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Thallium(III) Acetate-Mediated 3,3-Couplings of Indoles with the Formation of Indolocarbazoles

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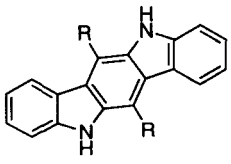
Abstract:

2,3-Dimethylindole, 2-ethyl-3-methylindole, and 2-methylindole have been oxidized with thallium(III) acetate (TTA). The structures of the products have been established by comparisons with products obtained previously with other oxidants as well as by independent syntheses, most notably double Fischer indolizations of the *bis*-phenylhydrazones of 2,5-dimethyl-1,4-cyclohexanedione and 2,3-dimethyl-1,4-cyclohexanedione.

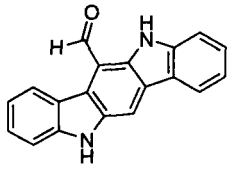
Keywords: thallium; indoles; oxidation; indolization

1. Background and Introduction[1]

The TCDD (2,3,7,8-tetrachlorodibenzo-*p*-dioxin) receptor is a ubiquitous, intracellular protein present in virtually all rodent tissues or human cells examined. Upon binding of a proper ligand the resulting receptor-ligand complex is translocated to the nucleus where activation of transcription of several genes will take place. These genes encode proteins involved in the metabolism of xenobiotica and in cell growth and differentiation. Several 5,11-dihydroindolo[3,2-*b*]carbazoles (most notably **1**, **2** and **4**) have been demonstrated to be exceptionally strong ligands to the receptor, and as part of a program to investigate further receptor function, we have recently developed more or less general synthetic methods to 6-mono-substituted[2] and 6,12-disubstituted derivatives[3] of this interesting class of compounds, including syntheses of **2**,[3] **3**[3] and **4**.[2,4]



1) R = H
2) R = CHO
3) R = Me



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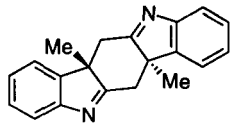

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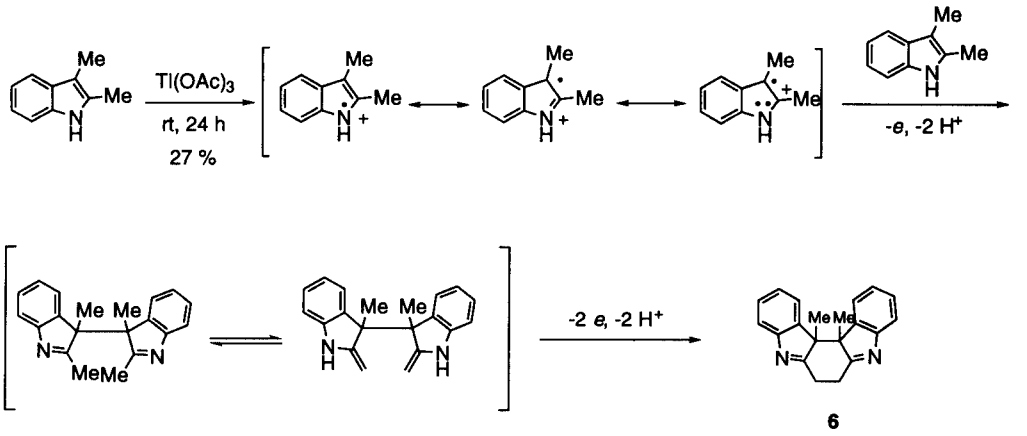
PII: S0040-4020(99)00734-6

In this context, an indolocarbazole isomeric with **3** aroused our interest. This isomer was obtained by oxidative dimerization of 2,3-dimethylindole induced by thallium(III) acetate (TTA) and the product was assigned the structure **5** based on NMR data.[5] The possible formation of the indolo[3,2-*b*]carbazole ring system through oxidation of 2,3-dialkylsubstituted indoles prompted us to reinvestigate this oxidative coupling of 2,3-dimethylindole.

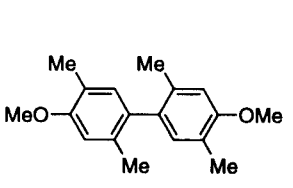
2. Results and discussion

The TTA-oxidation of 2,3-dimethylindole gave, apart from the main product (27 %), small amounts (≈2 %) of a second product. The spectral data of the main product was not in obvious disagreement with structure **5**, but from a mechanistic standpoint we felt that the NMR data could be equally well explained by the isomeric *bis*-indolenine structure **6**, whereby a 3,3-coupling would have played an important role (Scheme 1).



