CH_2), 2.61 (t, $^3J = 7.4$ Hz, 2 H, CH_2), 3.42 (s, 3 H, OCH_3), 7.06–7.12 (m, 2 H, 2 × CH_{Ph}), 7.31–7.35 (m, 2 H, 2 × CH_{Ph}), 7.51 (s, 1 H, CH_{Ar}), 11.59 (s, 1 H, OH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1 (CH_3), 22.6, 28.8, 29.2, 29.3, 29.4, 29.6, 31.9 (CH_2), 52.5 (OCH_3), 104.9 (*C*CN), 112.5 (*C*$COOCH_3$), 117.9 (CN), 128.3 (2 × CH_{Ph}), 129.5 (2 × CH_{Ph}), 132.7, 134.1 (C_{Ar}), 137.0 (CH_{Ar}), 137.4, 145.5 (C_{Ar}), 163.2 (COH), 170.6 (CO).

GC–MS (EI, 70 eV): *m*/*z* (%) = 399 (22) [M^+], 332 (38), 270 (10), 268 (21), 235 (18), 234 (100), 177 (15).

HRMS (EI): *m*/*z* [M^+] calcd for $C_{23}H_{26}O_3NCl$: 399.15957; found: 399.159574.

Methyl 4′-Chloro-6-cyano-3-hydroxy-4-isopentylbiphenyl-2-carboxylate (4s)

Starting with **2c** (0.353 g, 1.5 mmol) and **3j** (0.522 g, 1.7 mmol), **4s** was isolated after chromatography (silica gel; heptanes–EtOAc).

Yield: 0.319 g (62%); light-yellow solid; mp 74–76 °C.

IR (KBr): 2955 (m), 2928 (m), 2868 (w), 2224 (w), 1741 (w), 1665 (s), 1599 (m), 1575 (w), 1496 (m), 1436 (s), 1397 (m), 1385 (w), 1345 (m), 1325 (m), 1314 (m), 1263 (m), 1204 (s), 1169 (m), 1148 (m), 1089 (s), 1016 (m), 1000 (m), 981 (m), 945 (w), 904 (w), 888 (w), 861 (w), 820 (m), 771 (m), 738 (m), 660 (m), 634 (m), 545 (m) cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.89 (d, $^3J = 6.7$ Hz, 6 H, 2 × CH_3), 1.90–1.99 [m, 1 H, $CH(CH_3)_2$], 2.51 (d, $^3J = 7.2$ Hz, 2 H, CH_2), 3.43 (s, 3 H, OCH_3), 7.08–7.13 (m, 2 H, CH_{ClPh}), 7.32–7.36 (m, 2 H, CH_{ClPh}), 7.47 (s, 1 H, CH_{Ar}), 11.57 (s, 1 H, OH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.4 (2 × CH_3), 27.0 [$CH(CH_3)_2$], 37.8 (CH_2), 51.5 (OCH_3), 103.8 (*C*CN), 111.6 (*C*$COOCH_3$), 116.9 (CN), 127.3 (2 × CH_{ClPh}), 128.6 (2 × CH_{ClPh}), 130.5, 133.3, 136.4 (C_{Ar}), 137.0 (CH_{Ar}), 144.6 (C_{Ar}), 162.2 (COH), 169.6 (CO).

GC–MS (EI, 70 eV): *m*/*z* (%) = 343 (29) [M^+], 277 (20), 276 (100), 270 (16), 268 (44), 234 (39), 177 (24), 151 (5), 130 (2), 88 (2), 43 (5).

HRMS (EI): *m*/*z* [M^+] calcd for $C_{19}H_{18}O_3NCl$: 343.09697; found: 343.096981.

Methyl 4′-Bromo-6-cyano-3-hydroxy-4-methylbiphenyl-2-carboxylate (4t)

Starting with **2d** (0.420 g, 1.5 mmol) and **3c** (0.457 g, 1.7 mmol), the product was isolated after chromatography (silica gel; heptanes–EtOAc).

Yield: 0.301 g (58%); white crystalline solid; mp 199–200 °C.

IR (KBr): 3082 (w), 2957 (w), 2852 (w), 2227 (m), 1933 (w), 1667 (m), 1591 (w), 1555 (w), 1496 (w), 1435 (m), 1353 (m), 1331 (m), 1267 (m), 1201 (m), 1167 (m), 1146 (m), 1042 (w), 1012 (m), 987 (m), 902 (m), 861 (w), 807 (s), 770 (m), 659 (w), 600 (m), 548 (m) cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.24 (s, 3 H, CH_3), 3.42 (s, 3 H, OCH_3), 7.00–7.04 (m, 2 H, CH_{BrPh}), 7.47 (s, 1 H, CH_{Ar}), 7.50–7.52 (m, 2 H, CH_{BrPh}), 11.61 (s, 1 H, OH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.8 (CH_3), 52.6 (OCH_3), 104.9 (*C*CN), 112.2 (*C*$COOCH_3$), 117.8 (CN), 122.5, 128.3 (C_{Ar}), 129.9 (2 × CH_{BrPh}), 131.5 (2 × CH_{BrPh}), 137.7 (CH_{Ar}), 137.8, 145.4 (C_{Ar}), 163.2 (COH), 170.4 (CO).

GC–MS (EI, 70 eV): *m*/*z* (%) = 347 (29) [^{81}Br; M^+], 345 (29) [^{79}Br; M^+], 316 (10), 315 (60), 314 (12), 313 (60), 235 (20), 234 (100), 206 (12), 178 (10), 177 (19), 151 (17).

HRMS (EI): *m*/*z* [^{79}Br; M^+] calcd for $C_{16}H_{12}O_3BrN$: 344.99951; found: 344.999038.

HRMS (EI): *m*/*z* [^{81}Br; M^+] calcd for $C_{16}H_{12}O_3BrN$: 346.99746; found: 346.997318.

Ethyl 4′-Bromo-6-cyano-4-ethyl-3-hydroxybiphenyl-2-carboxylate (4u)

Starting with **2d** (0.420 g, 1.5 mmol) and **3d** (0.499 g, 1.7 mmol), **4u** was isolated after chromatography (silica gel; heptanes–EtOAc).

Yield: 0.453 g (60%); yellowish oil; mp 197–199 °C.

