Total Synthesis of RS-42358 and Analogs Using Lateral Lithiation

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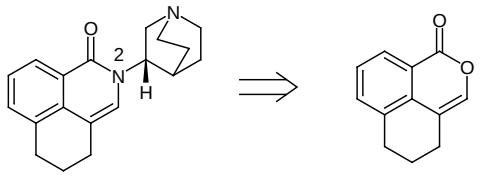
Abstract: A short synthesis of the 5-HT_3 receptor antagonist RS-42358 was developed based on the condensation of lactone **2** with *S*-3-aminoquinuclidine. The position 2 analogs of RS-42358 were made by condensing various primary amines with lactone **2**. The key step in the synthesis of lactone **2** was lateral lithiation of diethyl amide **7** using *n*-BuLi in THF.

Key words: lateral lithiation, 5-HT_3 receptor antagonist, RS-42358

Many pharmaceutical companies have vigorously pursued 5-HT_3 receptor antagonists because of their success in the clinic as anti-emetic agents and possible other uses.[1] One of our most promising 5-HT_3 receptor antagonists is the potent antagonist RS-42358 **1**. The dog and rat data are quite promising and the very high radioligand binding ($pK_i = 9.8$) for **1** make this compound and its general structure of great interest.[2] Analogs that were of great appeal contained the basic nucleus of **1** with a variety of substituents other than *S*-3-quinuclidinyl at position 2. Several syntheses of **1** exist, but none were easily amenable to rapid synthesis of position 2 analogs of **1**.[2,3]

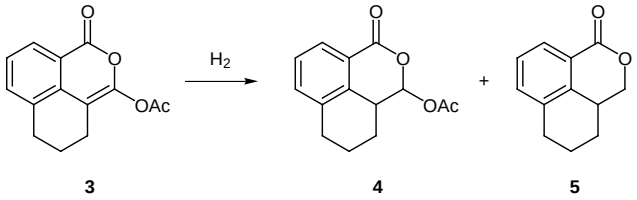
Our simple approach to synthesize position 2 analogs of **1** is outlined by the retrosynthetic analysis in Scheme 1. It was envisioned that lactone **2** could be condensed with *S*-3-aminoquinuclidine leading directly to **1**. Position 2 analogs of **1** would be synthesized by simply varying the choice of primary amine condensed with lactone **2**.



1 **2**

Scheme 1

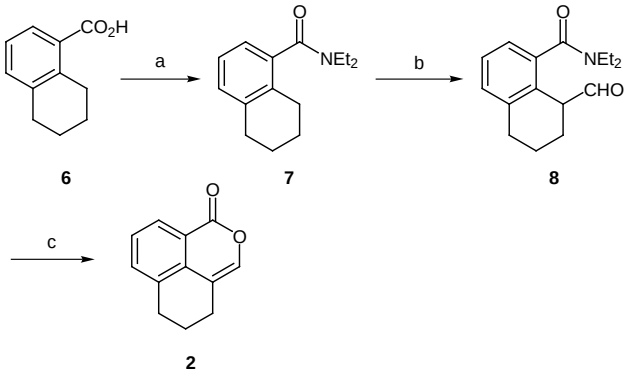
In the literature, there was one preparation of lactone **2**.[4] This route was quite attractive, because it started with inexpensive 1,8-naphthalic anhydride and was fairly short. The main difficulty with this route became our inability to cleanly hydrogenate olefin **3** to **4** without serious contamination by 30−50% of lactone **5** (Scheme 2). Therefore, a different approach to the synthesis of lactone **2** was desired.



3 **4** **5**

Scheme 2

Our new synthesis of lactone **2** is outlined in Scheme 3. Diethyl amide **7** was made from carboxylic acid **6** via the acid chloride. Treatment of a cold solution of diethyl amide **7** in THF with *n*-BuLi cleanly formed the laterally lithiated species, which was quenched with *N*,*N*-dimethylformamide to form aldehyde **8**. Aldehyde **8** was smoothly closed to desired lactone **2** by treatment with aqueous HCl.