Scheme 1

The fact that such couplings of indoles can be induced by a number of reagents (*e.g.* $FeCl_3$ in combination with secondary amines,[6] PbO_2,[7] but also electrochemical methods[8]) underscored this assumption. Furthermore, Tl(III)-induced couplings of activated aromatic systems have frequently been reported in the literature. For example, treatment of 2,5-dimethylanisole with Tl(III) trifluoroacetate gave the biphenyl derivative **7** in excellent yield.[9,10] Likewise, methyl *p*-methoxycinnamate gave the oxidatively coupled dimer **8**.[11]



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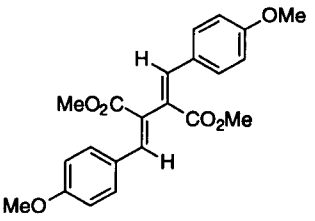

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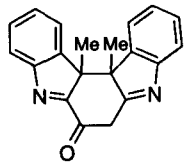
The minor secondary product in the reaction is formed from the *bis*-indolenine **6** and has been assigned the structure **9** based on NMR, IR and MS data. Compound **6** has apparently been oxidized to **9** by TTA. On the other hand, **5** might just as well have undergone the same type of oxidation giving the compound **10** with a ^{1}H NMR spectrum not much different from that of **9**.



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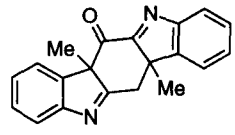

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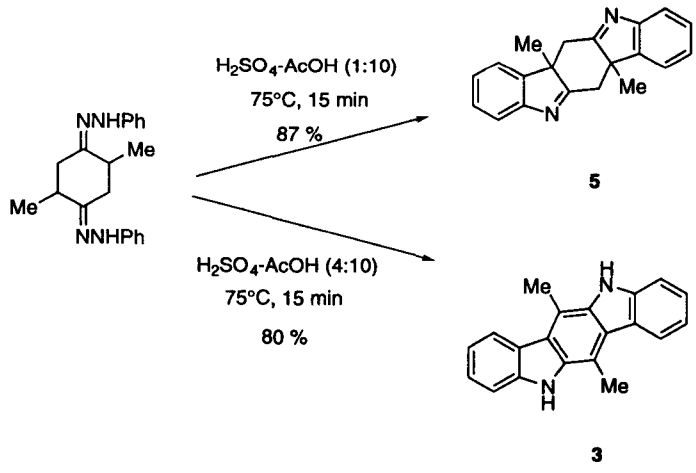
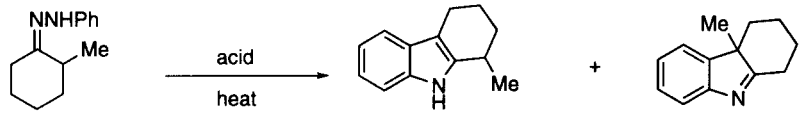
It should be possible to distinguish between the linear and the angular indolocarbazoles **5** and **6** by ^{1}H NMR spectroscopy: if **5** was formed one doublet from the CH_2 groups should be observed, while a more complicated coupling pattern should arise from **6**. The spectrum of the major product showed that one single isomer was formed (*cis* or *trans*), since only one signal from the CH_3 groups could be observed. The spectrum also showed two doublets from the CH_2 groups, in favour of **5**. However, the ^{1}H NMR spectrum does not render structure **6** impossible: with a certain conformation the coupling constant between two adjacent methylene protons could be zero and viewing a model of **6** suggests that it is not improbable. Since we recently have had some experience with Fischer indolization of the *bis*-phenylhydrazone of 2,5-dimethyl-1,4-cyclohexanedione to give dimethylindolocarbazole **3**,[3] we felt that by manipulating the reaction conditions it should be possible to synthesize **5** (an isomer of **3**) independently. Indeed, by lowering the concentration of H_2SO_4 in the reaction mixture previously used,[3,12] it was possible to obtain **5** (as a single stereoisomer) in high yield (Scheme 2). Conversely, increasing the concentration of H_2SO_4 gave **3**[3] in good amounts. It is remarkable that such a small change in acid concentration leads to completely different products.



