### A Straightforward Approach to Substituted 2-(Hydroxymethyl)-2,3-dihydrofuro[2,3-*b*]pyridines and 3-Hydroxy-3,4-dihydro-2*H*-pyrano[2,3-*b*]pyridines

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**Abstract:** An efficient route to 2-(hydroxymethyl)-2,3-dihydrofuro[2,3-*b*]pyridines and 3-hydroxy-3,4-dihydro-2*H*-pyrano[2,3*b*]pyridines is reported. The strategy is based on an intramolecular inverse electron demand Diels–Alder reaction starting from 1,2,4triazines. The hydroxy function comes from the glycidol ring opening with alkynyllithium or alkynylorganoalane.

Key words: alkynes, cycloadditions, Diels–Alder reactions, fusedring systems, heterocycles

The inverse electron demand Diels–Alder reaction – the [4+2] cycloaddition between electron-rich dienophiles and electron-poor dienes – is a versatile method for the construction of a wide variety of fused heterocyclic systems.<sup>1</sup> Electron-deficient heterocyclic azadienes are well-established reagents for this cycloaddition,<sup>2,3</sup> among which 1,2,4-triazines are the most reactive and most wide-ly used. Notably, they can be trapped by alkynes, providing straightforward access to a range of highly substituted heterocyclic systems.<sup>3</sup>

We recently reported an efficient method for the elaboration of substituted 2,3-dihydrofuro[2,3-*b*]pyridines and 3,4-dihydro-2*H*-pyrano[2,3-*b*]pyridines,<sup>3a,b</sup> of interest for their structural similarities to known biologically active quinolines, substituted pyridines, and chromanes,<sup>4</sup> taking advantage of the intramolecular Diels–Alder reaction between a 1,2,4-triazine and an alkyne tethered together by an ether linker. The two-step strategy (Scheme 1) involving aromatic nucleophilic substitution of a 3-(methylsulfonyl)-1,2,4-triazine by an alkoxyalkyne and the subsequent inverse electron demand Diels–Alder reaction under microwave heating gave access to fused heterocycles bearing various substituents on the pyridine ring in good yields.

Encouraged by these results, we decided to extend this methodology to the synthesis of substituted 2-(hydroxy-methyl)-2,3-dihydrofuro[2,3-*b*]pyridines and 3-hydroxy-3,4-dihydro-2*H*-pyrano[2,3-*b*]pyridines.

The formal total synthesis of 2-(hydroxymethyl)-2,3-dihydrofuro[2,3-*b*]pyridines was expected to be possible if

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**Scheme 1** Synthetic strategy towards functionalized 2,3-dihydrofuro[2,3-*b*]pyridines and 3,4-dihydro-2*H*-pyrano[2,3-*b*]pyridines

1,2,4-triazines 1 and 2 (Scheme 1)<sup>3a,b</sup> are used as starting materials and a  $\beta$ -hydroxyalkyne moiety is introduced.

Our strategy first required the preparation of the appropriate  $\beta$ -hydroxyalkynes (Scheme 2). 2-Substituted 1-(trityloxy)pent-4-yn-2-ols **4** and **5** were prepared by a protection/oxirane-opening sequence starting from racemic glycidol. After protection of the hydroxy as a trityl ether,<sup>5</sup> epoxide **3** was subjected to nucleophilic ring opening with (trimethylsilyl)acetylene or ethyl ethynyl ether in the presence of boron trifluoride–diethyl ether in tetrahydrofuran, to afford the corresponding  $\beta$ -hydroxyalkynes **4** and **5**.<sup>6</sup>



**Scheme 2** Synthesis of  $\beta$ -hydroxyalkynes **4** and **5**. *Reagents and conditions*: (a) TrCl, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>, r.t., 24 h; (b) TMSC=CH or EtOC=CH, *n*-BuLi, BF<sub>3</sub>·OEt<sub>2</sub>, THF, -78 °C to r.t., 12 h.

Nucleophilic displacement of the methylsulfonate from 1 and 2 by the lithium salts of alcohols 4 and 5 afforded, after hydrolysis, the desired Diels–Alder precursors 6–9 in 63–77% yields (Table 1). Treatment of compounds 6 and 8 with tetrabutylammonium fluoride in tetrahydrofuran furnished terminal alkynes 10 and 11 in high yields (93 and 97% yield, respectively).

With tethered triazines **6–11** in hand, we investigated the cycloaddition reaction. Under the reaction conditions previously developed in our laboratory<sup>3a,b</sup> for the synthesis of 2,3-dihydrofuro[2,3-*b*]pyridines and 3,4-dihydro-2*H*-pyrano[2,3-*b*]pyridines (microwave heating, chlorobenzene



<sup>a</sup> Yield of pure isolated product.

as solvent), the corresponding 2-(hydroxymethyl)-2,3-dihydrofuro[2,3-*b*]pyridines were obtained in excellent yields regardless of the substituent on the alkyne and on the triazine core. The results are collected in Table 2.<sup>7</sup>

Towards the elaboration of more complex molecules by manipulation of the hydroxy group, the trityl group was removed from **12** by using trifluoroacetic acid in dichloromethane<sup>8</sup> to yield the desired 2-(hydroxymethyl)-2,3-dihydrofuro[2,3-*b*]pyridine **18** in 63% yield (Scheme 3).



Scheme 3 Deprotection of trityl with trifluoroacetic acid in dichloromethane at room temperature

The successful synthesis of 2,3-dihydrofuro[2,3-*b*]pyridines then prompted us to investigate the use of glycidol for the synthesis of 3-hydroxy-3,4-dihydro-2*H*-pyrano[2,3-*b*]pyridines.

