Total Synthesis of Bruceolline I

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Abstract.

The first total synthesis of a natural product, Bruceolline I, isolated in very small amount from the ethanol extracts of *B. mollis* stems, was achieved in 29% over nine steps and with high enantiomeric purity (>98%). The key step of the process is the tandem gold-catalyzed rearrangement/Nazarov reaction of a propargylic acetate derivative. This synthesis provides sufficient amount of synthetic bruceolline I for further bioassays.

Introduction.

Two new indole alkaloids, possessing a cyclopenta[b]indole skeleton and named bruceollines D and E (Figure 1), were isolated in 1994 from the root wood of *Brucea mollis* Wall. var. *tonkinensis* Lecomte,[1] a plant which grows in southern China and North-East India (*Brucea mollis* Wall. ex Kurz.) and traditionally used for treating malaria and other parasitic diseases.[1,2]

More recently, some more bruceollines of the same type were isolated from the ethanol extracts of *B. mollis* stems, in particular bruceolline H, I and J (Figure 1).[3]

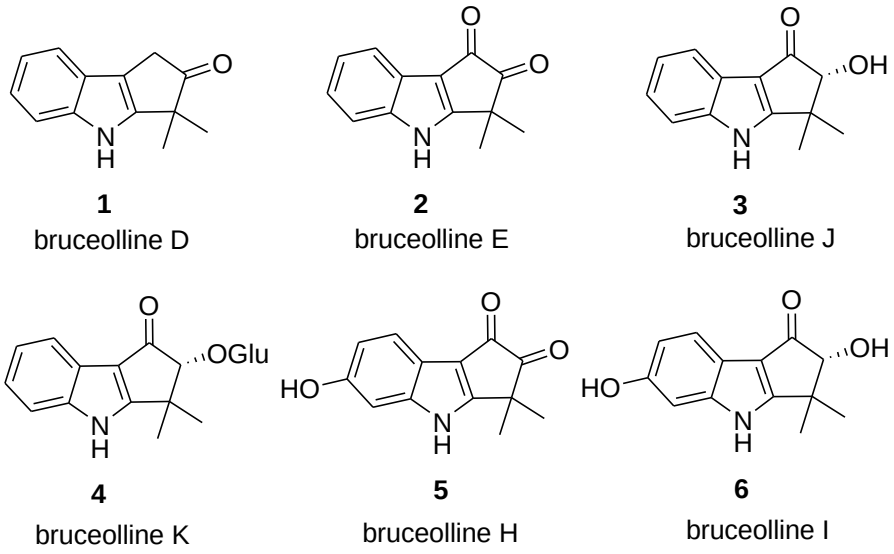


Figure 1. Cyclopenta[b]indole-based structures of bruceollines.

Despite their potential in medicinal chemistry, only a few syntheses of these natural alkaloids, as well as an extremely limited number of biological studies on the isolated compounds, have been reported so far.[3,4] The syntheses of bruceolline E (**2**) and J (**3**) have been first reported by Gribble and co-workers,[5,6] who also published the crystallographic structure of bruceolline E.[7] A concise asymmetric synthesis of bruceolline J (**3**) was reported in 2015 by Dethe and Kumar[8] and, more recently, the first synthesis of bruceolline H (**5**) was described by us.[9]

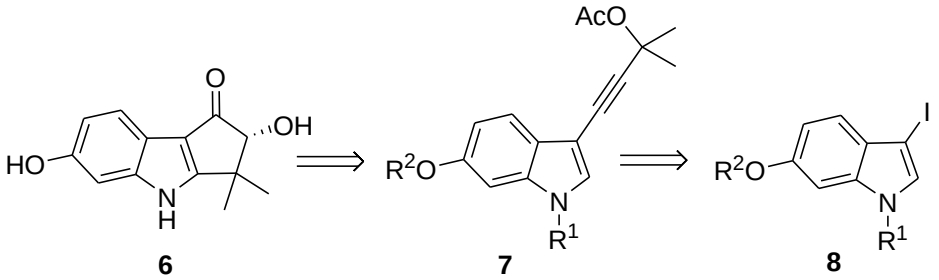
Bruceollines H (**5**) and I (**6**) differ from the other members of the family by the presence of an OH group on the indole ring. Their cytotoxicity has been tested in vitro against five human tumor cell lines but both compounds exhibited low activity.[3] On the other hand, these two alkaloids were isolated in very low quantities from the natural resource. For example, 5 and 32 mg of bruceolline I and H, respectively, were obtained from 6.5 kg of *B. mollis* stems in an

isolation process which included three chromatographic separations.[3] Clearly, this limited availability, together with the fact that the plant is endangered in NE India due to destruction of its habitat,[2] could hamper further and more extensive evaluations of compounds **5** and **6** (and their synthetic derivatives) towards a greater variety of biological targets. For this reason we decided to embark in the first synthesis of bruceolline I by exploiting the tandem gold-catalyzed rearrangement/Nazarov reactions of propargylic acetate derivatives we have recently described,[9,10] in order to establish a reliable method for obtaining sufficient amount of material for biological tests as well as for the confirmation of its structure.

