Single Electron Transfer Regioselective Photocatalytic Synthesis of 2-Cyano-1,2,5,6-tetrahydropyridines

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A mild and regioselective single electron transfer (SET) photocatalytic general synthesis of 2-cyano-1,2,5,6-tetrahydropyridines from 1,2,5,6-tetrahydropyridines is described. Cyanotrimethylsilane is used as cyanating agent in the presence of tetraphenylporphyrin (TPP) as photosensitizer.

There is continuing interest in α-amino nitriles, mainly because they are intermediates in convenient preparative methods for obtaining nitrogen-containing heterocycles, which are biologically important compounds. These derivatives have proven to be extremely versatile synthetic reagents: the carbon atom α to the nitrogen atom can be made nucleophilic or electrophilic at will, providing, in the former case, a masked carbonyl[1] or an ambident anion[2,3] and, in the latter, an iminium ion, by loss of cyanide ion.[2,4–6]

Specifically, 2-cyano-1,2,5,6-tetrahydropyridines, versatile synthetic equivalents of 5,6-dihydropyridinium salts, are potentially powerful synthons for the preparation of functionalized piperidines as one can envisage successive control over three of the ring carbon centers (C-2,3,4). In contrast to the unstable 5,6-dihydropyridinium salts, which can exist only under a very restricted set of conditions (i.e. acidic media), their cyano adducts, being more stable, are readily isolable entities. These synthons retain the reactivity of the parent dihydropyridinium salts without the inconveniences associated with its instability. The latter would account for the little attention the chemistry of these salts has received.

The only chemical preparation of these α-amino nitriles, using the classical modified Polonovski (Polonovski–Potier) reaction,[7] i.e. TFAA treatment of the 1,2,5,6-tetrahydropyridines *N*-oxides followed by cyanide trapping, has been developed by Husson and Grierson.[8] This potential reactivity has since been exploited in a number of syntheses, particularly in the indole alkaloid area.[9] Nevertheless, the Polonovski protocol suffers from several drawbacks: the necessary acidity of the medium, buffered to pH 4, during the formation of the α-amino nitrile is a problem when further *in situ* reactions are envisaged with carbon nucleophiles and other organometallic reagents; a purification is required. Moreover, in the case of *N*-tryptophyl-Δ^3-piperideines the indole nitrogen has to be deactivated by a suitable electron-withdrawing group to avoid the unwanted Grob-type fragmentation[10] of the tryptamine side chain which competes with α-amino nitrile formation. This deactivation would also prevent the intramolecular cyclization which could occur during the reaction of tetrahydropyridine *N*-oxides with TFAA, introducing two additional steps into synthetic sequences.

An alternative method to circumvent these drawbacks is the photoinduced single electron transfer (SET) method which allows the selective formation of an iminium cation under mild conditions.[11] We have recently reported that this intermediate can be trapped with cyanotrimethylsilane (TMSCN) allowing the regioselective preparation of 2-cyano-Δ^3-piperideines[12,13] as well as α-amino nitriles from various alkaloids.[14] We have pointed out that TMSCN is a superior trapping agent for these iminium ion intermediates and it also displays a suitable protection towards enamine moieties.[13,14] However, it was felt that the necessary acetonitrile medium[15] for these photocatalytic preparations, using 9,10-dicyanoanthracene (DCA)[11,12,14] or *N,N'*-dimethyl-2,7-diazapyreniumbis(tetrafluoroborate) (DAP^{2+}, $2\,BF_4^-$)[11,13] as electron acceptor, is not convenient for the synthesis of these α-amino nitriles as they are generally sensitive to heat.