Upon treatment of methyl sulfone **1** with glycidol in the presence of sodium hydride, the desired product **19** was isolated in good yield (81%) (Scheme 4). Next, the introduction of the alkynyl moiety by ring opening of the oxirane was investigated. With alkynyllithium reagents, no

 
 Table 2
 Intramolecular Inverse Electron Demand Diels–Alder Reactions under Microwave Irradiation

	R <sup>2</sup>			
	OTr	chlorobenze MW 170 °C, 1–2		
	6–11		1:	2–17
Entry	$\mathbb{R}^1$	$\mathbb{R}^2$	Product	Yield (%) <sup>a</sup>
1	Ph	TMS	12	89
2	Ph	OEt	13	95
3	Н	TMS	14	90
4	Н	OEt	15	93
5	Ph	Н	16	83
6	Н	Н	17	90

<sup>a</sup> Yield of pure isolated product.

product was obtained, despite attempts under numerous reaction conditions, and only the starting material and degradation products could be obtained by this reaction. With ethynylmagnesium bromide as the nucleophile under the conditions reported by Trost [ethynylmagnesium bromide (5 equiv), THF, -78 °C],<sup>9</sup> the starting material was recovered. Substitution of tetrahydrofuran as solvent to the less polar toluene did not change the outcome of the reaction. A hypothesis for these unsuccessful attempts



R = TMS, CH<sub>2</sub>OTHP, Bn

Scheme 4 *Reagents and conditions*: (a) glycidol, NaH, THF, r.t., 2 h; (b) RC=CH (2 equiv), *n*-BuLi (2 equiv), BF<sub>3</sub>·OEt<sub>2</sub> (2–5 equiv), THF, -78 °C to r.t., 12 h.

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<sup>a</sup> Yield of pure isolated product.

might be the competition between the epoxide and the triazine core for alkynylation, which, in the latter case, would result in the formation of an unstable product. To check this hypothesis, we planned to use a less nucleophilic alkynylmetal reagent.

 Table 3
 Nucleophilic Ring Opening of 19 with Alkynyldimethylalanes

Micouin et al. reported a straightforward procedure for the preparation of alkynylorganoalanes and have studied their reactivity with aldehydes and cyanooxazolopiperidine.<sup>10</sup> We therefore investigated these reagents for the ring-opening reaction. Various alkynyldimethylalanes were thus prepared and used for the nucleophilic ring opening of **19** to synthesize dienophiles **20** (Table 3). From hep-tyne, we were pleased to isolate the desired compound **20** in 36% yield (entry 1). Unfortunately, the use of an oxygenated alkyne or trimethylsilylacetylene was unsuccessful (entries 2 and 3).

Finally, the subsequent inverse electron demand Diels– Alder reaction with tethered triazine **20** was carried out under microwave irradiation in a sealed tube under our optimal conditions.<sup>3a,b</sup> 3-Hydroxy-3,4-dihydro-2*H*-pyrano[2,3-*b*]pyridine **21** was obtained in a remarkable 96% yield (Scheme 5).



Scheme 5 Intramolecular inverse electron demand Diels–Alder reaction under microwave irradiation

In summary, the intramolecular inverse electron demand Diels–Alder reaction has been applied to the synthesis of 2,3-dihydrofuro[2,3-*b*]pyridines and 3,4-dihydro-2*H*-pyr-ano[2,3-*b*]pyridines. This methodology involving the ring opening of racemic glycidol with various alkynes represents a viable route for the preparation of the dienophilic side chain. Intramolecular cycloaddition then proceeds in excellent yields from these compounds giving access to 2-(hydroxymethyl)-2,3-dihydrofuro[2,3-*b*]pyridines and 3-

hydroxy-3,4-dihydro-2*H*-pyrano[2,3-*b*]pyridine. Further investigations are ongoing to extend the scope of this methodology with an emphasis on the preparation of poly-functionalized, enantiopure scaffolds.

Microwave irradiations were carried out in sealed 2-5 mL vessels placed in a Biotage Initiator system using a standard absorbance level (300 W maximum power). The temperatures were measured externally by an IR probe that determined the temperature on the surface of the vial and could be read directly from the instrument screen. The reaction time was measured from when the reaction mixture reached the stated temperature for temperature-controlled experiments. Small-scale reactions were performed [triazine (0.3 mmol), 2-5 mL vial, 3-6 bar]. Pressure was measured by a non-invasive sensor integrated into the cavity lid. CAUTION: The microwave apparatus has to be equipped with a safety pressure shutoff when the reaction generates more than 20 bar. If the pressure develops too quickly, an explosion will occur. <sup>1</sup>H NMR (250 MHz) and <sup>13</sup>C NMR (63 MHz) spectra were recorded on a Bruker Avance DPX250 spectrometer; TMS was used as the internal standard and multiplicities were determined by the DEPT 135 sequence. IR spectra of samples prepared as NaCl films or KBr pellets were obtained on a Perkin-Elmer Paragon 1000 PC FTIR spectromenter. Low-resolution MS was carried out on a Perkin-Elmer SCIEX API 3000 spectrometer. HRMS (ESI-TOF) was performed on a Micromass LC TOF spectrometer. Triazine derivatives  $(R^1 = H)$  appear to be much more unstable than the others ( $R^1 \neq H$ ). Melting points were determined in open capillary tubes and are uncorrected. Flash chromatography was performed on silica gel 60 (40-63 mesh). TLC was carried out on Merck silica gel 60F254 precoated plates and UV light was used for visualization. Reactions requiring anhyd conditions were performed under argon. THF was freshly distilled from sodium/benzophenone, and CH2Cl2 from CaH2 under argon prior to use. Chemicals were obtained from Aldrich and Acros.

#### 3-(Trityloxy)-1,2-epoxypropane (3)

TrCl (5 g, 18.1 mmol) and Et<sub>3</sub>N (2.52 mL, 18.1 mmol) were added to a stirred soln of glycidol (1 mL, 15 mmol) in anhyd  $CH_2Cl_2$  under a N<sub>2</sub> atmosphere at 0 °C. Then the mixture was warmed to r.t. and the reaction was monitored by TLC. After complete conversion of the starting material, the reaction was quenched with sat. aq Na<sub>2</sub>CO<sub>3</sub> (15 mL). The aqueous layer was extracted with  $CH_2Cl_2$  (3 × 25 mL) and the combined organic extracts were dried (MgSO<sub>4</sub>), evaporated, and purified by column chromatography (silica gel, PE–EtOAc, 9:1); this afforded epoxide **3**.

Yield: 83%; white solid; mp 72-74 °C.

IR (KBr): 3061, 3018, 1448, 1212, 1145, 1017, 912, 774, 668 cm<sup>-1</sup>.

<sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.49–7.45 (m, 6 H), 7.34–7.22 (m, 9 H), 4.03–3.93 (m, 1 H), 3.78–3.41 (m, 2 H), 3.39–3.27 (m, 2 H). <sup>13</sup>C NMR (62.9 MHz, CDCl<sub>3</sub>):  $\delta$  = 145.6 (C<sub>Ar</sub>), 130.6 (CH<sub>Ar</sub>), 129.8 (CH<sub>Ar</sub>), 129.2 (CH<sub>Ar</sub>), 88.9 (C), 72.7 (CH), 66.3 (CH<sub>2</sub>), 48.7 (CH<sub>2</sub>). MS (ES): *m*/*z* = 317 [M + 1].

#### β-Hydroxyalkynes 4 and 5; General Procedure

A 1.6 M soln of *n*-BuLi in hexane (61.31 mL, 98.2 mmol) was added to a stirred soln of ethynyltrimethylsilane or ethyl ethynyl ether (98.2 mmol) in anhyd THF (310 mL) under a N<sub>2</sub> atmosphere at – 78 °C. After 30 min, oxirane **3** (15.5 g, 49.1 mmol) and BF<sub>3</sub>·OEt<sub>2</sub> (12.45 mL, 98.2 mmol) were added. Then the mixture was stirred overnight at –78 °C to r.t. The mixture was quenched with sat. aq Na<sub>2</sub>CO<sub>3</sub> (300 mL) and extracted with EtOAc (3 × 200 mL). The combined organic extracts were dried (MgSO<sub>4</sub>), evaporated, and purified by column chromatography (silica gel, PE–EtOAc, 6:4); this gave the corresponding β-hydroxyalkyne **4** or **5**.

### 5-(Trimethylsilyl)-1-(trityloxy)pent-4-yn-2-ol (4)

Yield: 75%; white solid; mp 82-84 °C.

IR (KBr): 3260, 3019, 2150, 1596, 1417, 1212, 911, 756 cm<sup>-1</sup>.

<sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.53 (d, *J* = 7.3 Hz, 6 H), 7.46–7.27 (m, 9 H), 4.02–3.91 (m, 1 H), 3.34–3.22 (m, 2 H), 2.55–2.48 (m, 3 H), 0.16 (s, 9 H).

<sup>13</sup>C NMR (62.9 MHz, CDCl<sub>3</sub>): δ = 143.7 (C<sub>Ar</sub>), 129.1 (CH<sub>Ar</sub>), 128.0 (CH<sub>Ar</sub>), 127.1 (CH<sub>Ar</sub>), 102.5 (C), 87.1 (C), 86.7 (C), 69.2 (CH), 66.0 (CH<sub>2</sub>), 25.2 (CH<sub>2</sub>), -0.45 (CH<sub>3</sub>-Si).

MS (ES): m/z = 415 [M + H].

ESI-HRMS: m/z [M + Na] calcd for C<sub>27</sub>H<sub>30</sub>O<sub>2</sub>NaSi: 437.1913; found: 437.1933.

#### 5-Ethoxy-1-(trityloxy)pent-4-yn-2-ol (5)

Yield: 35%; yellow oil.

IR (NaCl): 3454, 3052, 2267, 1723, 1447, 1211, 771 cm<sup>-1</sup>.

<sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.46–7.42 (m, 6 H), 7.42–7.16 (m, 9 H), 3.92–3.79 (m, 3 H), 3.20 (dd, *J* = 1.9, 4.3 Hz, 2 H), 2.49 (d, *J* = 5.0 Hz, OH), 2.40 (d, *J* = 6.2 Hz, 2 H), 1.21 (t, *J* = 6.9 Hz, 3 H). <sup>13</sup>C NMR (62.9 MHz, CDCl<sub>3</sub>):  $\delta$  = 144.9 (C<sub>Ar</sub>), 130.2 (CH<sub>Ar</sub>), 128.9 (CH<sub>Ar</sub>), 128.0 (CH<sub>Ar</sub>), 92.1 (C), 87.6 (C), 75.0 (CH<sub>2</sub>), 70.9 (CH), 67.2 (CH<sub>2</sub>), 34.0 (C), 23.8 (CH<sub>2</sub>), 15.3 (CH<sub>3</sub>).

MS (ES): m/z = 387 [M + H].

#### Alkynes 6-9; General Procedure

A 1.6 M soln of *n*-BuLi in hexane (5.14 mL, 8.2 mmol) was added dropwise to a soln of  $\beta$ -hydroxyalkyne **4** or **5** (6.8 mmol) in anhyd THF (5 mL) at -78 °C, and the mixture was stirred at 0 °C for 30 min. The appropriate triazine **1** or **2** (6.8 mmol) was then added, and the reaction was allowed to slowly reach r.t. After 2 h, the soln was poured into H<sub>2</sub>O (10 mL) and extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 × 10 mL). The combined organic extracts were dried (MgSO<sub>4</sub>), evaporated, and purified by column chromatography (silica gel, PE–EtOAc, 9:1); this gave the corresponding alkynes **6–9**.

### 5-Phenyl-3-[4-(trimethylsilyl)-1-(trityloxymethyl)but-3-ynyloxy]-1,2,4-triazine (6)

Yield: 63%; white solid; mp 65-67 °C.

IR (KBr): 3260, 3019, 2210, 1541, 1413, 1212, 1015, 776, 668  $\rm cm^{-1}.$ 

<sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>):  $\delta$  = 9.38 (s, 1 H), 8.18–8.15 (m, 2 H), 7.56–7.43 (m, 3 H), 7.23–7.25 (m, 6 H), 7.22–7.16 (m, 9 H), 5.79–5.70 (quin, *J* = 5.9 Hz, 1 H), 3.55–3.67 (m, 2 H), 3.06–2.28 (m, 2 H), 0.06 (s, 9 H).

