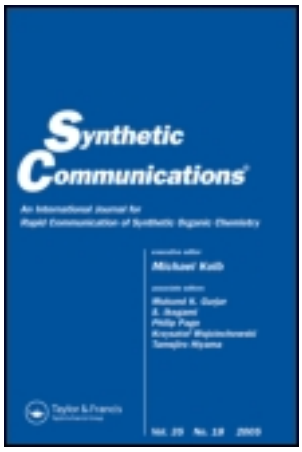

Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

SYNTHESIS OF NAPHTHALENIC MELATONIN RECEPTOR LIGANDS

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Published online: 16 Aug 2006.

To cite this article: Guo-Hua Chu & Pui-Kai Li (2001) SYNTHESIS OF NAPHTHALENIC MELATONIN RECEPTOR LIGANDS, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 31:4, 621-629, DOI: 10.1081/SCC-100000591

To link to this article: http://dx.doi.org/10.1081/SCC-100000591

SYNTHETIC COMMUNICATIONS, 31(4), 621–629 (2001)

SYNTHESIS OF NAPHTHALENIC MELATONIN RECEPTOR LIGANDS

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ABSTRACT

A highly efficient and versatile synthetic approach to the synthesis of naphthalenic analogs of melatonin, compound **7**, and its 2-alkyl substituted analog **8** is described. This approach features the novel synthesis of substituted 1-naphthyl acetonitrile **12** and **19** by nucleophilic addition of $LiCH_2CN$ to substituted 1-tetralone, followed by aromatization via a 2-step reaction sequence, dehydrogenation with DDQ and TsOH catalyzed dehydration.

The pineal hormone melatonin **1** is involved in circadian rhythms, retinal physiology, seasonal breeding, and cardiovascular regulation (1–3). Melatonin also appears to be involved in a number of pathological conditions, and there is strong evidence for its use in pathologies associated with disorders in circadian rhythm. The administration of melatonin in humans was shown to alleviate jet lag (4), to induce sleep (5), and to advance the sleep rhythm of subjects with delayed sleep phase syndrome (6). Melatonin may mediate its effect in vivo through melatonin receptors. Presently, two human melatonin receptor subtypes exist and are now defined as either the mt_1 (7) (formerly known as the Mel_{1a} receptor) (8) and the MT_2

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(7) (formerly known as the Mel_{1b} receptor) (9). The therapeutic use of melatonin is limited by its short biological half-life (10), despite its involvement in many possible physiological processes. Thus, synthetic analogs of melatonin were designed. It has been known that the indole ring of melatonin is not crucial for melatonin receptor recognition. For instance, the naphthalene ring (11–20) can serve as a bioisostere of the indole nucleus of melatonin, and analog **2** was reported to have equivalent affinity to melatonin for melatonin receptors in ovine pars tuberalis (11) and is currently in clinical trial. In addition to naphthalene, other groups such as amidotetralin (21), methoxychroman (22), amido indane (23), benzofuran (18,24), benzothiophene (18,24), and quinoline (25) can serve as a bioisostere of the indole nucleus of melatonin. Langlois et al. reported that the addition of a 2-methoxy group (OMe) to compound **2** to form **3** results in an order of magnitude increase in receptor affinity over compound **2** (Fig. 1) (12). It was postulated that the 2-OMe group binds to the accessory binding site of the receptor. Other 2-substituted naphthalenic melatonin receptor ligands were also reported (16). Two of the ligands are N-[2-(2-trimethylammoniumethyleneoxy-7-methoxy-1-naphthyl)ethyl]propionamide iodide **4** (TMEPI) (16) and N-[2-(2-bromo-acetoxy-7-methoxy-1-naphthyl) ethyl] propionamide **5** (BMNEP) (17). TMEPI is the first melatonin receptor analog that contains a permanently charged moiety and is a potential agent to study melatonin receptor regulation. BMNEP is the first irreversible melatonin receptor ligand that is reported to selectively alkylate MT_2 melatonin receptor. Recently, the synthesis of 3-alkyl substituted analog of **2** containing a fluorescent probe (compound **6**), a potential agent to be used to localize the cellular distribution of melatonin receptor, was reported (20). However, the strategy to synthesize 2-alkyl substituted naphthalenic melatonin analog has never been reported.