IR (KBr): 2970 (w), 2874 (w), 2224 (w), 1898 (w), 1659 (s), 1573 (w), 1492 (w), 1421 (m), 1393 (m), 1327 (s), 1268 (m), 1239 (m), 1190 (s), 1146 (m), 1100 (w), 1004 (m), 906 (w), 809 (s), 727 (m), 652 (w), 599 (m), 547 (m) cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.71 (t, $^3J = 7.5$ Hz, 3 H, CH_2CH_3), 1.19 (t, $^3J = 7.0$ Hz, 3 H, OCH_2CH_3), 2.65 (q, $^3J = 7.5$ Hz, 2 H, CH_2CH_3), 3.93 (q, $^3J = 7.5$ Hz, 2 H, OCH_2CH_3), 7.01–7.05 (m, 2 H, CH_{BrPh}), 7.47 (s, 1 H, CH_{Ar}), 7.50–7.52 (m, 2 H, CH_{BrPh}), 11.78 (s, 1 H, OH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.9, 13.0 (CH_3), 22.7, 62.0 (CH_2), 104.8 (*C*CN), 112.4 (*C*$COOCH_3$), 117.9 (CN), 122.3 (C_{Ar}), 129.5 (2 × CH_{BrPh}), 131.2 (2 × CH_{BrPh}), 133.8 (C_{Ar}), 136.0 (CH_{Ar}), 138.2, 145.5 (C_{Ar}), 163.2 (COH), 170.0 (CO).

GC–MS (EI, 70 eV): *m*/*z* (%) = 375 (20) [^{81}Br; M^+], 373 (21) [^{79}Br; M^+], 329 (32), 327 (32), 249 (19), 248 (100), 190 (10), 177 (12).

HRMS (EI): *m*/*z* [^{79}Br; M^+] calcd for $C_{18}H_{16}O_3BrN$: 373.03081; found: 373.030467.

HRMS (EI): *m*/*z* [^{81}Br; M^+] calcd for $C_{18}H_{16}O_3BrN$: 375.02876; found: 375.028656.

Methyl 4′-Bromo-6-cyano-4-hexyl-3-hydroxybiphenyl-2-carboxylate (4v)

Starting with **2d** (0.420 g, 1.5 mmol) and **3f** (0.568 g, 1.7 mmol), the product was isolated after chromatography (silica gel; *n*-heptane–EtOAc).

Yield: 0.343 g (55%); yellowish oil.

IR (KBr): 2954 (w), 2927 (m), 2856 (w), 2224 (w), 1666 (m), 1601 (w), 1573 (w), 1493 (w), 1438 (m), 1392 (w), 1340 (m), 1262 (w), 1206 (m), 1171 (w), 1101 (w), 1071 (w), 1013 (w), 908 (m), 817 (w), 770 (w), 730 (s), 649 (w), 621 (w) cm^{-1}.

^{1}H NMR (300 MHz, CDCl$_3$): δ = 0.73 [t, ^3J = 7.5 Hz, 3 H, (CH$_2$)$_7$CH_3], 1.07–1.20 (m, 6 H, 3 × CH$_2$), 1.42–1.50 (m, 2 H, CH$_2$), 2.51 (t, ^3J = 7.5 Hz, 2 H, CH$_2$), 3.42 (s, 3 H, OCH$_3$), 6.90–6.95 (m, 2 H, 2 × CH$_{\mathrm{Ph}}$), 7.36–7.39 (m, 3 H, 3 × CH$_{\mathrm{Ar}}$), 11.49 (s, 1 H, OH).

^{13}C NMR (75 MHz, CDCl$_3$): δ = 15.3 (CH$_3$), 23.8, 30.0, 30.3, 30.8, 32.9 (CH$_2$), 53.7 (OCH$_3$), 106.0 (*C*CN), 113.6 (*C*COOCH$_3$), 119.1 (CN), 123.6 (C$_{\mathrm{Ar}}$), 131.1, 132.4 (4 × CH$_{\mathrm{Ph}}$), 133.9 (C$_{\mathrm{Ar}}$), 138.2 (CH$_{\mathrm{Ar}}$), 139.0, 146.6 (C$_{\mathrm{Ar}}$), 164.2 (COH), 171.7 (CO).

GC–MS (EI, 70 eV): *m/z* (%) = 417 (17), 415 (17) [M$^+$], 304 (26), 235 (17), 234 (100), 205 (11), 177 (12).

HRMS (EI): *m/z* [^{79}Br; M$^+$] calcd for C$_{21}$H$_{22}$O$_3$NBr: 415.07776; found: 415.077792.

HRMS (EI): *m/z* [^{81}Br; M$^+$] calcd for C$_{23}$H$_{26}$O$_3$NBr: 417.07571; found: 417.076005.

Methyl 4′-Bromo-6-cyano-3-hydroxy-4-octylbiphenyl-2-carboxylate (4w)

Starting with **2d** (0.420 g, 1.5 mmol) and **3h** (0.614 g, 1.7 mmol), **4w** was isolated after chromatography (silica gel; heptanes–EtOAc).

Yield: 0.367 g (55%); yellowish solid; mp 73–75 °C.

IR (KBr): 2953 (w), 2924 (m), 2854 (w), 2224 (w), 1667 (m), 1602 (w), 1574 (w), 1493 (w), 1438 (m), 1392 (w), 1339 (m), 1259 (w), 1205 (m), 1172 (m), 1103 (w), 1071 (w), 1012 (w), 906 (m), 817 (w), 770 (w), 728 (s), 649 (w), 548 (w) cm^{-1}.

^{1}H NMR (300 MHz, CDCl$_3$): δ = 0.83 [t, ^3J = 7.4 Hz, 3 H, (CH$_2$)$_7$CH_3], 1.16–1.32 (m, 10 H, 5 × CH$_2$), 1.49–1.61 (m, 2 H, CH$_2$), 2.61 (t, ^3J = 7.6 Hz, 2 H, CH$_2$), 3.43 (s, 3 H, OCH$_3$), 7.01–7.05 (m, 2 H, 2 × CH$_{\mathrm{Ph}}$), 7.47–7.51 (m, 3 H, 3 × CH$_{\mathrm{Ar}}$), 11.59 (s, 1 H, OH).

^{13}C NMR (75 MHz, CDCl$_3$): δ = 14.1 (CH$_3$), 22.6, 28.8, 29.2, 29.4, 29.5, 29.6, 31.8 (CH$_2$), 52.5 (OCH$_3$), 104.8 (*C*CN), 112.4 (*C*COOCH$_3$), 117.9 (CN), 122.3 (C$_{\mathrm{Ar}}$), 129.8, 131.3 (4 × H$_{\mathrm{Ph}}$), 132.7 (C$_{\mathrm{Ar}}$), 137.0 (CH$_{\mathrm{Ar}}$), 137.8, 145.5 (C$_{\mathrm{Ar}}$), 163.1 (COH), 170.6 (CO).