<sup>13</sup>C NMR (62.9 MHz, CDCl<sub>3</sub>):  $\delta = 165.2$  (C<sub>triazine</sub>), 157.7 (C<sub>triazine</sub>), 143.7 (C<sub>Ar</sub>), 141.3 (CH<sub>triazine</sub>), 133.1 (C<sub>Ar</sub>), 132.7 (CH<sub>Ar</sub>), 129.3 (CH<sub>Ar</sub>), 128.7 (CH<sub>Ar</sub>), 127.8 (CH<sub>Ar</sub>), 127.1 (CH<sub>Ar</sub>), 127.0 (CH<sub>A</sub>), 101.7 (CO), 87.3 (C), 86.7 (C), 75.2 (CH), 63.4 (CH<sub>2</sub>O), 22.7 (CH<sub>2</sub>), 0.4 (CH<sub>3</sub>Si).

MS (ES): m/z = 570 [M + H].

ESI-HRMS: m/z [M + Na] calcd for  $C_{36}H_{35}N_3O_2NaSi$ : 592.2396; found: 592.2388.

# 3-[4-Ethoxy-1-(trityloxymethyl)but-3-ynyloxy]-5-phenyl-1,2,4-triazine (7)

Yield: 77%; yellow oil.

IR (NaCl): 3444, 3004, 2296, 1533, 1474, 1302, 1210, 1021, 752  $\rm cm^{-1}.$ 

<sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>):  $\delta$  = 9.30 (s, 1 H), 8.10–8.07 (m, 2 H), 8.07–7.43 (m, 3 H), 7.37–7.33 (m, 6 H), 7.23–7.05 (m, 9 H), 5.61–5.52 (m, 1 H), 3.80 (qd, *J* = 6.9, 14.1 Hz, 2 H), 3.48 (m, 2 H), 2.84–2.65 (m, 2 H), 1.17 (t, *J* = 6.9 Hz, 3 H).

<sup>13</sup>C NMR (62.9 MHz, CDCl<sub>3</sub>): δ = 165.4 (C<sub>triazine</sub>), 157.7 (C<sub>triazine</sub>), 143.9 (C<sub>Ar</sub>), 141.3 (CH<sub>triazine</sub>), 133.2 (C<sub>Ar</sub>), 132.7 (CH<sub>Ar</sub>), 129.4 (CH<sub>Ar</sub>), 128.8 (CH<sub>Ar</sub>), 127.9 (CH<sub>Ar</sub>), 127.8 (CH<sub>Ar</sub>), 127.0 (CH<sub>Ar</sub>), 90.8 (C), 86.7 (CO), 76.2 (CH), 74.0 (CH<sub>2</sub>O), 63.5 (CH<sub>2</sub>O), 32.7 (C), 20.1 (CH<sub>2</sub>), 14.3 (CH<sub>3</sub>).

MS (ES): m/z = 542 [M + H].

ESI-HRMS: m/z [M + Na] calcd for  $C_{35}H_{31}N_3O_3Na$ : 564.2263; found: 564.2263.

# 3-[4-(Trimethylsilyl)-1-(trityloxymethyl)but-3-ynyloxy]-1,2,4-triazine (8)

Yield: 70%; yellow oil.

IR (NaCl): 3055, 2944, 2183, 1527, 1399, 1206, 1012, 787, 637 cm<sup>-1</sup>.

<sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>):  $\delta$  = 8.89 (d, *J* = 2.2 Hz, 1 H), 8.33 (d, *J* = 2.2 Hz, 1 H), 7.48 (dd, *J* = 1.5, 8.4 Hz, 6 H), 7.31–7.18 (m, 9 H), 5.70 (quin, *J* = 5.9 Hz, 1 H), 3.64–3.52 (m, 2 H), 3.01–2.83 (m, 2 H), 0.08 (s, 9 H)

<sup>13</sup>C NMR (62.9 MHz, CDCl<sub>3</sub>): δ = 165.3 (C<sub>triazine</sub>), 150.7 (CH<sub>triazine</sub>), 144.7 (CH<sub>triazine</sub>), 143.6 (C<sub>Ar</sub>), 128.6 (CH<sub>Ar</sub>), 127.7 (CH<sub>Ar</sub>), 126.9 (CH<sub>Ar</sub>), 101.4 (C), 87.2 (C), 86.6 (CO), 75.3 (CH), 63.3 (CH<sub>2</sub>O), 22.4 (CH<sub>2</sub>), -0.09 (CH<sub>3</sub>Si).

MS (ES): m/z = 494 [M + H].

ESI-HRMS: m/z [M + Na] calcd for  $C_{30}H_{31}N_3O_2NaSi$ : 516.2083; found: 516.2086.

# 3-[4-Ethoxy-1-(trityloxymethyl)but-3-ynyloxy]-1,2,4-triazine (9)

Yield: 71%; yellow oil.

IR (NaCl): 3073, 2908, 2266, 1545, 1411, 1221, 697 cm<sup>-1</sup>.

<sup>1</sup>H NMR (250MHz, CDCl<sub>3</sub>):  $\delta = 8.84$  (d, J = 2.2 Hz, 1 H), 8.29 (d, J = 2.2 Hz, 1 H), 7.44 (dd, J = 1.5, 8.4 Hz, 6 H), 7.26–7.16 (m, 9 H), 5.56 (quin, J = 5.9 Hz, 1 H), 3.84 (q, J = 7.2 Hz, 2 H), 3.57–3.46 (m, 2 H), 2.86–2.68 (m, 2 H), 1.89 (t, J = 7.2 Hz, 3 H).

<sup>13</sup>C NMR (62.9 MHz, CDCl<sub>3</sub>): δ = 165.4 (C<sub>triazine</sub>), 150.7 (CH<sub>triazine</sub>), 144.6 (CH<sub>triazine</sub>), 143.7 (C<sub>Ar</sub>), 128.6 (CH<sub>Ar</sub>), 127.7 (CH<sub>Ar</sub>), 126.9 (CH<sub>Ar</sub>), 90.7 (C), 86.5 (C), 76.3 (CO), 73.9 (CH), 63.4 (CH<sub>2</sub>O), 32.4 (CH<sub>2</sub>O), 19.8 (CH<sub>2</sub>), 14.2 (CH<sub>3</sub>).

MS (ES): m/z = 466 [M + H].

