Synthesis of Polyalkylated Indoles Using a Thallium(III)-Mediated Ring-Contraction Reaction

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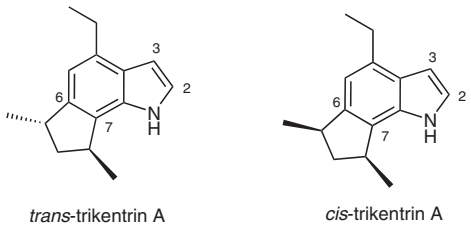
Abstract: A new approach to the synthesis of cyclopenta[*g*]indole derivatives possessing structural features of natural alkaloids, such as trikentrins and herbindols, is described. The key step in the sequence is a thallium(III)-mediated ring-contraction reaction to transform a cyclohexene moiety into a functionalized cyclopentyl unit.

Key words: cyclopenta[*g*]indoles, thallium trinitrate, ring contraction

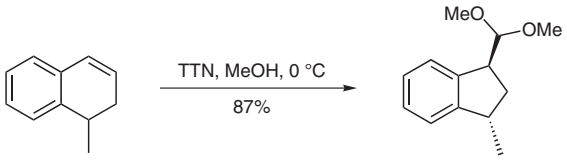
Cycloalkylindole alkaloids constitute a large number of compounds, on which usually the carbocyclic moiety is fused to the C2–C3 position.[1,2] However, the cytotoxic herbindoles and trikentrins, that were isolated from marine sponges, feature an unusual skeleton, on which the cyclopentane ring is fused to the C6–C7 position. In addition, there is no substituent at the C2 and the C3 positions (Figure 1).[3] Furthermore, synthetic molecules with similar tricyclic ring systems can inhibit the human nonpancreatic secretory phospholipase A_2, which is associated with some diseases including arthritis, septic shock and atherosclerosis.[4] Thus, several approaches have been developed to construct the challenging framework of these bioactive natural molecules.[5]



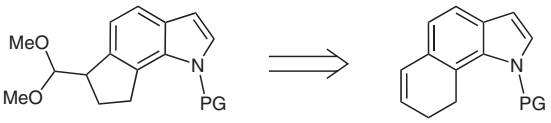
trans-trikentrin A *cis*-trikentrin A

Figure 1 Structure of *cis*- and *trans*-trikentrin A

We considered that a ring-contraction approach could be used to obtain the cyclopentane ring of this class of alkaloids. A reagent that could efficiently promote this rearrangement would be thallium trinitrate (TTN),[6,7] which has already been used in the synthesis of several indanes through the rearrangement of 1,2-dihydronaphthalenes (Scheme 1),[8] including the total synthesis of the sesquiterpene (±)-mutisianthol.[8b] Based on these results, we herein present the synthesis of new cyclopenta[*g*]indole derivatives, such as **1**, through the thallium(III)-mediated ring-contraction reaction of the six-membered-ring substrate **2** (Scheme **2**).



Scheme 1



1 **2**

Scheme 2

Indoles are known to be very reactive toward electrophilic species, particularly at the 3-position. Among the electrophiles utilized in functionalizations of indoles are thallium(III) salts, such as thallium tris-trifluoroacetate (TTFA) and thallium triacetate (TTA).[9] In this scenario, we started the present work investigating the reactivity of the N-protected indole **3** with TTN, using one of the standard conditions for the ring-contraction reaction.[8a] This reaction gave the indoline derivatives **4**, **5**, and **6** in 23%, 40%, and 9% isolated yields, respectively (Scheme 3). Considering the behavior of the indole **3,** the main challenge to obtain the desired cyclopenta[*g*]indole **1** using thallium(III) would be the discovery of a reaction condition that could promote the rearrangement of the indole **2**, avoiding the oxidation of its very reactive C3 position.

The indoline **4** is a crystalline solid, whose X-ray crystal structure analysis showed a *trans* relationship between the nitrate and methoxy groups (Figure 2). Thus, by analogy with the NMR data of compound **4**, the relative configuration of the *trans*-dimethoxy derivative **5** could be assigned. The NMR data of the indolines **4**, **5** and **6** deserve some comments. The signals of H_a in **4** and **5** are broad singlets. On the other hand, H_a appears as a doublet with a coupling constant of $J = 5.1$ Hz in the indoline **6**. Additionally, H_a and H_b of the *cis* isomer **6** are deshielded when compared to the same hydrogens of the corresponding

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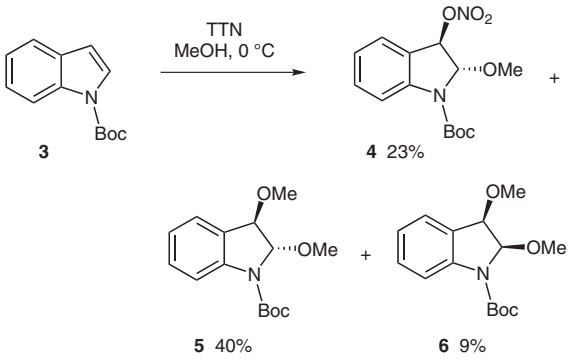
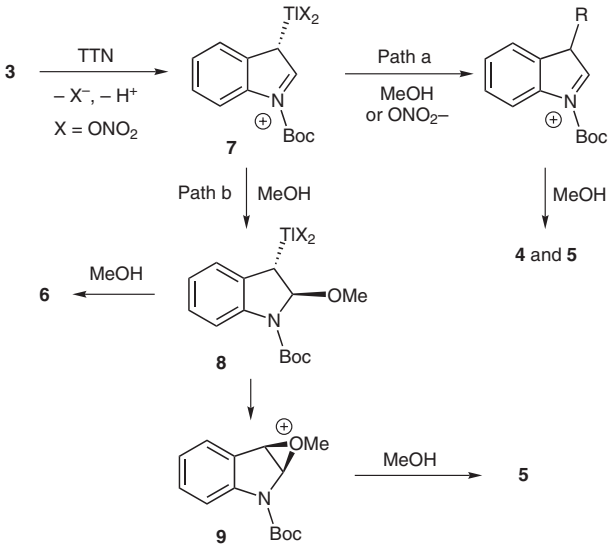