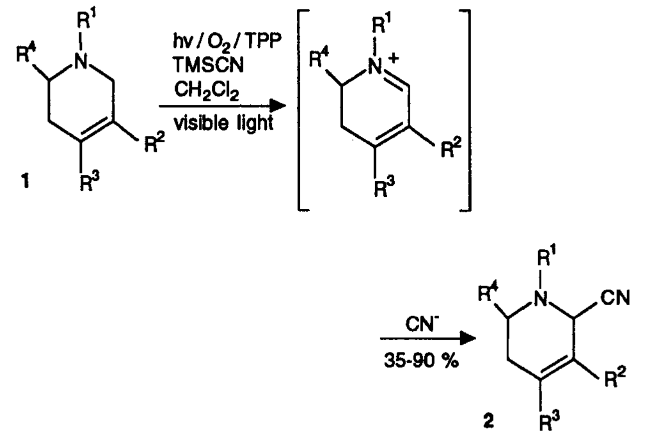
We now report a new general methodology for the preparation of 2-cyano-1,2,5,6-tetrahydropyridines involving use of 5,10,15,20-tetraphenyl-21*H*,23*H*-porphyrin (TPP, $\lambda > 500$ nm) as electron acceptor photosensitizer and dichloromethane as the medium. Under these very mild experimental conditions the corresponding α-amino nitrile is the only product formed. Due to the relative instability of certain derivatives, losses of up to 50% during the purification procedure were consistently encountered. Nevertheless, the crude products were pure enough for further synthetic use. Furthermore, the overall reaction rate is increased by a factor of 2 to 3 compared to our earlier experimental conditions.

It is noteworthy that, as might be expected for an electron-transfer reaction,[16] the α-amino nitrile products are not oxidized on irradiation. Indeed with an electron-withdrawing α-substituent such as CN on the nitrogen atom, the values of the quenching rate constants (k_q) between the acceptor and the amines are too low to achieve a second oxidation step.[17] The intermediate 5,6-dihydropyridinium salts are trapped through reaction with cyanide ion at a diffusion controlled rate,[11,17] thus avoiding oxidation by the oxygen bubbled into the solution.

The required tetrahydropyridines **1** were prepared by borohydride reduction of the corresponding pyridinium salts, which were themselves readily prepared by condensation of appropriate pyridines with alkyl or tryptophyl bromides according to known procedures.[18]

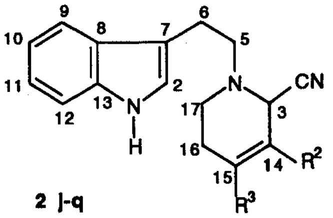
IR spectra were recorded on a Perkin-Elmer 457 spectrophotometer. ^{1}H and ^{13}C NMR spectra were obtained with a Brüker AC 200 spectrophotometer using $CDCl_3$ as a solvent and TMS as an internal reference. MS were determined on a quadrupole Nermag R 10-10 mass spectrometer.

2-Cyano-1,2,5,6-tetrahydropyridines (2a–q); Typical Procedure:
A solution of **1a** (1.2 g, 8 mmol) and TMSCN (2.12 mL, 16 mmol) in CH_2Cl_2 (25 mL) to which was added a catalytic amount of TPP



1,2	R^1	R^2	R^3	R^4
a	Me	Et	H	H
b	Me	Et	H	Me
c	Me	Me	Me	H
d	Me	OBn	H	H
e	Bn	Et	H	H
f	CH_2CO_2Et	Et	H	H
g	CH_2CO_2Et	Et	H	Me
h	CH_2CO_2Et	Me	Me	H
i	$CH(CO_2Et)_2$	Me	Me	H
j	tryptophyl	H	Me	H
k	tryptophyl	H	Et	H
l	tryptophyl	H	tBu	H
m	tryptophyl	Et	H	H
n	tryptophyl	Me	Me	H
o	tryptophyl	OBn	H	H
p	tryptophyl	—CH=CH—CH=CH—		H
q	tryptophyl	CH_2CO_2Et	H	H

Scheme 1



2 j-q

(0.020 g, 0.03 mmol) was irradiated, under oxygen bubbling, with a 1800 W Xenon lamp through a UV cut-off glass filter ($\lambda > 500$ nm) at about 20 °C. On completion of the reaction (TLC monitoring), the resulting mixture was evaporated under reduced pressure (water bath temperature 20–25 °C). The crude product was purified by flash chromatography on alumina [Merck (act. II–III); eluent, hexane–EtOAc 1 : 1] yielding pure product **2a** as a pale yellow liquid (1.26 g, 88 %) (Tables 1 and 2[19]).