#### Terminal Alkynes 10 and 11; General Procedure

TBAF (628  $\mu$ L, 0.6 mmol) was added dropwise to a soln of alkyne **6** or **8** (0.3 mmol) in anhyd THF (4 mL), and the mixture was stirred

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Dihydrofuropyridines and Dihydropyranopyridines 1353

overnight at r.t. The mixture was quenched with  $H_2O$  (10 mL) and extracted with  $CH_2Cl_2$  (3 × 10 mL). The combined organic extracts were dried (MgSO<sub>4</sub>), evaporated, and purified by column chromatography (silica gel, PE–EtOAc, 8:2); this gave the corresponding terminal alkynes **10** and **11**.

# 5-Phenyl-3-[1-(trityloxymethyl)but-3-ynyloxy]-1,2,4-triazine (10)

Yield: 93%; yellow solid; mp 65–67 °C.

IR (KBr): 3263, 3019, 2215, 2014, 1542, 1441, 1282, 1015, 998, 764, 668 cm<sup>-1</sup>.

<sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>):  $\delta$  = 9.38 (s, 1 H), 8.17–8.14 (m, 2 H), 7.59–7.51 (m, 3 H), 7.44–7.42 (m, 6 H), 7.25–7.16 (m, 9 H), 5.68 (m, 1 H), 3.57 (d, *J* = 4.0 Hz, 2 H), 2.98–2.85 (m, 2 H), 1.92 (s, 1 H).

<sup>13</sup>C NMR (62.9 MHz, CDCl<sub>3</sub>): δ = 165.7 (C<sub>triazine</sub>), 158.4 (C<sub>triazine</sub>), 144.2 (C<sub>Ar</sub>), 142.5 (CH<sub>triazine</sub>), 133.6 (C<sub>Ar</sub>), 133.3 (CH<sub>Ar</sub>), 129.9 (CH<sub>Ar</sub>), 129.2 (CH<sub>Ar</sub>), 129.0 (CH<sub>Ar</sub>), 128.1 (CH<sub>Ar</sub>), 127.6 (CH<sub>A</sub>), 87.3 (C), 80.0 (CH), 75.6 (CO), 71.3 (CHO), 63.8 (CH<sub>2</sub>O), 21.4 (CH<sub>2</sub>).

MS (ES): m/z = 498 [M + H].

ESI-HRMS: m/z [M + Na] calcd for  $C_{33}H_{27}N_3O_2Na$ : 520.2001; found: 520.2000.

### 3-[1-(Trityloxymethyl)but-3-ynyloxy]-1,2,4-triazine (11)

Yield: 97%; dark red oil.

IR (NaCl): 3036, 2917, 2238, 1729, 1633, 1414, 1210, 778, 637 cm<sup>-1</sup>.

<sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>):  $\delta$  = 8.93 (d, *J* = 2.2 Hz, 1 H), 8.39 (d, *J* = 2.2 Hz, 1 H), 7.42 (dd, *J* = 1.5, 8.4 Hz, 6 H), 7.29–7.19 (m, 9 H), 5.60 (quin, *J* = 5.9 Hz, 1 H), 3.58–3.46 (m, 2 H), 2.95–2.76 (m, 2 H), 1.89 (t, *J* = 2.5 Hz, 1 H).

<sup>13</sup>C NMR (62.9 MHz, CDCl<sub>3</sub>): δ = 165.4 (C<sub>triazine</sub>), 150.9 (CH<sub>triazine</sub>), 144.9 (CH<sub>triazine</sub>), 143.7 (C<sub>Ar</sub>), 128.7 (CH<sub>Ar</sub>), 127.9 (CH<sub>Ar</sub>), 127.1 (CH<sub>Ar</sub>), 86.8 (C), 79.2 (CH), 75.3 (CO), 70.8 (CHO), 63.2 (CH<sub>2</sub>O), 21.2 (CH<sub>2</sub>).

MS (ES): m/z = 422 [M + H].

#### Furo[2,3-b]pyridines 12-17; General Procedure

Triazines **6–11** (0.3 mmol) were dissolved in chlorobenzene (5 mL) and heated at 170 °C under microwave irradiation (pressure can reach 3–6 bar). The reaction was monitored by TLC. After complete conversion of the starting material (1–2 h), the product was purified by chromatography (silica gel, PE–EtOAc); this gave the desired products **12–17**.

#### 6-Phenyl-4-(trimethylsilyl)-2-(trityloxymethyl)-2,3-dihydrofuro[2,3-*b*]pyridine (12)

Purification by column chromatography (silica gel, PE–EtOAc, 9:1).

Yield: 89%; white solid; mp 145-147 °C.

IR (KBr): 3019, 1614, 1596, 1215, 1072, 921, 774, 668 cm<sup>-1</sup>.

<sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>):  $\delta = 8.07$  (d, J = 7.9 Hz, 2 H), 7.46–7.17 (m, 19 H), 5.01–4.95 (m, 1 H), 3.46 (dd, J = 3.7, 10.0 Hz, 1 H), 3.36–3.23 (m, 2 H), 3.07 (dd, J = 5.8, 10.0 Hz, 1 H), 0.30 (s, 9 H).

<sup>13</sup>C NMR (62.9 MHz, CDCl<sub>3</sub>):  $\delta$  = 167.5 (C), 154.1 (C-Si), 147.4 (C<sub>Ar</sub>), 143.8 (C<sub>Ar</sub>), 143.8 (C<sub>Ar</sub>), 139.5 (C), 128.7 (CH<sub>Ar</sub>), 127.9 (CH<sub>Ar</sub>), 127.1 (CH<sub>Ar</sub>), 127.1 (CH<sub>Ar</sub>), 125.9 (CH<sub>Ar</sub>), 123.4 (CH), 117.1 (CH), 86.6 (CO), 79.4 (CHO), 66.1 (CH<sub>2</sub>O), 31.8 (CH<sub>2</sub>), -0.9 (CH<sub>3</sub>-Si).

MS (ES): m/z = 542 [M + H].

ESI-HRMS: *m*/*z* [M + H] calcd for C<sub>36</sub>H<sub>36</sub>NO<sub>2</sub>Si: 542.2515; found: 542.2518.

### 4-Ethoxy-6-phenyl-2-(trityloxymethyl)-2,3-dihydrofuro[2,3b]pyridine (13)

Purification by column chromatography (silica gel, PE-EtOAc, 9:1).

