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Efficient Route to the Pineal Hormone Melatonin by Radical-Based Indole Synthesis

Douglas W. Thomson, Aurélien G. J. Commeureuc, Stefan Berlin, and John A. Murphy*

Department of Pure and Applied Chemistry,
University of Strathclyde, Glasgow, UK

ABSTRACT

The hormone melatonin, which is known to have a range of important biological effects, has been prepared in a high-yielding route that features formation of the indole nucleus by radical cyclization. Mediation of the radical cyclization by tristrimethylsilylsilane (TTMSS) is more efficient than by *N*-ethylpiperidine hypophosphite.

Key Words: Melatonin; Radical; Synthesis; Indole.

*Correspondence: J. A. Murphy, Merck-Pauson Professor, Department of Pure and Applied Chemistry, University of Strathclyde, 295 Cathedral St., Glasgow G1 1XL, UK; Fax: (+44) 141 548 4822; E-mail: john.murphy@strath.ac.uk.

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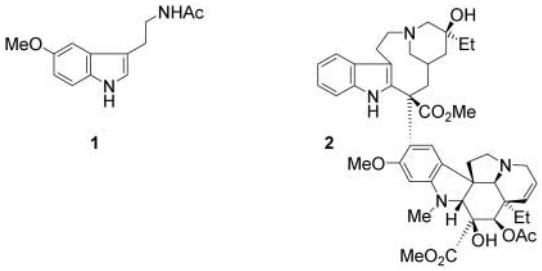
INTRODUCTION

Melatonin **1**[1] is a naturally occurring hormone produced by the pineal gland in vertebrates. Its synthesis and secretion is increased at night,[2] raising plasma levels, and leading to the onset of sleep. It is useful in treating some sleep disorders; oral administration of melatonin can lead to improved sleep patterns with accelerated onset of sleep. Recognition of this led to melatonin being widely used to overcome "jet-lag." Melatonin also has a role in protection against oxidative stress,[3] both by direct quenching of reactive free radicals and by regulating the activity of anti-oxidant enzymes. Another more recent discovery is melatonin's ability to inhibit a key step in the onset of Alzheimer's disease.[4] Thus the Alzheimer amyloid Aβ-peptide aggregates to form insoluble amyloid fibrils, which are essential pathological markers of the disease. Melatonin, in conjunction with other compounds, can inhibit fibril formation, leading to the suggestion that reduced levels of melatonin in the brain with ageing might be one of the contributing factors to the onset of the disease. Melatonin is freely available in some countries, but not in others due to fears about its possible side-effects. It is known to inhibit the assembly of microtubules,[5] the transient cytoskeletal structures that play a crucial role in many cell functions, notably mitosis.

In principle, this inhibition of microtubule formation can be turned to good effect, since many anti-cancer compounds act in this way, i.e., by inhibiting cell-division in rapidly dividing cancer cells, and this is what kindled our interest. Many of the current anti-cancer drugs that act in this way are highly complex structures e.g., vinblastine **2**, but a drive is underway to produce much simpler structures, and this is greatly aided both by the publication[6] of a detailed structure in 1998 for a tubulin-taxol complex, as well as by the rapid advances in computational methods allowing the rational planning of tubulin-binding structures.



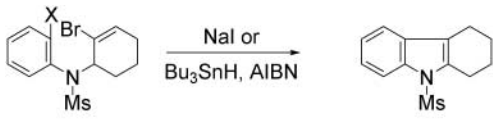
Scheme 1.

Moreover, a number of simpler anti-cancer leads have recently been discovered,[7] and for this reason, flexible routes to melatonin and related labelled and unlabelled structures are timely. A number of syntheses of melatonin have been accomplished,[8] but the recent elegant synthesis by Zard's group[9] demonstrated the first approach using radicals, although harsh conditions (conc. sulfuric acid) were needed for the final deprotection step; we now demonstrate an alternative but very simple and direct approach featuring radical cyclization as the key step.