Scheme 3



Scheme 4

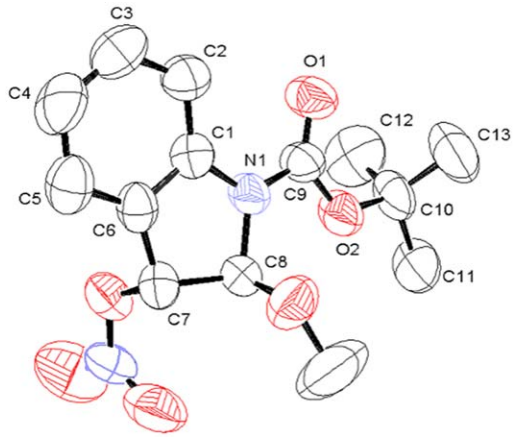


Figure 2 ORTEP diagram of **4**[11]

trans isomer **5**. This observation agrees with the data on some analogous indolines previously reported in the literature (Figure 3).[10]

The diastereoselectivity observed in the oxidation of the indole **3**, where the *trans* diastereoisomers (**4** and **5**) predominate over the *cis* (**6**), agrees with previous results[8c] and can be explained by the mechanism shown in Scheme 4.[8c,d,12] The electrophilic addition of a thallium(III) species at the C3 position of **3** would lead to the iminium ion **7**. This ion could either suffer a nucleophilic attack at C3 either by MeOH or by a nitrate ion, displacing thallium(I) nitrate, and thus giving the *trans*-indolines **4** and **5**, after addition of a second molecule of MeOH at C2 (Path a, Scheme **4**). Other possibility would be the attack at C2 of **7** by MeOH, which would lead to the oxythallated intermediate **8** (Path b). This organometallic species could suffer an intramolecular displacement of thallium(I) nitrate generating the oxonium ion **9**, that would give the *trans*-indoline **5**, after *anti* addition of a second molecule of solvent. Furthermore, the MeOH displacement of thallium(I) nitrate in **8** by MeOH would give the *cis*-isomer **6**.

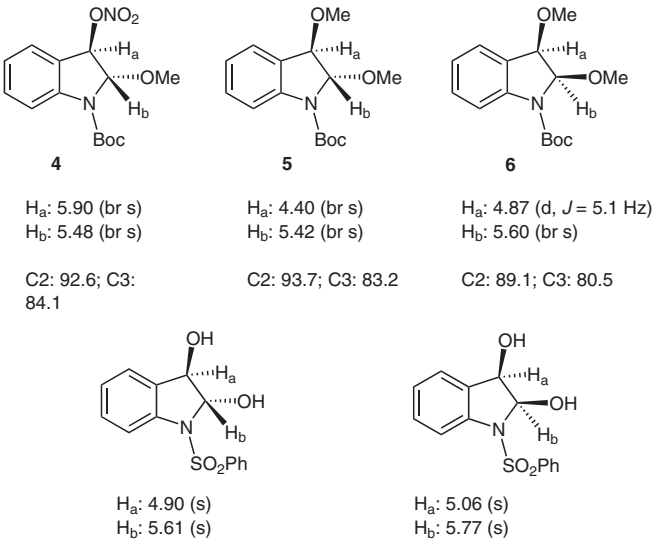
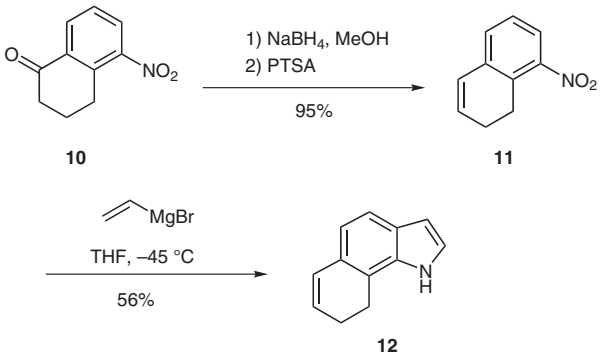


Figure 3 Selected NMR data for indolines

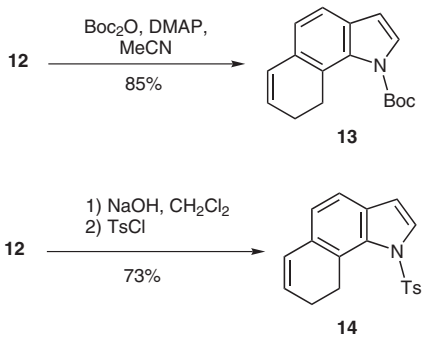
The tricyclic indole **12** was prepared from the tetralone **10**, which was obtained as described by Zhang et al.[13] Reduction of the ketone moiety of **10** was carried out using $NaBH_4$ in MeOH. The crude 1-tetralol was treated with *p*-toluenesulfonic acid (PTSA) in toluene, affording the desired 1,2-dihydronaphthalene **11**, in excellent yield. At this point, we had two possible routes: the rearrangement of the cyclohexene moiety could be performed before or after the formation of the indole skeleton. Considering that the thallium(III)-mediated oxidation of 1,2-dihydronaphthalenes bearing electron-withdrawing groups in the 7-position, analogous to **11**, led to several by-products,[8c] we rationalized that the best alternative would be the construction of the indole skeleton before the rearrangement. Thus, the indole **12** was prepared from the 1,2-dihydronaphthalene **11** using the Bartoli reaction,[14] which was best performed using six equivalents of the Grignard reagent (Scheme 5).