Scheme 2

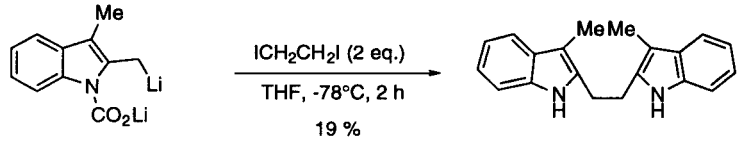
These results nicely fitted with those of Miller and Schinske,[13] who found that the ratio indole/indolenine (**11/12**) obtained when indolizing the phenylhydrazone of 2-methylcyclohexanone increased with enhanced acidity of the medium (Scheme 3).



11 **12**

Scheme 3

The NMR spectrum of compound **5** synthesized independently showed the same general features as those of the main product from the TTA-oxidation of 2,3-dimethylindole, although it was distinctly different. Nevertheless, it is theoretically possible that the *cis* isomer of **5** was formed in the Tl-experiment, and the *trans* isomer (or *vice versa*) was obtained by the Fischer indolization. So, to obtain a definitive proof of our assigned structure **6** we decided to confirm it by an independent synthesis. At first, we thought of using a new protocol developed in our laboratories involving homocoupling of 2-methylindoles.[14] Thus, 2,3-dimethylindole was doubly lithiated using the Katritzky protocol[14,15] then treated with diiodoethane to give the *bis*-indolylethane **13** in low yield (Scheme 4).



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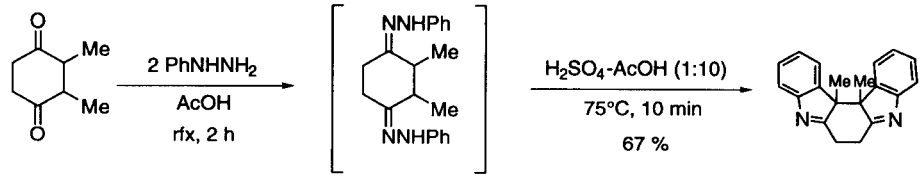
Scheme 4

Compound **13** was then treated with TTA in the hope of cyclization to the indolo[2,3-*c*]carbazole **6**. Disappointingly, not a trace of **6** could be detected, not even at elevated temperatures. Probably, the energy barrier for achieving the requisite conformation for the cyclization is too high. Therefore, we turned to the more conventional Fischer indolization. The required *bis*-phenylhydrazone **14** was obtained from 2,3-dimethyl-1,4-cyclohexanedione, a known compound[16-18] which was obtained from 2,3-dimethyl-1,4-benzoquinone by reduction to 2,3-dimethyl-1,4-cyclohexanediol followed by reoxidation to the dione. The *bis*-phenylhydrazone **14** was treated with a H_2SO_4-AcOH combination and from the reaction mixture **6** could be isolated in 67 % yield (once again as a single isomer), thus confirming the reassignment of the product obtained by Tl(III) oxidation of 2,3-dimethylindole (Scheme 5).

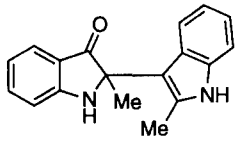


14 **6**

Scheme 5

The formation of the by-product **9** gave us an opportunity to ascertain whether the methyl groups in **6** have a *cis* or *trans* relationship (**9** is formed from **6** and can thus be viewed as a derivative thereof). A NOESY experiment revealed no nOes between the methyl groups whatsoever, thus strongly indicating a *trans* relationship. No efforts have been made to assign the stereochemistry of **5**.

Oxidation of 2-methylindole with TTA had also been previously studied[5] and apart from the well-known dimeric 2,3´-coupling product **15** a "trimer" (unassigned) had been isolated. This "trimer" has now been identified as **16** and has been previously obtained by electrochemical[8] as well as by $FeCl_3$-mediated[6] couplings of 2-methylindole. Finally, TTA-oxidation of 2-ethyl-3-methylindole gave the tetramethyl-substituted angular indolocarbazole **17**, the expected homologue of **6**, once again as a single isomer.



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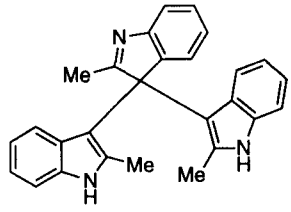

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3. Conclusion

In summary, we have studied Tl(III) acetate oxidation of 2,3-dimethylindole and 2-methylindole and corroborated the products with known compounds and independent syntheses, most notably double Fischer indolizations of the *bis*-phenylhydrazones of 2,5-dimethyl-1,4-cyclohexanedione and 2,3-dimethyl-1,4-cyclohexanedione.