We recently announced[10] a new synthesis of tricyclic indoles such as tetrahydrocarbolines **4** by cyclization of aryl radicals, derived from arenediazonium salts **3** ($X = N_2BF_4$) or from aryl iodides **3** ($X = I$), onto vinyl bromides (Sch. 2). The complementary approach[11] of cyclization onto an alkyne rather than a vinyl bromide could not be used to make such derivatives, but is attractive in the preparation of simpler indoles such as melatonin.

Our proposal was to cyclize the radical derived from iodoarene **9**, which in turn should be easily made from **5**.

In practice, iodoanisidine **5** was protected as its methanesulfonamide **6**. The protecting group also serves to acidify the N-H bond and activate it for the Mitsunobu coupling that follows. Thus coupling with 4-phthalimidobut-2-yn-1-ol **8**, in turn prepared by Mitsunobu coupling of 2-butyne-1,4-diol and phthalimide, afforded the product **9** ready for radical cyclization. Cyclization was attempted under different conditions, with ethylpiperidine hypophosphite (EPHP) and *tris*trimethylsilylsilane (TTMSS). Cyclization with EPHP was successful in initially producing a mixture of indole **11** and indolenine **10**; this mixture was easily converted in situ into the indole by addition of a trace of *p*-toluenesulfonic acid, but the overall reaction yield (45%) was disappointing; although no other product was detected, two plausible side-reactions could occur: (a) Addition of the phosphorus radicals to the alkyne and (b) Addition to the oxygen of the imide carbonyl group. Happily, TTMSS was much more successful. The product from the TTMSS reaction was again directly treated with *p*-toluenesulfonic acid to afford indole **11** in



3a, $X = N_2BF_4$
3b, X = I

4

Scheme 2.

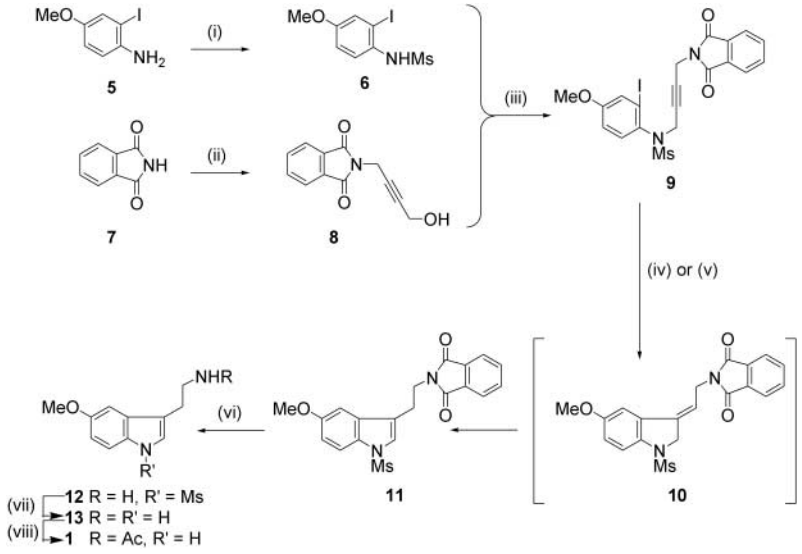
74% yield. Liberation of the two amine groups and selective acetylation led to melatonin **1**, identical to authentic material.

This route, featuring radical-induced indole synthesis as the key step therefore gives convenient and simple access to melatonin, and provides a trigger for further studies aimed at uncovering structure-activity relationships in its broad array of intriguing biological actions.

EXPERIMENTAL SECTION

General

NMR spectra were recorded on a Bruker DPX400 spectrometer, operating at 400 MHz for ^{1}H NMR and 100.61 MHz for ^{13}C NMR, respectively. All NMR experiments were carried out in $CDCl_3$. Chemical shifts are reported in parts per million (ppm). Coupling constants *J* are reported in Hertz (Hz). The following abbreviations are used for the multiplicities in ^{1}H NMR: s, singlet; d, doublet; t, triplet;