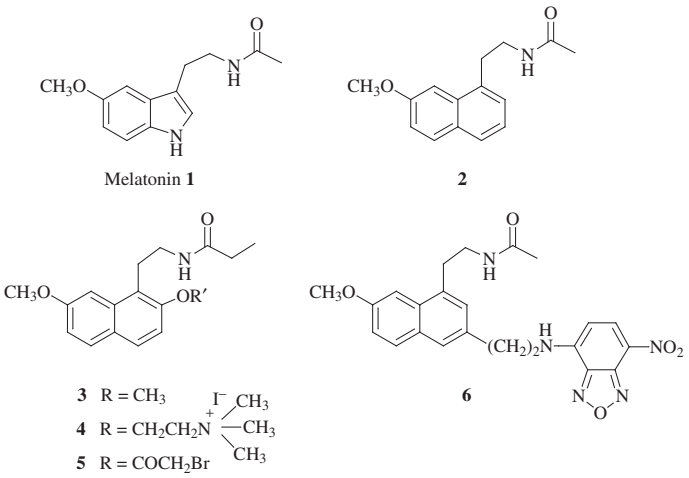

Figure 1.

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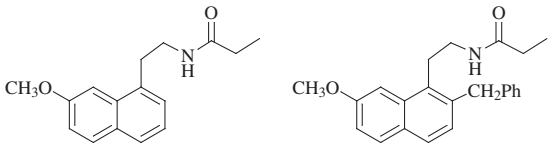
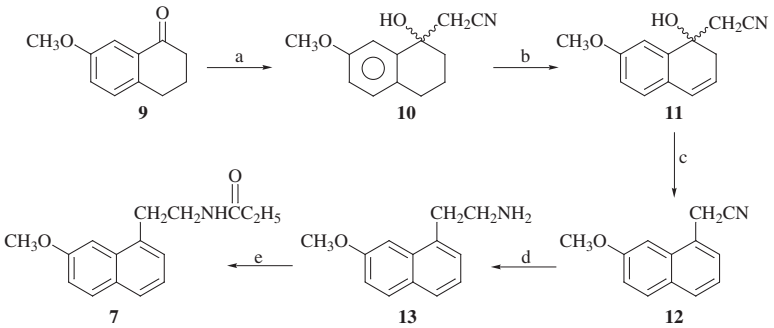
Due to the importance of the naphthalenic bioisostere **2** and its 2-substituted analogs, we report a new efficient synthetic scheme for naphthalene analog **7** (a homolog of **2**) and its 2 alkyl substituted analog **8** (N-[2-(2-Benzyl 7-methoxy-1-naphthyl)ethyl] propionamide).



7 **8**

For the synthesis of naphthalenic melatonin analog **7**, the commercially available 7-methoxy-1-tetralone (**9**) was used as the starting material (Scheme 1). Reaction of **9** with $LiCH_2CN$, which was prepared by treatment of acetonitrile with n-butyl lithium, gave the tertiary alcohol **10** (95%). Treatment of compound **9** with DDQ afforded the dehydrogenated product **11** (90.7%), which was unstable and immediately subjected to acid-catalyzed dehydrogenation, yielding the key intermediate: nitrile **12** (88.2%). Reduction of nitrile **12** with $LiAlH_4$ gave the amine **13**, which was acylated with propionyl chloride, furnishing target compound **7** (54% from **12**). Although there is a known procedure for the synthesis of the key intermediate, nitrile **12** (26), compared to the literature method, our method reported here is much more efficient and versatile. The versatility of this new method was further illustrated by its application to the synthesis of 2-alkyl substituted analog **8**.