Results and discussion.

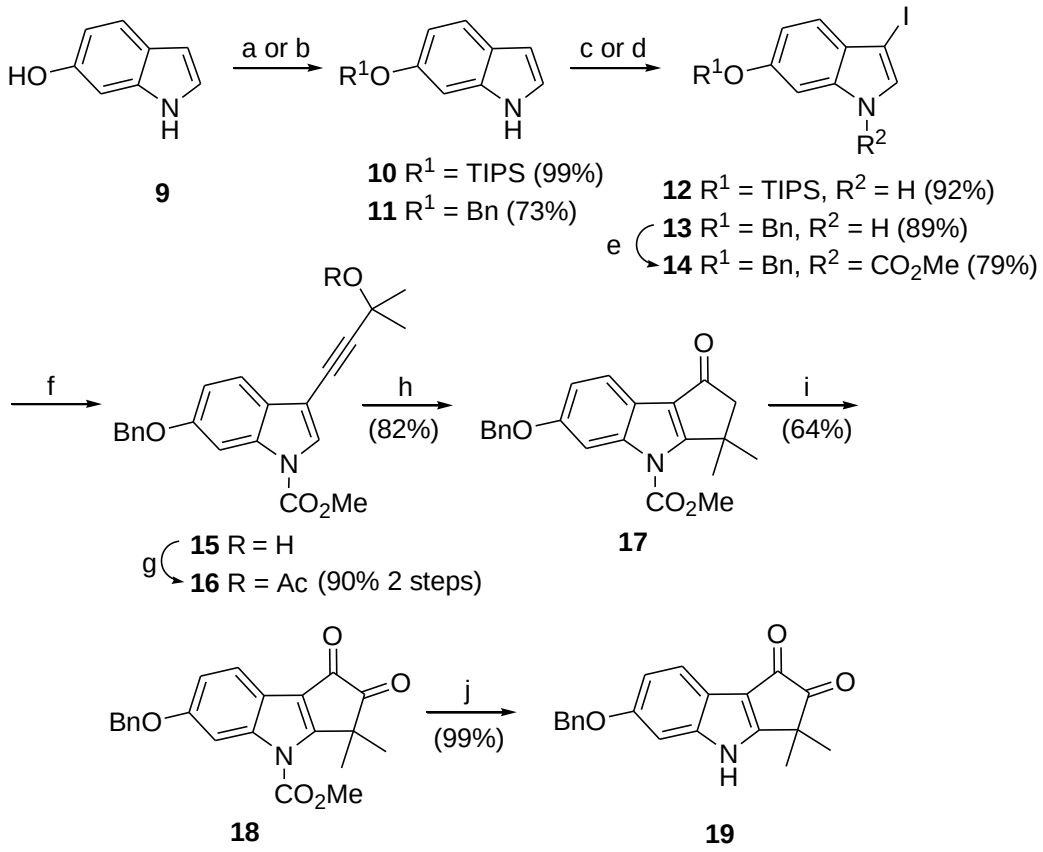
The synthesis would entail (Scheme 1) a Sonogashira coupling of suitably protected iodo-indole **8** to obtain propargylic acetate derivative **7**, which in the presence of a gold(I) catalyst rearranges and generates a pentadienyl cation with the proper electronic arrangement for the next Nazarov cyclization. Further oxidation of the so obtained cyclopenta[b]indol-1-one gives rise to *N*- and *O*-protected bruceolline H and, subsequent enantioselective reduction, bruceolline I (**6**).

Scheme 1. Retrosynthetic analysis.



The synthesis of bruceolline H we have described[9] included an unoptimized step and, moreover, BBr_3 was necessary for the removal of the methyl group from the oxygen atom at 6-position under harsh conditions. As we wanted especially to avoid the use of this nasty reagent, we planned our synthesis to include either a silyl ether or a benzyl O-protection (Scheme 2).

Scheme 2. Synthesis of precursor **19**.