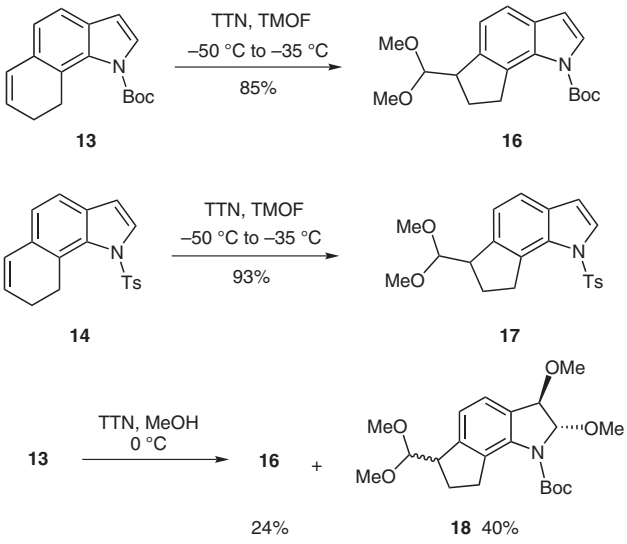
Scheme 5

Substrates bearing an N–H bond usually give complex mixtures when treated with thallium(III)[8c,15] and the same was observed for **12**.[16] Consequently, the indole was protected with the usual Boc and Ts groups. The N-protection with Boc_2O was performed as described by Ghren,[17] affording **13** in good yield. The reaction of **12** with TsCl using the procedure described by Ottoni and co-workers[18] led to two isomers, **14** and **15**, which were separated by column chromatography (Scheme 6).

In the thallium(III)-mediated oxidation of 1,2-dihydronaphthalenes lowering the temperature favors the ring contraction instead of addition.[8a,19] A similar tendency is observed when the solvent MeOH is replaced by trimethyl orthoformate (TMOF).[6a] Thus, we decided to perform the reaction of **12** with TTN using TMOF as solvent and at low temperature. The addition of TTN was made at –78 °C and the solution was allowed to warm up. Under these conditions, the cyclopenta[*g*]indole **16** was obtained as a single product in 85% yield. The reaction of **14** was performed in a similar manner affording the ring-contraction product **17**, also in excellent yield. These reaction conditions are crucial to obtain the desired product in good yields. For instance, when the oxidation of **12** was performed using TTN in MeOH at 0 °C which is the typical condition for the rearrangement of 1,2-dihydronaphthalenes, the ring-contraction product **16** was obtained in only 24% yield. In this case, the main product was the *trans*-indoline derivative **18** isolated in 40% yield, which was presumably formed by ring-contraction reaction and by an electrophilic addition to the double bond of the indole moiety. The compound **18** was isolated as a 1:1 mixture of diastereomers, which could not be separated (Scheme 7).



Scheme 6

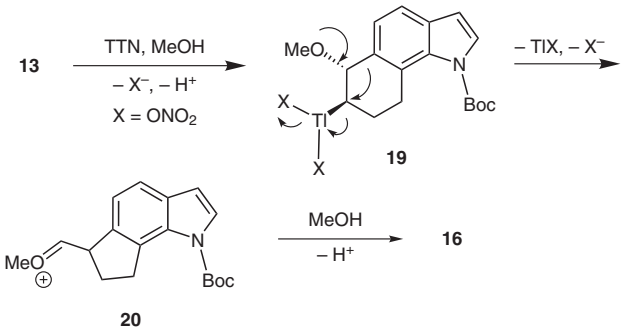


Scheme 7

The formation of **16** can be explained by the mechanism shown in Scheme 8.[8c,d,10] The *trans*-diaxial ring opening of a thallonium intermediate by a molecule of MeOH (formed by the reaction of TMOF with the hydration water of TTN) would generate the oxythallated adduct **19**. After the ring contraction, the oxonium ion intermediate **20** would be converted to the cyclopenta[*g*]indole **16** by addition of a second molecule of MeOH.

The relative configuration of the indoline moiety of the tricyclic **18** was assigned by comparison to the NMR data of the indolines **5** and **6**. Clearly, the ^1H and ^{13}C NMR data of the 1,2-dimethoxy moiety of **18** match with those of the indoline **5** (Figure 4).

In summary, a new and short approach for the synthesis of cyclopenta[*g*]indole derivatives was developed. The indoles obtained feature the carbocyclic ring system of nat-



Scheme 8

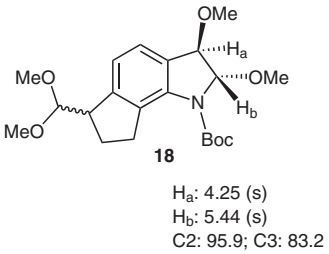


Figure 4 Selected NMR data for indoline **18**.

ural products and biologically active molecules, which makes this route attractive to the synthesis of those molecules. The key step in the sequence is a chemoselective ring-contraction reaction mediated by thallium trinitrate. Finally, new aspects of the reactivity and of the properties of indoles and indolines were discovered.

THF and MeCN were freshly distilled from sodium/benzophenone and from CaH_2, respectively. 3,4-Dihydro-5-nitronaphthalen-1-(2*H*)-one (10) was prepared as described by Zhang et al.[13] Other reagents were used as received. Column chromatography was performed using silica gel Acros 200–400 mesh. TLC analyses were performed with silica gel plates Merck, using UV-254 nm, *p*-anisaldehyde and phosphomolybdic acid solutions for visualization. ^1H and ^{13}C NMR spectra were recorded on Bruker and Varian spectrometers. IR spectra were measured on a PerkinElmer 1750-FT. The X-ray (monocrystal diffraction) crystal structure determination was performed on an Enraf-Nonius CAD4-Mach instrument. Gas chromatography analyses were performed in a HP-6890 series II. CG-MS analyses were performed using Finnigan-MAT INCOS 50B and GC Varian 2400. Elemental analyses were performed using PerkinElmer 2400 apparatus. High-resolution mass spectra were performed on a Bruker Daltonics Micro-TOF electrospray instrument.

tert-Butyl 1*H*-Indole-1-carboxylate (3)

To a stirred solution of 1*H*-indole (0.240 g, 2.05 mmol), MeCN (6 mL), and DMAP (cat.) in a two-necked flask was added Boc_2O (0.672 g, 3.08 mmol, 1.5 equiv). Liberation of CO_2 was then observed. After 1.5 h, the mixture was extracted with Et_2O (3 × 50 mL) and the organic layer was washed with H_2O (50 mL), aq sat. $NaHCO_3$ (50 mL), brine (50 mL), and dried ($MgSO_4$). The solvent was removed under reduced pressure and the residue was purified by flash chromatography (20% EtOAc in hexanes) to afford **3**[2] (0.436 g, 98%); colorless oil.