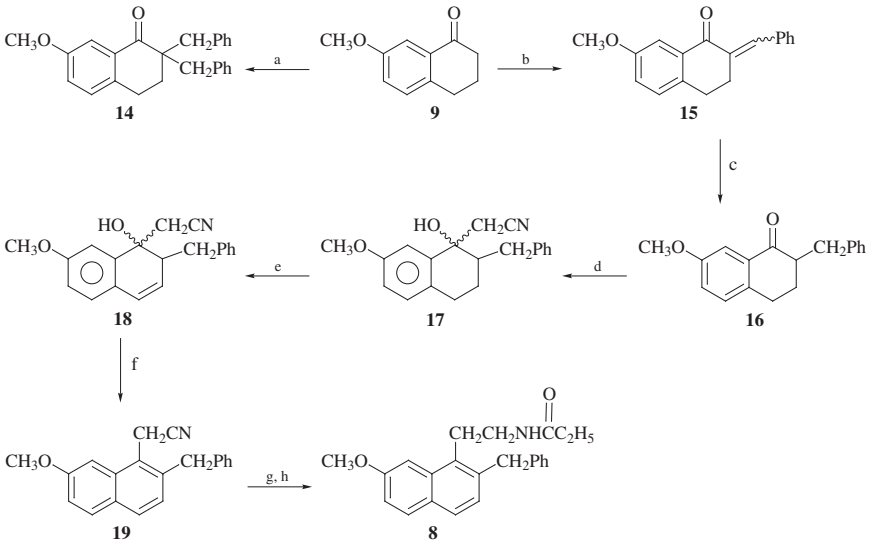
7-Methoxy-1-tetralone **9** was also used as the starting material for the synthesis of analog **8** (Scheme 2). Treatment of **9** with LiHMDS, followed by excess



9 **10** **11** **12** **13** **7**

Reagents and Conditions: a. $LiCH_2CN$, THF, −78°C, lh, 95%; b. DDQ, CH_2Cl_2, rt, overnight, 90.7%; c. TsOH, benzene, reflux, 1h, 88.2%; d. $LiAlH_4$, THF, 45–50°C, overnight; e. C_2H_5COCl, Et_3N, CH_2Cl_2, 0°C to r.t, 1h, 54% from **12**.

Scheme 1.



Reagents and Conditions: a. i. LiHMDS, THF, −78°C, 30 min; ii. $PhCH_2Br$, −78°C to r.t, overnight; b. PhCHO, NaOH, THF-EtOH-H_2O, r.t, 6 days, 88%; c. H_2, 10% Pd/C, r.t, 2h, 80%; d. $LiCH_2CN$, −78°C, 1h, 87%; e. DDQ, CH_2Cl_2, r.t, overnight; f. TsOH, PhH, reflux, 1h, 50.4% from **17**; g. $LiAlH_4$, THF, 50°C, overnight; h. C_2H_5COCl, Et_3N, CH_2Cl_2, 0°C to r.t, 1h, 31.3%.

Scheme 2.

benzyl bromide, gave the dibenzylated product **14** as the major product. Then a two-step reaction sequence was used to prepare the monobenzylated compound **16**. Condensation of **8** with benzaldehyde yielded α,β-unsaturated ketone **15** (88%), which was then hydrogenated to afford the desired compound **16** (80%). Reaction of ketone **16** with the anion generated from acetonitrile by treatment with LiHMDS yielded the nitrile **17** (87%). The configurations **5** of the hydroxy and benzyl group at C-1 and C-2 position were not elucidated; however, the nucleophilic attack at the C-1 position of compound **16** by the acetonitrile would favor the opposite side of the benzyl group at the C-2 position. Furthermore, it was unnecessary to determine the configuration at C-1 and C-2 position of compound **17** because it would be aromatized and the two stereo centers would be eliminated. Compound **17** was then treated with DDQ followed by acid-catalyzed dehydration, yielding the aromatized product **19** (50.4% for 2 steps). Finally, nitrile **19** was reduced with $LiAlH_4$ and the resulting amine was acylated by treatment with propionyl chloride, leading to the target compound **8** (31.3% for 2 steps).