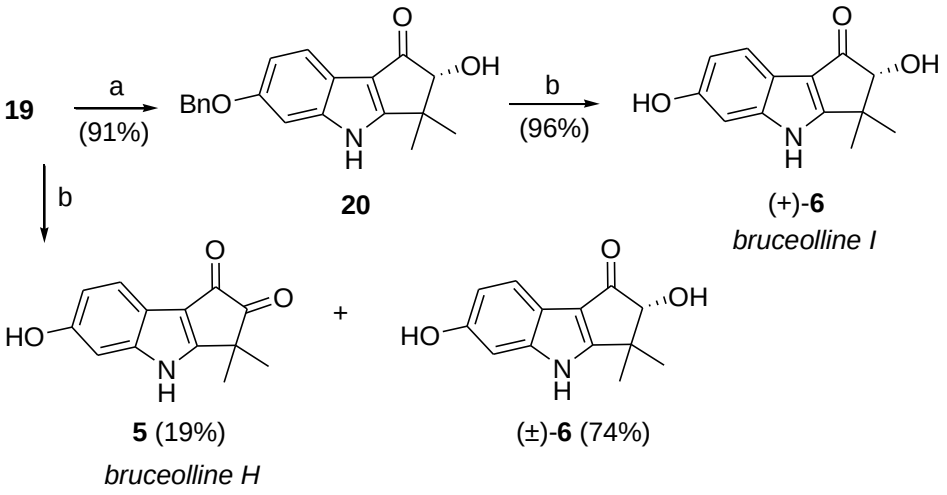


(a) TIPSCl, imidazole, CH_2Cl_2, 25 °C; (b) BnBr, Cs_2CO_3, THF, 0-25 °C, 15 h; (c) KOH, I_2, DMF, r.t., 1 h; (d) NIS, THF, 25 °C; (e) 1) LiHMDS -78°C, 15 min, 2) $ClCO_2Me$, -78 °C to r.t., 2 h; (f) 2-methyl-3-butyn-2-ol, 5 mol % $(Ph_3P)_2PdCl_2$, 3 mol % CuI, Et_3N-DMF 5:1, 40 °C, 1 h; (g) Ac_2O, Et_3N, cat. DMAP, DCM, 25 °C, 15 h; (h) $(4\text{-}CF_3C_6H_4)_3PAuSbF_6$ (3 mol %), DCM, 25 °C, 50 min; (i) SeO_2, 1,4-dioxane, 100 °C, 17 h; (j) *t*-Butylamine, MeOH, reflux, 1 h.

However, whereas the formation of the TIPS-protected iodo-indole **12** by treatment of **10**[11] with NIS (*N*-iodosuccinimide) in THF at room temperature[12] was uneventful (92%), the next N-protection step with methyl chloroformate in THF in the presence of Et_3N caused an almost complete degradation of this intermediate which therefore proved very unstable. Instead, commercially available benzyl-protected indole **11** (which we prepared from indole **9** as reported)[13] was easily converted into N-protected iodo-indole **14** (70% overall yield) ready for the Sonogashira coupling with 2-methyl-3-butyn-2-ol. The conditions for the N-protection were changed here compared to those already described, and treatment of **13** with a strong base (LiHMDS -78°C) before addition of methyl chloroformate allowed us to obtain **14** in very good yield. The coupling of the latter with the alkyne was carried out at 40 °C in the presence of 5 mol % $(Ph_3P)_2PdCl_2$ and 3 mol % CuI, in a mixed Et_3N-DMF (5:1) solvent, providing alcohol **15** and, after acetylation, propargylic acetate **16** in 90% yield after chromatography over two steps. The next gold-catalyzed step was carried out in the presence of $(4\text{-}CF_3C_6H_4)_3PAuSbF_6$ (3 mol %) as the catalyst in CH_2Cl_2 and furnished cyclopenta[b]indol-1-one **17** in 82% yield after chromatography. The conditions for the oxidation of **17** by SeO_2 we originally used in the synthesis of bruceolline H allowed us to obtain fully protected bruceolline H **18** in 64% yield. N-deprotection of **18** with *t*-butylamine in MeOH eventually provided intermediate **19** (99%) which was in part subjected to hydrogenation over 10% Pd/C in MeOH-THF 1:1 (Scheme 3) to provide the racemic bruceolline I [(±)-**6**] (74%) we needed for chiral HPLC analysis. We stopped the hydrogenation before completion in order to recover also a sufficient amount of bruceolline H (**5**) for X-ray structural determination, as this was to date unreported (see Supporting Information). The synthesis of enantiopure bruceolline I was finally attained by reduction of the carbonyl group of **19** by (+)-DIP-Cl (Chlorodiisopinocampheylborane) as reported for

bruceolline J,[6] envisioning that the presence of a OBn group on the six-membered ring would not change the stereochemical outcome of the reaction (i.e. it should provide the *S* enantiomer). The reduction with (+)-DIP-Cl was carried out in anhydrous THF at -45 °C and provided alcohol **20** in 91% yield.

Scheme 3. Synthesis of Bruceollines H and I.



(a) (+)-DIP-Cl, THF, - 45 °C, 10 min; (b) H_2, 10% Pd/C, MeOH-THF 1:1, 23 °C, 17 h.