Reaction of _tert_-Butyl-1*H*-indole-1-carboxylate (3) with TTN in MeOH at 0 °C

To a stirred cooled (0 °C) solution of **3** (0.469 g, 2.16 mmol) in MeOH (14 mL) was added $TTN{\cdot}3H_2O$ (1.06 g, 2.37 mmol, 1.1 equiv). After 10 min, a white precipitated was formed and the mixture was filtered through a silica gel pad (10 cm, 70–230 mesh) using CH_2Cl_2 as eluent (150 mL). The resulting solution was washed with H_2O (50 mL), brine (50 mL), and dried ($MgSO_4$). The solvent was removed under reduced pressure and the residue was purified by flash chromatography (10% EtOAc in hexanes) affording **4** (0.157 g, 23%), **5** (0.243 g, 40%), and **6** (0.0528 g, 9%).

***trans*-1-*tert*-Butoxycarbonyl-2-methoxyindoline 3-Nitrate (4)**

White solid; mp 97–98 °C.

IR (KBr): 2984, 2938, 1708, 1644, 1394, 1274, 1150 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.60 (s, 9 H), 3.58 (s, 3 H), 5.48 (br s, 1 H), 5.90 (s, 1 H), 7.08 (dt, *J* = 7.8, 1.2 Hz, 1 H), 7.43 (d, *J* = 7.8 Hz, 2H), 7.86 (br s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.3, 57.0, 82.7, 84.1, 92.6, 116.3, 122.3, 123.5, 127.3, 132.1, 144.0, 151.7.

LRMS: *m*/*z* (%) = 247 (9, $[M^+ – HNO_3]$), 57 (100).

HRMS: [ESI (+)]: *m*/*z* $[M + Na]^+$ calcd for $C_{14}H_{18}N_2O_6$: 333.1063; found: 333.1065.

***tert*-Butyl *trans*-2,3-Dimethoxyindoline-1-carboxylate (5)**

Light yellow oil.

IR (KBr): 2978, 2934, 1710, 1482, 1392, 1168, 1062 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.58 (s, 9 H), 3.43 (s, 3 H), 3.58 (s, 3 H), 4.40 (s, 1 H), 5.42 (br s, 1 H), 7.03 (dt, *J* = 7.2, 0.9 Hz, 1 H), 7.26–7.38 (m, 2 H), 7.80 (br s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.3, 56.0, 56.1, 81.9, 83.2, 93.7, 116.3, 122.8, 126.3, 128.3, 130.3, 142.7, 152.5.

LRMS: *m*/*z* (%) = 279 (6, $[M^+]$), 57 (100).

HRMS [ESI (+)]: *m*/*z* $[M + K]^+$ calcd for $C_{15}H_{21}NO_4$: 318.1108; found: 318.1093.

***tert*-Butyl *cis*-2,3-Dimethoxyindoline-1-carboxylate (6)**

Light yellow oil.

IR (KBr): 2978, 2934, 1710, 1482, 1392, 1168, 1062 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.59 (s, 9 H), 3.50 (s, 3 H), 3.63 (s, 3 H), 4.87 (d, *J* = 5.1 Hz, 1 H), 5.60 (br s, 1 H), 7.00–7.05 (m, 1 H), 7.21–7.32 (m, 2 H), 7.60 (br s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.3, 56.6, 58.7, 80.5, 81.8, 89.1, 115.7, 123.3, 124.0, 128.9, 130.4, 140.0, 152.6.

LRMS: *m*/*z* (%) = 279 (6, $[M^+]$), 57 (100).

HRMS [ESI (+)]: *m*/*z* $[M + Na]^+$ calcd for $C_{15}H_{21}NO_4$: 302.1368; found: 302.1357.

1,2-Dihydro-8-nitronaphthalene (11)

To a stirred cooled (0 °C) solution of 3,4-dihydro-5-nitronaphthalen-1-(2*H*)-one (**10**; 0.426 g, 2.22 mmol) in MeOH (10 mL) was added $NaBH_4$ (0.0830 g, 2.20 mmol). The mixture was stirred for 1 h. After this period, H_2O (10 mL) was added followed by neutralization with 10% aq HCl. Extraction was performed using EtOAc (3 × 50 mL). The organic phase was washed with H_2O (50 mL), brine (50 mL) and dried ($MgSO_4$). The solvent was removed under reduced pressure, affording 1,2,3,4-tetrahydro-5-nitronaphthalen-1-ol (0.425 g, 99%), as a brown oil, which was used in the next step without purification. An analytical sample was obtained for characterization.

1,2,3,4-Tetrahydro-5-nitronaphthalen-1-ol
IR (film): 3183, 2947, 1525, 1352, 1056 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.80–2.04 (m, 4 H), 2.38 (br s, 1 H), 2.89–2.99 (m, 2 H), 4.78 (m, 1 H), 7.32 (t, *J* = 7.9 Hz, 1 H), 7.70–7.76 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.1, 26.0, 31.2, 67.7, 123.5, 126.4, 131.9, 133.4, 141.6, 149.5.

LRMS: *m*/*z* (%) = 193 (2, $[M^+]$), 158 (100).

Anal. Calcd for $C_{10}H_{11}NO_3$: C, 62.17; H, 5.74; N, 7.25. Found: C, 61.83; H, 5.64; N, 7.01.