Scheme 3. Reagents and conditions: (i) MsCl, DMAP, py, rt, 14 h, 96%; (ii) Ph_3P, but-2-yn-1,4-diol, DIAD, THF, 0°C-rt, 62%; (iii) Ph_3P, DIAD, THF, 0°C-rt, 82%; (iv) TTMSS, AIBN, PhMe, Δ, 12 h, then TsOH (cat.), Δ, 2 h, 74%; (v) EPHP, AIBN, toluene, then TsOH, CH_2Cl_2, 8 h, Δ, 45%; (vi) N_2H_4, EtOH, Δ, 3 h, 85%; (vii) KOH, MeOH, 9 h, Δ, 84%; (viii) Ac_2O, 18 h, rt, 90%.

q, quartet; m, multiplet; dd, double doublet; b s, broad singlet. Infrared spectra are recorded on a Perkin Elmer "spectrum One FT-IR" spectrometer. Melting points were determined using either a Griffin or a Gallenkamp melting point apparatus and are uncorrected. Column chromatography was performed using Prolabo 35–75 μm particle sized silica gel 60 (200–400 mesh). All reagents were obtained from commercial suppliers and where necessary solvents were dried and/or distilled before use. All petroleum ether was of boiling range 40–60°C and distilled before use. Dichloromethane was distilled from calcium hydride, toluene from sodium, and THF from sodium/benzophenone. Diethyl ether was dried over sodium wire.

N-(2-Iodo-4-methoxyphenyl)methanesulfonamide 6

4-Amino-3-iodoanisole[12] **5** (4.025 g, 16.2 mmol, 1.00 equiv.) and 4-dimethylaminopyridine (197 mg, 1.62 mmol, 0.10 equiv.) were dissolved in pyridine (25 mL), under argon. The solution was cooled to 0°C when methanesulfonylchloride (1.31 mL, 17.0 mmol, 1.05 equiv.) was added dropwise. The solution was stirred at room temperature for 14 h. The pyridine was then removed in vacuo and the crude material diluted with CH_2Cl_2. The organic phase was extracted with hydrochloric acid (2 M), $NaHCO_3$ (sat.) and brine (sat.). The organic phase was then dried over $MgSO_4$, filtered and evaporated to afford pure *N*-(2-*iodo*-4-*methoxyphenyl*)*methanesulfonamide* **6** as a white solid (5.072 g, 96%). M.p. 116–117°C Found: $(MNH_4)^+$, 344.9770. $C_8H_{14}IN_2O_3S$ requires: (MNH_4), 344.9770. ν_{max} (KBr)/cm^{-1}: 3262 (NH), 3002 (Ar-H), 2836 (CH), 1594 (Ar), 1567 (Ar or NH), 1488 (CH), 1317, and 1147 (SO_2). δ_H ($CDCl_3$): 2.97 (3H, s, SO_2CH_3), 3.80 (3H, s, OCH_3), 6.34 (1H, b s, NH), 6.94 (1H, dd, *J* 8.9, 2.8, ArH), 7.36 (1H, d, *J* 2.8, ArH), and 7.55 (1H, d, *J* 8.9, ArH). δ_C ($CDCl_3$): 40.2 (CH_3), 56.0 (CH_3), 94.8 (C), 115.7 (CH), 124.5 (CH), 125.9 (CH), 130.8 (C), and 158.5 (C). *m*/*z*: (EI) 327 (M^+, 22%), 248 (100), 106 (100).

4-Phthalimidobut-2-yn-1-ol 8

2-Butyne-1,4-diol (1.755 g, 20 mmol, 1.50 equiv.), phthalimide **7** (2.000 g, 14.0 mmol, 1.00 equiv.) and triphenylphosphine (3.565 g, 14.0 mmol, 1.00 equiv.) were dissolved in dry THF (80 mL), under nitrogen, and cooled to 0°C. Diisopropyl azodicarboxylate (2.82 mL, 14.0 mmol, 1.00 equiv.) was added dropwise over 1 h. The mixture was

raised to room temperature and stirred additionally for 18 h. The solvent was removed in vacuo and the residue was purified by column chromatography (40:60 ethyl acetate-petroleum ether) to afford 4-phthalimidobut-2-yn-1-ol **8** as a white solid (1.81 g, 62%). M.p. 166–167°C [Lit.[13] 168–170°C]. ν_{max} (KBr)/cm^{-1}. 3449 (O-H), 1767 and 1719 (C=O), 1428, 1397, 1350, 1126, 724. δ_H ($CDCl_3$): 2.01 (1H, s, OH), 4.25 (2H, t, *J* 1.9, CH_2), 4.99 (2H, t, *J* 1.9, CH_2), 7.73–7.77 (2H, m, ArH), 7.87–7.91 (2H, m, ArH). δ_C ($CDCl_3$): 27.8 (CH_2), 51.6 (CH_2), 79.8 (C), 81.9 (C), 124.1 (CH), 132.5 (C), 134.8 (CH), 167.6 (C).