After quantitative debenzylation, a product with identical ^1H and ^{13}C NMR spectra to those reported for the natural compound was obtained (see Supporting Information) and its enantiomeric excess was determined by chiral HPLC analysis, resulting very high (98.7%; see Supporting Information). Moreover, we were glad to see that the sign of the optical rotation of this enantiopure compound was the same as that of the natural bruceolline I.[15] However, for our synthetic product (+)-**6** we measured an absolute value ($[\alpha]_D^{16}$ +38.5, c 0.47, MeOH) which was more than three times higher than that reported for natural bruceolline I ($[\alpha]_D^{20}$ +11.3, c 0.05,

MeOH),[3] a discrepancy which is likely due to the inaccuracy in the optical rotation measurement of a very low amount of the natural compound.

In conclusion we have described a short and efficient synthesis of bruceolline I which provides this natural compound in 29% overall yield over 9 steps. The key step of the process is a gold-catalyzed tandem sequence which allows for the rapid construction of the cyclopenta[b]indol-1-one core of the bruceolline in particularly high yield. This synthesis affords the synthetic bruceolline I in sufficient amount for its further evaluation in various biological tests.

Experimental Section

General Experimental Procedures. Melting points are uncorrected. Chromatographic separations were performed under pressure on silica gel by flash-column techniques; R_f values refer to TLC carried out on 0.25-mm silica gel plates (Merck F_{254}), with the same eluent as indicated for the column chromatography. ^{1}H NMR and ^{13}C NMR spectra were recorded at 400 and 100.4 MHz, respectively, in the specified deuterated solvent. Solvent reference lines were set at 7.26 and 77.00 ($CDCl_3$), 2.05 and 29.84 (acetone-d6), 3.31 and 49.00 (CD_3OD), 2.50 and 39.52 ppm (DMSO-d6) in ^{1}H and ^{13}C NMR spectra, respectively. Mass spectra were carried out by direct inlet of a 20 ppm solution in CH_3OH on a LCQ Fleet^{TM} Ion Trap LC/MS system with an electrospray ionization (ESI) interface in the positive mode, unless otherwise stated. Microanalyses were carried out with a CHN elemental analyzer. HPLC analyses were carried out with an HPLC instrument equipped with a Lux 5µ Cellulose-4 column, 250 x 4.60 mm and eluting at 0.3 mL/min flow rate in isocratic 15% IPA, 85% hexane. 6-((Triisopropylsilyl)oxy)indole[14] (**10**) and 6-benyzolyindole[13] (**11**) were prepared as reported.

Enynyl acetate **16** proved to be quite unstable when neat and elemental analysis could not be performed.

6-Benzyloxy-3-iodoindole-1-carboxylic acid methyl ester (14). Crushed KOH (205 mg, 3.7 mmol) was added to a solution of the 6-benzyloxyindole (327 mg, 1.46 mmol) in anhydrous DMF (1.7 mL) and the resulting suspension was stirred at room temperature for 20 min. A solution of I_2 (372 mg, 1.46 mmol) in anhydrous DMF (1.7 mL) was then dropwise added and, after 1 h, the reaction mixture was poured into ice water (34 mL) containing NH_4OH (0.5%) and $K_2S_2O_5$ (0.1%). A precipitate immediately formed and this was collected by filtration, washed with chilled water (30 mL) and dried under reduced pressure. The so obtained 3-iodo-6-benzyloxyindole-1*H*-indole **13** (455 mg, 89%) was immediately used in next step: ^{1}H NMR (400 MHz): δ = 8.19 (br s, 1 H), 7.48-7.42 (m, 2 H), 7.42-7.36 (m, 2 H), 7.35-7.31 (m, 2 H), 7.17 (d, *J* 2.4 Hz, 1 H), 6.95 (dd, *J* 8.4, 2.4 Hz, 1 H), 6.92 (d, *J* 2.0 Hz, 1 H), 5.12 (s, 2 H) ppm.

3-Iodo-6-benzyloxy-1*H*-indole **13** (450 mg, 1.29 mmol) was dissolved in anhydrous THF (8.6 mL) and, after cooling at -78°C (internal), LiHMDS 1.0 M in THF (1.35 mL, 1.35 mmol) was slowly added, keeping the temperature below -70 °C. After 15 min, methyl chloroformate (105 μL, 1.35 mmol) was slowly added and, after further 15 minutes, the cooling bath was removed and the reaction mixture was stirred at room temperature until complete consumption of the starting material (2 h). An 0.5 M aqueous solution of $NaHCO_3$ (15 mL) was added under vigorous stirring and the product extracted by EtOAc (3 x 15 mL). The combined organic extracts were dried over anhydrous Na_2SO_4. After filtration and evaporation of the solvent, crude **14** was isolated and purified by flash chromatography (eluent: *n*-hexane-EtOAc, 12:1; R_f = 0.26), affording pure **14** as a white solid (664 mg, 79%): m.p. = 94.1 - 94.8 °C; ^{1}H NMR (400 MHz): δ