GC–MS (EI, 70 eV): *m/z* (%) = 445 (15), 443 (15), 332 (29), 235 (20), 234 (100).

HRMS (EI): *m/z* [^{79}Br; M$^+$] calcd for C$_{23}$H$_{26}$O$_3$NBr: 443.10906; found: 443.109033.

HRMS (EI): *m/z* [^{81}Br; M$^+$] calcd for C$_{23}$H$_{26}$O$_3$NBr: 445.10701; found: 445.107259.

Methyl 4′-Bromo-6-cyano-3-hydroxy-4-nonylbiphenyl-2-carboxylate (4x)

Starting with **2d** (0.420 g, 1.5 mmol) and **3i** (0.638 g, 1.7 mmol), **4x** was isolated after chromatography (silica gel; heptanes–EtOAc).

Yield: 0.392 g (57%); yellow solid; mp 65–67 °C.

IR (KBr): 3333 (w), 2949 (m), 2921 (m), 2871 (m), 2847 (m), 2226 (w), 1911 (w), 1736 (m), 1714 (m), 1639 (w), 1599 (m), 1568 (m), 1493 (w), 1458 (m), 1428 (m), 1403 (m), 1392 (m), 1374 (w), 1356 (w), 1334 (w), 1301 (m), 1257 (m), 1237 (m), 1207 (m), 1187 (m), 1176 (m), 1148 (s), 1125 (m), 1072 (m), 1055 (w), 1038 (w), 1028 (w), 1012 (m) cm^{-1}.

^{1}H NMR (250 MHz, CDCl$_3$): δ = 0.82 [t, ^3J = 6.8 Hz, 3 H, (CH$_2$)$_8$CH_3], 1.18–1.24 (m, 12 H, 6 × CH$_2$), 1.51–1.59 (m, 2 H, CH$_2$), 2.62 (t, ^3J = 7.4 Hz, 2 H, CH$_2$), 3.43 (s, 3 H, OCH$_3$), 7.01–7.05 (m, 2 H, CH$_{\mathrm{BrPh}}$), 7.48 (s, 1 H, CH$_{\mathrm{Ar}}$), 7.49–7.51 (m, 2 H, CH$_{\mathrm{BrPh}}$), 11.60 (s, 1 H, OH).

^{13}C NMR (75 MHz, CDCl$_3$): δ = 13.1 (CH$_3$), 21.7, 27.8, 28.3, 28.4, 28.5, 28.6, 29.9, 30.9 (CH$_2$), 51.5 (OCH$_3$), 103.8 (*C*CN), 111.4 (*C*COOCH$_3$), 116.9 (CN), 121.4 (C$_{\mathrm{Ar}}$), 128.8 (2 × CH$_{\mathrm{BrPh}}$), 130.2 (2 × CH$_{\mathrm{BrPh}}$), 131.7 (C$_{\mathrm{Ar}}$), 136.0 (CH$_{\mathrm{Ar}}$), 136.9, 144.5 (C$_{\mathrm{Ar}}$), 162.1 (COH), 169.5 (CO).

GC–MS (EI, 70 eV): *m/z* (%) = 459 (41) [^{81}Br; M$^+$], 457 (41) [^{79}Br; M$^+$], 427 (9), 390 (5), 368 (4), 346 (90), 330 (7), 314 (22), 288 (14), 235 (73), 224 (11), 205 (22), 177 (22), 158 (13), 129 (42), 116 (100), 97 (21), 85 (34), 71 (48), 57 (74).

HRMS (EI): *m/z* [M$^+$] calcd for C$_{24}$H$_{28}$O$_3$NBr: 457.12471; found: 457.124229.

Ethyl 4′-Methoxy-6-cyano-3-hydroxy-biphenyl-2-carboxylate (4y)

Starting with **2e** (0.347 g, 1.5 mmol) and **3b** (0.453 g, 1.7 mmol), **4y** was isolated after chromatography (silica gel; heptanes–EtOAc).

Yield: 0.223 g (50%); yellow solid; mp 116–117 °C.

IR (KBr): 3306 (w, br), 3070 (w), 2987 (w), 2959 (w), 2921 (m), 2838 (w), 2537 (w), 2351 (w), 2225 (m), 2175 (w), 2050 (w), 1931 (w), 1682 (m), 1651 (w), 1609 (m), 1570 (m), 1517 (m), 1464 (m), 1455 (m), 1395 (m), 1372 (m), 1311 (m), 1294 (m), 1251 (m), 1174 (s), 1138 (m), 1112 (m), 1096 (m), 1028 (m), 1016 (m), 948 (m), 929 (w), 908 (w), 872 (w), 848 (m), 835 (s), 806 (m), 795 (m), 778 (m), 742 (m), 723 (m), 706 (m), 675 (m), 646 (m), 621 (m), 579 (m), 558 (m), 532 (m) cm^{-1}.

^{1}H NMR (250 MHz, CDCl$_3$): δ = 0.73 (t, ^3J = 7.0 Hz, 3 H, OCH$_2$CH_3), 3.79 (s, 3 H, OCH$_3$), 3.93 (q, ^3J = 7.0 Hz, 2 H, OCH_2CH$_3$), 6.86–6.91 (m, 2 H, CH$_{\mathrm{OMePh}}$), 6.99 (d, ^3J = 8.7 Hz, 1 H, CH$_{\mathrm{Ar}}$), 7.07–7.12 (m, 2 H, CH$_{\mathrm{OMePh}}$), 7.62 (d, ^3J = 9.0 Hz, 1 H, CH$_{\mathrm{Ar}}$), 11.36 (s, 1 H, OH).

^{13}C NMR (75 MHz, CDCl$_3$): δ = 13.1 (CH$_3$), 55.4 (OCH$_3$), 61.9 (OCH$_2$), 106.1 (*C*CN), 113.5 (2 × CH$_{\mathrm{OMePh}}$), 113.9 (*C*COOCH$_2$CH$_3$), 117.9 (CH$_{\mathrm{Ar}}$), 118.0 (CN), 129.4 (2 × CH$_{\mathrm{OMePh}}$), 131.2 (C$_{\mathrm{Ar}}$), 137.4 CH$_{\mathrm{Ar}}$), 149.5, 159.8 (C$_{\mathrm{Ar}}$), 164.7 (COH), 170.0 (CO).

GC–MS (EI, 70 eV): *m/z* (%) = 297 (44) [M$^+$], 251 (100), 236 (5), 223 (16), 208 (9), 180 (9), 152 (7), 126 (5), 101 (1), 75 (2), 63 (2).