N-[4-(1,3-Dioxodihydroisoindol-2-yl)but-2-ynyl]-*N*-(2′-iodo-4′-methoxyphenyl)methanesulfonamide 9

N-(2-Iodo-4-methoxyphenyl)methanesulfonamide **6** (1.40 g, 4.28 mmol, 1.20 equiv.), 4-phthalimidobut-2-yn-1-ol **8**, (767 mg, 3.57 mmol, 1.00 equiv.) and triphenylphosphine (1.160 g, 4.45 mmol, 1.25 equiv.) were dissolved in dry THF (20 mL), under nitrogen, and cooled to 0°C. Diisopropyl azodicarboxylate (0.88 mL, 4.45 mmol, 1.25 equiv.) was added dropwise over 20 min. The mixture was raised to room temperature and stirred for 18 h. The solvent was removed in vacuo and the residue purified by column chromatography (50:50 petroleum ether-ethyl acetate) to afford *N*-[*4*-(1,3-*dioxodihydroisoindol*-2-*yl*)-*but*-2-*ynyl*]-*N*-(2′-*iodo*-4′-*methoxyphenyl*)*methanesulfonamide* **9** as a white solid (1.530 g, 82%). M.p. 159–160°C (Found: $[MNH_4]^+$, 542.0243. $C_{20}H_{21}IN_3O_5S$ requires [*MNH4*], 542.0247). ν_{max} (KBr)/cm^{-1} 3091 (Ar-H), 2925 (CH), 1769 and 1721 (C=O), 1591 (Ar), 1486 (CH), 1341 and 1150 (SO_2). δ_H ($CDCl_3$): 3.13 (3H, s, SO_2CH_3), 3.77 (3H, s, OCH_3), 4.00 (1H, br d, *J* 18.3, SO_2NCH_2), 4.47 (2H, t, *J* 1.8, $CONCH_2$), 4.68 (1H, br d, *J* 18.3, SO_2NCH_2), 6.83 (1H, dd, *J* 8.7, 2.9, ArH), 7.39 (1H, d, *J* 2.9, ArH), 7.48 (1H, d, *J* 8.7, ArH), 7.75–7.79 (2H, m, ArH) and 7.88–7.91 (2H, m, ArH). δ_C ($CDCl_3$): 27.4 (CH_2), 41.1 (CH_2), 41.2 (CH_3), 55.9 (CH_3), 78.1 (C), 80.1 (C), 103.0 (C), 115.1 (CH), 123.8 (CH), 125.4 (CH), 131.3 (CH), 132.2 (C), 133.8 (C), 134.6 (CH), 160.2 (C) and 167.2 (C). *m*/*z*: (CI) 542 (M^+, 15%), 416 (18), 219 (100).

2-[2-(1-Methanesulfonyl-5-methoxy-1*H*-indol-3-yl)ethyl]isoindole-1,3-dione 11 (using TTMSS)

N-[4-(1,3-Dioxodihydroisoindol-2-yl)-but-2-ynyl]-*N*-(2′-iodo-4′-methoxyphenyl)methanesulfonamide **9**, (200 mg, 0.38 mmol, 1.00 equiv.)