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Table 1. Preparation of 2-Cyano-Δ^3-Piperideines **2a–q** from **1a–q**[a]

Product	Yield[b] (%)	Reaction time (h)	mp (°C) (solvent)	IR ($CHCl_3$) ν (cm^{-1})	MS (70 eV) *m/z* (%)
2a[2]	88	2	oil	2220	–
2b[2]	76	1.5	oil	2220	–
2c[2]	82	1.5	oil	2220	–
2d	76	1.5	oil	2220, 1680	229 (M^+ + 1, 40), 202 (100), 112 (4), 83 (6), 71 (7)
2e[2]	90	2	oil	2210	–
2f	77	1.25	oil	2220, 1750	222 (M^+, 7), 149 (62), 42 (100)
2g	78	2	oil	2220, 1750	236 (M^+, 8), 210 (37), 163 (100), 149 (98), 140 (74), 72 (39)
2h	80	1	oil	2220, 1750	222 (M^+, 19), 195 (6), 149 (100), 135 (74), 120 (29)
2i	72	0.5	67–68 (Et_2O)	2220, 1745[c]	294 (M^+, 50), 268 (89), 221 (100), 135 (52), 86 (54)
2j	35	2	oil	3400, 2230, 1630	265 (M^+, 24), 238 (19), 144 (25), 135 (100), 130 (57), 115 (19)
2k	60	2.5	oil	3400, 2220, 1630	279 (M^+, 31), 149 (100), 130 (27), 120 (12), 115 (5)
2l	45	2.5	141 (Et_2O)	3410, 2220, 1620	307 (M^+, 12) 250 (13), 177 (26), 163 (11), 144 (100), 130 (80)
2m	85	2	oil	3410, 2920, 2225, 1620	279 (M^+, 20), 252 (10), 181 (35), 176 (30), 149 (100), 130 (70)
2n	75	1.25	amorphous	3420, 2920, 2220, 1630	279 (M^+, 45), 252 (26), 176 (48), 149 (95), 130 (100), 115 (75)
2o[20]	82	2	oil	3410, 2220, 1675	–
2p	25	2	oil	3400, 2210, 1615	305 (M^+, 16), 278 (20), 175 (100), 148 (94), 130 (92), 115 (32), 103 (28), 91 (37)
2q	60	2.25	amorphous	3400, 2220, 1730, 1615, 1155	337 (M^+, 26), 264 (9), 207 (100), 179 (4), 144 (13), 130 (12), 115 (5)

[a] Satisfactory microanalysis obtained: C ± 0.4, N ± 0.3.

[b] Isolated by flash chromatography.

[c] KBr pellet.