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EXPERIMENTAL

Chemicals and silica gel were purchased from Aldrich Chemical Company (Milwaukee, WI). The chemicals were checked for purity by thin layer chromatography and NMR. Melting points were determined on a Thomas Hoover capillary melting point apparatus and are uncorrected. Proton NMR spectra were obtained with a Bruker WH-300 (300 MHz) spectrophotometer. Elemental analyses were performed by Atlantic Microlab Inc. (Norcross, GA).

1-Hydroxy-7-methoxy-1,2,3,4-tetrahydro-1-naphthyl Acetonitrile (10)

To a solution of acetonitrile (1.47 mL, 28 mmol) in anhydrous THF (50 mL) at 78°C was added dropwise 17.5 mL of n-BuLi (1.6 M in hexane, 28 mmol) under nitrogen. The mixture was then added a solution of 7-methoxy-1-tetralone **9** (3.52 g, 20 mmol) in THF (25 mL). After the addition, the solution was stirred at −78°C for 1 h and quenched with saturated aqueous solution of NH_4Cl(80 mL), extracted with EtOAc (3 × 80 mL). The organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by silical gel chromatography using petroleum ether: CH_2Cl_2: EtOAc (3:1:1) as eluent, yielding pure product **10** (4.13 g, 95%). m.p: 90.5°–91°C; ^{1}HNMR (300 MHz, $CDCl_3$) δ 1.78–2.25 (m, 4H), 2.40 (s, 1H, OH), 2.70 (m, 2H), 2.75, 2.87 (2d, 2H, J = 16.8 Hz), 3.77 (s, 3H, OCH_3), 6.77 (dd, 1H, J = 2.7, 8.4 Hz, ArH), 7.0 (d, 1H, J = 8.4 Hz, ArH), 7.07 (d, 1H, J = 2.7 Hz, ArH). Analysis calculated for $C_{13}H_{15}NO_2$: C, 71.87; H, 6.96; N, 6.45. Found: C, 71.62; H, 6.99; N, 6.57.

1-Hydroxy-7-methoxy-3,4-dihydro-1-naphthyl Acetonitrile (11)

To a solution of compound **10** (434 mg, 2 mmol) in CH_2Cl_2 (16 mL) was added DDQ (545 mg, 2.4 mmol). The reaction mixture was stirred at r.t overnight, then diluted with a mixture of petroleum ether : CH_2Cl_2 (2:1, 20 ml) and filtered. The filtrate was concentrated and the residue was purified by silica gel chromatography using petroleum ether : CH_2Cl_2 : EtOAc (3:1:1) as eluent, affording olefin **11** (390 mg, 90.7%) as an oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.45–2.77 (m, 5H), 3.79 (s, 3H, OCH_3), 5.83 [m, 1H, (HC = CH-CH_2)], 6.42 (dd, 1H, J = 2.7, 9.6 Hz, Ar-CH =), 6.77 (dd, 1H, J = 2.7, 8.4 Hz, ArH), 7.0 Hz (d, 1H, J = 8.4 Hz, ArH), 7.19 (d, 1H, J = 2.7 Hz, ArH). Olefin **11** was unstable and immediately used for the next step.

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7-Methoxy-1-naphthyl Acetonitrile (12)

To a solution of compound **11** (2.4 g, 11.2 mmol) in benzene (100 mL) was added $TsOH.H_2O$ (103 mg, 0.54 mmol). The reaction mixture was refluxed for 1 h, cooled down to r.t, and washed with saturated aqueous solution of $NaHCO_3$ (2×40 mL). The organic layer was dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by silica gel chromatography using petroleum ether : CH_2Cl_2: EtOAc (3:1:1) as eluent, furnishing pure nitrile **12** (1.94 g, 88.2%). m.p: 83.5°–84.5°C (lit. (27): 83°–85°C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.94 (s, 3H, OCH_3), 4.04 (s, 2H, $ArCH_2$), 7.04 (d, 1H, J = 2.1 Hz, ArH), 7.19–7.78 (m, 5H, ArH).