HRMS (EI): *m/z* [M$^+$] calcd for C$_{17}$H$_{15}$O$_4$N: 297.09956; found: 297.099391.

Methyl 6-Cyano-3-hydroxy-4′-methoxy-4-methylbiphenyl-2-carboxylate (4z)

Starting with **2e** (0.346 g, 1.5 mmol) and **3c** (0.457 g, 1.7 mmol), **4z** was isolated after chromatography (silica gel; heptanes–EtOAc).

Yield: 0.266 g (51%); yellowish solid; mp 85–87 °C.

IR (KBr): 2958 (w), 2843 (w), 2219 (w), 1659 (m), 1608 (m), 1555 (w), 1515 (m), 1427 (m), 1331 (m), 1308 (s), 1260 (m), 1202 (m), 1176 (m), 1145 (m), 1033 (m), 1019 (m), 983 (m), 902 (m), 862 (w), 808 (s), 767 (m), 661 (w), 648 (m), 535 (m) cm^{-1}.

^{1}H NMR (250 MHz, CDCl$_3$): δ = 2.23 (s, 3 H, CH$_3$), 3.42 (s, 3 H, OCH$_3$), 3.78 (s, 3 H, OCH$_3$), 6.85–6.89 (m, 2 H, CH$_{\mathrm{OMePh}}$), 7.05–7.09 (m, 2 H, CH$_{\mathrm{OMePh}}$), 7.49 (s, 1 H, CH$_{\mathrm{Ar}}$), 11.43 (s, 1 H, OH).

^{13}C NMR (75 MHz, CDCl$_3$): δ = 15.6 (CH$_3$), 52.4, 55.3 (OCH$_3$), 105.2 (*C*CN), 112.8 (*C*COOCH$_3$), 113.5 (2 × CH$_{\mathrm{OMePh}}$), 118.3 (CN), 127.4 (C$_{\mathrm{Ar}}$), 129.2 (2 × CH$_{\mathrm{OMePh}}$), 131.1 (C$_{\mathrm{Ar}}$), 137.7 (CH$_{\mathrm{Ar}}$), 146.9, 159.5 (C$_{\mathrm{Ar}}$), 162.9 (COH), 170.9 (CO).

GC–MS (EI, 70 eV): *m/z* (%) = 297 (45) [M$^+$], 266 (19), 265 (100), 264 (12), 250 (11), 222 (9), 166 (9), 140 (8), 39 (8).

HRMS (EI): *m/z* [M$^+$] calcd for C$_{17}$H$_{15}$O$_4$N: 297.09956; found: 297.099657.

Ethyl 6-Cyano-4-ethyl-3-hydroxy-4′-methoxybiphenyl-2-carboxylate (4aa)

Starting with **2e** (0.346 g, 1.5 mmol) and **3d** (0.499 g, 1.7 mmol), **4aa** was isolated after chromatography (silica gel; heptanes–EtOAc).

Yield: 0.237 g (49%); yellowish solid; mp 54–56 °C.

IR (neat): 2968 (w), 2875 (w), 2223 (w), 1658 (m), 1608 (m), 1566 (w), 1515(s), 1434 (m), 1399 (m), 1373 (m), 1326 (m), 1302 (m), 1268 (m), 1239 (s), 1189 (s), 1145 (s), 1109 (m), 1065 (w), 1030 (m), 906 (w), 808 (s), 770 (m), 643 (w), 534 (m).

^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.71 (t, $^3J = 7.2$ Hz, 3 H, CH_2CH_3), 1.19 (t, $^3J = 7.2$ Hz, 3 H, OCH_2CH_3), 2.65 (q, $^3J = 7.2$ Hz, 2 H, CH_2CH_3), 3.92 (q, $^3J = 7.2$ Hz, 2 H, OCH_2CH_3), 3.77 (s, 3 H, OCH_3), 6.85–6.88 (m, 2 H, CH_{OMePh}), 7.06–7.09 (m, 2 H, CH_{OMePh}), 7.49 (s, 1 H, CH_{Ar}), 11.60 (s, 1 H, OH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.9, 13.2 (CH_3), 22.7 (CH_2), 55.3 (OCH_3), 62.0 (OCH_2), 105.2 (*C*CN), 112.9 (*C*$COOCH_3$), 113.5 (2 × CH_{OMePh}), 118.3 (CN), 129.2 (2 × CH_{OMePh}), 132.5 (C_{Ar}), 133.8 (C_{Ar}), 136.9 (CH_{Ar}), 146.9, 159.8 (C_{Ar}), 163.0 (COH), 170.5 (CO).

GC–MS (EI, 70 eV): *m/z* (%) = 325 (84) [M$^+$], 280 (23), 279 (100), 264 (29), 262 (12), 261 (52), 251 (10), 250 (10), 249 (12), 248 (60), 247 (12), 246 (30), 236 (15), 208 (9), 193 (8), 177 (8), 165 (9), 152 (8), 29 (9).

HRMS (EI): *m/z* [M$^+$] calcd for $C_{19}H_{19}O_4N$: 325.13086; found: 325.130617.

Methyl 6-Cyano-4-hexyl-3-hydroxy-4′-methoxybiphenyl-2-carboxylate (4ab)

Starting with **2e** (0.346 g, 1.5 mmol) and **3f** (0.568 g, 1.7 mmol), **4ab** was isolated after chromatography (silica gel; heptanes–EtOAc).

Yield: 0.286 g (52%); yellowish solid; mp 43–44 °C.

IR (KBr): 2954 (w), 2927 (m), 2856 (w), 2223 (w), 1746 (w), 1665 (m), 1609 (m), 1579 (w), 1516 (m), 1436 (m), 1337 (m), 1289 (m), 1247 (s), 1205 (m), 1176 (m), 1147 (m), 1110 (w), 1034 (w), 906 (m), 830 (m), 768 (w), 728 (s), 649 (m) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.82 [t, $^3J = 7.5$ Hz, 3 H, $(CH_2)_5CH_3$], 1.18–1.32 (m, 6 H, 3 × CH_2), 1.50–1.59 (m, 2 H, CH_2), 2.61 (t, $^3J = 7.5$ Hz, 2 H, CH_2), 3.40 (s, 3 H, OCH_3), 3.77 (s, 3 H, OCH_3), 6.83–6.88 (m, 2 H, 2 × CH_{Ph}), 7.04–7.09 (m, 2 H, 2 × CH_{Ph}), 7.46 (s, 1 H, CH_{Ar}), 11.39 (s, 1 H, OH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1 (CH_3), 22.6, 28.8, 29.1, 29.5, 31.6 (CH_2), 52.4, 55.2 (OCH_3), 105.6 (*C*CN), 113.0 (*C*$COOCH_3$), 113.5 (2 × CH_{Ph}), 118.4 (CN), 129.4 (2 × CH_{Ph}), 131.1, 131.8 (C_{Ar}), 137.0 (CH_{Ar}), 146.6, 159.4 (C_{Ar}), 162.7 (COH), 170.9 (CO).