= 7.83 (br s, 1 H), 7.62 (s, 1H), 7.51-7.46 (m, 2 H), 7.44-7.37 (m, 2 H), 7.37-7.31 (m, 1 H), 7.28 (d, *J* 8.4 Hz, 1 H), 7.03 (dd, *J* 8.4, 2.4 Hz, 1 H), 5.15 (s, 2 H), 4.02 (s, 3 H) ppm; ^{13}C NMR (100.4 MHz): δ = 157.9 (s), 150.5 (s), 136.8 (s), 135.5 (s), 128.6 (d, 2 C), 128.4 (d), 128.0 (d), 127.6 (d, 2 C), 126.0 (s), 122.1 (d), 113.4 (d), 100.2 (d), 70.5 (t), 66.2 (s), 54.0 (q) ppm; MS/MS (ESI) *m/z* (%): 408 ($[M+1]^+$, 6), 281 ($[M+1-I]^+$, 100); elemental analysis calcd (%) for $C_{17}H_{14}INO_2$: C 50.14, H 3.47, N 3.44; found: C 50.35, H 3.50, N 3.54.

3-(3-Acetoxy-3-methylbut-1-ynyl)-6-benzyloxyindole-1-carboxylic acid methyl ester (16). A 5:1 (v/v) solution of Et_3N/DMF (7.2 mL) was added in a round bottom flask containing compound **14** (660 mg, 1.62 mmol), $(Ph_3P)_2PdCl_2$ (57 mg, 0.081 mmol) and CuI (9 mg, 0.049 mmol). Neat 2-methyl-3-butyn-2-ol (190 μL, 1.94 mmol) was then added and the reaction mixture heated at 40 °C under vigorous stirring until complete consumption of the starting material (TLC; 1 h). The mixture was then cooled at rt and quenched by water (22 mL). The product was extracted by EtOAc (3 x 20 mL) and the combined organic extracts dried over anhydrous K_2CO_3. After filtration and evaporation of the solvent, crude **15** was purified by flash chromatography (eluent: *n*-hexane-EtOAc, 2:1 + 1% Et_3N; R_f = 0.40) affording intermediate **15** that was immediately used in the next acetylation step: ^{1}H NMR (400 MHz): δ = 7.83 (br s, 1 H), 7.63 (s, 1 H), 7.52-7.47 (m, 3 H), 7.42-7.38 (m, 2 H), 7.35-7.33 (m, 1 H), 7.02 (dd, *J* 8.8, 2.4 Hz, 1 H), 5.14 (s, 2 H), 4.03 (s, 3 H), 1.66 (s, 6 H) ppm.

A solution of enynyl alcohol **15** (1.62 mmol) in anhydrous DCM (16.2 mL) was cooled at 0 °C (ice bath) and DMAP (30 mg, 0.24 mmol), Et_3N (1.13 mL, 8.1 mmol) and Ac_2O (605 μL, 4.9 mmol) were added. After 10 min, the ice bath was removed and the reaction mixture was stirred at 25 °C for 15 h, then quenched by addition of a satd solution of $NaHCO_3$ (15 mL). After

separation of the phases, the aqueous layer was extracted with DCM (2 x 15 mL) and the combined organic extracts were dried over anhydrous K_2CO_3. After filtration and evaporation of the solvent, crude **16** was obtained and purified by flash column chromatography (eluent: *n*-hexane-EtOAc, 7:1 + 1% Et_3N; R_f = 0.24), affording pure acetate **16** (591 mg, 90% over 2 steps) as a colorless oil. This was stored at 4°C as 0.1 M solution in the eluent until use: ^{1}H NMR (400 MHz): δ = 7.81 (br s, 1 H), 7.66 (s, 1 H), 7.54 (d, *J* 8.4 Hz, 1 H), 7.49-7.46 (m, 2 H), 7.42-7.37 (m, 2 H), 7.36-7.31 (m, 1 H), 7.02 (dd, *J* 8.8, 2.4 Hz, 1 H), 5.13 (s, 2 H), 4.02 (s, 3 H), 2.07 (s, 3 H), 1.79 (s, 6 H) ppm; ^{13}C NMR (100.4 MHz): δ = 169.3 (s), 157.7 (s), 150.9 (s), 136.9 (s), 135.5 (s), 128.5 (d, 2 C), 128.0 (d), 127.6 (d, 2 C), 127.3 (d), 124.5 (s), 120.7 (d), 113.3 (d), 103.6 (d), 100.6 (s), 94.0 (s), 75.8 (s), 72.5 (s), 70.5 (t), 54.0 (q), 29.2 (q, 2 C), 22.0 (q) ppm; MS (ESI) *m/z* (%): 428 ($[M+Na]^+$, 8), 346 ($[M-CO_2Me]^+$, 100).