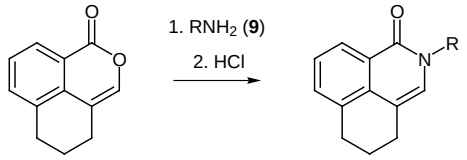


6 **7** **8** **2**

Scheme 3 Reagents and conditions:(a) 1) $SOCl_2$, 2) Et_2NH, 99%; (b) 1) *n*-BuLi, 2) DMF, 92%; (c) HCl, 77%

The diethyl amide derivative of carboxylic acid **6** was chosen for lateral lithiation because of success reported with the diethyl amide of *ortho*-toluic acid using *sec*-butyllithium or LDA as the base.[5] The lateral lithiation of the benzylic protons of an amide of 5,6,7,8-tetrahydro-1-naphthoic acid (**6**) derived from a secondary amine like diethylamine **7** was anticipated to work based on several known examples of successful lateral lithiations with primary amine derivatives of **6**.[2,6] It is of note the ease of lateral lithiation of **7** with *n*-BuLi instead of commonly used LDA or *s*-BuLi.[6] Alternatively, attempts to directly laterally lithiate carboxylic acid **6** with LDA, *n*-BuLi, or *t*-BuLi all met without success.[7]

The results of condensation of lactone **2** with various amines (Scheme 4) are presented in the Table. Amines **9a**, **b** with primary alkyl groups (entries 1, 2) condensed with lactone **2** under the mildest conditions of any of the amines providing products **10a**, **b**. Amines **9c**, **d**, **f** with secondary alkyl groups, both acyclic (entry 3) and cyclic (entries 4, 6), took slightly more forcing conditions to condense with lactone **2**. The most difficult condensation was with *tert*-butylamine (entry 5), clearly, steric crowding by the *tert*-butyl group slowed the condensation with lactone **2**. However, by using 5 equivalents of *tert*-butylamine and higher temperature a reasonable yield of **10e** was obtained. The condensation of *S*-3-aminoquinuclidine (entry 6) with lactone **2** provided a good yield of **1** as the HCl salt. This does constitute an efficient synthesis of **1** compared to the other known synthetic routes, and was especially attractive because expensive *S*-3-aminoquinuclidine was incorporated in the final step.



2 **10**

	R
a	n-butyl
b	i-butyl
c	i-propyl
d	cyclohexyl
e	t-butyl
f	S-3-quinuclidinyl

Scheme 4

In summary, lactone **2** was synthesized using lateral lithiation of diethyl amide **7** as the key step. The lateral lithiation was carried out using *n*-BuLi. The condensation of lactone **2** with *S*-3-aminoquinuclidine yielded potent 5-HT_3 antagonist **1**. The condensation of lactone **2** was also done with various primary amines producing position 2 analogs of **1**. The alkyl group of the primary amines used were quite varied ranging from primary, secondary acyclic, secondary cyclic, to tertiary.

Table Condensation of Various Amines with Lactone **2**

Entry	Amine	Reaction Conditions			Product Yield (%)
		Amine (Equiv)	Time (h)	Temp (°C)	
1	**9a**	2	18	80	**10a** (84)
2	**9b**	2	18	80	**10b** (92)
3	**9c**	3	43	100	**10c** (73)
4	**9d**	3	60	100	**10d** (77)
5	**9e**	5	7d	130	**10e** (63)
6	**9f**	2	45	110	**1** (71)

All materials were purchased form commercial suppliers and used without further purification. For the ^{1}H NMR spectral data, *J* values are in Hz. For the ^{13}C NMR spectral data, the resonances were assigned as CH_3, CH_2, CH, or C based on APT spectra.

***N,N*-Diethyl-5,6,7,8-tetrahydronaphthalene-1-carboxamide (7)**

A mixture of carboxylic acid **6**[8] (10.07 g, 57.1 mmol), toluene (50 mL), thionyl chloride (4.76 mL, 65.3 mmol), and DMF (15 drops) was stirred at r.t. for 1 h. The mixture was warmed to 45–50 °C for 25 min. The solution was concentrated in vacuo removing 10 mL of solvent. The concentrate was diluted with toluene (50 mL) and cooled in an ice/water bath. Four equal portions of diethylamine (13.0 mL, 126 mmol) were added over 40 min. The solution was stirred overnight letting the ice melt. To the mixture were added H_2O (50 mL) and EtOAc (50 mL). The resulting two phase mixture was separated and the organic layer was washed with H_2O (50 mL), dried ($MgSO_4$), filtered and concentrated in vacuo to give **7** (13.14 g, 99%) as a clear light yellow oil.