GC–MS (EI, 70 eV): *m/z* (%) = 368 (17), 367 (85) [M$^+$], 336 (13), 335 (54), 266 (17), 265 (100), 264 (44), 234 (22).

HRMS (EI): *m/z* [M$^+$] calcd for $C_{22}H_{25}O_4N$: 367.17781; found: 367.177574.

Methyl 6-Cyano-3-hydroxy-4′-methoxy-4-octylbiphenyl-2-carboxylate (4ac)

Starting with **2e** (0.346 g, 1.5 mmol) and **3h** (0.614 g, 1.7 mmol), **4ac** was isolated after chromatography (silica gel; heptanes–EtOAc).

Yield: 0.297 g (50%); yellowish oil.

IR (KBr): 2953 (w), 2924 (m), 2854 (w), 2223 (w), 1665 (m), 1609 (m), 1516 (m), 1436 (s), 1339 (m), 1290 (m), 1247 (s), 1205 (m), 1175 (m), 1034 (m), 991 (w), 906 (m), 829 (m), 767 (w), 729 (s), 649 (m), 536 (w) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.81 [t, $^3J = 7.4$ Hz, 3 H, $(CH_2)_7CH_3$], 1.17–1.32 (m, 10 H, 5 × CH_2), 1.50–1.59 (m, 2 H, CH_2), 2.61 (t, $^3J = 7.5$ Hz, 2 H, CH_2), 3.42 (s, 3 H, OCH_3), 3.78 (s, 3 H, OCH_3), 6.84–6.90 (m, 2 H, 2 × CH_{Ph}), 7.05–7.11 (m, 2 H, 2 × CH_{Ph}), 7.48 (s, 1 H, CH_{Ar}), 11.49 (s, 1 H, OH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.1 (CH_3), 21.6, 27.9, 28.2, 28.3, 28.4, 28.6, 30.9 (CH_2), 51.3, 54.3 (OCH_3), 104.1 (*C*CN), 111.9 (*C*$COOCH_3$), 112.4 (2 × CH_{Ph}), 117.4 (CN), 128.4 (2 × CH_{Ph}), 130.1, 130.8 (C_{Ar}), 136.1 (CH_{Ar}), 145.5, 158.4 (C_{Ar}), 161.7 (COH), 170.0 (CO).

GC–MS (EI, 70 eV): *m/z* (%) = 396 (21), 395 (97) [M$^+$], 364 (14), 363 (56), 266 (17), 265 (100), 264 (50), 234 (21).

HRMS (EI): *m/z* [M$^+$] calcd for $C_{24}H_{29}NO_4$: 395.20911; found: 395.209162.

Benzonitriles 6a–f; General Procedure

To a solution of **5** in CH_2Cl_2, was added $TiCl_4$ at –78 °C in the presence of molecular sieves (4 Å). The appropriate bis(silyl enol ether) **3** was subsequently added and the reaction mixture was allowed to warm to 20 °C during 20 h then stirred for a further 4 h. To this solution was added CH_2Cl_2, the molecular sieves were removed by filtration and sat. aq $NaHCO_3$ was added. The organic layer was separated and the aqueous layer was repeatedly extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were dried (Na_2SO_4), filtered, and the filtrate was concentrated in vacuo. The residue was purified by column chromatography (silica gel; heptanes–EtOAc) to give salicylates **6**.

Methyl 3-Cyano-6-hydroxy-2,4-dimethylbenzoate (6a)

Starting with **5** (188 mg, 1.0 mmol), CH_2Cl_2 (3.0 mL), molecular sieves (4 Å, 0.4 g), $TiCl_4$ (0.11 mL, 1.0 mmol), and **3a** (356 mg, 1.4 mmol), **6a** was obtained after 21 h and isolated by column chromatography (silica gel; heptanes–EtOAc, 10:1).

Yield: 67 mg (34%); colourless solid; mp 109–110 °C; $R_f = 0.21$ (heptanes–EtOAc, 10:1).

IR (KBr): 3431 (br, m), 2957 (m), 2217 (s), 1668 (s), 1601 (s), 1581 (s), 1442 (s), 1368 (s), 1358 (s), 1319 (s), 1241 (s), 810 (s) cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.48 (d, $^4J = 0.9$ Hz, 3 H, $ArCH_3$), 2.75 (s, 3 H, $ArCH_3$), 3.98 (s, 3 H, OCH_3), 6.76 (s, 1 H, CH_{Ar}), 11.72 (s, 1 H, OH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.4, 21.8 ($ArCH_3$), 52.7 (OCH_3), 107.0, 111.0, 117.3 (2 × C_{Ar}, CN), 117.4 (CH_{Ar}), 146.6, 148.4 (C_{Ar}), 165.1, 171.0 (C_{Ar}OH, CO).

MS (EI, 70 eV): *m/z* (%) = 205 (83) [M$^+$], 174 (76), 173 (100), 145 (66), 144 (37), 116 (20), 91 (14).

Anal. Calcd for $C_{11}H_{11}NO_3$: C, 64.38; H, 5.40; N, 6.83. Found: C, 64.64; H, 5.52; N, 6.65.

Ethyl 3-Cyano-6-hydroxy-2,4-dimethylbenzoate (6b)

Starting with **5** (196 mg, 1.0 mmol), CH_2Cl_2 (3.0 mL), molecular sieves (4 Å, 0.4 g), $TiCl_4$ (0.11 mL, 1.0 mmol), and **3b** (390 mg, 1.4 mmol), **6b** was obtained after 25 h and isolated by column chromatography (silica gel; heptanes–EtOAc, 10:1→7:1).

Yield: 90 mg (41%); colourless solid; mp 114–115 °C; $R_f = 0.22$ (*n*-heptane–EtOAc, 10:1).