To a solution of the above 1,2,3,4-tetrahydro-5-nitronaphthalen-1-ol (0.605 g, 3.12 mmol) in toluene (15 mL) was added some crystals of PTSA. The mixture was refluxed in a Dean–Stark apparatus for 1.5 h. After this period, the mixture was cooled to r.t. and 10% aq $NaHCO_3$ (10 mL) was added. The solution was washed with H_2O (30 mL), brine (30 mL) and dried ($MgSO_4$). The solvent was removed under reduced pressure and the residue was purified by flash chromatography (5% EtOAc in hexanes) to afford **11** (0.527 g, 96%); yellow oil.

11
IR (film): 3044, 2956, 1513, 1347 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 2.29–2.36 (m, 2 H), 3.03–3.06 (m, 2 H), 6.16 (dt, *J* = 9.6, 4.4 Hz, 1 H), 6.50 (dt, *J* = 9.6, 1.9 Hz, 1 H), 7.20–7.28 (m, 2 H), 7.64 (dd, *J* = 7.3, 2.1 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.2, 23.0, 122.5, 126.7, 126.7, 129.9, 130.1, 130.7, 136.3, 149.2.

LRMS: *m*/*z* (%) = 175 (63, $[M^+]$), 128 (100).

Anal. Calcd for $C_{10}H_9NO_2$: C, 68.56; H, 5.18; N, 8.00. Found: C, 68.54; H, 5.25; N, 7.76.

8,9-Dihydro-1*H*-benzo[*g*]indole (12)
To a stirred and cooled (–45 °C) solution of **11** (1.44 g, 8.20 mmol) in anhyd THF (15 mL) under N_2 was added a THF solution of vinylmagnesium bromide[20] (6.42 g, 49.0 mmol, 6 equiv) in one portion. After 45 min, sat. aq NH_4Cl (15 mL) was added and the mixture was allowed to warm to r.t. Extraction was performed with Et_2O (3 × 100 mL) and the organic layer was washed with sat. aq NH_4Cl (70 mL), H_2O (70 mL), brine (70 mL), and dried ($MgSO_4$). The solvent was removed under reduced pressure and the residue was purified by flash chromatography (gradient 10–20% EtOAc in hexanes) affording first the starting material (0.144 g, 10%) and then **12** (0.638 g, 51%) as a white solid, which turned yellow upon storage; mp 96–97 °C.

IR (film): 3520, 3026, 2924, 1431, 1318 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 2.34–2.42 (m, 2 H), 2.84 (t, *J* = 8.5, 2 H), 5.92 (dt, *J* = 9.6, 4.4 Hz, 1 H), 6.49 (dd, *J* = 2.0, 3.2 Hz, 1 H), 6.56 (dt, *J* = 9.6, 1.9 Hz, 1 H), 6.87 (d, *J* = 8.0 Hz, 1 H), 7.09 (dd, *J* = 1.5, 3.1 Hz, 1 H), 7.42 (dd, *J* = 8.0, 0.6 Hz, 1 H), 7.83 (br s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.9, 22.6, 103.1, 116.9, 118.1, 119.5, 124.6, 125.0, 127.5, 127.7, 128.5, 134.2.

LRMS: *m*/*z* (%) = 169 (97.5, $[M^+]$), 168 (100), 39 (62).

Anal. Calcd for $C_{12}H_{11}N$: C, 85.17; H, 6.55; N, 8.28. Found: C, 85.03; H, 6.52; N, 7.89.

***tert*-Butyl-8,9-dihydrobenzo[*g*]indole-1-carboxylate (13)**
To a stirred solution of **12** (0.196 g, 1.16 mmol), MeCN (5 mL), and DMAP (cat) in a two-necked flask was added Boc_2O (0.381 g, 1.74 mmol, 1.5 equiv). Liberation of CO_2 was then observed. After 1.5 h, the mixture was extracted with Et_2O (3 × 50 mL) and the organic layer was washed with H_2O (50 mL), sat. aq $NaHCO_3$ (20 mL), brine (20 mL), and dried ($MgSO_4$). The solvent was removed under reduced pressure and the residue was purified by flash chromatography (gradient 10–20% EtOAc in hexanes) to afford **13** (0.265 g, 85%); colorless oil.

IR (film): 3455, 3031, 2971, 1739, 1336, 1150 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.61 (s, 9 H), 2.23–2.31 (m, 2 H), 3.12 (m, 2 H), 6.01 (dt, *J* = 9.5, 4.4 Hz, 1 H), 6.47 (d, *J* = 3.7 Hz, 1 H), 6.57 (dt, *J* = 9.5, 1.7 Hz, 1 H), 6.97 (d, *J* = 7.8 Hz, 1 H), 7.32 (d, *J* = 7.8 Hz, 1 H), 7.48 (d, *J* = 3.7 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.0, 25.8, 28.1, 83.3, 107.6, 118.5, 122.7, 122.9, 127.0, 128.8, 128.9, 131.4, 131.5, 134.1, 149.9.

LRMS: *m*/*z* (%) = 169 (74, $[M^+ – Boc]$), 168 (100).

Anal. Calcd for $C_{17}H_{19}NO_2$: C, 75.81; H, 7.11; N, 5.20. Found: C, 76.04; H, 7.54; N, 4.92.

Reaction of 8,9-Dihydro-1*H*-benzo[*g*]indole (12) with Tosyl Chloride
To a stirred solution of **12** (0.0900 g, 0.530 mmol) in CH_2Cl_2 (5 mL) was added NaOH (0.032 g, 0.80 mmol, 1.5 equiv). After 25 min, TsCl (0.202 g, 1.06 mmol, 2.0 equiv) was added. The mixture was stirred for 24 h, diluted with CH_2Cl_2 (10 mL) and then washed with H_2O (3 × 10 mL) and dried ($MgSO_4$). The solvent was removed under reduced pressure and the residue was purified by flash chromatography (gradient 10–20% EtOAc in hexanes) affording **14** (0.0671 g, 39%) and **15** (0.0601 g, 35%), both as brown oils.