6-Benzyloxy-3,3-dimethyl-1-oxo-2,3-dihydro-1*H*-cyclopenta[*b*]indole-4-carboxylic acid methyl ester (17). The solution of **16** in the eluent was concentrated and dried under *vacuum* (no heating) for 30 minutes. Gold(I) complex $(4\text{-}CF_3C_6H_4)_3PAuCl$ (31 mg, 44 μmol) was dissolved in DCM (8.8 mL, 0.005 M) and $AgSbF_6$ (15 mg, 44 μmol) was added. The formed suspension was left to stir at 25 °C under nitrogen atmosphere. After 15 min a solution of enynyl acetate **16** (591 mg, 1.46 mmol) in DCM (20.2 mL; final concentration 0.05 M) was added and reaction mixture was stirred at 25 °C for 50 minutes. Water (50 mL) was added, the phases separated and the product extracted with DCM (2 x 25 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated. The oily residue was purified by flash chromatography (eluent: *n*-hexane-EtOAc, 4:1; R_f = 0.22), affording pure compound **17** (435 mg, 82%) as an orange solid: m.p. = 115.3-116.5 °C; ^{1}H NMR (400 MHz): δ = 7.78 (d, *J* 8.4 Hz,

1 H), 7.77 (d, *J* 2.4 Hz, 1 H), 7.49-7.45 (m, 2 H), 7.42-7.38 (m, 2 H), 7.36-7.31 (m, 1 H), 7.03 (dd, *J* 8.4, 2.4 Hz, 1 H), 5.14 (s, 2 H), 4.10 (s, 3 H), 2.90 (s, 2 H), 1.60 (s, 6 H) ppm; ^{13}C NMR (100.4 MHz): δ = 196.0 (s), 171.5 (s), 157.6 (s), 150.8 (s), 141.9 (s), 136.8 (s), 128.6 (d, 2 C), 128.0 (d), 127.5 (d, 2 C), 124.8 (s), 121.2 (d), 115.7 (s), 113.2 (d), 103.0 (d), 70.6 (t), 59.2 (s), 54.1 (q), 39.8 (t), 26.8 (q, 2 C) ppm; MS (ESI) *m/z* (%): 749 ([2M+Na]$^+$, 100), 364 ([M+1]$^+$, 52); elemental analysis calcd (%) for $C_{22}H_{21}NO_4$: C 72.71, H 5.82, N 3.85; found: C 72.67, H 5.72, N 3.54.

6-Benzyloxy-3,3-dimethyl-1,2-dioxo-2,3-dihydro-1*H*-cyclopenta[*b*]indole-4-carboxylic acid methyl ester (18). Compound **17** (420 mg, 1.16 mmol) was dissolved into 1,4-dioxane (13 mL) and SeO_2 (513 mg, 4.6 mmol) was then added in one portion to this solution. The mixture was heated at 100 °C (external) for 17 h; after cooling to room temperature, water (220 mL) was added and the product extracted with EtOAc (3 x 75 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated. Purification of the crude by flash chromatography (*n*-hexane/EtOAc, 4:1; R_f = 0.17) afforded pure **18** (236 mg, 64%) as a yellow solid: m.p. = 173.7-174.7 °C; ^{1}H NMR (400 MHz): δ = 7.91 (d, *J* 8.8 Hz, 1 H), 7.79 (d, *J* 2.0 Hz, 1 H), 7.49-7.46 (m, 2 H), 7.43-7.38 (m, 2 H), 7.37-7.33 (m, 1 H), 7.11 (dd, *J* 8.4, 2.0 Hz, 1 H), 5.17 (s, 2 H), 4.17 (s, 3 H), 1.59 (s, 6 H) ppm; ^{13}C NMR (100.4 MHz): δ = 204.7 (s), 177.7 (s), 169.7 (s), 158.9 (s), 150.1 (s), 139.8 (s), 136.4 (s), 128.6 (d, 2 C), 128.2 (d), 127.5 (d, 2 C), 127.4 (s), 122.4 (d), 115.6 (s), 114.1 (d), 103.0 (d), 70.7 (t), 54.8 (q), 45.9 (s), 22.5 (q, 2 C) ppm; MS (ESI) *m/z* (%): 777 ([2M+Na]$^+$, 100), 400 ([M+Na]$^+$, 21), 378 ([M+1]$^+$, 23); elemental analysis calcd (%) for $C_{22}H_{19}NO_5$: C 70.02, H 5.07, N 3.71; found: C 70.10, H 4.85, N 3.99.