IR (KBr): 3426 (br, w), 2995 (m), 2213 (s), 1662 (s), 1373 (s), 1315 (s), 1239 (s), 809 (m) cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.45 (t, $^3J = 7.2$ Hz, 3 H, OCH_2CH_3), 2.49 (s, 3 H, $ArCH_3$), 2.78 (s, 3 H, $ArCH_3$), 4.46 (q, $^3J = 7.2$ Hz, 2 H, OCH_2CH_3), 6.77 (s, 1 H, Ar), 11.83 (s, 1 H, OH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1 (OCH_2CH_3), 21.4, 21.9 ($ArCH_3$), 62.4 (OCH_2CH_3), 106.9, 111.2, 117.3 (2 × C_{Ar}, CN), 117.4 (CH_{Ar}), 146.7, 148.3 (C_{Ar}), 165.2, 170.6 (C_{Ar}OH, CO).

MS (EI, 70 eV): *m*/*z* (%) = 219 (64) [M$^+$], 174 (63), 173 (100), 145 (42), 144 (17).

Anal. Calcd for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98; N, 6.39. Found: C, 65.92; H, 6.01; N, 6.17.

Isobutyl 3-Cyano-6-hydroxy-2,4-dimethylbenzoate (6c)

Starting with **5** (188 mg, 1.0 mmol), CH_2Cl_2 (3.0 mL), molecular sieves (4 Å, 0.4 g), $TiCl_4$ (0.11 mL, 1.0 mmol), and **3l** (394 mg, 1.3 mmol), **6c** was obtained after 22 h and isolated by column chromatography (silica gel; heptanes–EtOAc, 10:1).

Yield: 91 mg (39%); colourless solid; mp 51–52 °C; R_f = 0.29 (heptanes–EtOAc, 10:1).

IR (KBr): 3427 (br, w), 2960 (s), 2930 (m), 2875 (m), 2216 (m), 1656 (s), 1318 (s), 1242 (s), 1080 (s), 814 (m) cm^{-1}.

^{1}H NMR (250 MHz, CDCl$_3$): δ = 1.04 [d, ^3J = 6.9 Hz, 6 H, CH(C*H*$_3$)$_2$], 2.12 (m, 1 H, OCH$_2$C*H*), 2.48 (s, 3 H, ArCH$_3$), 2.79 (s, 3 H, ArCH$_3$), 4.19 (d, ^3J = 6.4 Hz, 2 H, OC*H*$_2$CH), 6.77 (s, 1 H, Ar), 11.88 (s, 1 H, OH).

^{13}C NMR (75 MHz, CDCl$_3$): δ = 19.3 [CH(*C*H$_3$)$_2$], 21.4, 22.1 (ArCH$_3$), 27.6 (OCH$_2$*C*H), 72.7 (O*C*H$_2$CH), 106.9, 111.2, 117.3 (2 × C$_{Ar}$, CN), 117.5 (CH$_{Ar}$), 146.5, 148.3 (C$_{Ar}$), 165.3, 170.8 (C$_{Ar}$OH, CO).

MS (EI, 70 eV): *m*/*z* (%) = 247 (64) [M$^+$], 191 (55), 174 (81), 173 (100), 145 (26), 91 (14), 57 (23).

Anal. Calcd for $C_{14}H_{17}NO_3$: C, 68.00; H, 6.93; N, 5.66. Found: C, 67.95; H, 7.04; N, 5.36.

tert-Butyl 3-Cyano-6-hydroxy-2,4-dimethylbenzoate (6d)

Starting with **5** (300 mg, 1.52 mmol), CH_2Cl_2 (4.5 mL), molecular sieves (4 Å, 0.6 g), $TiCl_4$ (0.17 mL, 1.5 mmol), and **3m** (634 mg, 2.10 mmol), **6d** was obtained after 26 h and isolated by column chromatography (silica gel; *n*-heptane–EtOAc, 1:0→20:1).

Yield: 29 mg (8%); yellow solid; mp 92–94 °C; R_f 0.43 (*n*-heptane–EtOAc, 5:1).

IR (KBr): 2987 (m), 2928 (m), 2212 (m), 1661 (s), 1601 (m), 1575 (m), 1466 (m), 1377 (s), 1327 (s), 1245 (s), 1153 (s), 1080 (m), 839 (m), 813 (m) cm^{-1}.

^{1}H NMR (250 MHz, CDCl$_3$): δ = 1.63 [s, 9 H, C(CH$_3$)$_3$], 2.48 (d, ^4J = 0.7 Hz, 3 H, ArCH$_3$), 2.75 (s, 3 H, ArCH$_3$), 6.75 (s, 1 H, CH$_{Ar}$), 11.93 (s, 1 H, OH).

^{13}C NMR (75 MHz, CDCl$_3$): δ = 21.4, 22.1 (ArCH$_3$), 28.3 [OC(*C*H$_3$)$_3$], 85.0 [O*C*(CH$_3$)$_3$], 106.8, 112.5 (C), 117.4 (CH$_{Ar}$), 117.5 (C), 146.4, 147.9 (C$_{Ar}$), 165.2, 170.0 (C$_{Ar}$OH, CO).

MS (GC-EI, 70 eV): *m*/*z* (%) = 247 (4) [M$^+$], 191 (34), 174 (40), 173 (100), 57 (29).

HRMS (EI, 70 eV): *m*/*z* [M$^+$] calcd for $C_{14}H_{17}NO_3$: 247.12029; found: 247.12041.

Methyl 3-Cyano-5-ethyl-6-hydroxy-2,4-dimethylbenzoate (6e)

Starting with **5** (186 mg, 0.9 mmol), CH_2Cl_2 (3.0 mL), molecular sieves (4 Å, 0.4 g), $TiCl_4$ (0.10 mL, 0.9 mmol), and **3n** (371 mg, 1.29 mmol), **6e** was obtained after 21 h and isolated by column chromatography (silica gel; *n*-heptane–EtOAc, 10:1).

Yield: 96 mg (44%); colourless solid; mp 95–96 °C; R_f = 0.30 (heptanes–EtOAc, 10:1).

IR (KBr): 3432 (br, m), 2974 (s), 2962 (s), 2216 (s), 1660 (s), 1571 (s), 1366 (s), 1326 (s), 1209 (s), 947 (m) cm^{-1}.

^{1}H NMR (250 MHz, CDCl$_3$): δ = 1.07 (t, ^3J = 7.5 Hz, 3 H, CH$_2$C*H*$_3$), 2.49 (s, 3 H, ArCH$_3$), 2.67 (q, ^3J = 7.5 Hz, 2 H, C*H*$_2$CH$_3$), 2.70 (s, 3 H, ArCH$_3$), 3.97 (s, 3 H, OCH$_3$), 12.05 (s, 1 H, OH).