N-[2-(7-methoxy-1-naphthyl)ethyl]propionamide (7)

To a suspension of $LiAlH_4$ (1.3 g, 34.2 mmol) in anhydrous THF at 0°C was added dropwise a solution of nitrile **12** (2 g, 10.2 mmol). The reaction mixture was stirred at r.t for 30 min, then at 45°–50°C overnight. The reaction mixture was cooled with ice bath and quenched carefully by dropwise addition of water (4.0 mL). The resulting mixture was stirred at r.t for 30 min and filtered through a pad of celite. The filtrate was concentrated in vacuo, giving the crude amine **13**, which was used directly for the next step.

The crude amine **13** was dissolved in anhydrous CH_2Cl_2 (60 mL) and cooled with ice bath. To this solution was added triethylamine (3 mL, 21.6 mmol), followed by dropwise addition of propionyl chloride (1.4 mL, 16.1 mmol). The reaction mixture was allowed to warm to r.t and washed with saturated aqueous solution of $NaHCO_3$ (2×30 ml), dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by silica gel chromatography using petroleum ether: CH_2Cl_2 : EtOAc (1:1:1) as eluent, yielding the pure amide **7** (1.41 g, 54% for 2 steps) m.p: 103° – 104°C (lit. (11): 103°C). ^{1}HNMR (300 MHz, $CDCl_3$) δ 1.09 (t, 3H, J = 7.5 Hz, CH_3), 2.12 (q, 2H, J = 7.5 Hz, CH_2CO), 3.21 (t, 2H, J = 7.2 Hz, $ArCH_2$), 3.59 (m, 2H, CH_2N), 3.94 (s, 3H, OCH_3), 5.60 (br s, 1H, NH), 7.13 (dd, 1H, J = 2.4, 9.0 Hz, ArH), 7.20–7.65 (m, 4H, ArH), 7.72 (d, 1H, J = 9.0 Hz, ArH).

2-Phenylmethylene-7-methoxy-1-tetralone (15)

To the solution of tetralone **9** (2.12 g, 12 mmol) in a mixture of EtOH : THF (25 mL : 6 mL) was added a solution of NaOH (3.6 g, 90 mmol) in water (70 mL) and followed by the addition of benzaldehyde (1.28 g, 12.1 mmol). The reaction mixture was stirred at r.t for 6 days and diluted with water (160 mL). The crude product was obtained by filtration as a yellow solid, which was purified

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by silica gel chromatography using petroleum ether: CH_2Cl_2 : EtOAc (3:1:1) as eluent, yielding pure condensed product **15** (2.8 g, 88%). m.p: 115.5°−116.5°C. ^{1}HNMR (300 MHz, $CDCl_3$) δ 2.86 (t, 2H, J = 6.0 Hz, CH_2), 3.09 (t, 2H, J = 6.0 Hz, CH_2), 3.85 (s, 3H, OCH_3), 7.05 (dd, 1H, J = 2.7, 8.4 Hz, ArH), 7.15 (d, 1H, J = 8.4 Hz, ArH), 7.32–7.42 (m, 5H, ArH), 7.61 (d, 1H, J = 2.7 Hz, ArH), 7.85 (s, 1H, CH =). Analysis calculated for $C_{18}H_{16}O_2$: C, 81.79; H, 6.10. Found: C, 81.96; H, 5.98.