6-Benzyloxy-3,3-dimethyl-3,4-dihydrocyclopenta[*b*]indole-1,2-dione (19). Compound **18** (228 mg, 0.60 mmol) was suspended in MeOH (6 mL) and *tert*-butylamine (1.9 mL, 18 mmol) was added. The clear solution was heated at 90 °C (external) for 1 h and, after cooling, volatiles were removed under *vacuum*. The so obtained crude was triturated with *n*-hexane, affording pure compound **19** (190 mg, 99%) as an orange solid: m.p. = 262 °C (dec); ^{1}H NMR (400 MHz, CD_3OD): δ = 7.83 (d, *J* 8.8 Hz, 1 H), 7.48-7.46 (m, 2 H), 7.41-7.36 (m, 2 H), 7.34-7.29 (m, 1 H), 7.11 (d, *J* 2.4 Hz, 1 H), 7.04 (dd, *J* 8.8, 2.4 Hz, 1 H), 5.17 (s, 2 H), 1.47 (s, 6 H) ppm; ^{13}C NMR (100.4 MHz, CD_3OD): δ = 207.3 (s), 177.0 (s), 174.1 (s), 159.6 (s), 143.3 (s), 138.5 (s), 129.5 (d, 2 C), 128.9 (d), 128.6 (d, 2 C), 123.7 (s), 123.5 (d), 116.6 (s), 114.3 (d), 99.8 (d), 71.5 (t), 43.1 (s), 23.4 (q, 2 C) ppm; MS (ESI) *m/z* (%): 661 ($[2M+Na]^+$, 100), 342 ($[M+Na]^+$, 42), 320 ($[M+1]^+$, 42); elemental analysis calcd (%) for $C_{20}H_{17}NO_3$: C 75.22, H 5.37, N 4.39; found: C 75.14, H 5.23, N 4.17.

(+)-(2*R*)-6-Benzyloxy-2-hydroxy-3,3-dimethyl-3,4-dihydro-2*H*-cyclopenta[*b*]indol-1-one (20). A solution of (+)-DIP-Cl (362 mg, 1.13 mmol) in anhydrous THF (16 mL) was cooled at -45 °C and a solution of the substrate **19** (120 mg, 0.38 mmol) in anhydrous THF (16 mL) was added dropwise, keeping the temperature below -40 °C during the addition. After 10 minutes the reaction was quenched at -45 °C by adding diethanolamine (360 μL, 3.76 mmol), the cooling bath removed and the mixture left under vigorous stirring at room temperature for 1.5 h. The white precipitate was filtered off over a celite pad, washed with THF (2 x 4 mL) and the filtrate was concentrated under *vacuum* to afford crude **20**. This was purified by flash chromatography, eluting first with *n*-hexane-EtOAc, 2:1 and then with *n*-hexane-EtOAc, 1:2 (R_f = 0.16). Pure **20** was so obtained (110 mg, 91%) as a white solid: m.p. = 150.7-152.5 °C; $[\alpha]_D^{20}$ + 22.4 (*c* 0.37,

$CHCl_3$); ^{1}H NMR (400 MHz): δ = 8.42 (br s, 1 H), 7.78 (d, *J* 8.8 Hz, 1 H), 7.47-7.43 (m, 2 H), 7.42-7.37 (m, 2 H), 7.36-7.30 (m, 1 H), 7.00 (dd, *J* 8.8, 2.0 Hz, 1 H), 6.95 (d, *J* 2.0 Hz, 1 H), 5.12 (s, 2 H), 4.34 (s, 1 H), 1.57 (s, 3 H), 1.32 (s, 3 H) ppm; ^{13}C NMR (100.4 MHz): δ = 194.7 (s), 171.8 (s), 156.5 (s), 142.8 (s), 136.8 (s), 128.5 (d, 2 C), 127.9 (d), 127.4 (d, 2 C), 121.6 (s), 123.5 (d), 115.4 (d), 114.2 (s), 112.2 (d), 98.2 (d), 86.0 (d), 70.4 (t), 40.7 (s), 24.8 (q), 24.2 (q) ppm; MS (ESI) *m/z* (%): 665 ($[2M+Na]^+$, 100), 344 ($[M+Na]^+$, 50), 322 ($[M+1]^+$, 17); MS (ESI, negative mode) *m/z* (%): 320 ($[M-1]^-$, 100); elemental analysis calcd (%) for $C_{20}H_{19}NO_3$: C 74.75, H 5.96, N 4.36; found: C 74.47, H 5.88, N 4.06.