8,9-Dihydro-1-tosyl-1*H*-benzo[*g*]indole (14)
IR (film): 3034, 2928, 1355, 1173 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 2.11–2.19 (m, 2 H), 2.34 (br s, 3 H), 3.17 (t, *J* = 8.3 Hz, 2 H), 5.98 (dt, *J* = 9.5, 4.4 Hz, 1 H), 6.48 (dt, *J* = 9.5, 1.7 Hz, 1 H), 6.61 (d, *J* = 3.8 Hz, 1 H), 6.93 (d, *J* = 7.8 Hz, 1 H), 7.17 (d, *J* = 8.5 Hz, 2 H), 7.28 (d, *J* = 7.8 Hz, 1 H), 7.49 (m, 2 H), 7.70 (d, *J* = 3.8 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.6, 22.8, 24.6, 109.6, 119.6, 122.8, 123.5, 126.5, 127.5, 128.6, 129.7, 130.6, 131.9, 132.5, 134.6, 136.3, 144.5.

LRMS: *m*/*z* (%) = 323 (17, $[M^+]$), 168 (100), 167 (60).

HRMS [ESI (+)]: *m*/*z* $[M + H]^+$ calcd for $C_{19}H_{19}NO_2S$: 323.0980; found: 323.0982.

8,9-Dihydro-3-tosyl-1*H*-benzo[*g*]indole (15)
IR (film): 3169, 3.039, 2935, 1595, 1372, 1174 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 2.14–2.21 (m, 2 H), 2.35 (br s, 3 H), 3.19 (t, *J* = 8.3 Hz, 2 H), 6.03 (dt, *J* = 9.5, 4.4 Hz, 1 H), 6.49 (dt, *J* = 9.5, 1.7 Hz, 1 H), 7.01 (d, *J* = 7.9 Hz, 1 H), 6.93 (d, *J* = 7.8 Hz, 1 H), 7.20 (d, *J* = 8.5 Hz, 2 H), 7.30 (d, *J* = 7.9 Hz, 1 H), 7.50 (m, 2 H), 7.67 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.6, 22.7, 24.5, 114.7, 116.8, 123.4, 124.0, 126.4, 126.7, 128.4, 128.4, 129.8, 130.0, 133.1, 134.1, 135.5, 144.9.

***tert*-Butyl-7,8-dihydro-6-(dimethoxymethyl)cyclopenta[*g*]indole-1(6*H*)-carboxylate (16)**
To a stirred and cooled (–78 °C) solution of **13** (0.0726 g, 0.270 mmol) in TMOF (3 mL) was added TTN·$3H_2O$ (0.133 g, 0.290 mmol, 1.1 equiv). The solution was allowed to warm up (1.5 h) and TLC analysis was made during every change of 10 °C showing that all starting material was consumed between –50 °C and –35 °C. A white precipitate was formed and the mixture was filtered through a silica gel pad (10 cm, 70–230 Mesh) using CH_2Cl_2 as eluent (100 mL). The resultant solution was washed with H_2O (20 mL), brine (20 mL), and dried ($MgSO_4$). The solvent was removed under reduced pressure and the residue was purified by flash chromatogra-

phy (10% EtOAc in hexanes) to afford **16** (0.0760 g, 85%); colorless oil.

IR (film): 2977, 1746, 1337, 1160, 1099, 1059 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.63 (s, 9 H), 1.98–2.26 (m, 2 H), 3.31–3.39 (m, 1 H), 3.39 (s, 3 H), 3.42 (s, 3 H), 3.48–3.58 (m, 2 H), 4.35 (d, *J* = 7.4 Hz, 1 H), 6.51 (d, *J* = 3.8 Hz, 1 H), 7.34 (s, 2 H), 7.49 (d, *J* = 3.8 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 27.4, 28.2, 33.3, 47.9, 53.0, 54.6, 83.2, 107.4, 107.6, 118.9, 120.9, 126.7, 130.4, 130.7, 132.4, 140.7, 149.3.

LRMS: *m*/*z* (%) = 331 (2, $[M^+]$), 200 (9), 75 (100).

Anal. Calcd for $C_{19}H_{25}NO_4$: C, 68.86; H, 7.60; N, 4.23. Found: C, 68.47; H, 7.31; N, 4.29.

1,6,7,8-Tetrahydro-6-(dimethoxymethyl)-1-tosylcyclopenta[*g*]indole (17)

The reaction was performed as for **13**, but using **14** (0.125 g, 0.389 mmol), TMOF (3 mL), and TTN·$3H_2O$ (0.182 g, 0.410 mmol, 1.1 equiv). The resultant solution was washed with H_2O (20 mL), brine (20 mL), and dried ($MgSO_4$). The solvent was removed under reduced pressure and the residue was purified by flash chromatography (30% EtOAc in hexanes) to afford **17** (0.140 g, 93%); colorless oil.

IR (film): 3150, 2936, 1360, 1170, 1126, 1061 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.92–2.21 (m, 2 H), 2.34 (s, 3 H), 3.04–3.14 (m, 1 H), 3.25–3.35 (m, 4 H), 3.38 (s, 3 H), 3.41–3.48 (m, 1 H), 4.26 (d, *J* = 7.4 Hz, 1 H), 6.66 (d, *J* = 3.7 Hz, 1 H), 7.20 (d, *J* = 8.5 Hz, 2 H), 7.35 (d, *J* = 3.7 Hz, 2 H), 7.56 (d, *J* = 8.3 Hz, 2 H), 7.66 (d, *J* = 3.7 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.5, 27.4, 31.9, 47.9, 53.2, 54.5, 107.5, 108.8, 119.5, 121.5, 126.5, 128.3, 129.7, 131.5, 136.9, 141.2, 144.5.

LRMS: *m*/*z* (%)= 353 (74, $[M^+ - MeOH]$), 75 (100).