Yield: 95%; white solid; mp 174–176 °C.

IR (KBr): 3033, 1961, 1600, 1574, 1398, 1210, 1098, 939, 817, 761 cm<sup>-1</sup>.

<sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.90 (d, *J* = 7.9 Hz, 2 H), 7.87– 7.10 (m, 19 H), 4.96–4.85 (m, 1 H), 3.46 (q, *J* = 6.9 Hz, 2 H), 3.28 (dd, *J* = 2.8, 5.3 Hz, 2 H), 3.15 (dd, *J* = 9.4, 16.0 Hz, 1 H), 2.93 (dd, *J* = 6.6, 16.0 Hz, 1 H), 1.36 (t, *J* = 6.9 Hz, 3 H).

<sup>13</sup>C NMR (62.9 MHz, CDCl<sub>3</sub>): δ = 171.1 (C), 164.1 (C), 158.4 (C), 144.9 (C<sub>Ar</sub>), 140.6 (C<sub>Ar</sub>), 129.8 (CH<sub>Ar</sub>), 129.6 (CH<sub>Ar</sub>), 128.9 (CH<sub>Ar</sub>), 128.1 (CH<sub>Ar</sub>), 128.0 (CH<sub>Ar</sub>), 127.8 (CH<sub>Ar</sub>), 127.0 (CH<sub>A</sub>), 104.7 (C), 100.2 (CH), 87.7 (CO), 81.2 (CHO), 67.0 (CH<sub>2</sub>O), 65.0 (CH<sub>2</sub>O), 29.9 (CH<sub>2</sub>), 15.9 (CH<sub>3</sub>).

MS (ES): m/z = 514 [M + H].

ESI-HRMS: m/z [M + H] calcd for C<sub>35</sub>H<sub>32</sub>NO<sub>3</sub>: 514.2382; found: 514.2369.

### 4-(Trimethylsilyl)-2-(trityloxymethyl)-2,3-dihydrofuro[2,3b]pyridine (14)

Purification by column chromatography (silica gel, PE-EtOAc, 9:1).

Yield: 90%; white solid; mp 93-95 °C.

IR (KBr): 3012, 2910, 1450, 1378, 1214, 1065, 941, 822, 761, 680  $\rm cm^{-l}.$ 

<sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>):  $\delta = 8.00$  (d, J = 4.7 Hz, 1 H), 7.38 (dd, J = 1.5, 6.6 Hz, 6 H), 7.34–7.19 (m, 9 H), 6.87 (d, J = 4.7 Hz, 1 H), 4.96–4.87 (m, 1 H), (dd, J = 3.7, 10.0 Hz, 1 H), 3.28 (dd, J = 6.3, 16.0 Hz, 1 H), 3.19 (dd, J = 4.0, 10.0 Hz, 1 H), 3.06 (dd, J = 5.9, 16.0 Hz, 1 H), 0.26 (s, 9 H).

<sup>13</sup>C NMR (62.9 MHz, CDCl<sub>3</sub>):  $\delta$  = 167.3 (C), 146.9 (C-Si), 145.6 (CH), 143.8 (C<sub>Ar</sub>), 128.7 (CH<sub>Ar</sub>), 127.7 (CH<sub>Ar</sub>), 127.0 (CH<sub>Ar</sub>), 124.9 (C), 120.8 (CH), 86.5 (CO), 79.0 (CHO), 66.3 (CH<sub>2</sub>O), 31.9 (CH<sub>2</sub>), -1.4 (CH<sub>3</sub>-Si).

MS (ES): m/z = 466 [M + H].

ESI-HRMS: *m*/*z* [M + H] calcd for C<sub>30</sub>H<sub>32</sub>NO<sub>2</sub>Si: 466.2188; found: 466.2202.

# **4-Ethoxy-2-(trityloxymethyl)-2,3-dihydrofuro**[**2,3-***b*]**pyridine** (15)

Purification by column chromatography (silica gel, PE–EtOAc, 8:2 to 6:4).

Yield: 93%; yellow oil.

IR (NaCl): 3008, 2933, 1465, 1348, 1315, 1214, 1078, 935, 802, 764, 664  $\rm cm^{-1}.$ 

<sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.93 (d, *J* = 5.9 Hz, 1 H), 7.40 (dd, *J* = 1.6, 8.1 Hz, 6 H), 7.31–7.17 (m, 9 H), 6.37 (d, *J* = 5.9 Hz, 1 H), 4.99–4.89 (m, 1 H), 4.10 (q, *J* = 7.2 Hz, 2 H), 3.30 (d, *J* = 4.7 Hz, 2 H), 3.13 (dd, *J* = 9.7, 16.3 Hz, 1 H), 2.95 (dd, *J* = 10.0, 16.3 Hz, 1 H), 1.40 (t, *J* = 7.2 Hz, 3 H).

<sup>13</sup>C NMR (62.9 MHz, CDCl<sub>3</sub>): δ = 166.4 (C), 165.6 (C), 145.1 (CH), 143.8 (C<sub>Ar</sub>), 129.1 (CH<sub>Ar</sub>), 127.6 (CH<sub>Ar</sub>), 126.3 (CH<sub>Ar</sub>), 120.8 (C), 106.7 (CHO), 86.5 (CH), 78.7 (CH<sub>2</sub>O), 65.5 (CH<sub>2</sub>O), 48.9 (CO), 32.0 (CH<sub>2</sub>), 14.8 (CH<sub>3</sub>).

MS (ES): m/z = 438 [M + H].

# 6-Phenyl-2-(trityloxymethyl)-2,3-dihydrofuro[2,3-*b*]pyridine (16)

Purification by column chromatography (silica gel, PE-EtOAc, 6:4).

Yield: 83%; yellow oil.

IR (NaCl): 3018, 1606, 1437, 1337, 1214, 1015, 984, 764, 680 cm<sup>-1</sup>.

<sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>):  $\delta = 8.03-7.97$  (m, 2 H), 7.38-7.20 (m, 20 H), 5.03-4.93 (ddd, J = 4.7, 5.9, 9.7 Hz, 1 H), 3.43 (dd, J = 4.4, 10.0 Hz, 1 H), 3.33 (dd, J = 5.0, 10.0 Hz, 1 H), 3.26 (dd, J = 9.4, 16.3 Hz, 1 H), 3.05 (dd, J = 5.9, 16.3 Hz, 1 H).