^{13}C NMR (75 MHz, CDCl$_3$): δ = 12.8 (CH$_2$*C*H$_3$), 18.2 (ArCH$_3$), 19.5 (CH$_2$), 21.7 (ArCH$_3$), 52.6 (OCH$_3$), 107.0, 110.6, 118.0 (2 × C$_{Ar}$, CN), 130.1, 143.4, 145.3 (C$_{Ar}$), 163.1, 171.6 (C$_{Ar}$OH, CO).

MS (EI, 70 eV): *m*/*z* (%) = 233 (87) [M$^+$], 202 (73), 201 (100), 186 (62), 174 (49), 173 (97), 158 (34), 130 (17).

Anal. Calcd for $C_{13}H_{15}NO_3$: C, 66.94; H, 6.48; N, 6.00. Found: C, 66.99; H, 6.64; N, 5.80.

Ethyl 3-Cyano-5-ethyl-6-hydroxy-2,4-dimethylbenzoate (6f)

Starting with **5** (189 mg, 1.0 mmol), CH_2Cl_2 (3.0 mL), molecular sieves (4 Å, 0.4 g), $TiCl_4$ (0.11 mL, 1.0 mmol), and **3d** (400 mg, 1.3 mmol), **6f** was obtained after 26 h and isolated by column chromatography (silica gel; *n*-heptane–EtOAc, 10:1).

Yield: 138 mg (58%); colourless solid; mp 48–49 °C; R_f = 0.33 (heptanes–EtOAc, 10:1).

IR (KBr): 3441 (br, m), 2978 (s), 2943 (m), 2879 (m), 2218 (s), 1654 (s), 1399 (s), 1377 (s), 1208 (s), 824 (m).

^{1}H NMR (250 MHz, CDCl$_3$): δ = 1.07 (t, ^3J = 7.4 Hz, 3 H, ArCH$_2$C*H*$_3$), 1.44 (t, ^3J = 7.1 Hz, 3 H, OCH$_2$C*H*$_3$), 2.49 (s, 3 H, ArCH$_3$), 2.68 (q, ^3J = 7.4 Hz, 2 H, ArC*H*$_2$CH$_3$), 2.73 (s, 3 H, ArCH$_3$), 4.45 (q, ^3J = 7.1 Hz, 2 H, OC*H*$_2$CH$_3$), 12.14 (s, 1 H, OH).

^{13}C NMR (75 MHz, CDCl$_3$): δ = 12.8, 14.0 (CH$_2$*C*H$_3$), 18.2 (ArCH$_3$), 19.5 (ArCH$_2$), 21.8 (ArCH$_3$), 62.3 (OCH$_2$), 107.0, 110.7, 118.1 (2 × C$_{Ar}$, CN), 130.1, 143.4, 145.2 (C$_{Ar}$), 163.2, 171.2 (C$_{Ar}$OH, CO).

MS (EI, 70 eV): *m*/*z* (%) = 247 (40) [M$^+$], 202 (29), 201 (100), 186 (14), 173 (99), 158 (10).

Anal. Calcd for $C_{14}H_{17}NO_3$: C, 68.00; H, 6.93; N, 5.66. Found: C, 68.34; H, 7.07; N, 5.49.

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References

(1) Kleemann, A.; Engel, J.; Kutscher, B.; Reichert, D. *Pharmaceutical Substances: Syntheses, Patents, Applications*, 4th ed.; Thieme: Stuttgart, **2001**, 241, 488, 553, 825, 1154, 1598.

(2) Ford, R. E.; Knowles, P.; Lunt, E.; Marshall, S. M.; Penrose, A. J. *J. Med. Chem.* **1986**, *29*, 538.

(3) Klunder, J. M.; Hargrave, K. D.; West, M. A.; Cullen, E.; Pal, K. *J. Med. Chem.* **1992**, *35*, 1887.

(4) Collin, S.; El Tayar, N.; van de Waterbeemd, H.; Moureau, F.; Vercauteren, D. P.; Durant, F.; Langlois, M.; Testa, B. *Eur. J. Med. Chem.* **1989**, *24*, 163.

(5) Benedini, F.; Bertolini, G.; Cereda, R.; Dona, G.; Gromo, G. *J. Med. Chem.* **1995**, *38*, 130.

(6) Zwaagstra, M. E.; Timmerman, H.; Tamura, M.; Tohma, T.; Wada, Y. *J. Med. Chem.* **1997**, *40*, 1075.

(7) Zwaagstra, M. E.; Timmerman, H.; Abdoelgafoer, R. S.; Zhang, M. Q. *Eur. J. Med. Chem.* **1996**, *31*, 861.

(8) Pires, J. R.; Saito, C.; Gomes, S. L.; Giesbrecht, A. M.; Amaral, A. T. d. *J. Med. Chem.* **2001**, *44*, 3673.

(9) Fletcher, S. R.; Burkamp, F.; Blurton, P.; Cheng, S. K. F.; Clarkson, R.; O' Connor, D.; Spinks, D.; Tudge, M.; van Niel, M. B.; Patel, S.; Chapman, K. *J. Med. Chem.* **2002**, *45*, 492.

(10) Nielsen, F. E.; Jacobsen, P.; Worsaae, A.; Arkhammar, P. O. G.; Wahl, P.; Hansen, J. B. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 5727.

(11) van Zandt, M. C.; Sibley, E. O.; McCann, E. E.; Combs, K. J.; Flam, B.; Sawicki, D. R.; Sabetta, A.; Carrington, A.; Sredy, J.; Howard, E.; Mitschler, A.; Podjarny, A. D. *Bioorg. Med. Chem.* **2004**, *12*, 5661.

(12) Paulini, R.; Lerner, C.; Diederich, F.; Jakob-Roetne, R.; Zuercher, G.; Borroni, E. *Helv. Chim. Acta* **2006**, *89*, 1856.

(13) Zanon, J.; Klapars, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 2890.