2-Benzyl-7-methoxy-1-tetralone (16)

α, β-Unsaturated ketone **15** (3.9 g, 14.77 mmol) in EtOAc (200 mL) was hydrogenated at r.t in the presence of 10% Pd/C for 2 h. The reaction mixture was filtered and the filtrate was concentrated in vacuo. The residue was purified by silica gel chromatography using petroleum ether : EtOAc : CH_2Cl_2 (3:1:1) as eluent, giving pure compound **16** (3.15 g, 80%) m.p: 116°−117.5°C. ^{1}HNMR (300 MHz, $CDCl_3$) δ 1.77 (m, 1H), 2.09 (m, 1H), 2.60–2.89(m, 4H), 3.48 (dd, 1H, J = 3.0, 13.0 Hz), 3.84 (s, 3H, OCH_3), 7.04 (dd, 1H, J = 2.7, 8.4 Hz, ArH), 7.13 (d, 1H, J = 8.4 Hz, ArH), 7.19–7.33 (m, 5H, ArH), 7.55 (d, 1H, J = 2.7 Hz, ArH). Analysis calculated for $C_{18}H_{18}O_2$: C, 81.17; H, 6.81. Found: C, 81.02; H, 6.98.

1-Hydroxy-2-benzyl-7-methoxy-1,2,3,4-tetrahydro-1-naphthyl Acetonitrile (17)

The synthesis of acetonitrile **17** is similar to the procedure for the synthesis of **10**. From 2 g (7.52 mmol) of **16**, two grams (87%) of nitrile **17** were obtained after purification by silica gel chromatography. m.p: 187°−188°C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.61 (m, 2H), 2.04–2.74 (m, 4H), 2.92 (s, 2H), 3.25 (m, 1H), 3.79 (s, 3H, OCH_3), 5.69 (s, 1H, OH), 6.79 (dd, 1H, J = 2.1, 8.4 Hz, ArH), 6.97 Hz (d, 1H, J = 8.4 Hz, ArH), 7.19–7.31 (m, 6H, ArH). Analysis calculated for $C_{20}H_{21}NO_2$: C, 78.15; H, 6.89; N, 4.56. Found: C, 78.41; H, 6.76; N, 4.37.

2-Benzyl-7-methoxy-1-naphthyl Acetonitrile (19)

The synthesis of **19** is similar to the procedure for the synthesis of **12**. From 1.4 g (7.52 mmol) of **17**, 660 mg (50.4%) of compound **19** was obtained after purification by silica gel chromatography. m.p: 105°–106°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.95 (s, 3H, OCH_3), 4.24 (s, 2H, CH_2CN), 7.09–7.29 (m, 7H, ArH), 7.75 (m, 2H, ArH). Analysis calculated for $C_{20}H_{17}NO$: C, 83.60; H, 5.96; N, 4.87. Found: C, 83.78; H, 5.67; N, 4.55.

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N-[2-(2-Benzyl-7-methoxy-1-naphthyl)ethyl]propionamide (8)

The synthesis of **8** is similar to the procedure for the synthesis of **7**. From 0.66 g (7.52 mmol) of **19**, 250 mg (31.3%) of compound **8** was obtained after purification by silica gel chromatography. m.p: 117.5°−118.5°C; ^{1}HNMR (300 MHz, $CDCl_3$) δ 1.07 (t, 3H, J = 7.5 Hz, CH_3), 2.08 (q, 2H, J = 7.5 Hz, CH_2CO), 3.25 (m, 4H, $ArCH_2$ and CH_2CN), 3.97 (s, 3H, OCH_3), 4.18 (s, 2H, $ArCH_2Ph$), 5.45 (br s, 1H, NH), 7.10–7.22 (m, 7H, ArH), 7.57 (d, 1H, J = 2.7 Hz, ArH), 7.59 (d, 1H, J = 8.7 Hz, ArH), 7.68 (d, 1H, J = 8.7 Hz, ArH). Analysis calculated for $C_{23}H_{25}NO_2$: C, 79.51; H, 7.25; N, 4.03 Found: C, 79.52; H, 7.31; N, 4.09.

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Accepted March 29, 2000

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