<sup>13</sup>C NMR (62.9 MHz, CDCl<sub>3</sub>): δ = 168.5 (C), 155.2 (C), 143.8 (C<sub>Ar</sub>), 139.1 (C<sub>Ar</sub>), 133.9 (CH), 129.6 (CH<sub>Ar</sub>), 128.8 (CH<sub>Ar</sub>), 128.6 (CH<sub>Ar</sub>), 127.9 (CH<sub>Ar</sub>), 127.1 (CH<sub>Ar</sub>), 126.9 (CH<sub>Ar</sub>), 118.4 (C), 113.3 (CH), 86.7 (CHO), 79.9 (CO), 65.9 (CH<sub>2</sub>O), 30.8 (CH<sub>2</sub>).

MS (ES): m/z = 470 [M + H].

ESI-HRMS: m/z [M + H] calcd for C<sub>33</sub>H<sub>28</sub>NO<sub>2</sub>: 470.2120; found: 470.2124.

#### 2-(Trityloxymethyl)-2,3-dihydrofuro[2,3-b]pyridine (17)

Purification by column chromatography (silica gel, PE-EtOAc, 9:1).

Yield: 90%; orange oil.

IR (KBr): 2927, 1435, 1248, 1202, 1054, 917, 842, 768, 672 cm<sup>-1</sup>.

<sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.90–7.82 (m, 2 H), 7.28 (dd, J = 1.4, 7.9 Hz, 6 H), 7.21–7.09 (m, 9 H), 6.37–6.29 (m, 1 H), 4.90–4.81 (m, 1 H), 3.28 (d, J = 4.5 Hz, 2 H), 3.11 (dd, J = 10.0, 16.1 Hz, 1 H), 2.95 (dd, J = 9.8, 16.0 Hz, 1 H).

<sup>13</sup>C NMR (62.9 MHz, CDCl<sub>3</sub>): δ = 165.4 (C), 144.1 (CH), 143.2 (C<sub>Ar</sub>), 136.5 (CH), 130.9 (C), 129.1 (CH<sub>Ar</sub>), 128.7 (CH<sub>Ar</sub>), 126.7 (CH<sub>Ar</sub>), 112.4 (CH), 106.4 (CHO), 68.5 (CH<sub>2</sub>O), 48.9 (CO), 32.0 (CH<sub>2</sub>).

MS (ES): m/z = 394 [M + H].

# [6-Phenyl-4-(trimethylsilyl)-2,3-dihydrofuro[2,3-*b*]pyridin-2-yl]methanol (18)

TFA (110  $\mu$ L, 1.4 mmol) was added to a stirred soln of **12** (155 mg, 0.3 mmol) in anhyd CH<sub>2</sub>Cl<sub>2</sub> under a a N<sub>2</sub> atmosphere. The mixture was stirred at r.t. for 48 h. Then the reaction was quenched with H<sub>2</sub>O (10 mL) and the mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 × 10 mL). The combined organic extracts were dried (MgSO<sub>4</sub>), evaporated, and purified by column chromatography (silica gel, PE–EtOAc, 9:1); this afforded the desired product **18**.

Yield: 63%; yellow oil.

IR (NaCl): 3440, 3360, 3254, 3010, 1466, 1438, 1315, 1208, 1025, 981, 763, 682 cm<sup>-1</sup>.

<sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.92 (dd, *J* = 1.8, 8.3 Hz, 2 H), 7.46–7.34 (m, 3 H), 7.32 (s, 1 H), 5.02–4.91 (m, 1 H), 3.92 (dd, *J* = 3.2, 5.7 Hz, 1 H), 3.73 (dd, *J* = 5.7, 12.3 Hz, 1 H), 3.26 (dd, *J* = 9.5, 16.3 Hz, 1 H), 3.07 (dd, *J* = 7.4, 16.3 Hz, 1 H), 0.34 (s, 9 H).

<sup>13</sup>C NMR (62.9 MHz, CDCl<sub>3</sub>):  $\delta$  = 166.8 (C), 154.2 (C-Si), 148.3 (C), 139.2 (C<sub>Ar</sub>), 128.7 (CH<sub>Ar</sub>), 128.6 (CH<sub>Ar</sub>), 126.9 (CH<sub>Ar</sub>), 123.1 (C), 118.1 (CH), 80.9 (CHO), 64.9 (CH<sub>2</sub>OH), 30.7 (CH<sub>2</sub>), -1.31 (CH<sub>3</sub>Si).

MS (ES): m/z = 300 [M + H].

#### **3-(Oxiranylmethoxy)-5-phenyl-1,2,4-triazine (19)**

Glycidol (367  $\mu$ L, 5.5 mmol) was added to a stirred suspension of NaH (60% oil dispersion; 0.22 g, 5.5 mmol) under a N<sub>2</sub> atmosphere at 0 °C. After 10 min, the 5-phenyl-1,2,4-triazine **1** (1 g, 4.2 mmol) was added. The mixture was then warmed to r.t. and monitored by TLC. After complete conversion of the starting material, the reac-

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tion was quenched with  $H_2O(40 \text{ mL})$  and the mixture was extracted with EtOAc (3 × 60 mL). The organic layer was dried (MgSO<sub>4</sub>), evaporated, and purified by column chromatography (silica gel, PE–EtOAc, 4:6); this afforded **19**.

Yield: 81%; yellow solid; mp 74-76 °C.

IR (KBr): 3019, 1571, 1414, 1382, 1215, 998, 748, 668 cm<sup>-1</sup>.

<sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>):  $\delta$  = 9.44 (s, 1 H), 8.16–8.20 (m, 2 H), 7.56–7.59 (m, 3 H), 4.87 (dd, *J* = 3.5, 12.3 Hz, 1 H), 4.51 (dd, *J* = 6.0, 12.3 Hz, 1 H), 3.49–3.53 (m, 1 H), 2.90 (t, *J* = 4.6 Hz, 1 H), 2.83 (dd, *J* = 2.6, 4.6 Hz, 1 H).

