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 A2, 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

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.9 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

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 H2 in 4 and 5 are broad singlets. On the other hand, H2 appears as a doublet with a coupling constant of J = 5.1 Hz in the indoline 6. Additionally, H3 and H4 of the cis isomer 6 are deshielded when compared to the same hydrogens of the corresponding
This observation agrees with the data on some analogous indolines previously reported in the literature (Figure 3). 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 and can be explained by the mechanism shown in Scheme 4. 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-indole 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.

**Scheme 4**

**Figure 3** Selected NMR data for indolines

Desarbre et al., ref. 10
The tricyclic indole 12 was prepared from the tetralone 10, which was obtained as described by Zhang et al.\textsuperscript{13} Reduction of the ketone moiety of 10 was carried out using NaBH\textsubscript{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,\textsuperscript{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,\textsuperscript{14} which was best performed using six equivalents of the Grignard reagent (Scheme 5).

Substrates bearing an N–H bond usually give complex mixtures when treated with thallium(III)\textsuperscript{8c,15} and the same was observed for 12.\textsuperscript{16} Consequently, the indole was protected with the usual Boc and Ts groups. The N-protection with Boc\textsubscript{2}O was performed as described by Ghren,\textsuperscript{17} affording 13 in good yield. The reaction of 12 with TsCl using the procedure described by Ottoni and co-workers\textsuperscript{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.\textsuperscript{8a,19} A similar tendency is observed when the solvent MeOH is replaced by trimethyl orthofomrate (TMOF).\textsuperscript{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).

The formation of 16 can be explained by the mechanism shown in Scheme 8.\textsuperscript{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 indole moiety of the tricyclic 18 was assigned by comparison to the NMR data of the indolines 5 and 6. Clearly, the 1H and 13C 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-
aldehyde and phosphomolybdic acid solutions for visualization. After 1.5 h, the mixture was extracted with Et2O (3 × 50 mL), and DMAP (cat.) in a two-necked flask was added Boc 2O (0.436 g, 98%).

To a stirred cooled (0 °C) solution of 1 (0.240 g, 2.05 mmol), THF and MeCN were freshly distilled from sodium/benzophenone and from CaH2, respectively. 3,4-Dihydro-5-nitronaphthalen-1-one (11) was prepared as described by Zhang et al. Other reagents were used as received. Column chromatography was performed using silica gel Acros 200–400 mesh. TLC analyses were performed on an Enraf-Nonius CAD4-Mach instrument. Gas chromatography analyses were performed in a HP-6890 series II.

The X-ray (monocrystal diffraction) crystal structure determination was performed PerkinElmer 2400 apparatus. High-resolution mass spectra were recorded on Bruker and Varian spectrometers. IR spectra were measured on a PerkinElmer 1750-FT.

The key step in the sequence is a chemoselective ring-contraction reaction mediated by thallium trinitrate. Makes this route attractive to the synthesis of those molecular products and biologically active molecules, which are used as received. Column chromatography was performed on silica gel plates Merck, using UV-254 nm, p-anisaldehyde and phosphomolybdic acid solutions for visualization.

Finally, new aspects of the reactivity and of the properties of indoles and indolines were discovered.

**Scheme 8**

![Scheme 8](image)

**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 CaH2, respectively. 3,4-Dihydro-5-nitronaphthalen-1,2H-one (10) was prepared as described by Zhang et al. 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 NMR (300 MHz, CDCl3); δ = 1.59 (s, 3 H), 3.58 (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).**

**13C NMR (75 MHz, CDCl3); δ = 28.3, 56.0, 56.1, 81.9, 83.2, 93.7, 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]+ calc for C13H12NO3: 313.1063; found: 313.1057.

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

Light yellow oil.

**1H NMR (300 MHz, CDCl3); δ = 1.50 (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).**

**13C NMR (75 MHz, CDCl3); 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 + Na]+ calc for C13H12NO3: 318.1108; found: 318.1093.

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

Light yellow oil.