4. Experimental section

With the following exceptions all reagents and solvents were purchased from commercial suppliers and used without further purification: 2,3-dimethylcyclohexane-1,4-dione was synthesisized according to a known procedure;[16-18] and distilled solvents were used for flash chromatography. The petroleum ether used for chromatography had the boiling point range 60-80°C. Silica gel (230-400 mesh) for column chromatography and TLC plates were purchased from Merck. The expression "evaporation of solvent(s)" refers to the use of a rotatory evaporator at 30°C at reduced pressure. NMR experiments were performed on a Bruker DPX300 instrument. IR spectra were recorded on a Perkin-Elmer FT-IR 1600 spectrophotometer. Melting points (uncorrected) were determined on an Electrothermal IA9020 digital melting point apparatus or a Kofler Hotbench (Leica VM HB) when appropriate. The microanalyses were performed by H. Kolbe Mikroanalytisches Laboratorium, Mülheim an der Ruhr, Germany. High resolution mass spectroscopy (HRMS) experiments were performed by Sveriges Lantbruksuniversitet (SLU), Uppsala, Sweden.

2,3,8b,8c-Tetrahydroindolo[2,3-*c*]carbazole (6) and 2,3,8b,8c-Tetrahydroindolo[2,3-c]carbazol-2-one (9)

Method 1: TTA-oxidation of 2,3-dimethylindole (General TTA-oxidation procedure)

To a solution of 2,3-dimethylindole (1.452 g, 10.0 mmol) in acetic acid (40 mL) thallium triacetate (TTA) (3.815 g, 10.0 mmol) (CAUTION!: highly toxic!) was added in one portion to give an initially green solution. The solution was heated at 30°C for 24 h after which the acetic acid was evaporated. The residue was taken up in CH_2Cl_2 (150 mL) and washed with saturated aqueous $NaHCO_3$ (2×50 mL) before drying ($MgSO_4$). After evaporation of the solvent the residue was purified by column chromatography (1. CH_2Cl_2-petroleum ether, 0-100 %, 2. ethyl acetate-CH_2Cl_2, 0-50 %). The evaporated fractions containing the fastest eluting compound were triturated with diethyl ether-petroleum ether (50 %) to give pure **9** (30 mg) as a light-yellow powder, mp 196.5-199°C.
^1H NMR ($CDCl_3$, 300 MHz) δ 8.63 (d, 1H, J = 7.2 Hz), 7.95 (d, 1H, J = 7.6), 7.55-7.34 (m, 6H), 3.59 (d, 1H, J = 15.3 Hz), 2.60 (d, 1H, J = 15.3 Hz), 2.29 (s, 3H), 1.42 (s, 3H)
^{13}C NMR ($CDCl_3$, 75 MHz) δ 175.9 (s), 157.5 (s), 154.5 (s), 144.3 (s), 134.9 (s), 131.9 (s), 131.2 (s), 129.3 (d), 128.7 (d), 125.4 (d), 124.9 (d), 124.3 (d), 122.2 (d), 118.6 (d), 116.9 (d), 116.7 (s), 55.4 (s), 31.1 (t), 20.3 (q), 8.9 (q)
IR (KBr) 1700, 1459, 1395, 1370, 1358, 1338, 1325, 1315, 1204, 777, 756 cm^{-1}.
HRMS (EI+), calcd. for $C_{20}H_{16}N_2O$: 300.1263. Found: 300.1257.

The evaporated fractions containing the more polar compound were treated with ethyl acetate to give pure **6** (381 mg, 27 %) as a light-yellow powder. An analytical sample was obtained as a light-yellow powder by recrystallization from iso-PrCN, mp 294-297°C (Lit.[5] 282°C).