was dissolved in dry toluene (46 mL), under argon, and heated to reflux. A solution of *tris*trimethylsilylsilane (0.141 mL, 0.46 mmol, 1.20 equiv.) and azoisobutyronitrile (6 mg, 0.038 mmol, 0.01 equiv.) in dry toluene (7 mL) was added to the refluxing solution using a syringe pump over 5 h. The solution was refluxed overnight, after which *p*-toluenesulfonic acid (73 mg, 0.038 mmol, 1.00 equiv.) was added. The solution was refluxed for an additional 2 h. The solvent was removed in vacuo to afford a brown oil which was purified by column chromatography (75:25 petroleum ether-ethyl acetate) to afford *2-[2-(1-methanesulfonyl-5-methoxy-1H-indol-3-yl)ethyl]isoindole-1,3-dione* **11** as a yellow solid (111 mg, 74%). M.p. 176–178°C (Found: $[MNH_4]^+$, 416.1275. $C_{20}H_{22}N_3O_5S$ requires [*MNH4*], 416.1280). ν_{max} (KBr)/cm^{-1} 3026 (Ar-H), 2960 (CH), 1769 and 1710 (C=O), 1612 (Ar), 1478 (CH), 1364 and 1172 (SO_2). δ_H ($CDCl_3$): 2.99 (3H, s, SO_2CH_3), 3.08 (2H, t, *J* 7.4, CH_2), 3.87 (3H, s, OCH_3), 4.02 (2H, t, *J* 7.4, NCH_2), 6.96 (1H, dd, *J* 8.8, 2.4, ArH), 7.14 (1H, d, *J* 2.4, ArH), 7.28 (1H, s, ArH), 7.72–7.75 (2H, m, ArH), 7.78 (1H, d, *J* 8.8, ArH) and 7.79–7.85 (2H, m, ArH). δ_C ($CDCl_3$): 24.4 (CH_2), 37.8 (CH_2), 40.3 (CH_3), 55.9 (CH_3), 102.1 (CH), 114.5 (CH), 114.5 (CH), 119.5 (C), 123.5 (CH), 124.5 (CH), 130.2 (C), 131.9 (C), 132.3 (C), 134.3 (CH), 157.0 (C) and 168.4 (C). *m*/*z*: (EI) 398 (M^+, 14%), 319 (10), 251 (15), 238 (18), 160 (100).

2-[2-(1-Methanesulfonyl-5-methoxy-1*H*-indol-3-yl)ethyl]isoindole-1,3-dione 11 (Using 1-EPHP)

N -[4-(1,3-Dioxodihydroisoindol-2-yl)but-2-ynyl]-*N*-(2-iodo-4-methoxyphenyl) methanesulfonamide **9** (220 mg, 0.42 mmol, 1.00 equiv.), 1-ethylpiperidinium hypophosphite (751 mg, 4.20 mmol, 10.0 equiv.) and azoisobutyronitrile (27 mg, 0.17 mmol, 0.40 equiv.) were dissolved in dry toluene (30 mL), under nitrogen, and brought to reflux. The solvent was removed in vacuo and then diluted with CH_2Cl_2. After extraction with water, brine (sat.) and drying over $MgSO_4$, a yellowish oil was obtained. Subsequent purification by column chromatography (75:25 petroleum ether–ethyl acetate) gave an apparent mixture of the indolenine **10** along with 2-[2-(1-methanesulfonyl-5-methoxy-1H-indol-3-yl)ethyl] isoindole-1,3-dione **11**. The solid was dissolved in CH_2Cl_2 and a crystal of *p*-toluenesulfonic acid was added. After 8 h, the solution was filtered through a silica plug and eluted with ethyl acetate. Removal of the solvent gave the desired product **11** (75 mg, 45%). Spectral data were identical to those reported above.