**1H NMR (300 MHz, CDCl3); 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).**

**13C NMR (75 MHz, CDCl3); δ = 28.3, 56.0, 56.1, 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]+ calc for C13H12NO3: 320.1368; found: 320.1357.

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

To a stirred cooled (0 °C) solution of 3,4-dihydro-5-nitronaphthalen-1,2H-one (10; 0.426 g, 2.22 mmol) in MeOH (10 mL) was added NaH2PO4 (0.0830 g, 2.20 mmol). The mixture was stirred for 1 h. After this period, H2O (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 H2O (50 mL), brine (50 mL) and dried (MgSO4). The solvent was removed under reduced pressure, affording 1,2,3,4-tetrahydro-5-nitronaphthalene-1-ol (0.452 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, CDCl₃): 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).

13C NMR (75 MHz, CDCl₃): δ = 18.1. 26.0, 31.2, 67.7, 123.5, 126.4, 131.9, 133.4, 146.1, 149.5.
LRMS: m/z (%) = 193 (2, [M⁺]), 158 (100).
Anal. Calcd for C₁₉H₁₉NO₂: C, 75.81; H, 7.11; N, 5.20. Found: C, 76.04; H, 7.54; N, 4.92.

Reaction of 8,9-Dihydro-1H-benzo[g]indole (12) with Tosyl Chloride
To a stirred solution of 12 (0.0900 g, 0.530 mmol) in CH₂Cl₂ (5 mL) was added NaOH (0.032 g, 0.80 mmol, 1.5 equiv). After 25 min, the mixture was stirred for 24 h, diluted with CH₂Cl₂ (10 mL) and then washed with H₂O (3 × 10 mL) and dried (MgSO₄). 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-1H-benzo[g]indole (14)
IR (film): 3034, 2928, 1355, 1173 cm⁻¹.

1H NMR (300 MHz, CDCl₃): 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).

13C NMR (75 MHz, CDCl₃): 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, 145.4.
LRMS: m/z (%) = 323 (17, [M⁺]), 168 (100), 167 (60).
HRMS: [ESI (+)] m/z [M + H⁺] calcd for C₁₈H₁₈NO₃S: 323.0980; found: 323.0982.

8,9-Dihydro-3-tosyl-1H-benzo[g]indole (15)
IR (film): 3169, 3039, 2935, 1595, 1372, 1174 cm⁻¹.

1H NMR (300 MHz, CDCl₃): 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).

13C NMR (75 MHz, CDCl₃): δ = 21.6, 22.7, 24.5, 114.7, 116.8, 123.4, 124.0, 126.4, 126.7, 128.4, 129.8, 130.0, 131.3, 134.1, 135.5, 144.9.
tert-Butyl-7,8-dihydrobenz[a]indole-1(6H)-carboxylate (16)
To a stirred solution of 13 (0.0726 g, 0.270 mmol) in TMOF (3 mL) was added TTN·3H₂O (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 CH₂Cl₂ as eluent (100 mL). The resultant solution was washed with H₂O (20 mL), brine (20 mL), and dried (MgSO₄). The solvent was removed under reduced pressure and the residue was purified by flash chromatography (gradient 10–20% EtOAc in hexanes) to afford 16 (0.265 g, 85%); colorless oil.
IR (film): 3455, 3031, 2971, 1379, 1336, 1150 cm⁻¹.

1H NMR (300 MHz, CDCl₃): 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).

13C NMR (75 MHz, CDCl₃): δ = 23.0, 25.8, 28.1, 83.3, 107.6, 118.5, 122.7, 122.9, 127.0, 128.8, 131.4, 131.5, 143.1, 149.9.
LRMS: m/z (%) = 169 (74, [M⁺ – Boc]), 168 (100).
Anal. Calcd for C₁₇H₁₈NO₂: C, 76.04; H, 7.54; N, 4.92.

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ph (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, CDCl₃): 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), 3.42–3.84 (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).

¹³C NMR (75 MHz, CDCl₃): δ = 27.3, 28.3, 28.4, 31.5, 31.7, 42.2, 52.7, 52.9, 53.5, 55.0, 55.6, 55.77, 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).

References


(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).


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