<sup>13</sup>C NMR (62.9 MHz, CDCl<sub>3</sub>):  $\delta$  = 165.4 (C), 158.4 (C), 142.2 (C<sub>Ar</sub>), 133.2 (CH<sub>Ar</sub>), 129.7 (CH<sub>Ar</sub>), 128.2 (CH<sub>Ar</sub>), 126.2 (CH), 69.5 (CH<sub>2</sub>), 49.7 (CHO), 45.2 (CH<sub>2</sub>).

MS (ES): m/z = 230 [M + H].

ESI-HRMS: m/z [M + H] calcd for C<sub>12</sub>H<sub>12</sub>N<sub>3</sub>O<sub>2</sub>: 230.0930; found: 230.0916.

#### 1-(5-Phenyl-1,2,4-triazin-3-yloxy)dec-4-yn-2-ol (20)

A dry and argon-flushed flask equipped with a magnetic stirrer and a septum was charged with 2 M Me<sub>3</sub>Al in toluene (873  $\mu$ L, 1.7 mmol). Et<sub>3</sub>N (24  $\mu$ L, 0.2 mmol) was added at r.t. After 5 min, the alkyne (1.9 mmol) was then added dropwise, and the resulting mixture was heated to 60 °C for 4 h. The soln was then added by syringe to a soln of oxirane **19** (200 mg, 0.9 mmol) in anhyd toluene (10 mL) at 0 °C; the reaction mixture was stirred for 1 h at the same temperature, then allowed to slowly reach r.t., and stirred for 1 h before being poured into a cooled 2 M aq soln of Rochelle's salts (15 mL) (CAUTION: gas evolution). After 30 min of vigorous stirring, the organic phase was separated and the aqueous phase was extracted with Et<sub>2</sub>O (3 × 15 mL). The organic layer was dried (MgSO<sub>4</sub>), the solvent was evaporated, and the crude residue was purified by column chromatography (silica gel, PE–EtOAc, 8:2); this afforded compound **20**.

#### Yield: 36%; yellow oil.

IR (NaCl): 3422, 2954, 2187, 1666, 1542, 1425, 1256, 1014, 796, 668  $\rm cm^{-1}.$ 

<sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>):  $\delta$  = 9.43 (s, 1 H), 8.18–8.15 (m, 2 H), 7.64–7.51 (m, 3 H), 4.79–4.63 (ddd, *J* = 3.9, 6.4, 11.2 Hz, 2 H), 4.27 (s, 1 H), 3.07 (s, 1 H, OH), 2.62 (dd, *J* = 2.2, 8.6 Hz, 2 H), 2.13 (t, *J* = 2.2 Hz, 2 H), 1.52–1.46 (m, 2 H), 1.39–1.25 (m, 4 H), 0.87 (t, *J* = 7.0 Hz, 3 H).

<sup>13</sup>C NMR (62.9 MHz, CDCl<sub>3</sub>): δ = 165.5 (C), 158.2 (C), 141.8 (CH), 133.0 (C<sub>Ar</sub>), 133.0 (CH<sub>Ar</sub>), 129.5 (CH<sub>Ar</sub>), 128.0 (CH<sub>Ar</sub>), 83.8 (C), 74.8 (C), 71.4 (CH<sub>2</sub>O), 68.7 (CHOH), 31.2 (CH<sub>2</sub>), 28.7 (CH<sub>2</sub>), 24.1 (CH<sub>2</sub>), 22.3 (CH<sub>2</sub>), 18.8 (CH<sub>2</sub>), 14.0 (C H<sub>3</sub>).

MS (ES): m/z = 326 [M + H].

ESI-HRMS: m/z [M + Na] calcd for  $C_{19}H_{23}N_3O_2Na$ : 348.1688; found: 348.1673.

# 5-Pentyl-7-phenyl-3,4-dihydro-2*H*-pyrano[2,3-*b*]pyridin-3-ol (21)

Triazine **20** (0.98 g, 0.3 mmol) was dissolved in chlorobenzene (2 mL) and heated at 180 °C under microwave irradiation (pressure of up to 3–6 bar possible). The reaction was monitored by TLC. After complete conversion of the starting material, the product was purified by column chromatography (silica gel, PE–EtOAc, 5:5).

Yield 96%; yellow-orange oil.

IR (NaCl): 3400, 3260, 2960, 1730, 1680, 1458, 1284, 1215, 1098, 1022, 964, 784  $\rm cm^{-1}.$ 

<sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.93–7.90 (m, 2 H), 7.43–7.33 (m, 3 H), 7.07 (s, 1 H), 5.01–4.91 (m, 1 H), 3.92 (dd, *J* = 7.3, 11.9 Hz, 1 H), 3.75 (dd, *J* = 5.0, 11.9 Hz, 1 H), 3.20 (dd, *J* = 9.4, 16.3 Hz, 1

H), 3.02 (dd, J = 7.2, 16.3 Hz, 1 H), 2.91 (s, 1 H, OH), 2.52 (t, J = 7.5 Hz, 2 H), 1.64–1.56 (m, 2 H), 1.36–1.32 (m, 4 H), 0.90 (t, J = 6.5 Hz, 3 H).

<sup>13</sup>C NMR (62.9 MHz, CDCl<sub>3</sub>): δ = 167.9 (C), 155.0 (C), 150.2 (C), 139.0 (C<sub>Ar</sub>), 128.6 (CH<sub>Ar</sub>), 128.5 (CH<sub>Ar</sub>), 126.7 (CH<sub>Ar</sub>), 116.8 (C), 114.1 (CH), 81.2 (CHOH), 64.8 (CH<sub>2</sub>O), 33.2 (CH<sub>2</sub>), 31.6 (CH<sub>2</sub>), 28.8 (CH<sub>2</sub>), 28.5 (CH<sub>2</sub>), 22.5 (CH<sub>2</sub>), 14.0 (CH<sub>3</sub>).

MS (ES): m/z = 298 [M + H].

ESI-HRMS: m/z [M + H] calcd for C<sub>19</sub>H<sub>24</sub>NO<sub>2</sub>: 298.1807; found: 298.1796.

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