Table 2. NMR Data of 2-Cyano-Δ^3-Piperideines **2a–q**

Compound	^1H NMR ($CDCl_3$, TMS) δ, J (Hz)	^{13}C NMR ($CDCl_3$) δ
2a	1.05 (t, 3 H, $J = 6.0$, CH_3), 2.02 (m, 2 H, $C\mathit{H}_2CH_3$), 2.16 (m, 1 H, H-5), 2.29 (m, 1 H, H-5), 2.45 (s, 3 H, NCH_3), 2.49 (dd, 1 H, H-6), 2.67 (dd, 1 H, H-6), 3.87 (s, 1 H, H-2), 5.62 (m, 1 H, H-4)	11.83 ($\mathit{C}H_3CH_2$), 25.46 (C-5), 26.75 ($CH_3\mathit{C}H_2$), 43.33 (NCH_3), 47.41 (C-6), 56.55 (C-2), 116.10 (CN), 122.13 (C-4), 133.35 (C-3)
2d	2.10 (m, 1 H, H_e-5), 2.36 (m, 1 H, H_a-5), 2.51 (s, 3 H, NCH_3), 2.54 (m, 1 H, H_a-6), 2.72 (m, 1 H, H_e-6), 4.06 (s, 1 H, H-2), 4.83 (s, 2 H, OCH_2), 4.93 (m, 1 H, H-4), 7.37 (m, 5 H, H_{arom})	23.05 (C-5), 42.71 (NCH_3), 47.70 (C-6), 55.54 (C-2), 69.63 (CH_2O), 95.81 (C-4), 115.43 (CN), 127.32 (C_{arom}), 127.96 (C_{arom}), 128.44 (C_{arom}), 136.18 (C_{arom}), 147.23 (C-3)
2f	1.05 (t, 3 H, $J = 8.0$, $C\mathit{H}_3CH_2$), 1.25 (t, 3 H, $J = 8.0$, $C\mathit{H}_3CH_2O$), 1.70–3.00 (m, 6 H, H-5, H-6, $C\mathit{H}_2CH_3$), 3.80 (s, 2 H, NCH_2CO), 4.25 (q, 2 H, $J = 8.0$, $CH_3C\mathit{H}_2O$), 4.32 (s, 1 H, H-2), 5.45 (m, 1 H, H-4)	11.73 ($\mathit{C}H_3CH_2C{=}$), 14.20 ($\mathit{C}H_3CH_2O$), 25.24 (C-5), 26.65 ($CH_3\mathit{C}H_2C{=}$), 46.40 (C-6), 54.57 (C-2), 56.33 (NCH_2O), 61.11 ($CH_3\mathit{C}H_2O$), 116.26 (CN), 122.24 (C-4), 132.75 (C-3), 169.63 (CO)
2g	1.09 (t, 3 H, $J = 7.0$, $C\mathit{H}_3CH_2C{=}$), 1.15 (d, 3 H, $J = 6.0$, $C\mathit{H}_3CH$), 1.27 (t, 3 H, $J = 7.0$, $C\mathit{H}_3CH_2O$), 2.08 (m, 4 H, $CH_3C\mathit{H}_2C{=}$, H-5), 2.90 (m, 1 H, H-6), 3.68 (dt, 2 H, $J = 18.6$, NCH_2CO), 4.17 (m, 2 H, $CH_3C\mathit{H}_2O$), 4.45 (s, 1 H, H-2) 5.65 (m, 1 H, H-4)	11.81 ($\mathit{C}H_3CH_2$), 14.57 ($\mathit{C}H_3CH_2O$), 19.22 ($\mathit{C}H_3CH$), 26.42 (CH_3CH_2), 33.16 (C-5), 51.54 (C-6), 52.91 (C-2), 55.30 ($N\mathit{C}H_2CO$), 60.94 ($CH_3\mathit{C}H_2O$), 117.44 (CN), 121.67 (C-4), 131.92 (C-3), 170.43 (CO)
2h	1.26 (t, 3 H, $J = 7.0$, $C\mathit{H}_3CH_2$), 1.70 (s, 3 H, CH_3C-3), 1.76 (s, 3 H, CH_3C-4), 2.00–3.00 (m, 4 H, H-5, H-6), 3.43 (s, 2 H, NCH_2O), 4.23 (m, 3 H, H-2, $CH_3C\mathit{H}_2O$)	14.16 ($\mathit{C}H_3CH_2O$), 16.20 ($\mathit{C}H_3C$-3), 18.62 ($\mathit{C}H_3C$-4), 31.35 (C-5), 46.98 (C-6), 56.63 (C-2), 60.97 ($CH_3\mathit{C}H_2O$), 65.25 ($N\mathit{C}H_2CO$), 116.34 (CN), 119.23 (C-4), 130.00 (C-3), 169.55 (CO)