(14) (a) Ellis, G. P.; Romney-Alexander, T. M. *Chem. Rev.* **1987**, *87*, 779. (b) Sundermeier, M.; Zapf, A.; Beller, M. *Eur. J. Inorg. Chem.* **2003**, 3513. (c) Cassar, L.; Foà, M.; Montanari, F.; Marinelli, G. P. *J. Organomet. Chem.* **1979**, *173*, 335. (d) Sakakibara, Y.; Okuda, F.; Shimoyabashi, A.; Kirino, K.; Sakai, M.; Uchino, N.; Takagi, K. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 1985. (e) Sakakibara, Y.; Ido, Y.; Sasaki, K.; Sakai, M.; Uchino, N. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 2776. (f) Takagi, K.; Okamoto, T.; Sakakibara, Y.; Oka, S. *Chem. Lett.* **1973**, 471. (g) Sekiya, A.; Ishikawa, N. *Chem. Lett.* **1975**, 277. (h) Takagi, K.; Okamoto, T.; Sakakibara, Y.; Ohno, A.; Oka, S.; Hayama, N. *Bull. Chem. Soc. Jpn.* **1975**, *48*, 3298. (i) Dalton, J. R.; Regen, S. L. *J. Org. Chem.* **1979**, *44*, 4443. (j) Akita, Y.; Shimazaki, M.; Ohta, A. *Synthesis* **1981**, 974. (k) Chatani, N.; Hanafusa, T. *J. Org. Chem.* **1986**, *51*, 4714. (l) Takagi, K.; Sasaki, K.; Sakakibara, Y. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 1118. (m) Anderson, Y.; Långström, B. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1395. (n) Anderson, B. A.; Bell, E. C.; Ginah, F. O.; Harn, N. K.; Pagh, K. M.; Wepsiec, J. P. *J. Org. Chem.* **1998**, *63*, 8224. (o) Okano, T.; Kiji, J.; Toyooka, Y. *Chem. Lett.* **1998**, 425. (p) Maligres, P. E.; Waters, M. S.; Fleitz, F.; Askin, D. *Tetrahedron Lett.* **1999**, *40*, 8193. (q) Jin, F.; Confalone, P. N. *Tetrahedron Lett.* **2000**, *41*, 3271. (r) Sundermeier, M.; Zapf, A.; Beller, M.; Sans, J. *Tetrahedron Lett.* **2001**, *42*, 6707. (s) Ramnauth, J.; Bhardwaj, N.; Renton, P.; Rakhit, S.; Maddaford, S. *Synlett* **2003**, 2237. (t) Sundermeier, M.; Zapf, A.; Mutyala, S.; Baumann, W.; Sans, J.; Weiss, S.; Beller, M. *Chem. Eur. J.* **2003**, *9*, 1828. (u) Sundermeier, M.; Zapf, A.; Beller, M. *Angew. Chem. Int. Ed.* **2003**, *42*, 1661. (v) Sundermeier, J.; Mutyala, S.; Zapf, A.; Spannenberg, A.; Beller, M. *J. Organomet. Chem.* **2003**, *684*, 50. (w) Schareina, T.; Zapf, A.; Beller, M. *Chem. Commun.* **2004**, 1388.

(15) Houben, J.; Fischer, W. *Chem. Ber.* **1933**, *66*, 339.

(16) (a) Takashi, Y.; Shigeki, N.; Toshiyuki, O.; Toyoo, N.; Masateru, K. *Chem. Pharm. Bull.* **1984**, *32*, 4466. (b) van Zandt, M. C.; Sibley, E. O.; McCann, E. E.; Combs, K. J.; Flam, B.; Sawicki, D. R.; Sabetta, A.; Carrington, A.; Sredy, J.; Howard, E.; Mitschler, A.; Podjarny, A. D. *Bioorg. Med. Chem.* **2004**, *12*, 5661.

(17) (a) Nelson, P. H.; Carr, S. F.; Devens, B. H.; Eugui, E. M.; Franco, F. *J. Med. Chem.* **1996**, *39*, 4181. (b) Srivastava, R. R.; Collibee, S. E. *Tetrahedron Lett.* **2004**, *45*, 8895.

(18) Kopp, F.; Wunderlich, S.; Knochel, P. *Chem. Commun.* **2007**, *20*, 2075.

(19) (a) Taylor, E. C.; Katz, A. H.; McKillop, A. *Tetrahedron Lett.* **1984**, *25*, 5473. (b) Sargent, M. V. *J. Chem. Soc., Perkin Trans. 1* **1987**, 231.

(20) (a) Schmidt, H.-W.; Junek, H. *Liebigs Ann. Chem.* **1979**, 2005. (b) Schmidt, H.-W.; Klade, M. *Liebigs Ann. Chem.* **1988**, 257.

(21) Leaver, D.; Vass, J. D. R. *J. Chem. Soc.* **1965**, 1629.

(22) Baker, S. R.; Crombie, L.; Dove, R. V.; Slack, D. A. *J. Chem. Soc., Perkin Trans. 1* **1979**, 677.

(23) See for example: (a) Dilthey, W.; Schommer, W.; Trösken, O. *Chem. Ber.* **1933**, *66*, 1627. (b) Noland, W. E.; Kuryla, W. C.; Lange, R. F. *J. Am. Chem. Soc.* **1959**, *81*, 6010. (c) Boulton, A. J.; Mathur, S. S. *J. Org. Chem.* **1973**, *38*, 1054. (d) Ciganek, E. *J. Org. Chem.* **1969**, *34*, 1923. (e) Hopf, H.; Lenich, T. *Chem. Ber.* **1974**, *107*, 1891. (f) Sasaki, T.; Ishibashi, Y.; Ohno, M. *J. Chem. Res., Miniprint* **1984**, *7*, 1972.

(24) Barbero, A.; Pulido, F. J. *Synthesis* **2004**, 401.

(25) Fatunsin, O.; Shkoor, M.; Riahi, A.; Dede, R.; Reinke, H.; Langer, P. *Synlett* **2009**, 201.

(26) For the first [3+3] cyclizations of 1,3-bis(silyloxy)-1,3-butadienes, see: Chan, T.-H.; Brownbridge, P. *J. Am. Chem. Soc.* **1980**, *102*, 3534.

(27) For a review of [3+3] cyclizations of 1,3-bis(silyloxy)-1,3-butadienes, see: Feist, H.; Langer, P. *Synthesis* **2007**, 327.

(28) For a review of 1,3-bis(silyloxy)-1,3-butadienes in general, see: Langer, P. *Synthesis* **2002**, 441.

(29) Salon, J.; Milata, V.; Pronayova, N.; Lesko, J. *Monatsh. Chem.* **2000**, *131*, 293.

(30) (a) Brownbridge, P.; Chan, T. H.; Brook, M. A.; Kang, G. J. *Can. J. Chem.* **1983**, *61*, 688. (b) Hirai, K.; Ojima, I. *Tetrahedron Lett.* **1983**, *24*, 785.

(31) CCDC-716950 contain all crystallographic details of this publication and is available free of charge at: www.ccdc.cam.ac.uk/conts/retrieving.html or can be ordered from the following address: Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK; Fax: +44(1223)336033, or deposit@ccdc.cam.ac.uk.

(32) Buttke, K.; Niclas, H.-J. *Synth. Commun.* **1994**, *24*, 3241.