2-(1-Methanesulfonyl-5-methoxy-1H-indol-3-yl)ethylamine 12

2-[2-(1-Methanesulfonyl-5-methoxy-1*H*-indol-3-yl)ethyl]isoindole-1,3-dione **11** (800 mg, 2.00 mmol, 1.00 equiv.) and hydrazine monohydrate (0.389 mL, 8.03 mmol, 4.00 equiv.) were dissolved in ethanol (30 mL) and refluxed for 3 h. The solvent was removed in vacuo and the residue dissolved in CH_2Cl_2. The residue was extracted with aqueous NaOH (2 M) and subsequently with brine (sat). The combined organic extracts were dried over $MgSO_4$, filtered and evaporated to give a white solid which was purified by column chromatography (90:10:0, then 89:10:1 CH_2Cl_2-MeOH-Et_3N) to afford *2-(1-methanesulfonyl-5-methoxy-1H-indol-3-yl)ethylamine* **12** as a white solid (473 mg, 85%). M.p. 127–129°C (Found: $[MH]^+$, 269.0958. $C_{12}H_{17}N_2O_3S$ requires [*MH*], 269.0960). ν_{max} (KBr/cm^{-1}) 3429 and 3366 (NH_2), 3108 (Ar-H), 2930 (CH), 1612 (NH_2 or Ar), 1595 (NH_2 or Ar), 1477 (CH), 1353 and 1170 (SO_2). δ_H ($CDCl_3$): 1.51 (2H, b s, NH_2) 2.86 (2H, t, *J* 6.8, CH_2), 3.05 (3H, s, SO_2-CH_3), 3.05–3.11 (2H, m, NCH_2), 3.90 (3H, s, OCH_3), 7.01 (1H, dd, *J* 8.9, 2.4, ArH), 7.05 (1H, d, *J* 2.4, ArH), 7.27 (1H, s, ArH) and 7.82 (1H, d, *J* 8.9, ArH). δ_C ($CDCl_3$): 29.4 (CH_2), 40.3 (CH_3), 41.6 (CH_2), 56.0 (CH_3), 102.6 (CH), 114.0 (CH), 114.3 (CH), 120.7 (C), 124.1 (CH), 130.3 (C), 132.1 (C) and 156.8 (C). *m/z*: (CI) 286 (MNH_4^+, 10%), 269 (MH, 100), 191 (37).

5-Methoxytryptamine 13

2-(1-methanesulfonyl-5-methoxy-*1H*-indol-3-yl)ethylamine **12** (125 mg, 0.47 mmol, 1.00 equiv.) was dissolved in thoroughly degassed 5% KOH/MeOH solution and heated to reflux for 9 h. The solution was then diluted with water and extracted with diethyl ether. The combined organic layers were extracted with brine (sat) and dried over $MgSO_4$. The solvent was removed in vacuo to afford a purple solid which was purified by column chromatography (50:50:0, then 79:20:1 CH_2Cl_2-MeOH-Et_3N) to afford 5-methoxytryptamine **13** as white crystals (73 mg, 84%). M.p. 122–125°C (Lit.[14], 122°C). ν_{max} (KBr/cm^{-1}) 3335, 3284 (N-H), 3040, 2871 (C-H), 1623, 1585, 1489, 1239, 1218, 1010, 792, 639. δ_H ($CDCl_3$): 1.41 (2H, s, NH_2), 2.92 (2H, t, *J* 6.8, CH_2), 3.08 (2H, t, *J* 6.8, CH_2), 3.91 (3H, s, OMe), 6.90 (1H, dd, *J* 8.7, 2.4, Ar-H), 7.04 (s, 1H, Ar-H), 7.09 (1H, d, *J* 2.4, Ar-H), 8.23 (1H, s, N-H). δ_C ($CDCl_3$): 29.7 (CH_2), 42.5 (CH_2), 56.2 (CH_3), 101.0 (CH), 112.1 (CH), 112.4 (CH), 113.7 (C), 123.1 (CH), 128.1 (C), 131.8 (C), 154.1 (C).