IR (KBr): ν = 1634 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.03 (t, *J* = 7, 3H), 1.25 (t, *J* = 7, 3H), 1.73−1.83 (m, 4H), 2.40−2.52 (m, 1H), 2.74−2.92 (m, 3H), 3.12 (dq, *J* = 1, 7, 2H), 3.27−3.41 (m, 1H), 3.73−3.86 (m, 1H), 6.96 (dd, *J* = 2, 7, 1H), 7.03−7.12 (m, 2H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.87 (CH_3), 13.98 (CH_3), 22.87 (2 × CH_2), 26.10 (CH_2), 29.72 (CH_2), 38.52 (CH_2), 42.51 (CH_2), 122.65 (CH), 125.38 (CH), 129.35 (CH), 132.91 (C), 137.18 (C), 137.87 (C), 171.00 (C).

MS (EI): *m/z* = 231 (M^+).

Anal. Calcd for $C_{15}H_{21}NO$: C, 77.88; H, 9.15; N, 6.05. Found: C, 77.54; H, 9.04; N, 6.24.

***N,N*-Diethyl-8-formyl-5,6,7,8-tetrahydronaphthalene-1-carboxamide (8)**

Under a N_2 atm, a solution of amide **7** (6.98 g, 30.17 mmol) and THF (70 mL) was cooled in a CO_2/*i*-PrOH bath maintained at −70 °C to −65 °C. To the cold solution was slowly added *n*-BuLi in hexanes (1.6 M, 22.3 mL) creating a deep purple solution. After 40 min, DMF (3.0 mL, 38.7 mmol) was added to the solution, which quenched the purple color. The cold bath was removed and the reaction was warmed up to r.t. The solution was poured into 1 M HCl (100 mL). The mixture was extracted with EtOAc (2 × 200 mL). The extracts were combined, dried ($MgSO_4$), filtered, and concentrated in vacuo to give **8** (7.17 g, 92%) as a colorless oil. The material was used as is for further synthesis, but for analytical work, a small sample was further purified. A small sample was purified by flash chromatography (EtOAc/hexanes, 15/85) followed by crystallization from hexanes cooling to −10 °C.

Mp: 36.9−38.4 °C (hexanes).

IR (KBr): ν = 1721, 1626 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.04−1.15 (m, 3H), 1.19 (t, *J* = 7, 3H), 1.52−2.00 (m, 4H), 2.27−2.40 (m, 1H), 2.78−2.82 (m, 2H), 3.00−4.42 (m, 4H), 7.07 (d, *J* = 7, 1H), 7.14−7.23 (m, 2H), 9.68 (br s, 1H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.49, 13.87, 19.59, 22.86, 29.34, 38.52, 42.99, 48.64, 123.38, 126.67, 129.14, 130.02, 137.68, 139.12, 170.08, 201.18.

MS (EI): *m/z* = 259 (M^+).

Anal. Calcd for $C_{16}H_{21}NO_2 \cdot 0.2\ H_2O$: C, 73.08; H, 8.20; N, 5.33. Found: C, 73.13; H, 8.01; N, 5.52.

5,6-Dihydro-1*H*,4*H*-naphtho[1,8-*cd*]pyran-1-one (2)
A mixture of aldehyde **8** (6.95 g, 26.8 mmol) and 1 M HCl (200 mL) was refluxed for 45 min. The solution was cooled to r.t. and extracted with EtOAc (2 × 250 mL). The extracts were combined and concentrated in vacuo to a solid. The solid was purified by flash chromatography (CH_2Cl_2/toluene, 20/80) to give **2** (3.86 g, 77%) as a white crystalline solid.

Mp: 101.1−102.0 °C (toluene/hexanes).

IR (KBr): ν = 1723 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.91−1.99 (m, 2H), 2.64 (dt, *J* = 1.5, 6, 2H), 2.92 (t, *J* = 6, 2H), 7.09 (t, *J* = 1.5, 1H), 7.42 (dd, *J* = 8, 8, 1H), 7.51 (dd, *J* = 1, 8, 1H), 8.12 (dd, *J* = 1, 8, 1H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.29 (CH_2), 24.48 (CH_2), 29.30 (CH_2), 114.15 (C), 121.27 (C), 127.43 (CH), 127.89 (CH), 133.84 (C), 133.89 (CH), 135.59 (C), 139.05 (CH), 162.84 (C).

MS (EI): *m/z* = 186 (M^+).

Anal. Calcd for $C_{12}H_{10}O_2$: C, 77.40; H, 5.41. Found: C, 77.46; H, 5.39.