Anal. Calcd for $C_{21}H_{23}NO_4S$: C, 65.43; H, 6.01; N, 3.63. Found: C, 65.76; H, 5.69; N, 3.47.

Reaction of *tert*-Butyl-8,9-dihydrobenzo[*g*]indole-1-carboxylate (13) in MeOH at 0 °C

The reaction was performed as for **3**, but using **13** (0.0910 g, 0.340 mmol) in MeOH (2 mL), TTN·$3H_2O$ (0.165 g, 0.370 mmol, 1.1 equiv), and a reaction time of 5 min. The residue was purified by flash chromatography (10% EtOAc in hexanes) affording **16** (0.0268 g, 24%; for spectral and analytical data, see above) and **18** (0.0540 g, 40%), both as colorless oils.

***tert*-Butyl-2,3-dimethoxy-6-(dimethoxymethyl)-1,2,3,6,7,8-hexahydrocyclopenta[*g*]indole-1(6*H*)-carboxylate (18)**

IR (film): 2934, 2829, 1721, 1455, 1374, 1198, 1062 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.55 (s, 18 H), 1.71–1.82 (m, 1 H), 2.06–2.28 (m, 3 H), 2.63–2.82 (m, 2 H), 3.15–3.27 (m, 1 H), 3.32–3.54 (m, 3 H), 3.366 (s, 6 H), 3.374 (s, 3 H), 3.39 (s, 3 H), 3.40 (s, 3 H), 3.45 (s, 3 H), 3.47 (s, 3 H), 3.48 (s, 3 H), 4.25 (s, 1 H), 4.27 (s, 1 H), 4.30 (d, *J* = 7.7 Hz, 1 H), 4.34 (d, *J* = 7.7 Hz, 1 H), 5.438 (s, 1 H), 5.443 (s, 1 H), 7.14–7.21 (m, 3 H), 7.26 (dd, *J* = 7.6, 0.9 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 27.3, 28.3, 28.4, 31.5, 31.7, 47.2, 48.2, 52.7, 52.9, 53.5, 55.0, 55.6, 55.77, 55.81, 55.83, 81.6, 81.7, 83.1, 83.2, 95.8, 95.9, 106.7, 107.0, 120.7, 122.1, 124.37, 124.42, 128.5, 128.6, 134.0, 134.1, 138.99, 139.02, 146.9, 147.0, 152.9, 153,0.

LRMS: *m*/*z* (%) = 393 (2, $[M^+]$), 75 (100).

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References

(1) For some examples concerning the isolation of C2–C3 fused cycloalkylindoles, see: (a) Ondeyka, J. G.; Helms, G. L.; Hensens, O. D.; Goetz, M. A.; Zink, D. L.; Tsipouras, A.; Shoop, W. L.; Slayton, L.; Dombrowski, A. W.; Polishook, J. D.; Ostlind, D. A.; Tsou, N. N.; Ball, R. G.; Singh, S. B. *J. Am. Chem. Soc.* **1997**, *119*, 8809. (b) Kato, L.; Braga, R. M.; Koch, I.; Kinoshita, L. S. *Phytochemistry* **2002**, *60*, 315. (c) Singh, S. B.; Ondeyka, J. G.; Jayasuriya, H.; Zink, D. L.; Ha, S. N.; Dahl-Roshak, A.; Greene, J.; Kim, J. A.; Smith, M. M.; Shoop, W.; Tkacz, J. S. *J. Nat. Prod.* **2004**, *67*, 1496. (d) Carrol, A. R.; Hyde, E.; Smith, J.; Quinn, R. J.; Guymer, G.; Forster, P. I. *J. Org. Chem.* **2005**, *70*, 1096.

(2) For some examples concerning the synthesis of C2–C3 fused cycloalkylindoles, see: (a) Giannini, G.; Marzi, M.; Moretti, G. P.; Penco, S.; Tinti, M. O.; Pesci, S.; Lazzaro, F.; De Angelis, F. *Eur. J. Org. Chem.* **2004**, 2411. (b) Maertens, F.; Van den Bogaert, A.; Compernolle, F.; Hoornaert, G. J. *Eur. J. Org. Chem.* **2004**, 4648. (c) Smith, A. B. III.; Kurti, L.; Davulcu, A. H. *Org. Lett.* **2006**, *8*, 2167. (d) Sturino, C. F.; Lachance, N.; Boyd, M.; Berthelette, C.; Labelle, M.; Li, L.; Roy, B.; Scheigetz, J.; Tsou, N.; Brideau, C.; Cauchon, E.; Carriere, M.-C.; Denis, D.; Greig, G.; Kargman, S.; Lamontagne, S.; Mathieu, M.-C.; Sawyer, N.; Slipetz, D.; O'Neill, G.; Wang, Z.; Zamboni, R.; Metters, K. M.; Young, R. N. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 3043.

(3) (a) Capon, R. J.; MacLeod, J. K.; Scammels, P. J. *Tetrahedron* **1986**, *42*, 6545. (b) Herb, R.; Carrol, A. R.; Yoshida, W. Y.; Scheuer, P. J.; Paul, V. J. *Tetrahedron* **1990**, *46*, 3089.

(4) Sawyer, J. S.; Beight, D. W.; Smith, E. C. R.; Snyder, D. W.; Chastain, M. K.; Tielkin, R. L.; Hartley, L. W.; Carlson, D. G. *J. Med. Chem.* **2005**, *48*, 893.