Melatonin 1

5-Methoxytryptamine **13** (100 mg, 0.52 mmol, 1.00 equiv.) was dissolved in acetic anhydride (0.5 mL), under nitrogen, and the solution stirred for 18 h. Water (2 mL) was then added to the solution and this was stirred for 0.5 h. Solid sodium bicarbonate was added until the solution had a pH 6–7. The reaction mixture was extracted with CH_2Cl_2 and the combined extracts dried over $MgSO_4$, filtered and evaporated. The residue was purified by column chromatography (90:10 CH_2Cl_2-MeOH) to afford melatonin **1** as a white solid (108 mg, 90%). M.p. 112–114°C [Lit.[14] 117°C]. ν_{max} (KBr/cm^{-1}) 3304 (N-H), 3082, 2928, 2873, 2828 (C-H), 1629, 1587, 1557, 1489, 1213, 1041. δ_H ($CDCl_3$): 1.90 (3H, s, Ac), 2.96 (2H, t, *J* 6.6, CH_2), 3.61 (2H, dt, *J* 6, 6.6, CH_2), 3.89 (3H, s, CH_3), 5.68 (1H, s, N-H), 6.89 (1H, dd, *J* 8.8, 2.4, Ar-H), 7.02 (1H, m, Ar-H), 7.06 (1H, d, *J* 2.4, Ar-H), 7.28 (1H, d, *J* 8.8, Ar-H), 8.31 (1H, s, NH). δ_C ($CDCl_3$): 25.6 (CH_3), 25.5 (CH_2), 39.9 (CH_2), 56.1 (CH), 100.7 (CH), 112.2 (CH), 112.6 (C), 112.8 (CH), 123.0 (CH), 127.9 (C), 131.8 (C), 154.3 (C), 170.4 (C).

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REFERENCES

1. Lerner, B.; Case, J.D.; Takahashi, Y.; Lee, T.H.; Mori, W. Structure of melatonin. J. Am. Chem. Soc. **1959**, *80*, 6084–6085.
2. (a) Zhdanova, I.V.; Wartman, R.J.; Regan, M.M.; Taylor, J.A.; Shi, J.P.; Leclair, O.U. Melatonin treatment for age-related insomnia. J. Clin. Endocr. Metab. **2001**, *86*, 4727–4730; (b) Lynch, H.J.; Wurtman, R.J.; Moskowitz, M.A.; Archer, M.C.; Mo, M.H. Daily rhythm in human urinary melatonin. Science **1975**, *187*, 169–171.
3. (a) Reiter, R.J.; Acuna-Castroviejo, D.; Tan, D.X.; Burkhardt, S. Free radical-mediated molecular damage-mechanisms for the protective actions of melatonin in the central nervous system. Ann. N.Y. Acad. Sci. **2001**, *939*, 200–215; (b) Barlow-Walden, L.R.; Reiter, R.J.; Abe, M.; Pablos, M.; Menendez-Pelaez, A.; Chen, L.-D.; and

Poeggelar, B. Melatonin stimulates brain glutathione–peroxidase activity. Neurochem. Int. **1995**, *26*, 497–502; (c) Reiter, R.J. Functional pleiotropy of the neurohormone melatonin-antioxidant protection and neuroendocrine regulation. Front. Neuroendocrinol **1995**, *16*, 383; (d) Tan, D.X.; Poeggeler, B.; Reiter, R.J.; Chen, L.D.; Chen, S.; Manchester, L.C.; Barlow-Walden, L.R. The pineal hormone melatonin inhibits DNA-adduct formation induced by the chemical carcinogen safrole in vivo. Cancer Lett. **1993**, *70*, 65–71.