2-Substituted-2,4,5,6-tetrahydro-1-oxo-1*H*-benz[*de*]isoquinolines 10a−e; General Procedure
In a 5 mL Wheaton vial were combined the amine (see Table for equiv) and lactone **2** (0.248 g, 1.33 mmol). The vial was placed in an oil bath (see Table for time and temp). The vial was cooled and the contents were dissolved out with *i*-PrOH (10 mL) with, if necessary, the aid of CH_2Cl_2 (1 mL). To the solution was added concd HCl (0.42 g, 4.3 mmol) dropping the pH to <2. The solution was concentrated in vacuo removing most of the solvent. The residue was mixed with 1M HCl (10 mL). The solution was extracted with CH_2Cl_2 (2 × 15 mL). The extracts were combined, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by flash chromatography (CH_2Cl_2 followed by EtOAc/CH_2Cl_2, 5/95) to give **10a**−**e**. The yields are listed in the Table.

2-Butyl-2,4,5,6-tetrahydro-1-oxo-1*H*-benz[*de*]isoquinoline (10a)
The general procedure was used except that the eluent for chromatography was EtOAc/CH_2Cl_2 (10:90).

Mp: 71.1−72.3 °C (CH_2Cl_2).

IR (KBr): ν = 1597, 1614, 1655 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.96 (t, *J* = 7, 3H), 1.34−1.46 (m, 2H), 1.70−1.80 (m, 2H), 1.93−2.01 (m, 2H), 2.73 (dt, *J* = 1, 6, 2H), 2.96 (t, *J* = 6, 2H), 3.97 (t, *J* = 7, 2H), 6.83 (t, *J* = 1, 1H), 7.35−7.41 (m, 2H), 8.25−8.31 (m, 1H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.79 (CH_3), 20.07 (CH_2), 22.87 (CH_2), 27.06 (CH_2), 29.98 (CH_2), 31.49 (CH_2), 48.92 (CH_2), 113.69 (C), 125.76 (CH), 126.01 (C), 126.29 (CH), 126.94 (CH), 130.76 (CH), 133.88 (C), 135.29 (C), 161.87 (C).

MS (EI): *m/z* = 241 (M^+).

Anal. Calcd for $C_{16}H_{19}NO$: C, 79.63; H, 7.94; N, 5.80. Found: C, 79.41; H, 7.90; N, 6.00.

2-(2-Methylpropyl)-2,4,5,6-tetrahydro-1-oxo-1*H*-benz[*de*]isoquinoline (10b)
Mp: 89.5−91.4 °C (EtOAc/CH_2Cl_2).

IR (KBr): ν = 1595, 1618, 1653 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.96 (d, *J* = 7, 6H), 1.93−2.01 (m, 2H), 2.14−2.28 (m, 1H), 2.73 (dt, *J* = 1, 6, 2H), 2.96 (t, *J* = 6, 2H), 3.79 (d, *J* = 7, 2H), 6.79 (t, *J* = 1, 1H), 7.35−7.43 (m, 2H), 8.25−8.31 (m, 1H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.08 (2 × CH_3), 22.88 (CH_2), 27.06 (CH_2), 28.33 (CH), 29.98 (CH_2), 56.36 (CH_2), 113.24 (C), 125.86 (CH), 126.02 (C), 126.27 (CH), 127.51 (CH), 130.80 (CH), 133.87 (C), 135.29 (C), 162.11 (C).

MS (EI): *m/z* = 241 (M^+).

Anal. Calcd for $C_{16}H_{19}NO$: C, 79.63; H, 7.94; N, 5.80. Found: C, 79.79; H, 7.96; N, 6.02.

2-(1-Methylethyl)-2,4,5,6-tetrahydro-1-oxo-1*H*-benz[*de*]isoquinoline (10c)
Mp: 87.4−88.2 °C (EtOAc/CH_2Cl_2).

IR (KBr): ν = 1595, 1613, 1657 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.37 (d, *J* = 7, 6H), 1.92−2.02 (m, 2H), 2.76 (dt, *J* = 1, 6, 2H), 2.96 (t, *J* = 6, 2H), 5.36−5.50 (m, 1H), 6.89 (t, *J* = 1, 1H), 7.35−7.41 (m, 2H), 8.26−8.32 (m, 1H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.85 (2 × CH_3), 22.90 (CH_2), 27.38 (CH_2), 29.97 (CH_2), 45.48 (CH), 114.02 (C), 121.77 (CH), 125.87 (C), 126.00 (CH), 126.28 (CH), 130.77 (CH), 133.36 (C), 135.16 (C), 161.47 (C).