(+)-Bruceolline I (6). A solution of **20** (100 mg, 0.31 mmol) was prepared in a 1:1 mixture of anhydrous MeOH-THF (16 mL) and Pd/C 10% (33 mg, 0.031 mmol) was added under nitrogen. The resulting suspension was flushed with hydrogen under vigorous stirring and left under hydrogen atmosphere (balloon) at 23 °C for 17 h. The catalyst was filtered off over a celite pad, washed with methanol and the filtrate concentrated under vacuum. The so obtained crude was purified by flash chromatography (eluent: DCM-MeOH, 10:1; R_f = 0.14) and pure (+)-Bruceolline I **6** (69 mg, 96%) was obtained as a white solid: m.p. = 210 °C (dec); $[\alpha]_D^{16}$ + 38.5 (*c* 0.47, CH_3OH); ^{1}H NMR (400 MHz, acetone-d6):[3] δ = 10.92 (br s, 1 H), 8.27 (br s, 1 H), 7.54 (d, *J* 8.4 Hz, 1 H), 6.92 (d, *J* 2.0 Hz, 1 H), 6.78 (dd, *J* 8.4, 2.4 Hz, 1 H), 4.52 (br s, 1 H), 4.23 (s, 1 H), 1.53 (s, 3 H), 1.30 (s, 3 H) ppm; ^{13}C NMR (100.4 MHz, acetone-d6):[3] δ = 194.2 (s), 171.5 (s), 155.6 (s), 144.2 (s), 121.7 (d), 115.7 (s), 115.1 (s), 112.3 (d), 99.4 (d), 86.9 (d), 41.1 (s), 25.4 (q), 24.5 (q) ppm; ^{1}H NMR (400 MHz, CD_3OD): δ = 7.61 (dd, *J* 8.8, 0.8 Hz, 1 H), 6.83 (d, J 2.0 Hz, 1 H), 6.72 (dd, *J* 8.8, 2.0 Hz, 1 H), 4.28 (s, 1 H), 1.51 (s, 3 H), 1.30 (s, 3 H) ppm; ^{13}C NMR (100.4 MHz, CD_3OD): δ = 196.0 (s), 173.7 (s), 156.2 (s), 145.0 (s), 122.4 (d), 115.9 (s), 115.1

(s), 112.7 (d), 99.5 (d), 87.3 (d), 41.7 (s), 25.3 (q), 24.4 (q) ppm; MS (ESI) *m/z* (%): 485 ($[2M+Na]^+$, 68), 254 ($[M+Na]^+$, 100); MS (ESI, negative mode) *m/z* (%): 230 ($[M-1]^-$, 100); elemental analysis calcd (%) for $C_{13}H_{13}NO_3$: C 67.52, H 5.67, N 6.06; found: C 67.23, H 5.99, N 6.51.

(±)-Bruceolline I (6). Prepared subjecting **19** (70 mg, 0.22 mmol) to the same hydrogenation procedure reported for compound **20**. After 16 h the reaction was stopped and the crude mixture of **5** and (±)-**6** was separated by flash chromatography (eluent: DCM-MeOH, 1:1), affording pure (±)-**6** (38 mg, 74%) and a small amount of pure **5** (10 mg, 20%). Spectroscopical data of both compounds are identical to those already reported above (compound **6**) and in the literature (compounds **5** and **6**).[3,9]

Associated contents.

Supporting Information. The Supporting Information is available free of charge on the ACS Publications website at DOI:....

^1H and ^{13}C NMR spectra of all new compounds, HPLC chromatograms of both racemic and (+)-Bruceolline I, crystal structure determination and crystal data of Bruceolline H (PDF).

Crystallographic data of Bruceolline H (CIF).

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Notes

The authors declare no competing financial interest.

Acknowledgments

We gratefully acknowledge Università degli Studi di Firenze for financial support and Ente Cassa di Risparmio di Firenze for granting a 400 MHz NMR spectrometer. Dr Sandra Cencetti is acknowledged for technical support.

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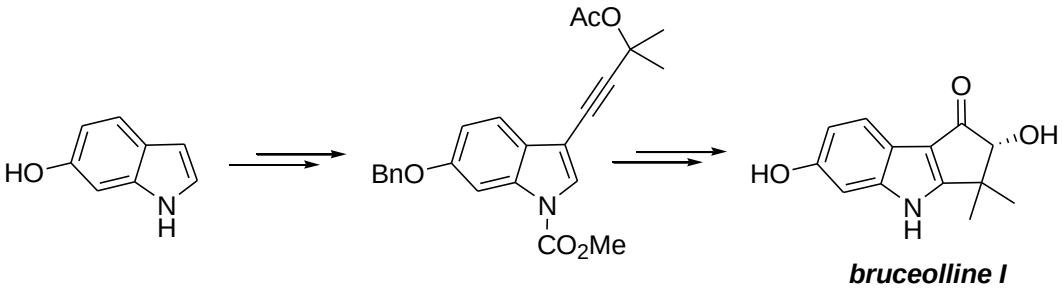
(15) Unfortunately, we could not manage to get crystals suitable for X-ray analysis of bruceolline I.

Graphical Abstract



bruceolline I
>99% e.e.