4. Poeggeler, B.; Miravalle, L.; Zagorski, M.G.; Wisniewski, T.; Chyan, Y.-J.; Zhang, Y.; Shao, H.; Bryant-Thomas, T.; Vidal, R.; Frangione, B.; Ghiso, J.; Pappolla, M.A. Melatonin reverses the profibrillogenic activity of apolipoprotein e4 on the alzheimer amyloid a beta peptide. Biochemistry **2001**, *40*, 14995–15001.
5. Jordan, A.; Hadfield, J.A.; Lawrence, N.J.; McGown, A.T. Tubulin as a target for anticancer drugs: agents which interact with the mitotic spindle. Med. Res. Rev. **1998**, *18*, 259–296; Banerjee, S.; Kerr, V.; Winston, M.; Kelleher, J.K.; Margulis, L. J. Protozool melatonin: inhibition of microtubule-based oral morphogenesis in Stento Coeruleus. **1972**, *19*, 108–113.
6. Nogales, E.; Wolf, S.G.; Downing, K.H. Structure of the alpha beta tubulin dimer by electron crystallography. Nature **1998**, *391*, 199–203.
7. Edmondson, S.; Danishefsky, S.J.; Sepp-Lorenzino, L.; Rosen, N. Total synthesis of spirotryprostatin A, leading to the discovery of some biologically promising analogues. J. Am. Chem. Soc. **1999**, *121*, 2147–2155.
8. (a) Somei, M.; Fukui, Y.; Hasegawa, M.; Oshikiri, N.; Hayashi, T. Syntheses of melatonin and its derivatives. Heterocycles **2000**, *53*, 1725–1725; (b) Hwang, K.J.; Lee, T.S. A practical synthesis of *N*-acetyl-5-methoxytryptamine (melatonin). Synth. Commun. **1999**, *29*, 2099–2104 and references therein.
9. (a) Quiclet-Sire, B.; Sortais, B.; Zard, S.Z. A convergent approach to 2-substituted-5-methoxyindoles. application to the synthesis of Melatonin. Chem. Commun. **2002**, 1692–1693 (and 1988).
10. (a) Murphy, J.A.; Scott, K.A.; Sinclair, R.S.; Lewis, N. A new synthesis of indoles. Tetrahedron Lett. **1997**, *38*, 7295–7298; (b) Murphy, J.A.; Scott, K.A.; Sinclair, R.S.; Martin, C.G.; Kennedy, A.R.; Lewis, N. A radical based addition–elimination route for the preparation of indoles. J. Chem. Soc. Perkin Trans. **2000**, *1*, 2395–2408.
11. (a) Dittami, J.P.; Ramanathan, H. Intramolecular radical cyclization reactions—an approach to the indole alkaloids. Tetrahedron

Lett. **1988**, *29*, 45–48; (b) Boger, D.L.; Ishizaki, T.; Kitos, P.A.; Suntornwat, O. Synthesis of *n*-(*tert*-butyloxycarbonyl)-CBI, CBI, CBI-$CDPI_1$, and CBI-$CDPI_2$-enhanced functional analogs of cc-1065 incorporating the 1,2,9,9a-tetrahydrocyclopropa[*c*]benz[*e*]-indol-4-one (CBI) left-hand subunit. J. Org. Chem. **1990**, *55*, 5823–5832; (c) Boger, D.L.; Coleman, R.S. Total synthesis of (±)-N^2-(Phenylsulfonyl)-CPI, (±)-CC-1065, (+)-CC-1065, *ent*-(-)-CC-1065, and the precise, functional agents (±)-CPI-$CDPI_2$, (+)-CPI-$CDPI_2$, and (−)-CPI-$CDPI_2$ [(±)-(3b*R**,4aS*)-, (+)-(3b*R*,4a*S*)- and (−)-(3b*S*,4a*R*)-Deoxy-CC-1065]. J. Amer. Chem. Soc. **1988**, *110*, 4796–4807; (d) Inanaga, J.; Ujikawa, O.; Yamaguchi, M. SmI_2-promoted aryl radical cyclization—a new synthetic entry into heterocycles. Tetrahedron Lett. **1991**, *32*, 1737–1740; (e) Hodgson, D.M.; Wells, C. Chromium(II)-mediated nickel(ii)-catalyzed cyclizations of (iodoaryl)-substituted alkynes and alkynals. Tetrahedron Lett. **1994**, *35*, 1601–1604.

12. Lizos, D.E.; Murphy, J.A. Concise synthesis of (±)-horsfiline and (±)-coerulescine by tandem cyclization of iodoaryl alkenyl azides. Org. Biomol. Chem. **2003**, *1*, 117–122.
13. Allan, R.D.; Johnston, G.A.R.; Twitchin, B. Synthesis of analogues of GABA. V. *trans* and *cis* isomers of some 4-amino-3-halogenobut-2-enoic Acids. Aust. J. Chem. **1980**, *33*, 1115–1122.
14. Revial, G.; Jabin, I.; Lirn, S.; Pfau, M. Aromatization of 1,6,7,7a-tetrahydro-2H-indol-2-ones by a novel process. Preparation of key-intermediate methyl 1-benzyl-5-methoxy-1H-indole-3-acetate and the syntheses of serotonin, melatonin, and bufotenin. J. Org. Chem. **2002**, *67*, 2252–2256.

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