2i	1.28 (dt, 6 H, $2\,C\mathit{H}_3CH_2$), 1.67 (s, 3 H, CH_3C-3), 1.74 (s, 3 H, CH_3C-4), 1.97 (d, 1 H, H-5), 2.38 (m, 1 H, H-5), 2.97 (m, 2 H, H-6), 4.24 (m, 6 H, H-2, NCH, $2\,CH_3C\mathit{H}_2O$)	13.87 ($2\,\mathit{C}H_3CH_2O$), 15.98 ($\mathit{C}H_3C$-3), 18.65 ($\mathit{C}H_3C$-4), 31.29 (C-5), 44.39 (C-6), 54.85 (C-2), 61.86 ($2\,CH_3\mathit{C}H_2O$), 68.84 (NCH), 116.73 (C-4), 119.52 (CN), 130.23 (C-3), 116.17 (2 CO)
2j	1.43 (s, 3 H, CH_3), 2.00 (t, 2 H, $J = 4.4$, H-16), 2.50 (t, 2 H, $J = 4.4$, H-17), 2.85–2.94 (m, 4 H, H-5, H-6), 3.24 (d, 1 H, $J = 5.2$, H-3), 4.36 (d, 1 H, $J = 5.2$, H-14), 7.03 (d, 1 H, $J = 2.3$, H-2), 7.13 (td, 1 H, $J = 7.0$, $J = 1.2$, H-10), 7.21 (td, $J = 7.0$, $J = 1.3$, H-11), 7.37 (d, 1 H, H-9), 7.62 (d, 1 H, H-12), 8.1 (s, 1 H, NH)	22.10 (CH_3), 22.76 (C-6), 30.56 (C-16), 42.74 (C-5), 52.40 (C-3), 111.10 (C-14), 113.12 (C-12), 113.90 (C-15, CN), 118.55 (C-7), 119.29 (C-9), 121.59 (C-10), 121.76 (C-11), 122.00 (C-2), 127.19 (C-8), 136.07 (C-13)
2k	1.06 (t, 3 H, $J = 7.0$, $CH_2C\mathit{H}_3$), 1.67 (m, 1 H, H-16), 2.05 (m, 2 H, $C\mathit{H}_2CH_3$), 2.23 (m, 1 H, H-16), 2.95 (m, 6 H, H-17, H-5, H-6), 4.04 (m, 1 H, H-3), 5.49 (m, 1 H, H-14), 7.05 (d, 1 H, $J = 2.5$, H-2), 7.14 (m, 1 H, H-10), 7.22 (m, 1 H, H-11), 7.37 (d, 1 H, $J = 7.0$, H-9), 7.63 (m, 1 H, H-12), 8.08 (s, 1 H, NH)	11.55 (CH_3), 23.13 (C-6), 29.00 (C-16), 32.53 ($\mathit{C}H_2{-}CH_3$), 48.71 (C-5), 49.95 (C-3), 56.37 (C-17), 111.07 (C-12), 113.39 (C-7), 116.75 (CN), 117.47 (C-14), 118.57 (C-9), 119.26 (C-10), 121.52 (C-11), 121.97 (C-2), 127.23 (C-8), 134.15 (C-15), 136.11 (C-13)
2l	1.07 (s, 9 H, $3\,CH_3$), 2.40 (m, 1 H, H-16), 2.50 (m, 1 H, H-16), 2.95 (m, 5 H, H-5, H-6, H-17), 3.45 (m, 1 H, H-17), 4.05 (m, 1 H, H-3), 5.52 (m, 1 H, H-14), 7.05 (m, 1 H, H-2), 7.15 (dt, 1 H, $J = 7.5$, $J = 2.5$, H-10), 7.22 (dt, 1 H, $J = 7.5$, $J = 2.5$, H-11), 7.37 (d, 1 H, $J = 7.5$, H-9), 7.62 (d, 1 H, $J = 7.5$, H-12), 8.10 (s, 1 H, NH)	23.08 (C-6), 28.29 ($3\,CH_3$), 29.10 (C-16), 34.67 (C-18), 49.19 (C-5), 50.26 (C-3), 56.38 (C-17), 111.10 (C-12), 113.35 (C-7), 115.81 (C-14), 116.59 (CN), 118.56 (C-9), 119.24 (C-10), 121.52 (C-11), 121.95 (C-2), 127.20 (C-8), 136.09 (C-13), 140.42 (C-15)
2m	1.12 (t, 3 H, $J = 7.3$, $CH_2C\mathit{H}_3$), 2.05 (m, 3 H, $C\mathit{H}_2CH_3$, H-16), 2.25 (m, 1 H, H-16), 2.59 (m, 1 H, H-17), 2.90 (m, 5 H, H-5, H-6, H-17), 4.14 (s, 1 H, H-3), 5.71 (m, 1 H, H-15), 7.04 (d, 1 H, $J = 2.5$, H-2), 7.2 (m, 2 H, H-10, H-11), 7.35 (d, 1 H, $J = 7.0$, H-9), 7.65 (d, 1 H, $J = 7.0$, H-12), 8.30 (s, 1 H, NH)	11.60 ($CH_2\mathit{C}H_3$), 23.41 (C-6), 25.40 (C-16), 26.64 ($\mathit{C}H_2CH_3$), 45.80 (C-5), 55.01 (C-3), 56.04 (C-17), 111.18 (C-12), 113.53 (C-7), 116.43 (CN), 118.68 (C-9), 119.30 (C-10), 121.74 (C-11), 121.96 (C-15), 122.52 (C-2), 127.45 (C-8), 133.25 (C-14), 136.34 (C-13)