Method 2: Double Fischer indolization of 2,3-dimethyl-1,4-cyclohexanedione, *bis*-phenylhydrazone

Phenylhydrazine (1.08 g, 10 mmol) was dissolved in EtOH (10 mL) and 2,3-dimethylcyclohexane-1,4-dione[16-18] (0.70 g, 5.0 mmol) was added followed by 3 drops of acetic acid. The solution was refluxed for 2 h and then cooled to room temperature. Since no precipitate was formed the solution containing the crude *bis*-phenylhydrazone **14** was evaporated. The residue obtained was redissolved in a mixture of acetic acid (10 mL) and H_2SO_4 (1 mL). The solution obtained was heated for 10 min at 75°C and then allowed to cool. After addition of water and ice (50 mL), the solution was neutralized with an aqueous 20 % NaOH-solution. The mixture obtained was extracted with ether. After washing (water) and drying ($MgSO_4$) the ether phase, the solvent was evaporated and the residue purified by column chromatography (CH_2Cl_2-petroleum ether, 0-100 %) to afford pure **6** (0.95 g, 67 %) as a light-yellow powder. An analytical sample was obtained as a light-yellow powder by recrystallization from iso-PrCN, mp 294-297°C (Lit.[5] 282°C).
^1H NMR ($CDCl_3$, 300 MHz) δ 7.69 (d, 2H, J = 7.9 Hz), 7.45-7.38 (m, 4H), 7.30 (dd, 2H, J = 7.5, 7.5 Hz), 3.27 (d, 2H, J = 13.3 Hz), 2.68 (d, 2H, J = 13.3 Hz), 1.30 (s, 6H)
^{13}C NMR ($CDCl_3$, 75 MHz) δ 185.3 (s), 154.8 (s), 145.2 (s), 128.6 (d), 126.1 (d), 121.8 (d), 121.2 (d), 56.1 (s), 38.9 (t), 21.3 (q)
IR (KBr) 2959, 1584, 1468, 1455, 1426, 1378, 776, 750 cm^{-1}.
Anal. calcd. for $C_{20}H_{18}N_2$: C: 83.88; H: 6.34; N: 9.78. Found: C: 83.70; H: 6.27; N: 9.74.

6a,12a-Dimethyl-6,6a,12,12a-tetrahydroindolo[3,2-*b*]carbazole (5)

2,5-Dimethylcyclohexane-1,4-dione *bis*-phenylhydrazone[3] (4.50 g, 14.0 mmol) was added portion-wise to a solution of conc. H_2SO_4 (2 mL) in AcOH (20 mL) at 30°C. The resulting red solution was treated as in the previous experiment and a small amount of 6,12-dimethylindolo[3,2-*b*]carbazole **3** was collected. The pH of the acidic mother liquor was now adjusted to 9-10 by the addition of sodium carbonate. The brownish precipitate obtained was purified by column chromatograpy (MeOH-CH_2Cl_2, 0-10 %) to give **5** (3.45 g, 87 %) as a brown powder. An analytical sample was obtained as brownish crystals by recrystallization from methyl acetate, mp 195-198°C.
^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.42-7.37 (m, 4H), 7.31-7.20 (m, 4H), 3.48 (d, 2H, J = 14.9 Hz), 3.34 (d, 2H, J = 14.9 Hz), 1.72 (s, 6H)
^{13}C NMR ($CDCl_3$, 75 MHz) δ 184.9 (s), 154.0 (s), 146.5 (s), 128.4 (d), 126.3 (d), 121.5 (d), 120.8 (d), 54.5 (s), 38.7 (t), 27.0 (q)
IR (KBr) 2962, 1575, 1468, 1448, 1429, 1190, 776, 755 cm^{-1}.
HRMS (EI+), calcd. for $C_{20}H_{18}N_2$: 286.1470. Found: 286.1465.

1,2-Di-(3-methylindol-2-yl)ethane (13)