(5) (a) MacLeod, J. K.; Monahan, L. C. *Tetrahedron Lett.* **1988**, *29*, 391. (b) Muratake, H.; Natsume, M. *Tetrahedron Lett.* **1989**, *30*, 5771. (c) Muratake, H.; Watanabe, M.; Goto, K.; Natsume, M. *Tetrahedron* **1990**, *46*, 4179. (d) MacLeod, J. K.; Monahan, L. C. *Aust. J. Chem.* **1990**, *43*, 329. (e) Boger, D. L.; Zhang, M. *J. Am. Chem. Soc.* **1991**, *113*, 4230. (f) Muratake, H.; Mikawa, A.; Natsume, M. *Tetrahedron Lett.* **1992**, *33*, 4595. (g) Muratake, H.; Seino, T.; Natsume, M. *Tetrahedron Lett.* **1993**, *34*, 4815. (h) Wiedenau, P.; Monse, B.; Blechert, S. *Tetrahedron* **1995**, *51*, 1167. (i) MacLeod, J. K.; Ward, A.; Willis, A. C. *Aust. J. Chem.* **1998**, *51*, 177. (j) Jackson, S. K.; Banfield, S. C.; Kerr, M. A. *Org. Lett.* **2005**, *7*, 1215. (k) Huntley, R. J.; Funk, R. L. *Org. Lett.* **2006**, *8*, 3403. (l) Jackson, S. K.; Kerr, M. A. *J. Org. Chem.* **2007**, *72*, 1405.

(6) For some reviews concerning thallium(III) in organic synthesis, see: (a) McKillop, A.; Taylor, E. C. In *Comprehensive Organometallic Chemistry*, Vol. 7; Wilkinson, G., Ed.; Pergamon Press: New York, **1982**, 465. (b) Ferraz, H. M. C.; Silva, L. F. Jr.; Vieira, T. O. *Synthesis* **1999**, 2001. (c) Uemura, S. In *Synthetic Reagents*, Vol. 5; Pizey, J. S., Ed.; Ellis Horwood: Chichester, **1983**, 164.

(7) For some examples of rearrangement of olefins with TTN, see: (a) McKillop, A.; Hunt, J. D.; Taylor, E. C.; Kienzle, F. *Tetrahedron Lett.* **1970**, *11*, 5275. (b) McKillop, A.; Hunt, J. D.; Kienzle, F.; Bigham, E.; Taylor, E. C. *J. Am. Chem. Soc.* **1973**, *95*, 3635. (c) Taylor, E. C.; Chiang, C.-S.; McKillop, A.; White, J. F. *J. Am. Chem. Soc.* **1976**, *98*,

6750. (d) Rigby, J. H.; Pigge, F. C. *J. Org. Chem.* **1995**, *60*, 7392. (e) Rigby, J. H.; Pigge, F. C. *Synlett* **1996**, 631. (f) Butkus, E.; Zilinskas, A.; Stoncius, S.; Rozembergas, R.; Urbanová, M.; Setnicka, V.; Boui, P.; Volka, K. *Tetrahedron: Asymmetry* **2002**, *13*, 633. (g) Singh, O. V.; Muthukrishnan, M.; Sundaravedivelu, M. *Synth. Commun.* **2006**, *36*, 946.

(8) (a) Ferraz, H. M. C.; Silva, L. F. Jr.; Vieira, T. O. *Tetrahedron* **2001**, *57*, 1709. (b) Ferraz, H. M. C.; Aguilar, A. M.; Silva, L. F. Jr. *Tetrahedron* **2003**, *59*, 5817. (c) Silva, L. F. Jr.; Sousa, R. M. F.; Ferraz, H. M. C.; Aguilar, A. M. *J. Braz. Chem. Soc.* **2005**, *16*, 1160. (d) Silva, L. F. Jr.; Quintiliano, S. A. P.; Craveiro, M. V.; Vieira, F. Y. M.; Ferraz, H. M. C. *Synthesis* **2007**, 355. (e) For a related reaction using iodine(III), see: Silva, L. F. Jr.; Siqueira, F. A.; Pedrozo, E. C.; Vieira, F. Y. M.; Doriguetto, A. C. *Org. Lett.* **2007**, *9*, 1433.

(9) (a) Somei, M.; Hasegawa, T.; Kaneko, C. *Heterocycles* **1983**, *20*, 1983. (b) Somei, M.; Saida, Y.; Funamoto, T.; Ohta, T. *Chem. Pharm. Bull.* **1987**, *35*, 3146. (c) Banerji, A.; Nandi, G. *Heterocycles* **1987**, *26*, 1221. (d) Tholander, J.; Bergman, J. *Tetrahedron* **1999**, *55*, 12595.

(10) Desarbre, E.; Savelon, L.; Cornec, O.; Mérour, J. Y. *Tetrahedron* **1996**, *52*, 2983.

(11) The X-ray crystal structure data have been deposited at the Cambridge Crystallographic Data Centre and allocated the deposition number CCDC 656449. Copies of the data can be obtained free of charge on application to The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Fax: + 44 1223 336 033; e-mail: deposit@ccdc.cam.ac.uk).

(12) (a) Anderson, C. B.; Winstein, S. *J. Org. Chem.* **1963**, *28*, 605. (b) Abley, P.; Byrd, J. E.; Halpern, J. *J. Am. Chem. Soc.* **1973**, *95*, 2591.

(13) Zhang, M.; Schuster, G. B. *J. Am. Chem. Soc.* **1994**, *116*, 4852.

(14) Bartoli, G.; Palmieri, G.; Bosco, M.; Dalpozzo, R. *Tetrahedron Lett.* **1989**, *30*, 2129.

(15) Michael, J. P.; Nkwelo, M. M. *Tetrahedron* **1990**, *46*, 2549.

(16) A complex mixture was obtained when **9** was treated with 1.1 equiv of TTN in MeOH at 0 °C.

(17) Ghren, L.; Ragnarsson, U. *Angew. Chem. Int. Ed.* **1984**, *23*, 296.

(18) Ottoni, O.; Cruz, R.; Alves, R. *Tetrahedron* **1998**, *54*, 13915.

(19) (a) Lee, J. B.; Price, M. J. *Tetrahedron* **1964**, *20*, 1017. (b) Sekizaki, H.; Ito, M.; Inoue, S. *Bull. Chem. Soc. Jpn.* **1978**, *51*, 2439.

(20) Seyferth, D. *Org. Synth. Coll. Vol. 4*; Wiley: New York, **1963**, 258.