2n	1.74 (s, 3 H, CH_3C-14), 1.82 (s, 3 H, CH_3C-15), 2.00 (d, 1 H, $J = 18.0$, H_e-16), 2.40 (m, 1 H, H_a-16), 2.62 (dt, 1 H, $J = 11.3$, $J = 4.3$, H_a-17), 3.00 (m, 5 H, H-5, H-6, H_e-17), 4.09 (s, 1 H, H-3), 7.00 (d, 1 H, $J = 2.0$, H-2), 7.20 (m, 2 H, H-10, H-11), 7.36 (d, 1 H, $J = 7.2$, H-9), 7.70 (d, 1 H, $J = 7.2$, H-12), 8.20 (s, 1 H, NH)	16.28 (CH_3C-14), 18.66 (CH_3C-15), 23.33 (C-6), 31.50 (C-16), 46.40 (C-5), 56.00 (C-17), 57.07 (C-3), 111,24 (C-12), 113.12 (C-7), 116.62 (CN), 118.64 (C-9), 119.23 (C-10), 119.52 (C-15), 121.80 (C-11), 121.90 (C-2), 127.29 (C-8), 130.40 (C-14), 136.17 (C-13)
2o[20]	2.33 (m, 2 H, H-16), 2.72 (t, 2 H, $J = 5.8$, H-17), 2.89 (m, 2 H, H-6), 3.08 (m, 2 H, H-5), 4.23 (s, 1 H, H-3), 4.82 (s br, 2 H, OCH_2), 6.99 (d, 1 H, $J = 2.3$, H-2), 7.17 (dt, 1 H, $J = 1.5$, $J = 7.0$, H-10), 7.24 (dt, 1 H, $J = 1.5$, $J = 7.0$, H-11), 7.35 (m, 1 H, H-9), 7.45 (m, 5 H, H_{arom}), 7.66 (m, 1 H, H-12), 8.10 (s br, 1 H, NH)	
2p	1.55–1.96 (m, 9 H, H-15, H-16, H-17, H-18, H_e-20), 2.2 (m, 1 H, H_a-20), 2.65 (dt, 1 H, $J = 4.4$, $J = 11.5$, H_a-21), 2.95 (m, 5 H, H-5, H-6, H_e-21), 4.04 (s, 1 H, H-3), 7.02 (d, 1 H, $J = 2.0$, H-2), 7.14 (dt, 1 H, $J = 2.0$, $J = 7.0$, H-10), 7.21 (dt, 1 H, $J = 2.0$, $J = 7.0$, H-11), 7.35 (d, 1 H, $J = 7.15$, H-9), 7.64 (d, 1 H, $J = 7.15$, H-12), 8.16 (s, 1 H, NH)	22.23–22.36 (C-19, C-20), 23.35 (C-6), 27.00 (C-18), 29.52 (C-21), 30.25 (C-16), 46.37 (C-5), 55.99 (C-17), 56.11 (C-3), 111.13 (C-12), 113.23 (C-7), 116.60 (CN), 118.62 (C-9), 119.23 (C-10), 121.65 (C-11), 121.90 (C-2), 122.31 (C-15), 127.25, (C-14), 132.40 (C-8), 136.12 (C-13)
2q	1.27 (t, 3 H, $CH_2C\mathit{H}_3$), 2.12 (m, 1 H, H_e-16), 2.40 (m, 1 H, H_a-16), 2.55 (dt, 1 H, $J = 11.0$, $J = 4.0$, H_a-17), 2.95 (m, 5 H, H-5, H-6, He-17), 3.20 (s, 2 H, CH_2CO), 4.15 (q, 2 H, $C\mathit{H}_2CH_3$), 4.55 (s, 1 H, H-3), 5.58 (s, 1 H, H-15), 7.05 (d, 1 H, $J = 2.0$, H-2), 7.12 (dt, 1 H, $J = 7.0$, $J = 2.5$, H-10), 7.20 (dt, 1 H, $J = 7{,}0$, $J = 2.5$, H-11), 7.35 (d, 1 H, $J = 7.2$, H-9), 7.65 (d, 1 H, $J = 7.2$, H-12), 8.20 (s, 1 H, NH)	14.03 (CH_3), 23.18 (C-6), 25.43 (C-16), 39.23 (C-5), 45.24 (C-17), 53.97 (C-3), 55.80 (CH_2CO), 61.03 ($\mathit{C}H_2CH_3$), 111.11 (C-12), 113.00 (C-7), 115.88 (CN), 118.60 (C-9), 119.18 (C-10), 121.79 (C-15), 121.85 (C-11), 125.20 (C-2), 127.50 (C-8), 128.89 (C-14), 136.14 (C-13), 170.40 (CO)

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