2,3-Dimethylindole (1.452 g, 10 mmol) was dissolved in dry THF (30 mL) under N_2. The solution was cooled to -78 °C and *n*-BuLi (12.5 mmol, 5.0 mL, 2.5 M in hexane) was added dropwise during 10 min. The lithium salt precipitated at the end of the addition. 1.5 h after the last drop of *n*-BuLi had been added the solution was protected with a drying tube and CO_2 was bubbled through the mixture during 20 min. A clear solution was obtained almost immediately. After the CO_2-bubbling was complete the solution was allowed to stir for 30 min to let most of the dissolved CO_2 to evaporate. A vacuum pump was then connected to the system. The pumping continued for 30 min at -78 °C, whereupon the CO_2-EtOH-bath was replaced with an ordinary ice-bath to remove the solvent completely (to ensure complete removal of CO_2). Freshly distilled THF (30 mL) was added to dissolve the solid residue and the solution was once again cooled to -78 °C. *tert*-BuLi (12.5 mmol, 7.4 mL, 1.7 M in hexane) was added dropwise during 10 min. The colour of the solution changed through yellow to deep orange. 1 h after the addition of *tert*-BuLi diiodoethane (2.819 g 10 mmol) was added in one portion and the mixture was stirred for 2 h at -78°C before quenching with saturated, aqueous NH_4Cl (1 mL). The solution was warmed to room temperature and diluted with CH_2Cl_2 (100 mL). The organic phase was washed with aqueous $Na_2S_2O_3$ (30 mL) and then dried ($MgSO_4$). Evaporation of the solvents gave a brownish residue which was treated with diethyl ether (30 mL) to give a cream-white powder (565 mg) consisting of desired **13** contaminated with unreacted 2,3-dimethylindole (12 mol %). Pure **13** (274 mg, 19 %) was obtained as a cream-white powder by recrystallization from iso-PrCN, mp 260-263°C.
^{1}H NMR (DMSO-*d6*, 300 MHz) δ 10.77 (s, 2H, N*H*), 7.35 (d, 2H, J = 7.5 Hz), 7.28 (d, 2H, J = 7.8 Hz), 7.01 (dd, 2H, J = 7.6, 7.6 Hz), 6.93 (dd, 2H, J = 7.6, 7.6 Hz), 3.04 (s, 4H), 2.09 (s, 6H).
^{13}C NMR (DMSO-*d6*, 75 MHz) δ 135.3 (s), 134.8 (s), 128.8 (s), 120.1 (d), 117.9 (d), 117.5 (d), 110.4 (d), 105.2 (s), 26.1 (t), 8.1 (q).
IR (KBr) 3383, 1464, 1440, 1334, 1312, 1244, 1004, 744, 678cm^{-1}.
Anal. calcd. for $C_{20}H_{20}N_2$: C: 83.30; H: 6.99; N: 9.71. Found: C: 83.18; H: 6.97; N: 9.57.

2-Methyl-2-(2-methyl-1*H*-3-indolyl)-3-indolinone (15) and 2-Methyl-3,3-di(2-methyl-1*H*-3-indolyl)-3*H*-indole (16)

2-Methylindole (1.31 g, 10 mmol) was oxidized with Tl(III) acetate (3.815 g, 10 mmol) following the general procedure (*vide supra*). The crude product mixture was separated by column chromatography on silica gel using CH_2Cl_2 with slowly increasing amounts of MeOH as eluent.

15: Yield: 95 mg of yellow powder, mp 210 °C (dec.) [Lit. 210 °C[5], 210 °C[8] (dec.), 212 °C[19] (dec.)].
The spectral data agreed with those already reported.[8]

16: Yield: 40 mg of white crystals, mp 203-204 °C [Lit. 193°C[5] (dec.), 201-203°C[8]].
The spectral data agreed with those already reported.[8]

2,3,8b,8c-Tetramethyl-2,3,8b,8c-tetrahydroindolo[2,3-*c*]carbazole (17)

The same (general) TTA-oxidation procedure as for the preparation of **6** and **9** was used, but with 2-ethyl-3-methylindole as substrate.

17: Yield: 20 % of off-white powder, mp 268-270°C (Lit.[5] 270°C).
^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.72 (d, 2H, J = 7.7 Hz), 7.49 (d, 2H, J = 7.0 Hz), 7.40 (dd, 2H, J = 7.6, 7.6 Hz), 7.26 (dd, 2H, J = 7.6, 7.6 Hz), 2.71 (q, 2H, J = 6.7 Hz), 1.67 (d, 6H, J = 6.7 Hz), 1.15 (s, 6H)
^{13}C NMR ($CDCl_3$, 100 MHz) δ 189.1 (s), 154.5 (s), 144.5 (s), 128.3 (d), 125.5 (d), 122.7 (d), 121.0 (d), 58.8 (s), 39.9 (d), 15.9 (q), 10.7 (q)
IR (KBr) 2978, 2919, 2861, 1574, 1452, 1383, 1197, 1071, 1014, 991, 772, 748 cm^{-1}.
HRMS calcd for $C_{22}H_{22}N_2$: 314.1783. Found: 314.1779.

5. References and notes

1. For a more thorough background with leading references to receptor structure and function, see the Introduction section of the preceding paper.
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