MS (EI): *m/z* = 227 (M^+).

Anal. Calcd for $C_{15}H_{17}NO$: C, 79.26; H, 7.54; N, 6.16. Found: C, 79.35; H, 7.48; N, 6.39.

2-Cyclohexyl-2,4,5,6-tetrahydro-1-oxo-1*H*-benz[*de*]isoquinoline (10d)
The general procedure was used except that the eluent for chromatography was MeOH/CH_2Cl_2, (5/95). Compound **10d** was obtained as an oil.

IR (KBr): ν = 1597, 1618, 1655 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.19−1.29 (m, 1H), 1.46−1.62 (m, 5H), 1.72−1.81 (m, 1H), 1.87−2.01 (m, 5H), 2.74 (dt, *J* = 1, 6, 2H), 2.95 (t, *J* = 6, 2H), 4.97−5.05 (m, 1H), 6.91 (br s, 1H), 7.34−7.41 (m, 2H), 8.26−8.32 (m, 1H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.82 (CH_2), 25.51 (CH_2), 25.86 (2 × CH_2), 27.27 (CH_2), 29.89 (CH_2), 32.33 (2 × CH_2), 53.31 (CH), 113.56 (C), 122.53 (CH), 125.74 (C), 125.96 (CH), 126.13 (CH), 130.65 (CH), 133.25 (C), 135.04 (C), 161.42 (C).

HRMS (EI): *m/z* calc 267.1623. Found: 267.1618 (M^+).

Anal. Calcd for $C_{18}H_{21}NO.0.25\ H_2O$: C, 79.52; H, 7.97; N, 5.15. Found: C, 79.42; H, 7.87; N, 5.50.

2-(1,1-Dimethylethyl)-2,4,5,6-tetrahydro-1-oxo-1*H*-benz[*de*]isoquinoline (10e)
The general procedure was used except that the HCl treatment was unnecessary.

Mp: 91−94 °C (EtOAc/CH_2Cl_2).

IR (KBr): ν = 1597, 1618, 1649 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.73 (s, 9H), 1.93−2.01 (m, 2H), 2.72 (dt, *J* = 1, 6, 2H), 2.95 (t, *J* = 6, 2H), 7.14 (t, *J* = 1, 1H), 7.32−7.39 (m, 2H), 8.22−8.27 (m, 1H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.06 (CH_2), 27.59 (CH_2), 28.82 (3 × CH_3), 29.87 (CH_2), 60.35 (C), 112.63 (C), 123.48 (CH), 125.73 (CH), 126.06 (CH), 127.41 (C), 130.47 (CH), 133.39 (C), 134.76 (C), 162.96 (C).

MS (EI): *m/z* = 241 (M^+).

Anal. Calcd for $C_{16}H_{19}NO$: C, 79.63; H, 7.94; N, 5.80. Found: C, 79.40; H, 7.88; N, 5.96.

(*S*)-2-(1-Azabicyclo[2.2.2]oct-3-yl)-2,4,5,6-tetrahydro-1*H*-benz[*de*]isoquinolin-1-one hydrochloride (1)

In a 5 mL Wheaton vial were combined *S*-3-aminoquinuclidine[9] (0.331 g, 2.62 mmol) and lactone **2** (0.248 g, 1.33 mmol). The vial was placed in an oil bath maintained at 110−115 °C for 45 h. The vial was cooled and the contents were dissolved out with *i*-PrOH (10 mL). To the solution was added concd HCl (0.42 g, 4.3 mmol). The solution was concentrated in vacuo removing most of the solvent. The residue was dissolved in H_2O (10 mL) and 50% NaOH (0.42 g, 5.3 mmol) was added. The mixture was extracted with EtOAc (3 × 10 mL). The combined extracts were washed with NaCl solution (10 mL), dried ($MgSO_4$), and concentrated in vacuo to an oil. The oil was dissolved in *i*-PrOH (6 mL) and concd HCl (0.142 g, 1.44 mmol) was added. The solution was concentrated by distillation removing 4 mL of solvent. The solution was cooled to r.t. and then left overnight at 5 °C. The resulting off-white crystals were filtered off, washed with *i*-PrOH (2 × 1 mL), and dried to give **1** (0.313 g, 71%) as an off-white crystalline solid. Compound **1** was identical to material prepared previously.[2,3]

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